Vibegron
(overactive bladder)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Vibegron (überaktive Blase) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Medical and scientific advice

- Winfried Vahlensieck

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Alfred Marenbach and 5 other people.

IQWiG thanks the respondents and the patient organizations 'Selbsthilfe Bund Blasenkrebs e. V. Bonn' and 'Deutsche Multiple Sklerose Gesellschaft' for participating in the written exchange and for their support. The respondents and the patient organizations 'Selbsthilfe Bund Blasenkrebs e. V. Bonn' and 'Deutsche Multiple Sklerose Gesellschaft' were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BPH	benign prostatic hyperplasia
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
FAS	full analysis set
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ICS	International Continence Society
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NCI	National Cancer Institute
OAB	overactive bladder
OAB-q LF	Overactive Bladder symptom and health-related quality of life questionnaire long form
PGI	Patient Global Impression
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SAF	safety analysis set
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics
SOC	System Organ Class
VAS	visual analogue scale
WPAI-US	Work Productivity and Activity Impairment Questionnaire-Urinary Symptoms

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug vibegron. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 3 March 2025.

Research question

The aim of this report is to assess the added benefit of vibegron in comparison with the appropriate comparator therapy (ACT) for the symptomatic treatment of adult patients with overactive bladder (OAB) syndrome.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of vibegron

Therapeutic indication	**ACT**[a]
Symptomatic treatment of adult patients with overactive bladder (OAB) syndrome	Darifenacin or desfesoterodine or fesoterodine or mirabegron or propiverine or solifenacin or tolterodine or trospium chloride[b]

a. Presented is the ACT specified by the G-BA.
b. Comments from the G-BA:
- The ACT specified here comprises several alternative treatment options. These alternative treatment options are equally appropriate for the comparator therapy.
- The added benefit can be proven in comparison with one of the cited alternative treatment options; this can typically be achieved in the context of a single-comparator study.
- Non-drug interventions as outlined in the German Remedies Directive or the Remedies Catalogue (e.g. physiotherapy) can help to alleviate symptoms and, if indicated, should be offered in both study arms. The type and scope of the interventions used must be documented.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAB: overactive bladder

The company's comparator therapy corresponded to the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used to derive the added benefit. This concurred with the company's inclusion criteria.

Study pool and study design

The studies RVT-901-3003 and RVT-901-3004 were included in the benefit assessment. The company excluded the 12-week study RVT-901-3003 in Module 4 A of the dossier due to the

short study duration (< 24 weeks treatment duration) and only included its extension study RVT-901-3004 (treatment over a further 40 weeks). However, the results presented by the company in Module 4 A referred to patients who received vibegron or tolterodine over a total period of 52 weeks by participating in both study RVT-901-3003 and extension study RVT-901-3004. The 2 studies RVT-901-3003 and RVT-901-3004 were therefore regarded as 1 continuous study for this dossier assessment. For this reason, study RVT-901-3003 is also described in this benefit assessment in addition to study RVT-901-3004.

Study RVT-901-3003

Study RVT-901-3003 is a double-blind RCT comparing vibegron with tolterodine or placebo, with a treatment duration of 12 weeks. Adult patients with medically diagnosed OAB for at least 3 months were enrolled. OAB was defined as urgency, with or without urge incontinence, usually associated with increased micturition frequency and nocturia. Patients had to have an OAB labelled either as 'OAB dry' or 'OAB wet'; the classification was based on the patients' micturition diary entries. An additional requirement for inclusion in study RVT-901-3003 was good general physical and mental health as determined by the investigator. Patients who had undergone bladder training or electrostimulation in the 28 days prior to screening or planned to start such treatment during the study were, among others, excluded from study participation.

The study comprised a screening phase of up to 5 weeks, a 2-week single-blind placebo run-in phase and a 12-week double-blind treatment phase. A 4-week follow-up phase followed for those patients who did not transfer to extension study RVT-901-3004. A total of 1518 patients were randomly assigned in a 5:5:4 ratio to treatment with vibegron, placebo or tolterodine.

Treatment with vibegron as a film-coated tablet at a dosage of 75 mg once daily and administration of tolterodine as a prolonged-release capsule at a dosage of 4 mg once daily (for patients without renal or hepatic impairment) concurred with the recommended dosages according to the respective summary of product characteristics (SmPC). According to the SmPC, the daily dose of tolterodine can be reduced from 4 mg to 2 mg if intolerances occur. However, all dose modifications were prohibited in the study.

The coprimary outcomes of study RVT-901-3003 were micturition frequency and urge incontinence episodes. Secondary outcomes included outcomes from the categories of morbidity, health-related quality of life and side effects.

Study RVT-901-3004

Study RVT-901-3004 is a randomized, double-blind extension study to RVT-901-3003, on the comparison of vibegron with tolterodine. The extension study comprised a 40-week treatment phase and a 4-week follow-up phase.

To participate, patients had to have completed study RVT-901-3003. In addition to the criteria for inclusion in study RVT-901-3003, RVT-901-3004 required that patients showed at least 80% compliance with self-administration of the study medication during the course of RVT-901-3003 and had at least 4 complete diary days in their micturition diary at Week 12. In addition, patients were excluded from participation in the extension study if new health problems or clinically relevant changes in an existing disease had occurred during the course of study RVT-901-3003, or if there was a change in the medical history or other circumstances which, in the opinion of the investigator, could falsify the results of the study.

The preliminary plan was to enrol around 500 patients with OAB who had participated in study RVT-901-3003 for 12 weeks into study RVT-901-3004. A total of 506 patients were enrolled in study RVT-901-3004. Patients who had been randomized to the vibegron or tolterodine arm in study RVT-901-3003 remained in their respective treatment arms in extension study RVT-901-3004. Patients who had been randomized to the placebo arm in study RVT-901-3003 were randomized 1:1 to the vibegron or tolterodine treatment arm. The number of patients who were continuously in the vibegron or tolterodine arm for 52 weeks was 182 and 141 patients respectively.

Treatment with vibegron and tolterodine in study RVT-901-3004 was concurrent with treatment in study RVT-901-3003 (see above).

The primary outcome of study RVT-901-3004 was adverse events (AEs). Secondary outcomes comprised outcomes from the morbidity and health-related quality of life categories.

No accompanying bladder training or electrostimulation

The results observed in studies RVT-901-3003/RVT-901-3004 refer to patients who, according to the inclusion and exclusion criteria of the study, did not conduct bladder training or electrostimulation in the 28 days prior to screening and did not plan to do so during the study.

No dose modification of tolterodine allowed

According to the SmPC, the daily dose of tolterodine can be reduced from 4 mg to 2 mg in case of intolerance. This option was not available to patients in study RVT-901-3003 and extension study RVT-901-3004, as any dose modifications were prohibited. This represents an uncertainty, as it remains unclear to what extent AEs could have been avoided in the comparator arm if the possibility of dose reduction had existed. This uncertainty was taken into account in the assessment of the risk of bias of the AE outcomes results.

Transition from study RVT-901-3003 to extension study RVT-901-3004

In order to be able to use the results of the extension study, the structural equality between the study arms, which was achieved at the beginning of the first study through the randomized allocation of patients to the study arms, needed to be maintained after the transition to the

extension study. The transition of patients from study RVT-901-3003 to extension study RVT-901-3004 was associated with the following uncertainties in particular.

Firstly, the study documents showed that around 10% of the 1518 patients enrolled in study RVT-901-3003 did not complete the study. These patients therefore did not have the opportunity to proceed to extension study RVT-901-3004. This may affect the certainty of results of the study if the reasons for early discontinuation of RVT-901-3003 were informative and the number of discontinuations or reasons for discontinuation were unevenly distributed between the study arms.

The study documents showed that the frequency and reasons for study discontinuations in study RVT-901-3003 were comparable between the study arms. However, with regard to the discontinuation reason withdrawal of consent to participate in the study, there was no information as to whether the reasons that led the patients to withdraw consent differed between the study arms. Overall, this did not completely call into question the interpretability of the data in the given data situation.

Secondly, of the patients who completed study RVT-901-3003, around 500 patients were to be enrolled in extension study RVT-901-3004. According to a publication on study RVT-901-3004 by Staskin 2021, 506 (86%) of the 587 patients from the 3 study arms who completed study RVT-901-3003 first decided to participate in study RVT-901-3004 and met the inclusion criteria. Based on this information, it is assumed that patients had the opportunity to participate in study RVT-901-3004 in the order in which they completed RVT-901-3003. One prerequisite was that the patients decided in favour of further participation and that none of the exclusion criteria were met. For the remaining 81 (14%) of the 587 patients from the 3 study arms, the specific reasons for not participating in the extension study were not clear from the available data. It thus remained unclear whether the distribution of these 81 patients differed between the study arms, or whether the reasons for non-participation were distributed very differently between the study arms.

The uncertainties described in the present situation did not lead to the exclusion of studies RVT-901-3003/RVT-901-3004. It was assumed that the structural equality of the study arms in the transition from study RVT-901-3003 to study RVT-901-3004 was not impaired to such an extent that the results could not be used for the benefit assessment. This uncertainty was, however, taken into account in the assessment of the risk of bias.

Subpopulation presented by the company

In line with the company, this benefit assessment considered the subpopulation of patients in studies RVT-901-3003/RVT-901-3004 who were treated with vibegron or tolterodine during both studies – and thus continuously over a period of 52 weeks. This subpopulation (N = 323) comprised 182 patients in the vibegron arm and 141 patients in the tolterodine arm.

The patients who received placebo in study RVT-901-3003 and who were newly randomized to the vibegron or tolterodine treatment arm in RVT-901-3004 (N = 183) were not taken into account. Although these patients made up a relevant proportion of the population enrolled in study RVT-901-3004 (183/506 [36%]), a 12-week placebo treatment prior to the start of the actual drug treatment does not concur with everyday practice overall. In addition, some of the patients in study RVT-901-3003 had already experienced an improvement in their OAB symptoms when taking placebo. When starting active therapy with vibegron or tolterodine, these patients may no longer have represented the population for whom treatment with vibegron or tolterodine is indicated.

Risk of bias

The risk of bias across outcomes was rated as high for the combination of studies RVT-901-3003/RVT-901-3004. The reason for this was uncertainty regarding the transition of patients from study RVT-901-3003 study to extension study RVT-901-3004. This led to a high risk of bias for the results for all outcomes.

In addition, there was uncertainty regarding outcomes in the side effects category, as the dosage of tolterodine in the study could not be reduced if intolerance occurred, contradicting the SmPC. It therefore remains unclear whether AEs could have been avoided in the comparator arm.

Results

Mortality

The results on all-cause mortality were based on data on fatal AEs. No events for the outcome of all-cause mortality occurred in study RVT-901-3004. There was no hint of an added benefit of vibegron in comparison with tolterodine; an added benefit is therefore not proven.

Morbidity

Symptoms (OAB-q LF, PGI-Change, PGI-Severity and PGI-Control)

For the outcomes on symptoms, recorded using the Overactive Bladder symptom and health-related quality of life questionnaire long form (OAB-q LF), and Patient Global Impression of Change (PGI-Change), Patient Global Impression of Severity (PGI-Severity) and Patient Global Impression of Control (PGI-Control), there was no statistically significant difference between the treatment groups. There was no hint of an added benefit of vibegron in comparison with tolterodine; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No statistically significant difference between treatment groups was shown for the outcome of health status. There was no hint of an added benefit of vibegron in comparison with tolterodine; an added benefit is therefore not proven.

Incontinence and urge incontinence

A statistically significant difference in favour of vibegron in comparison with tolterodine was shown for each of the outcomes of incontinence and urge incontinence, based on the mean differences. However, it was not possible to deduce from the associated effect estimates and associated 95% confidence intervals (CI) that for the mean difference for both outcomes of half an incontinence episode between the 2 treatment arms, there were clinically relevant effects. Considered together, there was no hint of an added benefit of vibegron in comparison with tolterodine for these outcomes; an added benefit is therefore not proven.

Micturition frequency

There was no statistically significant difference between the treatment groups for the outcome of micturition frequency. There was no hint of an added benefit of vibegron in comparison with tolterodine; an added benefit is therefore not proven.

Urgency

There was no statistically significant difference between the treatment groups for the outcome urgency. There was no hint of an added benefit of vibegron in comparison with tolterodine; an added benefit is therefore not proven.

Nocturia

There was no statistically significant difference between the treatment groups for the outcome nocturia. There was no hint of an added benefit of vibegron in comparison with tolterodine; an added benefit is therefore not proven.

Health-related quality of life (OAB-q LF)

For the outcome of health-related quality of life (recorded using the OAB-q LF), no statistically significant difference between treatment groups was found. However, there is an effect modification by the characteristic of age. For patients ≥ 65 years, there was a hint of an added benefit of vibegron in comparison with tolterodine. For patients < 65 years, there was no hint of an added benefit of vibegron in comparison to tolterodine; an added benefit is therefore not proven for patients < 65 years of age.

Side effects

SAEs, severe AEs, and discontinuation due to AEs

No statistically significant difference between treatment groups was found for any of the outcomes of SAEs, severe AEs, or discontinuation due to AEs. For each of these outcomes, there was no hint of greater or lesser harm from vibegron in comparison with tolterodine; greater or lesser harm is therefore not proven.

Urinary tract infection

There was no statistically significant difference between the treatment groups for the outcome urinary tract infection (AE). There was no hint of greater or lesser harm of vibegron in comparison with tolterodine; greater or lesser harm is therefore not proven.

Dry mouth

A statistically significant difference in favour of vibegron in comparison with tolterodine was shown for the outcome of dry mouth (AE). There was a hint of lesser harm from vibegron in comparison with tolterodine. However, it is unclear to what extent this AE could have been avoided or reduced in the tolterodine arm if the possibility of dose reduction in case of intolerance had existed in studies RVT-901-3003/RVT-901-3004. This also contributed to the reduced certainty of conclusions for this outcome.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of the added benefit of the drug vibegron versus the ACT was assessed as follows:

Overall, a positive effect for the outcome health-related quality of life (OAB-q LF) remains for vibegron compared with tolterodine for patients ≥ 65 years. Regardless of age, there was a positive effect for the outcome dry mouth (non-serious/non-severe side effects). The positive effect for the outcome dry mouth alone was not assessed to be sufficient in the present data situation to derive an added benefit for all patients. It is also unclear to what extent AEs could have been avoided or reduced in the tolterodine arm if the possibility of dose reduction in case of intolerance had existed in studies RVT-901-3003/RVT-901-3004.

Weighing up is therefore carried out separately for the 2 age categories. For patients aged 65 years and over, there was a hint of minor added benefit, but for patients < 65 years of age, the added benefit is not proven.

Table 3 presents a summary of the probability and extent of the added benefit of vibegron.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Vibegron – extent and probability of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Symptomatic treatment of adult patients with overactive bladder (OAB) syndrome	Darifenacin or desfesoterodine or fesoterodine or mirabegron or propiverine or solifenacin or tolterodine or trospium chloride[b]	▪ Patients ≥ 65 years: hint of a minor added benefit[c] ▪ Patients < 65 years: added benefit not proven[c]

a. Presented is the ACT specified by the G-BA.
b. Comments from the G-BA:
- The ACT specified here comprises several alternative treatment options. These alternative treatment options are equally appropriate for the comparator therapy.
- The added benefit can be proven in comparison with one of the cited alternative treatment options; this can typically be achieved in the context of a single-comparator study.
- Non-drug interventions as outlined in the German Remedies Directive or the Remedies Catalogue (e.g. physiotherapy) can help to alleviate symptoms and, if indicated, should be offered in both study arms. The type and scope of the interventions used must be documented.

c. Due to the inclusion criteria of studies RVT-901-3003/RVT-901-3004, it remains unclear whether the observed effects can be transferred to patients who do not have good general physical and mental health and to patients for whom additionally the initiation of non-drug measures such as bladder training or electrostimulation would be indicated.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAB: overactive bladder

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of vibegron in comparison with the ACT for the symptomatic treatment of adult patients with OAB syndrome.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of vibegron

Therapeutic indication	**ACT**[a]
Symptomatic treatment of adult patients with overactive bladder (OAB) syndrome	Darifenacin or desfesoterodine or fesoterodine or mirabegron or propiverine or solifenacin or tolterodine or trospium chloride[b]

a. Presented is the ACT specified by the G-BA.
b. Comments from the G-BA:
- The ACT specified here comprises several alternative treatment options. These alternative treatment options are equally appropriate for the comparator therapy.
- The added benefit can be proven in comparison with one of the cited alternative treatment options; this can typically be achieved in the context of a single-comparator study.
- Non-drug interventions as outlined in the German Remedies Directive or the Remedies Catalogue (e.g. physiotherapy) can help to alleviate symptoms and, if indicated, should be offered in both study arms. The type and scope of the interventions used must be documented.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAB: overactive bladder

The company's comparator therapy corresponded to the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used to derive the added benefit. This concurred with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on vibegron (status: 5 February 2025)
- Bibliographical literature search on vibegron (last search on 5 February 2025)
- Search of trial registries/trial results databases for studies on vibegron (last search on 5 February 2025)
- Search on the G-BA website for vibegron (last search on 5 February 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on vibegron (last search on 27 March 2025); for search strategies, see I Appendix A of the full dossier assessment

The review of completeness did not identify any additional relevant studies.

It should also be noted that the company excluded the 12-week study RVT-901-3003 in Module 4 A of the dossier due to the short study duration (< 24 weeks treatment duration) and only included its extension study RVT-901-3004 (treatment over a further 40 weeks). However, the results presented by the company in Module 4 A referred to patients who received vibegron or tolterodine over a total period of 52 weeks by participating in both study RVT-901-3003 and extension study RVT-901-3004. The 2 studies RVT-901-3003 and RVT-901-3004 were therefore regarded as 1 continuous study for this dossier assessment. For this reason, study RVT-901-3003 is also described in this benefit assessment in addition to study RVT-901-3004.

I 3.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: vibegron vs. ACT

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
RVT-901-3003/ RVT-901-3004 (52 weeks)	Yes	Yes[d]	No	RVT-901-3003: Yes [3] RVT-901-3004: Yes [4,5]	RVT-901-3003: Yes [6,7] RVT-901-3004: Yes [8,9]	RVT-901-3003: [10,11] RVT-901-3004: [11-19]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In 2022, the company acquired the licensing rights for vibegron from the study sponsor Urovant Sciences GmbH.

ACT: appropriate comparator therapy; CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

I 3.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, direct comparison: vibegron vs. tolterodine (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study implementation	Primary outcome; secondary outcomes[a]
RVT-901-3003[b]	RCT, double-blind, parallel	Adults (≥ 18 years) with OAB (≥ 3 months)[c], and presence of 'OAB dry'[d] or 'OAB wet'[e]	vibegron (N = 547) tolterodine (N = 431) placebo (N = 540)[f, g]	Screening: 1 to 5 weeks[h] Treatment: 12 weeks Monitoring: until 4 weeks after the end of study treatment[i, j]	199 study centres in Canada, Hungary, Latvia, Lithuania, Poland, United States 3/2018–2/2019	Coprimary: micturition frequency, urge incontinence episodes Secondary: morbidity, health-related quality of life, AEs
RVT-901-3004[b]	RCT, double-blind, parallel	Patients who had completed study RVT-901-3003 with ≥ 80% compliance with self-administration of the study treatment and at least 4 complete diary days at Week 12	vibegron (N = 274)[g] tolterodine (N = 232)[g] Subpopulation analysed by the company[k]: vibegron (n = 182) tolterodine (n = 141)	Treatment: 40 weeks[l] Monitoring: until 4 weeks after the end of study treatment[j]	109 study centres in the United States 6/2018–7/2019	Primary: AEs Secondary: morbidity, health-related quality of life

Table 6: Characteristics of the studies included – RCT, direct comparison: vibegron vs. tolterodine (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study implementation	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. In Module 4 A, the company only includes study RVT-901-3004; this is the extension study of the 12-week study RVT-901-3003. However, the results presented in Module 4 A on patients who were treated over a total period of 52 weeks also include data from study RVT-901-3003 (Weeks 1 to 12). Study RVT-901-3003 is therefore also included and its study design presented.
c. Defined as urgency, with or without urge incontinence, usually with increased micturition frequency and nocturia. Urodynamic evaluation was not required for the diagnosis.
d. The following criteria had to be met based on the patients' micturition diary entries: an average of ≥ 8 micturitions per diary day, an average of ≥ 3 urgency episodes per diary day, an average of < 1 urge incontinence episodes per diary day, and in the presence of stress incontinence, the total number of urge incontinence episodes had to be greater than the total number of stress incontinence episodes from the previous visit diary.
e. The following criteria had to be met based on the patients' micturition diary entries: an average of ≥ 8 micturitions per diary day, an average of ≥ 1 urge incontinence episodes per diary day, and in the presence of stress incontinence, the total number of urge incontinence episodes had to be greater than the total number of stress incontinence episodes from the previous visit diary.
f. The study arm is not relevant for the assessment and not presented in the tables to follow.
g. Following study RVT-901-3003, some of the patients were able to participate in extension study RVT-901-3004. In total, approximately 500 patients were to be enrolled in the extension study. Patients who had been randomized to the placebo arm in study RVT-901-3003 were randomized 1:1 to the vibegron or tolterodine treatment arm. Patients who had been randomized to the vibegron or tolterodine arm in study RVT-901-3003 remained in their respective treatment arms in extension study RVT-901-3004.
h. Following the screening phase of up to 5 weeks (including a 28-day washout period if necessary), all patients underwent a 2-week single-blind placebo run-in phase.
i. Alternatively, some of the patients could participate in extension study RVT-901-3004, provided they met the inclusion criteria for participation.
j. Efficacy outcomes were recorded up to Week 12 (RVT-901-3003) or Week 52 (RVT-901-3004). AEs were observed until 28 days after the end of treatment.
k. Patients with a treatment period of 52 weeks who had already been treated with vibegron or tolterodine in study RVT-901-3003. Patients who initially received placebo in study RVT-901-3003 are not included in the subpopulation.
l. In patients who had previously been treated with vibegron or tolterodine as part of the RVT-901-3003 study, the treatment period lasted a total of 52 weeks.

AE: adverse event; N: number of randomized patients; n: relevant subpopulation; OAB: overactive bladder; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: vibegron vs. tolterodine (multipage table)

Study	Intervention	Comparison
RVT-901-3003	Placebo (single-blind in the run-in phase): 14 days	
	Randomized treatment phase (12 weeks) ▪ vibegron 75 mg once daily, orally + placebo once daily, orally	Randomized treatment phase (12 weeks) ▪ tolterodine prolonged release 4 mg once daily, orally + placebo once daily, orally
	Dose modification: ▪ vibegron/tolterodine: no dose modifications allowed ▪ Treatment discontinuation in the event of treatment-associated toxicity grade ≥ 3 ▪ Interruption of ≤ 21 days possible if non-treatment-associated grade ≥ 3 AEs occur. Resumption of treatment possible if the side effects subside to a grade ≤ 2.	
	Concomitant treatment ▪ The following concomitant medications were permitted, provided they were used at a stable dose (≥ 28 days before baseline)[a]: ▫ Tricyclic antidepressants or combinations (including amitriptyline, imipramine and doxepin) ▫ Alpha-1 antagonists[b] ▫ Serotonin and/or norepinephrine reuptake inhibitors (including fluoxetine, paroxetine, duloxetine) ▫ Alpha-adrenergic agonists (including non-specific sympathomimetic amines, e.g. ephedrine, pseudoephedrine, phenylephrine) ▫ Diuretic treatment (including furosemide, hydrochlorothiazide) ▫ Inhaled anticholinergics (including tiotropium bromide, ipratropium bromide) ▫ Regular use of phosphodiesterase type 5 inhibitors (including tadalafil, sildenafil, vardenafil)[c] **Prohibited prior and concomitant treatment** ▪ Surgery to correct stress incontinence, pelvic organ prolapse or procedural treatments for BPH (≤ 6 months prior to screening) ▪ Current use of a pessary for the treatment of pelvic organ prolapse ▪ Bladder training or electrostimulation (≤ 28 days prior to screening)[a] ▪ Use of an indwelling catheter or intermittent catheterization ▪ Injection of botulinum toxin into the urinary bladder muscles (≤ 9 months prior to screening) ▪ Anticholinergics, spasmolytics, synthetic analogues of antidiuretic hormone, beta-3 sympathomimetics, beta-2 sympathomimetics for the treatment of stress incontinence (≤ 28 days prior to screening); systemic beta-2 sympathomimetics (no washout required) ▪ The following substances with narrow therapeutic indices ≤ 28 days prior to screening (e.g. warfarin, digoxin, lithium, phenytoin, theophylline)[d] ▪ Other investigational products or devices (≤ 28 days prior to the start of the study)	

Table 7: Characteristics of the intervention – RCT, direct comparison: vibegron vs. tolterodine (multipage table)

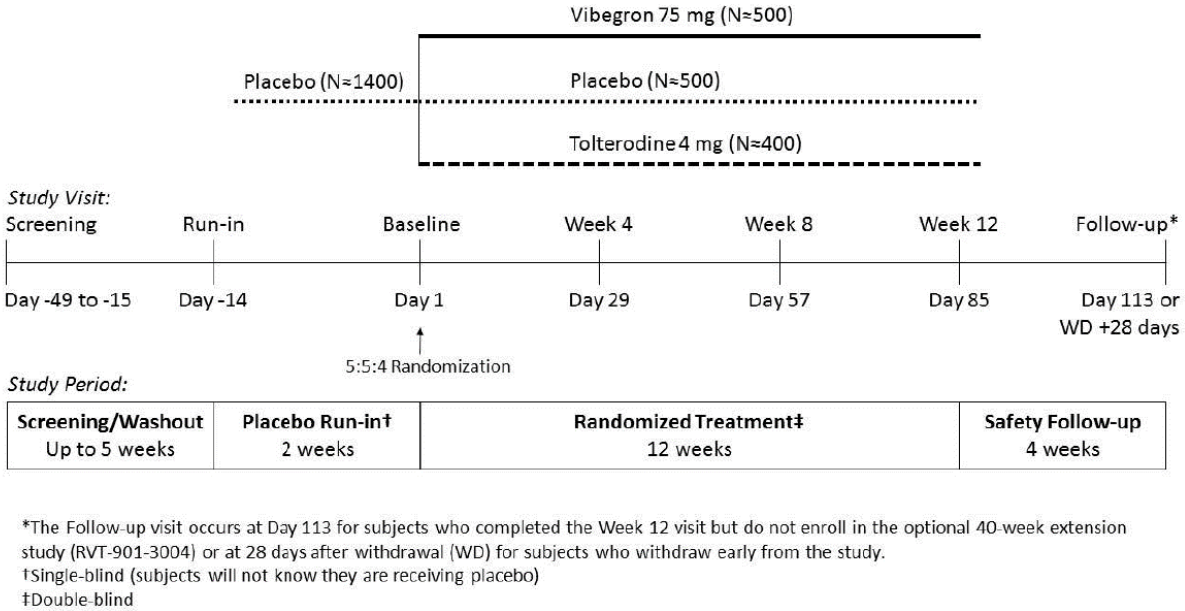
Study	Intervention	Comparison
RVT-901-3004[a]	Randomized treatment phase (40 weeks) ▪ See study RVT-901-3003	Randomized treatment phase (40 weeks) ▪ See study RVT-901-3003
	Dose modification: see study RVT-901-3003 **Pretreatment** ▪ 14 days placebo (single-blind in the run-in phase of study RVT-901-3003) ▪ 12 weeks of treatment with vibegron, tolterodine or placebo as part of study RVT-901-3003 **Concomitant treatment** ▪ See study RVT-901-3003 **Prohibited prior and concomitant treatment** ▪ See study RVT-901-3003	

a. Patients who were planning to start therapy with the respective medication or to modify the dose, or to start bladder training or electrostimulation were excluded from participation in the study.
b. Except for the treatment of BPH. In this case, a stable dose over a period of ≥ 3 months prior to baseline was required.
c. Occasional use (e.g. for the treatment of erectile dysfunction) was permitted throughout the study.
d. In study RVT-901-3004, only the use of the 5 drugs mentioned with narrow therapeutic indices was not permitted.

AE: adverse event; BPH: benign prostatic hyperplasia; RCT: randomized controlled trial

The studies RVT-901-3003 and the extension study RVT-901-3004 are described below.

Study RVT-901-3003



*The Follow-up visit occurs at Day 113 for subjects who completed the Week 12 visit but do 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 will not know they are receiving placebo)
‡Double-blind

The figure shows the planned number of patients per study arm.

Figure 1: Design of study RVT-901-3003 (from the study documents) [3]

Study RVT-901-3003 is a double-blind RCT comparing vibegron with tolterodine or placebo, with a treatment duration of 12 weeks. Adult patients with medically diagnosed OAB for at least 3 months were enrolled. OAB was defined as urgency, with or without urge incontinence, usually associated with increased micturition frequency and nocturia. Patients had to have an OAB labelled either as 'OAB dry' or 'OAB wet'; the classification was based on the patients' micturition diary entries. 'OAB dry' was defined as an average of ≥ 8 micturitions per day, an average of ≥ 3 urgency episodes per day and an average of < 1 urge incontinence episodes per day. 'OAB wet' was defined as an average of ≥ 8 micturitions per day and an average of ≥ 1 urge incontinence episodes per day. If stress incontinence was present, the total number of urge incontinence episodes had to be greater than the total number of stress incontinence episodes from the previous visit diary.

It was planned to include up to 25% of patients with 'OAB dry'. Additional requirements for inclusion in study RVT-901-3003 were ≥ 80% compliance with self-administration of the study treatment during the 2-week placebo run-in phase and, as determined by the investigator, good general physical and mental health. In total, up to 15% male patients were to be enrolled in the study.

Patients with previous surgery to correct stress incontinence, pelvic organ prolapse, treatment of benign prostatic hyperplasia (BPH) in the 6 months prior to screening, and patients who had received an injection of botulinum toxin into the urinary bladder muscles in the 9 months prior to screening were excluded from participation in the study. Furthermore, patients who had undergone bladder training or electrostimulation in the 28 days prior to screening or planned to start such treatment during the study were excluded from study participation. Also excluded were patients with previous injuries, surgery or neurodegenerative diseases (e.g. multiple sclerosis, Parkinson's disease) that could affect the lower urinary tract or its nerve supply, as well as patients with a history of liver disorder.

The study comprised a screening phase of up to 5 weeks (including a 28-day washout period for certain non-permitted concomitant medications defined in the study protocol), a 2-week single-blind placebo run-in phase and a 12-week double-blind treatment phase. A 4-week follow-up phase followed for those patients who did not transfer to extension study RVT-901-3004.

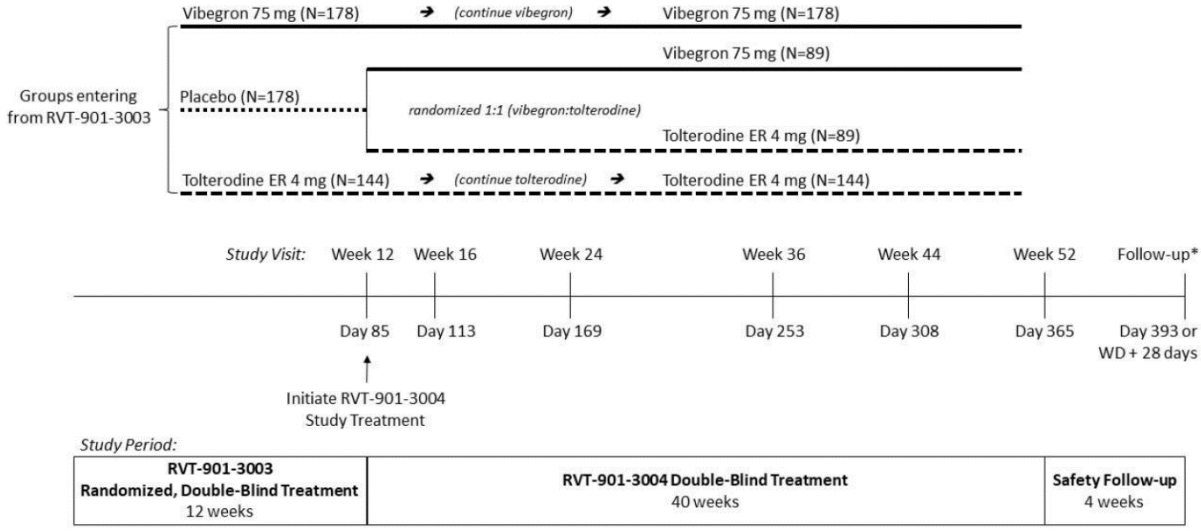
A total of 1518 patients were randomly assigned in a 5:5:4 ratio to treatment with vibegron, placebo or tolterodine. Randomization was stratified by sex (female, male) and OAB type (wet, dry).

Treatment with vibegron as a film-coated tablet at a dosage of 75 mg once daily and administration of tolterodine as a prolonged-release capsule at a dosage of 4 mg once daily (for patients without renal or hepatic impairment) concurred with the recommended dosages

according to the respective SmPC [20,21]. According to the SmPC, the daily dose of tolterodine can be reduced from 4 mg to 2 mg if intolerances occur. In the study, however, any dose modifications were prohibited, which presented an uncertainty for treatment in the tolterodine arm. The consequences that resulted from this deviation for the benefit assessment are described in the following section (see 'Notes on study population and dosing').

The coprimary outcomes of study RVT-901-3003 were micturition frequency and urge incontinence episodes. Secondary outcomes included outcomes from the categories of morbidity, health-related quality of life and side effects.

Study RVT-901-3004



*The follow-up visit took place on Day 393. For patients who discontinued treatment prematurely and stopped taking the trial medication, the follow-up visit took place on Day 28.
WD = withdrawal
The figure shows the planned number of patients per study arm (based on the planned enrolment of 500 patients).

Figure 2: Design of study RVT-901-3004 (figure from Module 4 A of the dossier)

Study RVT-901-3004 is a randomized, double-blind extension study to RVT-901-3003, on the comparison of vibegron with tolterodine. The extension study comprised a 40-week treatment phase and a 4-week follow-up phase.

To participate, patients had to have completed study RVT-901-3003. In addition to the criteria for inclusion in study RVT-901-3003, RVT-901-3004 required that patients showed at least 80% compliance with self-administration of the study medication during the course of RVT-901-3003 and had at least 4 complete diary days in their micturition diary at Week 12. The study documents showed that compliance with self-administration of the study medication was high overall for the entire population during the course of the RVT-901-3003 study (on average

around 98% and a median of 100% across the 3 study arms). In addition, patients were excluded from participation in the extension study if new health problems or clinically relevant changes in an existing disease had occurred during the course of study RVT-901-3003, or if there was a change in the medical history or other circumstances which, in the opinion of the investigator, could falsify the results of the study.

The preliminary plan was to enrol around 500 patients with OAB who had participated in study RVT-901-3003 for 12 weeks into study RVT-901-3004. A total of 506 patients were enrolled in study RVT-901-3004. Patients who had been randomized to the vibegron or tolterodine arm in study RVT-901-3003 remained in their respective treatment arms in extension study RVT-901-3004. Patients who had been randomized to the placebo arm in study RVT-901-3003 were randomized 1:1 to the vibegron or tolterodine treatment arm. The number of patients who were continuously in the vibegron or tolterodine arm for 52 weeks was 182 and 141 patients respectively.

Treatment with vibegron and tolterodine in study RVT-901-3004 was concurrent with treatment in study RVT-901-3003 (see above). The uncertainty resulting from the use of tolterodine is described in the following section.

The primary outcome of study RVT-901-3004 was AEs. Secondary outcomes comprised outcomes from the morbidity and health-related quality of life categories.

Notes on study population and dosage

Inclusion criteria for OAB syndrome

Study RVT-901-3003 enrolled patients with OAB who met the criteria for either ‘OAB wet’ or ‘OAB dry’. As described, these were based on criteria for the frequency of urgency and urge incontinence episodes, as well as micturition frequency (see study description). For the micturition frequency criterion, patients had to have at least 8 micturitions per day, as described above (see study description). In current guidelines, such as the S2k guidelines ‘Urinary incontinence in women’ and ‘Urinary incontinence in geriatric patients – diagnosis and treatment’, the diagnosis of OAB is not linked to specific requirements regarding the number of micturitions, or urgency or urge incontinence episodes [22,23]. The current definition of the International Continence Society (ICS) [24] also no longer determines increased micturition frequency by a specific number of micturitions, as according to the ICS, an increase in the frequency of daily micturition is a subjective assessment that can be confirmed by a micturition diary. When assessing the frequency, according to the ICS, the focus is rather on the degree of stress for patients. Even if, with regard to micturition frequency, the inclusion criteria of study RVT901-3003 do not correspond to the current criteria for diagnosis [22-24], they are considered sufficient for the presence of OAB in the given situation, as the inclusion criteria for OAB – defined as urgency, with or without urge

incontinence, combined with a generally increased micturition frequency and nocturia – sufficiently represent the definition of OAB according to the ICS and S2k guideline [22,24].

No accompanying bladder training or electrostimulation

According to the inclusion criteria of study RVT-901-3003, patients who had undergone bladder training or electrostimulation in the 28 days prior to screening or planned to start such treatment during the study were excluded from study participation.

In everyday practice, there is no such restriction on concomitant therapies, as can be deduced from the two S2k guidelines [22,23]. The company itself also described in Module 3 A of its dossier, with reference to these 2 guidelines, among others, that pelvic floor muscle training is recommended as a non-drug intervention for the treatment of OAB and that bladder training is another option for conservative therapy to gain control over urge incontinence and to strengthen confidence in one's own control of bladder function. The extent to which the non-drug interventions mentioned were indicated for the patient population presented by the company could not be determined on the basis of the available information. Even though according to the study protocol of RVT-901-3003 information on previous pelvic floor muscle training should have been recorded as part of the medical history, the study documents did not contain any specific information on the use of this measure before or during studies RVT-901-3003/RVT-901-3004. The patient population presented by the company was therefore limited to patients who did not conduct bladder training or electrostimulation in the 28 days prior to screening, or who did not plan to do so during the study.

No dose modification of tolterodine allowed

According to the SmPC, the daily dose of tolterodine can be reduced from 4 mg to 2 mg in case of intolerance [21]. This option was not available to patients in study RVT-901-3003 and extension study RVT-901-3004, as any dose modifications were prohibited. This represents an uncertainty, as it remains unclear to what extent AEs could have been avoided in the comparator arm if the possibility of dose reduction had existed. This uncertainty was taken into account in the assessment of the risk of bias of the AE outcomes results (see Section I 4.2).

Transition from study RVT-901-3003 to extension study RVT-901-3004

In order to be able to use the results of the extension study, the structural equality between the study arms, which was achieved at the beginning of the first study through the randomized allocation of patients to the study arms, needed to be maintained after the transition to the extension study. The transition of patients from study RVT-901-3003 to extension study RVT-901-3004 was associated with the following uncertainties in particular.

Firstly, the study documents showed that around 10% of the 1518 patients enrolled in study RVT-901-3003 did not complete the study. These patients therefore did not have the

opportunity to proceed to extension study RVT-901-3004. This may affect the certainty of results of the study if the reasons for early discontinuation of RVT-901-3003 were informative (e.g. lack of symptom relief, high number of AEs) and the number of discontinuations or reasons for discontinuation were also unevenly distributed between the study arms. In such cases, the patient population selected for continuation of the study may differ between the treatment groups at the time of transition to the extension study.

The study documents showed that study discontinuations in study RVT-901-3003 were comparably common between the study arms (vibegron, tolterodine and placebo) and occurred for similar reasons (e.g. due to withdrawal of consent to participate in the study, lost to follow-up, or AEs). However, in the case of withdrawal of consent to participate in the study, it was not possible to assess from the available documents whether the reasons that led patients to withdraw their consent differed between the study arms. The proportion of patients with such withdrawal was, however, rather low (vibegron arm: 2.6%, tolterodine arm: 3.0%, placebo arm: 3.9%). Overall, this did not completely call into question the interpretability of the data in the given data situation.

Secondly, of the patients who completed study RVT-901-3003, around 500 patients were to be enrolled in extension study RVT-901-3004. According to a publication on study RVT-901-3004 by Staskin 2021 [17], 506 (86%) of the 587 patients from the 3 study arms who completed study RVT-901-3003 first decided to participate in study RVT-901-3004 and met the inclusion criteria. Based on this information, it is assumed that patients had the opportunity to participate in study RVT-901-3004 in the order in which they completed RVT-901-3003. One prerequisite was that the patients decided in favour of further participation and that none of the exclusion criteria were met. This means that patients were not allowed to participate in the extension study if, for example, new health problems had arisen during the course of study RVT-901-3003 which, in the opinion of the investigator, could falsify the results of the study (for further information, see study description). The approach of including patients in study RVT-901-3004 solely on the basis of the order in which they completed RVT-901-3003 did not lead to an impairment of structural equality. However, the fact that further study participation depended on the patient's decision and the absence of an exclusion criterion could lead to an impairment of structural equality, as these points may differ between the 2 treatment groups.

In Module 4 A of the dossier, the company itself did not provide any information on the transition of patients into the extension study, apart from the number of patients enrolled in study RVT-901-3004. For 81 (14%) of the 587 patients from the 3 study arms, it therefore remained unclear for what reasons these patients were excluded from participation in the extension study (for example, whether new health problems as mentioned above had arisen) or for what reasons they decided not to participate in the extension study. In particular, it remained unclear whether the distribution of these patients differed between the study arms,

or whether the reasons for non-participation were distributed very differently between the study arms. These reasons may have been informative and may result in the structural equality of the study arms being compromised.

In summary, the uncertainties described in the present situation did not lead to the exclusion of studies RVT-901-3003/RVT-901-3004. It was assumed that the structural equality of the study arms in the transition from study RVT-901-3003 to study RVT-901-3004 was not impaired to such an extent that the results could not be used for the benefit assessment. This uncertainty was, however, taken into account when assessing the risk of bias (see Table 9 and Table 11).

Subpopulation presented by the company

In Module 4 A of the dossier, the company used the data on a subpopulation of patients who were treated with vibegron or tolterodine during both studies – and thus continuously over a period of 52 weeks. This subpopulation (N = 323) comprised 182 patients in the vibegron arm and 141 patients in the tolterodine arm.

For the analysis of the efficacy outcomes, the company considered the population referred to as the 'full analysis set (FAS)-Ext 52-week population' (N = 312) as the primary analysis population; this comprised 176 patients in the vibegron arm and 136 patients in the tolterodine arm who received at least 1 dose of the respective treatment and in whom there was at least one usable change versus the micturition measurement at baseline. For the analysis of the side effects outcomes, the company presented analyses for the population referred to as the 'safety analysis set (SAF)-Ext 52-week population' (N = 322); this population comprised 181 patients in the vibegron arm and 141 patients in the tolterodine arm who received at least 1 dose of the respective treatment.

In concurrence with the company, the data from patients treated with vibegron or tolterodine over a period of 52 weeks were considered for this benefit assessment (N = 323). The subpopulation of patients who received placebo in study RVT-901-3003 and were newly randomized to the vibegron or tolterodine treatment arm in RVT-901-3004 (referred to by the company in the dossier as the '40-week population'; N = 183) was therefore not taken into account. Although these patients made up a relevant proportion of the population enrolled in study RVT-901-3004 (183/506 [36%]), a 12-week placebo treatment prior to the start of the actual drug treatment does not concur with everyday practice overall. In addition, some of the patients in study RVT-901-3003 had already experienced an improvement in their OAB symptoms when taking placebo. When starting active therapy with vibegron or tolterodine, these patients may no longer have represented the population for whom treatment with vibegron or tolterodine is indicated.

For this benefit assessment, the subpopulation of patients treated with vibegron or tolterodine for 52 weeks presented by the company was used.

Patient characteristics

Table 8 shows the characteristics of the patients in the studies included.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: vibegron vs. tolterodine (multipage table)

Study **Characteristic** **Category**	**vibegron** **N[a] = 176**	**tolterodine** **N[a] = 136**
RVT-901-3003/RVT-901-3004 (52 weeks)[b]		
Age [years], mean (SD)	62 (12)	61 (13)
Age category [years], n (%)		
<65	87 (49)	74 (54)
≥ 65	89 (51)	62 (46)
Sex [F/M], %	78/22	79/21
Family origin, n (%)		
White	137 (78)	98 (72)[c]
Black	22 (13)	25 (18)
Asian	16 (9)	11 (8)
Other	1 (<1)	2 (1)
BMI [kg/m^2], mean (SD)	30.5 (7.2)	31.0 (6.3)
Patients with BPH, n (%)[d]	14 (36)	8 (28)
Diabetes mellitus, n (%)		
Yes	38 (22)	25 (18)
No	138 (78)	111 (82)
Hypertension[e], n (%)		
Yes	11 (6)	15 (11)
No	165 (94)	121 (89)
OAB type, n (%)		
'OAB wet'[f]	143 (81)	106 (78)
'OAB dry'[g]	33 (19)	30 (22)
Previous use of anticholinergics[h], n (%)		
Yes	26 (15)	14 (10)
No	150 (85)	122 (90)
Previous use of beta-3 agonists[h], n (%)		
Yes	9 (5)	10 (7)
No	167 (95)	126 (93)

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: vibegron vs. tolterodine (multipage table)

Study **Characteristic** **Category**	**vibegron** **N[a] = 176**	**tolterodine** **N[a] = 136**
Micturitions[i]		
Mean (SD)	11.3 (3.4)	11.3 (3.2)
Median [Q1; Q3]	10.4 [9.1; 12.7]	10.4 [8.9; 12.4]
Urge incontinence episodes[i]		
Mean (SD)	2.6 (2.8)	2.4 (2.1)[c]
Median [Q1; Q3]	1.6 [0.9; 3.6]	1.9 [1.0; 3.1]
Urgency episodes[i]		
Mean (SD)	8.0 (4.6)	8.0 (3.7)
Median [Q1; Q3]	7.1 [4.7; 10.0][c]	7.9 [5.1; 10.4]
Total incontinence episodes[i]		
Mean (SD)	3.1 (3.2)	2.9 (2.6)
Median [Q1; Q3]	1.9 [1.0; 4.1]	2.2 [1.1; 4.0]
Therapy/study discontinuation, n (%)[j, k]	26 (14)	18 (13)

a. Number of randomized patients who were treated with vibegron or tolterodine for 52 weeks, received at least 1 dose of the respective treatment and in whom there was at least one usable change versus the micturition measurement at baseline. Referred to as the FAS-Ext 52-week population in the running text. Values that are based on other patient numbers are marked in the corresponding line where the deviation is relevant.
b. Data refer to the baseline visits from RVT-901-3003.
c. Differing information between Module 4 A and the clinical study report. The above information is taken from the clinical study report.
d. Percentages refer to the proportion of male patients. These are n = 39 in the vibegron arm and n = 29 in the tolterodine arm.
e. Defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg at baseline, regardless of medical history. In addition, pre-existing high blood pressure was recorded based on the values at baseline or the medical history: 92 (52.3%) vs. 70 (51.5%).
f. The following criteria had to be met based on the patients' micturition diary entries: an average of ≥ 8 micturitions per diary day, an average of ≥ 1 urge incontinence episodes per diary day, and in the presence of stress incontinence, the total number of urge incontinence episodes had to be greater than the total number of stress incontinence episodes from the previous visit diary.
g. The following criteria had to be met based on the patients' micturition diary entries: an average of ≥ 8 micturitions per diary day, an average of ≥ 3 urgency episodes per diary day, an average of < 1 urge incontinence episodes per diary day, and in the presence of stress incontinence, the total number of urge incontinence episodes had to be greater than the total number of stress incontinence episodes from the previous visit diary.
h. Use within the 12 months prior to screening.
i. According to the patient diary before administration of the double-blind study medication.
j. Percentages refer to the number of randomized patients.
k. Frequent reasons for treatment discontinuation in the intervention arm vs. the control arm (percentages refer to randomized patients): withdrawal of patient consent (6.0% vs. 5.7%), loss to follow-up (3.3% vs. 1.4%), AEs (1.6% vs. 2.8%). In addition, 1 (0.5%) vs. 0 (0%) of the randomized patients never started treatment. 156 (85.7%) vs. 123 (87.2%) of the patients completed treatment as planned.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: vibegron vs. tolterodine (multipage table)

Study Characteristic Category	vibegron N[a] = 176	tolterodine N[a] = 136

BMI: body mass index; BPH: benign prostatic hyperplasia; F: female; M: male; n: number of patients in the category; N: number of randomized patients; OAB: overactive bladder; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation

The data on the characteristics of the patients referred to the values at baseline in study RVT-901-3003. The demographic and clinical characteristics were largely balanced between the 2 treatment arms. The patients were predominantly female (78% and 79% respectively), white and the mean age was around 61 years old. According to the inclusion criteria for study RVT-901-3003 (see Table 6), around 80% of patients in both treatment arms had type 'OAB wet'. This means that the proportion of patients with 'OAB wet' in the studies RVT-901-3003/RVT-901-3004 was slightly higher than is described for everyday practice [24]. A proportion of 15% of patients in the vibegron arm and 10% in the tolterodine arm had taken anticholinergics within the 12 months before enrolment in the study, and around 6% of patients in both treatment arms had taken beta-3 agonists during this period.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: vibegron vs. tolterodine

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
RVT-901-3003/RVT-901-3004[a]	Yes	Yes	Yes	Yes	Yes	No[b]	High

a. Patients randomized to the vibegron or tolterodine treatment arms in study RVT-901-3003 remained on their respective treatment, resulting in a total treatment duration of 52 weeks (12 weeks in study RVT-901-3003 + 40 weeks in study RVT-901-3004). For further study descriptions of the respective treatment arms, see the running text for Table 6 and Table 7.

b. With the exception of the number of patients, Module 4 A of the dossier contains no specific information on the transition of patients from study RVT-901-3003 to extension study RVT-901-3004 (see running text for further explanation).

RCT: randomized controlled trial

The risk of bias across outcomes was rated as high for the combination of studies RVT-901-3003/RVT-901-3004. The reason for this was uncertainty regarding the transition of patients from study RVT-901-3003 to extension study RVT-901-3004. Due to a lack of information, it remained unclear for 81 patients (14%) why they were excluded from participation in extension study RVT-901-3004 or why they decided not to participate. In particular, it remained unclear whether the distribution of these patients differed between the study arms, or whether the reasons for non-participation were distributed very differently between the study arms. These reasons may potentially be informative and may result in the structural equality of the study arms being impaired (see Section I 3.2).

Transferability of the study results to the German health care context

The company stated that the results of study RVT-901-3004 were transferable to the German health care context due to the study design and the study population. Study RVT-901-3004 was conducted in the United States. The company claimed that the health care context in the United States is comparable to that in Germany: the vast majority of patients belong to the Caucasian ethnic group. It maintained that the inclusion criteria of the studies ensured that the characteristics of the study population corresponded with the characteristics of the patient population with OAB syndrome treated with vibegron according to the SmPC in everyday practice in Germany. It also stated that the study population comprised adults ≥ 18 years, with the median age of the patients in the studies being 64.0 to 65.0 years. According to the company, in line with the relevance of OAB syndrome, transferability to the German health care context could therefore also be assumed with regard to the age of the patients. Overall, transferability to the German health care context could therefore be assumed, according to the company. From the company's point of view, there were no indications of limitations.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - All-cause mortality
- Morbidity
  - Symptoms, recorded using the OAB-q LF and PGI-Change, PGI-Severity and PGI-Control
  - Health status, recorded using the EQ-5D visual analogue scale (VAS)
  - Incontinence
  - Urge incontinence
  - Micturition frequency
  - Urgency
  - Nocturia
- Health-related quality of life
  - recorded using the OAB-q LF
- Side effects
  - Serious adverse events (SAEs)
  - Severe AEs
  - Discontinuation due to AEs
  - Urinary tract infection (Preferred Term [PT], AEs)
  - Dry mouth (PT, AEs)
  - Other specific AEs, if any

The selection of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A).

Table 10 shows for which outcomes data were available in the included studies.

Table 10: Matrix of outcomes – RCT, direct comparison: vibegron vs. tolterodine

Study	Outcomes														
	All-cause mortality[a]	Symptoms (OAB-q LF[b], PGI-Change, PGI-Severity, PGI-Control)	Health status (EQ-5D VAS)	Incontinence[c]	Urge incontinence[d]	Frequency of micturition[e]	Urgency[f]	Nocturia[g]	Health-related quality of life (OAB-q LF)	SAEs	Severe AEs[h]	Discontinuation due to AEs	Urinary tract infection (PT, AEs)	Dry mouth (PT, AEs)	Other specific AEs
RVT-901-3003/ RVT-901-3004	Y	Y	Y	y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N[i]

a. The results on all-cause mortality are based on the information on fatal AEs.
b: OAB-q LF symptom scale (Symptom Bother Score).
c. Number of total incontinence episodes/24 hours (measured over the 7 days before the last visit).
d. Number of urge incontinence episodes/24 hours (measured over the 7 days before the last visit).
e: Number of micturitions/24 hours: (measured over the 7 days before the last visit).
f. Number of urgency episodes/24 hours (measured over the 7 days before the last visit).
g. Number of nocturnal micturitions/24 hours (measured over the 7 days before the last visit).
h. Severe AEs are operationalized as severe or medically significant, not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disability; impairment of daily self-care activities; or life-threatening consequences; urgent intervention indicated; or death due to an adverse event. The wording of this definition corresponds to the criteria according to NCI-CTCAE grade ≥ 3.
i. No further specific AEs were identified based on the AEs occurring in the relevant studies.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; N: no; NCI: National Cancer Institute; OAB-q LF: Overactive Bladder symptom and health-related quality of life questionnaire long form; PGI: Patient Global Impression; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; Y: yes

Notes on outcomes

The instruments for recording morbidity and health-related quality of life are first described below. The analyses used for this benefit assessment are then explained.

Description of patient-reported outcomes on morbidity and health-related quality of life

Symptoms recorded using the OAB-q LF

In studies RVT-901-3003/RVT-901-3004, symptoms were recorded using the OAB-q LF Symptom Bother Score. This score measures the extent to which patients are affected by the following 8 specific symptoms: frequent micturition during the day, uncomfortable urge to urinate, sudden urge to urinate, accidental loss of small amounts of urine, nighttime urination, waking up at night due to urge to urinate, uncontrollable urge to urinate and urine loss associated with a strong urge to urinate. The score uses a scale of 1 to 6 (from 'not at all' to 'a very great deal') and can have values between 0 and 100, with higher values indicating the patient is affected to a greater extent.

Symptoms recorded with PGI-Change, PGI-Severity and PGI-Control

PGI-Change and PGI-Severity each consist of a single question that the patients could use to assess the severity of their symptoms or a change to them.

Using PGI-Change, patients were asked to indicate the change in symptom severity on a 7-point scale ('very much improved', 'much improved', 'slightly improved', 'no change', 'slightly worse', 'much worse', 'very much worse') in relation to the symptom severity at the start of the study.

Using PGI-Severity, patients were asked to indicate the severity of their symptoms on a 4-point scale ('no symptoms', 'mild', 'moderate', 'severe') for the previous week.

PGI-Control consists of a single question that allows patients to assess their symptom control on a 5-point scale ('complete control', 'a lot of control', 'some control', 'only a little control', 'no control') for the previous week.

Health status recorded using the EQ-5D VAS

Health status was recorded using the EQ-5D VAS. The recording was based on a scale from 0 to 100, on which patients answered the question about their current health status. A score of 0 indicates the worst and a score of 100 the best imaginable health status. The recording of the health status by means of a VAS is regarded as patient-relevant.

Activity impairment, recorded using the Work Productivity and Activity Impairment Questionnaire-Urinary Symptoms (WPAI-US) question 6

The WPAI-US was additionally used in studies RVT-901-3003/RVT-901-3004. Question 6 of the WPAI-US is used to record a patient's activity impairment. However, the company did not present any results for this outcome in Module 4 A. With the recording of the OAB-q LF in the studies RVT-901-3003/RVT-901-3004, question 6 of the WPAI-US on activity impairment was

considered to be covered, therefore the absence of these results in the present situation had no consequence for the assessment.

Health-related quality of life recorded using the OAB-q LF

In the OAB-q LF, health-related quality of life is shown using the 4 domains of coping with illness (8 items), concern (7 items), sleep (5 items) and social interaction (5 items) as well as a total score derived from these. The total score can achieve values between 0 and 100, with higher values correlating with a higher health-related quality of life.

Analyses of patient-reported outcomes on morbidity and health-related quality of life used for the benefit assessment

In Module 4 A, the company presented responder analyses for the patient-reported outcomes of the categories morbidity and health-related quality of life – recorded using: OAB-q LF, PGI-Change, PGI-Severity, PGI-Control, EQ-5D VAS; these were not predefined. The response criteria used in the analyses presented by the company fulfil the requirements for response criteria of reflecting with sufficient certainty a change that is perceivable for patients, as described in the *General Methods* of the Institute [1].

For some of the patient-reported outcomes, the company presented analyses of both improvement and worsening. Since the patients included in studies RVT-901-3003/RVT-901-3004 were symptomatic at the start of the study (symptomatic OAB) and the treatment goal of vibegron is to improve symptoms, the analyses on improvement were considered for the responder analyses for the patient-reported outcomes in the categories of morbidity and health-related quality of life.

For PGI-Change, the company presented responder analyses in its dossier in which the scale values from 1 (‘very much improved’) to 3 (‘mildly improved’) were seen as an improvement. This analysis of the proportion of patients with any improvement was adequate. For PGI-Severity, the company presented responder analyses in its dossier in which the improvement by at least one category was seen as an improvement (corresponds to at least 15% of the scale range). This analysis was adequate [1].

The company did not use the patient-reported outcome PGI-Control for its assessment without further justification. Accordingly, no analyses were available for this outcome in Module 4 A. Therefore, for this outcome – in contrast to the outcomes mentioned above – the predefined continuous analyses (mean difference) available in the clinical study report on the change at Week 52 versus baseline were used and supplemented by the Institute's calculation of the treatment effect.

Morbidity outcomes recorded using the micturition diary

Incontinence, urge incontinence, micturition frequency, urgency, nocturia

In studies RVT-901-3003/RVT-901-3004 the number of micturitions, urgency episodes, incontinence and urge incontinence episodes, and nocturia were documented by the patients using micturition diaries. Patients were asked to keep diaries for 7 days before the placebo run-in visit, the baseline visit, Week 2 and before the respective visits at Weeks 4, 8, 12, 16, 24, 44 and 52. The mean value per 24 hours was then calculated on the basis of the recordings.

The company presented predefined analyses of the change at Week 52 versus baseline for the outcomes incontinence, urge incontinence, micturition frequency, urgency and nocturia. These continuous analyses were used for this benefit assessment. I Appendix C of the full dossier assessment also shows the average change over time curves for the outcomes mentioned. On the basis of these curves, it is not assumed that fluctuations occurred between the time points considered in the continuous analyses (baseline and Week 52) that would call into question the interpretability of the results of the continuous analyses.

For the outcomes mentioned, the company also presented various – partly predefined, partly post hoc – responder analyses for the reduction of episodes by 50 %, 75 % or 100 % (depending on the outcome), or for reaching a micturition frequency within the normal range. The responder analyses that indicate freedom from symptoms (such as reduction by 100%) would in principle be a meaningful operationalization in terms of content. However, this was not predefined for the respective outcomes (with the exception of the urge incontinence outcome). Therefore, these responder analyses were not used, but rather the analyses of the continuous data predefined throughout. The responder analyses (reduction by 100% or reaching a normal range in micturition frequency) are presented in I Appendix B of the full dossier assessment.

For the outcome urge incontinence, a responder analysis was predefined for the reduction of episodes by 100% at Week 52. However, urge incontinence is only one component of the incontinence outcome and can only be interpreted together with this outcome. The continuous data were therefore also used here.

Adverse events

The study protocol of RVT-901-3004 describes that AEs that occurred before the start of the first dose of the study medication were still recorded in study RVT-901-3003. AEs that occurred after the first dose of study medication in study RVT-901-3004 were recorded in that study. In Module 4 A, the company specified the data collection period for AEs as the period between the screening (visit 1 of study RVT-901-3003) and the last follow-up visit after the last dose (of study RVT-901-3004). It was assumed that the results on AEs presented by the company in Module 4 A covered the entire period of both studies.

Severe AEs

According to the study protocols of studies RVT-901-3003/RVT-901-3004, the severity of AEs was assessed using the following criteria:

- Grade 1 (mild): asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated
- Grade 2 (moderate): minimal, localized or non-invasive intervention indicated; impairment of age-appropriate instrumental activities of daily living
- Grade 3 (severe or medically significant): not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disability; impairment of daily self-care activities
- Grade 4 (life-threatening): life-threatening consequences; urgent intervention indicated
- Grade 5 (death): death due to an adverse event

This definition corresponds to the overarching definition of the Common Terminology Criteria for Adverse Events (CTCAE) grades specified by the National Cancer Institute (NCI) [25]. The extent to which the full CTCAE scoring system, including the specific definitions for many PTs, was used was not clear from the study documents. Therefore, it cannot be assumed with enough certainty that the categorization of severe AEs was sufficiently reliable. However, in terms of overarching definitions, the definition of a Grade 3 to 5 severe AE available in the study protocol does cover the NCI CTCAE Grade 3 to 5. The results on severe AEs were used in this benefit assessment; however, if there were to be a statistically significant difference between the treatment groups, the extent of the effect would not be quantifiable.

I 4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: vibegron vs. tolterodine

Study	Study level	Outcomes														
		All-cause mortality[a]	Symptoms (OAB-q LF[b], PGI-Change, PGI-Severity, PGI-Control)	Health status (EQ-5D VAS)	Incontinence[c]	Urge incontinence[d]	Frequency of micturition[e]	Urgency[f]	Nocturia[g]	Health-related quality of life (OAB-q LF)	SAEs	Severe AEs[h]	Discontinuation due to AEs	Urinary tract infection (PT, AEs)	Dry mouth (PT, AEs)	Other specific AEs
RVT-901-3003/ RVT-901-3004	H	H[i]	H[i]	H[i]	H[i]	H[i]	H[i]	H[i]	H[i]	H[i]	H[i,j]	H[i,j]	H[i]	H[i,j]	H[i,j]	–

a. The results on all-cause mortality are based on the information on fatal AEs.
b: OAB-q LF symptom scale (Symptom Bother Score).
c. Number of total incontinence episodes/24 hours (measured over the 7 days before the last visit).
d. Number of urge incontinence episodes/24 hours (measured over the 7 days before the last visit).
e: Number of micturitions/24 hours: (measured over the 7 days before the last visit).
f. Number of urgency episodes/24 hours (measured over the 7 days before the last visit).
g. Number of nocturnal micturitions/24 hours (measured over the 7 days before the last visit).
h. Severe AEs are operationalized as severe or medically significant, not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disability; impairment of daily self-care activities; or life-threatening consequences; urgent intervention indicated; or death due to an adverse event. The wording of this definition corresponds to the criteria according to NCI-CTCAE grade ≥ 3.
i. High risk of bias across outcomes.
j. The dose of tolterodine was not allowed to be reduced if intolerance occurred, contradicting the SmPC. It therefore remains unclear whether AEs could have been avoided in the comparator arm.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; H: high; NCI: National Cancer Institute; OAB-q LF: Overactive Bladder symptom and health-related quality of life questionnaire long form; PGI: Patient Global Impression; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SmPC: summary of product characteristics; VAS: visual analogue scale

Due to the uncertainties in the transition of patients from study RVT-901-3003 to extension study RVT-901-3004, the risk of bias across outcomes for RVT-901-3003/RVT-901-3004 had to be rated as high (see Table 9). This led to a high risk of bias for the results of all outcomes.

In addition, there was uncertainty regarding outcomes in the side effects category, as the dosage of tolterodine in the study could not be reduced if intolerance occurred, contradicting the SmPC [21]. It therefore remains unclear whether AEs could have been avoided in the comparator arm.

I 4.3 Results

Table 12 and Table 13 summarize the results on the comparison of vibegron with tolterodine in patients with OAB syndrome. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

In addition, responder analyses for individual morbidity outcomes are presented in I Appendix B of the full dossier assessment. I Appendix C of the full dossier assessment additionally shows curves for the average change over time for the outcomes incontinence, urge incontinence, micturition frequency, urgency and nocturia. Results on common AEs, SAEs, severe AEs and discontinuations due to AEs are presented in I Appendix D of the full dossier assessment.

Table 12: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: vibegron vs. tolterodine (multipage table)

Study Outcome category Outcome	vibegron		tolterodine		vibegron vs. tolterodine
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p-value
RVT-901-3003/RVT-901-3004					
Mortality					
All-cause mortality[b]	181	0 (0)	141	0 (0)	–[c]
Morbidity					
Symptoms – improvement at Week 52					
OAB-q LF[d]	166	121 (72.9)	134	87 (64.9)	1.12 [0.97; 1.30]; 0.160[e]
PGI-Change[f]	166	140 (84.3)	134	112 (83.6)	1.02 [0.93; 1.12]; 0.923[e]
PGI-Severity[g]	166	123 (74.1)	134	87 (64.9)	1.13 [0.97; 1.32]; 0.092[e]
Health status (EQ-5D VAS – improvement at Week 52)	166	39 (23.5)	134	27 (20.1)	1.16 [0.75; 1.78]; 0.525[e]
Health-related quality of life					
OAB-q LF – improvement at Week 52[i]					
Total score	166	92 (55.4)	134	68 (50.8)	1.10 [0.89; 1.35]; 0.486[e]
Coping with illness	166	104 (62.6)	134	76 (56.7)	1.14 [0.95; 1.38][e]
Concern	166	94 (56.6)	134	72 (53.7)	1.06 [0.87; 1.30][e]
Sleep	166	94 (56.6)	134	72 (53.7)	1.06 [0.87; 1.30][e]
Social interaction	166	67 (40.4)	134	48 (35.8)	1.13 [0.84; 1.50][e]

Table 12: Results (mortality, morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: vibegron vs. tolterodine (multipage table)

Study	vibegron		tolterodine		vibegron vs. tolterodine
Outcome category Outcome	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p-value
Side effects					
AEs (supplementary information)	181	119 (65.8)	141	86 (61.0)	–
SAEs	181	4 (2.2)	141	4 (2.8)	0.78 [0.20; 3.06]; 0.720[j]
Severe AEs[k]	181	4 (2.2)	141	5 (3.5)	0.62 [0.17; 2.28]; 0.471[j]
Discontinuation due to AEs	181	3 (1.7)	141	4 (2.8)	0.58 [0.13; 2.57]; 0.472[j]
Urinary tract infection (PT, AEs)	181	10 (5.5)	141	13 (9.2)	0.60 [0.27; 1.33]; 0.202[j]
Dry mouth (PT, AEs)	181	3 (1.7)	141	10 (7.1)	0.23 [0.07; 0.83]; 0.014[j]

a. Number of analysed patients. For outcomes in the morbidity and health-related quality of life category, patients with baseline values and observations at Week 52 were included.
b. The results on all-cause mortality are based on the data on fatal AEs.
c. No presentation of effect estimation, as not informative.
d. Symptom scale of the OAB-q LF (Symptom Bother Score); lower values mean an improvement in symptoms. A decrease in the Symptom Bother Scores of ≥ 15 points in comparison to baseline is considered a clinically relevant improvement (scale range: 0 to 100).
e. RR and CI: logistic regression, adjusted for OAB type and sex; p-value: Cochran-Mantel-Haenszel test, stratified by OAB type and sex.
f. Proportion of patients with any improvement ("very much improved", "much improved" or "slightly improved").
g. Proportion of patients with any improvement in symptom severity on a 4-point scale ("no symptoms", "mild", "moderate" and "severe") compared to baseline.
h. An EQ-5D VAS score increase of ≥ 15 points in comparison to baseline is considered a clinically relevant improvement (scale range: 0 to 100).
i. An increase in the OAB-q LF score of ≥ 15 points compared to baseline is considered a clinically relevant improvement (scale range: 0 to 100).
j. RR and CI: logistic regression, unadjusted; p-value: Cochran-Mantel-Haenszel test, unstratified.
k. Severe AEs are operationalized as severe or medically significant, not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disability; impairment of daily self-care activities; or life-threatening consequences; urgent intervention indicated; or death due to an adverse event. The wording of this definition corresponds to the criteria according to NCI-CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; NCI: National Cancer Institute; OAB: overactive bladder; OAB-q LF: Overactive Bladder symptom and health-related quality of life questionnaire long form; PGI: Patient Global Impression; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale

Table 13: Results (morbidity, continuous) – RCT, direct comparison: vibegron vs. tolterodine

Study Outcome category Outcome	vibegron			tolterodine			vibegron vs. tolterodine
	N[a]	Values at baseline mean (SD)	Change at Week 52 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at week 52 mean[b] (SE)	MD [95% CI]; p-value[b]
RVT-901-3003/RVT-901-3004							
Morbidity							
Symptom (PGI-Control)[c]	166	3.3 (0.9)	Mean (SD): −1.1 (1.0)	134	3.2 (0.8)	mean (SD): −1.0 (1.1)	−0.10 [−0.33; 0.13]; 0.399[d]
Incontinence[e]	152	3.1 (3.2)	−2.1 (0.1)	120	2.9 (2.7)	−1.6 (0.2)	−0.48 [−0.84; −0.12]; 0.009
including:							
Urge incontinence[f]	152	2.6 (2.8)	-1.8 (0.1)	120	2.4 (2.2)	-1.4 (0.1)	−0.47 [−0.79; −0.14]; 0.005
Micturition frequency[g]	152	11.1 (3.3)	−2.4 (0.2)	120	11.3 (3.2)	−2.0 (0.3)	−0.43 [−1.06; 0.20]; 0.183
Urgency[h]	152	7.9 (4.6)	-3.4 (0.3)	120	8.1 (3.7)	−3.2 (0.4)	−0.15 [−1.07; 0.77]; 0.749
Nocturia[i]	152	1.4 (1.1)	−0.6 (0.1)	120	1.5 (1.2)	−0.5 (0.1)	−0.13 [−0.32; 0.07]; 0.202

a. Number of patients included in the effect estimation (patients with baseline value and observation at Week 52). The values at the start of the study may be based on other patient numbers.
b. Unless otherwise stated: mixed-effects model with repeated measures with covariates OAB type and sex.
c. Lower (decreasing) values mean improved symptoms; negative effects mean an advantage for the intervention (scale range: 1 to 5).
d: Institute's calculation from data on the change at Week 52.
e. Number of total incontinence episodes/24 hours (measured over the 7 days before the last visit).
f. Number of urge incontinence episodes/24 hours (measured over the 7 days before the last visit). Urge incontinence is a component of the incontinence outcome and is therefore interpreted together with this outcome.
g: Number of micturitions/24 hours: (measured over the 7 days before the last visit).
h. Number of urgency episodes/24 hours (measured over the 7 days before the last visit).
i. Number of nocturnal micturitions/24 hours (measured over the 7 days before the last visit).

CI: confidence interval; MD: mean difference; N: number of analysed patients; OAB: overactive bladder; PGI: Patient Global Impression; RCT: randomized controlled trial; SD: standard deviation; SE: standard error

Based on the available information, at most hints, e.g. of an added benefit, could be determined for all outcomes (see Table 9 and Table 11).

Mortality

The results on all-cause mortality were based on data on fatal AEs. No events for the outcome of all-cause mortality occurred in study RVT-901-3004. There was no hint of an added benefit of vibegron in comparison with tolterodine; an added benefit is therefore not proven.

Morbidity

Symptoms (OAB-q LF, PGI-Change, PGI-Severity and PGI-Control)

For the outcomes on symptoms, recorded using the OAB-q LF, PGI-Change, PGI-Severity and PGI-Control, there was no statistically significant difference between the treatment groups. There was no hint of an added benefit of vibegron in comparison with tolterodine; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No statistically significant difference between treatment groups was shown for the outcome of health status. There was no hint of an added benefit of vibegron in comparison with tolterodine; an added benefit is therefore not proven.

Incontinence and urge incontinence

A statistically significant difference in favour of vibegron in comparison with tolterodine was shown for each of the outcomes of incontinence and urge incontinence, based on the mean differences. However, it was not possible to deduce from the associated effect estimates and associated 95% confidence intervals (CI) that for the mean difference for both outcomes of half an incontinence episode between the 2 treatment arms, there were clinically relevant effects. Considered together, there was no hint of an added benefit of vibegron in comparison with tolterodine for these outcomes; an added benefit is therefore not proven.

Micturition frequency

There was no statistically significant difference between the treatment groups for the outcome of micturition frequency. There was no hint of an added benefit of vibegron in comparison with tolterodine; an added benefit is therefore not proven.

Urgency

There was no statistically significant difference between the treatment groups for the outcome urgency. There was no hint of an added benefit of vibegron in comparison with tolterodine; an added benefit is therefore not proven.

Nocturia

There was no statistically significant difference between the treatment groups for the outcome nocturia. There was no hint of an added benefit of vibegron in comparison with tolterodine; an added benefit is therefore not proven.

Health-related quality of life (OAB-q LF)

For the outcome of health-related quality of life (recorded using the OAB-q LF), no statistically significant difference between treatment groups was found. There was an effect modification by the characteristic of age, however (see Section I 4.4). For patients ≥ 65 years, there was a

hint of an added benefit of vibegron in comparison with tolterodine. For patients < 65 years, there was no hint of an added benefit of vibegron in comparison to tolterodine; an added benefit is therefore not proven for patients < 65 years of age.

Side effects

SAEs, severe AEs, and discontinuation due to AEs

No statistically significant difference between treatment groups was found for any of the outcomes of SAEs, severe AEs, or discontinuation due to AEs. For each of these outcomes, there was no hint of greater or lesser harm from vibegron in comparison with tolterodine; greater or lesser harm is therefore not proven.

Urinary tract infection

There was no statistically significant difference between the treatment groups for the outcome urinary tract infection (AE). There was no hint of greater or lesser harm of vibegron in comparison with tolterodine; greater or lesser harm is therefore not proven.

Dry mouth

A statistically significant difference in favour of vibegron in comparison with tolterodine was shown for the outcome of dry mouth (AE). There was a hint of lesser harm from vibegron in comparison with tolterodine. However, it is unclear to what extent this AE could have been avoided or reduced in the tolterodine arm if the possibility of dose reduction in case of intolerance had existed in studies RVT-901-3003/RVT-901-3004. This also contributed to the reduced certainty of conclusions for this outcome.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account in this benefit assessment:

- Age (< 65 years versus ≥ 65 years)
- Sex (female versus male)

The characteristics mentioned were prespecified in study RVT-901-3003. For outcomes in the outcome category morbidity, the company presented only subgroup analyses for the responder analyses, not for the continuous analyses, in its dossier. Subgroup analyses were also not available for all analyses of adverse events by System Organ Class (SOC)/PT with statistically significant results for the overall population.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

The subgroup results comparing vibegron with tolterodine for the treatment of OAB are shown in Table 14.

Table 14: Subgroups (morbidity) – RCT, direct comparison: vibegron vs. tolterodine

Study Outcome Characteristic Subgroup	vibegron N[a]	 Patients with event n (%)	tolterodine N[a]	 Patients with event n (%)	vibegron vs. tolterodine RR [95% CI][b]	 p-value[b]
RVT-901-3003/RVT-901-3004						
Health-related quality of life (OAB-q LF – improvement at Week 52[i])						
Age						
< 65 years	81	41 (50.6)	72	41 (56.9)	0.89 [0.66; 1.19]	0.435
≥ 65 years	85	51 (60.0)	62	27 (43.5)	1.38 [0.99; 1.92]	0.049
Total					Interaction:	0.049

a. Number of patients in the subgroups. Patients with a baseline value and observation at Week 52 were taken into account.
b. RR and CI: logistic regression, unadjusted; p-value: Cochran-Mantel-Haenszel test, unstratified; interaction p-value: test for interaction between treatment group and subgroup from the generalized linear model.
c. An increase in the OAB-q LF score of ≥ 15 points compared to baseline is considered a clinically relevant improvement (scale range: 0 to 100).

CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; OAB-q LF: Overactive Bladder symptom and health-related quality of life questionnaire long form; RCT: randomized controlled trial; RR: relative risk

Health-related quality of life

OAB-q LF

For the outcome of health-related quality of life, recorded using OAB-q LF, there was an effect modification by the characteristic of age.

For patients ≥ 65 years of age, a statistically significant difference was shown in favour of vibegron in comparison with tolterodine. There was a hint of added benefit of vibegron in comparison with tolterodine for this patient group.

However, no statistically significant difference between treatment groups was found for patients < 65 years. There was no hint of an added benefit of vibegron in comparison with tolterodine; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 15).

Table 15: Extent of added benefit at outcome level: vibegron vs. tolterodine (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**vibegron vs. tolterodine** **Proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0 vs. 0 RR: –[c]	Lesser benefit not proven/added benefit not proven
Morbidity		
Symptoms (OAB-q LF – improvement at Week 52)	72.9 vs. 64.9 RR: 1.12 [0.97; 1.30]; p = 0.160	Lesser benefit not proven/added benefit not proven
Symptoms (PGI-Change – improvement at Week 52)	84.3 vs. 83.6 RR: 1.02 [0.93; 1.12]; p = 0.923	Lesser benefit not proven/added benefit not proven
Symptoms (PGI-Severity – improvement at Week 52)	74.1 vs. 64.9 RR: 1.13 [0.97; 1.32]; p = 0.092	Lesser benefit not proven/added benefit not proven
Symptoms (PGI-Control – improvement at Week 52)	Mean change: –1.1 vs. –1.0 MD: −0.1 [−0.33; 0.13]; p = 0.399	Lesser benefit not proven/added benefit not proven
Health status (EQ-5D VAS – improvement at Week 52)	23.5 vs. 20.1 RR: 1.16 [0.75; 1.78]; p = 0.525	Lesser benefit not proven/added benefit not proven
Incontinence	Mean change: –2.1 vs. –1.6 MWD: −0.48 [−0.84; −0.12]; p = 0.009	Lesser benefit not proven/added benefit not proven[d]

Table 15: Extent of added benefit at outcome level: vibegron vs. tolterodine (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**vibegron vs. tolterodine** **Proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Urge incontinence	Mean change: −1.8 vs. −1.4 MWD: −0.47 [−0.79; −0.14]; p = 0.005	Lesser benefit not proven/added benefit not proven[d]
Micturition frequency	Mean change: –2.4 vs. –2.0 MWD: −0.43 [−1.06; 0.20]; p = 0.183	Lesser benefit not proven/added benefit not proven
Urgency	Mean change: −3.4 vs. −3.2 MWD: −0.15 [−1.07; 0.77]; p = 0.749	Lesser benefit not proven/added benefit not proven
Nocturia	Mean change: −0.6 vs. −0.5 MWD: −0.13 [−0.32; 0.07]; p = 0.202	Lesser benefit not proven/added benefit not proven
Health-related quality of life		
OAB-q LF total score – improvement at Week 52 Age		
< 65 years	50.6 vs. 56.9 RR: 0.89 [0.66; 1.19]; p = 0.435	Lesser benefit not proven/added benefit not proven
≥ 65 years	60.0 vs. 43.5 RR: 1.38 [0.99; 1.92]; RR: 0.72 [0.52; 1.01][e]; p = 0.049 Probability: hint	Outcome category: health-related quality of life Added benefit, extent: minor[f]

Table 15: Extent of added benefit at outcome level: vibegron vs. tolterodine (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**vibegron vs. tolterodine** **Proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	2.2 vs. 2.8 RR: 0.78 [0.20; 3.06]; p = 0.720	Greater/lesser harm not proven
Severe AEs	2.2 vs. 3.5 RR: 0.62 [0.17; 2.28]; p = 0.471	Greater/lesser harm not proven
Discontinuation due to AEs	1.7 vs. 2.8 RR: 0.58 [0.13; 2.57]; p = 0.472	Greater/lesser harm not proven
Urinary tract infection (AEs)	5.5 vs. 9.2 RR: 0.60 [0.27; 1.33]; p = 0.202	Greater/lesser harm not proven
Dry mouth (AEs)	1.7 vs. 7.1 RR: 0.23 [0.07; 0.83]; p = 0.014 Probability: hint	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ Lesser harm, extent: minor

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category and the scale of the outcome, effect size is estimated with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L).
c. No presentation of effect estimation, as not informative.
d. Although there is a statistically significant difference between the treatment groups, no clinically relevant effect can be derived from the effect estimate and associated CI.
e. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
f. Discrepancy between CI and p-value; the extent is rated as minor.

AE: adverse event; CI: confidence interval; CI_L: lower limit of confidence interval; CI_u: upper limit of confidence interval; MD: mean difference; OAB-q LF: Overactive Bladder symptom and health-related quality of life questionnaire long form; PGI: Patient Global Impression; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 16 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 16: Positive and negative effects from the assessment of vibegron compared with tolterodine

Positive effects	Negative effects
Health-related quality of life ▪ OAB-q LF total score – improvement at Week 52 ▫ ≥ 65 years: hint of an added benefit – extent: minor	–
Non-serious/non-severe side effects ▪ Dry mouth (AEs): hint of lesser harm – extent: minor	–
AE: adverse event; OAB-q LF: Overactive Bladder symptom and health-related quality of life questionnaire long form	

Overall, a positive effect for the outcome health-related quality of life (OAB-q LF) remains for vibegron compared with tolterodine for patients ≥ 65 years. Regardless of age, there was a positive effect for the outcome dry mouth (non-serious/non-severe side effects). The positive effect for the outcome dry mouth alone was not assessed to be sufficient in the present data situation to derive an added benefit for all patients. It is also unclear to what extent AEs could have been avoided or reduced in the tolterodine arm if the possibility of dose reduction in case of intolerance had existed in studies RVT-901-3003/RVT-901-3004.

Weighing up is therefore carried out separately for the 2 age categories. For patients aged 65 years and over, there was a hint of minor added benefit, but for patients < 65 years of age, the added benefit is not proven.

The result of the assessment of the added benefit of vibegron in comparison with the ACT is summarized in Table 17.

Table 17: Vibegron – extent and probability of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Symptomatic treatment of adult patients with overactive bladder (OAB) syndrome	Darifenacin or desfesoterodine or fesoterodine or mirabegron or propiverine or solifenacin or tolterodine or trospium chloride[b]	▪ Patients ≥ 65 years: hint of a minor added benefit[c] ▪ Patients < 65 years: added benefit not proven[c]

a. Presented is the ACT specified by the G-BA.
b. Comments from the G-BA:
- The ACT specified here comprises several alternative treatment options. These alternative treatment options are equally appropriate for the comparator therapy.
- The added benefit can be proven in comparison with one of the cited alternative treatment options; this can typically be achieved in the context of a single-comparator study.
- Non-drug interventions as outlined in the German Remedies Directive or the Remedies Catalogue (e.g. physiotherapy) can help to alleviate symptoms and, if indicated, should be offered in both study arms. The type and scope of the interventions used must be documented.

c. Due to the inclusion criteria of studies RVT-901-3003/RVT-901-3004, it remains unclear whether the observed effects can be transferred to patients who do not have good general physical and mental health and to patients for whom additionally the initiation of non-drug measures such as bladder training or electrostimulation would be indicated.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; OAB: overactive bladder

The assessment described above deviates from that of the company, which derived an indication of a minor added benefit for the total patient population from the marketing authorization – independent of age.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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