25 April 2024
EMA/226759/2024
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Obgemsa

International non-proprietary name: vibegron

Procedure No. EMEA/H/C/005957/0000

Note

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

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List of abbreviations

[14C]	Radiolabeled with carbon 14
[3H]	Radiolabeled with tritium
[I]max,b	Maximal total concentration in the blood at steady state
^{14}C	Radiolabelled with carbon 14
^{3}H	Radiolabelled with tritium
A50	50% of the lipid accumulation induced by 10 µM of amiodarone
ABPM	Ambulatory blood pressure monitoring
ADD	Average daily dose
ADME	Absorption, distribution, metabolism, and excretion
ADR	Adverse drug reaction
AE	Adverse event
AI	Acceptable intake
ALP	Alkaline phosphatase
ALT	Alanine transferase
ANCOVA	Analysis of covariance
AR	Adrenergic receptor
AUC	Area Under Curve
AUC0-24	Area under the concentration-time curve from time zero (pre-dose) to 24 hours post-dose or over 24 hours
AUC0-∞	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC0-t	Area-under-the-plasma-concentration vs. time curve from time zero to the last detectable plasma concentration
AUCτ	Area under the concentration-time curve over the dosing interval
BA	Bioavailability
BCS	Biopharmaceutics Classification System
BDC	Bile-duct cannulated
BE	Bioequivalence
BMAX	Maximum distribution capacity
BMI	Body mass index
BP	Blood pressure
BPH	Benign prostate hypertrophy
bpm	Beats per minute
C24h	Concentration 24 hours post dose
CAC	Carcinogenicity Assessment Committee
cAMP	Cyclic adenosine monophosphate
CFB	Change from baseline
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	Confidence interval
CL	Systemic clearance
CL/F	Apparent clearance following oral dosing
cLDA	constrained longitudinal data analysis

Cmax	Maximum concentration
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CPCA	Carcinogenic potency categorisation approach
CSR	Clinical study report
Ctrough	Plasma concentration at 24 hours after the morning dose on Study Day 14 or 28
CV	Cardiovascular
CV	Coefficient of variation
CVb	Between-subject variability (or coefficient of variation)
CVw	Within-subject variability (or coefficient of variation)
CYP	Cytochrome P450
D	Dose
DART	Developmental and reproductive toxicology
DDI	Drug-drug interaction
EC	European Commission
EC	European Community
EC_{50}	Half maximal effective concentration
ECG	Electrocardiogram
EDC	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide
EFD	Embryo-foetal development
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ER	Extended release
EU	European Union
F	Female
F0	Parental
F1	First filial
FAS	Full Analysis Set
FAS-Ext	Full Analysis Set-Extension
FAS-Ext-I	Full Analysis Set - Extension for Incontinence
FAS-I	Full Analysis Set for Incontinence
FDA	US Food and Drug Administration
FFA	Free fatty acids
Fg	Fraction of absorbed dose escaping gutwall extraction
FTIR	Fourier transform infrared spectroscopy
fu,b	Fraction unbound in blood
GC	Gas Chromatography
GCP	Good Clinical Practice
GD	Gestation day
GLP	Good Laboratory Practice
GMR	Geometric mean ratio
HCl	Hydrochloric acid
HDPE	High Density PolyEthylene
hERG	Human ether-à-go-go-related gene
HI	Hepatic impairment
HPLC	High performance liquid chromatography

HPLC-MS	High performance liquid chromatography-mass spectrometry
HR	Heart rate
IBD	International Birth Date
IBS	Irritable bowel syndrome
IC_{50}	Half-maximal inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human use
ICP-MS	inductively coupled plasma mass spectrometry
IIV	Interindividual variability
IND	Investigational New Drug
INN	International Nonproprietary Name
IPC	In-Process Control
IS	Internal standard
ISR	Incurred sample reanalysis
ISS	Integrated Summary of Safety
IV	Intravenous(ly)
ka	Absorption rate constant
KF	Karl Fischer titration
K_i	Inhibitory constant
LF	Long form
LOAEL	Lowest-observed-adverse-effect level
LS	Least-square
M	Metabolite
M	Male
M2	Muscarinic acetylcholine receptor 2
MAA	Marketing Authorisation Application
MACCE	Major adverse cardiac and cerebrovascular events
MAD	Multiple ascending dose
MATE	Multidrug and toxin extrusion transporter
MBP	Mean blood pressure
MedDRA	Medical Dictionary for Regulatory Activities
Merck	Merck Sharp & Dohme Corp
MF	Micturition frequency
MK-4618	Vibegron code used by Merck & Co., Inc. [Merck], previous Sponsor
MMRM	Mixed model for repeated measures
MP	Merck Process
MTT	Mean transit time
N	Number of subjects
NC	Not calculated
ND	Not Detected
NMR	Nuclear Magnetic Resonance
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
NPA	N-nitroso pyrrolidine aniline
NT	Not tested
N-Vib	N-Nitrosovibegron
OAB	Overactive bladder

OAB-d	Overactive bladder type (Wet, Dry, or Missing [categorised based on diary data])
OAB-q	Overactive Bladder Questionnaire
OAB-q LF	Overactive Bladder Questionnaire long-form
OATP	Organic anion-transporting polypeptide
OC	Oral contraceptive
OCT	Organic cation transporter
PD	Pharmacodynamic(s)
PDCO	Paediatric Committee
PDE	Permitted Daily Exposure
P-gp	Permeability glycoprotein
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PND	Postnatal Day
ppm	Parts per million
PPND	Pre- and postnatal development
PPS	Per-Protocol Set
PPS-I	PPS-Incontinence
PT	Preferred term
PVR	Post-void residual volume (urine)
Q	Every
Q	Specified amount of dissolved active substance, expressed as a percentage of the labelled content
QC	Quality control
QD	Once daily
QH	Total hepatic blood flow
QoL	Quality of life
QTc	Corrected QT
QTcF	Fridericia's corrected QT interval
QTcI	Individual-specific QT correction
PSUR	Periodic safety update report
R	Predicted ratio of the victim drug's AUC in the presence and absence of an inhibitor for basic models of enzyme
RH	Relative Humidity
RI	Renal impairment
RMP	Risk management plan
RPM	Rotations Per Minute
RSM	Regulatory Starting Material
RVT-901	Vibegron (Urovant code number)
SA	Safety Analysis
SAD	Single ascending dose
SAE	Serious adverse event
SAF	Safety population
SAF	Safety Analysis Set
SAF-Ext	Safety population-extension
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error

SmPC	Summary of Product Characteristics
SOC	System organ class
t½	Terminal phase half-life
Term	Definition
Tmax	Time of occurrence of Cmax
TSE	Transmissible spongiform encephalopathy
TX	Texas
TYMC	Total Yeast and Mold Count
UGT	Uridine Diphosphate Glucuronosyltransferase
URO-901	Vibegron code used by Urovant Sciences GmbH [Urovant]
Urovant	Urovant Sciences GmbH
US	United States
UUI	Urgency urinary incontinence
UV	Ultraviolet
UVR	Ultraviolet radiation
V2	Central volume of distribution
XRPD	X-Ray Powder Diffraction
β3-AR	Beta 3-adrenergic receptor

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pierre Fabre Medicament submitted on 19 April 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Obgemsa, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 June 2021.

The applicant applied for the following indication:

Vibegron is indicated in symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with Overactive Bladder (OAB) syndrome.

The name of this medicinal product was changed during the procedure from Vibegron to Obgemsa and both names might be referred to in this document.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0288/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0288/2022 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Applicant's request for consideration

1.5.1. New active Substance status

The applicant requested the active substance vibegron contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal

product previously authorised within the European Union

1.6. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
15 November 2012	EMEA/SAWP/698154/2012	*Prof Minne Casteels and Dr Andre Elferink*
21 July 2022	EMA/SA/0000086987	*Dina Apele-Freimane and Adriana Ammassari*

The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

Quality:

- the proposed regulatory starting materials (RSMs) for the synthesis of vibegron drug substance.
- the approach to use drug substance primary stability batches manufactured using the same process but with different starting points as RSMs compared to the proposed commercial process for determination of re-test period.
- evaluation of the risk of presence of nitrosamine impurities.

Non-clinical:

- Acceptability of the safety pharmacology, repeat-dose toxicology, genotoxicity, carcinogenicity, and developmental and reproductive toxicology programmes for phase III and MAA.

Multidisciplinary Non-clinical and Clinical:

- Characterisation of potential PK interactions with other medicines and information intended for product information.

Clinical:

- Clinical pharmacology programme.
- Evaluation of drug effects on PT/INR.
- Use of dried blood spot as a PK sampling method.
- Overall clinical development plan for MAA, in particular the primary endpoint, comparator, data collection regarding the possibility of bladder outflow obstruction and urinary retention, statistical analysis, type I error control, unblinding procedures, population, cardiovascular monitoring, long term exposure for safety, and dose selection for phase III.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Tomas Radimersky

The application was received by the EMA on	19 April 2023
The procedure started on	18 May 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 August 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 August 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 August 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 September 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 December 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	30 January 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 February 2024
The CHMP Rapporteurs circulated the CHMP and PRAC updated Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	15 February 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	22 February 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 March 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 April 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	18 April 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Obgemsa on	25 April 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	25 April 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Overactive bladder (OAB) syndrome is a clinical syndrome characterised by urinary urgency (i.e., a sudden compelling desire to void that is difficult to defer), with or without UUI, and usually accompanied by urinary frequency and nocturia [Scarneciu, 2021; Stewart, 2003; Abrams, 2002; Milsom, 2001] in the absence of urinary tract infection or other obvious pathology.

The proposed indication for Obgemsa is:

Obgemsa is indicated in symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with Overactive Bladder (OAB) syndrome.

2.1.2. Epidemiology

Overactive bladder (OAB) syndrome is a common disease among middle aged and elderly adults.

The prevalence of OAB in adults is difficult to estimate because of the negative social impact it may have, and most affected patients do not seek medical care. However, OAB is highly prevalent and may be affecting 1 in 7 adults (both men and women) in European and North American populations. This prevalence increases with age, and OAB affects approximately one-third of adults over 75 years of age [Sexton, 2009; Stewart, 2003; Milsom, 2001]. A recent review analysing 5 key studies on the epidemiology of OAB in several countries across Europe, the United States (US) and Canada showed that the prevalence in adults ranged from 11.8% to 35.6% in the EU and US [Eapen, 2016]. According to European studies, approximately 36% of men and 43% of women over 40 year of age have symptoms of OAB [Coyne, 2011].

2.1.3. Clinical presentation and diagnosis

OAB is a clinical syndrome characterised by urinary urgency (i.e., a sudden compelling desire to void that is difficult to defer), with or without UUI, and usually accompanied by urinary frequency and nocturia [in the absence of urinary tract infection or other obvious pathology. UUI is the involuntary loss of urine accompanied by urgency (referred to as OAB Wet) and is present in approximately one-third of patients with OAB [Stewart, 2003; Milsom, 2001]. In the absence of incontinence, OAB is referred to as OAB Dry. UUI is distinguished from stress urinary incontinence, which is the involuntary loss of urine on effort or physical exertion (e.g., sporting activities), or on sneezing or coughing. When both components are present, the classification is mixed urinary incontinence, with either urgency or stress specified as the predominant component. From a pathophysiological perspective, the OAB symptom complex is suggestive of detrusor overactivity, which may be intrinsic or may be secondary to neurological conditions such as stroke or spinal cord injury [Abrams, 2002].

2.1.4. Management

Several treatment options exist for OAB:

Anticholinergics

The most prescribed OAB medications are of the antimuscarinic drug class (e.g., tolterodine [Detrusitol], solifenacin [Vesicare], oxybutynin [Ditropan]).

B$_3$-AR Agonist

A first-generation β_3-AR agonist (mirabegron; Betmiga) has been approved in the EU in 2012 for the "symptomatic treatment of urgency, increased micturition frequency, and/or urgency incontinence as may occur in adult patients with OAB syndrome". It is an extended release (ER) product that cannot be crushed for administration in soft foods.

There is a guideline from 2013, "Guideline on the clinical investigation of medicinal products for the treatment of urinary incontinence" (CPMP/EWP/18/01/Rev. 1)

According to the Applicant, "there remains an unmet medical need for safe, effective, well tolerated, oral long-term therapies with rapid onset of action for treating OAB. The development programme of vibegron was designed to address the unmet medical needs of the currently existing therapies." This view is at least partly agreed to. The active compound in the present application, vibegron, has a similar mechanism of action as mirabegron. It is considered of advantage to have an alternative to mirabegron for patients achieving treatment with an β_3-AR agonist on the market if the product will subsequently be approved.

There is a disease burden in OAB, and although there is a diversity of therapies available, there is an unmet medical need for effective medicinal products with a benign safety profile.

2.2. About the product

Vibegron is a selective and potent human beta-3 adrenergic receptor agonist over β1-AR and β2-AR. Activation of the beta-3 adrenergic receptor located in the bladder detrusor muscle increases bladder capacity by relaxing the detrusor smooth muscle during bladder filling. Vibegron is β3-adrenergic receptor (β3-AR) agonist with more than 9000 times higher affinity to the β3 than to the β1 or β2 adrenergic receptor.

The pharmacological classification is: Urologicals, drugs for urinary frequency and incontinence, ATC code: G04BD15.

The initially claimed indication was "*Vibegron is indicated in symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with Overactive Bladder (OAB) syndrome.*"

The final approved indication is "*Obgemsa is indicated in symptomatic treatment of adult patients with overactive bladder (OAB) syndrome*".
The posology is 75 mg once daily for adults including elderly patients.

The pharmaceutical form is a film-coated tablet.

2.3. Type of Application and aspects on development

The development programme for Vibegron has included several sponsors.

In 2012, a Committee for Medicinal Products for Human Use (CHMP) Scientific Advice was provided on the non-clinical and clinical development of vibegron (MK-4618) in adult patients with OAB to the

original Sponsor Merck (EMA/CHMP/SAWP/698154/2012). CHMP scientific advice was also provided in 2022 with respect to the quality development (EMA/SA/0000086987).

In 2013, Merck submitted a Paediatric Investigation Plan (PIP) application to the European Medicines Agency (EMA) (EMEA-001415-PIP01-12). This PIP application was withdrawn in 2014 as Merck discontinued global development of vibegron.

In 2017, Urovant acquired the rights to develop and commercialise vibegron in multiple countries around the world. Of note, the vibegron clinical development programme planned by Urovant differed from the previous programme developed by Merck and discussed with EMA in 2012. This was undertaken to better align with recently released clinical guidelines, and with the new Sponsor's strategy as well as to consider US FDA requirements. In 2022, Pierre Fabre licensed from Urovant the rights for registration and commercialisation in the European Economic Area, the United Kingdom and Switzerland.

Urovant also updated the paediatric programme to focus on the treatment of detrusor overactivity as a monotherapy in children with neurogenic bladder dysfunction aged 6 months to <18 years. In 2020, a paediatric scientific advice was provided on CMC, non-clinical and clinical aspects to Urovant (EMA/CHMP/SAWP/465404/2020) and a PIP was agreed by the Paediatric Committee (PDCO) in June 2022 (EMEA-001415-PIP02-21) and was concluded with a positive EMA decision (P/0288/2022). The paediatric programme is out of the scope of the present MAA.

The submitted documentation in support of the approval of the product is extensive, with approximately 4300 individuals exposed to vibegron. Two of the performed clinical studies, studies 3003 and its extension study 3004, were performed with the dose proposed for marketing, 75 mg. These studies can be viewed in the table below.

For details of the above mentioned scientific advices please refer to previous section 1.6.

Table 1 Pivotal studies in support of the application Obgemsa

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
Study 3003	199 sites; Global (US, Poland, Hungary, Canada, Latvia, Lithuania)	Randomised, double-blind, placebo- and active controlled, multi centre parallel group study	Vibegron 75 mg, placebo, or tolterodine ER 4 mg Admini-stered once daily	Efficacy, safety, and PK profile of vibegron in patients with symptoms of OAB	vibegron (n=545/502) placebo (n=540/486) tolterodine (n=430/385)	12 weeks following a 2-week placebo run-in phase	M= 217 F=1246 Median age 60 years	OAB for at least 3 months prior to the screening visit	Two co-primary endpoints;change from baseline in micturitions, and average daily number of urge urinary incontinence episodes
Study 3004	109 Sites; US	Randomised, double-blind, active controlled, extension study for patients who completed Study 3003	Vibegron 75 mg, or tolterodine ER 4 mg Administered once daily	Safety, tolerability, and efficacy of vibegron in patients with symptoms of OAB	505[a] completers from Study 3003. vibegron (n=273[a]/235) tolterodine (n=232[a]/195)	40-weeks, following Week 12	M= 110 F=395 Median age at entry 61 years	OAB; having finalised study 3003	Incidence of TEAEs Secondary efficacy endpoints: CFB at Week 52 in the mean daily number of micturitions, UUI, urgency episodes, and total urinary incontinence episodes

Vibegron 50 mg was approved for the treatment of OAB in adult patients in Japan in September 2018. Vibegron 75 mg was approved for the treatment of OAB in adult patients in the US in December 2020 (Tradename GEMTESA, marketed in the US by Urovant).

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets containing 75 mg of vibegron as active substance.

Other ingredients are:

Tablet core: mannitol, microcrystalline cellulose, croscarmellose sodium, hydroxypropylcellulose, magnesium stearate.

Film-coating: hypromellose, triacetin, titanium dioxide, lactose monohydrate, iron oxide yellow and indigo carmine aluminium lake.

The product is available in white square or round high-density polyethylene (HDPE) bottles closed with an induction seal and child-resistant polypropene (PP) cap.

2.4.2. Active Substance

General information

The chemical name of vibegron is (6*S*)-*N*-[4-[[(2*S*,5*R*)-5-[(*R*)-hydroxy(phenyl)methyl]-pyrrolidin-2-yl]methyl]phenyl]-4-oxo-7,8-dihydro-6*H*-pyrrolo[1,2-a]pyrimidine-6-carboxamide corresponding to the molecular formula $C_{26}H_{28}N_4O_3$. It has a relative molecular mass of 444.54 g/mol and the following structure:

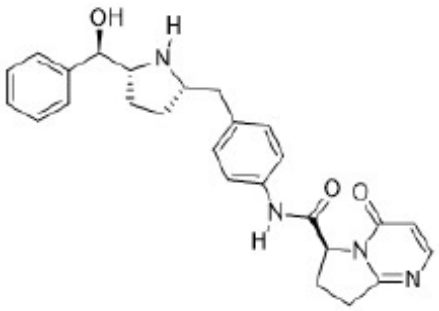


Figure 1: active substance structure

The chemical structure of vibegron was elucidated by a combination of ^{1}H- and ^{13}C-NMR spectroscopy, mass spectrometry, infrared spectroscopy, and UV spectroscopy. X-ray crystallography was used to confirm the absolute stereochemistry. The solid-state properties of the active substance were measured by thermogravimetric analysis, differential scanning calorimetry, and x-ray powder diffraction.

The active substance is a white to off-white to tan crystalline solid. Particle size is determined by the final manufacturing step conditions. Polymorphism has not been observed for vibegron.

Vibegron exhibits stereoisomerism due to the presence of 4 chiral centres. The correct enantiomer is ensured by the control strategy and diastereomers are controlled to appropriate levels.

Manufacture, characterisation and process controls

Vibegron is synthesised using well defined starting materials with acceptable specifications. Several manufacturers are involved in the process, conducting different synthetic steps and associated release testing.

Control of stereoisomers and other impurities were extensively discussed. Critical synthetic steps were defined along with associated process parameters and in-process controls (IPCs). The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of active substances. Potential and actual impurities, including potentially genotoxic impurities, were discussed with regards to their origin and characterised, however, several deficiencies were identified in the initial dossier resulting in 2 major objections as the control strategy for potentially mutagenic impurities had not been adequately justified. The applicant provided further justification and data during the procedure and the issues were considered resolved. The overall control strategy is considered appropriate.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. Changes introduced have been presented in sufficient detail and have been justified.

The active substance is packaged in double LDPE bags sealed with cable ties. The bags are stored in sealed HDPE drums. The primary contact materials comply with Commission Regulation (EU) 10/2011, as amended.

Specification

The active substance specification includes tests for appearance (visual), identity (FTIR, HPLC), water content (KF), elemental impurities (ICP-MS), residual solvents (GC), impurities including stereoisomers (GC, HPLC, chiral HPLC), genotoxic impurities (HPLC-MS), assay (HPLC), specific optical rotation (polarimetry), residue on ignition (Ph. Eur.), and particle size distribution (laser diffraction).

Acceptable justifications for the proposed specifications have been provided and the proposed acceptance criteria were set in line with ICH or Ph. Eur. standards.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. Limits for solvents, elemental and genotoxic impurities have been set according to the relevant ICH guidelines.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented.

Batch analysis data from 10 batches up to production scale from manufacturers responsible for the final active substance process steps and batch release are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 10 production scale batches of active substance from the proposed manufacturers stored in the intended commercial package according to the ICH guidelines were provided.

The following parameters were tested: appearance, water content, assay, impurities, genotoxic impurities, particle size and solid-state form (by XRPD as per characterisation data). The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications and no trends were observed.

Photostability testing following the ICH guideline Q1B was performed as part of the forced degradation studies, which demonstrated the stability indicating nature of the test methods. Additional conditions tested included acidic, basic and oxidative aqueous media and dry heat.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period and storage conditions.

2.4.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Obgemsa 75 mg film-coated tablets are light green, oval, debossed with V75 on one side and plain on the other. The qualitative composition is provided in SmPC section 6.1 and in paragraph 2.4.1 of this report. No overages are used.

The initial development of the finished product took place at a previous sponsor and was continued by the current applicant. The aim was to provide a once per day oral dosage form suitable for the intended patient population. The components of the tablets are described, the choice of excipients included in the composition is justified and their functions are explained. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report.

Pharmaceutical development is adequately described in the dossier, including studies carried out evaluating relevant manufacturing process parameters. Further development of the 75 mg tablet was conducted at the proposed commercial manufacturer, including scale up studies with adjustments of the manufacturing process parameters.

The development of the dissolution methods used for testing of the tablet formulations and for comparisons is described. A major objection was raised with respect to the acceptability of the QC dissolution method in the initial dossier and the demonstration of discriminatory power. The applicant provided further data and tightened the specification in response. The dissolution method and associated specification are considered suitable for the finished product.

The primary packaging is white HDPE bottles closed with a child resistant polypropylene (PP) cap and an inner seal containing a polyethylene (PE) layer in contact with the tablets. The materials in contact with the tablets comply with EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of blending of components, granulation, compression into tablets and film-coating. The process is considered to be a standard manufacturing process.

The applicant states that through development of the process, it was demonstrated that none of the process parameters are considered critical. Process control parameters and in-process controls have been established and will be used to monitor commercial manufacturing process.

Major steps of the manufacturing process have been validated on 3 consecutive production scale batches of the finished product. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance (visual), identification (UV, HPLC), water content (KF), assay (HPLC), content uniformity (Ph. Eur.), related substances (HPLC), *N*-nitrosovibegron (LCMS/MS) and dissolution (Ph. Eur.).

The proposed specifications are acceptable. The acceptance criteria were set on the basis of batch and stability data, and are in line with ICH guidelines and the Ph. Eur.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). *N*-nitrosovibegron was detected in some batches of finished product below the proposed acceptable intake (AI). Initially, no routine control was proposed and no information on root causes was provided resulting in a major objection. Furthermore, the AI had not been justified in line with latest policy. In response, the applicant proposed a limit of 1500 ng/day based on structural features in line with the carcinogenic potency categorisation approach (CPCA). Further data from stability batches was also provided, demonstrating compliance with the specification throughout the proposed shelf-life. A routine control for *N*-Vib is included in the finished product specification (20 ppm, equivalent to 1500 ng/day). The applied LCMS/MS analytical method has been suitably validated at the required sensitivity.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented.

Batch analysis results are provided for 5 production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 11 batches of finished product including production scale batches stored for up to 48 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches are identical to those proposed for marketing, with the exception of a few early batches which had a different film-coating colour and were packed in the primary packaging proposed for marketing. Samples were tested for appearance, assay, related substances, water content and dissolution, additional annual testing for microbiological quality according to Ph. Eur.

Generally, the results are well within the proposed specifications. A slight decrease in assay results was observed in some cases under long term conditions which justifies the wider shelf-life specification limits. A slight increase in the total related substances was seen over time, in particular under accelerated conditions. but results remain well within specification. Statistical trend analysis was performed confirming that water content is expected to remain within specification during shelf-life.

The photostability study results (according to ICH Q1B conditions) indicated that the finished product is not sensitive to light.

An in-use stability study has been conducted on one recent batch and one batch close to the end of shelf life applying an open dish design. Satisfactory in-use stability was shown.

Based on available stability data, the proposed shelf-life of 4 years without specific storage conditions as stated in the SmPC (section 6.3 and 6.4) is acceptable.

Adventitious agents

It is confirmed that the lactose used in the Opadry film-coating is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Four major objections were raised during the procedure concerning control of genotoxic impurities, and on the development and discriminatory power of the dissolution method. The applicant provided additional data demonstrating that the control strategy for genotoxic impurities (which includes specification limits for both active substance and finished product) is adequate, and that the dissolution method and associated release limit is suitable. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Vibegron is a small molecule β3-AR agonist that upon receptor binding leads to increased intracellular levels of cyclic adenosine monophosphate (cAMP) via activation of guanine nucleotide-binding (G) proteins and adenylyl cyclase. At a physiological level it leads to smooth muscle relaxation. The stimulation of β3-AR in adipose tissue has also as a consequence the release of free fatty acids (FFA) and glycerol due to lipolysis.

The non-clinical dossier included 7 PD combination studies with vibegron and the muscarin antagonist tolterodine and darifenacin. Co-treatment with these antagonists is not indicated in the Summary of Products Characteristics (SmPC) and as such is not within the scope of this MAA. Therefore, these studies have not been assessed.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Primary pharmacodynamics (PD) was evaluated in various *in vitro*, *ex vivo* and *in vivo* studies. Some of the studies were made in comparison with mirabegron (Betmiga) which is a β3-AR agonist that has been approved in the EU since 2012.

In vitro: species specificity and potency for β-AR was established through competition assays using membranes prepared from recombinant cells expressing β1, β2 or β3-AR.

The functional activity of vibegron was assessed by measurement of cAMP levels in CHO cells with stable expression of β3-AR from human and from rat, rabbit, rhesus monkey and dog. Normalisation of cAMP values were normalised against the known full agonist isoproterenol (a non-selective β-AR agonist) and subsequently EC50 and percent maximum activation was determined. Vibegron was shown to activate human β3-AR and to increase cAMP levels, with an EC of 1,1 nM and 87% activation. The selectivity for β3-AR over β1- and β2 was 9000-fold. The low plasma protein binding of vibegron was reflected in a small serum shift in the presence of 40% human serum.

Species selectivity of vibegron for the β3-AR with regards to potency was noted; similar potency was noted between monkey and human. A 10-fold less agonist activity relative to human potency was observed for the rabbit and dog receptor, and 100-fold less for the rat receptor.

Using radioligands in binding and functional studies (Study RVT-901-9009) the applicant compared the selectivity vibegron of mirabegron (a selective β3-AR agonist) for different AR types and subtypes. Both vibegron and mirabegron displayed potent agonist activity towards human β3-AR, 104% and 88% respectively. For β1 and β2-AR vibegron exhibited 0 and 2% agonist activity. The corresponding agonist activity of mirabegron for β1 and β2-AR was 3% and 15% respectively.

Ex vivo: Bladder contractility was examined *ex vivo* in both human and rat tissues using functional assays. Bladder muscle relaxation was observed in both species. In the rat study EC50 value was ~3.0μM and in the human study 0,087 μM, a difference that probably reflects the potency of 100-fold less in rat compared to human.

In vivo: the species tested in the *in vivo* studies were rat and monkeys. In the rat studies functional bladder capacity and micturition pressure were evaluated, but also levels of FFA and glycerol in order to obtain full dose response curves for the vibegron induced lipolysis. The functional studies utilised a model for bladder overactivity where acetic acid is administered to induce a hyperactive state of the bladder. Effects in decreased micturition pressure and increased bladder capacity was noted, although the effect on bladder capacity were not statistically significant. In addition, an increase of plasma glycerol was noted at the lowest dose 1 mg/kg and the increase in plasma glycerol and FFA levels was dose dependent.

In the primate studies effects of bladder capacity and micturition pressure were noted in anesthetised female Rhesus monkeys. In addition, there was a clear PK/PD relationship bladder capacity and serum glycerol levels, a relationship that was dose-dependent. The EC50 values for bladder capacity and serum glycerol was 2,9 nM and 9,9 nM. Similarity between vibegron and mirabegron was also evaluated in conscious cynomolgus monkeys, where similar affects were noted for bladder capacity between the two compounds. Regarding micturition pressure there was no effect on this endpoint after administration of vibegron and mirabegron.

These findings in primates suggests that: 1) vibegron exhibits a preference for β3-AR over β1, β2 and 2) circulating glycerol levels and FFA are reliable biomarkers for β3-AR in primates. There are however

discrepancies between species in terms of physiological responses and levels/correlation of circulating levels of glycerol and FFA. The cause of these discrepancies is most likely due to species differences in tissue distribution and expression of β3-AR leading. Expression of β3-AR is more elevated in rat adipose tissue leading to a more pronounced metabolic effects and thus affecting observed levels of glycerol and FFA in a species-specific manner.

2.5.2.2. Secondary pharmacodynamic studies

Off-target activity of vibegron was screened against a panel of 163 receptors, enzymes, ion-channels and transporters (study PD007). Vibegron was tested up to concentrations of 10 uM, corresponding a 36-fold higher concentration than the plasma concentration expected at a clinical exposure of 75mg/day i.e. 0,276 uM (study RVT-901-1002). In the study,vibegron interacted with the target receptor (β3AR) with IC50 value of 4.13 µM and 53% inhibition of the ligand. The determined interaction is weaker compared to the results from study PD001. Under these experimental conditions vibegron showed off-target activity for one target (>50 activity), namely the human serotonin transporter (hSERT) exhibiting an 89% inhibition, surpassing the inhibitory levels of the human β3-AR in this assay. In order to further evaluate this finding, the applicant proceeded with a follow up study PD008. The two-fold purpose of this study was to assess the inhibition human serotonin transporter (Serotonin (hSERT) and to assess the phospholipidosis potential of vibegron in two different assays. hSERT has been shown to play an important role in neuronal migration, differentiation, and synaptogenesis. No observations were made in the safety pharmacology studies or toxicology studies indicating a perturbation of hSERT. With regards to inhibition of the serotonin transporter, no inhibition at IC50 >9.5 was noted in this assay. In the PLD assay the applicant concludes that vibegron has a low potential to induce phospholipidosis with a A50 >70 µM.

Finally, in study PD009 an evaluation was made for the activity of vibegron to potassium channel [K_A] in an in vitro potassium channel radioligand binding assay. Vibegron had no activity on this neuron-specific potassium channel.

2.5.2.3. Safety pharmacology programme

Safety pharmacology was evaluated both *in vitro* and *in vivo* studies with the aim of determining neurobehavioural, respiratory, gastrointestinal and cardiovascular effects of vibegron. 8 studies were performed of which 3 are GLP compliant. One of these studies, TT09-1065, evaluating CNS safety in rats is part of the toxicology dossier and is covered more in depth in section 2.5.4. but in summary, no safety concern issues based on the non-clinical data was noted with regards to the CNS and gastrointestinal studies.

CNS safety studies

CNS safety was covered within the GLP compliant study TT09-1065 performed in rats. In this repeat dose study vibegron was administered orally for 14 days in order to study the toxicity and toxicokinetic profile. Neurobehavioural effects were evaluated after a single dose (2, 20, or 1000 mg/kg/day) on study day one.

At doses ≥ 20 mg/kg (with Cmax of 9.09 µM) decreased locomotion, abnormal gait and abnormal posture were observed. No-observed-effect level (NOEL) for neurobehavioural effects was 2 mg/kg, while no sustained drug-related CNS effects during the in-life phase or histological changes at post-mortem were noted with continued dosing at 20 mg/kg. This dose was therefore considered by the Applicant to be the no-observed-adverse-effect level (NOAEL) (with an associated exposure 33-fold of the steady state Cmax in humans treated with 75 mg/day).

Respiratory system

A study with vibegron in rhesus monkeys treated with single oral doses of the vehicle and 2.5, 15, and 135 mg/kg was performed to evaluate potential effects on respiratory function (Study TT09-5605). Vibegron-related transient increases in rate of respiration were observed at 2.5, 15, and 135 mg/kg vibegron. Increases in depth of respiration were observed only at 135 mg/kg. Based on the results of this study, no-observed-adverse-effect level (NOAEL) was considered to be 2.5 mg/kg. Mean vibegron Cmax values was 0.0598 µM, with no associated exposure margin to the steady state Cmax in humans treated with 75 mg/day. However, there are no indications from the studies in humans of any adverse effects on respiratory function.

Cardiovascular system

The studies for cardiovascular and respiratory system is based on *in vitro* studies and *in vivo* studies in dogs and monkeys.

In vitro: 2 studies were performed in order to study the effect of vibegron on hERG channel current. The first, GLP compliant study (TT09-4709), set out to examine the effects of the test article on hERG channels stably expressed in CHO cells. No statistically significant inhibitory effect on hERG channels at the concentration of 31 µM was noted, corresponding to a 111-fold of clinical levels. A statistically significant weak inhibitory effect was noted at the maximum testable actual concentration of 101 µM. This concentration corresponds to a 365-fold of the Cmax in the clinical study RVT-901-1002 in subjects dosed with 75mg/day. Similar inhibitory results were obtained in study TT08-3098 but here the lowest concentration tested was 30 µM.

In vivo: 3 cardiovascular safety studies were performed; 2 in anaesthetised, vagotomised, and ventilated dogs and 1 in conscious monkeys.

Study TT08-5311 (dog) non-GLP: 3 (n=3) anesthetised mixed breed dogs were treated with I.V. infusions with rising doses of 1,2 and 7 mg/kg of vibegron (mean Cmax of 2, 10 and 32 µM respectively), administered over 3 sequential 30-min periods. The lowest dose of 1 mg/kg corresponds to 3,6-fold margin of clinical plasma concentration. Heart rate, mean arterial pressure, and electrocardiographic parameters were monitored predose and after each infusion. Decreases were noted in mean arterial pressure and PR interval. An increase was noted in heart rate and QRS interval in all dogs, with one of the dogs exhibiting a marked increase in QRS interval compared to the other 2 dogs. There were no observed treatment related effects on QTc interval.

Study TT08-5314 (dog) non-GLP: the study designs of this study is in principle the same as for study TT08-5311 with the difference that only 2 dogs were studied and the administered doses of vibegron were lower, namely 0.3, 0.7, and 2 mg/kg (mean Cmax of 0.9, 2.2 and 7,2 µM respectively). Similar to the previous study a decrease in arterial pressure and PR interval was noted, and an increase in heart rate. No test article related effects were noted on QRS and QTc interval. The highest dose corresponds to a 26-fold to clinical Cmax.

In both studies, there were no effects on QTc interval using Bazetts correction, relative to the time-matched vehicle control at 1, 2, and 7 mg/kg. The mean peak plasma concentrations at dose 7 mg/kg were 32 µM, with exposure margin 115-fold to the Cmax in humans treated with 75 mg. Collectively, findings from the anaesthetised dog studies demonstrate that vibegron evokes decreases in MBP and increases in HR, with concomitant decreases in PR interval and dose-dependent QRS prolongation. Low-observed-adverse-effect level (LOAEL) for increases in QRS interval was observed at an IV dose of 1 mg/kg with QRS interval increase of 10% at this dose level. The NOAEL for increases in QRS interval was 0.7 mg/kg (with an associated exposure of 8-fold Cmax in humans treated with 75 mg). However, none of the evaluated vibegron doses had any effects on HR-corrected QTc interval. As positive control for QT evaluation in pre-clinical investigations, exploratory 1-month oral toxicity study in dogs

administered sotalol (Study TT10-1086), a racemic mixture of sotalol (a dual cardiac rapid hERG and β blocker), was used. Administration of ± sotalol at 10 mg/kg generally produced an approximately 10% increase in QT prolongation, an increase in PR interval, and a decrease in HR. Sotalol-related increases in the individual-specific QT correction (QTcI) interval were observed immediately following dose administration and, similar to increases in the PR interval, lasted approximately 8 to over 24 hours post-dose. The peak was approximately 2 to 3 hours post-dose (maximum value compared to time-matched vehicle value) with observed increases of approximately 7%, 9%, and 24%, at 3, 10, and 30 mg/kg/dose, respectively.

Study TT09-5605 (monkey)-GLP: To further evaluate potential effects on CV, vibegron was administered by the oral route to conscious, telemetered rhesus monkeys (n=4, 2 males and 4 females) with ascending doses starting with vehicle followed by 2.5, 15 and 135 mg/kg vibegron with at least 3 days between doses. HR, arterial BP, QRS, PR, and QT intervals, respiration rate and depth, and body temperature were monitored via radio-telemetry. In addition, a toxicokinetic evaluation was also performed.

The QTc was corrected for HR variation using an individual animal correction method (Miyazaki's correction). There were vibegron-related increases in HR at 2.5, 15, and 135 mg/kg vibegron (+38% bpm, +57% bpm, and +79% bpm). Increases in the QTc interval (+23 msec [+9%], +24 msec [+9%], and +15 msec [+6%]) were also observed at 2.5, 15, and 135 mg/kg of vibegron, respectively.

A NOAEL was determined to 2.5 mg/kg corresponding to an exposure 0,22-fold of the steady state Cmax in clinical study RVT-901-1002 in subjects dosed with 75mg/day.

In dogs and monkeys, a significant increase in HR at all studied doses were observed, while in humans at dose 75-mg no clinically relevant increases in HR were observed.

In the cardiovascular safety pharmacology studies in dog and monkey vibegron-related CV effects were observed. However, no CV effects were observed in the thorough QT study. Furthermore, CV parameters were monitored in additional clinical studies without adverse observations.

In addition, CV effects were noted in the repeat-dose toxicology studies in monkey. Similarly, QRS enlargement was noted, and coupled to mortality. Mortality was, however, noted at high concentrations that are not considered clinically relevant.

Gastrointestinal Safety Studies: Gastrointestinal safety pharmacology was evaluated in rat using a model for small intestinal charcoal powder transit. The powder in transit rate in the low dose group 30 and intermediate dose group 100 mg/kg was 60.1% and 61.3%, respectively. The control group had a transit rate of 65.2%

The transit rate at the highest dose group of 300 mg/kg was 42,1% and significantly lower than the control group, corresponding to 170-fold exposure.

2.5.2.4. Pharmacodynamic drug interactions

No studies on pharmacodynamic drug interactions have been performed.

2.5.3. Pharmacokinetics

Methods of analysis

No analytical method validation reports have been identified.

Absorption

After IV or oral administration of vibegron to rats, dogs and cynomolgus monkeys, vibegron exhibited relatively low clearance (14, 15 and 20 mL/min/kg, respectively), a large volume of distribution (6-15 L/kg,) that exceeds total body water, suggestive of extensive distribution to tissues, and a low-moderate oral bioavailability (20%, 44%, and 46%, respectively). The half-life for vibegron was 6.8, 13, and 7.4 hours in rats, dogs, and cynomolgus monkeys, respectively. Vibegron absorption was rapid following oral administration to the non-clinical species with Tmax ranging from 0.08-1 hour. The systemic exposure to vibegron increased with increasing dose over the dose ranges evaluated in the repeat-dose toxicity studies. To evaluate the impact of P-gp on vibegron transport, an *in-vivo* study was performed in wild type and 9 P-gp null mice. The P-gp null mice had significantly higher plasma levels compared to wild type mice suggesting that vibegron may be a mouse P-gp substrate.

Distribution

The Tmax occurred in most tissues at 2 hours post dose, suggesting extensive distribution and a rapid penetration of substance into tissues. The highest concentrations up to 12 hours was found in urine and bile indicating renal and biliary excretion of the substance. The highest Cmax tissue values were measured in liver, uveal tract, stomach mucosa, brown fat and kidney cortex. Radioactivity was eliminated in most tissues by 168 hours and at the late time points (336 and 840 hours) radioactivity was only measured in the eye, meninges, preputial gland, testis, and uveal tract, illustrating that elimination was not yet complete. While radioactivity was identified in the choroid plexus, the radioactivity was below the limit of quantitation in the circumventricular organs and the lens of the eye suggesting that the substance did not cross the blood-brain barrier.

The levels of radioactivity were only slightly higher in pigmented than non-pigmented skin but were not detected after the 168 hour time point. The highest concentrations in the eye and uveal tract were noted at 24 hours and then slowly declined. However, levels were still detectable 840 hours post dose, suggesting that vibegron is associated with eye melanin but not irreversibly bound.

The organ distribution in pregnant animals shows similar distribution pattern as in non-pregnant animals. In the fetal organs and tissues maximum concentrations occurred at 4 hours. Fetal maximum organ concentrations were lower than the concentrations in the analogous maternal organs. Four hours after administration, 4.37% of the administered amount of radioactivity (dose) was found in the liver. The radioactivity levels in other tissues were 0.50% or less of the administered dose. Collectively, it seems that there is placental passage of vibegron, but the levels reaching the fetus are considered relatively low. An oral single-dose study in nursing SD rats on lactation day 10 showed that vibegron levels reached a Cmax of 174.75 ± 134.60 ng eq [3H]vibegron/mL in milk after 12 hours, corresponding to a milk/plasma ratio of 2.2.

Protein binding of vibegron was moderate in the evaluated species with unbound fractions of 58% (CD-1 mouse), 20% (SD rat), 40% (dog), 50% (rhesus monkey), 56% (cynomolgus monkey), 49% (human), 37% (rasH2 mouse) and 7% (DB rabbit). In vitro blood-to-plasma ratios of vibegron were 0.7 (rat), 1.0 (dog), 1.0 (rhesus monkey), and 0.9 (human) over the concentration range tested, indicating a modest preferential distribution of vibegron to plasma over blood cells in rat, but not in the other tested species. This data indicates that measurement of drug concentration in plasma is representative of drug exposure in the evaluated species.

Metabolism

Vibegron was relatively stable across species. In human microsomes, six oxidised metabolites (M1-M6) were identified, and these were also identified in rat, dog and rhesus monkey microsomes. In the Cynomolgus monkey, the M2 metabolite was not recovered. In human hepatocytes, M3, M4 and M6

were identified, and these were also identified in rat, dog, Rhesus monkey and Cynomolgus monkey hepatocytes.

A CYP phenotyping study with chemical inhibitors in human liver microsomes identified M4 and M17 as prominent human metabolites (rvt-901-9003). In a subsequent experiment in rat and mouse microsomes using “improved analytical conditions” the M17 metabolite (formed by parent oxidation) was identified as the major metabolite also in rat and mouse (PK006).

In vivo metabolism was evaluated in BDC rats and monkeys. In the rat, unchanged vibegron (66-89%) and the oxidative metabolite M17 (8-30%) were the predominant species in both orally and intravenously treated rats, but M6 (2%, oral) and M22 (5-7%, intravenous) were also detected. In BDC Cynomolgus monkey the predominant drug related material after oral administration was vibegron (31-41%) followed by the O-glucuronide M7 (18-20%) and the oxidative metabolite M17 (10-14%). After intravenous administration, vibegron was the predominant species (42-50%) and M3 (5%), M7 (5-8%), M17 (7-8%) and M31 (5-9%) were also detected.

There are no human-specific metabolites, and in the human mass balance study vibegron was the predominant circulating component in human plasma, representing 78% and 73% in the pooled 0-2- and 2-4-hour plasma samples. Three human metabolites were also detected. M7 corresponded to 12% (2h) to 14% (4h) of the total circulating drug-related material (15-19% of parent drug). M4 and M17 accounted for below 10% of the total drug-related material in plasma and are minor metabolites.

Excretion

The predominant excretion route of radioactivity was faeces in Cynomolgus monkey after oral dosing, and urine was a minor route of excretion. In the rat, [3H]vibegron was excreted in similar amounts in urine, feces and bile after oral doses.

2.5.4. Toxicology

The toxicological profile of vibegron has been evaluated in a complete set of non-clinical safety studies which included repeat-dose toxicity studies (up to 6 months in rat and 9 months in cynomolgus monkey), *in vitro* and *in vivo* genetic toxicology, fertility/early embryonic in rats, embryo-foetal development in rats and rabbits, juvenile studies in rats, phototoxicity and impurity studies.

The oral route of administration was utilised in all toxicology studies to match the intended clinical administration route.

The metabolic profiles of vibegron in rats, monkeys and humans were similar which supports the selection of these animal species as the primary toxicology species.

The recommended clinical maximal dose of vibegron is an oral dose of 75 mg/kg/day and the applicant propose that this dose results in an AUC_{0-24} mean value of 1450µg•h/mL and a C_{max} value of 123 ng/mL.

The Sprague Dawley rat and cynomolgus monkey were selected as the main rodent and non-rodent species in the general toxicity studies. Sprague Dawley rat and New Zeeland White rabbits were selected for reproduction and developmental studies. The choice of toxicology species rats and monkeys was based on that the metabolic profile of these species is similar to that of human. Concerning the pharmacologic relevance, vibegron was shown to have a potency to rhesus monkey β3-AR (which is identical with the cynomolgus receptor) similar to the human receptor, while the rabbit and the rat receptor showed 10 and 100-fold, respectively, less potency than that of the human receptor. Regarding the low potency to the rat receptor this may be relevant for assessing off-target

toxicology. However, pharmacologic effect of vibegron in terms of accumulation of brown fat was seen in both rodents and monkeys accompanied by reduced bodyweight in adult and juvenile rats.

2.5.4.1. Single dose toxicity

No stand-alone single dose toxicity studies were conducted.

2.5.4.2. Repeat dose toxicity

Repeat-dose toxicity studies was conducted in rats and monkeys treated for up to 6 and 9 months, respectively. Generally, vibegron-related mortality and clinical signs occurred at high doses. Treatment-related organ effects was mainly found in the heart and liver and to some extent in female reproductive organs. In addition, pharmacological effects of vibegron in terms of bodyweight decrease and accumulation of brown fat were seen in both rats and monkeys.

Mortality
In rats, treatment-related mortality of 2 males and 1 female occurred at 1000 mg/kg/day dosed for 14 days and of 1 male at 180 mg/kg/day dosed for 6 months. The animals in 14-day study had physical signs preceding death such as decreased activity and skin turgor, distended abdomen and urine staining similar to the signs in remaining animals in the same dose group.

In the 3-months monkeys study, mortality occurred at 2 females dosed at 1000 mg/kg/day. Findings preceding death was decreased activity, decreased skin turgor, and/or coldness to the touch, and/or inappetence. The microscopic examination of these animals revealed no changes of the heart. A plausible explanation given by the applicant was that the sudden death was consequence of severe cardiac arrhythmias since ECG changes was recorded in 3 males dosed 1000 mg/kg/day at the same timepoint and also when the dose has been decreased to 360 mg/kg/day in 2 males consisting of QRS enlargement and/or distortion at both dosages. In the 6-months study, one female dosed at 300 mg/kg (and one control female) had physical signs of inappetence, absence of feces, distended abdomen, decreased activity, and/or weakness preceding death and was sacrificed due to poor physical condition. At necropsy these animals had inflammatory changes in the abdominal cavity and the reason to death was considered incidental. The mortality in monkeys occurred at an exposure marginal of approximately 114x (Cmax) and 725x (AUC) compared to recommended clinical dose.

Cardiac effects
Cardiac effects occurred only in monkeys with increased QRS interval at 300mg/kg/day in all animals (4M +4F) in the 9-months study. At this dose prolongation of QRS was observed in all animals at 2 hours post-dose (correlating to Tmax) without microscopic changes. These findings were transient and no longer observed approximately 24 hours postdosing. Moreover, test article-related conduction defects prevented QT interval measurement 2 hours postdosing at high dose 300 mg/kg. These effects occurred in all animals and were characterised by an increase in QRS duration, including "coving" of the S wave and P wave overlapping with the T wave. Absence of QT evaluation in high dose groups is acceptable, since it was not feasible to measure QT interval because of wave interference. In the 3-months study ECG changes were observed in males after approximately 3 weeks of dosing at 1 000 mg/kg/day (3/3 males) at approximately 1-hour and/or 24-hours post-dosing, and after approximately 1 month and 2 months of dosing at 360 mg/kg/day (2/3 males) at approximately 1-hour post-dosing. They consisted of QRS enlargement and/or distortion at both dosages. In 1 animal at 1 000 mg/kg/day, absence of P waves and PR prolongation were also observed. Near study termination, after approximately 2 months of dosing at 360 mg/kg/day, ECG changes were limited to QRS enlargement. These ECG changes are consistent with cardiac conduction defects affecting primarily ventricular conduction (QRS enlargement and/or distortion) with evidence of atrioventricular conduction defects

(PR prolongation) in 1 animal at 1 000 mg/kg/day. In neither study, no correlating histopathologic findings of the heart was observed. These heart changes occurred at an exposure marginal of approximately 75x (AUC) and 114x (Cmax) compared to the recommended human dose. No corresponding ECG changes have been reported in the clinic and the human relevance of these heart findings is therefore considered low.

Hepatic effects
An increase of liver enzymes was observed in rats at ≥180 mg/kg/day and in monkeys at ≥300 mg/kg/day. In both species, the increase of ALP and ALT was considered as slight generally ranging up to 2.0 – fold in rats and up to 4.0- fold in monkeys. These changes were generally accompanied with a decrease in triglyceride levels. No correlating histopathology was recorded in the liver of rats and monkeys. Changes of liver enzymes occurred at an exposure marginal of approximately 725x (Cmax and AUC) in rats, and 61x (Cmax) and 75x (AUC) in monkeys compared to recommended clinical dose.

Female reproduction organs effects
Atrophy in ovaries, uterus and cervix was seen at 300 mg/kg/day in the 3-monhts rat study. No corresponding changes were seen in monkeys or in other rat toxicology studies, reproductive studies or juvenile studies. The atrophy findings occurred at a high exposure marginal (approximately 200-fold and 400-fold AUC and Cmax exposure, respectively) compared to the recommended human dose.

Brown fat accumulation
Vibegron-related effects in terms of accumulation of brown fat was seen in both rodents and monkeys and accompanied by reduced bodyweight in adult and juvenile rats. However, these findings are related to the pharmacologic effects of vibegron commonly seen with beta 3-adrenergicreceptor (β3-AR) agonists and is considered of no significant toxicity.

2.5.4.3. Genotoxicity

The applicant has performed an adequate genotoxic package including Ames tests, and in vitro/vivo chromosomal aberration test. Vibegron showed no signs of mutagenicity or cyto- or genotoxicity in any of the studies.

2.5.4.4. Carcinogenicity

Vibegron was tested for its carcinogenic potential in 2 years studies in mice and rat with study designs as recommended by Carcinogenicity Assessment Committee (CAC). No treatment-related mortality or neo-plastic findings (i.e. no significant increasing or decreasing trends in tumour incidence) was recorded in mice and rats. Other finding observed in rats was decreased body weight gain at ≥ 60 mg/kg/day in females and at ≥20 mg/kg/day in males, salivation at ≥ 60 mg/kg/day in females only and dose-dependent incidence of transient post-dosing clinical signs such as lateral, sternal, or supine recumbency, occasionally in females at ≥20 mg/kg/day and in males at ≥ 3 mg/kg/day. This clinical sign was consistent with hyperthermia which was induced by treatment. When compared to predose values, mean increase in body temperature was 3.3°C (+9%) in the 30 mg/kg/day treated male group. Non-neo-plastic microscopic findings seen were vacuolation of zona glomerulosa of adrenals in rats and brown fat accumulation in rats and mice. The increased brown fat accumulation occurred at ≥30 mg/kg/day in male mice and at ≥50 mg/kg/day in female mice while in rats it occurred at ≥10 mg/kg/day in males and at ≥60 mg/kg/day in females.

2.5.4.5. Reproductive and developmental toxicity

A full programme of reproductive and developmental studies has been performed with vibegron in rats and rabbits. Reproductive and developmental toxicity studies with vibegron consisted of 9 in vivo studies, 7 in rat and 2 in rabbits.

FEED studies in rats

In females, a pivotal FEED study was performed at doses up to 1000 mg/kg/day (14D-GD7, Study TT11-7320). At the highest dose level vibegron-related decreased fecundity and fertility (72% as compared to 100% in control) and maternal toxicity were observed. Toxicity findings at the highest dose level included maternal mortality (two deaths), physical signs, transient changes in body weight and food consumption and distended colons. No effects of vibegron on embryo/foetal survival parameters were observed at any dose. Based on these data, the NOAEL was set to 300 mg/kg/day for general toxicity in females, female fertility and for early embryonic development. The corresponding exposure margins were determined to 230x (Cmax) and 275x (AUC).

In the rat 3-month repeat-dose study (TT09-6012) female reproductive organ atrophy (ovaries, uterus and cervix) accompanied by decreases in ovary weight (also of the pituitary) were noted at 300 mg/kg/d, i.e. a lower dose than that causing general toxicity and a decrease in fertility in females in the FEED study.

In males, a pivotal FEED study (exposure 15 days prior to cohabitation, during cohabitation, and until the day prior to scheduled sacrifice, approximately 6 weeks in total, Study TT11-7110) was performed at doses up to 300 mg/kg/day. Regarding general toxicity, the main findings were decreases in body weight gain in the 30 and 300 mg/kg groups, and salivation in the 300-mg/kg/day group. No vibegron-related effects were observed on fertility or early embryonic development based on data on copulation index, the number of days until copulation or the fertility index in male rats, number of corpora lutea, the number of implantations, pre-implantation loss index, post-implantation loss index, or number of live embryos in the bred females.

For general toxicity in males, the NOAEL was identified as 10 mg/kg corresponding to the exposure margins of approximately 9x (Cmax) and 4.8 x (AUC). The NOAEL for male fertility and early embryonic development was estimated to be ≥ 300 mg/kg/day corresponding to the exposure margins of 412x (Cmax) and 274x (AUC).

EFD studies

Rat

A pivotal EFD study was performed in Sprague Dawley rats at doses up to 1000 mg/kg/day. At the highest dose maternal toxicity was observed: 2 females were found dead on GD 14 or 16, 3 females were euthanised (GD 10 or 13) due to body weight loss and recumbency (1 of the 3 animals). The remaining females were euthanised due to unacceptable physical signs.

In offspring, no observed effects on postimplantation loss, the number of live foetuses, dead foetuses, and foetal sex ratio, external or visceral morphology. The Applicant reported that the numbers of fetuses with sites of incomplete ossification were present at low incidences that lacked a dose response relationship and/or were within the range of historical control incidences and were therefore considered to be unrelated to vibegron treatment. The number of fetuses (litter mean) with incomplete ossification of sternebra was increased in the 300 mg/kg group (the highest dose group of offspring) compared with the control. However, the reported incidence of 15% (% litter affected) with incomplete ossification of sternebra in the 300 mg/kg group is within the range for the historical control data (0% – 29.2%) and hence considered unrelated to vibegron exposure by the applicant.

The mean numbers of ossified sacrocaudal vertebrae were slightly decreased in the 100-mg/kg/day and 300-mg/kg/day groups (5% and 7% below control, respectively); however, since there were no concurrent effects on fetal weights or the incidence of fetuses with sites of incomplete ossification, these were considered by the Applicant to be spontaneous changes and not related to vibegron treatment.

Systemic exposure (AUC 0-24 h) and C max were greater than dose-proportional between 30 mg/kg/day and 100 mg/kg/day, approximately dose-proportional between 100 mg/kg/day and 300 mg/kg/day, and greater than dose-proportional between 300 mg/kg/day and 1000 mg/kg/day.

The NOAEL for dams as well as for embryo-foetal development was set to 300 mg/kg/day. On day GD 15/16, the systemic exposure of vibegron at this dose was 896 ± 95.5 uM·h (AUC_{24h}) and Cmax was 63.8 ± 10.9 µM, which was 275 and 230 times higher, respectively, than exposure in patients at the clinical dose of 75 mg/day.

Rabbit

A pivotal EFD study has been performed in Dutch Belted rabbit at doses up to 300 mg/kg/day (Study TT11-7170). At the highest dose there were transient, vibegron-related decreases in mean maternal food consumption on GD 8 and 13 (30% and 21% below the control group, respectively) while no effects on body weight gain were observed. No deaths occurred and no other vibegron-related maternal effects were detected.

Regarding embryo/foetal development, no vibegron-related effects on embryonic/foetal survival parameters were observed. There was a decrease in mean live fetal weight (14% and 9% below the control group in females and males, respectively) and an increased incidence of foetuses with sites of incomplete ossification in the 300-mg/kg/day group.

PPND study

A pivotal PPND study has been performed in pregnant Crl:CD (SD) rats at doses up to 500 mg/kg/day. In the dams, decreased body weight gain and food consumption were observed immediately after dosing at 500 mg/kg. At ≥ 100 mg/kg decreased body weight gain was observed during the lactation period. At 30 mg/kg an increase in food consumption was observed in dams.

In the F1 offspring, at 500 mg/kg a tendency toward increase in stillborn index was noted, and all offspring of 2 dams died on LDs 4 and 10. Furthermore, low values were noted in viability index on PND 4 and weaning index. As for surviving offspring, decreased mean body weights and body weight gains were noted during the lactation, maturation, and gestation periods at 500 mg/kg.

At 500 mg/kg, the differentiation indices of piliation, incisor eruption, eye opening, and/or preputial separation were tendency toward low or significantly low in males and females. In addition, the reflex indices of righting reflex and visual placing response showed a tendency toward low in males and females at this dose. The Applicant considered that the retardation of development and decreased reflexes were effects secondary to the decreased body weights, and not a direct effect of the test article.

The Applicant argued that the effects on bodyweight and bodyweight gain in male pups at 100 mg/kg/day were small and transitory, indicating that these effects were not adverse. The Applicant further argued that the body weights of pups in the 100 mg/kg/day group in the pivotal PPND study were within the range of historical control data supporting that they were not treatment-related.

Dilatation of pelvis in the kidney was observed in 1 and 2 female offspring at 30 and 100 mg/kg, respectively. However, this incidence was reported to be within the range of historical data and therefore judged by the Applicant to be not treatment-related.

The NOAEL for general maternal toxicity was set to 30 mg/kg, corresponding to exposure margins of 9.6 x (Cmax) and 9 x (AUC). The NOAEL for F1 development was set to 100 mg/kg, corresponding to exposure margins of 84.9x (Cmax) and 88.6x (AUC) to exposure in patients at the clinical dose of 75 mg/day.

Juvenile toxicity

The applicant has provided with rat juvenile toxicology studies as these were requested from FDA to support clinical investigations in children. However, it should be clarified that paediatric patients are not intended to be treated in the current application.

Treatment-related bone effects were seen at 125 mg/kg/day and 250 mg/kg/day in juvenile male and female rats, respectively. These effects consisted of decrease in bone mass and size (decreases of femur length, cortical thickness and area at the diaphysis site in males and decrease at the area of metaphysis site in females). After a recovery period of 4 weeks bone findings showed partial reversibility. Other effects seen were decreased body weight and changes in liver enzymes in the males at 50 mg/kg/day while the latter changes occurred at ≥125 mg/kg/day in females. Histopathological changes consisted similar findings seen in adult rats in terms of mild increase of brown fat in both genders.

To conclude, vibegron-related effects seen in juvenile rats comprised decrease in bone mass and size, that were partially resolved after a 4-week recovery period, and findings similar to those seen in adult rats.

Impurities

Elemental impurities and residual solvents

The Applicant identified several impurities which are routinely monitored. Relevant elemental impurities are controlled according to ICH Q3D. The residual solvents are controlled according to ICH Q3C. The details on impurity control are found in the quality section.

Organic impurities

According to the Applicant, the Vibegron Trans-Isomer has been qualified in the 6-month study and that the qualified impurity dose is 3-times the current specified level of 0.50%. In this study, rats were dosed with batch 000L018 (1.01% of trans-isomer for Weeks 1 to 13 and batch 000L021 (0.16% of trans-isomer) for Weeks 14 to 27 (Study TT10-6005). The NOAEL in the 6-month rat study was 10 mg/kg/day. Based on the level of impurity used in the 6-month rat study, and a maximum daily dose of 75 mg vibegron, the qualified impurity dose is 3-times the current specified level of 0.50%. The justification is in line with the ICH Q3A Guideline. However, Certificate of Analysis (CoA) for any of the listed batches was not provided by the applicant. The drug substance itself was not genotoxic in battery of ICH S2 studies which implies that based on structure similarity the vibegron trans-isomer should not pose a genotoxic potential as well.

As a part of the genotoxic risk assessment in module 3, the applicant considered one reagent as non-genotoxic in vivo despite in vitro mutagenic potential. The rationale was based on one review article secondarily referring to conducted studies.

The Applicant identified two N-nitroso derivatives that can be formed during drug substance synthesis, drug product formulation or during drug product storage and provided with a risk assessment based on read across to arrive at a proposed AI for the substances. However, from 7 July 2023 the Carcinogenic

Potency Categorisation Approach (CPCA) and the Enhanced Ames Test (EAT) should be applied to establish acceptable intakes (AI) for nitrosamines.

2.5.4.6. Toxicokinetic data

In rat studies, the TK measurements was recorded only at one time point (at week 2 in the 14-days study and at 13 weeks in the 3- and 6-months study) which make it not possible to evaluate the exposure profile over time. Overall, the TK recordings in rats revealed no obvious gender difference and generally a dose-proportionality (with some exceptions for Cmax). Also, in monkeys vibegron showed no obvious gender differences and a dose-proportionality with few exceptions (i.e. in the 9 months study the low dose in females the AUC exposure was 2.2 to 2.4-fold higher compared to males, and a Cmax that were greater than dose-proportional between the low and mid doses while it showed dose-proportional between the mid and high doses).

Generally, findings seen in repeated-dose studies occurred at high marginals. In rats, liver effects and findings of the female reproduction organs was seen at several hundred-folds margins and in monkeys the heart and liver effects occurred at 75-fold (AUC) and ≥61-fold margins compared to clinical dose. In rodent cancerogenic studies, animals were dosed up to 90 and 150mg/kg/day (mice), and 30 and 180 mg/kg/day without any neoplastic findings. These doses corresponding to ≥21-fold and ≥18-fold marginal. while the non-neo-plastic findings seen in rats (vacuolation in adrenals) occurred at doses at ≥20 mg/kg/day corresponding to -fold (AUC) marginal compared to the clinical dose.

2.5.4.7. Local Tolerance

No local tolerance studies have been conducted. This is considered acceptable because vibegron is intended as oral administration.

2.5.4.8. Other toxicity studies

Phototoxicity
In a GLP-compliant study in pigmented female rat, administrated up to 300 mg/kg/day and exposed to single solar simulated UVR exposure, vibegron showed no signs of phototoxicity.

2.5.5. Ecotoxicity/environmental risk assessment

The Applicant presents an experimentally determined log Pow value of 0.19 for vibegron using a method corresponding to the OECD TG107 shake-flask method (non-GLP). The log Pow value is below the action limit and, therefore, does not trigger a PBT assessment. The refined PECsw of 3.78 µg/L exceeds the action limit of 0.01 µg/L and thereby triggers a phase IIA assessment. No phase II related data for vibegron were submitted.

Table 2 Summary of main study results

Substance (INN/Invented Name): vibegron					
CAS-number (if available): 1190389-15-1					
PBT screening		Result			Conclusion
Bioaccumulation potential- log K_{ow}	Similar to OECD TG107 (non GLP)	0.19			Potential PBT N
Phase I					
Calculation	Value	Unit			Conclusion
PEC $_{surfacewater}$, refined (e.g. prevalence, literature)	3.78	µg/L			> 0.01 threshold Y
Other concerns (e.g. chemical class)					N
Phase II Physical-chemical properties and fate					
Study type	Test protocol	Results			Remarks
Adsorption-Desorption	OECD 106 or ...	K_{oc} =			*pending*
Ready Biodegradability Test	OECD 301				*pending*
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			*pending*
Phase IIa Effect studies					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC		µg/L	*pending* species
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	*pending*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	*pending* species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	*pending*
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/ kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/ kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/ kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/ kg	
Sediment dwelling organism		NOEC		mg/ kg	species

2.5.6. Discussion on non-clinical aspects

Pharmacology

The submitted *in vitro* studies evaluate the potential of vibegron to activate the β3 subtype of ARs. The potency was determined by the ability to increase an intracellular cAMP level. The test article is highly potent activator of the β3 AR with EC50 ranging from 1.1 nM (study PD001) or 1.2 nM (study RVT-901 9004) to 2.13 nM (study RVT 901 9009). Even though vibegron is a highly potent activator, the interaction with the receptor determined by the competition binding assay was only moderate (IC50 =

193 nM, study PD001). The discrepancy between the strong potency and the moderate binding affinity has been attributed to the ability of the test substance to compete for uncoupled vs. coupled receptor without any discussion on the suitability of the test conditions. Nonetheless, the interaction with the receptor has been confirmed. The submitted studies further demonstrate the specificity of vibegron to β3 AR versus β1 and β2 isotypes. The affinity and potency to the β1,2 ARs are negligible (study PD001, study RVT- 901 9009).

The functional activity of vibegron was assessed by measurement of cAMP levels in CHO cells with stable expression of human β3-AR and non-human species; rat, rabbit, rhesus and dog. Normalisation of cAMP values were normalised against the known full agonist isoproterenol (a non-selective β-AR agonist) and subsequently EC50 and percent maximum activation was determined. Vibegron was shown to activate human β3-AR and to increase cAMP levels, with an EC of 1,1 nM and 87% activation. The selectivity for β3-AR over β1- and β2 was 9000-fold. The low plasma protein binding of vibegron was reflected in a small serum shift in the presence of 40% human serum.

Species selectivity of vibegron for the β3-AR with regards to potency was noted; similar potency was noted between monkey and human. A 10-fold less agonist activity relative to human potency was observed for the rabbit and dog receptor, and 100-fold less for the rat receptor.

In animal species, the vibegron potency to the β3 isotype only has been evaluated. No other β ARs are discussed. However, this is acceptable as the applicant states that the β3-AR structural homology among species is higher than that among individual receptor subtypes. The homology between the human and monkey, rat, or mouse β3-ARs ranges between 80 to 90 %; the homology between β3- and β1-AR or β3- and β2-AR is about 50 %.

In vivo: the species tested in the *in vivo* studies were rat and monkeys. In the rat studies functional bladder capacity and micturition pressure were evaluated, but also levels of FFA and glycerol in order to obtain full dose response curves for the vibegron induced lipolysis.

In the primate studies effects of bladder capacity and micturition pressure were noted in anesthetised female Rhesus monkeys. In addition, there was a clear PK/PD relationship bladder capacity and serum glycerol levels, a relationship that was dose-dependent. The EC50 values for bladder capacity and serum glycerol was 2,9 nM and 9,9 nM. Similarity between vibegron and mirabegron was also evaluated in conscious cynomolgus monkeys, where similar effects were noted for bladder capacity between the two compounds. Regarding micturition pressure there was no effect on this endpoint after administration of vibegron and mirabegron.

According to the applicant, it is possible that acetylcholine released from the parasympathetic nerve endings during the urination phase stimulates muscarinic acetylcholine receptor 2 (M2), and the associated suppression of adenylate cyclase activation in the smooth muscle cells of the bladder and decreased cAMP concentration suppressed the bladder relaxation action of vibegron and micturition pressure decrease that is typically observed upon cAMP concentration elevation.

The applicant has provided a reasonable explanation, and the issue is considered addressed.

These findings in primates suggests that: 1) vibegron exhibits a preference for β3-AR over β1, β2 and 2) circulating glycerol levels and FFA are reliable biomarkers for β3-AR in primates. There are however discrepancies between species in terms of physiological responses and levels/correlation of circulating levels of glycerol and FFA. The applicant was asked to elaborate on these differences and provided a discussion outlining species differences and receptor tissue distribution as a plausible cause of the observed discrepancies. In summary, expression of β3-AR is more elevated in rat adipose tissue leading to a more pronounced metabolic effects and thus affecting observed levels of glycerol and FFA in a species-specific manner.

With respect to the suitability of individual animals for *in vivo/ex vivo* studies, the potency of the receptor activation but also the receptor tissue expression pattern should be taken into consideration (efficacy and potential adverse effects). It is known that the β AR subtype mediating detrusor muscle relaxation is species dependent. β3 AR is the dominant receptor in bladder smooth muscle in humans and monkeys. β3 and β2 receptor subtypes are expressed in rats. β2 receptors only are expressed in mice and rabbits. In studies with rats, rhesus and cynomolgus monkeys, receptor potency has been confirmed and the relevant subtype of the receptor is expressed in the target tissue. Although in rats, weaker potency to β3 AR was established and β3 AR is not the exclusive subtype in the target tissue. The species selection is acceptable for the primary pharmacology studies.

Off-target activity of vibegron was screened against a panel of 163 receptors, enzymes, ion-channels and transporters (study PD007, PD008). No off-target activity is anticipated at clinically relevant exposures. In study PD009 an evaluation was made for the activity of vibegron to potassium channel [K_A] in an *in vitro* potassium channel radioligand binding assay. Vibegron had no activity on this neuron-specific potassium channel. Safety pharmacology was evaluated both in in vitro and in vivo studies with the aim of determining neurobehavioural, respiratory, gastrointestinal and cardiovascular effects of vibegron. 8 studies were performed of which 3 are GLP compliant. One of these studies, TT09-1065, evaluating CNS safety in rats, as presented in section 2.5.4. No safety concern issues based on the non-clinical data was noted with regards to the CNS and gastrointestinal studies.

In vitro: 2 studies were performed in order to study the effect of vibegron on hERG channel current. The first, GLP compliant study (TT09-4709), set out to examine the effects of the test article on hERG channels stably expressed in CHO cells. No statistically significant inhibitory effect on hERG channels at the concentration of 31 µM was noted, corresponding to a 111-fold of clinical levels. A statistically significant weak inhibitory effect was noted at the maximum testable actual concentration of 101 µM. This concentration corresponds to a 365-fold of the Cmax in the clinical study RVT-901-1002 in subjects dosed with 75mg/day. Similar inhibitory results were obtained in study TT08-3098 but here the lowest concentration tested was 30 µM.

Based on in vitro data, no vibegron-induced inhibition of hERG channels is expected in humans at clinically relevant concentrations. In dogs and monkeys, a significant increase in HR at all studied doses were observed, while in humans at dose 75-mg no clinically relevant increases in HR were observed. In the dedicated cardiovascular study (Study TT09-5605) monkeys, HR increase was +57% bpm at vibegron dose 15 mg/kg (330 ng/ml), corresponding to a dose with 2,7x margin of safety in comparison to human subjects dosed with 75mg/day (123 ng/ml). The applicant was requested to update SmPC section 5.3 with the information on increase in HR in animal studies. The applicant provided a response concluding that the HR effects were transitory and limited in their increase and that an update of section 5.3 was not deemed necessary. Although the observation in dogs and monkeys of indicates increase in HR, and further, that experimental conditions in the toxicity studies were not optimal, consideration has been taken that this dedicated cardiovascular study in monkeys was performed on limited number of animals and no other findings in the studies support vibegron-induced cardiac effects. The updating of SmPC section 5.3 with the information on HR increases observed in dedicated cardiovascular animal studies is therefore not further pursued.

In the cardiovascular safety pharmacology studies in dog and monkey vibegron-related CV effects were observed. However, no CV effects were observed in the thorough QT study. Furthermore, CV parameters were monitored in additional clinical studies without adverse observations.

Pharmacokinetics

Vibegron absorption was rapid following oral administration to the non-clinical species with Tmax ranging from 0.08-1 hour. The half-life for vibegron was 6.8, 13, and 7.4 hours in rats, dogs, and cynomolgus monkeys, respectively. The systemic exposure to vibegron increased with increasing dose

over the dose ranges evaluated in the repeat-dose toxicity studies. The Tmax occurred in most tissues at 2 hours post dose, suggesting extensive distribution and a rapid penetration of substance into tissues. The highest concentrations up to 12 hours was found in urine and bile indicating renal and biliary excretion of the substance. The highest Cmax tissue values were measured in liver, uveal tract, stomach mucosa, brown fat and kidney cortex. Based on an oral single-dose study in nursing SD rats on lactation day 10 it can be concluded that vibegron is transferred into breastmilk in rat with a milk/plasma ratio of 2.2 after 12 hours.

There are no human-specific metabolites, and in the human mass balance study vibegron was the predominant circulating component in human plasma, representing 78% and 73% in the pooled 0-2- and 2-4-hour plasma samples. Three human metabolites were also detected. M7 corresponded to 12% (2h) to 14% (4h) of the total circulating drug-related material (15-19% of parent drug). M4 and M17 accounted for below 10% of the total drug-related material in plasma and are minor metabolites. All human metabolites were covered by non-clinical data.

The predominant excretion route of radioactivity was faeces in Cynomolgus monkey after oral dosing, and urine was a minor route of excretion. In the rat, [3H]vibegron was excreted in similar amounts in urine, feces and bile after oral doses. Based on a study of the potential for enterohepatic circulation in rat, approximately 15% of the [3H]vibegron-derived radioactivity was subject to reabsorption, suggesting enterohepatic recirculation of the vibegron-derived components. The human excretion is via a variety of pathways including urinary excretion, biliary excretion, and hepatic metabolism and of these, hepatic metabolism appears to play a minor part. Collectively, elimination pathways seem sufficiently similar to conclude that the rat and monkey are relevant species to assess potential human toxicity related to excretion organs.

Toxicology

No stand-alone single dose toxicity studies were conducted. The lack of single dose toxicity studies is acceptable. However, acute toxicity has been assessed in 3-days escalating study in monkey and 7- and 14-day rat repeat-dose toxicity studies. In rats, the findings observed after the first dose where neurobehavioural signs of decreased locomotion, abnormal gait, and abnormal posture at ≥ 20 mg/kg); and palpebral closure, constricted pupil size, decreased muscle tone, and decreased body temperature at 1000 mg/kg. In monkeys no acute toxicity was observed at doses up to 500 mg/kg.

Repeat-dose toxicity studies was conducted in rats and monkeys treated for up to 6 and 9 months, respectively. Treatment-related organ effects was mainly found in the heart and liver and in female reproductive organs that occurred at high marginals. The liver effects and findings of the female reproduction organs in rats was seen at several hundred-folds margins and in monkeys the heart and liver effects occurred at 75-fold (AUC) and ≥61-fold margins compared to clinical dose. In rodent cancerogenic studies, animals were dosed up to 90 and 150mg/kg/day (mice), and 30 and 180 mg/kg/day without any neoplastic findings. These doses corresponding to ≥21-fold and ≥18-fold marginal. However, vibegron shows diversity in potency to β3-AR in the studied species. Upon request the applicant submitted revised safety margins calculated with the lower β3-AR potency seen in monkeys, rabbits and rats compared to humans (i.e. 1.5, 8.7 and 78-fold lower factor when determined without serum). This resulted in no or low safety margins in rat studies and appropriate safety margins in the monkey chronic toxicology study and rabbit EFD study (see table below).

Table 3 showing the toxicity studies, NOAEL and systemic exposures, ratio of animal to human exposure (AUC_{0-24}) (clinical dose of 75 mg QD) and corrected safety margins considering β3-AR potency differences between human and animal species.

Species and Study Type	NOAEL (mg/kg/day)	AUC_{0-24} (ng × h/mL)	Ratio of Animal to Human Exposure (AUC_{0-24}) 75 mg QD*	Corrected Safety margin / β3-AR potency
Rat, 6 months	30	30895	21	0.3
Monkey, 9 months	100	24450	17	11
Rat, Carcinogenicity	30 (M)[µ]	25605	18	0.23
	180 (F)[µ]	170255	117	1.5
Rat – Male, Fertility	300	396972	274	3.5
Rat – Female, Fertility	300	398306	275	3.5
Rat, EFD	300	398306	275	3.5
Rabbit, EFD	100	412976	285	33
Rat, PPND	30 (F0 dams)	13247	9	0.12
	100 (F1 pups)	128471	89	1.1
Rat, Juvenile	50	50400	35	0.45

M: males; F: female; EFD : embryo-fœtal development
* Human Exposure 75 mg QD, AUC_{0-24} = 1450 ng/mL.h
[µ] NOEL

The applicant argues that the low safety margins in rat studies has little relevance for humans given that the pharmacological effect is more profound in rat compared to humans/NHPs as β3-AR expression occur in both brown and white rat adipose tissue while in humans/NHPs it occurs mainly in brown adipose tissue. Further, they consider this a relevant species as rat β3-AR plays a similar role as in humans (relaxation of bladder detrusor muscle) and that the rat has be used for development of other β3-AR agonists. This is acknowledged. The un-corrected safety marginals for β3-AR potency are stated in the SmPC section 5.3, however it is reflected also that vibegron showed considerably lower *in vitro* β3-AR potency for rabbits and rats compared to humans and that the safety margins for potential β3-AR-mediated effects on development or reproduction are accordingly lower than for non-β3-AR-related effects.

In rats, treatment-related mortality of 2 males and 1 female occurred at 1000 mg/kg/day dosed for 14 days and of 1 male at 180 mg/kg/day dosed for 6 months. The animals in 14-day study had physical signs preceding death such as decreased activity and skin turgor, distended abdomen and urine staining similar to the signs in remaining animals in the same dose group. The applicant claims that the unscheduled death of the animals the 14-day study was related to aspiration or reflux of vibegron which seems likely. No explanation was given for the death of the male in the 6-month study. The mortality in rats occurred at an exposure marginal of approximately 61x (Cmax) and 1640x (AUC) compared to recommended clinical dose.

Vibegron was tested for its carcinogenic potential in 2 years studies in mice and rat with study designs as recommended by Carcinogenicity Assessment Committee (CAC). Based on the results, it can be concluded that vbegron show no cancerogenic potential

Reproductive and developmental toxicology

A full programme of reproductive and developmental studies has been performed with vibegron in rats and rabbits. The studies were designed and conducted according to relevant ICH guidelines and the pivotal studies were GLP compliant.

In female rats, a pivotal FEED study was performed at doses up to 1000 mg/kg/day. At the highest dose level vibegron-related decreased fecundity and fertility (72% as compared to 100% in control) and maternal toxicity were observed. The NOAEL was thereby set to 300 mg/kg/day for general toxicity in females, female fertility and for early embryonic development, corresponding to exposure margins of 230x (Cmax) and 275x (AUC).

In male rats, a pivotal FEED study was performed at doses up to 300 mg/kg/day. Regarding general toxicity, the main findings were decreases in body weight gain in the 30 and 300 mg/kg groups, and salivation in the 300-mg/kg/day group. No vibegron-related effects were observed on fertility or early embryonic development. The NOAEL for general toxicity in males was therefore set to 10 mg/kg, corresponding to the exposure margins of approximately 9x (Cmax) and 4.8 x (AUC). The NOAEL for male fertility and early embryonic development was estimated to be ≥ 300 mg/kg/day corresponding to the exposure margins of 412x (Cmax) and 274x (AUC). The results of these studies indicate that there may be a sex difference with regard to vibegron-related effects on body weight gain as a markedly decreased body weight gain was observed at lower doses for males than for females.s, the numbers of fetuses with sites of incomplete ossification were present at incidences that lacked a dose response relationship and/or were within the range of historical control incidences and were therefore considered by the applicant to be unrelated to vibegron treatment. The number of fetuses (litter mean) with incomplete ossification of sternebra was increased in the 300 mg/kg group (the highest dose group of offspring) compared with the control. However, the reported incidence of 15% (% litter affected) with incomplete ossification of sternebra in the 300 mg/kg group is within the range for the historical control data provided by the Applicant and hence considered unrelated to vibegron exposure. The NOAEL for embryo-foetal development in the rat EFD study was set to 300 mg/kg/day which is agreed. This reflected in SmPC section 5.3.

In the pivotal EFD study (Study TT11-7170) in Dutch Belted rabbit at doses up to 300 mg/kg/day, no vibegron-related effects on embryonic/foetal survival parameters were observed. There was a decrease in mean live fetal weight and an increased incidence of foetuses with sites of incomplete ossification of the skull bone (primarily the hyoid), sternebra, metacarpal, and talus-calcaneus) in the 300-mg/kg/day group. No vibegron-related malformations in rabbits were reported. With regard to maternal toxicity, there were transient, vibegron-related decreases in mean maternal food consumption while no effects on body weight gain were observed in the 300 mg/kg/day group. Hence, the NOEL for both maternal toxicity and embryo/foetal development was set to 100 mg/kg/day in the rabbit EFD study. At this dose the AUC24h was 413 ug/ml·h (929 ± 75.5 µM·h) and Cmax was 93.8 ug/ml (211 ± 21 µM), which was approximately 285 and 762 times higher, respectively, than exposure in patients at the clinical dose of 75 mg/day.

In the PPND study in rats, the F1 offspring, at 500 mg/kg a tendency toward increase in stillborn index was noted, and all offspring of 2 dams died on LDs 4 and 10. Furthermore, low values were noted in viability index on PND 4 and weaning index. Significant decreases in body weight and/or body weight gain were observed in male F1 offspring at 500mg/kg. The NOAEL for offspring development was set to 100 mg/kg/day, corresponding to exposure margins of 84.9x (Cmax) and 88.6x (AUC) to exposure in patients at the clinical dose of 75 mg/day.

Embryo/fetal/postnatal exposure of the F1 offspring in the rat EFD and PPND studies is supported by data from pregnant rats demonstrating placental passage of vibegron albeit at low levels and that vibegron-derived material was transferred into milk.

It should be noted that there are significant species differences in the potency of vibegron on B3-AR, as discussed above in the toxicology discussion and reflected in SmPC 5.3.

Regarding the significance for labelling, the DART studies do not reveal findings of malformations or structural toxicity. The main developmental findings are related to reduced fetal body weight which may be due to the β3 -adrenergic agonistic effect of vibegron. Overall, the results of the DART studies suggest that there was a vibegron-related effect on fetal growth rather than organogenesis. Therefore, vibegron treatment is not recommended during pregnancy and should not be used during breast feeding. In addition, vibegron treatment is not recommended in women of childbearing potential not using contraception and a recommendation that vibegron treatment should be stopped and, if

appropriate, alternative therapy should be started when pregnancy is planned or diagnosed is included in SmPC 4.6. Furthermore, the applicant included specific adverse reaction follow-up questionnaires to monitor the important potential risk of embryo-foetal toxicity, see RMP section 2.7.

Impurities

The Applicant identified two N-nitroso derivatives that can be formed during drug substance synthesis, drug product formulation or during drug product storage and has provided with a risk assessment based on read across to arrive at a proposed AI for the substances. However, from 7 July 2023 the Carcinogenic Potency Categorisation Approach (CPCA) and the Enhanced Ames Test (EAT) should be applied to establish acceptable intakes (AI) for nitrosamines.

Assessment of paediatric data on non-clinical aspects

Juvenil toxicity studies were provided although paediatric patients are not intended to be treated in the current application.

In juvenile rats, treatment-related bone effects were seen at 125 mg/kg/day in males and 250 mg/kg/day in females consisted of decrease in bone mass and size (decreases of femur length, cortical thickness and area at the diaphysis site in males and decrease at the area of metaphysis site in females). Partial reversibility was seen after a recovery period of 4 weeks. The bone findings occurred at a 100-folds exposure marginal compared to the clinical dose. Other effects/findings were similar to those found in adult rats.

Environmental risk assessment (ERA)

The refined PECSW of 3.78 µg/L exceeds the action limit of 0.01 µg/L and thereby triggers a phase IIA assessment. No phase II related data for vibegron were submitted. Upon request, the Applicant has provided a commitment letter stating that it will submit a phase II ERA according to “Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2, 01 June 2006)” by Q4 2025.

Vibegron is not considered to be a PBT substance.

As a result of the above considerations, the available data do not allow to conclude on the potential risk of vibegron to the environment.

Upon request, the Applicant has provided a commitment letter stating that it will submit a phase II ERA according to “Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2, 01 June 2006)” by Q4 2025.

2.5.7. Conclusion on the non-clinical aspects

Overall, the non-clinical package is considered acceptable and in support of this marketing authorisation application (MAA).

Regarding the ERA, a phase II study will be submitted by the applicant by Q4 2025 in line with the “Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2, 01 June 2006)”.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

Tabular overview of clinical studies

Type of Study	Study Identifier	Study Objective(s)	Study Design and Type of Control	Test Product(s) Dosage Regimen Administration Route	Number of Subjects/Patients	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
BA	006[a]	To compare the PK properties between the Phase I and Phase II formulations of vibegron	Open-label, randomised, 2-period, crossover PK study	150 mg gelatine capsule and non-aqueous tablet formulations Single dose Oral	Total: 22 treated	Healthy subjects (male)	Single dose
BA	018[a]	To compare the PK properties between the non-aqueous and aqueous formulations of vibegron	Open-label, single-dose, randomised, 2-period, 2-treatment, 2-sequence, crossover study	50 mg (formulation: non-aqueous tablet), 50 mg (formulation: to-be-marketed tablet A) Single dose Oral	Total: 20 treated	Healthy subjects	Single dose
BA	1005[b]	To assess the plasma PK parameters of a single-dose oral vibegron 75 mg tablet and paediatric granule formulation	Open-label, randomized, -period, crossover PK study of vibegron tablet and paediatric granules formulation	75 mg tablet B and 75 mg granules Single dose Oral	Total: 40 treated	Healthy subjects	Single dose
PK/BA (Food)	001[a]	Safety, tolerability, and PK of single-rising oral doses of vibegron	Randomised, double-blind, placebo-controlled, rising single dose study	2, 5, 10, 20, 50, 100, 150, 200, 300, 450, 600 mg vibegron capsule, or placebo Single dose Oral	Total: 48 treated 40 vibegron 8 placebo	Healthy subjects (young male, elderly male, and elderly female)	Single dose

Type of Study	Study Identifier	Study Objective(s)	Study Design and Type of Control	Test Product(s) Dosage Regimen Administration Route	Number of Subjects/Patients	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
PK/BA (Food)	003[a]	Safety, tolerability, and PK study	Double-blind, randomised, placebo-controlled, alternating (Panels A and B), multiple-period, single rising oral dose study	10 to 300 mg, 50 mg vibegron capsule, or placebo Single dose Oral	Total: 19 treated 18 vibegron 1 placebo	Healthy subjects (young Japanese male)	Single dose
BA (Food)	1004[a]	Effect of food on vibegron 75 mg tablet (Part I) and comparison of PK after administration of an intact tablet and crushed in applesauce (Part II)	Open-label, randomised, 3-period, crossover PK study of vibegron tablet fasted, tablet administered with a high fat meal and tablet crushed and mixed in applesauce	75 mg vibegron tablet B Single dose Oral	Total: 48 treated 18 (Part I) 30 (Part II)	Healthy subjects	Single dose
BA (Food)	101[c]	Effect of food on final tablet formulation of vibegron	Open-label, randomised, uncontrolled, 2-period crossover study	50 mg vibegron tablet[d] Single dose Oral	Total: 8 treated	Healthy subjects (Japanese male)	Single dose
PK	002[a]	Safety, tolerability, and PK of multiple ascending doses of vibegron	Randomised, double-blind, placebo-controlled, multiple rising dose study	25, 50, 100, 150, 200, 300, 400 mg vibegron, or placebo Multiple dose, once daily Oral	Total: 129 treated 95 vibegron 34 placebo	Healthy subjects (young male, elderly male, and elderly female)	7-28 days
PK	011[a]	Mass-balance study to investigate the absorption, metabolism, and excretion of [^{14}C]-vibegron	Single dose, open-label study	100 mg [^{14}C]-vibegron (~100 µCi) Single dose Oral	Total: 6 treated	Healthy subjects (male)	Single dose

Type of Study	Study Identifier	Study Objective(s)	Study Design and Type of Control	Test Product(s) Dosage Regimen Administration Route	Number of Subjects/Patients	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
PK	009[a]	Safety, tolerability, and multiple dose PK study	A 2-part, randomised, double-blind, placebo-controlled, multiple rising dose study	50 to 200 mg, 100 mg vibegron, or placebo Multiple dose, once daily Oral	Total: 40 treated 30 vibegron 10 placebo	Healthy subjects (young male, elderly male, and elderly female Japanese)	14 days
PK	013[a]	Safety, tolerability and PK in subjects with hepatic impairment	A 2-part, open-label, single dose study	100 mg vibegron Single dose Oral	Total: 16 treated	Patients with hepatic insufficiency	Single dose
PK	014[a]	Safety, tolerability and PK in subjects with impaired renal function	Open-label, single-dose study	100 mg vibegron Single dose Oral	Total: 32 treated	Patients with renal insufficiency	Single dose
PK/PD DDI	007[a]	Safety, tolerability, and multiple dose PK of vibegron alone or in combination with tolterodine ER To evaluate the effect on HR at steady state	Double-blind, randomised, placebo-controlled, multiple dose study	100, 150 mg vibegron, or 4 mg tolterodine ER or placebo Multiple dose, once daily Oral	Total: 50 treated 49 vibegron 1 tolterodine	Healthy subjects (male)	7 days
DDI	015[a]	The effect of multiple oral doses of ketoconazole (Panel 1) and diltiazem (Panel 2) on the single dose PK and safety of vibegron	Two-panel, open-label, randomised, 2-period, fixed-sequence study	100 mg vibegron, 200 mg Q12h ketoconazole, 240 mg ER diltiazem, 180 mg diltiazem (60 mg TID every 8 hours) Single and multiple doses, once daily Oral	Total: 22 treated	Healthy subjects	1-16 days

Type of Study	Study Identifier	Study Objective(s)	Study Design and Type of Control	Test Product(s) Dosage Regimen Administration Route	Number of Subjects/Patients	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
DDI	024[a]	Safety, tolerability and effects of vibegron on the single-dose PK of digoxin	Open-label, single-dose and multiple dose, 2-period, single-sequence, 2-treatment study	0.25 mg digoxin, 100, 150 mg vibegron Single and multiple dose, once daily Oral	Total: 18 treated	Healthy subjects	1-6 days
DDI	022[a]	Safety and tolerability; Effect of multiple oral doses vibegron on the single-dose PK of OC components, EE and LNG	Open-label, 2-period, fixed-sequence study	OC, 100 mg vibegron Single and multiple dose, once daily Oral	Total: 18 treated	Postmenopausal or oophorectomised adult female subjects	13 days
DDI	1002[a]	Safety and tolerability; Effect of vibegron on metoprolol or warfarin	Open-label, single-sequence study of single dose oral warfarin and metoprolol succinate given alone, and in combination with repeat-dose oral vibegron	10 mg warfarin, 100 mg metoprolol succinate, 75 mg vibegron QD Single and multiple dose, once daily Oral	Total: 24 treated	Healthy subjects	1-16 days
DDI	1003[a]	Safety and tolerability; Effect of rifampin on vibegron	Open-label, single-sequence study of single dose oral vibegron alone and in combination with repeat-dose oral rifampin	75 mg vibegron, 600 mg rifampin Single and multiple dose, once daily Oral	Total: 20 treated	Healthy subjects	1-14 days

Type of Study	Study Identifier	Study Objective(s)	Study Design and Type of Control	Test Product(s) Dosage Regimen Administration Route	Number of Subjects/Patients	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
PD	012[a]	Safety and tolerability; TQT study to assess the effect of vibegron on QTc interval	Single dose, randomised, double-blind (with respect to vibegron only), placebo- and active-controlled, 4-period, balanced crossover study	200, 400 mg vibegron, or 400 mg moxifloxacin Single dose Oral	Total: 52 treated	Healthy subjects	Single dose
PD	010[a]	Safety, tolerability, PK and blood pressure following multiple oral doses of vibegron when co-administered with a beta-blocker or vasodilator	Two-panel, randomised, blinded (with respect to vibegron only), placebo-controlled 2-period crossover study	Metoprolol, 100 mg vibegron, amlodipine Multiple dose, once daily Oral	Total: 26 treated 24 vibegron 2 comparator	Patients on a stable dose of a beta-blocker or amlodipine for the treatment of uncomplicated essential or idiopathic hypertension	7 days
PD	1001[b]	Safety and tolerability; Ambulatory Blood Pressure Monitoring Study to assess the effect of vibegron on 24-hour blood pressure and HR	Double-blind, randomised, placebo-controlled, parallel-group study	75 mg vibegron or placebo Multiple dose, once daily Oral	Total: 214 treated 106 vibegron 108 placebo	Patients with OAB	28 days
PK/PD	004[a,e]	Safety and tolerability of multiple oral doses of vibegron	Randomised, double-blind, double-dummy, placebo- and active-controlled, multiple dose study	100 mg vibegron, 4 mg tolterodine ER, or placebo Multiple dose, once daily Oral	Total: 4 treated 3 vibegron 1 placebo	Adult female patients with OAB	7 days

Type of Study	Study Identifier	Study Objective(s)	Study Design and Type of Control	Test Product(s) Dosage Regimen Administration Route	Number of Subjects/Patients	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Safety and efficacy	008[a]	Efficacy, safety, and tolerability of selected vibegron doses either alone or dosed with tolterodine ER	Double-blind, randomised, placebo- and active comparator (tolterodine)-controlled, 2-part, parallel-group efficacy, and safety study with 52-week extension	3, 15, 50, 100 mg vibegron, 4 mg tolterodine ER, or placebo Multiple dose, once daily Oral	Base study: Total: 1393 treated 931 vibegron 257 tolterodine 205 placebo Extension study: Total: 845 treated 605 vibegron 240 tolterodine	Adult patients with OAB	8-52 weeks
Safety and efficacy	3003[b]	Safety, tolerability, and efficacy of vibegron	Double-blind, randomised, placebo- and active-controlled, multicentre parallel-group study	75 mg vibegron, 4 mg tolterodine ER, or placebo; Multiple dose, once daily Oral	Total: 1515 treated 545 vibegron 430 tolterodine 540 placebo	Adult patients with OAB	12 weeks

Type of Study	Study Identifier	Study Objective(s)	Study Design and Type of Control	Test Product(s) Dosage Regimen Administration Route	Number of Subjects/Patients	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Safety and efficacy	3004[b]	Long-term safety and tolerability of vibegron. Efficacy included as an exploratory objective	Double-blind, randomised, active-controlled, 40-week extension study for patients who complete RVT-901-3003; patients randomised in RVT-901-3003 to placebo are randomised 1:1 to blinded vibegron or tolterodine; patients randomised in RVT-901-3003 to vibegron or tolterodine continue to receive the same blinded treatment	75 mg vibegron, or 4 mg tolterodine ER Multiple dose, once daily Oral	Total: 505 treated 273 vibegron 232 tolterodine	Study completers from RVT-901-3003: Adult patients with OAB	40-week extension (52 weeks in total)
Safety and efficacy	301[c]	Safety and efficacy of vibegron	Double-blind, randomised, placebo-controlled study	50, 100 mg vibegron, placebo, or 0.2 mg imidafenacin Imidafenacin (twice daily), vibegron (once daily) Oral	Total: 1225 treated 739 vibegron 369 placebo 117 imidafenacin	Adult patients with OAB	12 weeks
Safety and efficacy	302[c]	Long-term safety and effectiveness of vibegron	Open-label, uncontrolled safety and efficacy study	50, 100 mg vibegron Multiple dose, once daily Oral	Total: 167 treated	Adult patients with OAB	52 weeks

[a] Conducted by Merck.
[b] Conducted by Urovant.
[c] Conducted by Kyorin.
[d] Information regarding the quantitative composition of the tablet formulation used in Study 101, and the validation report C-AT140015 related to the bioanalytical method used to test samples for this study are not available to the Applicant.
[e] Study 004 was terminated early due to insufficient enrolment.
BA = Bioavailability; DDI = Drug-drug interaction; EE = Ethinyl oestradiol; ER = Extended release; HR = Heart rate; LNG = Levonorgestrel; OAB = Overactive bladder; OC = Oral contraceptive; PD = Pharmacodynamic; PK = Pharmacokinetic; QD = Once a day; QTc = Corrected QT duration; TID = Three times a day; TQT = Thorough QT.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Vibegron is a new chemical entity, and the pharmacokinetic (PK) studies should thus aim at describing the disposition and also to identify subgroups where an altered exposure can be expected based on the PK properties. Potential interactions should also be evaluated.

Methods

Bioanalytical methods

Bioanalytical methods were developed and validated for the quantitation of vibegron in human plasma and urine, and the quantitation in plasma of drugs co-administered with vibegron in drug- drug interaction studies.

Non-compartmental data analysis

Standard non-compartmental analysis was performed in all studies where rich sampling was applied.

Population PK analysis

The objectives of the popPK model development were to describe vibegron PK and evaluate selected covariates on vibegron PK parameters. The model was utilised to simulate expected vibegron plasma concentrations in subpopulations (elderly, renally impaired, and underweight subjects) to illustrate and quantify potential differences across subgroups. In the evaluation of subject covariates, forward inclusion was followed by stepwise backward elimination of effects, until removal of a particular covariate resulted in a statistically important degradation in the model fit.

Standard model development and evaluation has been used in the development of a vibegron popPK model. The final popPK model was a three-compartment model with nonlinear distribution into one of the peripheral compartments and linear elimination from the central compartment, utilizing MTT and ntr1. Absorption was described by a transit compartment model with increasing relative bioavailability with dose. The model incorporated IIV on CL, V1, Bmax (Maximum capacity of peripheral distribution). The parameter estimates of the final model are given in Table 4.

Table 4. Parameter Estimates of the Final PopPK Model

Parameter	Alias	Estimate	Relative SE (%)	95% CI
θ_1	CL/F (L/h)	48.1	.....	(42.4 - 54.7)
θ_2	V_2/F (L)	575	.....	(521 - 635)
θ_3	V_3/F (L)	880	.....	(699 - $1.11 \cdot 10^3$)
θ_4	$Q2_2$/F (L/h)	3.33	.....	(2.66 - 4.16)
θ_5	MTT1 (h)	0.517	.....	(0.468 - 0.572)
θ_6	B_{max}/F (μg)	$1.61 \cdot 10^5$	.....	($1.37 \cdot 10^5$ - $1.88 \cdot 10^5$)
θ_7	K_m/F (μg)	$3.15 \cdot 10^4$	.....	($2.62 \cdot 10^4$ - $3.79 \cdot 10^4$)
θ_8	F_{base} (-)	0.204	.....	(0.171 - 0.241)
θ_9	F_{50} (mg)	71.2	.....	(50.4 - 101)
θ_{10}	Food study 001 and 003 (-)	0.482	10.8	(0.380 - 0.585)
θ_{11}	N_{tr1} (-)	3.38	.....	(2.39 - 4.78)
θ_{12}	k_p/F (/h)	0.0783	.....	(0.0704 - 0.0872)
θ_{13}	Food study 002 (-)	0.805	10.5	(0.640 - 0.971)
θ_{14}	Age on B_{max} (-)	0.372	16.6	(0.251 - 0.494)
θ_{15}	eGFR on CL (-)	0.312	17.9	(0.202 - 0.421)
θ_{16}	Healthy CL (-)	-0.195	10.8	(-0.236 - -0.154)
θ_{17}	WT on CL (-)	0.563	12.6	(0.424 - 0.701)
θ_{18}	WT on V_1 (-)	1.38	13.4	(1.02 - 1.74)
$\omega_{1.1}$	ω^2_{CL}	0.215	7.90	(0.182 - 0.249)
$\omega_{2.2}$	ω^2_{V1}	0.278	13.0	(0.207 - 0.348)
$\omega_{3.3}$	ω^2_{MTT1}	0.500	19.4	(0.310 - 0.690)
$\omega_{4.4}$	ω^2_{BMAX}	0.116	15.5	(0.0809 - 0.152)
$\sigma_{1.1}$	Proportional residual error healthy	0.0865	3.80	(0.0800 - 0.0930)
$\sigma_{2.2}$	Proportional residual error patients	0.130	5.80	(0.115 - 0.145)

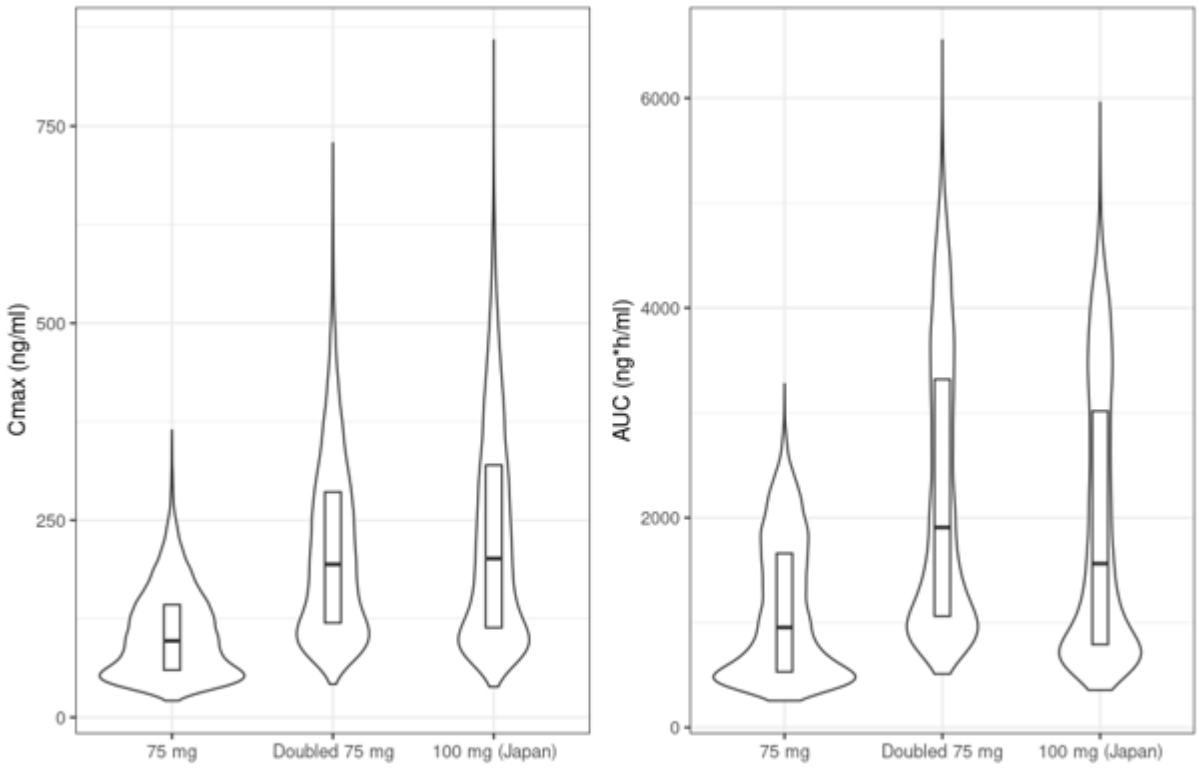
Parameter values for the final PopPK model. CL: systemic clearance. F: Bioavailability ("/F" denotes apparent). V_1: central volume of distribution. V_2: first peripheral volume of distribution. Q_1: first intercompartment clearance. V_3: second peripheral volume of distribution. Q_2: second intercompartment clearance. ω^2_X: variance of the IIV of parameter X, IIV is derived from variance according to $\sqrt{\omega^2_X} \cdot 100$, covariance $\omega^2_{X,Y}$: covariance of the IIV of parameters X and Y, IIV is derived from variance according to $\sqrt{\omega^2_X} \cdot 100$, SE: standard error, CI: Confidence interval. Relative SE is only shown for parameters estimated on normal scale; ellipses denote a parameter not on a normal scale. Uncertainties are determined by the covariance step in NONMEM.

The median appears relatively well captured in most stratified pcVPCs. In the OAB patient studies the outer percentiles are adequately captured. However, in the two phase 1 repeated dose studies the variability is overpredicted. The pcVPC of OAB Patient Studies MK-4618-008 (phase 2 dose finding study, patient given 3, 15, 50 and 100 mg vibegron) and RVT-901-3003 (Phase 3 study, patients given 75 mg vibegron) shows trends in the outer percentiles over time. However, these trends go in opposite direction for study MK-4618-008 and RVT-901-3003 indicating that it is not a PK trend but rather an effect of study related character. The median is slightly underpredicted for study RVT-901-3003 and well described for study MK-4618-008 (samples collected only at Ctrough on 1 to 3 occasions) and URO-901-1001 (Phase 1 Systolic Blood Pressure study in patients given 75 mg vibegron and samples were collected around Cmax).

Simulations

The model was used for simulation of exposures in special populations (see section on Special population) and to support comparison of doubled exposure with 75 mg to 100 mg exposures. A simulation was performed to enable comparison of 75 mg versus 100 mg once daily vibegron and explore what a doubling of exposure from 75 mg in a population reflective of the EU would compare to 100 mg once daily in Japanese subjects (Figure 2, Figure 7 and Table 6). The simulation dataset consisted of 10,000 subjects for which their WT, eGFR and age were sampled from Study RVT-901-3003 (75 mg and doubled 75 mg) and Study 301 (100 mg). Study 301 is a study in Japanese patients. The difference in steady state Cmax and AUC after 75 mg and 100 mg of vibegron was illustrated using the covariate distributions in the OAB patient studies (RVT-901-3003) to achieve a reasonable comparison. The same subjects (10000) were simulated with both dose level 75 and 100 mg of

vibegron. After multiplying the exposures of once daily 75 mg by two, the results were compared to simulated multiple exposure of 100 mg.



The violin shows the density of the simulated data. The box shows the median and interquartile range.

Figure 2 Simulated Vibegron Cmax and AUC for doses of 75, doubled 75 and 100 mg. The 100 mg dose was simulated using covariates from the Japanese population in Study 301 whereas the 75 mg and doubled 75 mg was simulated using the covariates from the population in Study 3003.

Table 5 Summary of simulated Cmax (ng/mL) per dose. The 100 mg dose was simulated using covariates from the Japanese population in Study 301 whereas the 75 mg and doubled 75 mg was simulated using the covariates from the population in Study 3003.

Dose	Minimum	p05	p10	Median	Mean	SD	p90	p95	Maximum
75 mg (3003 population)	21.07	38.92	44.7	97.05	106.8	55.37	184.6	210.1	364.3
Doubled 75 mg (3003 population)	42.14	77.83	89.41	194.1	213.5	110.7	369.2	420.2	728.6
100 mg (301population)	38.88	75.27	84.86	201.5	231.5	135.8	428.8	489	859

*Table 6 Summary of simulated AUC (ng*h/mL) per dose. The 100 mg dose was simulated using covariates from the Japanese population in Study 301 whereas the 75 mg and doubled 75 mg was simulated using the covariates from the population in Study 3003.*

Table 12: Summary of simulated AUC_T (ng.h/mL) per dose

Dose	Minimum	p05	p10	Median	Mean	SD	P89	p90	p95	Maximum
75 mg (3003 population)	254.9	382.6	422.4	953.7	1122	648.7	2057	2094	2285	3276
Doubled 75 mg (3003 population)	509.8	765.1	844.9	1907	2244	1297	4114	4188	4569	6553
100 mg (301population)	356.9	567.2	620.4	1562	1938	1246	3777	3835	4147	5960

Absorption

Following oral administration of the 75 mg film-coated tablet formulation, vibegron absorption is rapid with a median t_{max} of approximately 1 to 3 hours.

No human absolute bioavailability study has been performed. The mass-balance study indicates incomplete absorption. In vitro permeability studies show that vibegron is a low-permeability compound and a substrate of the efflux transporter P-gp. The applicant claims that vibegron is a Biopharmaceutics Classification System (BCS) Class 3 drug substance.

The to-be-marketed formulation (tablet A) was used in the pivotal and supportive phase 3 studies. Two relative bioavailability studies were performed to compare different formulations used during the clinical development programme. Study 006 demonstrated similar AUC and C_{max} of two earlier formulations, non-aqueous tablet and capsule formulation, at a dose of 150 mg. Study 018 demonstrated similar AUC and C_{max} of non-aqueous tablet and tablet A (to-be-marketed formulation) at a dose of 50 mg.

Study 1004 investigated the effect of a high-fat meal on tablet B, which is very similar to the final commercial formulation tablet A (differ only in colorant used in film-coating). In this study, a high-fat meal decreased the vibegron $AUC_{0-\infty}$ by 37%, the AUC_{0-t} by 34% and the C_{max} by 63%. Previous studies with the capsule formulation indicate a similar food effect. In the MAD study 002 multiple doses of vibegron at a dose of 150 mg given with a high fat meal resulted in similar AUC and 30% lower C_{max} compared to the same dose in the fasted state (between group-comparison).

Study 1004 compared vibegron PK of a crushed tablet in applesauce to administration of the intact tablet. In this comparison, $AUC_{0-\infty}$ and AUC_{0-t} are within BE acceptance criteria while C_{max} is 30% lower for crushed tablet with applesauce compared to intact tablet.

Distribution

The mean apparent volume of distribution following oral administration of the tablet formulation is estimated at 9120 L (hepatic impairment study 013, data from healthy controls).

Plasma protein binding was determined by equilibrium dialysis. Vibegron plasma protein binding is 50%, and independent of concentration. The average blood-to-plasma concentration ratio is 0.9 in human blood.

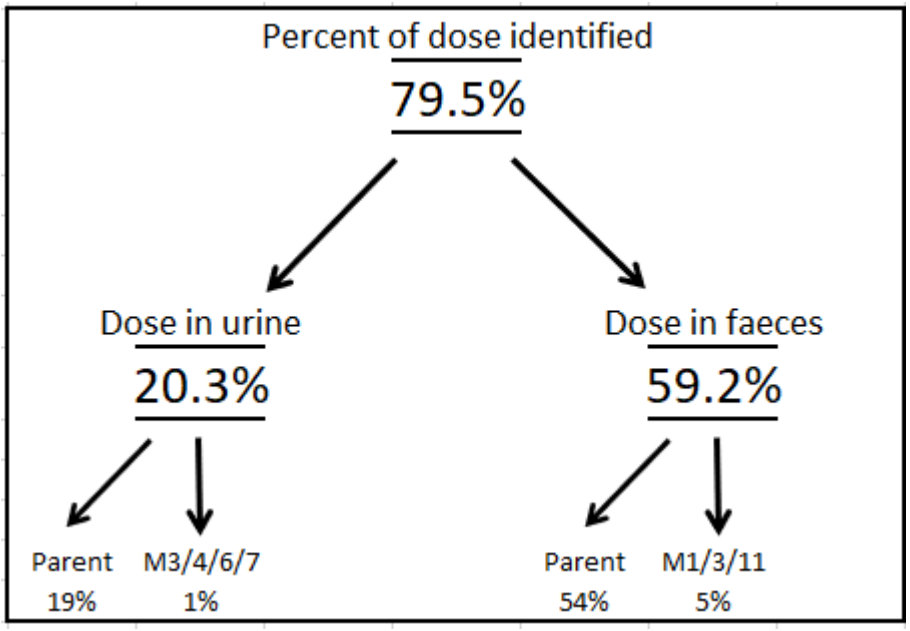
Elimination

Vibegron has an apparent terminal t½ ranging from 59 to 94 hours in young and elderly subjects; whereas the effective half-life across all populations is 30.8 hours.

Based on the pop-PK analysis, CL/F for an OAB patient was estimated to be 48.1 L/h with IIV of 46.4% CV (reported IIV value for the entire population, not only for OAB patients).

In the mass balance study (study 011) healthy male subjects (N=6) received a single oral dose of 100 mg carbon-14-radiolabeled ([^{14}C])-vibegron (~92 µCi) (given as an oral solution in the fasted state). The mean total recovery of radioactivity following the oral dose was 79.5% over the 20-day collection interval, with 20.3% in urine and 59.2% in faeces. The majority of the vibegron dose was eliminated as the unchanged parent drug. Nineteen percent (19%) of the radioactive dose was recovered in urine and 54% of the dose was recovered in feces as unchanged parent radioactive drug. Mean apparent vibegron terminal elimination phase t½ was 135 hours. Vibegron renal clearance following oral administration was 157 mL/minute (9.42 L/h).

In the mass balance study, 7 minor metabolites were detected in urine and faeces. In urine (0-120 h pooled urine samples) parent drug vibegron was the major drug-related component, accounting for 19% of the dose. M3, M4, M6, M17 and the glucuronide conjugate M7 accounted for 0.2%, 0.2%, 0.3%, <0.2%, and 0.3% of the dose, respectively. In faeces (0-120 h pooled faeces samples) parent drug vibegron was the major drug-related component, accounting for 54% of the dose. The oxidative metabolites M1, M3, M11, and M17 were also observed and accounted for 1%, 2%, 2%, and <1% of the dose, respectively.



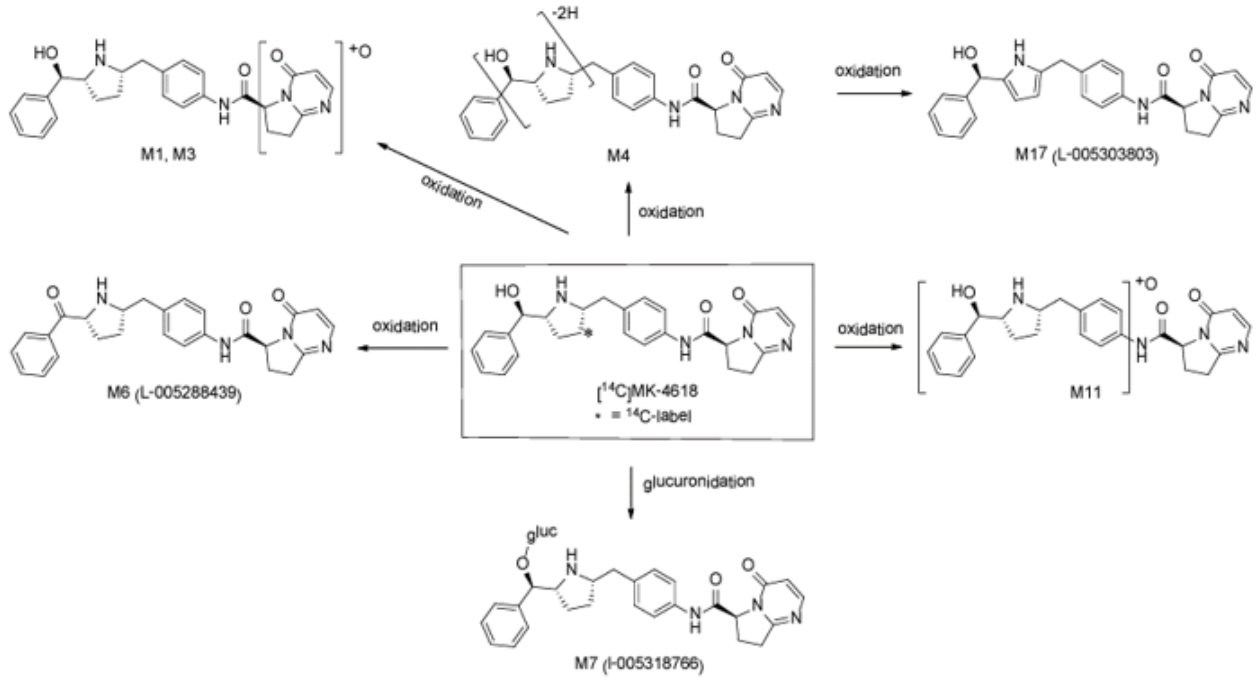
Vibegron was the predominant circulating component in human plasma, representing 78% and 73% of the total circulating vibegron-related material in the pooled 0-2 and 2-4 hour plasma samples, respectively. M7, an O-glucuronide conjugate, was the major circulating metabolite in plasma accounting for approximately 12% (2h) to 14% (4h) of the total circulating drug-related material. Two oxidative metabolites, M4 and M17, accounted for 4 to 6% and 6 to 7%, respectively, of total drug-related material in plasma.

Vibegron has been evaluated as a substrate for both renal and hepatic transporters as both renal and hepatic elimination pathways are important. Vibegron is not a substrate of any other transporter than P-gp.

Vibegron is rather stable in microsomes and hepatocytes precluding robust CYP phenotyping. The available data indicate that vibegron is a substrate mainly for CYP3A4 and CYP3A5. In addition, all the recombinant UGT enzymes evaluated demonstrated some metabolism of vibegron (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B10, UGT2B15, UGT2B17).

The Applicant concludes that vibegron is eliminated by a variety of pathways including urinary excretion, biliary excretion, and hepatic metabolism, where metabolism appears to only play a minor role. In the mass balance study, the majority of the recovered dose was eliminated as unchanged vibegron.

Figure 3: Proposed Metabolic Scheme for [^{14}C] Vibegron



Dose proportionality and time dependencies

In SAD study 001, investigating vibegron doses from 2 to 600 mg, vibegron exhibited greater than dose proportional increases in exposure over a dose range of 5 to 200 mg (slope estimates 1.3-1.6), with a trend towards a more dose proportional increase between 200 to 600 mg (slope estimates 1.1-1.3). Results are presented in Table 7.

Table 7. Mean ± SD Vibegron Plasma Pharmacokinetic Parameters Following a Single Dose of Vibegron to Healthy Young Males in a Fasted State (Part 1, Panels A and B, Part 3, Panels D and E) and Elderly Males and Females (Part 2, Panel C) (study 001)

Dose (mg) [a]	N	$AUC_{0-\infty}$ (ng·h/mL)	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	t_{max} [b] (hr)	$t_{½}$ [c] (hr)
2	3 [d]	-- [e]	-- [e]	0.14 ± 0.15	3.0 (1.0-3.0)	-- [e]
5	6	-- [e]	14.3 ± 1.27 [f]	0.79 ± 0.30	1.0 (0.5-6.0)	-- [e]
10	6	71.6 ± 37.5	28.0 ± 12.6	4.76 ± 4.58	2.5 (1.0-6.0)	45.5 (36.7)
20	6	119 ± 48.0	40.0 ± 21.1	5.25 ± 4.25	0.8 (0.5-6.0)	64.1 (19.8)
50	6	542 ± 262	219 ± 124	31.7 ± 35.0	2.0 (0.5-6.0)	50.4 (13.7)
50 (Elderly)	12	948 ± 304	313 ± 119	50.2 ± 23.6	1.0 (0.5-3.0)	95.1 (16.5)
100	6	1890 ± 698	845 ± 401	142 ± 108	2.0 (1.0-4.0)	73.5 (15.2)
150	6	2280 ± 893	1050 ± 551	195 ± 185	1.0 (1.0-6.0)	68.4 (27.8)
200	18	3620 ± 1110	1740 ± 747	274 ± 138	1.0 (1.0-4.0)	75.8 (12.2)
300	6	7380 ± 1410	4430 ± 996	618 ± 231	2.5 (2.0-3.0)	63.8 (4.6)
450	6	9160 ± 1860	5510 ± 1440	645 ± 165	3.0 (0.5-6.0)	60.5 (16.8)
600	5	15500 ± 3440	10800 ± 2770	1330 ± 529	3.0 (2.0-6.0)	60.7 (8.7)

Source: Study 001 CSR, Table 14-3, 14-4, 14-5, 14-6, 14-7, 14-8, 14-9, 14-10, 14-11, 14-12, 14-13, 14-14
$AUC_{0-\infty}$ = Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time; AUC_{0-24} = Area under the concentration-time curve from time zero (pre-dose) to 24 hours post dose or over 24 hours; C_{max} = Maximum observed concentration; CSR = Clinical study report; CV = Coefficient of variation; GCV = Geometric mean coefficient of variation; N = Number; SD = Standard deviation; $t_{½}$ = Elimination half-life; t_{max} = Time of occurrence of C_{max}.
Note: Concentration data converted from molar to ng/mL (molecular weight of vibegron = 444.538 g/mol)
[a] Dosed in healthy young males unless otherwise indicated
[b] Median (minimum-maximum)
[c] Geometric mean (geometric mean CV% [GCV%])
[d] Only 3 of 6 subjects had any concentrations above the limit of quantitation at the 2 mg dose. Summary statistics for C_{max} and t_{max} are based only on data from these subjects.
[e] The duration of sampling was too short for 2 and 5 mg, precluding an accurate determination of the apparent terminal $t_{1/2}$ and $AUC_{0-\infty}$
[f] N=2

In the MAD study 002, vibegron exhibited greater than dose proportional increases in exposure over a dose range of 25 to 400 mg once daily. The mean accumulation ratio over the dosing range was 1.7 for C_{max} and 2.4 for area under the concentration time curve from 0 to 24 hours (AUC_{0-24}). Steady state concentrations are achieved within 7 days of once daily dosing. Results are presented in Table 8.

Table 8. Mean ± SD Vibegron Plasma Pharmacokinetic Parameters Following Multiple-Dose Administration of Vibegron to Healthy Young Males, Elderly Males, Elderly Females and Middle-Aged Males and Females after 14 Days of Dosing (Except for Panel F at Day 28) (study 002)

Dose (mg)[a]	N	AUC_{0-24} (ng.h/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)	t_{max}[b] (hr)	$t_{1/2}$[c] (hr)	R_{ac}[b]
25 (Panel A)	5	164 ± 25.9	15.6 ± 6.93	5.07 ± 0.71	1.0 (0.5-2.0)	94.9 (10.6)	2.35 (2.04-2.42)
50 (Panel B)	6	507 ± 176	41.6 ± 12.3	15.3 ± 5.07	2.5 (0.5-6.0)	78.0 (7.9)	2.14 (1.41-3.74)
100 (Panel C)	6	1280 ± 529	169 ± 80.9	31.9 ± 11.5	1.0 (0.5-4.0)	80.8 (10.6)	2.06 (1.56-2.76)
100 (Panel E-Elderly Males and Females)	12	2230 ± 671	224 ± 92.0	54.2 ± 15.4	1.0 (0.5-6.0)	89.4 (10.5)	2.78 (1.94-3.90)
150 (Panel D)	6	2410 ± 1140	305 ± 215	54.2 ± 16.6	1.5 (0.5-4.0)	80.0 (8.9)	2.01 (1.04-4.37)
150[d] (Panel F-Middle-Aged Males and Females)	18	2370 ± 796	276 ± 88.5	50.2 ± 12.7	1.0 (0.5-6.0)	78.6 (14.5)	2.04 (1.77-2.35)
150 (Panel J-Fed Middle-Aged and Elderly Females	11	2560 ± 858	216 ± 125	64.0 ± 12.8	6.0 (3.0-6.1)	80.4 (9.54)	2.92 (1.50-4.43)
200 (Panel G)	5	3200 ± 1120	313 ± 168	61.8 ± 12.4	2.0 (1.0-3.0)	65.1 (6.8)	1.60 (1.03-2.31)
300 (Panel H)	6	6980 ± 1040	733 ± 164	129 ± 23.6	2.0 (2.0-3.0)	58.8 (10.4)	2.38 (1.66-3.11)
400 (Panel I)	6	10400 ± 2140	1400 ± 257	189 ± 54.7	1.5 (1.0-3.0)	59.4 (5.72)	2.26 (1.56-2.84)

Source: Study 002 CSR, Table 14-15, 14-16, 14-17, 14-18, 14-19, 14-20, 14-21, 14-22, 14-23, 14-24
Note: Concentration data converted from molar to ng/mL (molecular weight of vibegron = 444.538 g/mol)
AUC_{0-24} = Area under the concentration-time curve from time zero (pre-dose) to 24 hours post dose or over 24 hours; C_{max} = Maximum observed concentration; C_{trough} = Plasma concentration at 24 hours after the morning dose on Study Day 14 or 28; N = Number of subjects; R_{ac} = Accumulation Ratio (ratio of AUC_{0-24} on Study Day 14 to that on Study Day 1); SD = Standard deviation; $t_{½}$ = Elimination half-life; t_{max} = Time of occurrence of C_{max}.
[a] Dosed in healthy young males for 14 days unless otherwise indicated
[b] Median (minimum-maximum)
[c] Arithmetic mean (SD)
[d] 28 days of dosing; $t_{½}$ determined after 28 days of dosing

SAD and MAD studies were also performed in Japanese population (study 003 and study 009). Vibegron exhibited greater than dose proportional increases in exposure over a single dose range of 10 to 300 mg (for AUC_{inf} regression slope 1.252, for C_{max} regression slope 1.632) and over a multiple dose range of 50 mg to 200 mg (for AUC_{0-24h} and Cmax the slopes were 1.46 and 1.83, respectively, with corresponding 95% CIs above 1).

Data on systemic exposure following multiple dose administration of vibegron at the therapeutic dose of 75 mg (not included in SAD/MAD studies) is available from study 1002 (DDI study). Geometric mean (%CV) values for $AUC_{0-24\ h}$ was 1450 (51) ng*h/ml, for C_{max} 123 (72) ng/ml and for C_{24h} 37.0 (43) ng/ml.

Variability

The between subject variability (%CVb) for vibegron C_{max} ranged from 32.1 to 67.2% and AUC ranged from 37.2 to 59.1%, across studies evaluating 50 mg once daily. Vibegron %CVb for C_{max} ranged from 25.2 to 88.0% and AUC ranged from 12.3 to 48.3%, across studies evaluating 100 mg once daily.

Intensive pharmacokinetic sampling of vibegron 75 mg at steady-state was performed in a DDI study (1002). In this study, %CVb for Cmax was 72% and for AUC_{0-24h} it was 51%.

Within subject variability (%CVw) was determined from 3 Phase 1 studies in which subjects received the same dose on two occasions separated by a washout period. The %CVw for vibegron C_{max} and AUC ranged from 36 to 55% and 18 to 40%, respectively.

Pharmacokinetics in target population and therapeutic window

In the population pharmacokinetic analysis, patient status was a statistically significant covariate on clearance. The significance, however, should be interpreted with caution due to potential factors such as food intake decreasing exposures and no physiologic basis for the disease state of OAB to alter exposures.

In the pivotal phase 3 study (where a 75 mg dose was given), C_{trough} samples were collected in a PK subset of the population at certain time points. Results are presented in Table 9. Note that the PK data from the pivotal phase 3 study was included in the population PK analysis (see section Population PK analysis).

Table 9. Summary of Plasma Concentrations 24 Hours Post Dose for Vibegron 75 mg Once Daily at Week 4, Week 8, and Week 12 – PK Set

Vibegron Treatment	n	C24h (ng/mL)[a]
Week 4	140	22.9 (20.5 ± 19.6)
Week 8	147	16.9 (19.4 ± 26.2)
Week 12	128	21.0 (21.2 ± 31.6)

Source: Table 14.2.22.1.1

[a] C24h (concentration 24 hours post dose) data are shown as geometric mean (arithmetic mean ± standard deviation)

The Applicant claims that from an efficacy perspective, the decrease in exposure when administered with a high-fat mealis not clinically relevant. The phase 3 studies (3003 and 3004) were performed with drug administration without regards to food.

From a safety perspective, the Applicant claims that a 2-fold increase in vibegron AUC and C_{max} with a 75 mg dose (which is the magnitude of increase observed in the DDI study with ketoconazole and in patients with moderate or severe RI in the RI study) is not considered clinically relevant. A vibegron dose of 100 mg has been evaluated with respect to safety in the supportive Phase 3 (Study 301 and 302) studies in the Japanese population and also in the phase 2 study 008. The Applicant also refers to the use of supratherapeutic doses in the clinical programme. In addition, reference is made to safety data in patients with moderate RI from the phase 3 studies. See discussion on clinical pharmacology section 2.6.3.

Renal impairment

A dedicated renal impairment study (study 014) has been performed. Subjects were originally classified based on body-surface adjusted eGFR but a reclassification was made using the Cockroft-Gault formula (ml/min). Following this reclassification, mild, moderate and severe RI resulted in 1.6-fold, 2.0-fold and 1.8-fold higher AUC_{inf} and 2.1-fold, 1.6-fold and 1.2-fold higher C_{max}, respectively, compared to healthy controls. Patients with mild, moderate, and severe renal insufficiency had mean CL/F values 37%, 49%, and 44% lower, respectively, compared to the healthy matched control subjects. The applicant concludes that no dose adjustment is needed when vibegron is administered to patients with mild, moderate or severe renal impairment. Vibegron has not been evaluated in patients

with End Stage Renal Disease including those requiring haemodialysis; thus it is not recommended in these patient populations.

Hepatic impairment

A dedicated hepatic impairment study (013) has been performed, comparing the exposure of vibegron in subjects with moderate HI to that of healthy controls. Relative to volunteers with normal hepatic function, administration of a 100 mg single dose of vibegron increased mean C_{max} and AUC by 1.3- and 1.3-fold, respectively in volunteers with moderate hepatic impairment (Child-Pugh Class B). No dose adjustment for vibegron is proposed in OAB patients with mild or moderate hepatic impairment. Vibegron has not been evaluated in subjects with severe hepatic impairment (Child Pugh C) and therefore, is not recommended in this population.

Gender, race, weight, age

Based on comparison of SAD/MAD studies, exposure in Japanese subjects was 30-40% higher than in non-Japanese subjects (likely due to differences in weight).

Sex, race (including Japanese versus non-Japanese) and age were not found to impact the exposure of vibegron to a clinically relevant extent in patients with OAB, based on population PK model assessment.

Weight was found to have a significant impact on exposure in the population PK model, however, as subjects in the Phase 3 study weighed 46 to 161 kg the efficacy and safety, the clinical relevance in the OAB population, is considered covered.

Number of older subjects included in studies (PK subset)

Study	Age 65-74 (N = 385)	Age 75-84 (N = 61)	Age 85+ (N = 3)
001	10	2	0
002	24	2	0
003	0	0	0
004	0	0	0
008	199	9	0
009	11	1	0
010	3	0	0
013	1	0	0
014	13	2	0
015	0	0	0
022	2	0	0
1001	17	0	0
1002	0	0	0
1003	0	0	0
3003	105	45	3

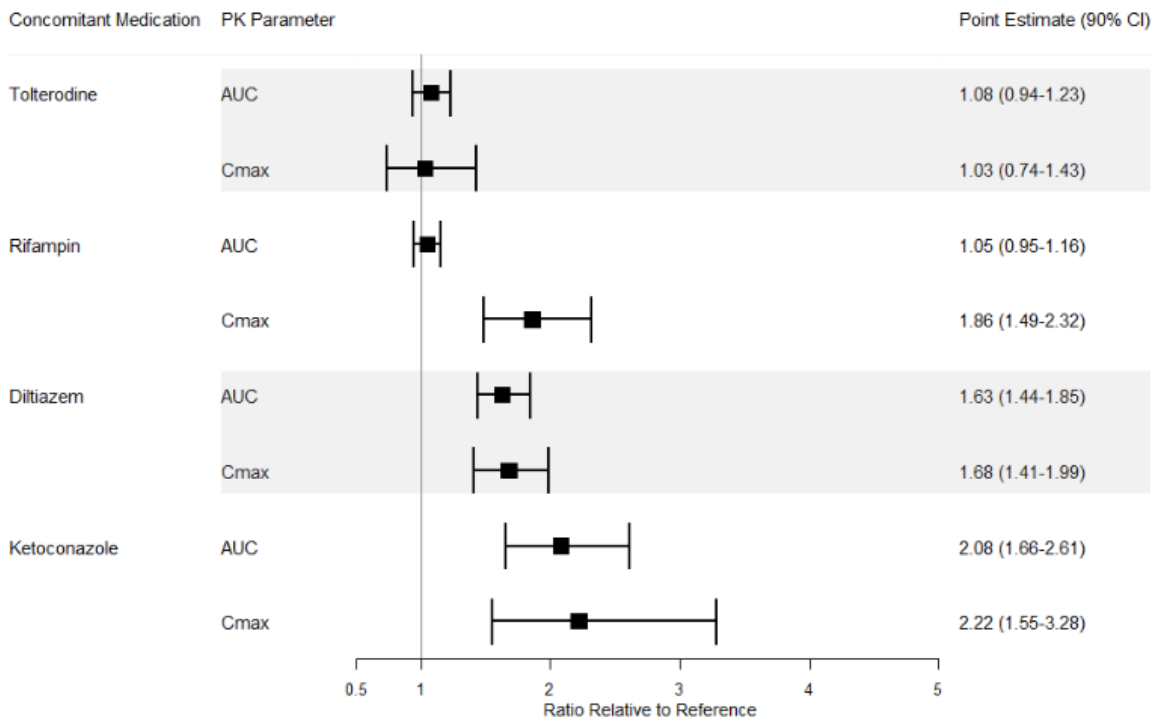
No data in children are included in the current application. The paediatric programme is out of the scope of the present MAA.

Pharmacokinetic interaction studies

Effect of other Co-administered drugs on Vibegron pharmacokinetics (Victim)

Co-administration of vibegron with multiple doses of a moderate (diltiazem) and a strong (ketoconazole) CYP3A/P-gp inhibitor and a strong CYP3A4 and P-gp inducer (rifampicin) has been studied to confirm metabolic pathways as well as p-gp involvement in vibegron absorption. A study with tolterodine, a commonly prescribed medication for OAB, has also been performed. Results are presented in Figure 4.

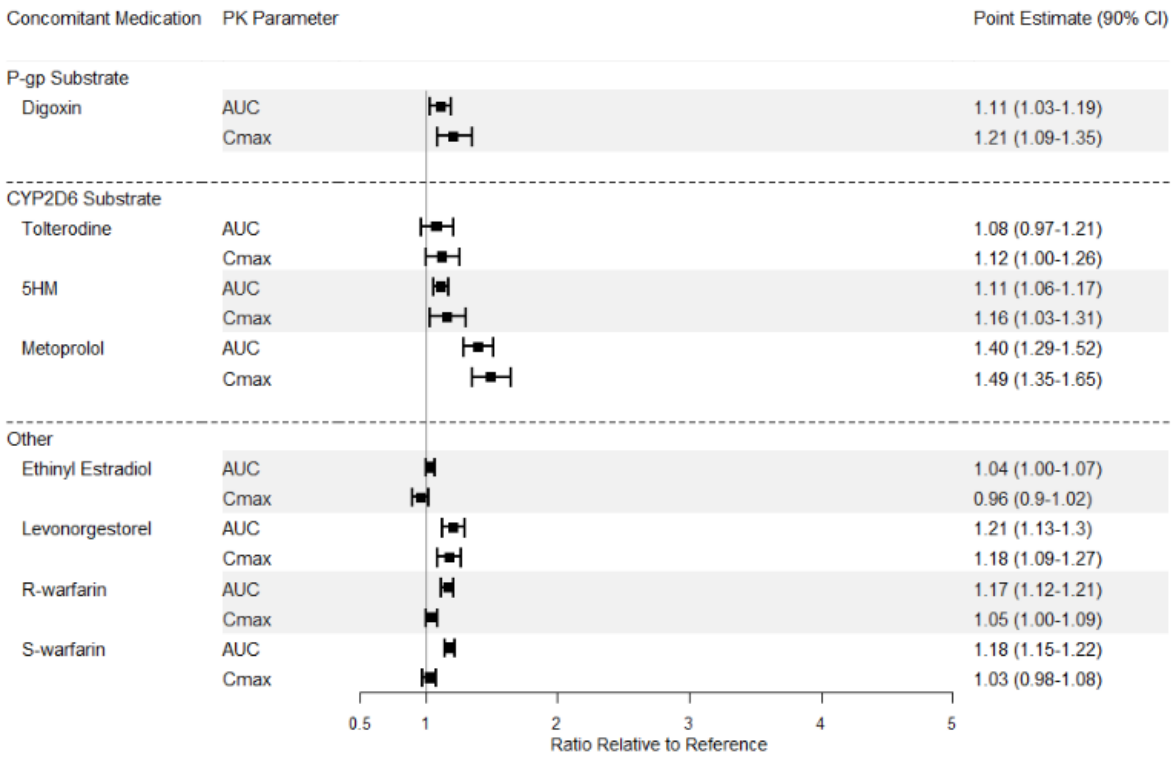
Figure 4. Geometric Mean Ratio (90% Confidence Interval) AUC and Cmax of Vibegron with and without the Co-Administered Drug



Effect of Vibegron on the pharmacokinetics of co-administered drugs (Perpetrator)

Four clinical studies have investigated the effect of multiple doses of Vibegron on the pharmacokinetics of Co-administered drugs namely, single-dose warfarin (a CYP2C9/CYP2C19 substrate), metoprolol (a CYP2D6 substrate), the components (Ethinyl Estradiol and Levonorgestrel) of an oral contraceptive pill, tolterodine (a sensitive CYP2D6 substrate) and digoxin (a P-gp substrate). The study evaluating the effect on warfarin and metoprolol was a cocktail study. Results are presented below.

Figure 5: Geometric Mean Ratio (90% Confidence Interval) AUC and Cmax of the Co-Administered Drug with and without vibegron



Pharmacokinetics using human biomaterials

Table 10: Cut-offs relevant for signal evaluation in in vitro studies

$50\times C_{max(u)}$ (µM)	$25\times$Inlet $C_{max(u)}$ (µM)	0.1×Dose/250 ml (µM)
6,9	149,9	67,5

The cut-offs are based on a of Cmax 123 ng/ml from study 1002 (DDI study with warfarin and metoprolol), MW 444,54 g/mol and the dose 75 mg. For the hepatic cut-off the worst-case F=1 has been used as presently the absolute bioavailability is unknown. Considering all the data F is likely less than 1. An F of 0.5 would generate a hepatic inlet cut-off of 77 µM. The default ka of 0.1 min-1 has also been employed in the calculation.

All mandatory CYP enzymes and transporters has been studied in vitro. Vibegron is not an inhibitor (direct or time-dependent) or inducer of any studied CYP enzyme. Neither is vibegron an inhibitor of the evaluated UGTs (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, UGT2B15 and UGT2B17).

In vitro vibegron is an inhibitor of OCT2 with an IC_{50} of 36 µM and MATE1 with a k_i of 9 µM; both these values are above the systemic cut-off.

Vibegron is also an inhibitor of OCT1 in vitro with an IC_{50} of 23 µM, this is below the relevant hepatic cut-off but the positive signal has not been further evaluated.

All other mandatory transporters have been evaluated *in vitro* without positive signals.

2.6.2.2. Pharmacodynamics

Mechanism of action

Vibegron is a selective and potent human beta-3 adrenergic receptor agonist over β1-AR and β2-AR Edmondson, 2016]. Activation of the beta-3 adrenergic receptor located in the bladder detrusor muscle increases bladder capacity by relaxing the detrusor smooth muscle during bladder filling.

β_3-ARs are prototypic G-protein coupled receptors expressed on the surface of cells, and mediate intracellular signaling via coupling to G-proteins and increasing levels of intracellular cyclic adenosine monophosphate (cAMP). β_3-ARs are widely distributed in humans and are the most prevalent β-AR subtype expressed on human detrusor smooth muscle [Takeda, 2000]. In isolated human bladder smooth muscle, activation of β_3-AR using subtype-selective agonists results in smooth muscle relaxation, suggesting a role for β_3-AR agonists during the filling phase of the micturition cycle [Yamaguchi, 2002; Biers, 2006]. In rodent models of bladder overactivity, β_3-AR agonists relax bladder smooth muscle and suppress detrusor smooth muscle instability and hyperreflexia [Takeda, 2000; Woods, 2001; Takeda, 2002; Kaidoh, 2002]. In conscious cynomolgus monkeys, vibegron demonstrated dose-dependent increases in adder capacity with minimal effect on voiding pressure [Study 15539-2; Module 2.4].

Primary and Secondary pharmacology

Vibegron is a human beta-3 adrenergic receptor agonist. Activation of the beta-3 adrenergic receptor located in the bladder detrusor muscle increases bladder capacity by relaxing the detrusor smooth muscle during bladder filling.

Secondary pharmacology

Study 012 (thorough QT study)

Study 012 was a single-dose, randomised, double-blind (with respect to MK-4618), placebo- and active-controlled, 4-period balanced crossover study to assess the effect of MK-4618 on QTc interval. The study has been performed in accordance with the recommendations in the ICH E14 guidance. QTc assay sensitivity has been demonstrated based on the results for moxifloxacin 400 mg.

The effect of vibegron on QTc was tested at 2 dose levels, 200 and 400 mg, representing supratherapeutic doses based on 3.3- and 9-fold higher C_{max} levels compared with 75 mg vibegron at steady state, respectively.

A total of 52 healthy adult male and female subjects, between 18-55 years (inclusive) of age and with a body mass index (BMI) ≤32 kg/m^2 (inclusive), were enrolled and 50 subjects completed the study.

At 1-hour post-dose, the maximum LS mean difference (90% CI) from placebo in QTcF was 4.98 (3.07, 6.88) msec for 200 mg and 4.60 (2.71, 6.48) msec for 400 mg. For both dose levels, the upper limit of the 90% CI was less than 10 msec, indicating that vibegron at supratherapeutic doses does not cause a clinically relevant prolongation of the QTcF interval. No QTcF intervals ≥450 msec or increases in QTcF interval of ≥30 msec were reported following either dose of vibegron.

Study 1001 (ambulatory blood pressure monitoring study)

Study 1001 was a double-blind, placebo-controlled, parallel study in subjects with OAB to study the effect of vibegron at steady state on ambulatory BP and HR.

A total of 214 subjects were randomised and received at least one dose of double-blind study medication (placebo, N=108; vibegron, N=106). ABPM assessments were collected over 24 hours before subjects were randomised to vibegron 75 mg or placebo and following 28 days of treatment.

For the primary endpoint, mean daytime ambulatory systolic BP compared with placebo in the FAS population, the treatment difference in LS mean CFB was 0.81 mmHg (90% CI: -0.88 mmHg, 2.49 mmHg). The upper limit of the CI was below the pre-specified threshold of 3.5 mmHg and the primary endpoint was met. The results for sensitivity analyses and secondary endpoints (mean 24-hour vital signs and maximum vital signs at 0.5 to 6.5 hours post-dose) were consistent with the analysis of the primary endpoint.

Relationship between plasma concentration and effect

To inform the selection of the MK-4618 dose level for Phase 3, pharmacokinetic-pharmacodynamic (PKPD) modelling of micturition frequency (MF), urinary urge incontinence (UUI), and strong urgency (SU) data from Protocol 008-Part 1 was conducted. The doses administered in this study were 3, 15, 50 and 100 mg vibegron. From the PK/PD dose-exposure modelling, the Vibegron dose of 75 mg was chosen to be used in the phase 3 clinical trials.

2.6.3. Discussion on clinical pharmacology

Methods

The bioanalytical methods used are considered adequately validated. The method for analysis of vibegron in human plasma was partially validated after a transfer to further laboratories (associated with changes in a method). ISR was performed for several studies, including SAD studies, HI and RI studies, food effect study and some of the DDI studies. Available long-term stability data in plasma covers storage of study samples from all studies.

The applicant developed a population PK model of vibegron with the objectives to describe vibegron PK and evaluate selected covariates on vibegron PK parameters. The population PK model (RD-19-004) was developed using plasma concentrations of all subjects providing PK data in 10 clinical studies (MK-4618-001, MK-4618-002, MK-4618-003, MK-4618-009, MK-4618-014, MK-4618-015, URO-901-1001, RVT-901-1003, MK-4618-008 and RVT-901-3003). Data both from healthy volunteers and overactive bladder (OAB) patients were used. The model was utilised to simulate expected vibegron plasma concentrations in subpopulations (elderly, renally impaired, and underweight subjects) to illustrate and quantify potential differences across subgroups. However, dedicated studies with respect to renal impairment and hepatic impairment have been conducted, therefore the impact of these simulations are limited as the population PK analysis does not add further information. The methods used to develop the model in a stepwise manner were appropriate, as well as the reasoning regarding handling of data. The final model was described by a 3-compartment model with one saturable distribution compartment, linear elimination and nonlinear dose-dependent relative bioavailability increasing with dose. The structural part of 3-compartment model included inter-individual variability (IIV) on clearance (CL), on central volume of distribution (V2), on mean transit time (MTT) and on maximum distribution capacity (Bmax) and a proportional error model was used to describe residual variability. A nonlinear dose dependent relative bioavailability is a reasonable implementation of the non-linearity based on the results from the DDI studies. The covariate selection was done in a stepwise manner. These statistically significant effects (on 5% significance level) were identified: effect of WT both on CL and V2, effect of age on Bmax, effect of eGFR on CL and effect of OAB patient status on CL. Modest statistically significant impact (on 5% significance level) of WT on vibegron exposure given by AUC_T and Cmax was reported (31% for AUC_T if the WT "<60 kg" was compared to WT "75<90 kg", 71% for

Cmax if the WT "<60 kg" was compared to WT "75<90 kg"). However, this effect is not considered clinically relevant. The statistical methods used for model diagnostics are acceptable. The PopPK model was developed on 9795 PK observations from 1179 patients (including 669 PK samples from 252 patients in the Phase III study RVT-901-3003). The covariate distributions appear reasonable given the objectives of the PopPK analysis, which included evaluation of covariates. The use of stepwise covariate modelling is accepted. The stepwise covariate modelling approach may be sensitive to highly correlated covariates, however, the degree of correlation between the covariates was reasonable (the strongest correlation was between age and eGFR with a correlation coefficient of -0.358). The final model demonstrated appropriate agreement between predicted and observed data values, however, low concentrations appear to be overestimated for some individuals. Inspection of pcVPCs indicate that it could be samples collected in the Phase 1 single dose studies (Studies MK-4618-001 and -003). The model appears to adequately capture the median in the patient population studies, given the objectives of the model, except for study -3003 (Efficacy and safety in OAB, N=311, patients received 75 mg). Only Ctrough (1-3) samples were collected in both study -008 (N=650) and -3003. In study 1001 (where patient received 75 mg, samples also collected at time of Cmax) the median is well described. Information from the model is mainly supportive to clinical data, therefore the model is considered good enough for the purpose in this application and the noted issues are not further pursued.

When calculating the increase in Frel, based on the model equations and estimated parameters, Frel only increases 9.2%. The dose is increased by 33% between 75mg to 100mg. The AUC is then expected to be approximately 40-50% higher (simplified calculation using AUC = F*Dose/CL, where F increases approximately 10% and dose 33%. This is in line with what is observed when comparing exposure from SAD and MAD studies. This was shown using clinical trial simulations when all patients were simulated from the same population (data not shown). However, the PK exposure following 100 mg from Study KRP114V-T301 appears to be more than 50% higher than the PK exposure following 75 mg e.g. in Study RVT-901-3003. This may be due to differences in the included study population of each respective study. Study KRP114V-T301 (where 100 mg was studied) included mainly Japanese subjects with generally lower body weight than in Study RVT-901-3003 (where 75 mg was studied). The finding that the PK exposure for 100 mg in Study KRP114V-T301 was more than 50% higher than the exposure following 75 mg in Study RVT-901-3003 was confirmed by clinical trial simulations, when accounting for the different baseline/demographics between these studies. Comparing the doubled 75 mg exposure with the highest studied dose level (100 mg) may be used to inform the handling of dosing recommendations in these subgroups (see discussion on therapeutic window below).

ADME

From a PK perspective, vibegron can be classified as a BCS class 3 drug substance. As high solubility has been demonstrated, it is agreed that vibegron can be classified as a BCS class 3 substance.

The applicant did not conduct any absolute bioavailability study as no formulation for intravenous administration was developed for use in humans. In the mass balance study (with oral administration of vibegron in the fasted state), 54% of the dose was recovered as unchanged drug in faeces. Based on available information, the fraction absorbed is at least 25% but it is not possible to firmly conclude on how high the fraction absorbed is. This is not further pursued.

During clinical development, different formulations of vibegron were used and compared using *in vitro* dissolution tests and BA studies in healthy subjects. Study 006 compared bioavailability of capsule (used in Phase 1 studies) and non-aqueous tablet formulation (used in Phases 1 and 2 studies). The 90% CI for the GMR for C_{max} was slightly below the 0.8 lower bioequivalence limit (i.e., 0.75) but the 90% CI of the GMR for $AUC_{0-\infty}$ was within the classic bioequivalence range of 0.8 to 1.25. It can be concluded that bioavailability of these formulations is comparable.

Bioavailability of non-aqueous tablet (used in Phase 1 and 2 studies) and the to-be-marketed tablet A (used in Phase 1 and 3 studies) at dose of 50 mg was compared in Study 018. The 90% CI of the GMR for $AUC_{0-\infty}$ and AUC_{0-24} were within the 0.8 to 1.25 bioequivalence range. For C_{max}, the upper limit of the 90% CI was slightly above the upper limit of the bioequivalence range (i.e., 1.33 compared to 1.25). However, comparable bioavailability of these formulations can be concluded.

Tablet A (to be marketed formulation) and tablet B (used in food effect study and study of the effect of crushing the tablet) differ in colorant in film-coating, and the applicant refers to a BCS-based biowaiver for the comparison of these formulations. Considering the very small change in formulation between tablet A and B, a strict BCS-based biowaiver is not considered necessary.

Overall, it is thus agreed that comparable rate and extent of exposure has been demonstrated between the different capsule and tablet formulations used during clinical development.

Although the effect of food on single dose PK of vibegron is rather large ($AUC_{0-\infty}$ decreased by 37%, AUC_{0-t} by 34% and C_{max} by 63%), it is agreed that the effect appears to be smaller at steady state (mainly supported by data from MAD study 002, demonstrating unchanged AUC and 30% lower C_{max} with a high-fat meal compared to the fasted state although this is not a cross-over comparison). The most important aspect to consider is however that the phase 3 studies were performed with drug administration without regards to food, and thus the efficacy and safety of vibegron is established in this way. It is therefore agreed that no restriction regarding food is needed in the SmPC section 4.2. However, it cannot generally be concluded that a decrease in exposure of the magnitude observed in the single dose food effect study can be considered as not clinically relevant.

Crushing the tablet only affects C_{max} and not AUC and, similar to the effect of food, the effect on C_{max} of crushing a tablet would also likely be smaller at steady state than following a single dose. Acceptable stability for immediate use of vibegron crushed tablets in apple sauce was shown. It is agreed that tablets may be crushed and administered with soft food in accordance with the statement in the SmPC section 4.2 and as reflected in SmPC section 5.2.

In the mass balance study, the total recovery was 79.5%, which is below the 90% limit recommended according to the Guideline on interactions, which is not optimal, but it can be agreed that this does not cause major concerns considering also that almost all the recovered radioactivity has been identified.

It is difficult to completely characterise the routes of elimination based on the oral mass balance study since a large fraction of the oral dose is recovered as unchanged drug in faeces and since no absolute bioavailability study or IV mass balance study is available. Based on the oral mass balance study, renal elimination of unchanged drug is a major route of elimination (accounting for 24-75% of the elimination of the recovered radioactive dose, depending on how much of the dose excreted as unchanged drug in faeces that is unabsorbed drug). Metabolism could contribute to 8-24% of the elimination and biliary excretion of unchanged drug to 0-68% of the elimination. In the HI study the effect of moderate HI was not large but data in subjects with severe HI, which might have provided valuable information in the evaluation of elimination pathways of vibegron, is missing. In the RI study, up to 2-fold increase in exposure was seen in subjects with renal impairment compared to healthy controls, which might indicate that this route contributes to approximately 50% of the elimination of absorbed drug. Data from in vivo victim DDI studies (no decrease in vibegron exposure with inducer rifampicin, increase in vibegron exposure with CYP3A4/P-gp inhibitors to a noticeable extent due to an effect on absorption via P-gp) support that CYP-mediated metabolism is not a major elimination pathway of vibegron. It is thus a weakness that no absolute bioavailability study or IV mass balance study was performed, and there is also some additional uncertainty considering that 20% of the radioactive dose in the mass balance study was not recovered. However, considering the results from DDI studies as well as studies in special populations, there is no concern that there might be an unknown major route of elimination. It can be agreed that vibegron is eliminated by a variety of

pathways including urinary excretion, biliary excretion, and hepatic metabolism and that of these, hepatic metabolism appears to play a minor part. Renal elimination of parent drug is a major route of elimination, probably accounting for around 50% of the elimination of absorbed drug.

No pharmacology studies have been performed with the metabolites, and thus it is not known if any of them are active. However, the main component in plasma is parent drug and it is not considered likely that the metabolites would contribute significantly to the effect. There are no human-specific metabolites in plasma.

No metabolite needs to be investigated for CYP inhibiting potential. The only metabolite that accounted for more than 10% of the drug-related exposure in plasma was the glucuronide metabolite M7, but as this metabolite had an AUC that was below 25% of parent drug and as it is not a phase I metabolite there is no need to investigate the enzyme inhibitory potential of this metabolite according to the Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev.1 Corr.2**).

There are unclarities with the performed in vitro metabolism experiments regarding CYPs involved in the metabolism of vibegron, e.g. choice of CYP inhibitors, these uncertainties are however not considered of high importance. The amount of phase-1 metabolites found in excreta in the mass balance study was low. The concomitant use of vibegron and both a strong and a moderate inhibitor of CYP3A4 has been studied in vivo with a doubling of vibegron exposure which to a substantial extent is dependent on p-gp inhibition. Further Rifampicin, a strong inducer of CYP3A4 and also an inducer of several other CYP enzymes, did not affect the AUC of vibegron, results in line with CYP-mediated metabolism not being a major eliminaiton pathway. The performed in vitro evaluation of the CYPs involved in the metabolism of vibegron is considered sufficient.

The M7 metabolite correspond to 12-14% of circulating drug material, and while not detected in the excreta to any large extent glucuronides are known to be unstable in the gut where they may be de-glucuronidated by microbes. Several different UGTs appear involved in the glucuronidation of vibegron.

Clearance by hepatic metabolism and biliary secretion is together a major elimination pathway. The renal clearance is 9.4 L/H and renal filtration clearance is 3 L/H, thus there are indications of active secretion. Due to this, vibegron has been evaluated as a substrate for both hepatic and renal transporters. Vibegron is not a substrate of any transporter apart from P-gp.

As CYP-mediated metabolism is not a major route of elimination, no consequences of genetic polymorphism are expected.

Vibegron contains 4 chiral centres and is given as a pure enantiomer. There is no relevant interconversion of vibegron in vivo.

Dose proportionality, time dependency, variability

Overall, data following both single and multiple dose administration indicate that mean C_{max} and AUC increase in a greater than dose-proportional manner over the studied range. The non-linearity is likely due to non-linearity in absorption. As vibegron is a P-gp substrate, the reason for the non-linearity is likely saturation of P-gp at higher doses.

The clinical dose of 75 mg was not included in the SAD/MAD studies. The Applicant claimed that the exposure with 100 mg vibegron would be approximately twice that of 75 mg due to the non-linearity. This conclusion is however not agreed on based on the MAD studies which do not indicate a 2-fold increase in exposure with this 33% increase in dose from 75 to 100 mg. Based on the slope estimates for the SAD and MAD studies, AUC and C_{max} would rather be expected to increase by 40-50% when increasing the dose by 33% from 75 to 100 mg. See discussion regarding Therapeutic window below.

The Applicant did not specifically discuss time dependency of vibegron PK. Based on observed half-lives in study 002, a larger accumulation than the observed accumulation would be expected (4-6-fold rather than 2-3-fold). However, the Applicant discusses an effective half-life of 30.8 hours which would be consistent with an accumulation ratio of 2.4. By comparing AUC_{inf} following a single dose (from study 001) to AUC_{tau} following multiple doses (from study 002) there are no signs of major time-dependency. Also, by comparing data from the SAD and MAD study in Japanese subjects in the same way, the results do not indicate major time-dependency.

Rich sampling multiple dose PK data with the clinical dose 75 mg is mainly available from DDI study 1002 (in healthy volunteers). There is also some PK data with the clinical dose from study 1001 in OAB patients, where rich sampling occurred up to 4.5 hours post-dose at steady state. PK parameters from this study are not presented, only mean plasma concentrations at the different time points, but the highest value observed (100 ng/ml) is largely similar to the $C_{max,ss}$ value observed in study 1002 (123 ng/ml). In addition, C_{trough}-data is available from the pivotal phase 3 study 3003. The measured C_{trough}-values from the pivotal study were lower than those in study 1002.

The observed between-subject variability for vibegron was moderate to high. It is not clear which phase 1 studies that were used to determine the within-subject variability. It is stated that subjects received the same dose on two occasions separated by a washout period, but it is assumed that different formulations were given at these two occasions (or the mode of administration differed). However, no concern is raised regarding the lack of data of true intra-subject CV (ie from a replicate-design study).

Therapeutic window

From an efficacy perspective, reduced exposures are observed when vibegron is administered with food (AUC and C_{max} after a 75 mg single dose decreased by approximately 37% and 63%, respectively, in the presence of a high fat meal compared to the fasted state, but the effect seems to be smaller at steady state). As the phase 3 studies (3003 and 3004) were performed with drug administration without regards to food, and thus the efficacy and safety of vibegron is established in this way, it is agreed that no restriction regarding food is needed in the SmPC section 4.2. However, it cannot generally be concluded that the decrease in exposure observed in the single dose food effect study is not clinically relevant. In the current application, it is not considered critical to define the lower boundary of the therapeutic window (which should be based on the exposure range of the phase 3 study), as the situations with reduced exposure are already covered by efficacy and safety data. Thus, the lower boundary of the therapeutic window issue is not further pursued.

From a safety perspective, the Applicant claims that a 2-fold increase in vibegron AUC and C_{max} is not clinically relevant and is covered by the 100 mg dose-cohort in 301/302 (Japanese phase 3 studies, no PK data collected) where long-term safety data exist. The SAD/MAD studies do not indicate that doubling the exposure of a 75 mg dose would correspond to a 100 mg dose (~40-50% increase in exposure due to non-linearity). However, the 100 mg data (study 301) was obtained in a Japanese population and exposure is expected to be relatively higher due to lower weight in the Japanese population. The safety profile for 100 mg in Japanese subjects is considered similar to 75 mg (study 3003). The 75 mg and doubled 75 mg were simulated using study 3003 covariates whereas the 100 mg was simulated using covariates from Study 301 and the expected exposure for moderate/severe renal impairment and concomitant strong CYP3A4/P-gp inhibitors indicated that the Cmax is below the expected Cmax for 100 mg in Study 301 whereas the AUC is slightly above the expected AUC for 100 mg in Study 301. Specifically, a 1.7-1.8-fold increase in AUC is deemed covered by safety data from the Japanese phase 3-study A clinical safety concern was therefore raised regarding patients with moderate or severe renal impairment and in patients treated with concomitant strong CYP3A4/P-gp inhibitors, as a doubling of AUC is expected in these patients and as this increase in exposure was not

entirely covered by safety data (see clinical safety section 2.6.8.). In summary, no relevant differences in the safety profile were observed for patients with moderate renal impairment compared to those with normal renal function at baseline, and as the exposure is expected to be similar in this group as in patients with severe renal impairment or patients with concomitant use of a strong CYP3A4/P-gp inhibitor, the safety profile in all three subgroups is expected to be comparable. Also considering the safety data from the 100 mg dose in Japanese subjects, the proposal that no dose adjustment is needed in these settings with 2-fold increase in AUC can be agreed. It is thus agreed that a 2-fold increase in vibegron AUC and C_{max} is not clinically relevant.

Special populations

As no subjects with severe RI were included in the phase 3 studies and thus informed the analysis, the model-based analysis does not add additional information to the results from the dedicated RI study.

Based on the dedicated RI study, up to 2-fold increases in vibegron AUC in subjects with moderate or severe renal impairment was observed. As discussed above, up to 2-fold increases in vibegron exposure can be considered safe and thus no dose adjustment is needed. As vibegron has not been studied in patients with end-stage renal disease, it is adequate that it is not recommended in this group. This has been adequately reflected in SmPC section 4.2.

There were no large effects of moderate HI (27% higher AUC_{inf} and 35% higher C_{max} compared to healthy controls) and thus it is acceptable that no study in mild HI was performed. Data in subjects with severe HI are however missing, which is a weakness, considering that these subjects would likely have a larger increase in exposure, and it is thus not known if the increase in these subjects would be clinically relevant or not. Most subjects in the moderate HI group were mainly affected in aspects not primarily related to elimination capacity of drugs (such as encephalopathy and ascites) while only 3 of the subjects were affected in laboratory markers likely to be relevant for elimination capacity of drugs (all having decreased albumin levels). Thus, it is possible that a larger effect would have been seen if more subjects with effects on albumin, bilirubin and prothrombin times had been included. As discussed above, it is agreed that up to 2-fold increases in vibegron exposure are safe. The exposure increase observed in subjects with moderate HI (27% higher AUC_{inf} and 35% higher C_{max}) is also considered well covered by the available safety data with a 100 mg dose and the wording in section 4.2 regarding patients with mild and moderate HI can be agreed. As pharmacokinetics of vibegron was not evaluated in patients with severe hepatic impairment, it is considered adequate that the use of the medicinal product is not recommended in this group.

Population PK analysis have been conducted to assess importance of covariates. A drawback is the incorporation of covariates without presenting correlations, which hampers the interpretations of the impact of some covariates on the exposure and subsequent clinical relevance. However, as there is a dedicated RI study, and subjects in the phase 3 study 3003 weighed 46 to 161 kg the exposure in these subjects is considered covered from a clinical perspective, this issue is thus not pursued further. The effect of weight on the PK of vibegron have been added in the SmPC section 5.2. Sex, race and age were not found to impact the exposure of vibegron to a clinically relevant extent in patients with OAB. No dose adjustment is considered necessary based on gender, age, body weight or race in adult patients.

Interactions

To evaluate vibegron's interaction potential the Applicant has studied all mandatory enzymes and transporters in vitro. There are no in vitro signals of vibegron being an inhibitor (direct or time-dependent) or inducer of any studied CYP-enzyme. Regarding transporters the interaction potential for vibegron also appears low. For OATPB1/B3 the studied concentration span (up to 100 μM) does not cover the hepatic cut-off of 150 μM. This cut-off is however calculated by using the default

bioavailability where F is set to 1. This F-value is not likely relevant for vibegron which appears to have a lower bioavailability. Considering this and the presented in vitro data for OATPB1/B3 no further evaluation of these transporters are required. In vitro vibegron is an inhibitor of OCT2 and MATE1 at high concentrations, the IC50 or ki is above the relevant cut-off and no further studies are required. Vibegron is also an inhibitor of OCT1 with a IC50 below the hepatic cut-off which is likely the most relevant cut-off for this transporter (though this is not discussed in the Guideline on the investigation of drug interactions as OCT1 is not a mandatory transporter to study). The SmPC section 4.5. has been updated with this information. Other mandatory transporters were studied at relevant concentrations and not inhibited by vibegron in vitro.

In vitro vibegron is not an inhibitor of the studied UGTs (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, UGT2B15 and UGT2B17).

Despite the lack of positive in vitro signals several clinical DDI studies with vibegron as a perpetrator have been performed as well as victim studies.

Multiple doses with the strong CYP3A4 and P-gp inhibitor ketoconazole resulted in an approximately 2-fold increase of vibegron exposure, while the moderate CYP3A4 and p-gp inhibitor diltiazem resulted in an approximately 1.6-fold increase of vibegron exposure. As vibegron $t_{½}$ was not affected (77 h alone vs. 75 h with ketoconazole), it suggests that effect was on inhibition of intestinal P-gp resulting in increased absorption, rather than on elimination of vibegron. As discussed above, it is agreed that the increases in exposure observed with ketoconazole and diltiazem are not clinically relevant.

Coadministration of multiple doses of rifampicin, a strong inducer of CYP3A4 (and also an inducer of several other CYP-enzymes and certain UGTS) as well as both an inducer and inhibitor of p-gp, did not change vibegron AUC, however Cmax was increased almost 1.9-fold. The mechanism for this increase is not clear, even though vibegron was coadministered with rifampicin (staggered dosing was not applied in the study) and the effect on P-gp likely a net-effect of both induction and inhibition, the increase in Cmax is surprisingly high. However, this increase in Cmax is considered covered by available safety data and thus not considered to be clinically relevant.

Vibegron exposure was not affected by coadministration with tolterodine, a commonly used substance for OAB, neither did vibegron affect the exposure of tolterodine which is a sensitive CYP2D6 substrate.

Vibegron did affect the exposure of metoprolol, coadministration led to an approximately 1.4-fold increase in AUC and a 1.5-fold increase of Cmax of metoprolol. Metoprolol t½ was considered similar when administered alone and in combination with vibegron. The mechanism is not entirely clear, metoprolol is a moderate sensitive CYP2D6 substrate, but vibegron did not affect the sensitive CYP2D6 susbtrate tolterodine, making 2D6-inhibition an unlikely reason. Still the increase in metoprolol exposure does not warrant dose adjustments.

Coadministration of vibegron with the P-gp substrate digoxin resulted in a slight increase in AUC (11%) and Cmax (21%). Due to the elderly target population and the narrow therapeutic index of digoxin the SmPC section 4.5 recommends monitoring of serum digoxin concentrations.

Further vibegron did not affect the exposure of oral contraceptives (ethinyl estradiol or levonorgestrel) or warfarin.

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics of vibegron were evaluated in *in vitro* studies, clinical pharmacology studies and by modelling and simulation studies. The pharmacokinetics of vibegron are considered to have been adequately assessed.

No clinically relevant effect of vibegron 75 mg on the QT/QTc interval is foreseen based on the results from the QT study. No clinically relevant effect of vibegron 75 mg on systolic/diastolic BP or heart rate was observed in the ambulatory blood pressure study in OAB patients.

Overall, the clinical pharmacology package is considered acceptable and in support of this marketing authorisation application (MAA).

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

Phase 2b study 008: a phase IIb randomised, placebo- and active comparator (tolterodine)-controlled, 2-part clinical study of the efficacy and safety of MK-4618 in patients with overactive bladder

The study objectives were to investigate the 8-week efficacy and safety of increasing daily doses (3, 15, 50 and 100mg) of vibegron as monotherapy and in combination with tolterodine 4mg in comparison to placebo.

In addition, in an extension over 52 weeks, vibegron 100mg or tolterodine 4mg as monotherapies and vibegron 100mg in combination with tolterodine 4mg and placebo were studied. The study aims were dose-ranging, safety, and efficacy of vibegron and proof-of-concept for concomitant dosing of vibegron with tolterodine ER 4 mg.

The dose that subsequently was chosen for MAA, 75mg, was not included.

The primary endpoint was reduction in the daily number of micturitions at Week 8 compared to baseline. Further, several secondary efficacy endpoints at Week 8 of clinical relevance for OAB were also included, whereas safety and QoL were studied in the extension over 52 weeks.

Eligibility criteria were adequately reflecting the target patient group for treatment of OAB. Patients were required to have had OAB for >3 months before screening and meet predefined OAB-wet or OAB-dry criteria. OAB-wet was defined as an average of 8 or more micturitions and one or more urgency incontinence episodes per voiding diary day, while OAB-dry was defined as an average of eight or more micturitions, three or more urgency episodes and less than one daily urgency incontinence episode per voiding diary day.

Most patients were women (almost 90%), the mean age was 58.6 years and around 80% of patients were classified as OAB wet.

Results

Results are presented for vibegron 50mg and vibegron 100mg and for tolterodine as active comparator and placebo, whereas results from the lower doses of vibegron and the combination with tolterodine are not presented.

	Placebo	Vibegron 50 mg	Vibegron 100 mg	Tolterodine ER
Baseline Daily Number of Micturitions				
n	141	148	148	134
Mean (SD)	10.86 (2.84)	11.21 (3.16)	11.15 (2.32)	11.00 (2.17)
CFB at Week 8 in Average Daily Number of Micturitions				
LS means (95% CI)	-1.16 (-1.50, -0.82)	-1.80 (-2.13, -1.47)	-2.07 (-2.40, -1.74)	-1.71 (-2.05, -1.36)
Active – Placebo				
LS means difference (95% CI)		-0.64 (-1.11, -0.18)	-0.91 (-1.37, -0.44)	-0.54 (-1.02, -0.07)
P-value		0.007	0.000	0.026

CFB = change from baseline; CI = confidence interval; cLDA = constrained longitudinal data analysis; LS = least squares; OAB = overactive bladder; SD = standard deviation
Notes: Constrained longitudinal data analysis (cLDA) model included terms for time, region, study part, and interaction of time by treatment.

After 8 weeks, the average daily number of micturitions was reduced from baseline (of mean 11 micturitions) by around 2 episodes among patients on the higher dose (100mg) and slightly less in patients on the 50mg dose. Both those primary endpoint reductions from baseline were statistically significantly superior to placebo.

Also, a modest but statistically significant reduction from baseline at Week 8 in the secondary endpoint number of urge urinary incontinence episodes was seen with both doses as well as in total urinary incontinence episodes in patients with OAB Wet

The results from the extension study at Week 52 support that the efficacy remains after long-term treatment.

in QoL domain scores based on King's Health Questionnaire, treatment with vibegron (100 mg) was reported to result in numerical increases in individual sub scores relative to placebo.

Vibegron was generally well tolerated in the study. There were no clear dose-dependent effects on heart rate or blood pressure across vibegron treatment groups or compared with placebo.

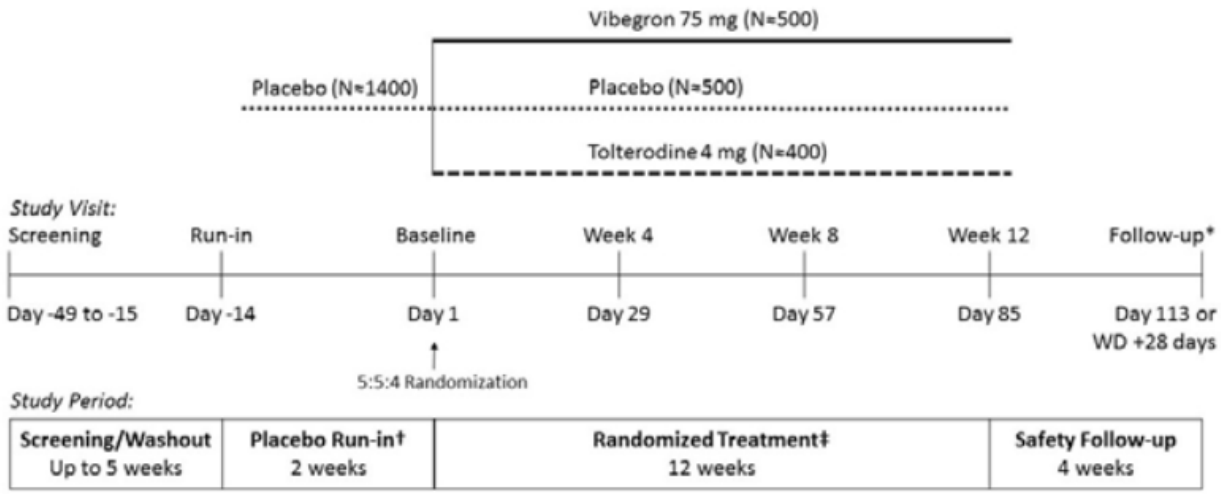
2.6.5.2. Main studies

Study 3003 - an international phase 3, randomised, double-blind, placebo- and active (tolterodine)-controlled multicentre study to evaluate the safety and efficacy of vibegron in patients with symptoms of overactive bladder

Methods

A figure describing the study design of the pivotal clinical study 3003 can be seen below.

Figure 6. Study design of the pivotal Phase 3 study 3003



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

Main inclusion criteria were:

1. Males or females ≥ 18 years of age. Note: Up to 15% of subjects could be male.

2. Had a history of OAB (as diagnosed by a physician) for at least 3 months prior to the Screening Visit. Note: OAB was defined as urgency, with or without urge urinary incontinence (UUI), usually associated with frequency and nocturia. Urodynamic evaluation was not required.
4. Meeting OAB Wet criteria or OAB Dry criteria (up to 25% of subjects meeting OAB Dry criteria were allowed), based on the Patient Voiding Diary
– *OAB Wet criteria:*
♣ An average of ≥ 8.0 micturitions per Diary Day*; and
♣ An average of ≥ 1.0 UUI episodes per Diary Day; and
♣ If stress urinary incontinence was present, the total number of UUI episodes must have been greater than the total number of stress urinary incontinence episodes from the previous visit diary
– *OAB Dry criteria:*
♣ An average of ≥ 8.0 micturitions per Diary Day; and
♣ An average of ≥ 3.0 urgency episodes per Diary Day; and
♣ An average of < 1.0 UUI episodes per Diary Day; and
♣ If stress urinary incontinence was present, the total number of UUI episodes must have been greater than the total number of stress urinary incontinence episodes from the previous visit diary.
*Note: A Diary Day was defined as the time between when the subject got up for the day each morning and the time the subject got up for the day the next morning as recorded in the Patient Voiding Diary.

Main exclusion criteria were:

1. History of 24-hour urine volume greater than 3,000 mL in the past 6 months, or a Urine Volume Diary day measurement greater than 3,000 mL during the Run-in Period.
2. Lower urinary tract pathology that could be responsible for urgency, frequency, or incontinence.

3. History of surgery to correct stress urinary incontinence, pelvic organ prolapse, or procedural treatments for benign prostatic hypertrophy (BPH) within 6 months of screening.
4. Had a current history or evidence of Stage 2 or greater pelvic organ prolapse (prolapse extending beyond the hymenal ring).
5. Was currently using a pessary for the treatment of pelvic organ prolapse.
6. Had a known history of elevated post-void residual volume defined as greater than 150 mL.
7. Underwent bladder training or electrostimulation within 28 days prior to Screening or planned to initiate either during the study.
8. Had active or recurrent (> 3 episodes per year) urinary tract infection by clinical symptoms or laboratory criteria.
9. Had a requirement for an indwelling catheter or intermittent catheterisation.
10. Received an intradetrusor injection of botulinum toxin within 9 months prior to screening.

Treatments

Subjects included in the study were treated with either vibegron 75 mg one daily in the morning, the matching placebo, or the comparator compound, tolterodine ER 4 mg. Tolterodine (Detrusitol) is a muscarinic receptor antagonist, indicated for the treatment of OAB which received marketing authorisation in Sweden in 1997.

The 75 mg dose of vibegron was selected based the Phase 2 dose-ranging study 008, two Phase 3 studies (301 and 302) performed in Japan, PK/PD modelling and supportive nonclinical data.

The duration of treatment was 12 weeks.

Objectives

The primary objective was to evaluate the efficacy of vibegron compared with placebo in subjects with symptoms of OAB. The statistical hypothesis was superiority over placebo for the two co-primary endpoints. The secondary objective was to evaluate the overall efficacy of vibegron compared to placebo in subjects with symptoms of OAB. In the estimation of sample size, the applicant referred to data obtained in the Phase 2 study 008 in which two other doses (50 and 100 mg) were tested.

Outcomes/endpoints

The co-primary efficacy endpoints of the Phase 3 clinical study 3003 were:

1) change from baseline at Week 12 in average numbers of micturition's per 24 hours in all OAB subjects and

2) change from baseline at Week 12 in average number of UUI episodes per 24 hours in OAB Wet subjects

Seven key secondary efficacy endpoints were by the applicant suggested to be tested sequentially.

• CFB at Week 12 in average number of urgency episodes (need to urinate immediately) over 24 hours in all OAB subjects.
• Percent of OAB Wet subjects with at least a 75% reduction from baseline in UUI episodes per 24 hours at Week 12.
• Percent of OAB Wet subjects with a 100% reduction from baseline in UUI episodes per 24 hours at Week 12.

• Percent of all OAB subjects with at least a 50% reduction from baseline in urgency episodes (need to urinate immediately) per 24 hours at Week 12.

• CFB at Week 12 in average number of total incontinence episodes over 24 hours in OAB Wet subjects.
• CFB at Week 12 in Coping Score from the Overactive Bladder Questionnaire Long Form (OAB-q LF, 1-week recall) in all OAB subjects.
• CFB at Week 12 in average volume voided per micturition in all OAB subjects.

Sample size

The planned total sample size was 1,400 patients: 500 patients in the vibegron and placebo treatment groups, and 400 patients in the tolterodine treatment group.

Power calculations were performed for both co-primary endpoints and for the comparison of vibegron versus placebo alone using a two-sided α of 0.05. With the assumptions made the study was expected to have a power of 96% to reject both co-primary hypotheses.

For change from baseline in the number of daily micturitions a true underlying between-group treatment difference of 0.6 was assumed with an estimated variability of 2.20 based on vibegron Study 008 data.

For change from baseline in urge urinary incontinence (UUI) episodes a true underlying between-group treatment difference of 0.51 was assumed with an estimated variability estimate of 1.68 based on vibegron Study 008 data.

Assuming that a total of 10% patients were to discontinue prior to Week 12, there was to be approximately 450 evaluable patients in the vibegron and placebo treatment groups at the end of Week 12. Further, assuming 75% of the population was to have OAB Wet, there was to be approximately 337 evaluable patients in the vibegron and placebo treatment groups for the incontinence endpoints.

Randomisation and blinding (masking)

Randomisation was performed centrally by the use of an interactive voice or web response system (IV/WRS). The randomised allocation schedule was to be generated by an external vendor and implemented by the vendor of the study IV/WRS.

Randomisation was stratified based on baseline OAB category (OAB Wet or OAB Dry) and sex (female or male) with enrolment to be capped based on OAB Dry criteria and sex as follows:

Up to 25% of the patients enrolled may meet OAB Dry criteria.

The proportion of OAB Dry patients and male patients during screening was to be monitored (via IV/WRS). Overall, 14.8% were male and 77.0% fulfilled the OAB wet criteria (Baseline characteristics).

The placebo run-in was single-blind; all subjects were to receive placebo (1 tablet + 1 capsule) orally, once daily for 2 weeks.

The randomised treatment period was to be performed double-blind implying that the patient, the investigator, and sponsor personnel or delegate(s) involved in the treatment or clinical evaluation of the patients were to be unaware of the treatment group assignments. For this to be achieved Vibegron and its matching placebo and tolterodine ER and its matching placebo were to be packaged identically

and all subjects were to take 1 tablet (vibegron or its matching placebo) and 1 capsule (tolterodine or its matching placebo) once daily.

Masking of assigned treatment was by the use of double-dummy technique and is expected to have been successful. As was reported in the CSR, no subjects were unblinded during the study.

Statistical methods

The primary analysis of efficacy and the analysis of safety and PK were planned after all patients had completed the final study visit or terminated early from the study.

At the end of the study (including the period of 28 days follow-up), the official, final database was to be frozen and unblinded after medical/scientific review had been performed, and data had been declared final and complete. As reported in the CSR, database lock occurred on 08 March 2019.

A Reporting and Statistical Analysis Plan was to be approved prior to data being unblinded. The submitted SAP is version 3.1, dated 06 March 2019. Changes made have been accounted for and raise no concerns. There was no planned interim analysis for efficacy.

Primary efficacy analysis populations

The primary efficacy analysis was the Full Analysis Set (FAS) population.

FAS was to include all randomised OAB patients who took at least one dose of double-blind Study Treatment and had at least one evaluable change from baseline micturition measurement.

Analyses of endpoints related to incontinence only applied to patients who meet the definition of incontinence at study entry and, hence, a separate FAS for incontinence (FAS-I) was defined.

FAS-I was to include all randomised OAB Wet patients who took at least one dose of double-blind Study Treatment and had at least one evaluable change from baseline UUI measurement.

Primary analysis of co-primary efficacy endpoints

In order for a subject to have an evaluable change from baseline, the subject must have had both a complete baseline diary (based on placebo run-in data) and a complete post-baseline diary from any post-baseline timepoint (i.e., Week 2, Week 4, Week 8, or Week 12).

For the analysis of the co-primary endpoints (change from baseline in average number of daily micturitions at Week 12 and change from baseline in average number of daily urge urinary incontinence episodes at Week 12), a mixed model for repeated measure (MMRM) with restricted maximum likelihood estimation with Kenward-Roger adjustment was used under the assumption of missing data being missing at random (MAR). The analysis model for each endpoint was to include terms for treatment, visit, OAB Type (wet/dry), sex (female/male), region (US/Rest of World), baseline score, and interaction of visit by treatment. Adjusted treatment means and the treatment differences (active-placebo) have been presented with a two-sided 95% CI and the corresponding p-value.

Analysis of secondary efficacy endpoints

The change from baseline efficacy endpoints were to be analysed using the same MMRM model described above for the analysis of each co-primary endpoint. Change from baseline for the OAB-q LF Coping Score was to be calculated at Week 12 and analysed in a similar manner as the primary endpoints, but with only one post-baseline assessment using a mixed model with the same terms as the primary analysis, but without any repeated measures.

For the efficacy endpoints of proportion of patients with at least 75% reduction or a 100% reduction in the average number of daily UUI episodes at Week 12 and proportion of patients with at least 50% reduction in the average number of daily urgency episodes at Week 12, the estimated difference in the proportion of responders and 95% confidence interval for the difference was to be calculated using the Cochran-Mantel-Haenszel risk difference estimate stratified by OAB Type (wet or dry, as applicable [i.e., for endpoints relevant to both types]) and sex (female vs male), with weights proposed by Greenland and Robins. Missing Week 12 data were to be replaced using multiple imputation.

Sensitivity analyses

Sensitivity analyses for the co-primary endpoints had been planned as follows:

An analysis of covariance (ANCOVA) model including terms for treatment, OAB Type (wet vs dry), sex (female vs male), region (US vs non-US), and baseline score. For patients with missing Week 12 assessment due to any reason, the Week 12 value was to be imputed using multiple imputation (MI).

An analysis of covariance (ANCOVA) model including terms for treatment, stratified by OAB Type (wet vs dry), sex (female vs male) and baseline score. For patients with missing Week 12 assessment due to any reason, the Week 12 value was to be imputed using Last Observation Carried Forward (LOCF).

The primary MMRM analysis repeated but excluding duplicate patients (index cases), i.e., patients who were screened or randomised at multiple sites were to be excluded in the analysis.

The primary MMRM analysis repeated but using OAB-d Type instead of OAB Type.

Multiplicity

Hypothesis testing was only planned to be performed for the comparison of vibegron and placebo.

No multiplicity adjustment was required for the co-primary endpoints since both endpoints needed to be statistically significant at the 0.05 level in order to test the key secondary endpoints.

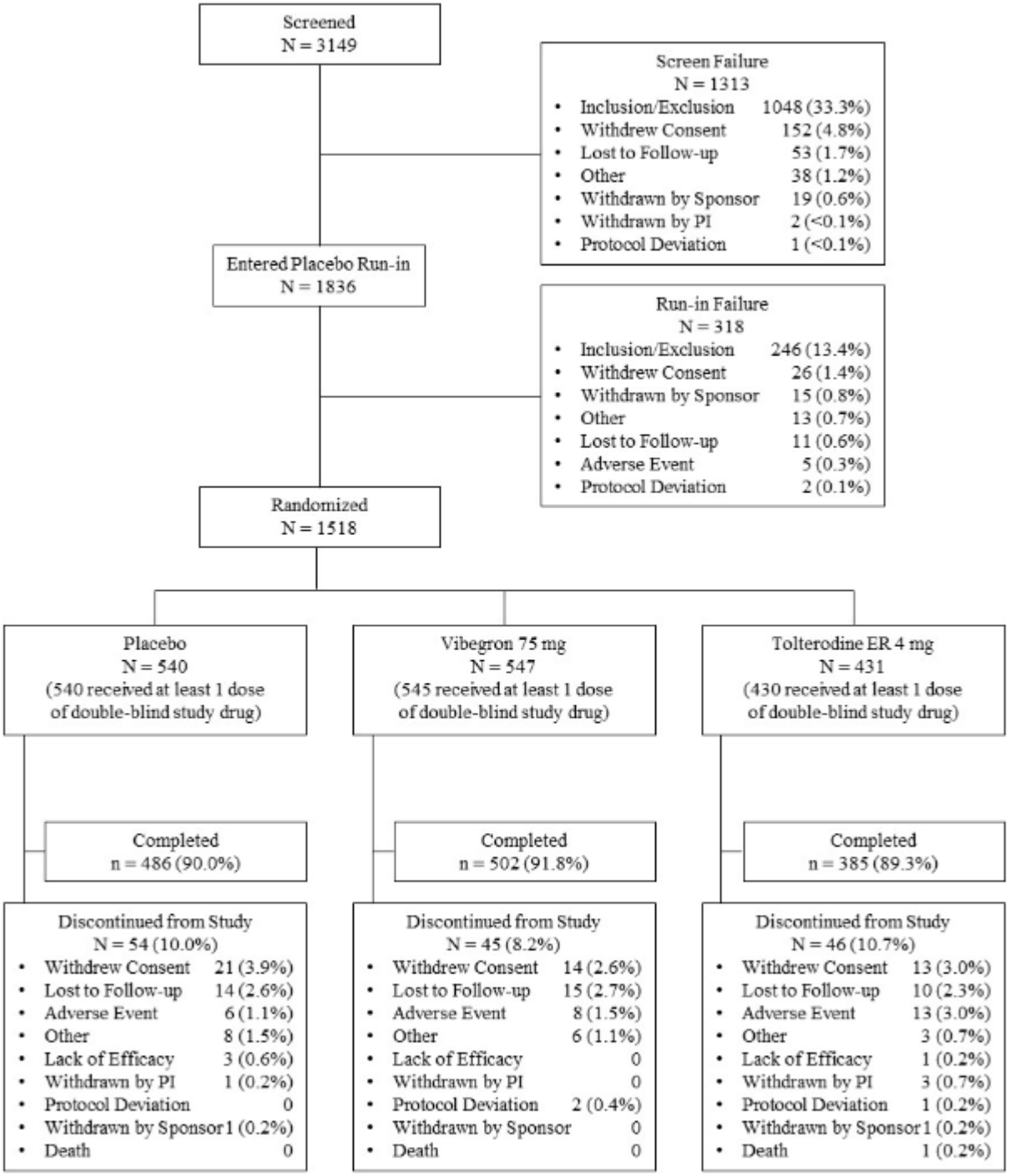
To control the overall type-I error rate at $\alpha=0.05$ (two-sided) over the 7 key secondary hypotheses, a stepwise gate-keeping procedure was used. If both co-primary null hypotheses could be rejected, the key secondary endpoints were to be tested sequentially in a predefined order. If statistical significance was achieved for all previous key secondary endpoints, the next sequential key secondary endpoint was to be tested. Once a key secondary endpoint was found to be not statistically significant (p-value ≥ 0.05), the testing procedure was to stop. For all subsequent key secondary endpoints, nominal p-values were then to be provided.

Results

Participant flow

A scheme of the participant flow can be seen below:

Figure 7. Study 3003: Schematic of Subject Disposition



Source: Table 14.1.1.1, Table 14.1.1.2, Table 14.1.1.3

Recruitment

The first subject was enrolled in the study on 26 Mars 2018. The last subject completed the study on 4 February 2019. The clinical study report was signed on 15 October 2019.

Randomised subjects were enrolled across 199 sites in 6 countries: United States (176), Canada (7), Poland (6), Hungary (5), Latvia (3), and Lithuania (2).

Conduct of the study

Major protocol deviations were reported for 11% of subjects, 8.1% of subjects had a major efficacy-related protocol deviation, which excluded them from the efficacy evaluation. results.

Baseline data

Demographic and baseline characteristics

The subject demographic and baseline OAB characteristics for the FAS and FAS-I populations can be seen in the tables below.

Table 11. Study 3003: Subject Demographic and Baseline Characteristics – FAS

	Placebo N = 520	**Vibegron 75 mg N = 526**	**Tolterodine ER 4 mg N = 417**	**Overall N = 1463**
Age (years), mean (SD)	59.9 (13.33)	60.8 (13.30)	59.8 (13.19)	60.2 (13.28)
Age category (years), n (%)				
< 40	45 (8.7)	40 (7.6)	36 (8.6)	121 (8.3)
≥ 40 to < 55	111 (21.3)	112 (21.3)	95 (22.8)	318 (21.7)
≥ 55 to < 65	144 (27.7)	132 (25.1)	120 (28.8)	396 (27.1)
≥ 65 to < 75	163 (31.3)	167 (31.7)	119 (28.5)	449 (30.7)
≥ 75	57 (11.0)	75 (14.3)	47 (11.3)	179 (12.2)
Sex, n (%)				
Male	75 (14.4)	77 (14.6)	65 (15.6)	217 (14.8)
Female	445 (85.6)	449 (85.4)	352 (84.4)	1246 (85.2)
Benign prostate hyperplasia, yes (male only), n (%)	16 (21.3)	29 (37.7)	22 (33.8)	67 (30.9)

	Placebo N = 520	Vibegron 75 mg N = 526	Tolterodine ER 4 mg N = 417	Overall N = 1463
Race, n (%)				
American Indian or Alaska Native	3 (0.6)	1 (0.2)	0	4 (0.3)
Asian	29 (5.6)	27 (5.1)	26 (6.2)	82 (5.6)
Black or African American	79 (15.2)	74 (14.1)	69 (16.5)	222 (15.2)
White	406 (78.1)	422 (80.2)	317 (76.0)	1145 (78.3)
Other	3 (0.6)	2 (0.4)	5 (1.2)	10 (0.7)
Region, n (%)				
US	463 (89.0)	472 (89.7)	376 (90.2)	1311 (89.6)
Non-US	57 (11.0)	54 (10.3)	41 (9.8)	152 (10.4)
OAB type, n (%)				
Wet	405 (77.9)	403 (76.6)	319 (76.5)	1127 (77.0)
Dry	115 (22.1)	123 (23.4)	98 (23.5)	336 (23.0)
Prior anticholinergic use in the last 12 months, n (%)				
Yes	85 (16.3)	77 (14.6)	51 (12.2)	213 (14.6)
Prior beta-3 agonist use in the last 12 months, n (%)				
Yes	27 (5.2)	21 (4.0)	32 (7.7)	80 (5.5)

Source: Table 14.1.3.1.2

Table 12. Study 3003: OAB Characteristics at Baseline, Last Voiding Diary Data Prior to Double-Blind Study Medication – FAS

	Placebo N = 520	Vibegron 75 mg N = 526	Tolterodine ER 4 mg N = 417	Overall N = 1463
Micturitions[a]				
n	520	526	417	1463
Mean (SD)	11.75 (4.007)	11.31 (3.420)	11.48 (3.153)	11.51 (3.573)
Median	10.43	10.43	10.67	10.57
Q1, Q3	9.15, 13.14	9.00, 12.57	9.13, 12.86	9.13, 12.86
Min, Max	0.1, 30.9	0.0, 30.0	4.1, 24.0	0.0, 30.9

	Placebo N = 520	Vibegron 75 mg N = 526	Tolterodine ER 4 mg N = 417	Overall N = 1463
Urge Urinary Incontinence Episodes[a]				
n	520	526	417	1463
Mean (SD)	2.82 (2.994)	2.73 (2.883)	2.72 (2.635)	2.76 (2.854)
Median	2.00	2.00	2.00	2.00
Q1, Q3	1.00, 3.57	0.86, 3.71	1.00, 3.57	1.00, 3.67
Min, Max	0.0, 23.7	0.0, 27.9	0.0, 17.0	0.0, 27.9
Urgency Episodes[a]				
n	520	526	417	1463
Mean (SD)	8.13 (4.668)	8.11 (4.400)	7.92 (3.883)	8.06 (4.357)
Median	8.00	7.75	8.00	7.86
Q1, Q3	4.59, 10.50	4.60, 10.71	4.86, 10.33	4.71, 10.57
Min, Max	0.0, 30.7	0.1, 30.0	0.7, 21.8	0.0, 30.7
Total Incontinence Episodes[a]				
n	520	526	417	1463
Mean (SD)	3.37 (3.713)	3.29 (3.578)	3.24 (3.109)	3.31 (3.499)
Median	2.25	2.14	2.29	2.25
Q1, Q3	1.13, 4.46	1.00, 4.43	1.14, 4.57	1.00, 4.50
Min, Max	0.0, 30.5	0.0, 28.4	0.0, 20.4	0.0, 30.5
Voided Volume per Micturition[b]				
n	514	524	415	1453
Mean (SD)	148.3 (60.67)	155.4 (63.07)	147.0 (60.79)	150.5 (61.65)
Median	141.7	150.0	143.3	144.4
Q1, Q3	107.1, 183.9	112.8, 193.4	104.3, 177.8	108.4, 184.3
Min, Max	7, 383	2, 406	18, 356	2, 406

Source: Table 14.1.3.2.2

[a] Daily Averages were calculated as the sum of the event type on Complete Diary Days divided by the number of Complete Diary Days

[b] Average volume voided per micturition was calculated as the arithmetic mean of all voids for which a subject recorded the volume.

Table 13. Study 3003: OAB Characteristics at Baseline, Last Voiding Diary Data Prior to Double-Blind Study Medication – FAS-I

	Placebo N = 405	Vibegron 75 mg N = 403	Tolterodine ER 4 mg N = 319	Overall N = 1127
Micturitions[a]				
n	405	403	319	1127
Mean (SD)	11.69 (4.074)	11.33 (3.410)	11.45 (3.189)	11.49 (3.606)
Median	10.43	10.43	10.57	10.43
Q1, Q3	9.00, 13.14	9.14, 12.56	9.13, 12.71	9.14, 12.71
Min, Max	0.1, 30.9	2.4, 30.0	4.1, 24.0	0.1, 30.9
Urge Urinary Incontinence Episodes[a]				
n	405	403	319	1127
Mean (SD)	3.49 (3.053)	3.43 (2.894)	3.42 (2.592)	3.45 (2.869)
Median	2.50	2.63	2.43	2.57
Q1, Q3	1.57, 4.43	1.57, 4.14	1.71, 4.57	1.57, 4.43
Min, Max	0.0, 23.7	0.0, 27.9	0.0, 17.0	0.0, 27.9
Urgency Episodes[a]				
n	405	403	319	1127
Mean (SD)	7.99 (4.559)	7.97 (4.389)	7.77 (3.875)	7.92 (4.311)
Median	7.86	7.67	7.86	7.86
Q1, Q3	4.57, 10.29	4.57, 10.57	4.71, 10.14	4.57, 10.29
Min, Max	0.3, 30.7	0.1, 30.0	0.7, 19.7	0.1, 30.7
Total Incontinence Episodes[a]				
n	405	403	319	1127
Mean (SD)	4.17 (3.823)	4.14 (3.631)	4.06 (3.071)	4.13 (3.552)
Median	3.00	3.14	3.00	3.00
Q1, Q3	1.78, 5.00	1.78, 5.29	1.88, 5.40	1.86, 5.29
Min, Max	0.0, 30.5	0.0, 28.4	0.1, 20.4	0.0, 30.5

	Placebo N = 405	Vibegron 75 mg N = 403	Tolterodine ER 4 mg N = 319	Overall N = 1127
Voided Volume per Micturition[b]				
n	400	401	318	1119
Mean (SD)	150.8 (59.99)	157.5 (64.21)	146.4 (61.45)	152.0 (62.05)
Median	144.2	150.8	141.3	145.8
Q1, Q3	111.6, 186.3	115.0, 193.7	101.7, 179.3	109.7, 187.5
Min, Max	25, 371	2, 406	18, 356	2, 406

Source: Table 14.1.3.2.3

[a] Daily Averages were calculated as the sum of the event type on Complete Diary Days divided by the number of Complete Diary Days.

[b] Average volume voided per micturition was calculated as the arithmetic mean of all voids for which a subject recorded the volume.

Numbers analysed

The table below summarizes the numbers of subjects included in each analysis set.

Table 14. Study 3003: Numbers of Subjects from the Randomised Set Included in the Other Analysis Sets

	Placebo N = 540[a] n (%)	Vibegron 75 mg N = 547[a] n (%)	Tolterodine ER 4 mg N = 431[a] n (%)	Overall N = 1518[a] n (%)
Safety Set (SAF)	540 (100)	545 (99.6)	430 (99.8)	1515 (99.8)
Full Analysis Set (FAS)	520 (96.3)	526 (96.2)	417 (96.8)	1463 (96.4)
Full Analysis Set for Incontinence (FAS-I)	405 (75.0)	403 (73.7)	319 (74.0)	1127 (74.2)
Per-Protocol Set (PPS)	483 (89.4)	476 (87.0)	386 (89.6)	1345 (88.6)
Per-Protocol Set for Incontinence (PPS-I)	373 (69.1)	368 (67.3)	291 (67.5)	1032 (68.0)
Pharmacokinetic Set (PK Set)	(not applicable)	308 (56.3)	(not applicable)	308 (20.3)

Source: Table 14.1.2.2

[a] Total number (N) of subjects in the Randomized Set

Outcomes and estimation

All analyses of efficacy separately compared each active treatment (vibegron or tolterodine) with placebo treatment. No formal statistical analyses were pre-specified to compare treatment with vibegron versus tolterodine, and thus, all assessments between these two active treatment groups are descriptive only.

The main timepoint for the evaluation of efficacy was at Week 12, and additional assessments were conducted at Week 2, Week 4, and Week 8. The FAS and FAS-I populations served as the primary populations for the analyses of efficacy data.

Co-Primary Efficacy Endpoints

- Change from Baseline in Micturitions

Table 15. Study 3003: Primary Efficacy Analysis (MMRM): Change from Baseline in Average Daily Number of Micturitions at Week 12 – FAS

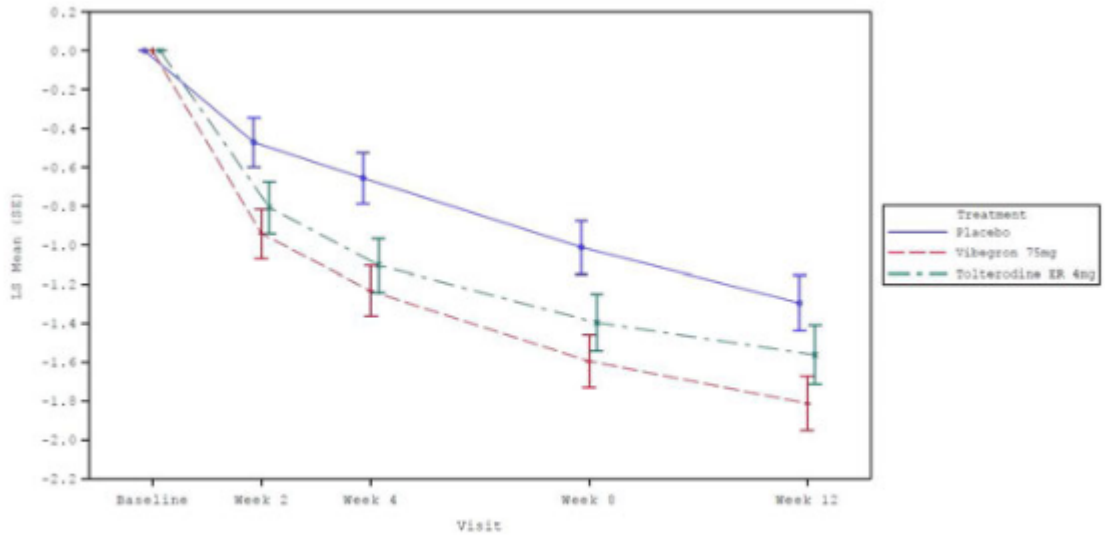
Statistic	Placebo N = 520	Vibegron 75 mg N = 526	Tolterodine ER 4 mg N = 417
Baseline			
n	520	526	417
Mean (SD)	11.75 (4.007)	11.31 (3.420)	11.48 (3.153)
Week 12			
n	475	492	378
Mean (SD)	10.05 (3.336)	9.32 (3.482)	9.58 (3.298)
Change from Baseline at Week 12			
n	475	492	378
LS means (standard error [SE])	-1.3 (0.14)	-1.8 (0.14)	-1.6 (0.15)
95% CI	-1.6 to -1.0	-2.1 to -1.5	-1.9 to -1.3
Active – Placebo			
LS means difference (SE)		-0.5 (0.15)	-0.3 (0.16)
95% CI		-0.8 to -0.2	-0.6 to 0.1
P-value		< 0.001	0.0988

Source: Table 14.2.1.1.2

Notes: Covariates included in the mixed model for repeated measures were study visit, OAB type, sex, region, baseline number of micturitions and treatment by study visit interaction.
Hypothesis testing was only performed for vibegron – placebo. Comparisons between tolterodine ER and placebo are considered descriptive.

Analyses of Change from Baseline in Average Daily Micturitions at Week 2, Week 4, and Week 8.

Table 16. Study 3003: Primary Efficacy Analysis (MMRM): Plot of LS Means (SE) of Change from Baseline in Average Daily Number of Micturitions – FAS



Source: Figure 14.2.1.1.13

Note: LS means (SE) are computed from the MMRM model displayed in Table 14.2.1.1.2.

- Change from Baseline in Urge Urinary Incontinence Episodes

Table 17. Study 3003: Primary Efficacy Analysis (MMRM): Change from Baseline in Average Daily Number of Urge Urinary Incontinence Episodes at Week 12 – FAS-I

Statistic	Placebo N = 405	Vibegron 75 mg N = 403	Tolterodine ER 4 mg N = 319
Baseline			
n	405	403	319
Mean (SD)	3.49 (3.053)	3.43 (2.894)	3.42 (2.592)
Week 12			
n	372	383	286
Mean (SD)	2.01 (2.478)	1.46 (2.446)	1.55 (2.040)

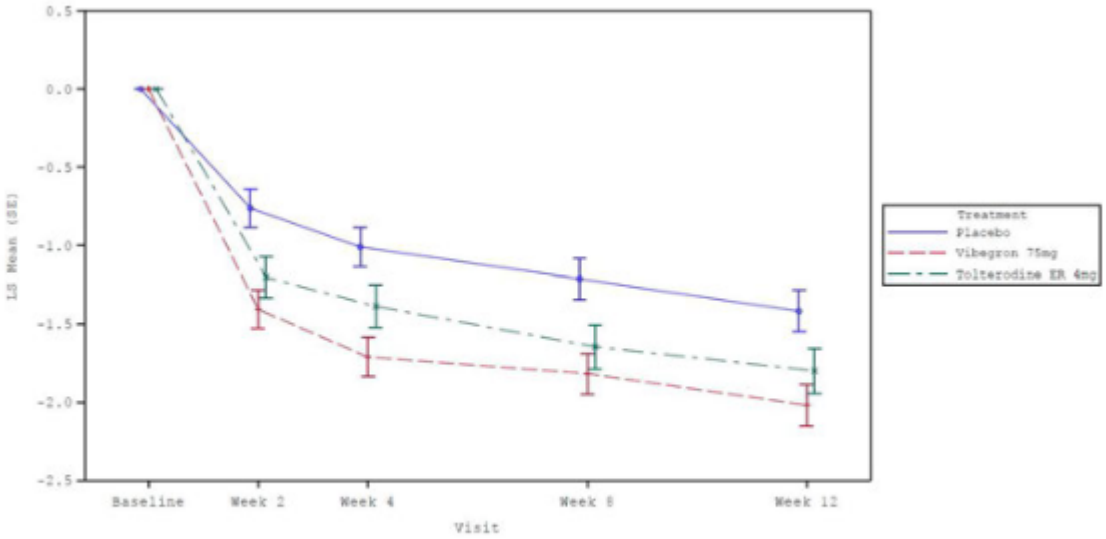
Statistic	Placebo N = 405	Vibegron 75 mg N = 403	Tolterodine ER 4 mg N = 319
Change from baseline at Week 12			
n	372	383	286
LS means (SE)	-1.4 (0.13)	-2.0 (0.13)	-1.8 (0.14)
95% CI	-1.7 to -1.2	-2.3 to -1.8	-2.1 to -1.5
Active – Placebo			
LS means difference (SE)		-0.6 (0.14)	-0.4 (0.15)
95% CI		-0.9 to -0.3	-0.7 to -0.1
P-value		< 0.0001	0.0123

Source: Table 14.2.2.1.2

Notes: Covariates included in the mixed model for repeated measures were study visit, sex, region, baseline number of UUI episodes and treatment by study visit interaction.
Hypothesis testing was only performed for vibegron – placebo. Comparisons between tolterodine ER and placebo are considered descriptive.

Analyses for Change from Baseline in Average Daily UUI Episodes at Week 2, Week 4, and Week 8.

Table 18. Study 3003: Primary Efficacy Analysis (MMRM): Plot of LS Means (SE) of Change from Baseline in Average Daily Number of Urge Urinary Incontinence Episodes –FAS-I



Source: Figure 14.2.2.1.13

Note: LS means (SE) were computed from the MMRM model displayed in Table 14.2.2.1.2.

Key Secondary Efficacy Endpoints

Each key secondary endpoint was tested sequentially. The table below summarizes the predefined key secondary endpoint

Table 19. Study 3003: Summary of Placebo-adjusted Key Secondary Efficacy Endpoints at Week 12 - FAS and FAS-I

	Vibegron 75 mg			Tolterodine ER 4 mg		
CFB analyses	**n**	**LS means difference (SE)**	**P-value**	**n**	**LS means difference (SE)**	**P-value**
Total incontinence episodes	383	-0.7 (0.16)	<0.0001	286	-0.5 (0.17)	0.0074
OAB-q LF Coping Score	512	3.6 (1.24)	0.0039	400	3.1 (1.32)	0.0210
Average voided volume per micturition (mL)	490	21.2 (3.52)	<0.0001	375	13.3 (3.76)	<0.001
Responder analyses	**n**	**CMH difference; % (95% CI)**	**P-value**	**n**	**CMH difference; % (95% CI)**	**P-value**
≥75% reduction in UUI	403	16.5 (9.7, 23.4)	<0.0001	319	9.4 (2.1, 16.7))	0.0120
100% reduction in UUI	403	6.3 (0.4, 12.1)	0.0360	319	1.9 (-4.1, 7.8)	0.5447
≥50% reduction in urgency episodes	526	6.8 (0.9, 12.7)	0.0235	417	3.7 (-2.5, 10.0)	0.2400

Source: Study 3003 CSR, Tables 14.2.7.1.2, 14.2.8.1.4, 14.2.9.1.2, 14.2.4.1.1, 14.2.5.1.1, 14.2.6.1.1.

CFB = Change from baseline; CI = Confidence interval; CMH = Cochran-Mantel-Haenszel; CSR = Clinical study report; ER = Extended release; FAS = Full Analysis Set; FAS-I = Full Analysis Set for Incontinence; LS = Least squares; OAB = Overactive bladder; OAB-q LF = Overactive Bladder Questionnaire long-form; SE = Standard error; UUI = Urge urinary incontinence.

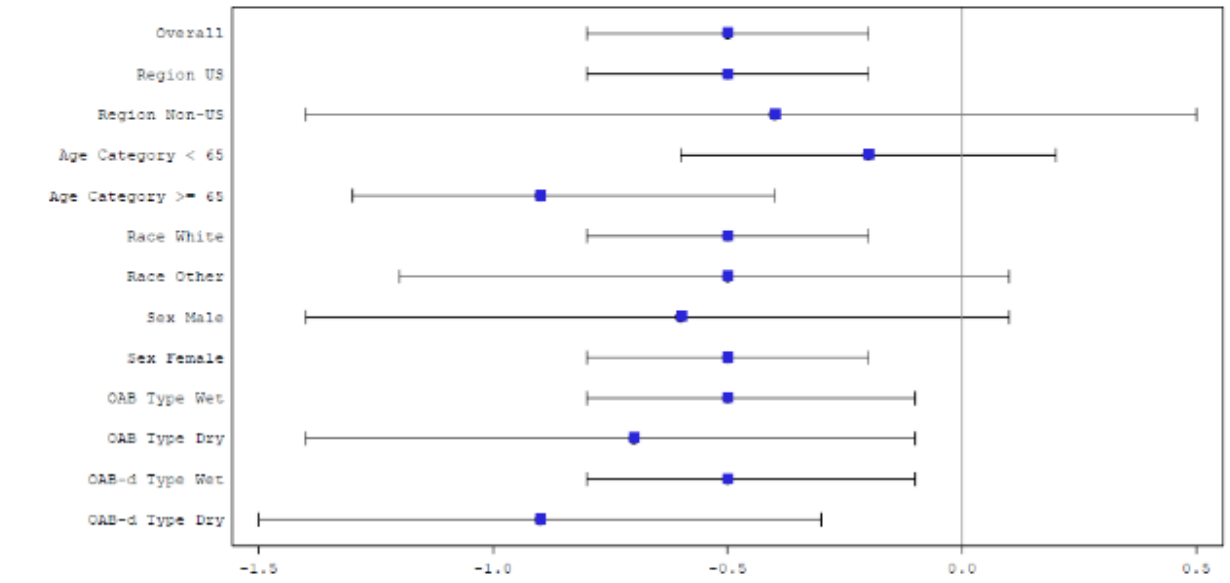
Notes: LS means results shown are for active (vibegron or tolterodine) minus placebo. Covariates included in the model were study visit, OAB type (for FAS only), gender, region, baseline, and treatment by study visit interaction. Hypothesis testing was only performed for vibegron – placebo. Comparisons between tolterodine ER and placebo are considered descriptive. See source tables for sample sizes in placebo groups.

Ancillary analyses

A subgroup analyses was performed in study 3003 of the co-primary efficacy endpoints. A forest plot showing the results can be seen below.

- Change from Baseline in Micturitions

Table 20. Study 3003: Forest Plot of Vibegron Treatment Effect vs Placebo on Average Daily Number of Micturitions at Week 12 by Subgroup. Primary Efficacy Analysis (MMRM) by Subgroup – FAS

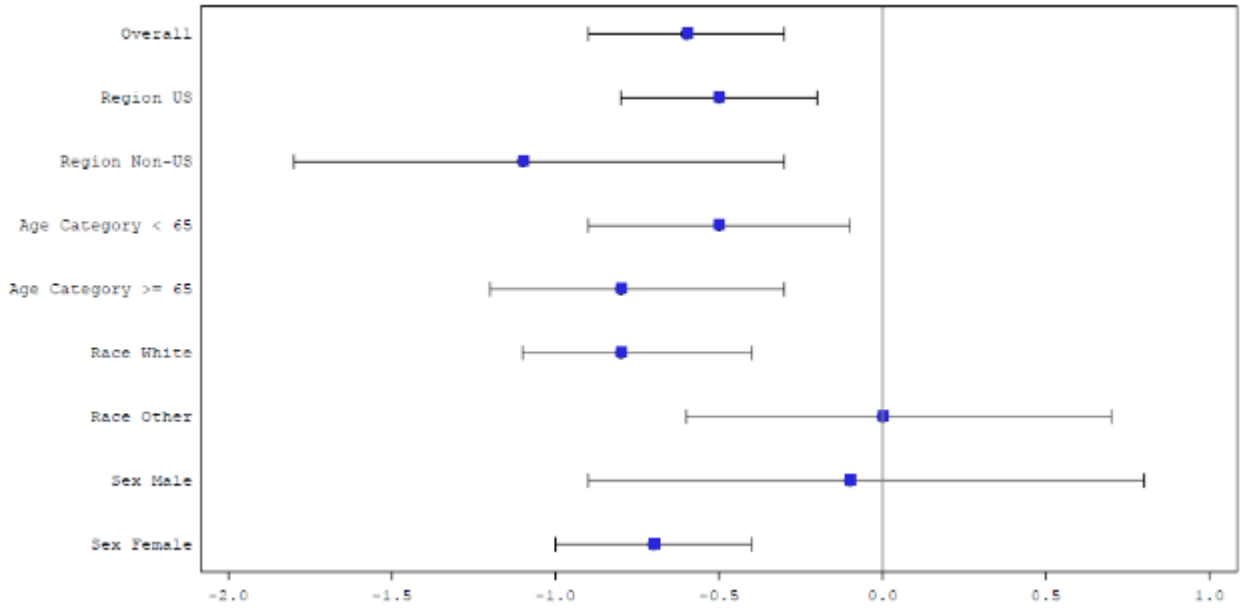


Source: Study 3003 CSR, Figure 14.2.1.1.14

- Change from Baseline in Urge Urinary Incontinence Episodes

A forest plot showing the results can be seen below.

Table 21. Study 3003: Forest Plot of Vibegron Treatment Effect vs Placebo on Average Daily Number of UUI Episodes at Week 12 by Subgroup. Primary Efficacy Analysis (MMRM) by Subgroup – FAS-I

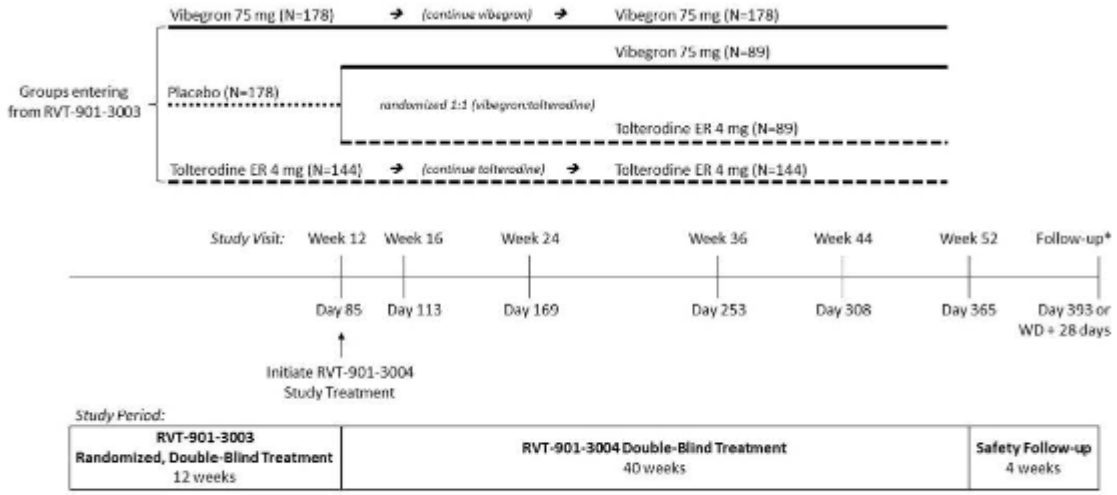


Study 3004 - An International Phase 3, Randomized, Double-Blind, Active (Tolterodine) Controlled Multicentre Extension Study to Evaluate the Long-Term Safety and Efficacy of Vibegron in Patients with Symptoms of Overactive Bladder

Methods

The study was an extension for subjects who had completed the Phase 3, double-blind, randomised, 12-week Study 3003.

Figure 8. Schematic of Design in study 3004



*The Follow-up visit occurred at Day 393 for subjects who completed the Week 52 visit or at 28 days after withdrawal (WD) for subjects who withdraw early from the study.

Study Participants

Key inclusion criterium was:
1. Had completed participation in Study 3003.

Key exclusionary criteria were:
1. Was unable to complete participation in Study 3003 for any reason.
2. Had a change in history or current evidence of any clinically significant condition, therapy, lab abnormality, or other circumstance that might, in the opinion of the Investigator, confound the results of the study, interfere with the subject's ability to comply with study procedures, or make participation in the study not in the subject's best interest. Included any serious or unstable, clinically relevant change in gastrointestinal, renal, hepatic, cardiovascular, lymphatic, or psychiatric, or other medical disorder during Study 3003.

Treatments

Subjects that had been taken vibegron 75 mg or tolterodine ER 4 mg during the 12-week study (study 3003) continued with their previous treatment. All subjects randomised to placebo were randomised 1:1 to take vibegron 75 mg or tolterodine ER 4 mg during the 40-week extension study.

Study treatments could be taken regardless of food. The first dose was taken at the study site, while all other doses were administered at home.

Objectives

Safety was the primary objective in this long-term extension study. The secondary objectives were related to efficacy and subject perceived outcomes.

Outcomes/endpoints

The primary efficacy endpoints of the Phase 3 clinical extension study 3004 were related to safety.

The key secondary efficacy endpoints were: 1) change from baseline (CFB) at Week 52 in average number of micturition's per 24 hours in all OAB subject, 2) CFB at Week 52 in average number of UUI episodes per 24 hours in OAB Wet subjects, 3) CFB at Week 52 in average number of urgency episodes (need to urinate immediately) over 24 hours in all OAB subjects and 4) CFB at Week 52 in average number of total urinary incontinence episodes over 24 hours in OAB Wet subjects.

Sample size

The enrolment in the extension study was to be capped at approximately 500 patients. There was no formal sample size calculation. Collecting data from approximately 500 patients rolling over from study RVT-901-3003 was considered sufficient to characterize the long-term safety profile of vibegron 75 mg (OD) while satisfying ICH guidance for 1-year exposure.

Randomisation and blinding (masking)

All subjects who had been randomised in Study 3003 to receive either vibegron 75 mg or tolterodine extended release (ER) 4 mg were to continue their same treatment. Subjects who had been randomised in Study 3003 to the placebo group were to be centrally randomised 1:1 to receive vibegron 75 mg or tolterodine ER 4 mg using IV/WRS. Randomisation was stratified based on baseline OAB type (Wet vs Dry) and sex (female vs male).

Study RVT-901-3003 was performed under double-blind conditions achieved using double-dummy technique. It is endorsed that this extension study was to continue in a double-blind manner. To maintain blinding, placebo to match the vibegron 75-mg tablet and placebo to match the tolterodine ER 4-mg capsule was to be administered in addition to active treatment. Vibegron and its matching placebo and tolterodine ER and its matching placebo were packaged identically.

It is acknowledged that specific Sponsor personnel and delegate(s) were partially unblinded once (the parent study) study 3003 reached database lock. However, Sponsor personnel and delegates involved in subject-level decisions were to remain blinded.

Statistical methods

The submitted SAP was version 2.0 (dated 09 August 2019) including the revision history. The initial release version of this document was 21 December 2018. It was revised several times but there were no major changes made.

All safety and efficacy analyses were to occur after all patients had completed all study visits or discontinued the study. No interim analyses were to be performed.

Study RVT-901-3004 primary objective was to evaluate the safety and tolerability. Efficacy was a secondary objective.

No formal comparisons of vibegron vs. tolterodine were planned; all between-treatment analyses were to be descriptive.

Analysis sets

The population for efficacy analysis was the Full Analysis Set Extension (FAS-Ext) for micturition endpoints and urgency episodes while the FAS Extension for Incontinence (FAS-Ext-I) was to be used for the following incontinence endpoints: UUI and total incontinence episodes.

FAS-Ext: all randomised OAB patients who took at least one dose of double-blind study treatment in RVT-901-3004 and had at least one subsequent evaluable change from baseline micturition measurement in the extension study.

FAS-Ext-I: all randomised OAB Wet patients who were included in the FAS-I population in the RVT-901-3003 study, who took at least one dose of double-blind Study Treatment in RVT-901-3004 and had at least one subsequent evaluable change from baseline (RVT-901-3004) urge urinary incontinence measurement.

Efficacy data

Throughout the trial, patients were required to fill out an event and volume diary. It was intended for the patients to fill out the voiding diary for 7 days prior to the Baseline (during Run-in), Week 2, 4, 8, and 12 visits (RVT-901-3003) and Week 16, Week 24, Week 44, and Week 52 visits (RVT-901-3004), and to fill out the volume portion of the diary for 1 of the 7 diary days for each visit.

In order for a patient to have an evaluable change from baseline, the patient must have had both a complete baseline diary and a complete post-baseline diary from any post-baseline timepoint (i.e., Week 16, Week 24, Week 44 or Week 52). Change from baseline was defined as the post-baseline assessment minus the baseline assessment.

For all endpoints the definition of baseline was the baseline value from the RVT-901-3003 study.

Key secondary efficacy endpoints

The secondary efficacy endpoints of change from baseline in average number of micturitions, average number of UUI episodes, average number of urgency episodes, and average number of total incontinence episodes were analysed separately using a mixed model for repeated measure (MMRM) with restricted maximum likelihood estimation. The analysis model for each efficacy endpoint was to include terms for treatment, visit, baseline stratification factors (only those that were statistically significant in RVT-901-3003 were included in the models), baseline score, and interaction of visit by treatment.

Only patients on active treatment in both RVT-901-3003 and RVT-901-3004 were to be included in these analyses.

Adjusted means for each treatment group and visit were estimated along with 95% confidence intervals. No formal statistical comparisons were made. No p-values and no treatment differences were to be presented.

Missing Data

For all change from baseline analyses of the secondary efficacy endpoints no imputation of missing data was to be performed as the Mixed Model for Repeated Measures (MMRM) accounts for this.

Subgroups

No subgroup analyses were to be performed for any efficacy endpoints.

Safety analysis

The SAF-Ext was to be used for all safety analyses. The Safety Analysis Set Extension (SAF-Ext) was to include all patients who received at least one dose of double-blind study treatment during RVT-901-3004. All safety data were to be presented by treatment received in RVT-901-3004, that is, Vibegron 75mg and Tolterodine ER 4mg with 52 weeks and 40 weeks scheduled treatment combined. Patients were to be included in the treatment group corresponding to the study treatment they actually received in RVT-901-3004.

Safety was to be assessed on the basis of AE reports, clinical laboratory data, extent of exposure and compliance, ECGs, physical examinations, and vital signs.

No inferential statistical testing was planned on the safety data, all data were to be summariszed and listed only. No imputation was to be performed for missing safety data (except for the case of partially missing dates in order to assign to study periods). Baseline was to be defined as the last non-missing value before treatment in RVT-901-3003.

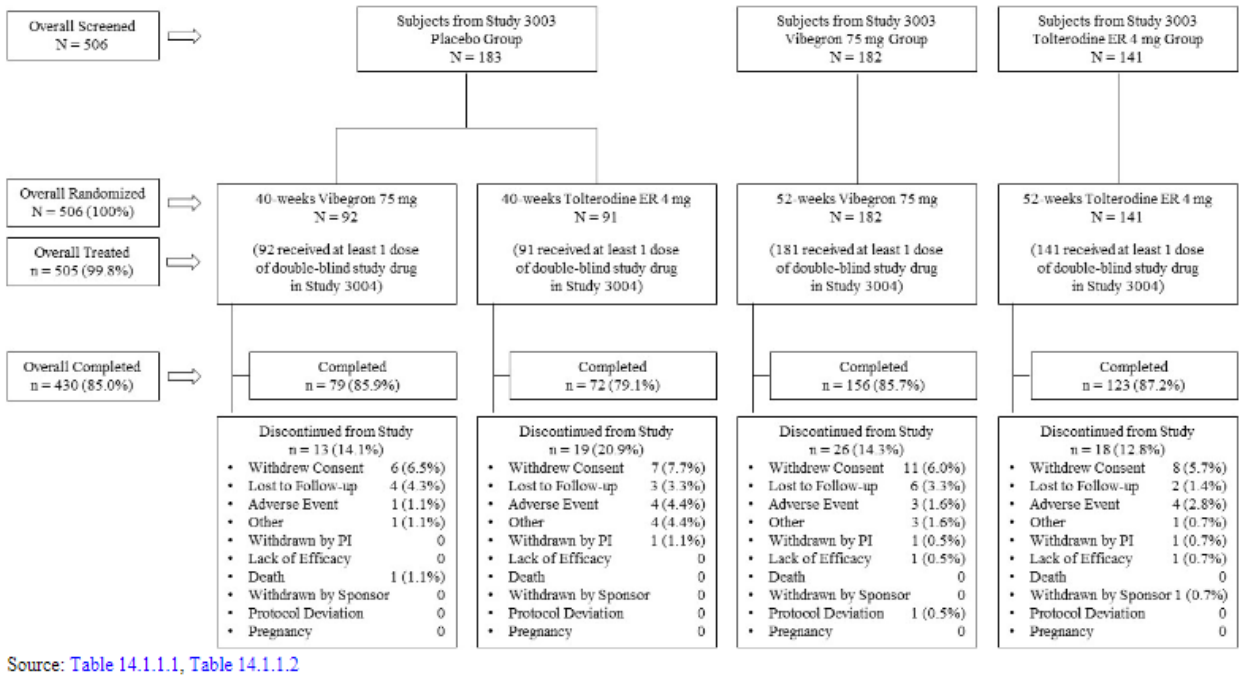
Results

Participant flow

A total of 274 subjects were randomised to the vibegron group and 232 to the tolterodine group (see table below).

A table of subject disposition can be seen below.

Figure 9. Study 3004: Schematic of subject disposition



Source: Table 14.1.1.1, Table 14.1.1.2

Recruitment

The first subject was enrolled in the study on 14 June 2018. The last subject completed the study on 25 July 2019. The clinical study report was signed on 3 December 2019. The study population was enrolled from a total of 109 sites, all located in the US.

Conduct of the study

Major protocol deviations were reported for 13% of subjects, 5.6% of subjects had a major efficacy-related protocol deviation, which excluded them from the efficacy evaluation. The protocol deviations are well balanced between the study groups and considered not to seriously affect the assessment of the results.

Baseline data

The demographic and baseline characteristics for the SAF-Ext are summarized in the table below.

Table 22. Study 3004: Subject Demographic and Baseline Characteristics – SAF-Ext

Variable Statistic/Response	40-weeks Vibegron 75mg (N=92) n (%)	52-weeks Vibegron 75mg (N=181) n (%)	Overall Vibegron 75mg (N=273) n (%)	40-weeks Tolterodine ER 4mg (N=91) n (%)	52-weeks Tolterodine ER 4mg (N=141) n (%)	Overall Tolterodine ER 4mg (N=232) n (%)	Overall (N=505) n (%)
Age at study entry (years), mean (SD)	58.8 (13.69)	62.1 (12.39)	61.0 (12.91)	62.1 (12.14)	60.6 (12.98)	61.2 (12.65)	61.1 (12.78)
Age category (years), n (%)							
< 40	9 (9.8)	11 (6.1)	20 (7.3)	5 (5.5)	11 (7.8)	16 (6.9)	36 (7.1)
≥ 40 to < 55	22 (23.9)	34 (18.8)	56 (20.5)	16 (17.6)	27 (19.1)	43 (18.5)	99 (19.6)
≥ 55 to < 65	25 (27.2)	43 (23.8)	68 (24.9)	27 (29.7)	40 (28.4)	67 (28.9)	135 (26.7)
≥ 65 to < 75	28 (30.4)	70 (38.7)	98 (35.9)	30 (33.0)	47 (33.3)	77 (33.2)	175 (34.7)
≥ 75	8 (8.7)	23 (12.7)	31 (11.4)	13 (14.3)	16 (11.3)	29 (12.5)	60 (11.9)
Sex, n(%)							
Male	19 (20.7)	41 (22.7)	60 (22.0)	21 (23.1)	29 (20.6)	50 (21.6)	110 (21.8)
Female	73 (79.3)	140 (77.3)	213 (78.0)	70 (76.9)	112 (79.4)	182 (78.4)	395 (78.2)
Benign prostate hyperplasia (male only), n (%)[a], yes	4 (21.1)	16 (39.0)	20 (33.3)	6 (28.6)	8 (27.6)	14 (28.0)	34 (30.9)
Baseline hypertension[b], n (%), yes	9 (9.8)	11 (6.1)	20 (7.3)	8 (8.8)	15 (10.6)	23 (9.9)	43 (8.5)
Pre-existing hypertension[c], n (%), yes	39 (42.4)	97 (53.6)	136 (49.8)	31 (34.1)	72 (51.1)	103 (44.4)	239 (47.3)
OAB type[d], n (%)							
Wet	71 (77.2)	146 (80.7)	217 (79.5)	70 (76.9)	108 (76.6)	178 (76.7)	395 (78.2)
Dry	21 (22.8)	35 (19.3)	56 (20.5)	21 (23.1)	33 (23.4)	54 (23.3)	110 (21.8)
Prior anticholinergic use, n (%), yes	11 (12.0)	27 (14.9)	38 (13.9)	16 (17.6)	15 (10.6)	31 (13.4)	69 (13.7)
Prior beta-3 agonist use, n (%), yes	7 (7.6)	9 (5.0)	16 (5.9)	9 (9.9)	10 (7.1)	19 (8.2)	35 (6.9)

Variable Statistic/Response	40-weeks Vibegron 75mg (N=92) n (%)	52-weeks Vibegron 75mg (N=181) n (%)	Overall Vibegron 75mg (N=273) n (%)	40-weeks Tolterodine ER 4mg (N=91) n (%)	52-weeks Tolterodine ER 4mg (N=141) n (%)	Overall Tolterodine ER 4mg (N=232) n (%)	Overall (N=505) n (%)
Race, n (%)							
American Indian or Alaska Native	2 (2.2)	0	2 (0.7)	0	0	0	2 (0.4)
Asian	4 (4.3)	16 (8.8)	20 (7.3)	8 (8.8)	11 (7.8)	19 (8.2)	39 (7.7)
Black or African American	14 (15.2)	23 (12.7)	37 (13.6)	10 (11.0)	26 (18.4)	36 (15.5)	73 (14.5)
White	72 (78.3)	141 (77.9)	213 (78.0)	72 (79.1)	102 (72.3)	174 (75.0)	387 (76.6)
Other	0	1 (0.6)	1 (0.4)	1 (1.1)	2 (1.4)	3 (1.3)	4 (0.8)

Source: Table 14.1.3.1.1

Note: Baseline refers to the baseline visit (Visit 3) in Study 3003.

[a] For benign prostate hyperplasia, percentages are based on the number of males.
[b] Baseline hypertension is based on baseline vitals.
[c] Pre-existing hypertension is based on baseline vitals and prior medical history.
[d] OAB type is as randomized.

Table 23. Study 3004: OAB Characteristics at Baseline, Last Voiding Diary Data Prior to Double-Blind Study Medication – FAS-Ext

Variable Statistic	40-weeks Vibegron 75mg (N=90)	52-weeks Vibegron 75mg (N=176)	Overall Vibegron 75mg (N=266)	40-weeks Tolterodine ER 4mg (N=83)	52-weeks Tolterodine ER 4mg (N=136)	Overall Tolterodine ER 4mg (N=219)
Micturitions[a]						
n	90	176	266	83	136	219
Mean (SD)	12.20 (3.803)	11.32 (3.415)	11.62 (3.568)	11.30 (3.072)	11.33 (3.218)	11.32 (3.157)
Median	10.94	10.43	10.57	10.14	10.43	10.43
Q1, Q3	9.86, 13.29	9.06, 12.71	9.29, 12.88	9.40, 12.43	8.89, 12.43	9.14, 12.43
Min, Max	7.9, 26.4	4.3, 28.9	4.3, 28.9	7.9, 23.6	7.0, 21.9	7.0, 23.6
UUI Episodes[a]						
n	90	176	266	83	136	219
Mean (SD)	2.76 (2.907)	2.62 (2.809)	2.67 (2.838)	2.26 (2.367)	2.39 (2.148)	2.34 (2.229)
Median	1.93	1.63	1.73	1.67	1.86	1.86
Q1, Q3	1.00, 3.43	0.85, 3.57	0.86, 3.57	1.00, 3.00	1.00, 3.12	1.00, 3.00
Min, Max	0.0, 13.6	0.0, 16.1	0.0, 16.1	0.0, 12.9	0.0, 9.4	0.0, 12.9
Urgency Episodes[a]						
n	90	176	266	83	136	219
Mean (SD)	8.56 (4.933)	8.00 (4.586)	8.19 (4.704)	7.61 (3.823)	8.03 (3.706)	7.87 (3.748)
Median	8.25	7.07	7.57	6.71	7.93	7.75
Q1, Q3	5.00, 10.86	4.71, 10.00	4.71, 10.29	4.71, 10.00	5.14, 10.43	5.00, 10.29
Min, Max	1.4, 26.4	1.0, 28.9	1.0, 28.9	0.4, 21.1	1.7, 21.8	0.4, 21.8

Variable Statistic	40-weeks Vibegron 75mg (N=90)	52-weeks Vibegron 75mg (N=176)	Overall Vibegron 75mg (N=266)	40-weeks Tolterodine ER 4mg (N=83)	52-weeks Tolterodine ER 4mg (N=136)	Overall Tolterodine ER 4mg (N=219)
Total Incontinence Episodes[a]						
n	90	176	266	83	136	219
Mean (SD)	3.24 (3.643)	3.08 (3.192)	3.13 (3.346)	2.72 (2.846)	2.86 (2.602)	2.80 (2.692)
Median	2.00	1.86	2.00	2.00	2.17	2.13
Q1, Q3	1.00, 4.13	1.00, 4.14	1.00, 4.14	1.00, 3.71	1.14, 3.99	1.14, 3.75
Min, Max	0.0, 16.1	0.0, 16.1	0.0, 16.1	0.0, 15.9	0.0, 11.9	0.0, 15.9
Volume Voided per Micturition (mL)[b]						
n	87	171	258	81	130	211
Mean (SD)	143.5 (60.52)	160.1 (61.98)	154.5 (61.88)	152.6 (60.52)	146.0 (57.47)	148.6 (58.61)
Median	125.6	153.1	150.0	144.0	142.2	142.7
Q1, Q3	102.7, 180.0	121.4, 191.5	113.3, 182.8	110.0, 187.5	106.0, 175.6	107.9, 179.2
Min, Max	47, 383	41, 353	41, 383	39, 363	32, 326	32, 363

Source: Table 14.1.3.2.2

Note: Baseline refers to the baseline visit (Visit 3) in Study 3003.

[a] Daily Averages was calculated as the sum of the event type on Complete Diary Days divided by the number of Complete Diary Days.

[b] Average volume voided per micturition was calculated as the arithmetic mean of all voids for which a subject had recorded the volume.

Table 24. Study 3004: OAB Characteristics at Baseline, Last Voiding Diary Data Prior to Double-Blind Study Medication – FAS-Ext -I

	40-weeks Vibegron 75mg (N=69)	52-weeks Vibegron 75mg (N=143)	Overall Vibegron 75mg (N=212)	40-weeks Tolterodine ER 4mg (N=64)	52-weeks Tolterodine ER 4mg (N=106)	Overall Tolterodine ER 4mg (N=170)
Micturitions[a]						
n	69	143	212	64	106	170
Mean (SD)	11.87 (3.118)	11.20 (3.190)	11.42 (3.175)	11.54 (3.372)	11.20 (3.170)	11.33 (3.242)
Median	10.86	10.43	10.57	10.14	10.29	10.29
Q1, Q3	10.00, 13.20	9.14, 12.56	9.36, 12.79	9.39, 13.07	8.88, 12.43	9.00, 12.43
Min, Max	8.0, 21.9	4.3, 28.9	4.3, 28.9	7.9, 23.6	7.0, 21.9	7.0, 23.6
UUI Episodes[a]						
n	69	143	212	64	106	170
Mean (SD)	3.51 (2.924)	3.18 (2.837)	3.29 (2.863)	2.83 (2.405)	3.00 (2.038)	2.94 (2.178)
Median	2.43	2.25	2.29	2.07	2.29	2.14
Q1, Q3	1.71, 3.71	1.29, 3.86	1.33, 3.86	1.43, 3.54	1.57, 4.00	1.50, 3.57
Min, Max	0.9, 13.6	0.0, 16.1	0.0, 16.1	0.1, 12.9	0.0, 9.4	0.0, 12.9
Urgency Episodes[a]						
n	69	143	212	64	106	170
Mean (SD)	7.85 (4.002)	7.86 (4.392)	7.85 (4.259)	7.56 (3.971)	7.78 (3.647)	7.69 (3.762)
Median	7.86	7.00	7.50	6.75	7.71	7.58
Q1, Q3	4.71, 10.29	4.63, 10.00	4.67, 10.27	4.66, 10.00	5.11, 10.14	4.86, 10.00
Min, Max	1.4, 20.0	1.0, 28.9	1.0, 28.9	0.4, 21.1	1.7, 19.7	0.4, 21.1

	40-weeks Vibegron 75mg (N=69)	52-weeks Vibegron 75mg (N=143)	Overall Vibegron 75mg (N=212)	40-weeks Tolterodine ER 4mg (N=64)	52-weeks Tolterodine ER 4mg (N=106)	Overall Tolterodine ER 4mg (N=170)
Total Incontinence Episodes[a]						
n	69	143	212	64	106	170
Mean (SD)	4.13 (3.725)	3.71 (3.221)	3.85 (3.390)	3.35 (2.937)	3.56 (2.521)	3.48 (2.679)
Median	2.71	2.50	2.54	2.25	2.54	2.46
Q1, Q3	1.71, 5.00	1.43, 5.14	1.50, 5.00	1.54, 4.07	1.86, 5.14	1.71, 4.57
Min, Max	0.9, 16.1	0.0, 16.1	0.0, 16.1	0.1, 15.9	0.3, 11.9	0.1, 15.9
Volume Voided per Micturition (mL)[b]						
n	68	139	207	62	101	163
Mean (SD)	143.3 (55.52)	161.3 (59.75)	155.4 (58.87)	159.9 (61.90)	145.1 (55.64)	150.7 (58.36)
Median	125.3	154.5	150.8	153.0	138.6	142.7
Q1, Q3	104.4, 179.3	123.0, 191.5	117.5, 184.6	121.0, 194.6	107.9, 175.6	111.7, 185.6
Min, Max	65, 371	41, 331	41, 371	39, 363	32, 306	32, 363

Source: Table 14.1.3.2.3

Note: Baseline refers to the baseline visit (Visit 3) in Study 3003.

[a] Daily Averages will be calculated as the sum of the event type on Complete Diary Days divided by the number of Complete Diary Days.

[b] Average volume voided per micturition was calculated as the arithmetic mean of all voids for which a subject had recorded the volume.

Numbers analysed

The table below summarizes the numbers of subjects included in each analysis set.

Table 25. Study 3004: Numbers of Subjects from the Randomized Set Included in the Other Analysis Sets

	40-weeks Vibegron 75mg (N=92) n (%)	52-weeks Vibegron 75mg (N=182) n (%)	Overall Vibegron 75mg (N=274) n (%)	40-weeks Tolterodine ER 4mg (N=91) n (%)	52-weeks Tolterodine ER 4mg (N=141) n (%)	Overall Tolterodine ER 4mg (N=232) n (%)	Overall (N=506) n (%)
Safety Set Extension (SAF-Ext)	92 (100)	181 (99.5)	273 (99.6)	91 (100)	141 (100)	232 (100)	505 (99.8)
Full Analysis Set Extension (FAS-Ext)	90 (97.8)	176 (96.7)	266 (97.1)	83 (91.2)	136 (96.5)	219 (94.4)	485 (95.8)
Full Analysis Set Extension for Incontinence (FAS-Ext-I)	69 (75.0)	143 (78.6)	212 (77.4)	64 (70.3)	106 (75.2)	170 (73.3)	382 (75.5)
Per-Protocol Set Extension (PP-Ext)	83 (90.2)	162 (89.0)	245 (89.4)	75 (82.4)	126 (89.4)	201 (86.6)	446 (88.1)
Per-Protocol Set Extension for Incontinence (PP-Ext-I)	64 (69.6)	130 (71.4)	194 (70.8)	58 (63.7)	97 (68.8)	155 (66.8)	349 (69.0)

Source: Table 14.1.2.2

Notes: Presented frequencies and the denominator used for percentages are based on subjects in the Randomized Set and the treatment randomized.
Only major protocol deviations related to efficacy, efficacy and safety, and compliance excluded a subject from the PP-Ext and PP-Ext-I populations.

Outcomes and estimation

Efficacy was evaluated as secondary and exploratory objectives. No formal statistical analyses were pre-specified to compare treatment with vibegron versus tolterodine, and thus, all assessments between these two active treatment groups are considered descriptive only.

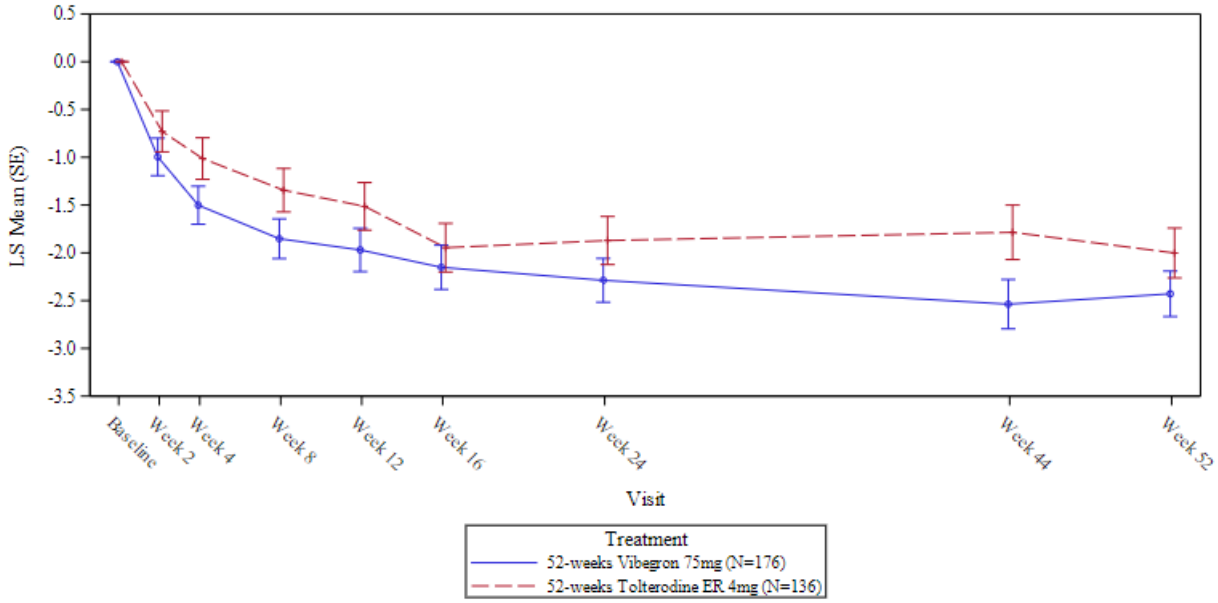
For all endpoints, the definition of baseline was the baseline value from Study 3003. The main timepoint for the evaluation of efficacy in this extension study was Week 52, and additional assessments were conducted at Weeks 2, 4, 8, 12 (under the Study 3003 protocol) and Weeks 16, 24, and 44 (under the Study 3004 protocol). The focus of the analysis was on subjects on active treatment in both Study 3003 and Study 3004 (ie, the 52-week treatment groups). The FAS-Ext and FAS-Ext-I populations served as the primary populations for the analyses of efficacy data.

In this Overview AR, the results with the secondary efficacy endpoints are shown as figures at assessments weeks 16, 24, 44, and 52. Further data are presented in the Clinical AR.

Secondary Efficacy Endpoints

- Change from Baseline in Micturitions

Figure 10. Secondary Endpoint Analysis (MMRM): Plot of LS Means (SE) of Change from Baseline in Average Daily Number of Micturitions – FAS-Ext

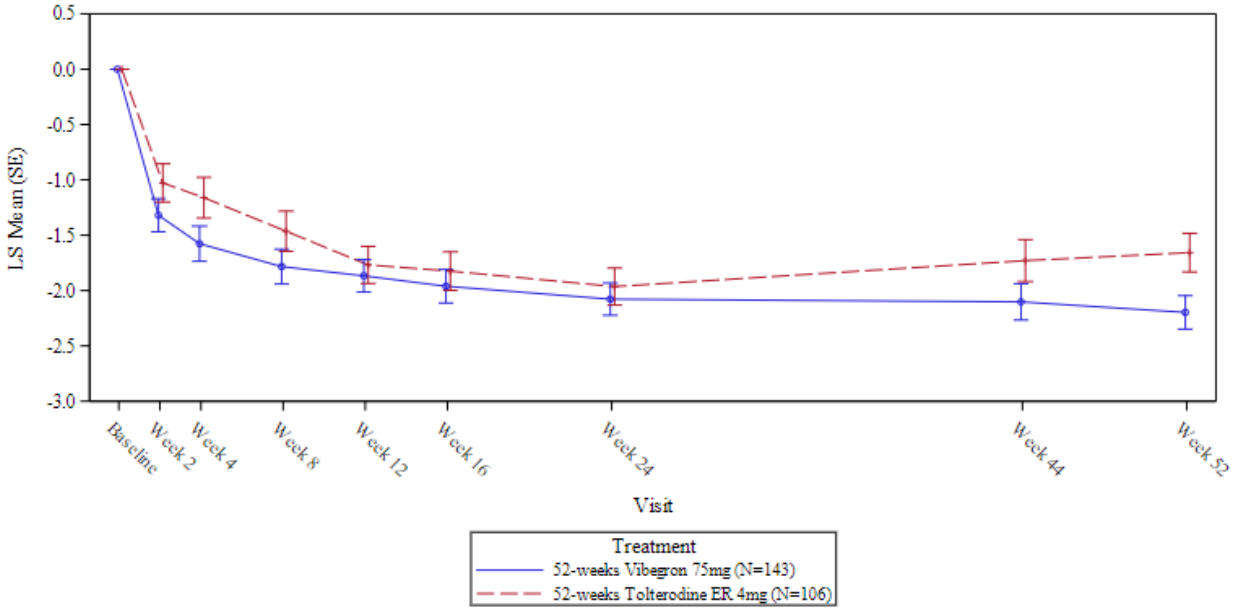


Source: Figure 14.2.1.5

Notes: Baseline value based on run-in diaries from Study 3003.
LS means (SE) were computed from the MMRM model displayed in Table 14.2.1.2 for 52-week groups only.

- Change from Baseline in Urge Urinary Incontinence Episodes

Figure 11. Study 3004: Secondary Endpoint Analysis (MMRM): Plot of LS Means (SE) of Change from Baseline in Average Daily Number of Urge Urinary Incontinence Episodes – FAS-Ext-I

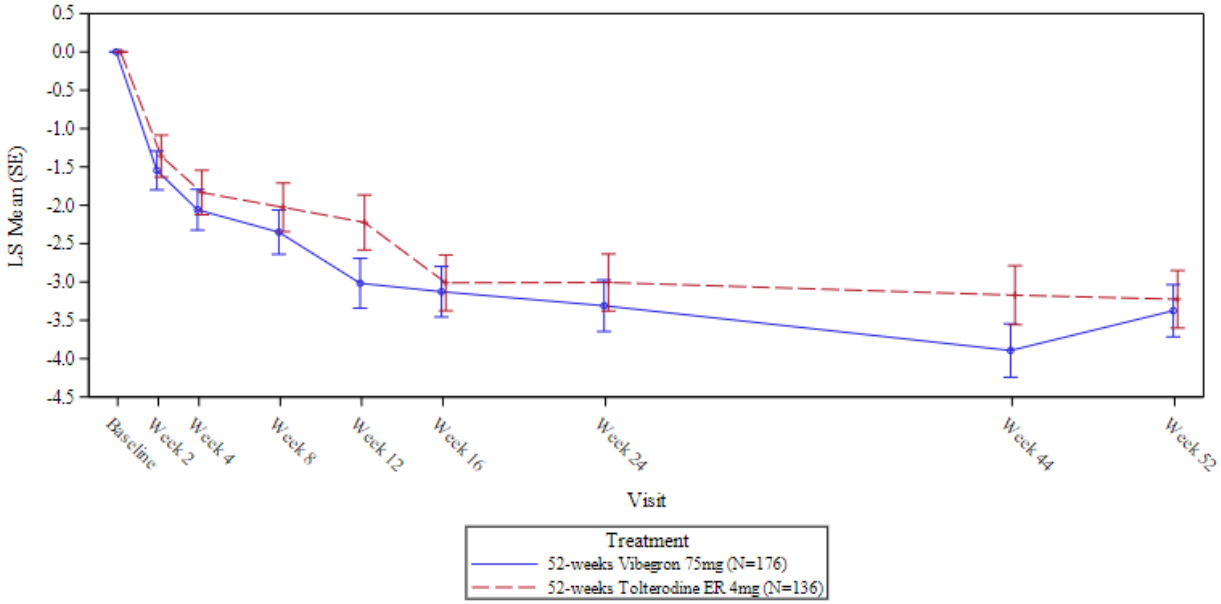


Source: Figure 14.2.2.5

Note: Baseline value based on run-in diaries from Study 3003.
LS means (SE) were computed from the MMRM model displayed in Table 14.2.2.2 for 52-week groups only.

- Change from Baseline in Urgency Episodes

Figure 12. Study 3004: Secondary Endpoint Analysis (MMRM): Plot of LS Means (SE) of Change from Baseline in Average Daily Number of Urgency Episodes – FAS-Ext

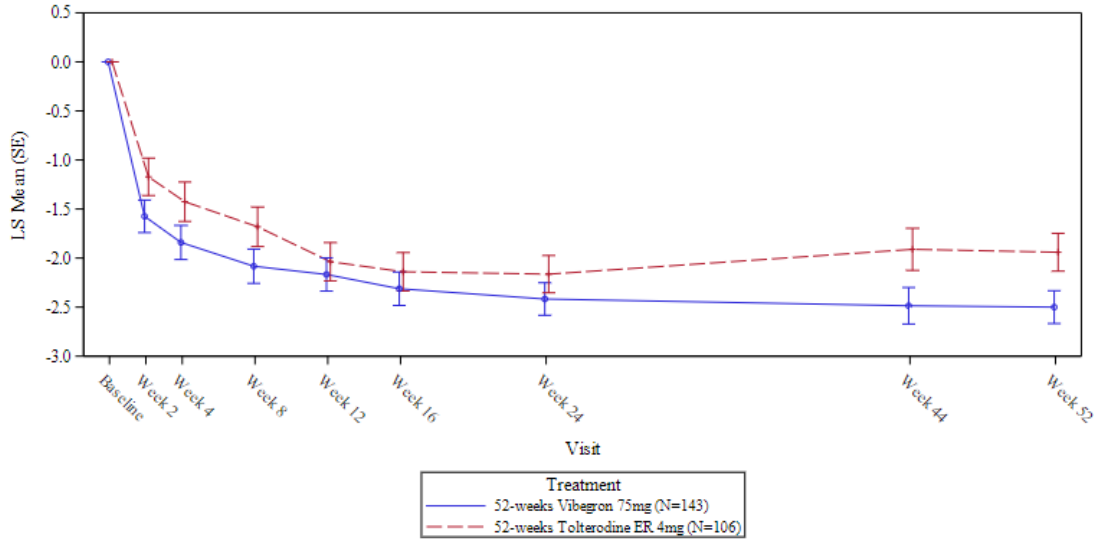


Source: Figure 14.2.3.5

Note: Baseline value based on run-in diaries from Study 3003.
LS means (SE) were computed from the MMRM model displayed in Table 14.2.3.2 for 52-week groups only.

- Change from Baseline in Total Urinary Incontinence Episodes

Figure 13. Study 3004: Secondary Endpoint Analysis (MMRM): Plot of LS Means (SE) of Change from Baseline in Average Daily Number of Total Urinary Incontinence Episodes – FAS-Ext-I



Source: Figure 14.2.4.5

Note: Baseline value based on run-in diaries from Study 3003.
LS means (SE) were computed from the MMRM model displayed in Table 14.2.4.2 for 52-week groups only.

Ancillary analyses

No ancillary analyses of study 3004 have been performed.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies RVT-901-3003. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 26. Summary of efficacy for trial RVT-901-3003

Title: An International Phase 3, Randomised, Double-Blind, Placebo- and Active (Tolterodine)-Controlled Multicentre Study to Evaluate the Safety and Efficacy of Vibegron in Patients with Symptoms of Overactive Bladder			
Study identifier	RVT-901-3003 IND# 106,410 EudraCT# 2017-003293-14 Clinicaltrials.gov NCT03492281 also known as EMPOWUR study		
Design	International, Phase 3, randomised, double-blind, placebo-controlled with active control (tolterodine), parallel-group, multicentre study		
	Duration of main phase: Duration of Run-in phase: Duration of Safety Follow-up phase:		12 weeks 2 weeks 4 weeks
Hypothesis	Superiority		
Treatments groups (n= number of randomised patients)	Vibegron		Vibegron 75 mg once daily for 12 weeks (n=547)
	Placebo		Placebo for 12 weeks (n=540)
	Tolterodine		Tolterodine ER 4mg once daily for 12 weeks (n=431)
Endpoints and definitions	Co-primary endpoint	CFB daily Micturition_w12	Change from baseline (CFB) at Week 12 in average number of micturitions per 24 hours in all OAB subjects
	Co-primary endpoint	CFB daily UUI_w12	CFB at Week 12 in average number of urge urinary incontinence (UUI) episodes per 24 hours in OAB Wet subjects.
	Key Secondary endpoint	CFB daily urgency episodes_ w12	CFB at Week 12 in average number of urgency episodes (need to urinate immediately) over 24 hours in all OAB subjects
	Key Secondary endpoint	75% reduction in daily UUI episodes_ w12	Percent of OAB Wet subjects with at least a 75% reduction from baseline in UUI episodes per 24 hours at Week 12
	Key Secondary endpoint	100% reduction in daily UUI episodes_ w12	Percent of OAB Wet subjects with a 100% reduction from baseline in UUI episodes per 24 hours at Week 12

	Key Secondary endpoint	50% reduction in daily urgency episodes_ w12	Percent of all OAB subjects with at least a 50% reduction from baseline in urgency episodes (need to urinate immediately) per 24 hours at Week 12
	Key Secondary endpoint	CFB daily total incontinence episodes w12	CFB at Week 12 in average number of total incontinence episodes over 24 hours in OAB Wet subjects
	Key Secondary endpoint	CFB OAB-q LF_coping score w12	CFB at Week 12 in Coping Score from the Overactive Bladder Questionnaire Long Form (OAB-q LF, 1-week recall) in all OAB subjects
	Key Secondary endpoint	CFB volume voided per micturition w12	CFB at Week 12 in average volume voided per micturition in all OAB subjects
	Exploratory endpoint	CFB daily Micturition w2	CFB at Week 2 in average number of micturitions per 24 hours in all OAB subjects
	Exploratory endpoint	CFB daily UUI_w2	CFB at Week 2 in average number of urge urinary incontinence (UUI) episodes per 24 hours in OAB Wet subjects.

Database lock	08MAR2019
Analysis description and results	Primary Analysis
Analysis population and time point description	Full Analysis Set (FAS) population: The FAS population served as the primary population for the analysis of efficacy data and was defined as all randomised OAB subjects who took at least 1 dose of double-blind study treatment and had at least 1 evaluable change from baseline micturition measurement. Subjects were included in the treatment group to which they were randomised. A separate FAS definition with an additional criterion was used to define the primary analysis population for incontinence endpoints, since incontinence endpoints only apply to subjects meeting the definition of OAB Wet at study entry. The FAS-I population was defined as all randomised OAB Wet subjects who took at least 1 dose of double-blind study treatment and had at least 1 evaluable change from the baseline UUI measurement. Subjects were included in the treatment group to which they were randomised.

Descriptive statistics and estimate variability	Treatment group	Placebo	Vibegron 75 mg	Tolterodine ER 4mg
	Number of subjects in FAS	N=520	N=526	N=417
	CFB daily Micturition w12 n	475	492	378
	Least Squares (LS) means	-1.3	-1.8	-1.6

	Standard error (SE)	0.14	0.14	0.15
	95% CI	-1.6, -1.0	-2.1, -1.5	-1.9, -1.3
Effect estimate per comparison	CFB daily Micturition w12	Comparison groups	Vibegron 75 mg vs Placebo	
		LS means difference	-0.5	
		SE	0.15	
		95% CI	-0.8, -0.2	
		MMRM P-value	<0.001	
		Comparison groups	Tolterodine ER 4mg vs Placebo	
		LS means difference	-0.3	
		SE	0.16	
		95% CI	-0.6, 0.1	
		MMRM P-value	0.0988	
Descriptive statistics and estimate variability	Treatment group	Placebo	Vibegron 75 mg	Tolterodine ER 4mg
	Number of subjects in FAS-I	N=405	N=403	N=319
	CFB daily UUI_w12 n	372	383	286
	Least Squares (LS) means	-1.4	-2.0	-1.8
	Standard error (SE)	0.13	0.13	0.14
	95% CI	-1.7, -1.2	-2.3, -1.8	-2.1, -1.5
Effect estimate per comparison	CFB daily UUI_w12	Comparison groups	Vibegron 75 mg vs Placebo	
		LS means difference	-0.6	

		SE	0.14	
		95% CI	-0.9, -0.3	
		MMRM P-value	<0.0001	
		Comparison groups	Tolterodine ER 4mg vs Placebo	
		LS means difference	-0.4	
		SE	0.15	
		95% CI	-0.7, -0.1	
		MMRM P-value	0.0123	
Analysis description	Secondary Analysis			
Analysis population and time point description	The FAS and FAS-I populations served as the population for the analysis of key secondary and exploratory efficacy data.			
Descriptive statistics and estimate variability	Treatment group	Placebo	Vibegron 75 mg	Tolterodine ER 4mg
	Number of subjects in FAS	N=520	N=526	N=417
	CFB daily Micturition w2 n	499	508	406
	Least Squares (LS) means	-0.5	-0.9	-0.8
	Standard error (SE)	0.13	0.13	0.13
	95% CI	-0.7, -0.2	-1.2, -0.7	-1.1, -0.5
Effect estimate per comparison	CFB daily Micturition w12	Comparison groups	Vibegron 75 mg vs Placebo	
		LS means difference	-0.5	
		SE	0.12	
		95% CI	-0.7, -0.2	

		MMRM P-value	<0.001	
		Comparison groups	Tolterodine ER 4mg vs Placebo	
		LS means difference	-0.3	
		SE	0.13	
		95% CI	-0.6, -0.1	
		MMRM P-value	0.0113	
Descriptive statistics and estimate variability	Treatment group	Placebo	Vibegron 75 mg	Tolterodine ER 4mg
	Number of subjects in FAS-I	N=405	N=403	N=319
	CFB daily UUI_w2 n	 391	 390	 310
	Least Squares (LS) means	-0.8	-1.4	-1.2
	Standard error (SE)	0.12	0.12	0.13
	95% CI	-1.0, -0.5	-1.6, -1.2	-1.5, -0.9
Effect estimate per comparison	CFB daily UUI_w2	Comparison groups	Vibegron 75 mg vs Placebo	
		LS means difference	-0.6	
		SE	0.12	
		95% CI	-0.9, -0.4	
		MMRM P-value	<0.0001	
		Comparison groups	Tolterodine ER 4mg vs Placebo	
		LS means difference	-0.4	
		SE	0.13	
		95% CI	-0.7, -0.2	
		MMRM P-value	<0.001	

Descriptive statistics and estimate variability	Treatment group	Placebo	Vibegron 75 mg	Tolterodine ER 4mg
	Number of subjects in FAS	N=520	N=526	N=417
	CFB daily urgency episodes_ w12 n	475	492	378
	Least Squares (LS) means	-2.0	-2.7	-2.5
	Standard error (SE)	0.19	0.19	0.21
	95% CI	-2.4, -1.7	-3.1, -2.3	-2.9, -2.

Effect estimate per comparison	CFB daily urgency episodes_ w12	Comparison groups	Vibegron 75 mg vs Placebo
		LS means difference	-0.7
		SE	0.22
		95% CI	-1.1, -0.2
		MMRM P-value	0.0020
		Comparison groups	Tolterodine ER 4mg vs Placebo
		LS means difference	-0.4
		SE	0.23
		95% CI	-0.9, 0.0
		MMRM P-value	0.0648

Descriptive statistics and estimate variability	Treatment group	Placebo	Vibegron 75 mg	Tolterodine ER 4mg
	Number of subjects on FAS-I	N=405	N=403	N=319
	75% reduction in daily UUI episodes_w12			
	Patients with at least 75% reduction in UUI (%)	36.8	52.4	47.6

Effect estimate per comparison	75% reduction in daily UUI episodes_w12	Comparison groups	Vibegron 75 mg vs Placebo
		CMH difference	16.5

		95% CI	9.7, 23.4	
		CMH P-value	<0.0001	
		Comparison groups	Tolterodine ER 4mg vs Placebo	
		LS means difference	9.4	
		95% CI	2.1, 16.7	
		CMH P-value	0.0120	
Descriptive statistics and estimate variability	Treatment group	Placebo	Vibegron 75 mg	Tolterodine ER 4mg
	Number of subjects in FAS-I	N=405	N=403	N=319
	100% reduction in daily UUI episodes_w12			
	Patients with 100% reduction in UUI (%)	22.5	28.8	26.6
Effect estimate per comparison	100% reduction in daily UUI episodes_w12	Comparison groups	Vibegron 75 mg vs Placebo	
		CMH difference	6.3	
		95% CI	0.4, 12.1	
		CMH P-value	0.0360	
		Comparison groups	Tolterodine ER 4mg vs Placebo	
		LS means difference	1.9	
		95% CI	-4.1, 7.8	
		CMH P-value	0.5447	
Descriptive statistics and estimate variability	Treatment group	Placebo	Vibegron 75 mg	Tolterodine ER 4mg
	Number of subjects in FAS	N=520	N=526	N=417
	Patients with at least 50% reduction in daily urgency episodes_w12 (%)	38.3	43.2	41.2

Effect estimate per comparison	50% reduction in daily urgency episodes_w12	Comparison groups	Vibegron 75 mg vs Placebo	
		CMH difference	6.8	
		95% CI	0.9, 12.7	
		CMH P-value	0.0235	
		Comparison groups	Tolterodine ER 4mg vs Placebo	
		LS means difference	3.7	
		95% CI	-2.5, 10.0	
		CMH P-value	0.2400	
Descriptive statistics and estimate variability	Treatment group	Placebo	Vibegron 75 mg	Tolterodine ER 4mg
	Number of subjects in FAS-I	N=405	N=403	N=319
	CFB daily total incontinence episodes w12 n	372	383	286
	Least Squares (LS) means	-1.6	-2.3	-2.0
	Standard error (SE)	0.15	0.15	0.16
	95% CI	-1.9, -1.3	-2.6, -2.0	-2.4, -1.7
Effect estimate per comparison	CFB daily total incontinence episodes w12	Comparison groups	Vibegron 75 mg vs Placebo	
		LS means difference	-0.7	
		SE	0.16	
		95% CI	-1.0, -0.4	
		MMRM P-value	<0.0001	
		Comparison groups	Toleterodine ER 4mg vs Placebo	
		LS means difference	-0.5	
		SE	0.17	
		95% CI	-0.8, -0.1	

		MMRM P-value	0.0074	
Descriptive statistics and estimate variability	Treatment group	Placebo	Vibegron 75 mg	Tolterodine ER 4mg
	Number of subjects in FAS	N=520	N=526	N=417
	CFB OAB-q LF_coping score w12 n	504	512	400
	Least Squares (LS) means	12.9	16.5	16.0
	Standard error (SE)	1.32	1.31	1.39
	95% CI	10.4, 15.5	14.0, 19.1	13.3, 18.7.
Effect estimate per comparison	CFB OAB-q LF_coping score w12	Comparison groups	Vibegron 75 mg vs Placebo	
		LS means difference	3.6	
		SE	1.24	
		95% CI	1.2, 6.0	
		MMRM P-value	0.0039	
		Comparison groups	Toleterodine ER 4mg vs Placebo	
		LS means difference	3.1	
		SE	1.32	
		95% CI	0.5, 5.7	
		MMRM P-value	0.0210	
Descriptive statistics and estimate variability	Treatment group	Placebo	Vibegron 75 mg	Tolterodine ER 4mg
	Number of subjects in FAS	N=520	N=526	N=417
	CFB volume voided per micturition w12 n	478	490	375
	Least Squares (LS) means	2.2	23.5	15.5
	Standard error (SE)	3.28	3.26	3.52

	95% CI	-4.2, 8.7	17.1, 29.9	8.6, 22.4.
Effect estimate per comparison	CFB volume voided per micturition w12	Comparison groups	Vibegron 75 mg vs Placebo	
		LS means difference	21.2	
		SE	3.52	
		95% CI	14.3, 28.1	
		MMRM P-value	<0.0001	
		Comparison groups	Tolterodine ER 4mg vs Placebo	
		LS means difference	13.3	
		SE	3.76	
		95% CI	5.9, 20.7	
		MMRM P-value	<0.001	
Notes	A total of 1515 patients were randomised and received at least 1 dose of double-blind study drug in the treatment period (540 placebo, 545 vibegron 75 mg, 430 tolterodine). Overall, there was a high completion rate, and similar percentages of patients completed the study across the treatment groups (91.8% in the vibegron 75 mg group and 90.0% in the placebo group, respectively).			

2.6.5.3. Clinical studies in special populations

There were a considerable number of elderly subjects included in the performed clinical studies with vibegron. This is shown in the following table and includes four controlled studies (n=4145) (Studies 008, 301, 3003 and 3004) and one uncontrolled study (n=169) (Study 302).

Table 27 Summary of Age Group by Type of Trial [Randomised]

	Controlled Trials (N=4145)	Non-Controlled Trials (N=169)
Age Group - n/N(%)		
<65 years	2641/4145 (63.7)	95/169 (56.2)
65-74 years	1189/4145 (28.7)	55/169 (32.5)
75-84 years	298/4145 (7.2)	17/169 (10.1)
>=85 years	17/4145 (0.4)	2/169 (1.2)

1/1
Controlled Trials: MK4618008, RVT9013003, RVT9013004 and KRP114VT301
Non-Controlled Trials: KRP114VT302
Note #1: The table includes all subjects randomised whatever the treatment group.
Note #2: Study 3004 is an extension of Study 3003. Patients who participated in both studies are counted only once in "Controlled Trials" column.
Sources: F00019_OAB - Version date: 07NOV2023 18:11 - File Name: Q104_1_c1_AgeGrTri_fas_t.rtf
Sources: Cut-off date KRP114VT301: 19OCT2016 / Cut-off date KRP114VT302: 14SEP2016 / Cut-off date MK4618008: 15NOV2013 / Cut-off date RVT9013003: 08MAR2019 / Cut-off date RVT9013004: 21AUG2019 - Dataset AD008.ADSL:10FEB2023 AD3003.ADSL:10OCT2022 AD3004.ADSL:10OCT2022 AD301.ADSL:09FEB2023 AD302.ADSL:09FEB2023 - PGM Q104_1_c1_AgeGrTri_fas_t.sas 07NOV2023 18:05

In those clinical studies, a total of 36.3% of patients in controlled trials and 43.8% of patients in uncontrolled trials) were aged ≥65 years. Overall, 7.6% of participants in controlled trials and 11.3% of participants in uncontrolled trials were aged ≥75 years.

In addition, the following table presents the number of elderly patients included in the clinical trials conducted with vibegron by treatment groups.

Table 28 Summary of Age Group by Type of Trial and by Treatment Group [Randomised]

Placebo	(N=1116)	Vibegron 50 mg (N=835)	Vibegron 75 mg (N=639)	Vibegron 100 mg (N=759)	Tolterodine ER 4 mg (N=858)
Age Group by Type of Trial - n/N(%)					
Controlled Trials					
<65 years	694/1116 (62.2)	439/666 (65.9)	356/639 (55.7)	474/708 (66.9)	540/858 (62.9)
65-74 years	320/1116 (28.7)	188/666 (28.2)	200/639 (31.3)	203/708 (28.7)	253/858 (29.5)
75-84 years	97/1116 (8.7)	39/666 (5.9)	78/639 (12.2)	29/708 (4.1)	59/858 (6.9)
>=85 years	5/1116 (0.4)	0/666 (0.0)	5/639 (0.8)	2/708 (0.3)	6/858 (0.7)
Non-Controlled Trials					
<65 years	0	95/169 (56.2)	0	31/51 (60.8)	0
65-74 years	0	55/169 (32.5)	0	15/51 (29.4)	0
75-84 years	0	17/169 (10.1)	0	5/51 (9.8)	0
>=85 years	0	2/169 (1.2)	0	0/51 (0.0)	0

1/1

Controlled Trials: MK4618008, RVT9013003, RVT9013004 and KRP114VT301
Non-Controlled Trials: KRP114VT302
Note #1: For Vibegron, only doses >= 50 mg are displayed in the table. The combinations of "Vibegron + Tolterodine ER 4 mg" are excluded from the table, as well as the "Imidafenacin" group.
Note #2: Study 3004 is an extension of Study 3003. Patients who received the same treatment in both studies are counted only once in the corresponding treatment group.
Note #3: For studies 008 and 302 including several treatment periods, patients who received different doses during each treatment period are counted in the different treatment groups, as patients who received placebo in study 3003, then active treatment in study 3004.
Sources: F00019_OAB - Version date: 10NOV2023 11:10 - File Name: Q104_2_c1_AgeGrTriTrt_fas_t.rtf
Sources: Cut-off date KRP114VT301: 19OCT2016 / Cut-off date KRP114VT302: 14SEP2016 / Cut-off date MK4618008: 15NOV2013 / Cut-off date RVT9013003: 08MAR2019 / Cut-off date RVT9013004: 21AUG2019 - Dataset AD008.ADSL:10FEB2023 AD3003.ADSL:10OCT2022 AD3004.ADSL:10OCT2022 AD301.ADSL:09FEB2023 AD302.ADSL:09FEB2023 - PGM Q104_2_c1_AgeGrTriTrt_fas_t.sas 10NOV2023 10:03

A total of 838 patients aged ≥65 years were treated with vibegron at any dose, including 283 patients treated at the proposed dose of 75 mg. The percentage of patients at baseline over 65 years of age was 42.6% and over 75 years of age was 12.1%.

Overall, among patients treated with vibegron 75 mg the dose proposed for marketing, 200 patients out of in total 639 were between 65-74 years, 78 patients were 75-84 years, and 5 patients were above 85 years of age.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

Analysis performed across trials is not considered relevant since the present application consists of one pivotal Phase 3 study, study 3003 and its extension phase, study 3004.

2.6.5.6. Supportive study(ies)

Not applicable.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical efficacy programme of vibegron consists of five clinical studies. Pivotal phase 3, double-blind, randomised, Placebo- and Active (Tolterodine)-Controlled Multicentre study RVT-901-3003 evaluated efficacy and safety of vibegron 75 mg in patients with symptoms of overactive bladder (OAB) and its extension programme, clinical study RVT-901-3004. The phase 2b dose-finding study 008 evaluated vibegron doses of 50 mg or 100 mg compared with placebo or an active comparator (tolterodine ER 4 mg). In addition, two clinical studies 301 and 302 were designed to evaluate the efficacy and safety of vibegron at doses 50-100 mg conducted in Japanese population. These studies are considered as supportive only since the doses of the vibegron were different with the dose the Applicant applied for (i.e. 75 mg).

The initially proposed indication was *symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with Overactive Bladder (OAB) syndrome.*

Non-clinical pharmacodynamic (PD) studies (*in vitro* and *in vivo*) have demonstrated vibegron to be a selective human beta-3 adrenergic receptor (β3AR) agonist. Activation of the β3AR increases bladder capacity by relaxing the detrusor smooth muscle during bladder filling.

Performed secondary PD studies are a thorough QT study, study 012 in healthy volunteers, and study 1001, an ambulatory blood pressure monitoring study. Pharmacodynamic interaction with other substances was investigated in study 010, when co-administration of vibegron with antihypertensive agents was investigated. Moreover, study 007 is a DDI study with the CYP2D6 substrate, tolterodine.

Study 008

The study was a 2-part, randomised, double-blind, placebo- and active-controlled (tolterodine ER 4 mg), parallel-group study of vibegron in men and women with OAB.

The study objectives were to investigate the 8-week efficacy and safety of increasing daily doses (3, 15, 50 and 100mg) of vibegron as monotherapy, and in combination with tolterodine 4mg in comparison with placebo. In addition, in an extension over 52 weeks, vibegron 100mg or tolterodine 4mg as monotherapies and vibegron 100mg in combination with tolterodine 4mg and placebo were studied. The dose that subsequently was chosen for MAA, 75mg, was not included in the study.

The design of the study was acceptable, part 1 being a dose ranging study over several doses. Part 2 was a separate study on efficacy and safety of the higher doses (50 and 100mg) for 4 weeks. Both studies also included a placebo arm, a tolterodine-only arm as well as a combination arm of tolterodine-vibegron 100 mg. In addition, patients from both part 1 and 2 could continue into an extension study over 52 weeks, in which those having been treated with 3 and 15 mg were assigned to 50 and 100 mg, respectively. The comparator product tolterodine, a muscarinic receptor antagonist, has extensive clinical use in OAB, is considered appropriate. Although there is another ß3-AR agonist

marketed for treatment of OAB (mirabegron), muscarinic receptor antagonists represent the golden standard of OAB treatment and therefore preferred as an active comparator product.

Eligibility criteria were adequately reflecting the target patient group for treatment of OAB. Most patients were women (almost 90%), the mean age was 58,6 years and around 80% of patients were classified as OAB wet.

Study 3003

The application contains one pivotal phase 3 study, 3003. This was a randomised, double-blind, placebo and active-controlled, multicentre study. Each subject was to participate for 12 weeks in randomised treatment with vibegron, placebo, or tolterodine followed by a 4-week safety follow-up period. At the end of the study, subjects were invited to enter the extension study 3004 with vibegron and tolterodine treatmentThe overall design with a placebo-controlled trial is considered adequate. Only descriptive statistics was used in the comparison between vibegron and tolterodine.

The protocol was amended 5 times. Most of the amendments to the study protocol were performed prior the commencement of the trial. Protocol #3 went into effect after study initiation. The most important changes were made related to the changes in secondary and exploratory efficacy endpoints. As all safety and efficacy data were blinded during the implementation of these changes, no significant impact on study results is expected.

To be eligible for the study, adult subjects (≥18 years old) should have had a history of OAB for at least 3 months prior to the screening visit. OAB was defined as urgency, with or without urge urinary incontinence, usually associated with frequency and nocturia. Urodynamic evaluation was not required. Most patients (≥ 75%) should have OAB Wet (an average of ≥ 8.0 micturitions and ≥ 1.0 UUI episodes per Diary Day), and not more than 25% should have OAB Dry (an average of ≥ 8.0 micturitions, ≥ 3.0 urgency episodes, and < 1.0 UUI episodes per Diary Day). Up to 15% of the patient enrolled could be male. The inclusion and exclusion criteria are overall found acceptable. Eligibility criteria were adequately reflecting the target patient group.

The randomisation procedure was appropriate. Eligible subjects were randomised at baseline in a 5:5:4 ratio to receive either vibegron 75 mg, placebo, or the active comparator tolterodine ER 4 mg. Randomisation was stratified based on baseline OAB category (OAB Wet or OAB Dry) and sex (female or male) with enrolment to be capped to limit the proportion of subjects meeting OAB Dry criteria (at most 25%) . Overall, 14.8% were male and 77.0% fulfilled the OAB wet criteria.

For comments on choice of comparator, please see above study 008. The study drugs were all to be taken in the morning at the subject's home, except for the first dose which was taken at study centre.

Masking of assigned treatment was achieved using double-dummy technique. All subjects were to take one tablet and one capsule once daily: active treatment or its matching placebo. No subjects were unblinded during the study.

The 75 mg dose was selected based on a Phase 2 dose-ranging study, Phase 3 studies (301 and 302) performed in Japan, PK/PD modelling and supportive nonclinical data. However, neither the Phase 2b study, nor the Japanese Phase 3 studies, did evaluate the 75 mg dose of vibegron. Doses up to 100 mg have been evaluated (studies 301 and 302). It was by the applicant estimated that a 75 mg dose will achieve approximately 90% of the efficacy of the 100 mg dose. Concerning safety, doses of vibegron up to 100 mg was well tolerated in subjects with OAB. To conclude, there are no outstanding issues on the proposed dosing. The 75 mg dose was chosen for the clinical Phase 3 programme, and its efficacy and safety in subjects with OAB is the topic of this assessment.

The primary objective was to evaluate the efficacy of vibegron compared with placebo in subjects with symptoms of OAB. The secondary objectives were to evaluate the overall efficacy of vibegron compared with placebo.

The co-primary efficacy endpoints were 1) change from baseline at Week 12 in average number of micturition's per 24 hours in all OAB subjects and 2) change from baseline at Week 12 in average number of UUI episodes per 24 hours in OAB Wet subjects. If these endpoints are met, they are considered of clinical relevance in the proposed therapeutic indication of vibegron. Additional assessments were performed at weeks 2, 4 and 8. The duration of the study could be considered short. However, the onset of efficacy of ß3-receptor agonists in OAB seems to be rapid.). Moreover, the co-primary efficacy endpoints in the development programme of another agent in the same class and indication were also evaluated at week 12 .

The choice of these endpoints was not discussed and agreed in any scientific advice. There is a "Guideline on the clinical investigation of medicinal products for the treatment of urinary incontinence" (CPMP/EWP/18/01/Rev. 1). It is stated in this guideline that if a design with two co-primary endpoints is considered, it is recommended that one of them should strongly be related to the patient perceived effect (for example QoL). In the present application, both co-primary endpoints were "objective" (e.g. number of incontinence episodes) although patient reported. Formerly, these endpoints are against the guideline but were accepted for another agent in the class and therefore can be accepted in this application as well.

Several secondary endpoints have been evaluated, and considered appropriate: seven of them being classified as key secondary efficacy endpoints which were tested sequentially. These were 1) change from baseline in average number of urgency episodes (need to urinate immediately) in all OAB subjects, 2) percent of OAB Wet subjects with at least a 75% reduction from baseline in UUI episodes, 3) percent of OAB Wet subjects with a 100% reduction from baseline in UUI episodes, 4) percent of all OAB subjects with at least a 50% reduction from baseline in urgency episodes. Moreover, 5) change from baseline in average number of total incontinence episodes in OAB Wet subject, 6) change from baseline in Coping Score from the Overactive Bladder Questionnaire Long Form (OAB-q LF, 1-week recall) in all OAB subjects, and 7) change from baseline in average volume voided per micturition in all OAB subjects were evaluated. All evaluations were performed at week 12 and covered a 24-hour period. Additional assessments were performed at weeks 2, 4 and 8. Results with the Overactive Bladder Long Form (OAB-qLF) coping score is not considered for inclusion in the SmPC section 5.1. OAB-qLF is a multiplicity adjusted secondary endpoint, however the validity of this scale is uncertain. The results are not considered clinically relevant, statistically robust, and informative for the prescriber.

Statistical considerations

The planned total sample size was 1,400 patients: 500 patients in the vibegron and placebo treatment groups, and 400 patients in the tolterodine treatment group. Power calculations were performed for both co-primary endpoints. They were based on the comparison of vibegron versus placebo alone and implied that the study was expected to have a power of 96% to reject both co-primary hypotheses. The calculations were appropriate acknowledging that no formal comparisons of vibegron versus tolterodine were planned and also that one of the co-primary endpoints was defined for the OAB Wet stratum alone expected to constitute approximately 75% of the study population (that is, approximately 337 evaluable subjects in the vibegron and placebo arm, respectively). The type I error was set to α 0.05 (2-sided) for each endpoint in line with that both were required to be positive for the study to be successful while the impact on the type II error and study power was considered.

The original SAP was finalised only shortly after enrolment of the first subject. Submitted is version 3.1 (dated 06 March 2019), i.e., before DBL (08 March 2019). Changes made have been accounted for and

raise no concerns. Formal testing of hypotheses was only planned for comparing vibegron and placebo. There was no planned interim analysis for efficacy, and none was performed.

The primary analysis population was the full analysis set (FAS) and the primary analysis model used for all change from baseline endpoints was MMRM including terms for e.g., the stratification factors used at randomisation. The difference in proportion of responders for binary (responder) endpoints have been analysed using Cochran-Mantel-Haenszel risk difference estimate.Multiplicity was handled over seven key secondary endpoints by a stepwise gate-keeping procedure. This is supported, and the use of FAS, MMRM and the CMH risk difference estimate is agreed. However, the definition of FAS is not fully endorsed; requiring at least one dose of double-blind treatment and a complete baseline diary is accepted but not the requirement that a patient to be included had to have at least one complete post-baseline diary. The proportions of subjects excluded from FAS was 3.8% (21/547): vibegron, and 3.7% (20/540): placebo. It can be argued that both minor and similar across arms, additional analyses were nonetheless requested based on a full analysis set more in line with the intention-to-treat principle, see below. Another concern is that in the MMRM analyses, missing data has been assumed to be missing at random (MAR). In the responder analyses, missing Week 12 data were handled through the use of multiple imputation (interpreted as based on an assumption of MAR). The number of subjects with missing week 12 data requiring imputation should be reported and new analyses were performed as requested for the key secondary responder endpoints, ≥75% reduction and 100% reduction, respectively, in the average daily number of UUI episodes at 12 weeks.

Based on the above, additional analyses of the co-primary and multiplicity corrected secondary change from baseline endpoints, as well as above-mentioned responder endpoints, were performed upon CHMP's request. The proportion initially excluded was both limited and balanced. Comparing the outcomes from the primary analysis with the outcomes from the additional analyses now performed for which FAS2 comprised almost all randomised subjects (>99%), only minor differences were seen confirming the statistical outcomes seen in the primary analysis.

Overall, the proportion of subjects who completed the study was approximately 90% and approximately similar, irrespective of randomised treatment. In addition, the reasons for not completing the study followed a similar pattern.

For the majority of the highest ranked endpoints, data were collected from a subject-completed diary. No information was found on diary compliance. Upon CHMP's request, summaries were provided. For change from baseline endpoints, diary compliance was sufficiently high not to raise any concern. Diary compliance for the majority of endpoints were overall approximately 80% and 85% in the placebo and vibegron treatment arm, respectively, and always higher in the vibegron than in the placebo arm. Diary data availability per clinic visit based on the number of complete diary days and the following categories "0-3", "4-5" and "6-10" showed overall that diary compliance was high with no alarming differences between arms. Regarding binary endpoints, the proportion of patients without missing data at week 12 was >90% and in line with the high proportion of subjects completing the study.

Study conduct

During the study it was discovered that 19 (unique) patients enrolled into the study multiple times at different sites. These are notated as index and non-index cases. All analysis sets removed the non-index cases, i.e., the subsequent additional instances of screening/randomisation at any site. No information has been found regarding e.g., the randomisation outcome for the index cases. In a pre-planned sensitivity analysis performed for each co-primary endpoint also excluding index cases, only 2 (placebo), 1 (vibegron) and 3 (tolterodine) additional patients were excluded from the FAS, that is, only 6 out of the reported total of 19, implying that the majority (13/19) had already been excluded due to not fulfilling FAS requirements. Although it is agreed that index cases should be included in the primary analysis, further details were requested. Upon CHMP's request, randomisation outcome in case

applicable with information on treatment compliance, diary data availability, study status and length of follow-up for both the index and non-index cases were presented. The response clarified that out of the 19 index cases, the majority (13/19) were either screening (10) or run-in (3) failures.

In addition, post-hoc sensitivity analyses of the co-primary endpoints had been performed excluding subjects randomised at two study sites: site 10-156 (US) which randomised 70 subjects and site 27-105 (PL) which randomised 8 subjects. Together they represent 5.1% out of all randomised patients (78/1518). The only explanation found in the CSR was that it was "due to potential subject data anomalies" and the Applicant was requested to clarify, see below. Concerning all subjects at a site it can be assumed that they were fairly well balanced between arms, depending eventually on the nature of suspected data anomalies. Judging from the post-hoc sensitivity analysis that implied the additional exclusion from FAS of a total of 74 (out of 78 possible): 26, 28 and 20 from the placebo, vibegron and tolterodine arm respectively, there is support that similar proportions of approximately 5% was concerned irrespective of treatment arm. Based on the sensitivity analyses outcomes their inclusion or exclusion appears to have had only minor impact on estimated differences between vibegron and placebo.

An FDA Clinical Inspection Summary had been made available and its scope covered clinical inspection of five clinical investigators (three for study 3003 and two for study 3004) in support of the New Drug Application (NDA) for Gemtesa (vibegron) 75 mg oral tablets in the treatment of OAB. The FDA Clinical Inspection Summary conclusion was that Study RVT-901-3003 and RVT-901-3004 appear to have been conducted adequately, and that the data generated by these sites and submitted by the sponsor appear acceptable. However, the applicant was requested to fill in the details regarding the circumstances which led to the performance of this post-hoc analysis and elaborate on whether the issue with potential data anomalies had been confirmed or could be denied. More details have now been provided and for each of the two sites, a "Quality issue full report" has been submitted. The nature of the data anomalies included study assessments performed at other location than the approved site and suspicious of serious non-compliance (site 27-105) and potential serious mal practise by site personnel (site 10-156). In both cases the actions taken once anomalies were discovered appear appropriate and potentially sufficient. For both the sites the applicant conclusion was that all issues had been resolved.

For the site 27-105 the quality issues may or may not have been fully resolved. However, site 27-105 randomised a total of 8 patients whereof five were included in the primary analysis, three in the Vibegron arm and two in the placebo arm. Their impact on the primary conclusion is negligible.

At the site 10-156 a total of 71 patients were randomised: vibegron: 26 patients, placebo: 27 patients and tolterodine: 18 patients. Together they constituted approximately 5% of the study population.

Site 10-156 was suspected to complete diaries on behalf of existing patients or creating fake patients in order to randomise more qualifying patients than actually existed. However, the site was audited by the sponsor with no findings substantiating that patients did not exist. For the site 10-156 the quality issues appear resolved with support also from the earlier submitted FDA Clinical Inspection Summary conclusion.

Initially, two analyses had been presented. The primary analysis including the subjects from site 27-105 and site 10-156 and the post-hoc analysis excluding the same subjects. The best way to handle data in the analyses coming from subjects recruited at sites with potential GCP issues could be discussed. The two approaches used by the applicant resulted in very similar outcomes. Together with the clarifying details and the expected minor impact on primary conclusion irrespective how these data are handled in the analysis, this potential issue is not further pursued.

Study 3004

Study 3004 was a Phase 3, double-blind, active (tolterodine)-controlled, parallel-group, multicentre, 40-week extension study to evaluate the safety, tolerability, and efficacy of vibegron 75 mg in men and women with symptoms of OAB. The study was an extension for subjects who had completed the Phase 3, double-blind, randomised, 12-week Study 3003. Given the primary study objective, the design of the study is considered adequate.

The sample size in the extension study was based on considerations what regards the collection of safety data. No formal samples size estimation was performed. This is acknowledged given the study design and that the primary objective was long-term safety and tolerability. Efficacy was a secondary objective and no formal comparisons between treatments had been planned. The fact that the number of subjects entering study 3004 was to be capped at 500 is interpreted as to pertain solely to requirements regarding the safety database.

Study RVT-901-3003 was performed under double-blind conditions achieved using double-dummy technique. It is endorsed that the extension study was to continue in a double-blind manner, however, one important difference being that all subjects will have been aware of that there was no placebo arm.

All subjects who had been randomised in Study 3003 to receive either vibegron 75 mg or tolterodine ER 4 mg continued the same treatment once daily in a blinded fashion for an additional 40 weeks. Subjects who had been randomised in Study 3003 to the placebo group were randomised 1:1 to receive blinded study treatment of vibegron 75 mg or tolterodine ER 4 mg once daily for 40 weeks during the extension. Study 3004 consisted of a randomised double-blind treatment period (40 weeks), and a safety follow-up period (4 weeks). The study was performed in the US.

Included subjects should be adult (≥18 years old) and had completed participation in study 3003. Key exclusion criteria included a change in history or current evidence of any clinically significant condition, therapy, lab abnormality, or other medical disorder during study 3003.

The key secondary efficacy endpoints were change from baseline at Week 52 in average number of micturition's in all OAB subject, change from baseline at Week 52 in average number of UUI episodes in OAB Wet subjects, change from baseline at Week 52 in average number of urgency episodes (need to urinate immediately) in all OAB subjects and change from baseline at Week 52 in average number of total urinary incontinence episodes in OAB Wet subjects. All evaluations covered a 24-hour period. Additional assessments were conducted at weeks 15, 24, and 44.

Moreover, several endpoints were related to quality of life and coping strategies. The endpoints are considered to have a clinical relevance.

There was no intention to perform any formal comparisons; all between-treatment analyses are stated to have been for descriptive purposes only. Besides primary safety endpoints, four "key" secondary efficacy endpoints had been defined. Baseline was the RVT-901-3003 baseline and only subjects on active treatment in both study 3003 and 3004 have been included in the analyses of these four efficacy endpoints. The analysis approach is similar to the approach planned and used in the primary study 3003 analysis. This is *per se* reasonable although analogous study 3003 could be questioned. However, no additional efficacy analyses are requested: without formally tested efficacy hypotheses, claims pertaining to long-term efficacy have not been accepted.

Efficacy data and additional analyses

Study 008

987 subjects with OAB were randomised to Part 1 (dose ranging study) and 408 subjects to Part 2 of study 008. Results are presented for vibegron 50mg and vibegron 100mg and for tolterodine as active comparator and placebo, whereas results from the lower doses of vibegron and the combination with tolterodine are not presented, presumably as the Applicant has decided to develop vibegron only as monotherapy at the dose 75mg.

Treatment with vibegron 50 mg or 100 mg once daily resulted in statistically significant difference versus placebo in the change from baseline (CFB) in average daily number of micturitions at Week 8 (-0.64 [-1.11, -0.18], p = 0.007, and -0.91 [-1.37, -0.44], p = 0.000 for the 2 doses, respectively). That means that after 8 weeks treatment, the average daily number of micturitions was reduced from baseline (of mean 11 micturitions) by around 2 episodes among patients on the higher dose (100mg) and slightly less in patients on the 50mg dose. Also, a modest but statistically significant reduction from baseline at Week 8 in the secondary endpoint number of urge urinary incontinence episodes was seen with both doses as well as in total urinary incontinence episodes in patients with OAB Wet.

The results from the extension study at Week 52 support that the efficacy remains after long-term treatment.

Whether the rather modest improvement could be translated into improved quality of life (QoL) is unclear. However, in QoL domain scores based on King's Health Questionnaire, treatment with vibegron (100 mg) was reported to result in numerical increases in individual sub scores relative to placebo.

Study 3003

A total of 3149 subjects were screened for study 3003. 547 subjects were randomised to the vibegron group, 540 to the placebo group, and 431 to the tolterodine group. Randomised subjects were enrolled across 199 sites in 6 countries and geographic regions, including the US, Canada, and Europe. Overall, the completion rate was high (90,3%) in all treatment groups. The most common reasons for discontinuation were withdrawal of consent and lost to follow-up.

Major protocol deviations were reported for 11% of subjects, 8.1% of subjects had a major efficacy-related protocol deviation, which excluded them from the efficacy evaluation. The protocol deviations seem to be well balanced between the study groups and are considered not too seriously.

Prohibited medications during the study were, among others, anticholinergics, beta-2 adrenergic agonists for treatment of stress urinary incontinence, synthetic diuretic hormone, and beta-3 adrenergic agonists. The prohibited medications seem adequate considering the aim of the study.

Percentage of participants who were on prior anticholinergic use and prior beta-3 agonist use in the last 12 months was 14.6% and 5.5 %, respectively. Fewer patients on vibegron had prior anticholinergic and beta-3 agonist medication compared to placebo, namely 14.6% and 4.0% vs 16.3% and 5.2% in vibegron and placebo groups, respectively.

The demographics were well balanced between the three treatment groups. 15% of subjects were male and 85% were female. Men with mild to moderate BPH without evidence of bladder obstruction as determined by the investigator were allowed to participate, but patients were required to remain on stable medication prior screening and throughout the study. The mean age was 60 years (ranging from 18 to 93). Divided by age categories, 8% of subjects were <40 years of age, 22% were 40 to <55 years, 27% were ≥55 to <65 years, 31% were ≥65 years of age <75 years, and 12% were 75 years or older. The majority (75%) of subjects were White. Thus, most of the subjects were white middle-aged or elderly females, reflecting a typical population with OAB.

Demographic and baseline characteristics for the FAS-I (OAB Wet) were like the FAS (OAB Dry). As could be expected, the number of incontinence episodes were higher in the FAS-I group. Demographic and baseline characteristics for the SAF were also like those in the FAS.

Overall, the treatment groups were well balanced with respect to age, gender, race, region, OAB type (Wet vs Dry), and prior use of anticholinergic drugs or beta-3 agonists in the last 12 months. For the subgroup of male subjects (n = 217), a slightly higher proportion of subjects in the vibegron and tolterodine treatment groups entered the study with BPH compared with subjects in the placebo group. However, given the small sample size of this subgroup, this difference is not considered clinically meaningful.

Alhtoughvidence obtained from study 3003 is based on a predominantly female population (n=1246) vs(n=217) in the male population, the effect is not expected to differ depending on gender.

The datasets analysed for the vibegron 75 mg groups included the SAF where 545 completed out of 547 patients that started treatment. The other datasets analysed were FAS (526/547), FAS-I (403/547), PPS (476/547), PPS-I (368/547) and the pharmacokinetic set (308/547).

The corresponding datasets for the tolterodine ER 4 mg groups were SAF (430/431), FAS (417/431), FAS-I (319/431), PPS (386/431), and PPS-I set (291/431).

The datasets for the placebo group were SAF (540/540), FAS (520/540), FAS-I (405/540), PPS (483/540), and PPS-I set (373/540).

Efficacy results, study 3003

Both co-primary efficacy endpoints were met at week 12 as the number of micturition's was reduced compared with baseline in all OAB subjects, as well as the number of urge urinary incontinence (UUI) episodes decreased in OAB Wet subjects, both endpoints evaluated per 24 hours. The differences between vibegron and placebo are statistically significant ($p < 0.001$) for both co-primary efficacy endpoints although the LS means difference for active – placebo was -0.5 (SE 0.15, 95% CI -0.8 to -0.2) for change in number of micturition's, and -0.6 (SE 0.14, 95% CI -0.9 to -0.3) for change in number of UUI episodes. From a numerical perspective, the differences between active and placebo are assessed as modest but of clinical relevance. The onset of clinical efficacy was rapid, with a reduction from baseline observed already after 2 weeks and maintained over the duration of the study.

The primary MMRM analysis of all change from baseline endpoints including the co-primary endpoints and 4/7 key secondary multiplicity corrected endpoints, have been performed based on the assumption of missing data being missing at random. This is an seldom appropriate assumption. Sensitivity analyses of the co-primary endpoints were planned and have been presented. They were however questioned as not being sufficiently challenging. The outcomes from the analysis using ANCOVA (FAS) and a method for multiple imputation (MI) were similar/identical to the primary analysis of the co-primary endpoints. An analysis based on ANCOVA (FAS) using last-observation-carried-forward (LOCF) implied a larger difference in favour of vibegron versus placebo compared with the primary analysis. Generally, LOCF is not endorsed as it can be assumed to rely on the reason for why data is missing and tend therefore to imply that efficacy is overestimated. Hence, additional analyses assuming MNAR were requested. Comparing the outcomes from the primary analysis with the outcomes from the additional analyses now performed, the primary analysis outcomes were confirmed. Since statistical significance was found at the 0.05 level for both co-primary endpoints, each key secondary endpoint was tested sequentially.

Statistical superiority of vibegron over placebo was demonstrated for all 7 key secondary OAB endpoints which were tested sequentially at week 12. In the SmPC section 5.1 the following three key secondary endpoints are labelled. The first key secondary endpoint is average daily number of 'need to

urinate immediately (urgency) episodes. The LS means difference (SE; 95% CI) for active – placebo was -0.7 (0.22; -1.1 to -0.2). The second key secondary endpoint labelled is sverage daily number of total incontinence episodes, the result for which was (SE; 95% CI) for active – placebo was -0.7 (0.16; -1.0 to -0.4). The third key secondary to be labelled is average volume voided (ml) per micturition. The result for this key secondary endpoint was (SE; 95% CI) for active – placebo was 21 mL (3.5; 14 to 28). Also, the key secondary endpoint, Percent of OAB Wet subjects with at least a 75% reduction from baseline in UUI episodes, and Percent of OAB Wet subjects with a 100% reduction from baseline in UUI episodes as responders have been presented in a table in SmPC section 5.1.

Daily dosing of vibegron 75 mg for 12 weeks resulted in a statistically significant increase (representing an improvement) from baseline at Week 12 in the adjusted mean OAB-q LF Coping Score (quality of life questionnaire) as compared with placebo treatment (p = 0.0039).

Considering the size of this 12-week study, the convincing results obtained which were statistically significant in favour of vibegron 75 mg, and the well-known mechanism of action, a single pivotal trial is accepted. The overall design with a placebo-controlled trial is considered adequate.

Sub-group results, study 3003

With respect to the subgroups analysed in study 3003 of the two co-primary efficacy endpoints, no impact of age, race, gender, or disease factors on the efficacy of vibegron 75 mg could be demonstrated.

Study 3004

A total of 506 subjects were screened and randomised for this study. 274 subjects were randomised to the vibegron group and 232 to the tolterodine group. The study population was enrolled from a total of 109 sites, all located in the US. The completion rate was 85%. The most common reasons for discontinuation were withdrew consent and lost to follow-up in both treatment groups. The protocol deviations were well balanced between the study groups and are considered not to seriously affect the assessment of the results.

The mean age of subjects included in study 3004 was 61 years old. 46% of the included subjects were above 65 years of age, 78% of the subjects were female and 22% were male. The demographic characteristics is considered well representative of the target population.

Demographic and baseline characteristics were well balanced across the treatment groups. Comparing baseline OAB characteristics between the FAS-Ext and the FAS-Ext-I, as expected, the latter analysis group had a higher mean number of UUI episodes and total incontinence episodes. There were no large differences in prior OAB medication.

Treatment compliance was high in both the vibegron and tolterodine treatment groups.

The datasets analysed for the vibegron 75 mg groups included the SAF-Ext where 273 completed out of 274 patients that started treatment. The other datasets analysed were FAS-Ext (266/274), FAS-Ext-I (212/274), PP-Ext (245/274), and PP-Ext-I (194/274).

The corresponding datasets for the tolterodine ER 4 mg groups were SAF-Ex (232/232), FAS-Ext (219/232), FAS-Ext-I (170/232), PP-Ext (201/232), and PP-Ext-I set (155/232).

Efficacy results, study 3004

Efficacy was evaluated as a secondary and exploratory objectives. No formal statistical analyses were pre-specified to compare treatment with vibegron versus tolterodine, and thus, all assessments between the two active treatment groups are considered descriptive only.

It can overall be concluded that the efficacy of vibegron seemed to be maintained over the 52-week period for those subject's that completed the pivotal study 3003, entered and completed study 3004. However as stated above, no efficacy claims can be made as there was no intention to perform any formal comparisons; all between-treatment analyses are descriptive only.

Clinical studies in special populations

There were a considerable number of elderly subjects included in the performed clinical studies with vibegron. The Applicant has presented the age distribution of elderly subjects in tables as requested by the CHMP.

The applicant agreed to revise the wording of the indication in SmPC 4.1 in line with the guidance *"Wording of therapeutic indication - A guide for assessors of centralised applications". The agree indication is "*Obgemsa is indicated in symptomatic treatment of adult patients with overactive bladder (OAB) syndrome."

2.6.7. Conclusions on the clinical efficacy

The overall design of the single pivotal Phase 3 study 3003 is endorsed. The efficacy of vibegron 75 mg compared with placebo was evaluated at week 12 in study 3003. Comparison with the active comparator tolterodine ER 4 mg is only descriptive.

In study 3003, both co-primary efficacy endpoints were met with statistically significant results compared with placebo. Furthermore, seven key secondary endpoints were similarly statistically significant, and thus supportive of the co-primary endpoints. A clinically relevant efficacy of vibegron has thus been demonstrated, although the efficacy is considered modest in numerical values.

The CHMP concluded that the efficacy data available supports the following indication:

Vibegron is indicated in symptomatic treatment of adult patients with overactive bladder (OAB) syndrome.

2.6.8. Clinical safety

The clinical safety data of vibegron in patients with OAB is derived from 6 clinical studies:

- 5 completed Phase 2 and 3 studies: Studies 3003, 3004, 301, 302, and 008, with the pivotal Studies 3003 and 3004 assessing the 75-mg vibegron dose and supportive Studies 301, 302, and 008 assessing vibegron doses of 50 mg and 100 mg.
- 1 Phase 1 study (Study 1001) that evaluated the effects of 75-mg vibegron once daily on BP and HR in patients with OAB at 28 days.

Assessment of safety is primarily based on the pivotal study 3003 and its 40-week extension study, study 3004, using the 75 mg dose of vibegron proposed for marketing. Studies 301, 302 and 008 are considered supportive as using different doses of vibegron and are presented as pooled data; assessment of the pooled data primarily focused on a comparison of the 100 mg dose of vibegron with the 75 mg dose.

Short-term safety data, up to 12 weeks, is derived from study 3003, with supportive data from pool 1, presenting data from studies 301 and 3003. Long-term safety data, up to 52 weeks, is derived from study 3004, with supportive data from pool 3, presenting data from studies 008, 302 and 3003/3004.

The clinical safety database providing data for safety assessment consists of 2625 patients, with 651 patients having received at least 1 dose of vibegron 75 mg and 131 patients being exposed to vibegron 75 mg for 52 weeks or more.

2.6.8.1. Patient exposure

Please refer to the tabular overview of clinical studies in clinical aspects section 2.6. for an overview of the studies contributing to exposure data.

Study 3003

Table 29. Study 3003: Subject Disposition

	Placebo (N = 540) n (%)	Vibegron 75 mg (N = 547) n (%)	Tolterodine ER 4 mg (N = 431) n (%)	Overall (N = 1518) n (%)
Randomised Patients	540 (100)	547 (100)	431 (100)	1518 (100)
Took at Least 1 Dose of Study Drug	540 (100)	545 (99.6)	430 (99.8)	1515 (99.8)
Patients Completing the Study	486 (90.0)	502 (91.8)	385 (89.3)	1373 (90.4)
Patients Discontinuing Treatment	54 (10.0)	45 (8.2)	46 (10.7)	145 (9.6)
Wthdrawal of consent	21 (3.9)	14 (2.6)	13 (3.0)	48 (3.2)
Lost to Follow-Up	14 (2.6)	15 (2.7)	10 (2.3)	39 (2.6)
AE	6 (1.1)	8 (1.5)	13 (3.0)	27 (1.8)
Other	8 (1.5)	6 (1.1)	3 (0.7)	17 (1.1)
Lack of Efficacy	3 (0.6)	0	1 (0.2)	4 (0.3)
Patient Withdrawn (Investigator's Decision)	1 (0.2)	0	3 (0.7)	4 (0.3)
Protocol Deviation	0	2 (0.4)	1 (0.2)	3 (0.2)
Patient Withdrawn (Sponsor's decision)	1 (0.2)	0	1 (0.2)	2 (0.1)
Death	0	0	1 (0.2)	1 (0.1)

Source: Study 3003 CSR Table 14.1.1.3
AE = adverse event; CSR = clinical study report; ER = extended release

Study 3004

Table 30. Study 3004: Subject Disposition

	40-Weeks Vibegron 75 mg (N = 92) n (%)	52-Weeks Vibegron 75 mg (N = 182) n (%)	Overall Vibegron 75 mg (N = 274) n (%)	40-Weeks Tolterodine ER 4 mg (N = 141) n (%)	52-Weeks Tolterodine ER 4 mg (N = 141) n (%)	Overall Tolterodine ER 4 mg (N = 232) n (%)	Overall (N = 516) n (%)
Randomised Patients	92 (100)	182 (100)	274 (100)	91 (100)	141 (100)	232 (100)	506 (100)
Dispensed Double-Blind Study Drug in Study 3004	92 (100)	182 (100)	274 (100)	91 (100)	141 (100)	232 (100)	506 (100)
Took at Least 1 Dose of Study Drug in Study 3004	92 (100)	181 (99.5)	273 (99.6)	91 (100)	141 (100)	232 (100)	505 (99.8)
Patients Completing the Study	79 (85.9)	156 (85.7)	235 (85.8)	72 (79.1)	123 (87.2)	195 (84.1)	430 (85.0)
Patients Discontinuing Treatment	13 (14.1)	26 (14.3)	39 (14.2)	19 (20.9)	18 (12.8)	37 (15.9)	76 (15.0)
Wthdrawal of consent	6 (6.5)	11 (6.0)	17 (6.2)	7 (7.7)	8 (5.7)	15 (6.5)	32 (6.3)
Lost to Follow-Up	4 (4.3)	6 (3.3)	10 (3.6)	3 (3.3)	2 (1.4)	5 (2.2)	15 (3.0)
AE	1 (1.1)	3 (1.6)	4 (1.5)	4 (4.4)	4 (2.8)	8 (3.4)	12 (2.4)
Other	1 (1.1)	3 (1.6)	4 (1.5)	4 (4.4)	1 (0.7)	5 (2.2)	9 (1.8)
Patient Withdrawn (Investigator's Decision)	0	1 (0.5)	1 (0.4)	1 (1.1)	1 (0.7)	2 (0.9)	3 (0.6)
Lack of Efficacy	0	1 (0.5)	1 (0.4)	0	1 (0.7)	1 (0.4)	2 (0.4)
Death	1 (1.1)	0	1 (0.4)	0	0	0	1 (0.2)
Patient Withdrawn (Sponsor's decision)	0	0	0	0	1 (0.7)	1 (0.4)	1 (0.2)
Protocol Deviation	0	1 (0.5)	1 (0.4)	0	0	0	1 (0.2)
Pregnancy	0	0	0	0	0	0	0

Source: Study 3004 CSR Table 14.1.1.2
AE = adverse event; CSR = clinical study report; ER = extended release

Study 3004 was an extension of study 3003, enrolling patients who completed the 12-week treatment in study 3003. Patients who had received vibegron or tolterodine continued on the same treatment for 40 weeks in study 3004; patients on placebo in study 3003 were randomised 1:1 to receive vibegron or tolterodine. Discontinuation rate in study 3004 was similar between treatment arms (vibegron vs.

tolterodine: 14.2% vs. 15.9%). The most common reasons for discontinuation were withdrawal of consent and lost to follow-up.

Extent of exposure

Pool 1 (12-week Double-blind Studies 301 and 3003)

Table 31. Pool 1 (12-week Double-blind Studies 301 and 3003): Extent of Exposure

	Placebo (N = 909)	Vibegron 75 mg (N = 545)	Tolterodine ER 4 mg (N = 430)	Vibegron 100 mg (N = 369)
Duration of Treatment (weeks)				
Mean (SD)	11.5 (1.90)	11.6 (2.27)	11.4 (2.31)	11.7 (1.61)
Median (Q1, Q3)	12.0 (11.7, 12.1)	12.0 (11.9, 12.1)	12.0 (11.9, 12.1)	12.0 (11.6, 12.1)
Min, Max	0.1, 16.1	0.1, 17.7	0.1, 14.9	0.3, 13.0
Any Duration (>0 weeks), n (%)	909 (100)	545 (100)	430 (100)	369 (100)
≥ 4 weeks, n (%)	892 (98.1)	529 (97.1)	414 (96.3)	364 (98.6)
≥ 8 weeks, n (%)	864 (95.0)	515 (94.5)	401 (93.3)	358 (97.0)
≥ 12 weeks, n (%)	579 (63.7)	390 (71.6)	299 (69.5)	234 (63.4)
≥ 24 weeks, n (%)	0	0	0	0

Source: ISS Table 2.1a
ER = extended release; ISS = integrated summary of safety; Max = maximum; Min = minimum; Q1 = first interquartile; Q3 = third interquartile; SD = standard deviation

Pool 3 (Long-term Studies 008 Base and Extension, 302, 3004)

Table 32. Pool 3 (Long-term Studies 008 Base and Extension, 302, 3004): Extent of Exposure

	Vibegron 75 mg (N = 273) n (%)	Tolterodine ER 4 mg (N = 472) n (%)	Vibegron 100 mg (N = 299) n (%)	Vibegron 75 + 100 mg (N = 572) n (%)
Duration of Treatment (weeks)				
Mean (SD)	44.7 (11.13)	46.0 (14.27)	47.0 (14.95)	45.9 (13.31)
Median (Q1, Q3)	51.9 (40.0, 52.1)	52.0 (40.1, 54.8)	52.6 (43.3, 57.0)	52.0 (40.1, 53.1)
Min, Max	3.4, 55.1	0.1, 68.0	0.3, 63.9	0.3, 63.9
Any Duration (>0 weeks), n (%)	273 (100)	472 (100)	299 (100)	572 (100)
≥ 4 weeks, n (%)	272 (99.6)	465 (98.5)	297 (99.3)	569 (99.5)
≥ 8 weeks, n (%)	269 (98.5)	457 (96.8)	293 (98.0)	562 (98.3)
≥ 12 weeks, n (%)	267 (97.8)	449 (95.1)	288 (96.3)	555 (97.0)
≥ 24 weeks, n (%)	252 (92.3)	422 (89.4)	261 (87.3)	513 (89.7)
≥ 48 weeks, n (%)	158 (57.9)	310 (65.7)	188 (62.9)	346 (60.5)
≥ 52 weeks, n (%)	131 (48.0)	265 (56.1)	174 (58.2)	305 (53.3)

Source: ISS Table 2.1c
ER = extended release; ISS = integrated summary of safety; Max = maximum; Min = minimum; Q1 = first interquartile; Q3 = third interquartile; SD = standard deviation

Median treatment duration was identical across the treatment groups in studies 3003 (12 weeks) and 3004 (40 or 52 weeks) as well as in pools 1 and 3.

2.6.8.2. Adverse events

Study 3003

Table 33. Study 3003: Overall Summary of Adverse Events – SAF

Category	Placebo N = 540 n (%)	Vibegron 75 mg N = 545 n (%)	Tolterodine ER 4 mg N = 430 n (%)
Any AE	180 (33.3)	211 (38.7)	166 (38.6)
Any study drug-related AE	56 (10.4)	73 (13.4)	68 (15.8)
Any Grade ≥ 3 AE	8 (1.5)	6 (1.1)	9 (2.1)
Any Grade ≥ 3 study drug-related AE	3 (0.6)	1 (0.2)	2 (0.5)
Any SAE	6 (1.1)	8 (1.5)	10 (2.3)
Any study drug-related SAE	0	2 (0.4)	0
Any fatal AE	0	0	1 (0.2)
Any AE leading to discontinuation of study drug	6 (1.1)	9 (1.7)	14 (3.3)
Any AECI	40 (7.4)	36 (6.6)	38 (8.8)
Any study drug-related AECI	11 (2.0)	7 (1.3)	11 (2.6)

Source: Study 3003 CSR, Table 14.3.1.1
AE = adverse event; AECI = adverse event of clinical interest; CSR = clinical study report; eCRF= electronic case report form; ER = extended release; SAE = serious adverse event; SAF = safety population
Notes: If severity was missing, then severity was derived as severe (Grade 3).
If relationship to study drug for an AE was missing, then the relationship was derived as study drug related.
AECIs were those marked by the Investigator on the eCRF as an AECI.

Study 3004

Table 34. Study 3004: Overall Summary of Adverse Events – SAF-Ext

Category	Overall Vibegron 75 mg (N=273) n (%)	Overall Tolterodine ER 4 mg (N=232) n (%)
Any AE	171 (62.6)	126 (54.3)
Any study drug-related AE	59 (21.6)	46 (19.8)
Any Grade ≥ 3 AE	10 (3.7)	8 (3.4)
Any Grade ≥ 3 study drug-related AE	1 (0.4)	1 (0.4)
Any SAE	9 (3.3)	10 (4.3)
Any study drug-related SAE	1 (0.4)	2 (0.9)
Any fatal SAE	1 (0.4)	0
Any AE leading to discontinuation of study drug	4 (1.5)	8 (3.4)
Any AECI	41 (15.0)	32 (13.8)
Any study drug-related AECI	14 (5.1)	10 (4.3)

Source: Study 3004 CSR, Table 14.3.1.1
AE = adverse event; AECI = adverse event of clinical interest; eCRF= electronic case report form; ER = extended release; SAE = serious adverse event; SAF-Ext = safety population extension
Notes: Overall vibegron 75 mg includes patients who received 52-weeks and 40-weeks vibegron 75 mg and overall tolterodine ER 4 mg includes patients who received 52-weeks and 40-weeks tolterodine ER 4 mg.
If severity was missing, then severity was derived as severe (Grade 3).
If relationship to study drug for an AE was missing, then the relationship to study drug was derived as study drug-related.
AECIs were those marked by the Investigator on the eCRF as an AECI.

The general AE profile of vibegron 100 mg was similar to placebo for the 12-week pooled data; for the long-term pooled data no relevant differences in AE profile were observed between both doses of vibegron.

Common adverse events

Study 3003

Table 35. Study 3003: Adverse Events Reported in ≥2% of Patients Receiving Vibegron 75 mg – SAF

PT	Placebo N = 540 n (%)	Vibegron 75 mg N = 545 n (%)	Tolterodine ER 4 mg N = 430 n (%)
Any AE	**180 (33.3)**	**211 (38.7)**	**166 (38.6)**
Urinary tract infection	33 (6.1)	27 (5.0)	25 (5.8)
Headache	13 (2.4)	22 (4.0)	11 (2.6)
Nasopharyngitis	9 (1.7)	15 (2.8)	11 (2.6)
Diarrhoea	6 (1.1)	12 (2.2)	9 (2.1)
Nausea	6 (1.1)	12 (2.2)	5 (1.2)
Upper respiratory tract infection	4 (0.7)	11 (2.0)	2 (0.5)

Source: Study 3003 CSR, Table 14.3.1.14
AE = adverse event; ER = extended release; PT = preferred term; SAF = safety set
Notes: Descriptions of AEs are coded using Medical Dictionary for Regulatory Activities version 20.1.
Presented frequencies and the denominator used for percentages are based on patients in the SAF and the actual treatment received.
Patients with multiple AEs within the same PT are only counted once within the respective category.

Study 3004

Table 36. Study 3004: Adverse Events Reported in ≥2% of Patients Receiving Vibegron 75 mg – SAF-Ext

PT	Vibegron 75 mg N = 273 n (%)	Tolterodine ER 4 mg N = 232 n (%)
Any AE	**171 (62.6)**	**126 (54.3)**
Hypertension	24 (8.8)	20 (8.6)
Urinary tract infection	18 (6.6)	17 (7.3)
Headache	15 (5.5)	9 (3.9)
Nasopharyngitis	13 (4.8)	12 (5.2)
Diarrhoea	13 (4.8)	4 (1.7)
Upper respiratory tract infection	10 (3.7)	1 (0.4)
Constipation	10 (3.7)	6 (2.6)
Nausea	10 (3.7)	7 (3.0)
Bronchitis	8 (2.9)	3 (1.3)
Anaemia	7 (2.6)	2 (0.9)
Residual urine volume increased	7 (2.6)	3 (1.3)
Hyperglycaemia	7 (2.6)	2 (0.9)
Back pain	6 (2.2)	3 (1.3)
Musculoskeletal pain	6 (2.2)	1 (0.4)

Source: Study 3004 CSR, Table 14.3.1.13
AE = adverse event; ER = extended release; PT = preferred term; SAF-Ext = safety population extension; SOC = system organ class
Notes: Includes cumulative data from Study 3003 for patients who received vibegron or tolterodine in Study 3003.
Overall vibegron 75 mg includes patients who received 52-weeks and 40-weeks vibegron 75 mg and overall tolterodine ER 4 mg includes patients who received 52-weeks and 40-weeks tolterodine ER 4 mg. Only data for patients on active treatment were included.
Descriptions of AEs are coded using Medical Dictionary for Regulatory Activities version 20.1.
Presented frequencies and the denominator used for percentages are based on patients in the SAF-Ext and the actual treatment received.
Patients with multiple AEs within the same SOC and/or PT are only counted once within the respective category.

Pool 1 (12-week Double-blind Studies 301 and 3003)

Table 37. Pool 1 (12-week Double-blind Studies 301 and 3003): Adverse Events Reported in ≥2% of Patients Receiving Vibegron 75 mg and With Higher Patient Incidence Than Placebo

PT	Placebo (N = 909) n (%)	Vibegron 75 mg (N = 545) n (%)	Tolterodine ER 4 mg (N = 430) n (%)	Vibegron 100 mg (N = 369) n (%)
Any AE Occurring in ≥ 2% of the Vibegron 75 mg Arm and More than Placebo Arm	**61 (6.7)**	**76 (13.9)**	**48 (11.2)**	**3 (0.8)**
Urinary tract infection	33 (3.6)	27 (5.0)	25 (5.8)	0
Headache	13 (1.4)	22 (4.0)	11 (2.6)	1 (0.3)
Diarrhoea	10 (1.1)	12 (2.2)	9 (2.1)	2 (0.5)
Nausea	6 (0.7)	12 (2.2)	5 (1.2)	0
Upper respiratory tract infection	4 (0.4)	11 (2.0)	2 (0.5)	0

Source: ISS Table 2.12a
AE = adverse event; ER = extended release; ISS = integrated summary of safety; PT = preferred term; SOC = system organ class
Notes: AEs are coded to SOC and PT using Medical Dictionary for Regulatory Activities coding dictionary version 21.1.
Patient is counted only once in each PT.

Pool 3 (Long-term Exposure Studies: 008, 302, 3004)

Table 38. Pool 3 (Long-term Studies 008 Base and Extension, 302, 3004): Adverse Events Reported in ≥2% of Patients Receiving Vibegron 75 mg

PT	Vibegron 75 mg (N = 273) n (%)	Tolterodine ER 4 mg (N = 472) n (%)	Vibegron 100 mg (N = 299) n (%)	Vibegron 75 + 100 mg (N = 572) n (%)
Any AE Occurring in ≥2% of the Vibegron 75 mg Arm	**115 (42.1)**	**177 (37.5)**	**111 (37.1)**	**226 (39.5)**
Hypertension	24 (8.8)	23 (4.9)	6 (2.0)	30 (5.2)
Urinary tract infection	18 (6.6)	51 (10.8)	25 (8.4)	43 (7.5)
Headache	15 (5.5)	20 (4.2)	12 (4.0)	27 (4.7)
Diarrhoea	13 (4.8)	18 (3.8)	14 (4.7)	27 (4.7)
Nasopharyngitis	13 (4.8)	33 (7.0)	33 (11.0)	46 (8.0)
Upper respiratory tract infection	11 (4.0)	13 (2.8)	17 (5.7)	28 (4.9)
Constipation	10 (3.7)	19 (4.0)	10 (3.3)	20 (3.5)
Nausea	10 (3.7)	21 (4.4)	8 (2.7)	18 (3.1)
Bronchitis	8 (2.9)	8 (1.7)	9 (3.0)	17 (3.0)
Anaemia	7 (2.6)	5 (1.1)	0	7 (1.2)
Hyperglycaemia	7 (2.6)	3 (0.6)	2 (0.7)	9 (1.6)
Residual urine volume increased	7 (2.6)	3 (0.6)	0	7 (1.2)
Back pain	6 (2.2)	13 (2.8)	8 (2.7)	14 (2.4)
Musculoskeletal pain	6 (2.2)	5 (1.1)	3 (1.0)	9 (1.6)

Source: ISS Table 2.12c
AE = adverse event; ER = extended release; ISS = integrated summary of safety; PT = preferred term; SOC = system organ class
Notes: AEs are coded to SOC and PT using Medical Dictionary for Regulatory Activities coding dictionary version 21.1.
Patient is counted only once in each PT.

The most commonly reported AEs with vibegron (≥4%) were urinary tract infection and headache in study 3003 and hypertension, urinary tract infection, headache, nasopharyngitis and diarrhoea in study 3004. Most AEs were mild or moderate in severity in both studies. In study 3003, severe AEs were reported in 1.1% of patients with vibegron and with a similar incidence as in the placebo and tolterodine arms (1.5% and 1.9%, respectively). In study 3004, severe AEs were reported at similar frequency in both study arms (vibegron vs. tolterodine: 3.3% vs. 3.0%). One death was reported with vibegron.

In both pooled analyses, AEs in the 100 mg vibegron arm were reported at a lower or similar frequency compared with vibegron 75 mg, except for nasopharyngitis in pool 3 (100 mg vs. 75 mg: 11.0% vs. 4.8%).

Adverse reactions

In Study 3003, ADRs were derived based on either of the following criteria:

An AE reported in ≥2% of patients receiving vibegron 75 mg with:
- at least 1% higher patient incidence compared with placebo.
- a pharmacologic rationale for being an ADR.
- medical importance.

An AE reported in <2% of patients receiving vibegron 75 mg with:
- occurrence in at least 2 patients receiving vibegron 75 mg.
- higher patient incidence compared with placebo.

- pharmacologic rationale for being an ADR.
- medical importance.

In Study 3004, AEs were considered potential ADRs if they met the following criteria:

- Reported in ≥2% of patients receiving vibegron 75 mg.
- Pharmacologic rationale for being an ADR.
- Medical importance.

The criteria for identification of potential ADRs are acceptable.

The frequencies for the AEs proposed as ADR, estimated based on the totality of patients treated with vibegron in both studies 3003 and 3004, are presented in the table below.

Table 39. Adverse Drug Reactions by System Organ Class and Preferred Term in Studies 3003 and 3004 [Safety Population]

	Study 3003			Study 3004		Pool of studies 3003/3004
System Organ Class Preferred Term	Placebo (N= 540) n(%)	Vibegron 75 mg (N= 545) n(%)	Tolterodine ER 4 mg (N= 430) n(%)	Overall* Vibegron 75 mg (N= 273) n(%)	Overall* Tolterodine ER 4 mg (N= 232) n(%)	Vibegron 75 mg All Exposure (N= 637) n(%)
Any Adverse Drug Reaction	66 (12.2)	90 (16.5)	59 (13.7)	71 (26.0)	44 (19.0)	137 (21.5)
Gastrointestinal disorders						
Diarrhoea	6 (1.1)	12 (2.2)	9 (2.1)	13 (4.8)	4 (1.7)	20 (3.1)
Nausea	6 (1.1)	12 (2.2)	5 (1.2)	10 (3.7)	7 (3.0)	19 (3.0)
Constipation	7 (1.3)	9 (1.7)	6 (1.4)	10 (3.7)	6 (2.6)	14 (2.2)
Infections and infestations						
Urinary tract infection	33 (6.1)	27 (5.0)	25 (5.8)	18 (6.6)	17 (7.3)	42 (6.6)
Nervous system disorders						
Headache	13 (2.4)	22 (4.0)	11 (2.6)	15 (5.5)	9 (3.9)	32 (5.0)
Investigations						
Residual urine volume increased	2 (0.4)	4 (0.7)	6 (1.4)	7 (2.6)	3 (1.3)	9 (1.4)
Skin and subcutaneous tissue disorders						
Rash	4 (0.7)	4 (0.7)	1 (0.2)	4 (1.5)	2 (0.9)	6 (0.9)
Vascular disorders						
Hot flush	2 (0.4)	4 (0.7)	1 (0.2)	0	1 (0.4)	4 (0.6)
Renal and urinary disorders						
Urinary retention	2 (0.4)	3 (0.6)	3 (0.7)	3 (1.1)	1 (0.4)	5 (0.8)

* This includes "40-weeks" and "52-weeks" treatment groups.
N = Number of participants
MedDRA Dictionary Version 21.1 is used.
A participant with more than one occurrence of the same adverse event in a particular Preferred Term (PT) is counted only once in the total of those experiencing adverse events in that particular PT.
Terms are sorted in descending frequency for SOCs and PTs according to Vibegron 75mg in study 3003.
Note 1: Any ADR observed in both 3003 study and 3004 study for a same patient is counted once.
Sources: F00019_OAB - Version date: 01MAR2024 17:18 - File Name: Q023_01_p1_ADRSOCPT_saf_t.rtf
Sources: Cut-off date DOSSIER_PF: 21JUN2022 - Dataset ADSP1.ADADR:24APR2023 ADSP1.ADSL:24APR2023 - PGM Q023_01_p1_ADRSOCPT_saf_t.sas 01MAR2024 17:07

Urinary retention

In study 3003, residual urine volume increased was reported as an AE at a higher frequency with vibegron 75mg (0.7%) compared with placebo (0.4%); frequencies for urinary retention in study 3003 were (vibegron vs. placebo): 0.6% vs. 0.4%.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

Study 3003

One 75-year-old female patient receiving tolterodine died 62 days after initiating study drug. The patient had fatal AEs of urinary tract infection, sepsis, and cerebrovascular accident around the time of the death, none of which were considered related to study drug by the Investigator. The main cause of death was assessed as cerebrovascular accident.

Study 3004

One 63-year-old female patient receiving vibegron 75 mg died 102 days after initiating study drug. The death was attributed to the fatal AE of arteriosclerosis. The patient was enrolled in the 40-week vibegron group after receiving placebo in Study 3003. No relevant medical history or other AEs were reported. Throughout the study, the patient had normal vital signs and was not taking any concomitant medications. The death certificate listed arteriosclerotic disease as the cause of death, and no autopsy was performed. The death was considered unrelated to study treatment by the Investigator and the Sponsor.

Study 302

One 69-year-old female patient receiving vibegron 50 mg died approximately 29 days after initiating study drug. The death was attributed to cervical spinal cord injury resulting from a fall. The patient had been drinking alcohol on the day of the death, and the fall was considered an accident. The Investigator considered the event unrelated to study drug.

Other serious events

Study 3003

SAEs were reported at similar frequency across study arms (placebo vs. vibegron vs. tolterodine: 1.1% vs. 1.5% vs. 2.3%). Individual SAEs were reported in 1 patient only in each of the treatment arms; no cluster or pattern of SAEs was noted.

In 2 patients receiving vibegron, SAEs (pneumonia and non-cardiac chest pain) were assessed as related by the investigator and as unrelated by the sponsor, for the following reasons. The SAE of pneumonia in an 85-year-old male patient was reported with a time to onset of 36 days. The sponsor assessed the event as unrelated considering the presence of risk factors for pneumonia including advanced age (85) and gastroesophageal reflux disease treated with a proton pump inhibitor (omeprazole); in addition, pneumonia responded promptly to antibiotics. The SAE of non-cardiac chest pain was reported in a 75-year-old female patient, with a time to onset of 29 days. The cardiovascular workup was reported as negative. The sponsor considered the non-cardiac chest pain not related to study drug, noting the multiple reports of chest, back and arm pain for the prior two weeks and the presence of degenerative changes on chest X-ray. The causality assessment is agreed in both cases.

Study 3004

SAEs were reported at similar frequency across study arms (vibegron vs. tolterodine: 3.3% vs. 4.3%). Individual SAEs were reported in 1 patient only in each of the treatment arms; no cluster or pattern of SAEs was noted.

In 3 patients, SAEs were assessed as related to study drug by the investigator, including one SAE of colitis microscopic in a 49-year-old female patient receiving vibegron. The sponsor assessed this event as not related to vibegron based on confounding concomitant medications (sertraline, ranitidine and ibuprofen); the sponsor's causality assessment is agreed.

Pool 1 (12-week Double-blind Studies 301 and 3003)

In Pool 1, the patient incidence of SAEs was low across all treatment groups (1.0% placebo, 1.5% vibegron 75 mg, 2.3% tolterodine, 0.3% vibegron 100 mg). SAEs reported in >1 patient were cerebrovascular accident, which was reported in 1 patient receiving vibegron 75 mg and 1 patient receiving tolterodine, and pneumonia, which was reported in 1 patient receiving placebo and 1 patient receiving vibegron 75 mg. In addition to cerebrovascular accident and pneumonia, SAEs reported in the vibegron 75 mg treatment group were abdominal pain, appendix disorder, atrial fibrillation, cardiac failure congestive, colitis, colorectal adenocarcinoma, non-cardiac chest pain, and pleural effusion (all reported in 1 patient [0.2%] each).

Two patients, both in the vibegron 75 mg group, had SAEs (non-cardiac chest pain and pneumonia, respectively) that were considered related to study treatment by the Investigator. Neither was considered study drug-related per the Sponsor's assessment, and both events resolved.

Pool 3 (Long-term Exposure Studies: 008, 302, 3004)

In Pool 3, 9 patients (3.3%) receiving vibegron 75 mg, 29 patients (6.1%) receiving tolterodine, and 8 patients (2.7%) receiving vibegron 100 mg had SAEs. SAEs reported in >1 patient overall were appendicitis, breast cancer, chest pain, and pneumonia. SAEs reported in the vibegron 75-mg group were angina unstable, appendicitis, arteriosclerosis, breast cancer, chest pain, colitis, colitis microscopic, pelvic fracture, and urosepsis (all reported in 1 patient [0.4%] each). One patient (0.4%) in the vibegron 75-mg group and 3 patients (0.6%) in the tolterodine group had SAEs that were considered related to study treatment by the Investigator: colitis microscopic in the vibegron 75 mg group and cardiac failure, ileus paralytic, syncope in the tolterodine group.

Adverse events of clinical interest

Study 3003 and 3004

Table 40. Adverse Events of Clinical Interest by Category and Preferred Term as defined in the ISS database, in Studies 3003 and 3004 [Safety Population]

	Study 3003			Study 3004	
AECI Preferred Term	**Placebo (N= 540) n(%)**	**Vibegron 75 mg (N= 545) n(%)**	**Tolterodine ER 4 mg (N= 430) n(%)**	**Overall* Vibegron 75 mg (N= 273) n(%)**	**Overall* Tolterodine ER 4 mg (N= 232) n(%)**
Any Treatment Emergent AECI	61 (11.3)	44 (8.1)	52 (12.1)	47 (17.2)	41 (17.7)
Cystitis or Urinary Tract Infection	37 (6.9)	28 (5.1)	28 (6.5)	20 (7.3)	17 (7.3)
Costovertebral angle tenderness	1 (0.2)	0	0	0	0
Cystitis	1 (0.2)	1 (0.2)	1 (0.2)	0	0
Dysuria	3 (0.6)	0	0	2 (0.7)	0
Escherichia urinary tract infection	0	0	1 (0.2)	0	0
Kidney infection	0	0	1 (0.2)	0	0
Urinary tract infection	33 (6.1)	27 (5.0)	25 (5.8)	18 (6.6)	17 (7.3)
Urosepsis	0	0	0	1 (0.4)	0
Elevated AST or ALT	3 (0.6)	2 (0.4)	3 (0.7)	3 (1.1)	1 (0.4)
Alanine aminotransferase increased	2 (0.4)	1 (0.2)	1 (0.2)	2 (0.7)	0
Aspartate aminotransferase increased	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.7)	0
Blood bilirubin increased	0	0	1 (0.2)	0	0
Hepatic enzyme increased	1 (0.2)	0	1 (0.2)	0	1 (0.4)
Transaminases increased	0	1 (0.2)	0	1 (0.4)	0
Hypertension	14 (2.6)	12 (2.2)	20 (4.7)	25 (9.2)	23 (9.9)
Blood pressure diastolic increased	0	0	1 (0.2)	0	0
Blood pressure increased	5 (0.9)	4 (0.7)	8 (1.9)	2 (0.7)	4 (1.7)
Hypertension	9 (1.7)	9 (1.7)	11 (2.6)	24 (8.8)	20 (8.6)
MACCE	3 (0.6)	3 (0.6)	1 (0.2)	2 (0.7)	3 (1.3)
Angina pectoris	0	0	0	1 (0.4)	0
Angina unstable	0	0	0	1 (0.4)	0
Cardiac failure	0	0	0	0	1 (0.4)
Cardiac failure congestive	0	1 (0.2)	0	0	0
Cerebrovascular accident	0	1 (0.2)	1 (0.2)	0	0
Chest pain	3 (0.6)	0	0	1 (0.4)	2 (0.9)
Ejection fraction decreased	1 (0.2)	0	0	0	0
Vertebrobasilar insufficiency	0	1 (0.2)	0	0	0

	Study 3003			Study 3004	
AECI Preferred Term	**Placebo (N= 540) n(%)**	**Vibegron 75 mg (N= 545) n(%)**	**Tolterodine ER 4 mg (N= 430) n(%)**	**Overall* Vibegron 75 mg (N= 273) n(%)**	**Overall* Tolterodine ER 4 mg (N= 232) n(%)**
Orthostatic hypotension	8 (1.5)	5 (0.9)	4 (0.9)	4 (1.5)	3 (1.3)
Dizziness	6 (1.1)	5 (0.9)	4 (0.9)	4 (1.5)	2 (0.9)
Syncope	2 (0.4)	0	1 (0.2)	0	1 (0.4)

** This includes "40-weeks" and "52-weeks" treatment groups.*
AECI = Adverse Event of Clinical Interest
N = Number of participants
MedDRA Dictionary Version 21.1 is used.
A participant with more than one occurrence of the same adverse event in a particular Category or Preferred Term (PT) is counted only once in the total of those experiencing adverse events in that particular Category or PT.
Terms are sorted alphabetically for Category and PT.
Sources: F00019_OAB - Version date: 06OCT2023 10:46 - File Name: Q112_1_c1_AECICatPT_saf_t.rtf

Sources: Cut-off date DOSSIER_PF: 21JUN2022 - Dataset ADSP1.ADAE:24APR2023 ADSP1.ADSL:24APR2023 - PGM Q112_1_c1_AECICatPT_saf_t.sas 05OCT2023 15:32

Pool 1 (12-week Double-blind Studies 301 and 3003) and Pool 3 (Long-term Exposure Studies: 008, 302, 3004)

Table 41. Adverse Events of Clinical Interest by Category and Preferred Term as defined in the ISS database, in Pool 1 and Pool 3 [Safety Population]

	Pool 1				Pool 3			
AECI Preferred Term	**Placebo (N= 909) n(%)**	**Vibegron 75 mg (N= 545) n(%)**	**Tolterodine ER 4 mg (N= 430) n(%)**	**Vibegron 100 mg (N= 369) n(%)**	**Vibegron 75 mg (N= 273) n(%)**	**Tolterodine ER 4 mg (N= 472) n(%)**	**Vibegron 100 mg (N= 299) n(%)**	**Vibegron 75mg and 100 mg (N= 572) n(%)**
Any Treatment Emergent AECI	70 (7.7)	44 (8.1)	52 (12.1)	20 (5.4)	47 (17.2)	96 (20.3)	49 (16.4)	96 (16.8)
Cystitis or Urinary Tract Infection	41 (4.5)	28 (5.1)	28 (6.5)	10 (2.7)	20 (7.3)	56 (11.9)	31 (10.4)	51 (8.9)
Costovertebral angle tenderness	1 (0.1)	0	0	0	0	0	0	0
Cystitis	4 (0.4)	1 (0.2)	1 (0.2)	8 (2.2)	0	1 (0.2)	5 (1.7)	5 (0.9)
Dysuria	3 (0.3)	0	0	0	2 (0.7)	3 (0.6)	0	2 (0.3)
Escherichia urinary tract infection	0	0	1 (0.2)	0	0	0	1 (0.3)	1 (0.2)
Kidney infection	0	0	1 (0.2)	0	0	0	0	0
Pyelonephritis	0	0	0	1 (0.3)	0	0	0	0
Urethritis	0	0	0	0	0	1 (0.2)	0	0
Urinary tract infection	33 (3.6)	27 (5.0)	25 (5.8)	0	18 (6.6)	51 (10.8)	25 (8.4)	43 (7.5)
Urosepsis	0	0	0	0	1 (0.4)	0	0	1 (0.2)
White blood cells urine positive	1 (0.1)	0	0	1 (0.3)	0	2 (0.4)	0	0
Elevated AST or ALT	5 (0.6)	2 (0.4)	3 (0.7)	5 (1.4)	3 (1.1)	6 (1.3)	1 (0.3)	4 (0.7)
Alanine aminotransferase increased	2 (0.2)	1 (0.2)	1 (0.2)	0	2 (0.7)	2 (0.4)	0	2 (0.3)
Aspartate aminotransferase increased	1 (0.1)	1 (0.2)	1 (0.2)	0	2 (0.7)	2 (0.4)	1 (0.3)	3 (0.5)
Blood bilirubin increased	1 (0.1)	0	1 (0.2)	0	0	0	0	0
Drug-induced liver injury	0	0	0	0	0	1 (0.2)	0	0
Gamma-glutamyltransferase increased	1 (0.1)	0	0	2 (0.5)	0	0	0	0
Hepatic enzyme increased	1 (0.1)	0	1 (0.2)	0	0	1 (0.2)	0	0
Hepatic function abnormal	0	0	0	2 (0.5)	0	0	0	0
Hepatic steatosis	0	0	0	0	0	1 (0.2)	0	0
Liver function test abnormal	0	0	0	1 (0.3)	0	0	0	0
Liver function test increased	0	0	0	0	0	1 (0.2)	0	0
Transaminases increased	0	1 (0.2)	0	0	1 (0.4)	0	0	1 (0.2)
Hypertension	15 (1.7)	12 (2.2)	20 (4.7)	4 (1.1)	25 (9.2)	28 (5.9)	7 (2.3)	32 (5.6)
Blood pressure diastolic increased	0	0	1 (0.2)	0	0	0	0	0
Blood pressure increased	5 (0.6)	4 (0.7)	8 (1.9)	3 (0.8)	2 (0.7)	6 (1.3)	1 (0.3)	3 (0.5)
Hypertension	10 (1.1)	9 (1.7)	11 (2.6)	1 (0.3)	24 (8.8)	23 (4.9)	6 (2.0)	30 (5.2)

	Pool 1				Pool 3			
AECI Preferred Term	**Placebo (N= 909) n(%)**	**Vibegron 75 mg (N= 545) n(%)**	**Tolterodine ER 4 mg (N= 430) n(%)**	**Vibegron 100 mg (N= 369) n(%)**	**Vibegron 75 mg (N= 273) n(%)**	**Tolterodine ER 4 mg (N= 472) n(%)**	**Vibegron 100 mg (N= 299) n(%)**	**Vibegron 75mg and 100 mg (N= 572) n(%)**
MACCE	3 (0.3)	3 (0.6)	1 (0.2)	0	2 (0.7)	5 (1.1)	5 (1.7)	7 (1.2)
Angina pectoris	0	0	0	0	1 (0.4)	0	0	1 (0.2)
Angina unstable	0	0	0	0	1 (0.4)	0	0	1 (0.2)
Cardiac failure	0	0	0	0	0	1 (0.2)	0	0
Cardiac failure congestive	0	1 (0.2)	0	0	0	0	0	0
Cerebral haematoma	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Cerebrovascular accident	0	1 (0.2)	1 (0.2)	0	0	0	0	0
Cerebrovascular disorder	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Chest pain	3 (0.3)	0	0	0	1 (0.4)	4 (0.8)	2 (0.7)	3 (0.5)
Ejection fraction decreased	1 (0.1)	0	0	0	0	0	0	0
Myocardial ischaemia	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Vertebrobasilar insufficiency	0	1 (0.2)	0	0	0	0	0	0
Orthostatic hypotension	11 (1.2)	5 (0.9)	4 (0.9)	1 (0.3)	4 (1.5)	15 (3.2)	7 (2.3)	11 (1.9)
Dizziness	9 (1.0)	5 (0.9)	4 (0.9)	1 (0.3)	4 (1.5)	12 (2.5)	6 (2.0)	10 (1.7)
Dizziness exertional	0	0	0	0	0	2 (0.4)	0	0
Orthostatic hypotension	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Syncope	2 (0.2)	0	1 (0.2)	0	0	1 (0.2)	0	0

AECI = Adverse Event of Clinical Interest
N = Number of participants
MedDRA Dictionary Version 21.1 is used.
A participant with more than one occurrence of the same adverse event in a particular Category or Preferred Term (PT) is counted only once in the total of those experiencing adverse events in that particular Category or PT.
Terms are sorted alphabetically for Category and PT.
Sources: F00019_OAB - Version date: 06OCT2023 10:47 - File Name: Q112_2_c1_AECICaPTP1P3_saf_t.rtf
Sources: Cut-off date DOSSIER_ISS: 21JUN2022 - Dataset ADSX1.ADAE:11OCT2022 ADSX1.ADSL:11OCT2022 - PGM Q112_2_c1_AECICaPTP1P3_saf_t.sas 05OCT2023 15:35

Hypertension

The incidence of hypertension with vibegron (2.2%) was similar to placebo (2.6%) and lower than tolterodine (4.7%) in study 3003. In study 3004, incidences were similar for vibegron (9.2%) and tolterodine (9.9%).

In study 3004, pre-existing hypertension was reported in 49.8% of patients on vibegron and in 44.4% of patients on tolterodine. In this subpopulation, hypertension was reported in 7.3% of patients on vibegron and in 9.9% of patients on tolterodine. To be noted that hypertension or increased blood pressure is not labelled for tolterodine.

In study 3004, hypertension was assessed as treatment related by both investigator and sponsor for 10 patients in the vibegron arm. Based on the assessment of the case narratives, causality between vibegron and hypertension is not supported given the long latency time, the presence of underlying risk factors and resolution of the event while on vibegron treatment.

No events of hypertensive crisis have been reported in association with vibegron, neither in clinical studies (3003, 3004, 008, 301, 302 or 1001) nor in the post-marketing setting.

MACCE

In study 3003, the incidence of MACCE events with vibegron (0.6%) was similar to placebo (0.6%) and higher than with tolterodine (0.2%). In study 3004, the frequency of MACCE events with vibegron (0.7%) was lower than with tolterodine (1.3%). Based on the assessment of the case narratives for MACCE events reported with vibegron, causality between vibegron and MACCE events is not supported given the presence of previous and/or concurrent conditions possibly explaining the occurrence of MACCE events and underlying risk factors reported in those patients.

2.6.8.4. Laboratory findings

Study 3003

Assessments of safety laboratory parameters (haematology, clinical chemistry, urinalysis, serum β-choriogonadotropin, and urine culture) in Study 3003 showed no clinically meaningful differences in patients treated with vibegron vs. placebo in terms of descriptive statistics at Week 12, changes in parameters over time, and, as applicable, incidence of abnormal results (overall or by grade) or evaluations of shift in (low/normal/high) classification during the study.

Study 3004

Assessments of safety laboratory parameters in Study 3004 showed no clinically meaningful differences in patients treated with vibegron compared with tolterodine ER in terms of descriptive statistics at Week 52, changes over time, and, as applicable, incidence of abnormal results (overall or by grade) or evaluations of shift in (low/normal/high) classification during the study.

Integrated Data Analyses

In the integrated Phase 2b or 3 data (Pool 1, Pool 3), no clinically meaningful differences in laboratory results were observed between patients receiving vibegron and patients receiving placebo or tolterodine. Few patients in any pool had increased liver enzymes, and no patients met the laboratory criteria for Hy's Law.

2.6.8.5. Vital signs and other observations related to safety

Systolic blood pressure

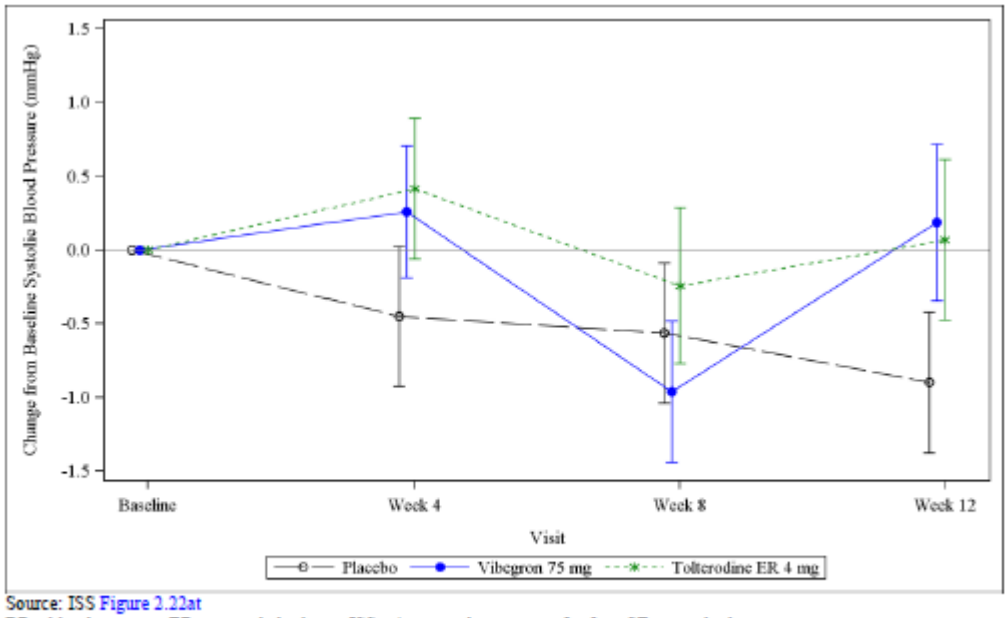
Study 3003

Table 42. Triplicate Vital Signs Study 3003: Summary of Systolic Blood Pressure at Baseline and Change from Baseline (Safety Population)

	Placebo N = 540	Vibegron 75 mg N = 545	Tolterodine ER 4 mg N = 430
Baseline			
n	540	545	430
Mean (SD), mmHg	123.3 (12.33)	124.3 (11.92)	124.0 (12.15)
Change from Baseline to Week 12			
n	493	503	388
Mean (SD), mmHg	-0.9 (10.56)	0.2 (11.89)	0.1 (10.74)
Change from Baseline to Maximum Post-baseline Value Across Visits (Through Week 12)			
n	527	535	420
Mean (SD), mmHg	4.7 (10.11)	5.5 (10.69)	5.4 (9.91)

Source: ISS Table 2.48at
ER = extended release; ISS = integrated summary of safety; SD = standard deviation
Note: Baseline is defined as the last non-missing value prior to the first dose of the study treatment.

Figure 14. Triplicate Vital Signs Study 3003: Mean (SE) of Change from Baseline Systolic Blood Pressure by Visit (Safety Population)



Source: ISS Figure 2.22at
BP = blood pressure; ER = extended release; ISS = integrated summary of safety; SE = standard error
BP measurements taken up to 3 times and averaged at each visit.
Number of patients at each visit (placebo, vibegron 75 mg, tolterodine) - Baseline: 540, 545, 430; Week 4: 520, 529, 415; Week 8: 512, 518, 413; Week 12: 493, 503, 388 (ISS Table 2.48at).

Table 43. Triplicate Vital Signs Study 3003: Area Under the Curve Minus Baseline Through Week 12 in Systolic Blood Pressure (Safety Population)

	Placebo N = 540	Vibegron 75 mg N = 545	Tolterodine ER 4 mg N = 430
Area Under the Curve Minus Baseline			
LS Means, mmHg			
n	526	534	420
LS Mean (SE) 95% CI	-0.5 (0.32) -1.1, 0.1	-0.0 (0.32) -0.6, 0.6	0.2 (0.34) -0.5, 0.9
Treatment – Placebo*			
Difference in LS Mean Change from Baseline, mmHg (SE) 95% CI		0.5 (0.38) -0.2, 1.3	0.7 (0.41) -0.1, 1.5

Source: ISS Table 2.58at
CI = confidence interval; ER = extended release; LS = least squares; ISS = integrated summary of safety; SE = standard error
Notes Linear model with treatment, age, sex (Male, Female), pre-existing hypertension (Yes, No), and baseline value.
Pre-existing hypertension subgroup is based on medical history and/or baseline hypertension. Baseline hypertension is defined as baseline SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg.

Table 44. Triplicate Vital Signs Study 3003: Categorical Analysis of Systolic Blood Pressure Increase ≥15 mmHg, by 3 Consecutive Post-baseline Visits and Maximum Post baseline Value (Safety Population)

Systolic Blood pressure Increase ≥ 15 mmHg	Placebo n/N (%)	Vibegron 75 mg n/N (%)	Tolterodine ER 4 mg n/N (%)
At 3 consecutive visits	4/527 (0.8)	7/535 (1.3)	9/420 (2.1)
Maximum post-baseline across visits through Week 12	75/527 (14.2)	81/535 (15.1)	70/420 (16.7)

Source: ISS Table 2.49at and ISS Table 2.52at
ISS = integrated summary of safety.
Note: n is the number of patients who met the condition and N is the number ofpatients with non-missing post-baseline values.

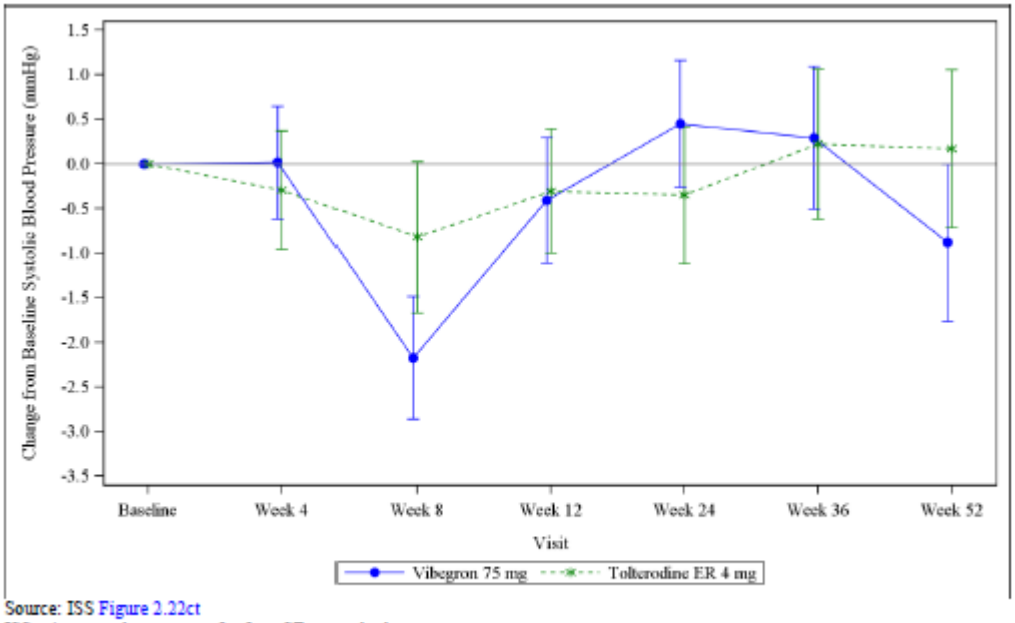
Study 3004

Table 45. Triplicate Vital Signs Study 3004: Summary of Systolic Blood Pressure at Baseline and Change from Baseline (Safety Population)

	Vibegron 75 mg N = 273	Tolterodine ER 4 mg N = 232
Baseline		
n	273	232
Mean (SD), mmHg	124.6 (12.16)	123.6 (11.58)
Change from Baseline to Week 52		
n	204	170
Mean (SD), mmHg	-0.9 (12.56)	0.2 (11.56)
Change from Baseline to Maximum Post-baseline Value Across Visits		
n	273	231
Mean (SD), mmHg	9.1 (11.06)	9.0 (10.30)

Source: ISS Table 2.48ct
ER = extended release; ISS = integrated summary of safety; SD = standard deviation
Note: Baseline is defined as the last non-missing value prior to the first dose of the study treatment.

Figure 15. Triplicate Vital Signs Study 3004: Mean (SE) of Change from Baseline Systolic Blood Pressure by Visit (Safety Population)



Source: ISS Figure 2.22ct
ISS = integrated summary of safety; SE = standard error
Number of patients at each visit (vibegron 75 mg, tolterodine) – Baseline: 273, 232; Week 4: 270, 227; Week 8: 183, 146; Week 12: 269, 225; Week 24: 258, 217; Week 36: 246, 208; Week 52: 204, 170 (ISS Table 2.48ct).

Table 46. Triplicate Vital Signs Study 3004: Analysis of Covariance for Change from Baseline to Week 52 in Systolic Blood Pressure (Safety Population)

	Vibegron 75 mg	Tolterodine ER 4 mg
Change from Baseline to Week 52 LS Means, mmHg		
n	204	170
LS Mean (SE) 95% CI	-0.6 (0.81) -2.2, 1.0	-0.2 (0.88) -1.9, 1.6

Source: ISS Table 2.63ct
DBP = diastolic blood pressure; ISS = integrated summary of safety; LS = least square; SBP = systolic blood pressure; SE = standard error
Linear model with treatment, age, sex (Male, Female), pre-existing hypertension (Yes, No), and baseline value. Pre-existing hypertension subgroup is based on medical history and/or baseline hypertension. Baseline hypertension is defined as baseline SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg.

Table 47. Triplicate Vital Signs Study 3004: Categorical Analysis of Systolic Blood Pressure Increase ≥15 mmHg, by 3 Consecutive Post-baseline Visits (Safety Population)

Systolic Blood pressure Increase ≥ 15 mmHg	Vibegron 75 mg n/N (%)	Tolterodine ER 4 mg n/N (%)
At 3 consecutive visits	9/273 (3.3)	5/231 (2.2)

Source: ISS Table 2.52ct
ISS = integrated summary of safety.
Note: n is the number of patients who met the condition and N is the number ofpatients with non-missing post-baseline values.

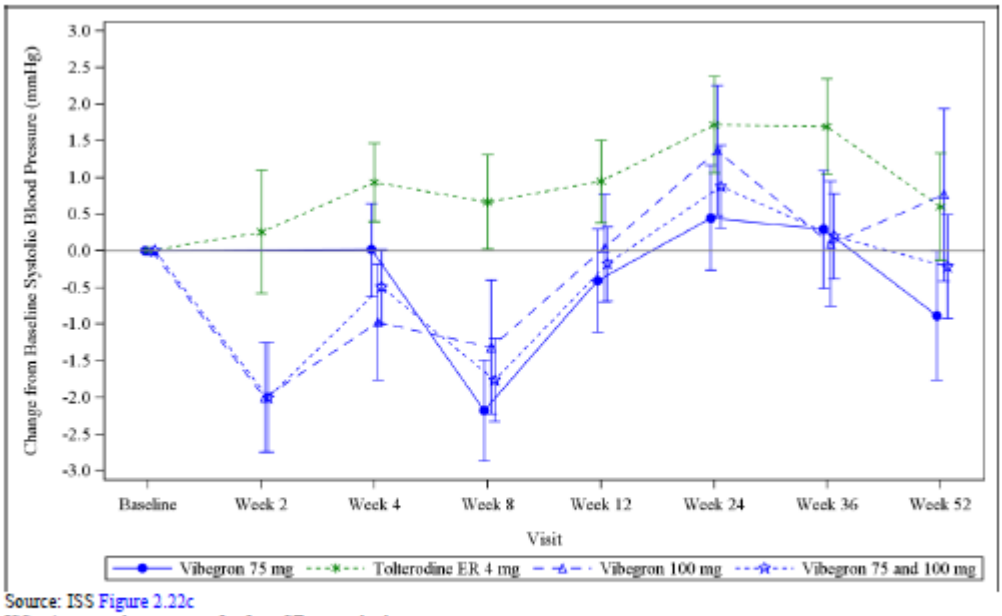
Pool 3 (Long-term Exposure Studies: 008, 302, 3004)

Table 48. Pool 3 (Studies 008 Base and Extension, 302, and 3004): Summary of Systolic Blood Pressure at Baseline and Change from Baseline (Safety Population)

	Vibegron 75 mg N = 273	Tolterodine ER 4 mg N = 472	Vibegron 100 mg N = 299	Vibegron 75 and 100 mg N = 572
Baseline				
n	273	471	299	572
Mean (SD), mmHg	124.6 (12.16)	122.8 (13.29)	124.9 (15.69)	124.8 (14.11)
Change from Baseline to Week 52				
n	204	297	139	343
Mean (SD), mmHg	-0.9 (12.56)	0.6 (12.61)	0.8 (13.89)	-0.2 (13.12)
Change from Baseline to Maximum Post-baseline Value Across Visits				
n	273	469	298	571
Mean (SD), mmHg	9.1 (11.06)	11.6 (11.54)	10.7 (11.76)	9.9 (11.45)

Source: ISS Table 2.48c
ER = extended release; ISS = integrated summary of safety; SD = standard deviation
Note: Baseline is defined as the last non-missing value prior to the first dose of the study treatment.

Figure 16. Pool 3 (Studies 008 Base and Extension, 302, 3004) Mean (SE) of Change from Baseline Systolic Blood Pressure by Visit (Safety Population)



Source: ISS Figure 2.22c
ISS = integrated summary of safety; SE = standard error
Number of patients at each visit (vibegron 75 mg, tolterodine, vibegron 100 mg, vibegron 75 +100 mg) - Baseline: 273, 471, 299, 572; Week 2: 0, 239, 260, 260: Week 4: 270, 462, 290, 560; Week 8: 183, 305, 170, 353; Week 12: 269, 435, 280, 549; Week 24: 258, 395, 223, 481; Week 36: 246, 410, 234, 480; Week 52: 204, 297, 139, 343 (ISS Table 2.48c).

Table 49. Pool 3 (Studies 008 Base and Extension, 302, 3004): Analysis of Covariance for Change from Baseline to Week 52 in Systolic Blood Pressure (Safety Population)

	Vibegron 75 mg	Tolterodine ER 4 mg	Vibegron 100 mg	Vibegron 75 and 100 mg
Change from Baseline to Week 52 LS Means, mmHg				
n	204	297	139	343
LS Mean (SE) 95% CI	-0.8 (0.85) -2.4, 0.9	0.3 (0.77) -1.2, 1.9	1.9 (1.10) -0.2, 4.1	-0.4 (0.86) -2.1, 1.3

Source: ISS Table 2.63c
DBP = diastolic blood pressure; ER = extended release; ISS = integrated summary of safety; LS = least squares; SBP = systolic blood pressure; SE = standard error
Linear model with treatment, age, sex (Male, Female), pre-existing hypertension (Yes, No), and baseline value. Pre-existing hypertension subgroup is based on medical history and/or baseline hypertension. Baseline hypertension is defined as baseline SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg.

Source: SCS Table 67

Table 50. Pool 3 (Studies 008 Base and Extension, 302 and 3004): Categorical Analysis of Systolic Blood Pressure Increase ≥15 mmHg, by 3 Consecutive Post-baseline Visits (Safety Population)

Systolic Blood pressure Increase ≥ 15 mmHg	Vibegron 75 mg n/N (%)	Tolterodine ER 4 mg n/N (%)	Vibegron 100 mg n/N (%)	Vibegron 75 and 100 mg n/N (%)
At 3 consecutive visits	9/273 (3.3)	19/469 (4.1)	11/298 (3.7)	20/571 (3.5)

Source: ISS Table 2.52c
ISS = integrated summary of safety
Note: n is the number of patients who met the condition and N is the number ofpatients with non-missing post-baseline values.

Vital signs were measured in triplicate in both pivotal studies. In studies 3003 and 3004, no clinically relevant changes from baseline in systolic blood pressure were observed with vibegron 75 mg; changes were similar to those reported with tolterodine or placebo. These results were confirmed by ANCOVA analysis. The frequency of increases of ≥15 mmHg in systolic blood pressure (at 3 consecutive visits in both studies and maximum value across visits in study 3003) was similar between the vibegron and placebo or tolterodine arms in both studies.

Results for increases in systolic blood pressure were similar between the vibegron 100 mg and 75 mg treatment groups.

Increases in systolic blood pressure were analysed in subpopulations at risk for increases in systolic blood pressure, i.e., older age (≥75th percentile), pre-existing hypertension, low body weight (≤25th percentile) and reduced eGFR (≤25th percentile). The frequency of increases of ≥15 mmHg in systolic blood pressure (at 3 consecutive visits) in the at-risk subpopulations was similar between the vibegron and placebo or tolterodine arms in both studies and pool 3.

In the pivotal phase 3 study and its extension, no clinically relevant changes from baseline in diastolic blood pressure were observed with vibegron 75 mg; changes were similar to those reported with tolterodine or placebo. These results were confirmed by ANCOVA analysis. The frequency of increases of ≥10 mmHg in diastolic blood pressure (at 3 consecutive visits in both studies and maximum value across visits in study 3003) was similar between the vibegron and placebo or tolterodine arms in both studies.

Results for increases in diastolic blood pressure were similar between the vibegron 100 mg and 75 mg treatment groups.

No relevant differences in the frequency of increases of ≥10 mmHg in diastolic blood pressure (at 3 consecutive visits) in the at-risk subpopulations were observed between the vibegron and placebo or tolterodine arms in both studies and pool 3.

Heart rate

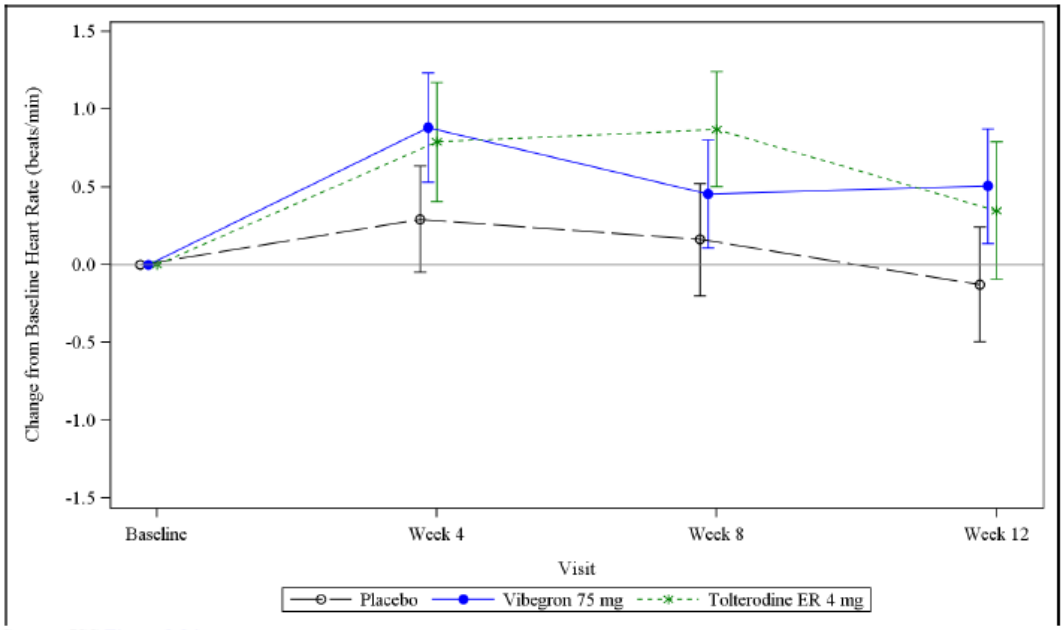
Study 3003

Table 51. Triplicate Vital Signs Study 3003: Summary of Heart Rate at Baseline and Change from Baseline (Safety Population)

	Placebo N = 540	Vibegron 75 mg N = 545	Tolterodine ER 4 mg N = 430
Baseline			
n	540	545	430
Mean (SD), bpm	71.6 (9.12)	72.1 (9.08)	72.5 (9.15)
Change from Baseline to Week 12			
n	493	503	388
Mean (SD), bpm	-0.1 (8.16)	0.5 (8.27)	0.3 (8.69)
Change from Baseline to Maximum Post-baseline Value Across Visits			
n	527	535	420
Mean (SD), bpm	4.6 (7.91)	5.0 (7.78)	4.9 (7.10)

Source: ISS Table 2.48at
bpm = beats per minutes; ER = extended release; ISS = integrated summary of safety; SD = standard deviation
Note: Baseline is defined as the last non-missing value prior to the first dose of the study treatment.

Figure 17. Triplicate Vital Signs Study 3003: Mean (SE) of Change from Baseline Heart Rate by Visit (Safety Population)



Source: ISS Figure 2.24at
ISS = integrated summary of safety; SE = standard error
Number of patients at each visit (placebo, vibegron 75 mg, tolterodine) - Baseline: 540, 545, 430; Week 4: 520, 529, 415; Week 8: 512, 518, 413; Week 12: 493, 503, 388 (ISS Table 2.48at).

Table 52. Triplicate Vital Signs Study 3003: Categorical Analysis of Heart Rate Increases ≥10 bpm at 3 Consecutive Post-baseline Visits and at Maximum Post-baseline Value Across Visits (Safety Population)

Heart Rate Increases ≥ 10 bpm	Placebo n/N (%)	Vibegron 75 mg n/N (%)	Tolterodine ER 4 mg n/N (%)
At 3 consecutive visits	8/527 (1.5)	10/535 (1.9)	9/420 (2.1)
Maximum post-baseline value across visits	124/527 (23.5)	120/535 (22.4)	100/420 (23.8)

Source: ISS Table 2.51at, and ISS Table 2.54at
bpm = beats per minute; ER = extended release; ISS = integrated summary of safety
Note: n is the number of patients who met the condition and N is the number ofpatients with non-missing post-baseline values.

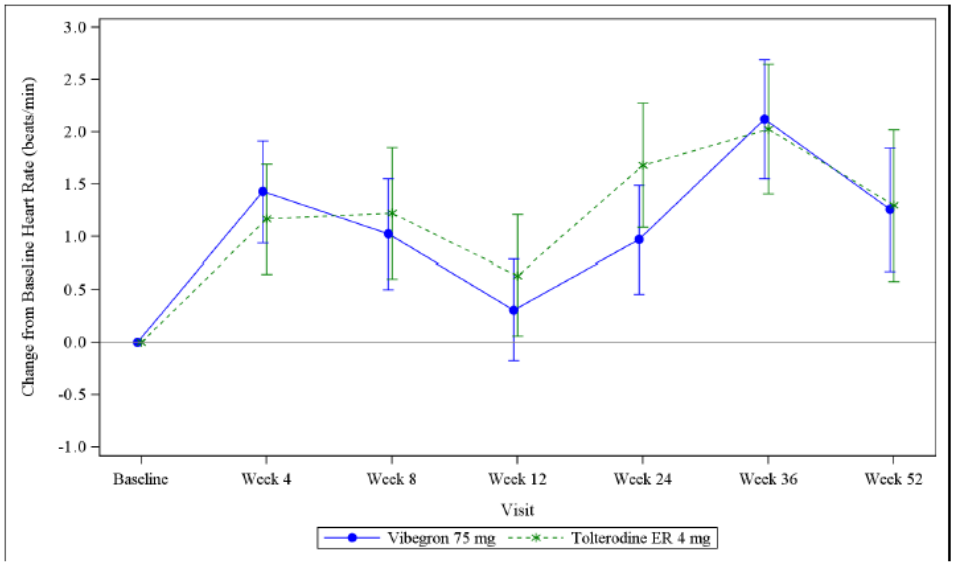
Study 3004

Table 53. Triplicate Vital Signs Study 3004: Summary of Heart Rate at Baseline and Change from Baseline (Safety Population)

	Vibegron 75 mg N = 273	Tolterodine ER 4 mg N = 232
Baseline		
n	273	232
Mean (SD), bpm	71.4 (8.15)	71.6 (8.66)
Change from Baseline to Week 52		
n	204	170
Mean (SD), bpm	1.3 (8.37)	1.3 (9.40)
Change from Baseline to Maximum Post-baseline Value Across Visits		
n	273	231
Mean (SD), bpm	9.0 (7.65)	8.6 (8.12)

Source: ISS Table 2.48ct
bpm = beats per minute; ER = extended release; ISS = integrated summary of safety; SD = standard deviation
Note: Baseline is defined as the last non-missing value prior to the first dose of the study treatment.

Figure 18. Triplicate Vital Signs Study 3004: Mean (SE) of Change from Baseline Heart Rate by Visit (Safety Population)



Source: ISS Figure 2.24ct
ISS = integrated summary of safety; SE = standard error
Number of patients at each visit (vibegron 75 mg, tolterodine) – Baseline: 273, 232; Week 4: 270, 227; Week 8: 183, 146; Week 12: 269, 225; Week 24: 258, 217; Week 36: 246, 208; Week 52: 204, 170 (ISS Table 2.48ct)

Table 54. Triplicate Vital Signs Study 3004: Analysis of Covariance for Change from Baseline to Week 52 in Heart Rate (Safety Population)

	Vibegron 75 mg	Tolterodine ER 4 mg
Change from Baseline to Week 52 LS Means, bpm		
n	204	170
LS Mean (SE) 95% CI	1.1 (0.62) -0.1, 2.4	1.1 (0.68) -0.2, 2.4

Source: ISS Table 2.65ct
bpm = beats per minute; CI = confidence interval; DBP = diastolic blood pressure; ER = extended release; ISS = integrated summary of safety; LS = least square; SBP = systolic blood pressure
Linear model with treatment, age, sex (Male, Female), pre-existing hypertension (Yes, No), and baseline value. Pre-existing hypertension subgroup is based on medical history and/or baseline hypertension. Baseline hypertension is defined as baseline SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg.

Table 55. Triplicate Vital Signs Study 3004: Categorical Analysis of Heart Rate Increases ≥10 bpm at 3 Consecutive Post-baseline Visits (Safety Population)

Heart Rate Increases ≥ 10 bpm	Vibegron 75 mg n/N (%)	Tolterodine ER 4 mg n/N (%)
At 3 consecutive visits	15/273 (5.5)	15/231 (6.5)

Source: ISS Table 2.54ct
bpm = beats per minute; ER = extended release; ISS = integrated summary of safety
Note: n is the number of patients who met the condition and N is the number ofpatients with non-missing post-baseline values.

Pool 3 (Long-term Exposure Studies: 008, 302, 3004)

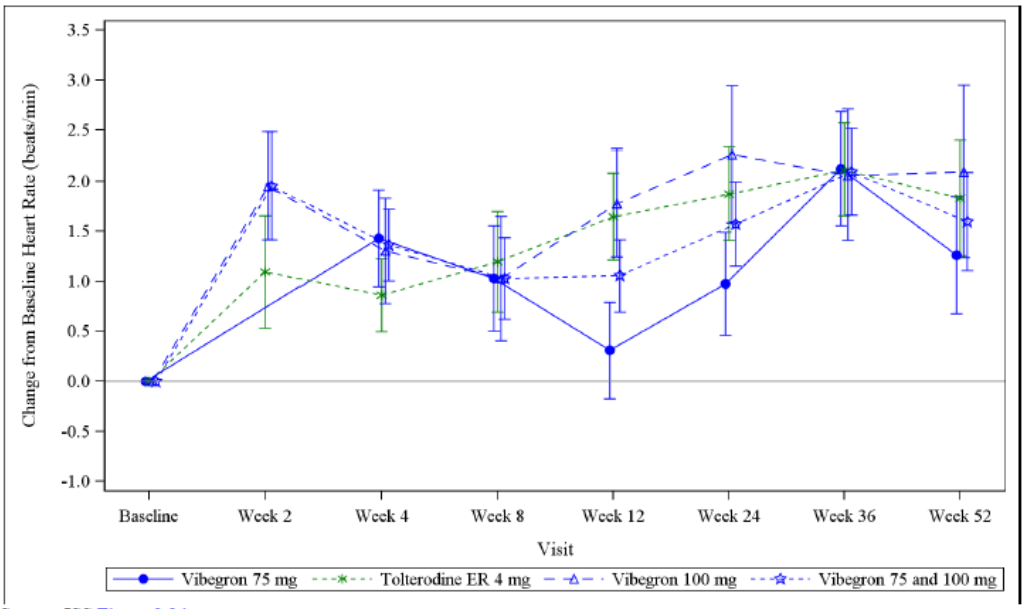
Table 56. Pool 3 (Studies 008 Base and Extension, 302, and 3004): Summary of Heart Rate at Baseline and Change from Baseline (Safety Population)

	Vibegron 75 mg N = 273	Tolterodine ER 4 mg N = 472	Vibegron 100 mg N = 299	Vibegron 75 and 100 mg N = 572
Baseline				
n	273	471	299	572
Mean (SD), bpm	71.4 (8.15)	71.2 (9.05)	70.0 (10.08)	70.7 (9.23)
Change from Baseline to Week 52				
n	204	297	139	343
Mean (SD), bpm	1.3 (8.37)	1.8 (9.88)	2.1 (10.11)	1.6 (9.11)
Change from Baseline to Maximum Post-baseline Value Across Visits				
n	273	469	298	571
Mean (SD), bpm	9.0 (7.65)	9.5 (8.34)	10.0 (9.29)	9.5 (8.55)

Source: ISS Table 2.48c
bpm = beats per minute; ER = extended release; ISS = integrated summary of safety; SD = standard deviation
Note: Baseline is defined as the last non-missing value prior to the first dose of the study treatment.

Source: SCS Table 90

Figure 19. Pool 3 (Studies 008 Base and Extension, 302, 3004): Mean (SE) of Change from Baseline Heart Rate by Visit (Safety Population)



Source: ISS Figure 2.24c
ER = extended release; ISS = integrated summary of safety; SE = standard error
Number of patients at each visit (vibegron 75 mg, tolterodine, vibegron 100 mg, vibegron 75 +100 mg) - Baseline: 273, 471, 299, 572; Week 2: 0, 239, 260, 260: Week 4: 270, 462, 290, 560; Week 8: 183, 305, 170, 353; Week 12: 269, 435, 280, 549; Week 24: 258, 395, 223, 481; Week 36: 246, 410, 233, 479; Week 52: 204, 297, 139, 343 (ISS Table 2.48c)

Table 57. Pool 3 (Studies 008 Base and Extension, 302, 3004): Analysis of Covariance for Change from Baseline to Week 52 in Heart Rate (Safety Population)

	Vibegron 75 mg	Tolterodine ER 4 mg	Vibegron 100 mg	Vibegron 75 and 100 mg
Change from Baseline to Week 52 LS Means, bpm				
n	204	297	139	343
LS Mean (SE) 95% CI	1.3 (0.64) 0.1, 2.6	1.7 (0.58) 0.6, 2.8	1.3 (0.83) -0.4, 2.9	1.8 (0.61) 0.6, 3.0

Source: ISS Table 2.65c
bpm = beats per minute; CI = confidence interval; DBP = diastolic blood pressure; ER = extended release; ISS = integrated summary of safety; LS = least square; SBP = systolic blood pressure; SE = standard error
a Linear model with treatment, age, sex (Male, Female), pre-existing hypertension (Yes, No), and baseline value. Pre-existing hypertension subgroup is based on medical history and/or baseline hypertension. Baseline hypertension is defined as baseline SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg.

Table 58. Pool 3 (Studies 008 Base and Extension, 302 and 3004): Categorical Analysis of Heart Rate Increases ≥10 bpm at 3 Consecutive Post-baseline Visits (Safety Population)

Heart Rate Increases ≥ 10 bpm	Vibegron 75 mg n/N (%)	Tolterodine ER 4 mg n/N (%)	Vibegron 100 mg n/N (%)	Vibegron 75 and 100 mg n/N (%)
At 3 consecutive visits	15/273 (5.5)	32/469 (6.8)	19/298 (6.4)	34/571 (6.0)

Source: ISS Table 2.54c
bpm = beats per minute; ER = extended release; ISS = integrated summary of safety
Note: n is the number of patients who met the condition and N is the number of patients with non-missing post-baseline values.

In the pivotal phase 3 study and its extension, no clinically relevant changes from baseline in heart rate were observed with vibegron 75 mg; changes were similar to those reported with tolterodine or placebo. These results were confirmed by ANCOVA analysis. The frequency of increases of ≥10 bpm in heart rate (at 3 consecutive visits in both studies and maximum value across visits in study 3003) was similar between the vibegron and placebo or tolterodine arms in both studies.

Results for increases in diastolic blood pressure were similar between the vibegron 100 mg and 75 mg treatment groups.

The frequency of increases of ≥10 bpm in heart rate (at 3 consecutive visits) in the at-risk subpopulations was similar between the vibegron and placebo or tolterodine arms in both studies and pool 3.

Post-void residual volume

Study 3003

Table 59. Study 3003: Summary of Post-void Residual Urine Volume (Safety Population)

	Placebo N = 540	Vibegron 75 mg N = 545	Tolterodine ER 4 mg N = 430
Baseline			
n	593	544	430
Mean (SD), mL	27.1 (31.05)	28.8 (32.49)	27.9 (37.94)
Change from Baseline at Week 12			
n	503	511	400
Mean (SD), mL	2.1 (37.25)	0.4 (38.27)	3.1 (40.93)

Source: Study 3003 CSR, Table 14.3.1.20
SD = Standard deviation

Study 3004

Table 60. Study 3004: Summary of Post-void Residual Urine Volume (Safety Population)

	Overall Vibegron 75 mg N = 273	Overall Tolterodine ER 4 mg N = 232
Baseline		
n	273	231
Mean (SD), mL	30.4 (30.29)	28.1 (30.09)
Change from Baseline at Week 40		
n	78	69
Mean (SD), mL	3.3 (33.91)	5.3 (35.01)
Change from Baseline at Week 52		
n	147	117
Mean (SD), mL	3.3 (51.96)	-0.6 (41.19)

Source: Study 3004 CSR, Table 14.3.1.20
SD = Standard deviation

Pool 1 (12-week Double-blind Studies 301 and 3003)

Table 61. Pool 1 (Studies 3003 and 301): Summary of Post-void Residual Urine Volume (Safety Population)

	Placebo N = 909	Vibegron 75 mg N = 545	Tolterodine ER 4 mg N = 430	Vibegron 100 mg N = 369
Baseline				
n	908	544	430	369
Mean (SD), mL	19.8 (26.83)	28.8 (32.49)	27.9 (37.94)	7.7 (12.17)
Baseline Categorical Summary				
< 100 mL, n (%)	883 (97.1)	518 (95.0)	409 (95.1)	369 (100)
≥ 100 and < 200 mL, n (%)	25 (2.8)	26 (4.8)	19 (4.4)	0
≥ 200 and < 350 mL, n (%)	0	0	0	0
≥ 350 mL, n (%)	0	0	2 (0.5)	0
Change from Baseline to Week 12				
n	865	496	391	368
Mean (SD), mL	1.5 (31.02)	0.3 (38.65)	3.3 (41.33)	0.9 (13.65)
Week 12 Categorical Summary				
< 100 mL, n (%)	843 (92.7)	476 (87.3)	363 (84.4)	367 (99.5)
≥ 100 and < 200 mL, n (%)	19 (2.1)	18 (3.3)	25 (5.8)	1 (0.3)
≥ 200 and < 350 mL, n (%)	4 (0.4)	3 (0.6)	3 (0.7)	0
≥ 350 mL, n (%)	0	0	0	0
Change from Baseline to Maximum Post-baseline Value Across Visits				
n	865	496	391	368
Mean (SD), mL	3.7 (31.41)	0.3 (38.65)	3.3 (41.33)	4.9 (15.21)
Maximum Post-baseline Value Categorical Summary				
< 100 mL, n (%)	843 (92.7)	476 (87.3)	363 (84.4)	367 (99.5)
≥ 100 and < 200 mL, n (%)	19 (2.1)	18 (3.3)	25 (5.8)	1 (0.3)
≥ 200 and < 350 mL, n (%)	4 (0.4)	3 (0.6)	3 (0.7)	0
≥ 350 mL, n (%)	0	0	0	0

Source: ISS Table 2.59a
ER = extended release; ISS = integrated summary of safety; SD = standard deviation
Note: Baseline is defined as the last non-missing value prior to the first dose of the study treatment.

Pool 3 (Long-term Exposure Studies: 008, 302, 3004)

Table 62. Pool 3 Studies (008 Base and Extension, 302, 3004): Summary of Post-void Residual Urine Volume (Safety Population)

	Vibegron 75 mg N = 273	Tolterodine ER 4 mg N = 232	Vibegron 100 mg N = 51	Vibegron 75 and 100 mg N = 324
Baseline				
n	273	231	51	324
Mean (SD), mL	30.4 (30.28)	28.1 (30.72)	5.6 (9.58)	26.5 (29.47)
Baseline Categorical Summary				
< 100 mL, n (%)	262 (96.0)	219 (94.4)	51 (100)	313 (96.6)
≥ 100 and < 200 mL, n (%)	11 (4.0)	12 (5.2)	0	11 (3.4)
≥ 200 and < 350 mL, n (%)	0	0	0	0
≥ 350 mL, n (%)	0	0	0	0
Change from Baseline to Week 52				
n	229	190	48	277
Mean (SD), mL	3.1 (46.10)	1.3 (38.81)	1.0 (10.68)	2.7 (42.14)
Week 52 Categorical Summary				
< 100 mL, n (%)	212 (77.4)	181 (78.0)	48 (94.1)	260 (80.0)
≥ 100 and < 200 mL, n (%)	12 (4.4)	9 (3.9)	0	12 (3.7)
≥ 200 and < 350 mL, n (%)	4 (1.5)	1 (0.4)	0	4 (1.2)
≥ 350 mL, n (%)	1 (0.4)	0	0	1 (0.3)
Change from Baseline to Maximum Post-baseline Value Across Visits				
n	269	227	51	320
Mean (SD), mL	17.8 (49.15)	17.6 (41.54)	6.7 (13.14)	16.0 (45.53)
Maximum Post-baseline Value Categorical Summary				
< 100 mL, n (%)	238 (87.2)	208 (89.7)	51 (100)	289 (89.2)
≥ 100 and < 200 mL, n (%)	24 (8.8)	15 (6.5)	0	24 (7.4)
≥ 200 and < 350 mL, n (%)	6 (2.2)	5 (2.2)	0	6 (1.9)
≥350 mL, n (%)	1 (0.4)	0	0	1 (0.3)

Source: ISS Table 2.59c
ER = extended release; ISS = integrated summary of safety; SD = standard deviation
Note: Baseline is defined as the last non-missing value prior to the first dose of the study treatment.

In study 3003, the mean change in PVR urine volume from baseline at week 12 was similar across study arms (placebo vs. vibegron vs. tolterodine: 2.1 mL vs. 0.4 mL vs. 3.1 mL). Similar results across study arms were also observed in study 3004 (vibegron vs. tolterodine: at week 40, 3.3 mL vs. 5.3 mL; and at week 52, 3.3 mL vs. -0.6 mL).

In pools 1 and 3 results for mean change in PVR urine volume from baseline to week 12 and week 52, respectively, were similar across treatment groups. The mean change from baseline to maximum post-baseline value in pool 1 was small and similar across treatment groups (placebo vs. vibegron 75mg vs. tolterodine vs. vibegron 100mg: 3.7 mL vs. 0.3 mL vs. 3.3 mL vs. 4.9 mL). Compared with the short-term data pool, mean change from baseline to maximum post-baseline value in pool 3 was considerably higher with vibegron 75mg and tolterodine (vibegron 75mg vs. tolterodine vs. vibegron 100mg: 17.8 mL vs. 17.6 mL vs. 6.7 mL). The data with vibegron 100mg should be interpreted with cautions considering the relatively small number of patients (N=53).

Categorical data were presented for pools 1 and 3 only. In both pools, the incidence of patients with a PVR urine volume of <100 mL was lower in all treatment groups at week 12 and week 52, respectively,

compared with baseline. No relevant differences in incidence across treatment groups were observed for the categories ≥100 mL and <200 mL and ≥200 mL and <350 mL.

Patients with BPH at baseline

Study 3003

Table 63. Study 3003: Post-Void Residual Urine Volume (mL) by Subgroup – SAF

Subgroup Timepoint	**Placebo** **N = 540**	**Vibegron 75 mg** **N = 545**	**Tolterodine ER 4 mg** **N = 430**
Men with BPH			
Baseline			
n	17	29	22
Mean (SD)	27.3 (26.73)	35.3 (33.57)	41.0 (43.17)
Change from Baseline at Week 12			
n	17	29	21
Mean (SD)	28.6 (62.36)	-3.4 (42.45)	3.7 (50.64)
Men without BPH			
Baseline			
n	63	53	44
Mean (SD)	27.9 (30.36)	40.7 (39.22)	26.8 (25.81)
Change from Baseline at Week 12			
n	57	49	40
Mean (SD)	8.5 (35.72)	5.5 (51.81)	13.7 (40.75)

Source: Table 14.3.1.21

Notes: Baseline results for post-void residual urine volume were collected at the Run-in Visit.
Change from baseline is calculated by: Visit Value - Baseline Value

Study 3004

Table 64. Study 3004: Post-Void Residual Urine Volume (mL) by Subgroup – SAF-Ext

Subgroup Timepoint	Overall Vibegron 75mg	Overall Tolterodine ER 4mg
Males with BPH, N	**20**	**14**
Baseline[a]		
n	20	14
Mean (SD)	43.3 (35.60)	25.4 (26.64)
Change from Baseline Week 40[b]		
n	4	4
Mean (SD)	-19.5 (33.37)	30.8 (19.99)
Change from Baseline Week 52[c]		
n	14	8
Mean (SD)	25.8 (76.34)	17.8 (69.15)
Males without BPH, N	**40**	**36**
Baseline[a]		
n	40	35
Mean (SD)	35.4 (31.99)	29.9 (32.37)
Change from Baseline Week 40[b]		
n	15	9
Mean (SD)	3.3 (41.34)	21.1 (38.52)
Change from Baseline Week 52[c]		
n	23	17
Mean (SD)	-1.2 (34.24)	19.4 (43.43)

Source: Table 14.3.1.21

Note: Change from baseline was calculated by: Visit Value - Baseline Value.

[a] Baseline results for PVR urine volume were collected at the Run-in Visit of Study 3003.

[b] Includes data from the 40-weeks treatment groups only; the visit window for subjects who received 40-weeks treatment was mapped relative to the start of active treatment.

[c] Includes data from the 52-weeks treatment groups only

In study 3003, the mean change in PVR urine volume from baseline at week 12 in patients with vs. without BPH at baseline was as follows: placebo: 28.6 mL vs. 8.5 mL; vibegron: -3.4 mL vs. 5.5 mL; tolterodine: 3.7 mL vs. 13.7 mL.

In study 3004, the mean change in PVR urine volume from baseline in patients with vs. without BPH at baseline was as follows: at week 40, vibegron: -19.5 mL vs. 3.3 mL; tolterodine: 30.8 mL vs. 21.1 mL; at week 52, vibegron: 25.8 mL vs. -1.2 mL; tolterodine: 17.8 mL vs. 19.4 mL.

The results of these analyses should be interpreted with caution, given the small number of patients with BPH at baseline in each study, 68 patients in study 3003 and 34 patients in study 3004.

ECG

ECGs were not routinely collected in studies 3003 and 3004;

In Study 301, the incidence of treatment-emergent ECG abnormalities was 0.5% with placebo, 0.8% with vibegron 50 mg, 0.5% with vibegron 100 mg, and 0.0% with imidafenacin and similar in the vibegron and placebo groups.

In Study 302, clinically significant ECG findings were noted in 3.0% of patients (5/166 patients) after initiation of study drug, 3.5% of patients (4/115 patients) during maintenance, and 2.0% of patients (1/51 patients) after increasing the dose of study drug. Among the 4 patients with abnormalities during maintenance, 2 (left anterior branch block, mild ST T abnormality) were recovered at 52 weeks, 1 had an abnormal ECG pre-study and throughout the study, and 1 (ST elevation) discontinued the study due to angina. The patient with an abnormal ECG (ST decline) after increasing the dose of study drug had the same abnormality on repeat testing, but no subsequent abnormality on further testing.

Pregnancy

Three patients have become pregnant while participating in clinical studies:

- In Study 008, 1 patient (receiving vibegron 100 mg + tolterodine) became pregnant during the extension study and discontinued from the study (Day 236). The pregnancy outcome was a healthy infant.
- In Study 3003, 1 patient (randomised to placebo) became pregnant between the End of Treatment Visit and the Follow-up Visit. The pregnancy went to term with a normal, vaginal delivery on 26 June 2019. The outcome was reported as a live birth of a normal male infant at approximately 38 weeks gestation (weight 2.8 kg, length 48.3 cm).
- In the completed IBS Study 2001, 1 patient had an ectopic pregnancy. The patient had a positive pregnancy test approximately 1 month after initiating study drug (baseline urine pregnancy test was negative). The patient received 75-mg vibegron. The event was reported as an SAE, and the pregnancy was terminated. The event was considered to be unrelated to study drug by both the Investigator and the Sponsor.

In the post-marketing experience, up to 20 September 2022 (Data Lock Point of the last PBRER), 2 events related to pregnancy and lactation (PTs: pregnancy, and exposure during pregnancy) were reported. Both events were non-serious.

No safety concern is raised based on pregnancies reported in the post-marketing setting.

2.6.8.6. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.7. Safety in special populations

Age

Age <65 Years and ≥65 Years

Table 65. Pool 1 (12-week Double-blind Studies 301 and 3003): Adverse Events Reported in ≥2% of Patients Receiving Vibegron 75 mg by Age <65 Years and ≥65 Years

PT	Placebo n (%)	Vibegron 75 mg n (%)	Tolterodine ER 4 mg n (%)	Vibegron 100 mg n (%)
Patients Aged < 65 Years	**N =550**	**N =299**	**N =259**	**N =239**
Any AE	144 (26.2)	101 (33.8)	93 (35.9)	65 (27.2)
Urinary tract infection	15 (2.7)	13 (4.3)	14 (5.4)	0
Headache	8 (1.5)	11 (3.7)	7 (2.7)	1 (0.4)
Nasopharyngitis	17 (3.1)	9 (3.0)	5 (1.9)	24 (10.0)
Nausea	3 (0.5)	7 (2.3)	4 (1.5)	0
Diarrhoea	6 (1.1)	6 (2.0)	3 (1.2)	1 (0.4)
Hypertension	2 (0.4)	6 (2.0)	6 (2.3)	0
Patients Aged ≥ 65 Years	**N =359**	**N =246**	**N =171**	**N=130**
Any AE	137 (38.2)	110 (44.7)	73 (42.7)	47 (36.2)
Urinary tract infection	18 (5.0)	14 (5.7)	11 (6.4)	0
Headache	5 (1.4)	11 (4.5)	4 (2.3)	0
Dry mouth	4 (1.1)	8 (3.3)	12 (7.0)	2 (1.5)
Upper respiratory tract infection	2 (0.6)	8 (3.3)	1 (0.6)	0
Diarrhoea	4 (1.1)	6 (2.4)	6 (3.5)	1 (0.8)
Nasopharyngitis	19 (5.3)	6 (2.4)	6 (3.5)	11 (8.5)
Nausea	3 (0.8)	5 (2.0)	1 (0.6)	0

Source: ISS Table 2.29a
AE = adverse event; ER = extended release; ISS = integrated summary of safety; PT = preferred term; SOC = system organ class
AEs are coded to SOC and PT using Medical Dictionary for Regulatory Activities coding dictionary version 21.1.
Patient is counted only once in each PT.

Table 66. Pool 3 (Long-term Studies 008 Base and Extension, 302 and 3004): Adverse Events Reported in ≥5% of Patients Receiving Vibegron 75 mg by Age <65 Years and ≥65 Years

PT	Vibegron 75 mg n (%)	Tolterodine ER 4 mg n (%)	Vibegron 100 mg n (%)	Vibegron 75 and 100 mg n (%)
Patients Aged < 65 Years	**N =144**	**N =293**	**N =209**	**N =353**
Any AE	79 (54.9)	179 (61.1)	135 (64.6)	214 (60.6)
Hypertension	10 (6.9)	13 (4.4)	2 (1.0)	12 (3.4)
Urinary tract infection	8 (5.6)	30 (10.2)	15 (7.2)	23 (6.5)
Patients Aged ≥ 65 Years	**N =129**	**N =179**	**N =90**	**N =219**
Any AE	92 (71.3)	116 (64.8)	55 (61.1)	147 (67.1)
Hypertension	14 (10.9)	10 (5.6)	4 (4.4)	18 (8.2)
Urinary tract infection	10 (7.8)	21 (11.7)	10 (11.1)	20 (9.1)
Headache	9 (7.0)	9 (5.0)	2 (2.2)	11 (5.0)
Constipation	8 (6.2)	15 (8.4)	3 (3.3)	11 (5.0)
Diarrhoea	8 (6.2)	8 (4.5)	5 (5.6)	13 (5.9)

Source: ISS Table 2.29c
AE = adverse event; ER = extended release; ISS = integrated summary of safety; PT = preferred term; SOC = system organ class
AEs are coded to SOC and PT using Medical Dictionary for Regulatory Activities coding dictionary version 21.1.
Patient is counted only once in each PT.

Age <75 Years and ≥75 Years

Table 67. Pool 1 (12-week Double-blind Studies 301 and 3003): Adverse Events Reported in ≥2% of Patients Receiving Vibegron 75 mg by Age <75 Years and ≥75 Years

	Placebo n (%)	Vibegron 75 mg n (%)	Tolterodine ER 4 mg n (%)	Vibegron 100 mg n (%)
Patients Aged < 75 Years	**N = 809**	**N = 470**	**N = 382**	**N = 343**
Any AE	246 (30.4)	174 (37.0)	142 (37.2)	100 (29.2)
Urinary tract infection	29 (3.6)	21 (4.5)	21 (5.5)	0
Headache	11 (1.4)	20 (4.3)	10 (2.6)	1 (0.3)
Nasopharyngitis	31 (3.8)	13 (2.8)	10 (2.6)	33 (9.6)
Nausea	4 (0.5)	10 (2.1)	5 (1.3)	0
Patients Aged ≥ 75 Years	**N = 100**	**N = 75**	**N = 48**	**N= 26**
Any AE	35 (35.0)	37 (49.3)	24 (50.0)	12 (46.2)
Urinary tract infection	4 (4.0)	6 (8.0)	4 (8.3)	0
Diarrhoea	3 (3.0)	3 (4.0)	2 (4.2)	0
Dyspnoea	0	3 (4.0)	0	0
Upper respiratory tract infection	1 (1.0)	3 (4.0)	0	0
Back pain	3 (3.0)	2 (2.7)	1 (2.1)	0
Flatulence	0	2 (2.7)	0	0
Headache	2 (2.0)	2 (2.7)	1 (2.1)	0
Nasopharyngitis	5 (5.0)	2 (2.7)	1 (2.1)	2 (7.7)
Nausea	2 (2.0)	2 (2.7)	0	0
Rash	1 (1.0)	2 (2.7)	0	0
Somnolence	0	2 (2.7)	1 (2.1)	0
Urinary retention	0	2 (2.7)	2 (4.2)	0

Source: ISS Table 2.30a
AE = adverse event; ER = extended release; ISS = integrated summary of safety; PT = preferred term; SOC = system organ class
AEs are coded to SOC and PT using Medical Dictionary for Regulatory Activities coding dictionary version 21.1.
Patient is counted only once in each PT.

Table 68. Pool 3 (Long-Term Exposure Studies 008 base and Extension, 302 and 3004): Adverse Events Reported in ≥2% of Patients Receiving Vibegron 75 mg by Age <75 Years and ≥75 Years

	Vibegron 75 mg n (%)	Tolterodine ER 4 mg n (%)	Vibegron 100 mg n (%)	Vibegron 75 and 100 mg n (%)
Patients Aged < 75 Years	**N = 242**	**N = 441**	**N = 290**	**N = 532**
Any AE	148 (61.2)	274 (62.1)	182 (62.8)	330 (62.0)
Hypertension	20 (8.3)	22 (5.0)	6 (2.1)	26 (4.9)
Urinary tract infection	16 (6.6)	48 (10.9)	24 (8.3)	40 (7.5)
Headache	15 (6.2)	16 (3.6)	12 (4.1)	27 (5.1)
Nasopharyngitis	12 (5.0)	33 (7.5)	32 (11.0)	44 (8.3)
Diarrhoea	9 (3.7)	18 (4.1)	13 (4.5)	22 (4.1)
Nausea	9 (3.7)	19 (4.3)	8 (2.8)	17 (3.2)
Upper respiratory tract infection	9 (3.7)	13 (2.9)	17 (5.9)	26 (4.9)
Anaemia	7 (2.9)	5 (1.1)	0	7 (1.3)
Bronchitis	7 (2.9)	7 (1.6)	9 (3.1)	16 (3.0)
Constipation	7 (2.9)	17 (3.9)	10 (3.4)	17 (3.2)
Residual urine volume increased	7 (2.9)	3 (0.7)	0	7 (1.3)
Back pain	6 (2.5)	13 (2.9)	8 (2.8)	14 (2.6)
Hyperglycaemia	6 (2.5)	1 (0.2)	2 (0.7)	8 (1.5)
Muscloskeletal pain	6 (2.5)	5 (1.1)	3 (1.0)	9 (1.7)
Influenza	5 (2.1)	5 (1.1)	5 (1.7)	10 (1.9)
Vomiting	5 (2.1)	5 (1.1)	2 (0.7)	7 (1.3)
Patients Aged ≥ 75 Years	**N = 31**	**N = 31**	**N = 9**	**N = 40**
Any AE	23 (74.2)	21 (67.7)	8 (88.9)	31 (77.5)
Diarrhoea	4 (12.9)	0	1 (11.1)	5 (12.5)
Hypertension	4 (12.9)	1 (3.2)	0	4 (10.0)
Constipation	3 (9.7)	2 (6.5)	0	3 (7.5)
Flatulence	2 (6.5)	0	0	2 (5.0)
Upper respiratory tract infection	2 (6.5)	0	0	2 (5.0)
Urinary retention	2 (6.5)	0	0	2 (5.0)
Urinary tract infection	2 (6.5)	3 (9.7)	1 (11.1)	3 (7.5)

Source: ISS Table 2.30c
AE = adverse event; ER = extended release; ISS = integrated summary of safety; PT = preferred term; SOC = system organ class
AEs are coded to SOC and PT using Medical Dictionary for Regulatory Activities coding dictionary version 21.1.
Patient is counted only once in each PT.

Overall, the incidence of any AE was higher for patients ≥75 years of age compared with those <75 years in all treatment groups. The AE profile was generally similar between both age groups, although small differences in incidences were observed; however, these should be interpreted with caution due to the smaller number of patients ≥75 years.

Age ≥85 Years

No dedicated subgroup analyses were planned for this age category due to the low number of patients in the ≥85 years category exposed to vibegron (n=9). However, a post-hoc review of safety data was performed for patients aged ≥85 years in the pivotal Studies 3003 and 3004.

In Study 3003, among the 4 patients exposed to vibegron 75 mg and aged ≥85 years, 1 was withdrawn for pneumonia and the other 3 patients completed the study. In those 3 completers, out of the reported AEs, the followings were considered possibly related to study drugs: acute sinusitis, dyspnoea, hypersensitivity and urinary retention. No AEs of hypertension were reported in patients aged ≥85 years.

In Study 3004, 1 patient aged ≥85 years was enrolled and exposed to vibegron 75 mg over 52 weeks. Only 1 AE of nausea was reported and considered related to study drug.

Although no concern is raised regarding the reported events in patients ≥85 years of age included in studies 3003 (n=4) and 3004 (n=1), the small number of patients does not allow for conclusions on the general safety profile in this age group.

Table 69. Study 3003 - Summary of adverse events by Age group – Subgroup of patients with Vibegron 75mg [Safety Population]

MedDRA Terms	<65 years (N=299) n(%)	65-74 years (N=171) n(%)	75-84 years (N=71) n(%)	>=85 years (N=4) n(%)
At least one TEAEs	101 (33.8)	73 (42.7)	33 (46.5)	4 (100.0)
At least one SAEs	3 (1.0)	1 (0.6)	3 (4.2)	1 (25.0)
Fatal	0	0	0	0
Hospitalisation/prolong existing hospitalisation	2 (0.7)	1 (0.6)	3 (4.2)	1 (25.0)
Life-threatening	0	0	0	0
Disability/incapacity	0	0	0	0
Other (medically significant)	1 (0.3)	0	1 (1.4)	0
AEs leading to treatment discontinuation	5 (1.7)	1 (0.6)	2 (2.8)	1 (25.0)
SOC Psychiatric disorders	5 (1.7)	3 (1.8)	0	0
SOC Nervous system disorders	18 (6.0)	11 (6.4)	6 (8.5)	0
Accidents and injuries (SMQ)	7 (2.3)	5 (2.9)	4 (5.6)	0
SOC Cardiac disorders	1 (0.3)	1 (0.6)	2 (2.8)	0
SOC Vascular disorders	7 (2.3)	4 (2.3)	2 (2.8)	0
Cerebrovascular disorders[a] (SMQ)	0	0	2 (2.8)	0
SOC Infections and infestations	42 (14.0)	19 (11.1)	18 (25.4)	2 (50.0)
PT Anticholinergic syndrome	0	0	0	0
PT Quality of life decreased	0	0	0	0
Sum of following events:	3 (1.0)	5 (2.9)	1 (1.4)	0
Postural hypotension[b]	0	0	0	0
Fall	0	1 (0.6)	1 (1.4)	0
Loss of consciousness	0	0	0	0
Syncope	0	0	0	0
Dizziness	3 (1.0)	2 (1.2)	0	0
Ataxia	0	0	0	0
Fracture[c]	0	2 (1.2)	0	0

Other AE appearing more frequently in older patients[d]				
Acute sinusitis	1 (0.3)	0	0	1 (25.0)
Back pain	0	1 (0.6)	2 (2.8)	0
Cholelithiasis	0	0	0	1 (25.0)
Diarrhoea	6 (2.0)	3 (1.8)	3 (4.2)	0
Dry mouth	1 (0.3)	7 (4.1)	1 (1.4)	0
Dyspnoea	0	1 (0.6)	1 (1.4)	2 (50.0)
Flatulence	0	0	2 (2.8)	0
Hyperglycaemia	1 (0.3)	1 (0.6)	0	1 (25.0)
Pneumonia	1 (0.3)	0	0	1 (25.0)
Pulmonary fibrosis	0	0	0	1 (25.0)
Rash	1 (0.3)	1 (0.6)	2 (2.8)	0
Somnolence	0	0	2 (2.8)	0
Upper respiratory tract infection	3 (1.0)	5 (2.9)	3 (4.2)	0
Urinary retention	0	1 (0.6)	1 (1.4)	1 (25.0)
Urinary tract infection	13 (4.3)	8 (4.7)	6 (8.5)	0

N = Number of participants

MedDRA Dictionary Version 21.1 is used.

a The selected PTs corresponds to the following SMQ: Central nervous system vascular disorders, Central nervous system haemorrhages and cerebrovascular conditions, Ischaemic central nervous system vascular conditions, Haemorrhagic central nervous system vascular conditions, Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic, Conditions associated with central nervous system haemorrhages and cerebrovascular accidents.
The PTs identified in the database are Cerebrovascular accident and Vertebrobasilar insufficiency.

b Postural Hypotension corresponds to preferred term Orthostatic hypotension in the database.

c Fracture corresponds to the following preferred term in the database: Sternal fracture and Upper limb fracture.

d The selection of AEs appearing in the elderly population were selected with the following algorithm: PTs with a difference ≥ 2% between "<65 years" and one of the other groups.

Sources: F00019_OAB - Version date: 06OCT2023 10:48 - File Name: Q115_1_1_c1_AEAgeVib3003_saf_t.rtf Sources: Cut-off date DOSSIER_ISS: 21JUN2022 - Dataset ADSX1.ADAE:11OCT2022 ADSX1.ADSL:11OCT2022 – PGM Q115_1_1_c1_AEAgeVib3003_saf_t.sas 05OCT2023 15:14

Table 70. Study 3004 - Summary of adverse events by Age group – Subgroup of patients with Vibegron 75mg [Safety Population]

MedDRA Terms	<65 years (N=144) n(%)	65-74 years (N=98) n(%)	75-84 years (N=29) n(%)	>=85 years (N=2) n(%)
At least one TEAEs	79 (54.9)	69 (70.4)	21 (72.4)	2 (100.0)
At least one SAEs	5 (3.5)	2 (2.0)	1 (3.4)	1 (50.0)
Fatal	1 (0.7)	0	0	0
Hospitalisation/prolong existing hospitalisation	4 (2.8)	2 (2.0)	1 (3.4)	0
Life-threatening	0	0	0	0
Disability/incapacity	0	0	0	0
Other (medically significant)	0	0	0	1 (50.0)
AEs leading to treatment discontinuation	1 (0.7)	2 (2.0)	1 (3.4)	0
SOC Psychiatric disorders	2 (1.4)	2 (2.0)	1 (3.4)	0
SOC Nervous system disorders	12 (8.3)	14 (14.3)	1 (3.4)	0
Accidents and injuries (SMQ)	7 (4.9)	9 (9.2)	1 (3.4)	0
SOC Cardiac disorders	1 (0.7)	2 (2.0)	0	0
SOC Vascular disorders	11 (7.6)	10 (10.2)	4 (13.8)	0
Cerebrovascular disorders[a] (SMQ)	0	0	0	0
SOC Infections and infestations	33 (22.9)	20 (20.4)	9 (31.0)	0
PT Anticholinergic syndrome	0	0	0	0
PT Quality of life decreased	0	0	0	0
Sum of following events:	4 (2.8)	3 (3.1)	1 (3.4)	0
Postural hypotension[b]	0	0	0	0
Fall	0	2 (2.0)	0	0
Loss of consciousness	0	0	0	0
Syncope	0	0	0	0
Dizziness	2 (1.4)	1 (1.0)	1 (3.4)	0
Ataxia	1 (0.7)	0	0	0

Fracture[c]	1 (0.7)	0	0	0
Other AE appearing more frequently in older patients[d]				
Abdominal discomfort	0	1 (1.0)	1 (3.4)	0
Abdominal distension	0	0	1 (3.4)	0
Abdominal pain	0	3 (3.1)	1 (3.4)	0
Appendicitis	0	0	1 (3.4)	0
Asthma	0	2 (2.0)	0	0
Back pain	2 (1.4)	4 (4.1)	0	0
Blood cholesterol increased	0	2 (2.0)	0	0
Breast cancer	0	0	0	1 (50.0)
Conjunctivitis	0	0	1 (3.4)	0
Constipation	2 (1.4)	5 (5.1)	3 (10.3)	0
Dehydration	1 (0.7)	0	1 (3.4)	0
Diarrhoea	5 (3.5)	4 (4.1)	4 (13.8)	0
Diverticulum	0	2 (2.0)	0	0
Dizziness	2 (1.4)	1 (1.0)	1 (3.4)	0
Dry mouth	0	4 (4.1)	1 (3.4)	0
Dyspnoea	2 (1.4)	0	1 (3.4)	0
Dyssomnia	0	0	1 (3.4)	0
Fall	0	2 (2.0)	0	0
Flatulence	0	0	2 (6.9)	0
Gastrooesophageal reflux disease	1 (0.7)	0	1 (3.4)	0
Headache	6 (4.2)	9 (9.2)	0	0
Helicobacter gastritis	0	0	1 (3.4)	0
Herpes zoster	0	0	1 (3.4)	0
Hyperglycaemia	2 (1.4)	4 (4.1)	0	1 (50.0)
Hypertension	10 (6.9)	10 (10.2)	4 (13.8)	0
Influenza	1 (0.7)	4 (4.1)	0	0
Intervertebral disc protrusion	0	0	1 (3.4)	0
Iron deficiency anaemia	0	0	1 (3.4)	0
Large intestine polyp	0	0	1 (3.4)	0
Meniscus injury	0	0	1 (3.4)	0
Nausea	4 (2.8)	5 (5.1)	0	1 (50.0)
Pain in extremity	0	0	1 (3.4)	0
Peripheral swelling	0	2 (2.0)	1 (3.4)	0
Pleural effusion	0	0	1 (3.4)	0
Seasonal allergy	1 (0.7)	0	1 (3.4)	0
Tooth infection	0	0	1 (3.4)	0
Upper respiratory tract infection	7 (4.9)	2 (2.0)	2 (6.9)	0
Urinary hesitation	0	0	1 (3.4)	0
Urinary retention	0	1 (1.0)	2 (6.9)	0
Urinary tract infection	8 (5.6)	8 (8.2)	2 (6.9)	0
Urine flow decreased	0	0	1 (3.4)	0
Viral infection	0	0	1 (3.4)	0

N = Number of participants
MedDRA Dictionary Version 21.1 is used.
a The selected PTs corresponds to the following SMQ: Central nervous system vascular disorders, Central nervous system haemorrhages and cerebrovascular conditions, Ischaemic central nervous system vascular conditions, Haemorrhagic central nervous system vascular conditions, Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic, Conditions associated with central nervous system haemorrhages and cerebrovascular accidents.
There is no PT identified in the database.
b Postural Hypotension corresponds to preferred term Orthostatic hypotension in the database.
c Fracture corresponds to the following preferred term in the database: Pelvic fracture.
d The selection of AEs appearing in the elderly population were selected with the following algorithm: PTs with a difference >= 2% between "<65 years" and one of the other groups.

Sources: F00019_OAB - Version date: 06OCT2023 10:49 - File Name: Q115_1_2_c1_AEAgeVib3004_saf_t.rtf Sources: Cut-off date DOSSIER_ISS: 21JUN2022 - Dataset ADSX1.ADAE:11OCT2022 ADSX1.ADSL:11OCT2022 – PGM Q115_1_2_c1_AEAgeVib3004_saf_t.sas 05OCT2023 15:15

Safety in other special populations

Renal impairment

No relevant differences in AE profile were observed for the patient populations with reduced renal clearance, based on the 25th percentile for eGFR of 74.1, 74.4, 72.0, and 75.3 mL/min/1.73 m^2 in pools 1, 2, 3, and 4.

In order to address the question regarding the therapeutic window raised in the pharmacokinetics part (section 3.3.1), a more detailed analysis of safety in patients with renal impairment was undertaken.

In the pivotal studies, the distribution of patients across the RI categories (with eGFR based on the Cockcroft-Gault method) for vibegron was as follows:

- study 3003: normal n=317 (58.1%); mild n=175 (32.1%); moderate n=52 (9.5%) and severe n=1 (0.3%).
- study 3004: normal n=151 (55.3%); mild n=93 (34.1%); moderate n=29 (10.6%); no patients with severe renal impairment were included.

Patients with severe renal impairment were excluded from clinical studies. However, following re-estimation of GFR using the Cockcroft-Gault method, 4 patients were re-classified as having severe renal impairment, including 1 patient in the vibegron arm.

Based on the summary of TEAEs, there is a trend for increasing incidence of any AE with increasing grade of renal impairment in the vibegron arm for both studies. A similar trend was observed for the placebo arm in study 3003, but not for tolterodine in both studies. For incidences of any grade ≥3 AEs, serious AEs and AEs leading to discontinuation, the assessment for a trend across RI categories is hampered in both studies by the low incidence of AEs in each RI category as well as the relatively smaller sample size in the moderate RI category.

The assessment for a trend in individual PTs focused on the AEs designated as adverse reactions and AEs reported in association with overdose. For study 3003, no trend for increasing incidence in these AEs across the RI categories can be discerned. For study 3004, there is a trend for increasing incidence across the RI categories in the vibegron arm for urinary tract infection (4.6%, 7.5% and 13.8% for normal, mild and moderate renal impairment, respectively) and for diarrhoea (2.6%, 6.5% and 10.3%, respectively).

In the patient population with pre-existing hypertension, the incidence of AEs of hypertension in pool 3 was higher in patients with pre-existing hypertension compared to those with no hypertension at baseline; no relevant differences between treatment groups were observed.

No relevant differences in AE profile were observed for the patient populations with lower body weight or other subgroups based on sex, diabetes mellitus or BMI at baseline. Evaluation of AEs by region (US vs. non-US) was affected by the differences in dosing in studies 301 and 302 (conducted in Japan and administered 50- and 100-mg vibegron) and studies 3003 and 3004 (conducted in the US and EU and administered 75-mg vibegron). The small number of patients receiving 75-mg vibegron in the non-US region make comparisons between regions difficult.

2.6.8.8. Immunological events

Rash has been identified as an ADR and is proposed to be included in section 4.8 of the SmPC. Hypersensitivity to the active substance or any of the excipients is addressed as a contraindication in the SmPC section 4.3.

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

In study 010, exploring the pharmacodynamic effect of vibegron 100 mg on blood pressure when used concomitantly with either metoprolol or amlodipine, no clinically relevant changes in systolic blood pressure, either increases or decreases, were observed.

In study 007, no clinically relevant changes in heart rate were observed in healthy male subjects with co-administration of either 100 mg or 150 mg vibegron and tolterodine ER 4 mg.

2.6.8.10. Discontinuation due to adverse events

Study 3003

The incidence of AEs leading to discontinuation of study drug was low across the 3 treatment groups: 6 patients (1.1%) with placebo, 9 patients (1.7%) with vibegron 75 mg and 14 patients (3.3%) with tolterodine.

The incidence of AE-related discontinuations reported with vibegron 75 mg was similar to that observed with placebo. Headache was the most frequently reported AE leading to study drug discontinuation (1 patient [0.2%] in the placebo group, 3 patients [0.6%] in the vibegron 75 mg group and 2 patients [0.5%] in the tolterodine group), followed by dry mouth (4 patients [0.9%] in the tolterodine group only), diarrhoea (2 patients [0.5%] in the tolterodine group only) and hypertension (2 patients [0.4%] in the placebo group and 1 patient [0.2%] in the vibegron group). All the other AEs leading to study discontinuation were reported in 1 patient only in any treatment group. The incidence of discontinuation due to an AE was highest in the tolterodine group, with dry mouth being the most common reported PT.

Study 3004

The incidence of AEs leading to discontinuation of study drug was low in both the overall vibegron and tolterodine treatment groups: 4 patients (1.5%) and 8 patients (3.4%), respectively, with fewer patients discontinuing in the overall vibegron group compared with the overall tolterodine group.

No individual PT was reported as an AE leading to discontinuation by more than 1 patient and thus, there were no discernible patterns of AEs leading to discontinuation for either treatment group. The only AEs reported in the overall vibegron treatment group in 1 patient (0.4%) were: amnesia, constipation, diarrhoea, blood creatinine increased, and blood urea increased.

Pool 1 (12-week Double-blind Studies 301 and 3003)

Table 71. Pool 1 (12-week Double-blind Studies 301 and 3003): Adverse Events Leading to Treatment Discontinuation in >1 Patient Overall

PT	Placebo (N = 909) n (%)	Vibegron 75 mg (N = 545) n (%)	Tolterodine ER 4 mg (N = 430) n (%)	Vibegron 100 mg (N = 369) n (%)
Any AE Leading to Treatment Discontinuation	**8 (0.9)**	**9 (1.7)**	**14 (3.3)**	**3 (0.8)**
Headache	1 (0.1)	3 (0.6)	2 (0.5)	0
Cerebrovascular accident	0	1 (0.2)	1 (0.2)	0
Hypertension	2 (0.2)	1 (0.2)	0	0
Nausea	1 (0.1)	1 (0.2)	0	0
Palpitations	0	1 (0.2)	1 (0.2)	0
Rash	1 (0.1)	1 (0.2)	0	0
Diarrhoea	0	0	2 (0.5)	0
Dry mouth	0	0	4 (0.9)	0
Fatigue	1 (0.1)	0	1 (0.2)	0
Somnolence	1 (0.1)	0	0	1 (0.3)

Source: ISS Table 2.21a
AE = adverse event; ER = extended release; ISS = integrated summary of safety; PT = preferred term; SOC = system organ class
Notes: AEs are coded to SOC and PT using Medical Dictionary for Regulatory Activities coding dictionary version 21.1.
Patient is counted only once in each PT.

Pool 3 (Long-term Exposure Studies: 008, 302, 3004)

Table 72. Pool 3 (Long-term Studies 008 Base and Extension, 302, 3004): Adverse Events Leading to Treatment Discontinuation in >1 Patient Overall

PT	Vibegron 75 mg (N = 273) n (%)	Tolterodine ER 4 mg (N = 472) n (%)	Vibegron 100 mg (N = 299) n (%)	Vibegron 75 + 100 mg (N = 572) n (%)
Any AE Leading to Treatment Discontinuation	**4 (1.5)**	**32 (6.8)**	**15 (5.0)**	**19 (3.3)**
Constipation	1 (0.4)	0	1 (0.3)	2 (0.3)
Abdominal pain upper	0	1 (0.2)	1 (0.3)	1 (0.2)
Breast cancer	0	1 (0.2)	1 (0.3)	1 (0.2)
Depression	0	1 (0.2)	1 (0.3)	1 (0.2)
Dizziness	0	2 (0.4)	0	0
Dry eye	0	2 (0.4)	0	0
Oedema peripheral	0	3 (0.6)	0	0

Source: ISS Table 2.21c
AE = adverse event; ER = extended release; ISS = integrated summary of safety; PT = preferred term; SOC = system organ class
Notes: AEs are coded to SOC and PT using Medical Dictionary for Regulatory Activities coding dictionary version 21.1.
Patient is counted only once in each PT.

The discontinuation rate in the vibegron 75 mg arm was low (1.7% in study 3003 and 1.5% in study 3004) and comparable to placebo in study 3003. In study 3003, the most frequently reported AE leading to discontinuation with vibegron was headache (0.6%); the remaining AEs in study 3003 and all AEs in study 3004 leading to discontinuation were reported in a single patient.

Compared with vibegron 75 mg the discontinuation rate with vibegron 100 mg was numerically lower in pool 1 (0.8%) and higher in pool 3 (5.0%). AEs leading to discontinuation of vibegron 100 mg were reported in single patients.

2.6.8.11. Post marketing experience

Vibegron has been approved in Japan for the treatment of adults with OAB since 21 September 2018 (International Birthdate) and in the US since 23 December 2020. With a data lock point of 20 September 2022, the cumulative worldwide exposure to commercial vibegron was estimated at 1,054,013 patient-treatment years.

Cumulatively, as of 20 September 2022, 4899 ADRs (177 serious; 4722 non-serious) have been reported from spontaneous reports from individual case safety reports, healthcare professionals, consumers, scientific literature, regulatory authorities, and non-interventional studies in the post-marketing setting.

Among these ADRs, 34 serious and 273 non-serious events of urinary retention (PTs urinary retention, residual urine volume increased, and urinary straining) were reported. Other serious renal-related ADRs were observed in more than 1 patient: urinary tract infection (6 events), and dysuria (3 events). Two serious and 52 non-serious events of rash were reported with vibegron (PTs rash, rash pruritic and rash erythematous). Other serious ADRs reported more than once were: death (6 events), pneumonia, fall (5 events each), cerebral infarction (4 events), hospitalisation (4 events); diarrhoea, ileus, peripheral swelling, hepatic function abnormal, headache, pruritus, loss of consciousness, seizure and flushing (2 events each), in addition to the PT: Adverse event (8 events).

Urinary retention and rash are considered ADRs for vibegron. In addition, a warning for urinary retention is included in the SmPC section 4.4 for vibegron.

Among the non-serious ADRs, 31 events related to overdose were reported.

2.6.9. Discussion on clinical safety

Vibegron is a novel β3-adrenoreceptor agonist, proposed for the indication of symptomatic treatment of symptomatic treatment of adult patients with overactive bladder (OAB) syndrome.

Vibegron has been approved in Japan (tradename: Beova) since 21 September 2018 and in the US (tradename: Gemtesa) since 23 December 2020.

The safety database for vibegron is based on 5 completed phase 2 and 3 studies: studies 3003, 3004, 301, 302, and 008. Assessment of safety is primarily based on both pivotal studies 3003 and 3004 (40-week extension study) using the 75 mg dose of vibegron proposed for marketing. Studies 301, 302 and 008 are considered supportive as using different doses of vibegron and were presented as part of the pooled data analysis. Short-term safety data, up to 12 weeks, is derived from study 3003, with supportive data from pool 1, presenting data from studies 301 and 3003. Long-term safety data, up to 52 weeks, is derived from study 3004, with supportive data from pool 3, presenting data from studies 008, 302 and 3003/3004.

The clinical safety database consists of 2625 patients, with 651 patients having received at least 1 dose of vibegron 75 mg and 131 patients being exposed to vibegron 75 mg for 52 weeks or more. The size of the safety database and the extent of exposure is considered adequate for assessment of safety.

The patient population enrolled in studies 3003 and 3004 is representative for the OAB population in terms of age (mean age of 60 and 61 years, respectively) and proportion of patients more than 65 years of age (42.6% and 46.5%, respectively) and ≥75 years of age (13.8% and 12.7%, respectively).

Median treatment duration was identical across the treatment groups in studies 3003 (12 weeks) and 3004 (40 or 52 weeks) as well as in pools 1 and 3.

Overall safety profile

Common AEs with vibegron (≥4%) were urinary tract infection and headache in study 3003 and hypertension, urinary tract infection, headache, nasopharyngitis and diarrhoea in study 3004. Most AEs were mild or moderate in severity in both studies.

The discontinuation rate with vibegron 75 mg was low (1.7% in study 3003 and 1.5% in study 3004) and comparable to placebo in study 3003 and lower compared with tolterodine in study 3004. In study 3003, the most frequently reported AE leading to discontinuation with vibegron was headache (0.6%); the remaining AEs in study 3003 and all aEs in study 3004 leading to discontinuation were reported in a single patient.

Three deaths were reported in the clinical studies. One death occurred with tolterodine and was attributed to urinary tract infection, sepsis, and cerebrovascular accident. Two deaths were reported for patients receiving vibegron; both events were considered as unrelated to study medication by the investigator/sponsor. The death in study 3004 was attributed to arteriosclerotic disease; no autopsy was performed. There was no relevant medical history, no AEs were reported and the patient was not taking any concomitant medications. The fatal event in study 302 was attributed to cervical spinal cord injury resulting from a fall; the patient had been using alcohol and the death was considered an accident.

Serious AEs in study 3003 were reported at similar frequency across study arms (placebo vs. vibegron vs. tolterodine: 1.1% vs. 1.5% vs. 2.3%). Individual SAEs were reported in 1 patient only in each of the treatment arms; no cluster or pattern of SAEs was noted. In 2 patients receiving vibegron, SAEs (pneumonia and non-cardiac chest pain) were assessed as related by the investigator and as unrelated by the sponsor, for the following reasons. The SAE of pneumonia was assessed as unrelated considering the presence of risk factors for pneumonia including advanced age and gastroesophageal reflux disease treated with a proton pump inhibitor (omeprazole). The SAE of non-cardiac chest pain was reported in a patient with multiple reports of chest, back and arm pain for the prior two weeks and the presence of degenerative changes on chest X-ray; the cardiovascular workup was reported as negative.

In study 3004, serious AEs were reported at similar frequency across study arms (vibegron vs. tolterodine: 3.3% vs. 4.3%). Individual SAEs were reported in 1 patient only in each of the treatment arms; no cluster or pattern of SAEs was noted. In 3 patients, SAEs were assessed as related to study drug by the investigator, including one SAE of colitis microscopic in an adult (40-50 years old) female patient receiving vibegron. The sponsor assessed this event as not related to vibegron based on confounding concomitant medications (sertraline, ranitidine and ibuprofen).

No relevant differences in safety profile were observed between vibegron 75 mg and 100 mg.

Dry mouth is a well-known risk for antimuscarinics. No off-target activity for muscarinic receptors (M1-M5) was observed with vibegron in non-clinical study PD007. Thus, there is no pharmacological rationale for vibegron to cause symptoms of dry mouth.

For nasopharyngitis, bronchitis and upper respiratory tract infection an imbalance in AEs reported with vibegron compared with the placebo arm (study 3003) or the tolterodine arm (study 3004). While acknowledging the imbalance in AEs, there is, however, no pharmacological rationale for identifying these events as an ADR taking into account that no evidence for the presence of β3-AR in the respiratory tract has been identified. Furthermore, no immunomodulatory activity has been described in literature for β3-AR agonists.

Based on non-clinical data, similar frequencies of hyperglycaemia in the vibegron and placebo arms in study 3003 and the lack of a pharmacological rationale, hyperglycaemia is not considered an adverse reaction.

Hypertension was not considered as ADR based on similar incidences for vibegron vs. placebo in the short-term studies and vs. tolterodine in the short- and long-term studies as well as the results from the ambulatory blood pressure study 1001. Furthermore, vibegron has a 9000-fold selectivity for β3-AR over β1- and β2-AR, with negligible agonist activity at human β1- and β2-AR (0% and 2%, respectively). Consequently, there is a lack of pharmacological rationale for vibegron to cause increased blood pressure or hypertension.

Two cases of vaginal infection have been reported during study 3003, only one of them was considered as possibly related to the vibegron treatment. The vaginal infection resolved within 7 days without any change in the study treatment dosing. No recurrence was observed. No information on potential confounding factors were provided, therefore, the investigation of other causes, unrelated to the treatment, was not possible. Moreover, there is no relevant literature source available and no pharmacological rationale to support the insertion of vaginal infection in the section 4.8.

Anaemia (11 unique patients in both pivotal studies) was not considered as an ADRs based on no clear temporal relationship, the presence of pre-existing anaemia or other confounding factors (e.g., concomitant AEs of chronic gastritis, gastrointestinal tract bleeding, or pelvic fracture, which likely led to blood loss), minimal decreases in red blood cell counts, no clear pharmacological rationale and laboratory pooled data without any clinically relevant changes in haemoglobin levels.

Back pain and musculoskeletal pain were not considered as ADR based on the lack of a pharmacological rationale.

The criteria for identification of potential ADRs are acceptable. The proposed ADRs as included in section 4.8 of the SmPC are acceptable.

Vital signs

The effect of vibegron on vital signs was explored in detail given that hypertension is an identified risk for mirabegron, another β3-adrenoreceptor agonist. In an ambulatory blood pressure study (study 1001) in OAB patients, no statistically significant or clinically relevant effect of vibegron 75 mg on mean daytime ambulatory systolic/diastolic BP or heart rate was observed. The results for the secondary analyses (mean 24-hour vital signs and maximum vital signs at 0.5 to 6.5 hours post-dose) were consistent with the primary analysis.

In both pivotal studies, vital signs were measured in triplicate. In studies 3003 and 3004, no clinically relevant mean changes from baseline at week 12 (study 3003) or week 52 (study 3004) in vital signs were observed with vibegron 75 mg; changes were similar to those reported with tolterodine or placebo. Results for mean change from baseline to maximum post-baseline value were also similar across treatment arms. These results were confirmed by ANCOVA analysis.

Analysis of categorical increases in vital signs (≥15 mmHg in systolic blood pressure, ≥10 mmHg in diastolic blood pressure and ≥10 bpm in heart rate) did not result in relevant differences between vibegron 75mg and placebo or tolterodine, both for results at 3 consecutive visits and for the maximum value across visits (study 3003 only). The incidence of increases in vital signs (at 3 consecutive visits) in subpopulations at risk, i.e., older age, pre-existing hypertension, low body weight and reduced eGFR was similar between the vibegron and placebo or tolterodine arms in both pivotal studies and pool 3.

ECG

In a thorough QT study (study 012) the effect of vibegron on QTc was tested at 2 dose levels, 200 and 400 mg, representing supratherapeutic doses based on 3.3- and 9-fold higher C_{max} levels, respectively, compared with 75 mg vibegron at steady state. The maximum LS mean difference (90% CI) from placebo in QTcF was 4.98 (3.07, 6.88) msec for 200 mg and 4.60 (2.71, 6.48) msec for 400 mg. For both dose levels, the upper limit of the 90% CI was less than 10 msec, indicating that vibegron at supratherapeutic doses does not cause a clinically relevant prolongation of the QTcF interval. No QTcF intervals ≥450 msec or increases in QTcF interval of ≥30 msec were reported following either dose of vibegron. Study 012 is a negative thorough QT study; no clinically relevant effect of vibegron 75 mg on the QT/QTc interval is foreseen.

ECGs were not routinely collected in studies 3003 and 3004; this is acceptable given the negative thorough QT/QTc study (study 012). The ECG results from the supportive clinical studies do not raise a safety concern.

Post-void residual urine volume

In both pivotal studies, the mean change in post-void residual urine volume from baseline at week 12 and 52 was low and similar across study arms. Categorical data were presented for pools 1 and 3 only. In both pools, the incidence of patients with a PVR urine volume of <100 mL was lower in all treatment groups at week 12 and week 52, respectively, compared with baseline. No relevant differences in incidence across treatment groups were observed for the categories ≥100 mL and <200 mL and ≥200 mL and <350 mL. In study 3003, 2 [0.4%] patients in placebo arms reported of residual volume increased, 4 [0.7%] patients with vibegron and 6 [1.4%] patients in tolterodine arm. In study 3004, 7 [2.6%] patients with vibegron reported a total of 8 events vs 3 [1.3%] patients with tolterodine reported a total of 3 events.

Urinary retention and residual urine volume increased are proposed as adverse reactions to be included in section 4.8; this is overall acceptable, based on an imbalance versus placebo and pharmacological rationale.

With regard to data on post-void residual volume in patients with benign hyperplasia at baseline, no firm conclusions can be drawn due to the small number of patients in the pivotal studies.

Urinary retention is also proposed to be addressed in section 4.4 of the SmPC, based on data from clinical studies and post-marketing reporting. The proposed warning concerns an increased risk of urinary retention in patients with bladder outlet obstruction and patients taking antimuscarinic medicinal products. A search for patients with a medical condition or history predisposing for bladder outlet obstruction at baseline (e.g., calculus urinary, urethral stenosis, benign urinary tract neoplasm or benign prostate hyperplasia) identified 102 patients in study 3003 (placebo vs. vibegron vs. tolterodine: 33 vs. 39 vs. 30) and 40 patients is study 3004 (vibegron vs. tolterodine: 23 vs. 17). In the subgroup at-risk for bladder outlet obstruction, urinary retention was reported in 1 patient (2.6%) in the vibegron arm in study 3003 and in 2 patients (8.7%) on vibegron in study 3004; none of the patients on placebo or tolterodine in either study reported urinary retention. None of these events were serious. Although data is too limited to draw any firm conclusions, an increased risk of urinary retention in patients with conditions predisposing for bladder outlet obstruction is plausible; thus, there is a need for a warning and precautionary measures. None of the patients in studies 3003 and 3004 used antimuscarinics (prohibited concomitant medication as per protocol). In part 2 of study 008, urinary retention was reported at a higher incidence with the combination treatment vibegron 100 mg + tolterodine 4 mg (2.2%) versus 0% with vibegron 100 mg. Overall, based on the data from study 008, a warning for urinary retention in patients taking antimuscarinics concomitantly with vibegron is justified. The proposal for text in section 4.4 is acceptable.

Laboratory evaluation

No clinically meaningful differences were observed between patients receiving vibegron, placebo or tolterodine. Only few patients in any pool had increased liver enzymes, and no patients met the laboratory criteria for Hy's law.

Adverse events of clinical interest

The following adverse events of clinical interest (AECIs) were pre-defined: major cardiac and cerebrovascular events (MACCE), hypertension, orthostatic hypotension, cystitis or urinary tract infection and alanine transferase (ALT) and aspartate transferase (AST) elevations.

Of the AECIs, urinary tract infections, including cystitis, is proposed to be included as an ADR in section 4.8, based on similar frequency to tolterodine and a pharmacological rationale.

Even if data for vibegron does not support hypertension as a risk, such risk is recommended as important potential risk in the context of the PSUR for further evaluations.

Safety in special populations

Safety in special populations was analysed for both pooled analyses. For the age categories with a cut-off of 65 years and 75 years, the incidence of any AEs was higher for patients ≥65 years and ≥75 years of age compared with those <65 or 75 years, respectively. The AE profile was generally similar between in both age categories, although small differences in incidences were observed.

In the patient population with pre-existing hypertension, the incidence of AEs of hypertension in pool 3 was higher in patients with pre-existing hypertension compared to those with no hypertension at baseline; no relevant differences between treatment groups were observed.

No relevant differences in AE profile were observed for the patient populations with lower body weight, reduced renal clearance or other subgroups based on sex, diabetes mellitus or BMI at baseline.

No relevant differences in safety profile were observed for patients with mild or moderate renal impairment compared to those with normal renal function at baseline. No conclusion can be drawn regarding safety in patients with severe renal impairment based on safety data for 1 patient in study 3003. The recommendation not to use vibegron in these patients is thus endorsed, as outlined in SmPC section 4.2.

Therapeutic window

A concern regarding the therapeutic window for patients with moderate or severe renal impairment and in patients treated with concomitant strong CYP3A4/P-gp inhibitors has been raised, as a doubling of AUC is expected in these patients. Although there are no (or very limited) safety data from the pivotal studies for patients with severe renal impairment or patients with concomitant use of a strong CYP3A4/P-gp inhibitor, the safety profile in both subgroups is expected to be similar to the moderate renal impairment group based on the expected doubling of AUC for all 3 subgroups. Furthermore, no specific safety concerns were raised with the 100 mg dose in the long-term Japanese study 301. Although the expected exposure with the 100 mg dose is slightly lower (i.e., 1.7 to 1.8-fold increase in AUC) than in both renal impairment groups, the safety data in this study provide further support for the conclusion regarding safety in both renal impairment groups and concomitant use of a strong CYP3A4/P-gp inhibitor. Consequently, the Applicant's proposal for sections 4.2 and 4.5 of the SmPC, informing that no dose adjustment is needed, is acceptable. In addition, as vibegron has not been studied in patients with end-stage renal disease (GFR < 15 mL/min with or without haemodialysis) it is therefore not recommended in these patients, as stated in section 4.2. and 5.2. of the SmPC.

2.6.10. Conclusions on the clinical safety

The size of the safety database and the extent of exposure is considered adequate to allow for safety assessment. The patient population included in the pivotal studies, with at least 40% of patients aged 65 years or older, is representative for the general patient population with overactive bladder syndrome.

From a safety perspective, no specific concerns are raised, including for the patient population aged 65 years or older. The most frequent adverse events with vibegron 75 mg in the treatment of OAB were urinary tract infection, gastrointestinal events and headache. No clinically relevant effects of vibegron on the QTc interval or blood pressure have been observed. Based on the low incidence of AEs leading to discontinuation, treatment with vibegron is well tolerated.

Even if data for vibegron does not support hypertension as a risk, such risk is recommended as important potential risk in the context of the PSUR for further evaluations.

Vibegron treatment is not recommended during pregnancy and should not be used during breast feeding. In addition, vibegron treatment is not recommended in women of childbearing potential not using contraception and a recommendation that vibegron treatment should be stopped and, if appropriate, alternative therapy should be started when pregnancy is planned or diagnosed is included in SmPC 4.6. Overall, from a safety perspective the application for marketing authorisation for vibegron in the proposed indication is approvable.

2.7. Risk Management Plan

2.7.1. Safety concerns

Important identified risks	None
Important potential risks	Embryo-foetal toxicity
Missing information	None

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities are planned to be conducted.

2.7.3. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk		
None	Not applicable	Not applicable
Important potential risk		
Embryo-foetal toxicity	Routine risk minimisation measures: - SmPC section 4.6 and section 5.3: - PL section 2 Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up forms Additional pharmacovigilance activities: None.
Missing information		
None	Not applicable	Not applicable

PL = Package leaflet; SmPC = Summary of Product Characteristics.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 21.09.2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. *Product information*

2.9.1. User consultation

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

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Obgemsa (Vibegron) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Vibegron is a ß3 adrenergic receptor agonist. Activation of the beta-3 adrenergic receptor located in the bladder detrusor muscle increases bladder capacity by relaxing the detrusor smooth muscle during bladder filling.

Overactive bladder is a clinical syndrome characterised by urinary urgency (i.e., a sudden compelling desire to void that is difficult to defer) with or without urge urinary incontinence (UUI). The aim of therapy is to increase bladder control and thereby decrease the daily number of urinary urgency and/or incontinence episodes.

3.1.2. Available therapies and unmet medical need

The most prescribed OAB medications are of the antimuscarinic drug class.

The first-generation β3-AR agonist (mirabegron; Betmiga) was approved in the EU in 2012 for the “symptomatic treatment of urgency, increased micturition frequency, and/or urgency incontinence as may occur in adult patients with OAB syndrome”.

There is a disease burden in OAB, and although there is a diversity of therapies available., there is an unmet need for more efficacious therapy in this common medical condition. However, the active compound in the present application, vibegron, has a similar mechanism of action as mirabegron.

3.1.3. Main clinical studies

The main evidence of efficacy and safety submitted is a single pivotal phase 3 randomised, double-blind, placebo and active-controlled, multicentre study (study 3003) comparing vibegron (n=547) vs. placebo (n=540) and the active control tolterodine (n=431) in adult patients with OAB. At the end of the study, subjects were invited to enter the extension study 3004 with vibegron and tolterodine treatments. Only descriptive statistics was used in the comparison between vibegron and tolterodine.

To be eligible for the study, adult subjects (≥18 years old) should have had a history of OAB for at least 3 months prior to the screening visit. OAB was defined as urgency, with or without urge urinary incontinence, usually associated with frequency and nocturia. Most patients (≥ 75%) should have OAB Wet and not more than 25% should have OAB Dry. Eligibility criteria were adequately reflecting the target patient group.

The subjects were randomised in a 5:5:4 ratio to receive either vibegron 75 mg, placebo, or the active comparator tolterodine ER 4 mg.

The co-primary efficacy endpoints were change from baseline at Week 12 in average numbers of micturition's per 24 hours in all OAB subjects and change from baseline at Week 12 in average number of UUI episodes per 24 hours in OAB Wet subjects.

3.2. Favourable effects

Placebo controlled phase

Both co-primary efficacy endpoints were met at week 12. The co-primary efficacy endpoints were evaluated at week 12, and additional evaluations were performed at week 2, week 4, week 8. A statistically significant ($p < 0.001$) reduction from baseline was demonstrated regarding change from baseline in number of micturition's following 12 weeks of dosing with vibegron 75 mg in all OAB subjects. The LS means difference (SE; 95% CI) for active – placebo was -0.5 (0.15; -0.8 to -0.2). Similarly, for the other co-primary efficacy endpoint, change from baseline in UUI per 24 hours, a statistically significant ($p < 0.001$) reduction from baseline was demonstrated after 12 weeks of dosing with vibegron 75 mg in OAB Wet subjects. The LS means difference (SE; 95% CI) for active – placebo was -0.6 (0.14; -0.9 to -0.3).

Onset of clinical efficacy was observed after 2 weeks and was maintained over the duration of the 12-week study ($p < 0.001$ at all timepoints).

Statistical superiority of vibegron over placebo was demonstrated for all 7 key secondary OAB endpoints which were tested sequentially at week 12. The LS means difference (SE; 95% CI) for Average daily number of 'need to urinate immediately (urgency) episodes for active – placebo was -0.7 (0.22; -1.1 to -0.2). The result for Average daily number of total incontinence episodes (SE; 95% CI) for active – placebo was -0.7 (0.16; -1.0 to -0.4). The result for Average volume voided (ml) per micturition (SE; 95% CI) for active – placebo was -21 (3.5; 14 to 28). Also, the key secondary endpoints, Percent of OAB Wet subjects with at least a 75% reduction from baseline in UUI episodes, and Percent of OAB Wet subjects with a 100% reduction from baseline in UUI episodes as responders.

3.3. Uncertainties and limitations about favourable effects

The application is supported by only one single pivotal phase 3 study. Nevertheless, considering the size of this 12-week study, the convincing results obtained which were statistically significant in favour of vibegron 75 mg, and the well-known mechanism of action, a single pivotal trial is accepted.

Long-term efficacy data are limited. Available data have been measured as secondary parameters and are descriptive only. Although the results obtained at week 52 do not suggest a loss of efficacy, these data do not allow to firmly conclude regarding the maintenance of effect of vibegron.

3.4. Unfavourable effects

The safety database providing safety data for the 75 mg dose of vibegron includes 651 patients (of which 131 patients with long-term exposure data of at least 52 weeks) and is mainly based on the pivotal study 3003 and its 40-week extension, study 3004.

The most commonly reported AE with vibegron was urinary tract infection (study 3003: 5% with vibegron, vs. 6.1% with placebo and 5.8% with tolterodine; study 3004: 6.6% with vibegron vs. 7.3% with tolterodine). In line with the mechanism of action of vibegron, urinary retention was reported in

0.6% of patients with vibegron compared with 0.4% in the placebo arm and 0.7% in the tolterodine arm in study 3003; frequencies for urinary retention in study 3004 were 1.1% with vibegron and 0.4% with tolterodine.

In study 3003, the frequency of AEs leading to discontinuation was 1.7% with vibegron compared with 1.1% with placebo and 3.3% with tolterodine. The most frequently reported AE leading to discontinuation with vibegron was headache (0.6%). In study 3004, the frequency of AEs leading to discontinuation was 1.5% with vibegron compared with 3.4% with tolterodine.

Even if data for vibegron does not support hypertension as a risk, such risk is recommended as important potential risk in the context of the PSUR for further evaluations.

Vibegron treatment is not recommended during pregnancy and should not be used during breast feeding. In addition, vibegron treatment is not recommended in women of childbearing potential not using contraception and a recommendation that vibegron treatment should be stopped and, if appropriate, alternative therapy should be started when pregnancy is planned or diagnosed is included in SmPC 4.6.

3.5. Uncertainties and limitations about unfavourable effects

Based on differences in β3-AR potency across species in the non-clinical studies, the safety margins for embryofoetal toxicity are considered to be of potential relevance for use in humans; consequently, embryofoetal toxicity is included in the RMP as an important potential risk and relevant statements included in SmPC section 4.6., i.e. vibegron treatment is not recommended during pregnancy and should not be used during breast feeding, not recommended in women of childbearing potential not using contraception and a recommendation that vibegron treatment should be stopped and, if appropriate, alternative therapy should be started when pregnancy is planned or diagnosed. Furthermore, the applicant included specific adverse reaction follow-up questionnaires to monitor the important potential risk of embryo-foetal toxicity, see RMP section 2.7. Furthermore, hypertension will be followed-up post-approval (in future PSURs).

3.6. Effects Table

Table 73. Effects Table for Obgemsa (Vibegron) indicated in OAB.

Effect	Short Description	Unit	Vibegron	Placebo	Tolterodine	Uncertainties/ Strength of evidence	References
	Favourable Effects						
Co-primary endpoints	Change from baseline in micturition's	LS means (SE) 95% CI	-1.8 (0.14) -2.1 - -1.5	-1.3 (0.14) -1.6 - -1.0	-1.6 (0.15) -1.9 - -1.3	The effect of vibegron 75 mg was robustly documented albeit with a modest magnitude, like the magnitude of the antimuscarinic agent tolterodine.	Study 3003
	Change from baseline in urge urinary incontinence episodes	LS means (SE) 95% CI	-2.0 (0.13) -2.3 - -1.8	-1.4 (0.13) -1.7 - -1.2	-1.8 (0.14) -2.1 - -1.5		
Key secondary endpoints	Change from baseline in micturition's 52-weeks treatment	LS means (SE) 95% CI	-2.4 (0.24) -2.9 - -2.0	N/A	-2.0 (0.26) -2.5 - -1.5		Study 3003
	Change from baseline in UUI 52-weeks treatment	LS means (SE) 95% CI	-2.2 (0.15) -2.5 - -1.9	N/A	-1.7 (0.17) -2.0 - -1.3		
	Change from baseline in urgency episodes 52-weeks treatment	LS means (SE) 95% CI	-3.4 (0.34) -4.0 - -2.7	N/A	-3.2 (0.37) -4.0 - -2.5		
	Change from baseline in total urinary incontience episodes 52-weeks treatment	LS means (SE) 95% CI	-2.5 (0.17) -2.8 - -2.2	N/A	-1.9 (0.19) -2.3 - -1.6		
	Unfavourable Effects						
AE summary	Any AE	%	38.7	33.3	38.6		Study 3003
	Grade ≥3	%	1.1	1.5	2.1		
	SAE	%	1.5	1.1	2.3		

Effect	Short Description	Unit	Vibegron	Placebo	Tolterodine	Uncertainties/ Strength of evidence	References
	Fatal AE	%	0	0	0.2		
	AE leading to drug discontinuation	%	1.7	1.1	3.3		
AE summary	Any AE	%	62.6	NA	54.3		Study 3004
	Grade ≥3	%	3.7	NA	3.4		
	SAE	%	3.3	NA	4.3		
	Fatal AE	%	0.4	NA	0		
	AE leading to drug discontinuation	%	1.5	NA	3.4		

Abbreviations: Adverse event (AE), Confidence interval (CI), Least-square (LS), Serious adverse event (SAE), Standard error (SE), Urgency urinary incontinence (UUI)

3.6.1. Importance of favourable and unfavourable effects

The main evidence of efficacy comes from a single pivotal phase 3 study. Considering the size of this 12-week study, the convincing results obtained which were statistically significant in favour of vibegron 75 mg, and the well-known mechanism of action, a single pivotal trial is accepted. The overall design with a placebo-controlled trial is considered adequate.

The efficacy endpoints chosen for this application are also considered clinically relevant.

Both co-primary efficacy endpoints were met as well as all key secondary efficacy endpoints. Considering the magnitude of the absolute change in number of micturition's and change in number of UUI, the effect of vibegron albeit modest, is considered to be clinically relevant for OAB patients.

The originally applied indication was *"symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with Overactive Bladder (OAB) syndrome.'* During the course of the evaluation, upon the CHMP request, the applicant agreed that the indication should define the target disease/condition and that references to study endpoints should not be included. Therefore the finally agreed indication for vibegron is '*symptomatic treatment of adult patients with overactive bladder (OAB) syndrome'.* The proposed posology is 75 mg once daily.

The size of the safety database and the extent of exposure is considered adequate to allow for safety assessment. The patient population included in the pivotal study, with at least 40% of patients aged 65 years or older, is representative for the general patient population with OAB syndrome. Based on the overall safety data presented, no specific concerns are raised.

Even if data for vibegron does not support hypertension as a risk, such risk is recommended as important potential risk in the context of the PSUR and will be closely monitored post-approval.

Vibegron treatment is not recommended during pregnancy and should not be used during breast feeding, not recommended in women of childbearing potential not using contraception and a recommendation is given that vibegron treatment should be stopped and, if appropriate, alternative therapy should be started when pregnancy is planned or diagnosed. Furthermore, the applicant included specific adverse reaction follow-up questionnaires to monitor the important potential risk of embryo-foetal toxicity, see RMP section 2.7.

3.6.2. Balance of benefits and risks

The efficacy of vibegron has been sufficiently demonstrated. Considering that vibegron has a benign safety profile, the effect, although modest, can be considered clinically relevant and sufficient to conclude on the positive benefit-risk balance in OAB.

3.6.3. Additional considerations on the benefit-risk balance

Not applicable.

3.7. Conclusions

The overall benefit/risk balance of Obgemsa is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Obgemsa is favourable in the following indication:

Obgemsa is indicated in symptomatic treatment of adult patients with overactive bladder (OAB) syndrome.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- Risk Management Plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Vibegron is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

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