Daridorexant (insomnia)

Addendum to Project A22-123 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
BWSQ	Benzodiazepine Withdrawal Symptom Questionnaire
CBT	cognitive behavioural therapy
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ISI	Insomnia Severity Index
MedDRA	Medical Dictionary for Regulatory Activities
PSG	polysomnography
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SDQ	sleep diary questionnaire
SDS	Sheehan Disability Scale
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics

1 Background

On 28 March 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A22-123 (Daridorexant – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprises the assessment of study 201 taking into account the information in the dossier [2] and the additional information regarding this study submitted in the commenting procedure.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

As explained in detail in dossier assessment A22-123 [1], study 201 comparing daridorexant with zolpidem, which was presented by the company, was not included in the benefit assessment.

This was particularly due to the lack of information on pretreatment with cognitive behavioural therapy (CBT) or the unsuitability of CBT for the patients. Furthermore, there was no information available on the extent to which pretreatment with CBT has an influence on the effects of subsequent drug therapy. In addition, study 201 was assessed as too short (for the detailed justification for the study exclusion, see dossier assessment A22-123 [1]).

According to the G-BA, however, it is assumed in the present therapeutic indication that CBT was carried out before the start of drug treatment and that the patient did not respond sufficiently or that CBT could not be carried out.

Neither the comments of the company [3] nor the oral hearing [4] provided new information on the patients' CBT pretreatment in study 201. In addition, no further information was provided on the extent to which CBT pretreatment can be classified as a possible effect modifier, or on the extent to which the results of a patient population without CBT pretreatment can be transferred to a patient population with CBT pretreatment. The relevant points of criticism have thus not been resolved even after completion of the commenting procedure. Therefore, study 201 is still not rated as relevant for the benefit assessment.

In accordance with the commission, the following Sections 2.1 to 2.4 describe study 201 and present its results.

Table 1: Study pool of the company – RCT, direct comparison: daridorexant vs. zolpidem

Study	Study category			Available sources		
	Study for the approval 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 (yes/no [citation])
Study AC-078A201 (201[c])	Yes	Yes	No	Yes [5]	Yes [6,7]	Yes [8,9]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

CSR: clinical study report; RCT: randomized controlled trial

2.1 Study characteristics

Table 2 and Table 3 describe study 201.

Table 2: Characteristics of the study included by the company – RCT, direct comparison: daridorexant vs. zolpidem

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
201	RCT, double-blind, parallel	Adults (18–64 years) with chronic sleep disorder according to DSM-5 criteria, as well as ▪ ISI score ≥ 15 ▪ the following self-reported sleep parameters[b]: ▫ ≥ 30 minutes to fall asleep ▫ total time spent awake after sleep onset ≥ 30 minutes ▫ total sleep time ≤ 6.5 h ▪ the following sleep parameters (using PSG on 2 nights[c]): ▫ mean latency to sleep onset (LPS) ≥ 20 minutes (minimum 15 minutes), and ▫ mean total time spent awake after sleep onset (WASO) ≥ 30 minutes (minimum 20 minutes), and ▫ mean total sleep time (TST) < 420 minutes	Daridorexant 50 mg (N = 61) zolpidem (N = 60) daridorexant 5 mg[d] (N = 60) daridorexant 10 mg[d] (N = 59) daridorexant 25 mg[d] (N = 60) placebo[d] (N = 60)	Screening: 14–28 days Treatment : 30 days[e] Follow-up for AEs: 30 days	38 centres in Germany, Hungary, Israel, Spain, Sweden and USA 9/2016–6/2017[f]	Primary: total time spent awake after sleep onset (WASO) Secondary: mortality, morbidity, AEs

a. Primary outcomes comprise information without consideration of the relevance for this benefit assessment. Secondary outcomes comprise exclusively data based on the information provided by the company's Module 4 A.
b. On ≥ 3 nights/week for ≥ 3 months before the start of the screening phase and on ≥ 3 nights within 7 consecutive nights between visits 1 and 2 (screening phase).
c. During the screening phase, PSG was performed on 2 consecutive nights (visit 2) after placebo administration between day 14 and day 6 before randomization.
d. This arm is irrelevant for the assessment and is not presented in the following tables.
e. On day 30, placebo was administered before bedtime in a single-blinded fashion (patients remained blinded).
f. According to the CSR, first visit of the first patient and last visit of the last patient.

AE: adverse event; CSR: clinical study report; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition; ISI: Insomnia Severity Index; LPS: latency to persistent sleep; N: number of randomized patients; PSG: polysomnography; RCT: randomized controlled trial; TST: total sleep time; WASO: wake after sleep onset

Table 3: Characteristics of the intervention – RCT, direct comparison: daridorexant vs. zolpidem

Study	Intervention	Comparison
201	Daridorexant, 50 mg, orally, once daily at bedtime	Zolpidem, 10 mg, orally, once daily at bedtime
	Dose adjustments were not allowed; short treatment interruption allowed in case of AEs	
	Pretreatment Not allowed ▪ CBT within 1 month before study start ▪ prohibited CNS-active drugs (including OTC and herbal drugs) for 5 half-lives of the respective drug (but at least 2 weeks prior to the start of the screening phase (visit 1) and until 24 hours after the last visit (e.g. sedating antihistamines, psychotropic substances, antidepressants, anxiolytics, other sleeping pills) ▪ moderate to strong CYP3A4 inhibitors and inducers, sensitive CYP3A4 substrates, (P-gP) substrates, BCRP substrates and CYP2B6 substrates, grapefruit juice within 1 week before the start of the screening phase (visit 1) and until 24 hours after the last visit **Concomitant treatment** Not allowed ▪ see non-permitted pretreatment ▪ caffeine consumption: ▫ > 600 mg caffeine/day; ▫ after 4 pm on non-PSG nights or after 2 pm on the days of PSG nights ▪ alcohol consumption: ▫ > 2 drinks/day, ▫ < 3 hours before going to bed on non-PSG nights ▫ within 24 hours prior to PSG night and during all PSG visits ▪ heavy tobacco use (≥ 10 cigarettes per day), and smoking during PSG assessment at night; at home, it is recommended not to smoke or to use other tobacco products, including oral snuff tobacco, from 10 pm to 8 am Allowed ▪ common advices related to sleep hygiene	

AE: adverse event; BCRP: breast cancer resistance protein; CBT: cognitive behavioural therapy; CNS: central nervous system; CYP: cytochrome P450; OCT: over the counter; P-gP: P-glycoprotein; PSG: polysomnography; RCT: randomized controlled trial

Study 201 is a multicentre, double-blind, randomized study with daridorexant, zolpidem and placebo. The study included adult patients between 18 and 64 years of age with chronic insomnia disorder according to Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria and poor sleep quality (Insomnia Severity Index [ISI] score ≥ 15). In addition, patients had to have insufficient sleep quantity. In their self-reported history, patients had to fulfil the following criteria on at least 3 nights per week and for at least 3 months prior to study start: ≥ 30 minutes to fall asleep, total time spent awake after sleep onset ≥ 30 minutes, and total sleep time ≤ 6.5 h. Prior to study inclusion, sleep quantity criteria had to be confirmed by polysomnography (PSG) on 2 nights. Patients who had received CBT

within 1 month prior to study start were excluded from the study. CBT and other psychological therapies, excluding common advice related to sleep hygiene, were also not allowed during the study.

It should be noted that patients were excluded who had psychiatric disease or neurological disorders which may impact sleep, motor performance, or cognition, (including Parkinson disease, predementia, dementia, other neurodegenerative disorders, and stroke).

The study consisted of a screening phase of 2 to a maximum of 4 weeks, a double-blind treatment phase of 4 weeks, and a follow-up phase of 4 weeks.

In the study, a total of 360 patients were randomly allocated in a 1:1:1:1:1:1 ratio to treatment with different dosages of daridorexant (5 mg [N = 60], 10 mg [N = 59], 25 mg [N = 60], 50 mg [N = 61]), 10 mg zolpidem (N = 60), or placebo (N = 60). Randomization was stratified by sex. In accordance with the respective Summaries of Product Characteristics (SPCs) [10,11], the treatment arms with 50 mg daridorexant and 10 mg zolpidem are considered for the present assessment.

As described in dossier assessment A22-123 [1], treatment in study 201 partly deviated from the recommendations of the corresponding SPC. According to the SPC [11], the treatment duration with daridorexant should be as short as possible and the appropriateness of continued treatment should be assessed within 3 months and periodically thereafter. However, the study protocol specified a fixed period of 4 weeks for treatment with daridorexant. Since the appropriateness should be assessed within the first 3 months and treatment only covered 1 month in total, it is ultimately unclear whether, and if so, how many patients were treated for a shorter or longer period than necessary. According to the SPC [10], the duration of treatment with zolpidem should also be as short as possible, but in contrast to daridorexant, it should not exceed 4 weeks including a period of tapering off. However, analogous to daridorexant, the study protocol specified a fixed period of 4 weeks of treatment. In addition, neither Module 4 A nor the study documents provide any information on the implementation of a tapering phase. The possible effects of the fixed treatment duration in the study and the lack of a tapering phase (e.g. rebound effect) for the patients are unclear.

Primary outcome of the study was the total time spent awake after sleep onset. Secondary outcomes were outcomes from the categories of mortality, morbidity and side effects.

Patient characteristics

Table 4 shows the characteristics of the patients in study 201.

Table 4: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: daridorexant vs. zolpidem

Study **Characteristic** **Category**	**Daridorexant** **N[a] = 61**	**Zolpidem** **N[a] = 60**
Study 201		
Age [years], mean (SD)	45 (12)	44 (12)
Sex [F/M], %	64/36	63/37
Family origin, n (%)		
African American	5 (8)	6 (10)
Caucasian	56 (92)	54 (90)
Insomnia Severity Index (ISI), mean (SD)	21.1 (2.7)	21.3 (2.9)
Disease duration: time from first diagnosis to randomization [months], mean (SD)	ND	ND
Pretreatment with CBT[b], n (%)	ND	ND
Medical history (recorded as SOC/PT[c]), n (%)		
Psychiatric disorders (SOC)	7 (11)	6 (10)
Tobacco abuse (PT)	4 (7)	3 (5)
Depression (PT)	2 (3)	3 (5)
Drug abuse (PT)	1 (2)	0 (0)
Drug dependence (PT)	0 (0)	1 (2)
Treatment discontinuation, n (%)	3 (5)	1 (2)
Study discontinuation, n (%)	0 (0)	2 (3)

a. Number of randomized patients. Values that are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. Patients who had received CBT within 1 month prior to study start were excluded from the study.
c. MedDRA version 19.0. SOC and PT from MedDRA without adaptation.

CBT: cognitive behavioural therapy; F: female; M: male; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients in the category; N: number of randomized (or included) patients; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SD: standard deviation; SOC: System Organ Class

The most important demographic and disease-specific characteristics of the patients in the study are largely balanced between the study arms. There is no information on the duration of the disease or on previous treatment with CBT. About 10% of patients reported psychiatric disorders in their medical history, with depression accounting for 3% and 5%. No data are available on accompanying diseases.

Risk of bias across outcomes (study level)

Table 5 shows the risk of bias across outcomes (risk of bias at study level).

Table 5: Risk of bias across outcomes (study level) – RCT, direct comparison: daridorexant vs. zolpidem

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
Study 201	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low.

2.2 Results

2.2.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - severity of insomnia recorded with ISI
  - daytime wakefulness recorded with the visual analogue scale (VAS) of the sleep diary questionnaire (SDQ) (VASDAY)
  - depth of sleep recorded with the SDQ VAS (VASDEPTH)
  - daytime functioning recorded with the SDQ VAS (VASFUNC)
  - quality of sleep recorded with the SDQ VAS (VASQUAL)
  - morning sleepiness recorded with the SDQ VAS (VASSLEEP)
- Health-related quality of life
  - No data were recorded for this outcome
- Side effects
  - serious adverse events (SAEs)
  - discontinuation due to adverse events (AEs)
  - withdrawal symptoms

- further specific AEs, if any

The choice of patient-relevant outcomes deviates from that taken by the company, which used further outcomes in the dossier (Module 4 A).

Table 6 shows for which outcomes data were available in the included study.

Table 6: Matrix of outcomes – RCT, direct comparison: daridorexant vs. zolpidem

Study	Outcomes											
	All-cause mortality	Severity of insomnia (ISI)	Daytime wakefulness (SDQ VAS VASDAY)	Depth of sleep (SDQ VAS VASDEPTH)	Daytime functioning (SDQ VAS VASFUNC)	Quality of sleep (SDQ VAS VASQUAL)	Morning sleepiness (SDQ VAS VASSLEEP)	Health-related quality of life	SAEs	Discontinuation due to AEs	Withdrawal symptoms	Specific AEs
Study 201	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[a]	Yes	Yes	No[b]	No[c]

a. Outcome not recorded.
b. No usable data available; for reasoning, see body of text below.
c. No specific AEs identified based on the AEs occurring in the relevant study.

AE: adverse event; ISI: Insomnia Severity Index; RCT: randomized controlled trial; SAE: serious adverse event; SDQ: sleep diary questionnaire; VAS: visual analogue scale

Outcomes on morbidity

Insomnia Severity Index (ISI)

In study 201, the severity of insomnia was recorded using the ISI and was also used as an inclusion criterion (ISI score ≥ 15 points). The ISI is an established and sufficiently valid instrument for measuring the severity of insomnia [12-15]. It includes the following 7 items: difficulty falling asleep, difficulty staying asleep, problem waking up too early, satisfaction with current sleep pattern, interference of sleep problems with daily functioning, noticeability of sleep problems by others, and worry/distress caused by current sleep problems. The 7 items are each rated on a 5-point Likert scale, where higher scores indicate greater severity (0 = no impairment, 4 = very severe/very impairing) [16]. The item scores are added together to give a total score of 0 to 28 [15]. A higher total score thus reflects greater severity of insomnia (0 to 7 points: no insomnia, 8 to 14 points: subthreshold insomnia, 15 to 21 points: moderate insomnia, and 22 to 28 points: severe insomnia).

The study participants completed the ISI 2 times: at the beginning of the screening phase (visit 1) and at the end of the double-blind treatment phase (visit 5). The company presented the change in total ISI score between baseline (visit 1) and the end of treatment after 4 weeks (visit 5) as an analysis. This analysis is used for the present assessment.

Disease-related symptoms, self-reported sleep parameters using the SDQ

At the beginning of the screening phase (visit 1) of study 201, patients were given a sleep diary (SDQ), which they were asked to complete electronically every day until week 4 (visit 6). Between visit 1 and visit 2 and between visit 2 and randomization, patients had to fully document their sleep parameters on ≥ 7 consecutive days. The period between visit 2 and randomization was used to determine the values at baseline. In the further course of the study, weekly mean values were calculated if data were available on at least 3 days of a week. The sleep diary contains one questionnaire for the morning and one for the evening. These contain both questions on the patient-reported recording of sleep quantity and an assessment of the burden of the sleep disturbances using various visual analogue scales: 3 VAS recordings in the morning measurement and 2 VAS recordings in the evening measurement.

The patients used the respective VAS in the morning to assess their perceived sleep quality, sleep depth and morning sleepiness, and in the evening to assess their perceived daytime wakefulness and daytime functioning. The results recorded by means of the different VAS are used for the assessment, reporting treatment effects at the time point of 4 weeks. Due to the patients' daily self-assessment of their perceived quality of sleep at night and the perceived wakefulness during the day, there is a direct relevance for the patients.

The individual questions on sleep quantity provided in the morning questionnaire record in particular points in time and time spans such as the time point of going to bed, the duration of time spent awake, the time point of waking up and the total sleep duration of the previous night. The total duration of wake after sleep onset, delayed sleep onset and total sleep duration were recorded on the basis of the times indicated by the patient. The individual questions of the evening questionnaire document the frequency and duration of the sleep phases during the day.

The patient-reported outcomes on total time spent awake after sleep onset, latency to sleep onset and total sleep time, reported by means of the 2 questionnaires (in the morning and in the evening), only record sleep quantity. It is unclear to what extent these sleep parameters allow direct conclusions to be drawn about sleep quality, so the analyses of these outcomes for the treatment effect at the 4-week time point are presented as supplementary information in Appendix B.

In addition, it should be noted that study 201 also used PSG measurements to characterize quantitative sleep parameters. Recording started after the light was turned off (within

30 minutes of the usual bedtime) and continued every 30 seconds for 8 hours until the light was turned on. The PSG was used to record the same sleep quantity outcomes as the questionnaires mentioned above. These outcomes are also presented as supplementary information in Appendix B.

Outcomes on side effects

Withdrawal symptoms (physical dependence) assessed with the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ)

The BWSQ is a questionnaire for the assessment of benzodiazepine withdrawal symptoms by the patients themselves or by medical staff [17]. The questionnaire is composed of 20 items on symptoms, although the question on "shaking or trembling" was inadvertently not included in study 201. The patient rates each symptom as severe (2 points), moderate (1 point) or absent (0 points). The patients completed the questionnaire themselves at visits 2, 4, 5 and visit 6. The company presented the changes in BWSQ total score and in the individual symptoms from visit 5 (corresponds to the end of treatment) to visit 6 (corresponds to the end of treatment + 1 day) as analysis. In Module 4 A, the company did not address the impact of the absence of the question on the interpretation of the total score. The company also did not submit any sources showing the BWSQ to be suitable for use of daridorexant or zolpidem, which are not benzodiazepines. Furthermore, it is questionable to record withdrawal symptoms only 1 day after discontinuation of the study medication. According to the SPC [10], zolpidem should be discontinued gradually. It does not seem reasonable to record withdrawal symptoms without adherence to the gradual discontinuation phase of zolpidem. The BWSQ is disregarded in the present assessment.

Comments on further outcomes from the category of morbidity and side effects

The company included various other outcomes and instruments for the recording of morbidity or side effects in its assessment and rated them as being patient-relevant or validated. They are commented on below.

Disease symptoms, assessed using the Sheehan Disability Scale [SDS]

For its benefit assessment, the company used results on the SDS as an outcome in the morbidity category, justifying this by stating that the validity and reliability of the SDS had been investigated in several studies. However, the SDS was developed as a generic instrument to examine functional impairment in the life domains of work, social life, and family life in patients with psychiatric disorders [18,19]. Validity was not investigated in patients with chronic insomnia. The SDS is therefore not validated in the therapeutic indication of chronic insomnia. Rather, patients with psychiatric disorders that may impact sleep, motor performance, or cognition were excluded from study 201. Only about 10% of the patients had a history of a psychiatric disorder (see also Table 4). The results obtained from the SDS are therefore not used for the present assessment.

Next-day residual effect, assessed with the Digit Symbol Substitution Test

To assess the next-day residual effect, the company used the Digit Symbol Substitution Test and assigned the results to the side effect category. According to the company, this cognitive function test can be used, for example, to detect impairments in attention, motor speed and memory, regardless of their type and cause or changes in the patients. The company added that the test was sensitive to both the presence of cognitive dysfunction and changes in cognitive function in a wide range of study populations. However, the company did not submit any sources showing this test to be validated for use in patients with chronic insomnia. The Digit Symbol Substitution Test is therefore not used for the present assessment.

2.2.2 Risk of bias

Table 7 describes the risk of bias for the results of the considered outcomes.

Table 7: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: daridorexant vs. zolpidem

Study		Outcomes											
	Study level	All-cause mortality	Severity of insomnia (ISI)	Daytime wakefulness (SDQ VAS VASDAY)	Depth of sleep (SDQ VAS VASDEPTH)	Daytime functioning (SDQ VAS VASFUNC)	Quality of sleep (SDQ VAS VASQUAL)	Morning sleepiness (SDQ VAS VASSLEEP)	Health-related quality of life	SAEs	Discontinuation due to AEs	Withdrawal symptoms	Specific AEs
Study 201	L	L	L	L	L	L	L	L	–[a]	L	L	–[b]	–

a. Outcome not recorded.
b. No usable data available; see Section 2.2.1 for reasons.

AE: adverse event; ISI: Insomnia Severity Index; L: low; RCT: randomized controlled trial; SAE: serious adverse event; SDQ: sleep diary questionnaire; VAS: visual analogue scale

The risk of bias for the results of the patient-relevant outcomes is rated as low.

2.2.3 Results

Patient-relevant outcomes

Table 8 and Table 9 summarize the results of the comparison of daridorexant with zolpidem. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Tables on common AEs, common SAEs and discontinuations due to AEs are presented in Appendix A. Supplementary results on the morbidity outcomes of perceived and measured total sleep time, latency to persistent sleep and total duration of wake after sleep onset are presented in Appendix B. For patient-reported outcomes, figures showing the time course of the mean values by treatment arm are additionally provided in Appendix C.

Table 8: Results (mortality, side effects) – RCT, direct comparison: daridorexant vs. zolpidem

Study	**Daridorexant**		**Zolpidem**		**Daridorexant vs. zolpidem**
Outcome category **Outcome**	**N**	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
Study 201					
Mortality					
All-cause mortality[a]	61	0 (0)	60	0 (0)	–
Side effects					
AEs (supplementary information)[b]	61	21 (34.4)	60	24 (40.0)	–
SAEs	61	1 (1.6)	60	0 (0)	–[c]; 0.529[d]
Discontinuation due to AEs	61	1 (1.6)	60	1 (1.7)	0.98 [0.06; 15.37]; 0.991
Withdrawal symptoms	No usable data[e]				

a. Recording of deaths in the framework of the recording of side effects
b. Discrepancy between the dossier's Module 4 A and 5. The presented data are from Module 5.
c. No presentation of effect estimation and CI, as these are not informative.
d. Institute's calculation, unconditional exact test (CSZ method according to [20])
e. See Section 2.2.1 for reasons.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Table 9: Results (morbidity, health-related quality of life) – RCT, direct comparison: daridorexant vs. zolpidem

Study Outcome category	Daridorexant			Zolpidem			Daridorexant vs. zolpidem
Outcome	**N[a]**	**Values at baseline mean (SD)**	**Change by treatment end mean (SD)**	**N[a]**	**Values at baseline mean (SD)**	**Change by treatment end mean (SD)**	**MD [95% CI]; p-value[b]**
Study 201							
Morbidity							
Severity of insomnia (ISI)[c]	55	21.2 (2.7)	−8.5 (6.3)	56	21.2 (2.7)	−9.0 (5.0)	0.54 [−1.58; 2.67]; 0.613[d]
Daytime wakefulness (SDQ VAS VASDAY)[e]	57	32.8 (20.1)	16.0 (15.9)	59	32.4 (17.7)	17.3 (17.9)	−2.02 [−7.95; 3.9]; 0.501
Depth of sleep (SDQ VAS VASDEPTH)[e]	57	30.2 (17.3)	20.1 (17.6)	59	31.8 (15.9)	20.5 (17.4)	−1.9 [−8.08; 4.28]; 0.545
Daytime functioning (SDQ VAS VASFUNC)[e]	57	33.6 (20.5)	17.1 (16.6)	59	34.3 (17.0)	16.6 (17.3)	−0.62 [−6.54; 5.31]; 0.838
Quality of sleep (SDQ VAS VASQUAL)[e]	57	30.5 (17.9)	20.9 (17.7)	59	31.6 (15.8)	19.3 (15.6)	0.23 [−5.77; 6.23]; 0.939
Morning sleepiness (SDQ VAS VASSLEEP)[e]	57	30.2 (19.7)	17.0 (17.6)	59	32.1 (16.9)	16.2 (15.8)	−0.87 [−6.51; 4.78]; 0.762
Health-related quality of life	Outcomes from this category were not recorded						

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
b. Effect, CI and p-value: mixed-effects model with repeated measures (MMRM) adjusted for baseline, sex and interaction of time and treatment.
c. Values at baseline refer to visit 1 at the beginning of the screening phase. c. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus control) indicate an advantage for the intervention (scale range 0 to 28).
d. The calculation is based on an unpaired t-test.
e. Patient-reported sleep parameters using the SDQ; values at baseline refer to the mean value of the entries between the screening phase (visit 2) and randomization (visit 3) over 7 consecutive days; recorded until the end of the double-blind treatment phase (week 4); weekly mean values are calculated if data are available on ≥ 3 days.
Higher (increasing) values indicate improved symptoms; positive effects (intervention minus control) indicate an advantage for the intervention (scale range 0 to 100).

CI: confidence interval; ISI: Insomnia Severity Index; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SDQ: sleep diary questionnaire; VAS: visual analogue scale

Mortality

No deaths occurred in study 201.

Morbidity

Severity of insomnia (ISI)

No statistically significant difference between treatment groups was found for the outcome of severity of insomnia, recorded using the ISI.

Daytime wakefulness (SDQ VAS VASDAY), depth of sleep (SDQ VAS VASDEPTH), daytime functioning (SDQ VAS VASFUNC), quality of sleep (SDQ VAS VASQUAL), morning sleepiness (SDQ VAS VASSLEEP)

No statistically significant difference between treatment groups was found for any of the outcomes of daytime wakefulness (SDQ VAS VASDAY), depth of sleep (SDQ VAS VASDEPTH), daytime functioning (SDQ VAS VASFUNC), quality of sleep (SDQ VAS VASQUAL), and morning sleepiness (SDQ VAS VASSLEEP).

Health-related quality of life

Health-related quality of life outcomes were not recorded in study 201.

Side effects

SAEs and discontinuation due to AEs

No statistically significant difference was found between treatment groups for either of the outcomes of SAEs or discontinuation due to AEs.

Withdrawal symptoms

Study 201 provides no usable data for the outcome of withdrawal symptoms (see Section 2.2.1).

2.3 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present analysis:

- sex (male versus female)
- severity of ISI (ISI score < 22 versus ≥ 22)

The subgroup analysis by sex was prespecified. No subgroup analyses by age were available. The company justified this by stating that no adults ≥ 65 years of age were included in study 201.

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 presented only if there is a statistically significant and relevant effect in at least one subgroup.

Using the methods described above, the available subgroup results do not reveal any effect modifications.

2.4 Summary

Overall, there are neither advantages nor disadvantages for daridorexant compared with zolpidem.

The G-BA decides on the added benefit.

3 References

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Appendix A Results on side effects

For the overall rates of AEs and SAEs, the tables below present events for System Organ Classes (SOCs) and Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA), each on the basis of the following criteria:

- overall rate of AEs (irrespective of severity grade): events that occurred in at least 10% of patients of one study arm
- overall rates of SAEs: events that occurred in at least 5% of patients in one study arm
- in addition, for all events irrespective of severity grade: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

Table 10: Common AEs[a] – RCT, direct comparison: daridorexant vs. zolpidem

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Daridorexant** **N = 61**	**Zolpidem** **N = 60**
Study 201		
Overall rate of AEs[c]	21 (34.4)[d]	24 (40.0)[d]
General disorders and administration site conditions[c]	0 (0.0)	6 (10.0)
Gastrointestinal disorders	4 (6.6)[d]	9 (15.0)
Nervous system disorders	9 (14.8)[d]	11 (18.3)[d]
Headache	5 (8.2)[d]	6 (10.0)[d]

a. Events that occurred in ≥ 10% of the patients in at least one study arm.
b. MedDRA version 19; SOCs and PTs used unmodified from the clinical study report.
c. Contains events of the underlying disease.
d. Unexplained discrepancy between the dossier's Module 4 A and 5. The data presented are from Module 5. The overall rates of AEs provided in Module 4 A were 20 versus 22 patients.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 11: Common SAEs[a] – RCT, direct comparison: daridorexant vs. zolpidem

Study	Patients with event n (%)	
SOC **PT**	**Daridorexant N = 61**	**Zolpidem N = 60**
Study 201		
Overall rate of SAEs[b]	1 (1.6)	0 (0.0)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. From the SAEs, no MedDRA SOCs and PTs met the criterion for presentation.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 12: Discontinuations due to AEs – RCT, direct comparison: daridorexant vs. zolpidem

Study	Patients with event n (%)	
SOC[a] **PT[a]**	**Daridorexant N = 61**	**Zolpidem N = 60**
Study 201		
Overall rate of discontinuations due to AEs	1 (1.6)	1 (1.7)
Skin and subcutaneous tissue disorders	1 (1.6)	0 (0.0)
Angioedema	1 (1.6)	0 (0.0)
Psychiatric disorders	0 (0.0)	1 (1.7)
Anxiety	0 (0.0)	1 (1.7)

a. MedDRA version 19.0; SOCs and PTs used unmodified from Module 4 A.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Appendix B Supplementary presentation of the results

Table 13: Results (morbidity, supplementary presentation) – RCT, direct comparison: daridorexant vs. zolpidem

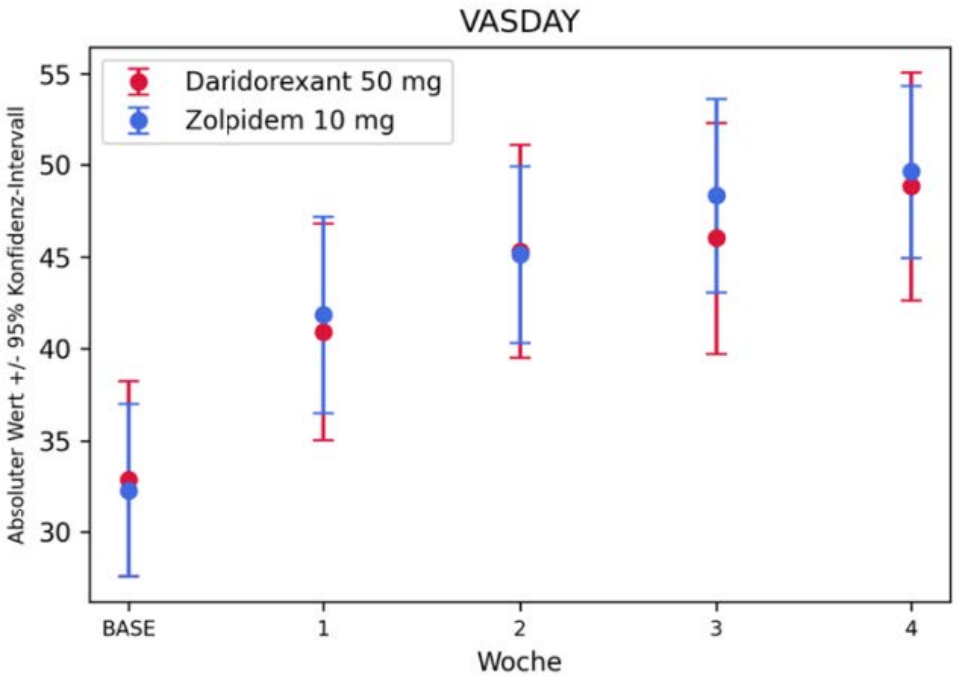
Study Outcome category Outcome	Daridorexant			Zolpidem			Daridorexant vs. zolpidem
	N[a]	Values at baseline mean (SD)	Change by treatment end mean (SD)	N[a]	Values at baseline mean (SD)	Change by treatment end mean (SD)	MD [95% CI]; p-value[b]
Study 201							
Morbidity							
Total duration of wake after sleep onset[c] (minutes)	58	95.1 (32.3)	–47.0 (34.0)	59	99.3 (39.1)	–37.1 (36.9)	–12.1 [–22.4; –1.8]; 0.021
Patient-reported total duration of wake after sleep onset[d] (minutes)	49	81.3 (48.7)	–35.5 (37.5)	48	78.6 (42.9)	–29.1 (27.3)	–3.4 [–13.5; 6.7]; 0.505
Latency to persistent sleep[c] (minutes)	58	70.2 (30.8)	–35.7 (37.6)	59	73.0 (35.0)	–45.8 (37.8)	7.9 [–0.04; 15.8]; 0.051
Patient reported delayed sleep onset[d] (minutes)	57	58.3 (30.8)	–23.7 (24.1)	59	51.6 (25.0)	–20.0 (19.3)	0.13 [–5.7; 6.0]; 0.964
Total sleep time[c] (minutes)	58	321.7 (46.0)	80.8 (53.4)	59	316.3 (55.3)	78.7 (54.0)	5.4 [–7.7; 18.6]; 0.416
Patient-reported total sleep time[d, e] (minutes)	57	316.1 (49.3)	77.4 (58.7)	59	321.9 (53.0)	53.2 (35.5)	21.5 [5.7; 37.3]; 0.008

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
b. Effect, CI and p-value: mixed-effects model with repeated measures (MMRM) adjusted for baseline, sex and interaction of time and treatment.
c. Recorded by PSG, mean value of 2 consecutive nights each; values at baseline refer to the PSG measurement during the screening phase between day 14 and day 6 before randomization (visit 2); last PSG measurement was conducted at week 4 (day 28 and day 29).
d. Patient-reported sleep parameters using the SDQ; values at baseline refer to the mean value of the entries between the screening phase (visit 2) and randomization (visit 3) over 7 consecutive days; recorded until the end of the double-blind treatment phase (week 4); weekly mean values are calculated if data are available on ≥ 3 days.
e. For the outcome, the company presented an additional responder analysis for the change in sleep duration by 55 minutes per night. The responder analysis is not presented because the response criterion (change ≥ 55 minutes) was not prespecified.

CI: confidence interval; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; PSG: polysomnography; RCT: randomized controlled trial; SD: standard deviation; SDQ: sleep diary questionnaire

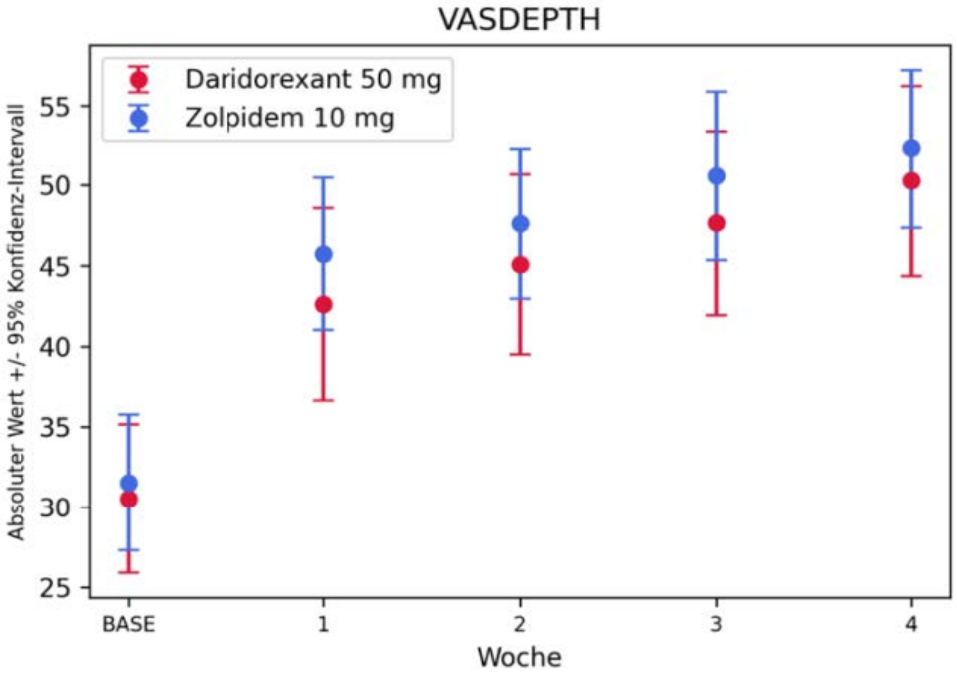
Appendix C Figures on the mean observed values over time by treatment arm

C.1 Morbidity – patient-reported outcomes



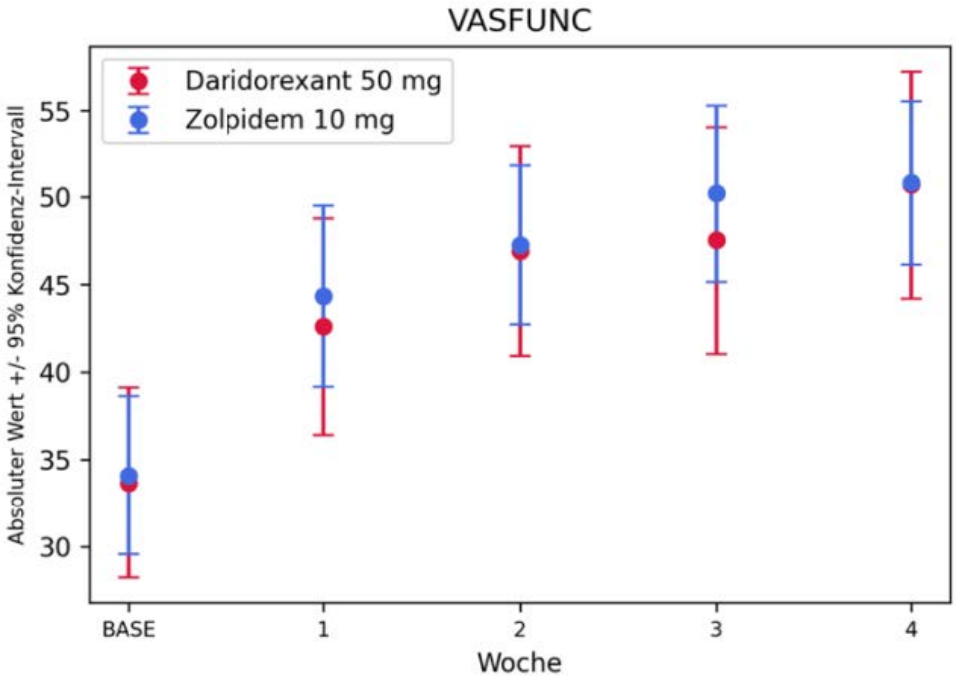
Absoluter Wert +/- 95% Konfidenz-Intervall = Absolute value +/- 95% confidence interval; Woche = Week

Figure 1: Mean values of observations with corresponding 95% confidence intervals over time for the outcome of daytime wakefulness (SDQ VAS VASDAY) by treatment arm in study 201



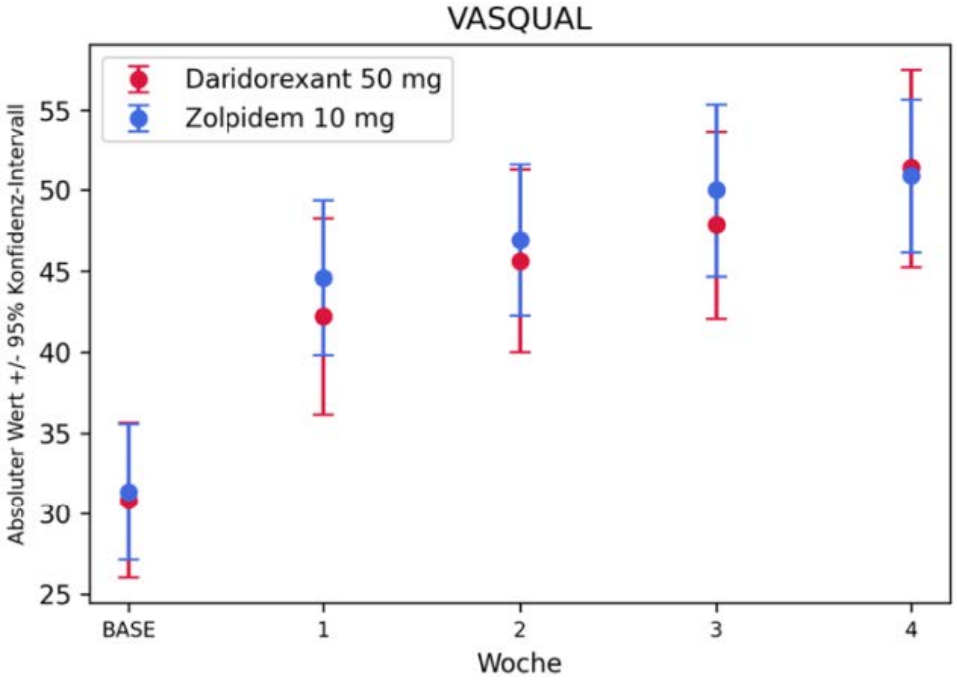
Absoluter Wert +/- 95% Konfidenz-Intervall = Absolute value +/- 95% confidence interval; Woche = Week

Figure 2: Mean values of observations with corresponding 95% confidence intervals over time for the outcome of depth of sleep (SDQ VAS VASDEPTH) by treatment arm in study 201



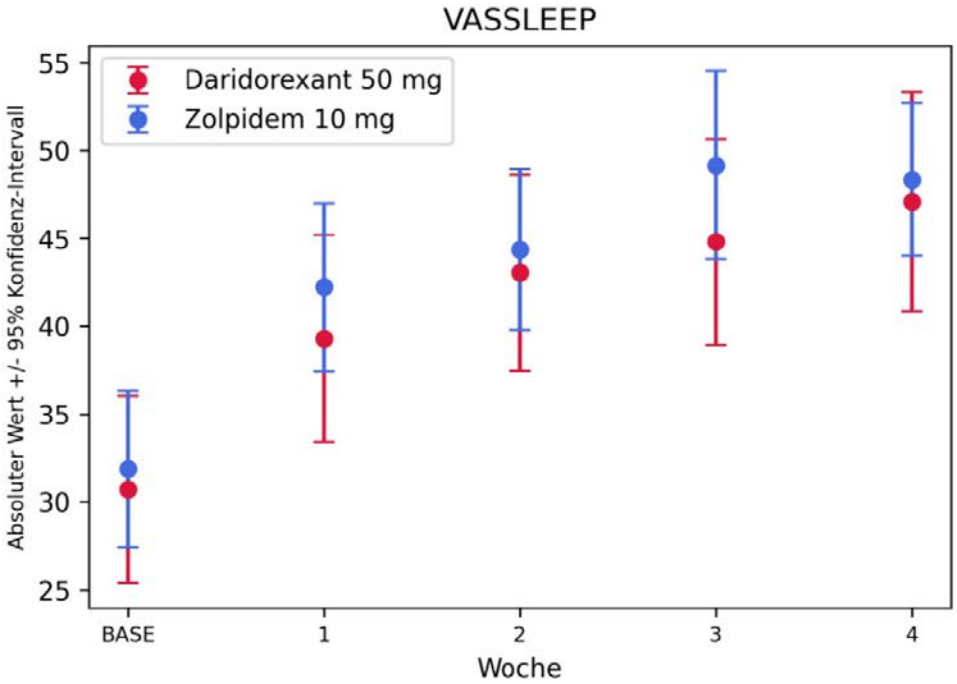
Absoluter Wert +/- 95% Konfidenz-Intervall = Absolute value +/- 95% confidence interval; Woche = Week

Figure 3: Mean values of observations with corresponding 95% confidence intervals over time for the outcome of daytime functioning (SDQ VAS VASFUNC) by treatment arm in study 201



Absoluter Wert +/- 95% Konfidenz-Intervall = Absolute value +/- 95% confidence interval; Woche = Week

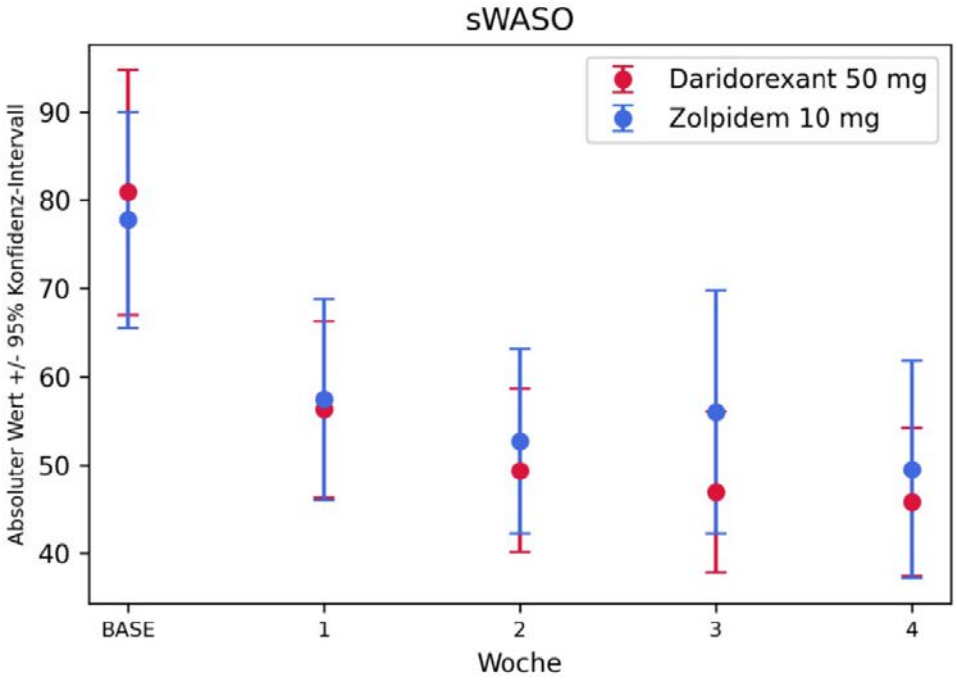
Figure 4: Mean values of observations with corresponding 95% confidence intervals over time for the outcome of quality of sleep (SDQ VAS VASQUAL) by treatment arm in study 201



Absoluter Wert +/- 95% Konfidenz-Intervall = Absolute value +/- 95% confidence interval; Woche = Week

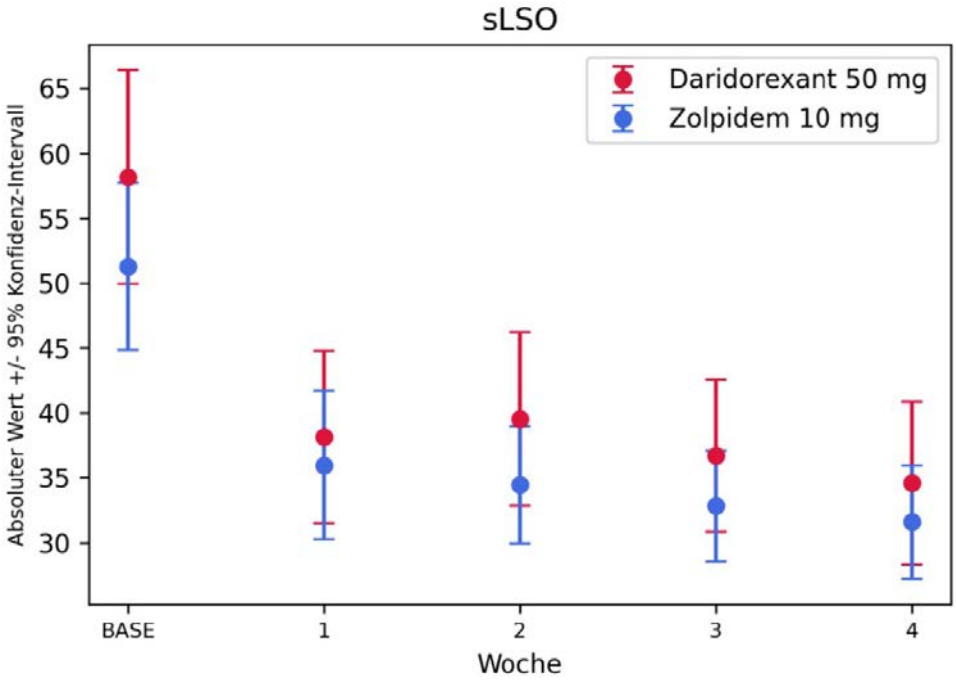
Figure 5: Mean values of observations with corresponding 95% confidence intervals over time for the outcome of morning sleepiness (SDQ VAS VASSLEEP) by treatment arm in study 201

C.2 Morbidity – patient-reported outcomes presented as supplementary information



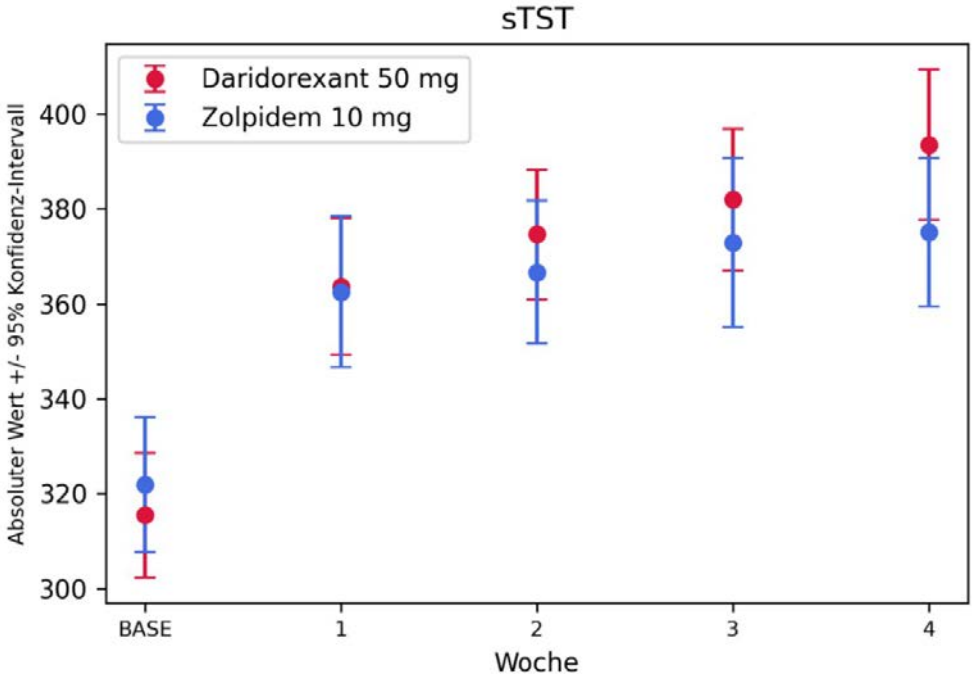
Absoluter Wert +/- 95% Konfidenz-Intervall = Absolute value +/- 95% confidence interval; Woche = Week

Figure 6: Mean values of observations with corresponding 95% confidence intervals over time for the supplementary outcome of patient-reported total duration of wake after sleep onset by treatment arm in study 201



Absoluter Wert +/- 95% Konfidenz-Intervall = Absolute value +/- 95% confidence interval; Woche = Week

Figure 7: Mean values of observations with corresponding 95% confidence intervals over time for the supplementary outcome of patient-reported delayed sleep onset by treatment arm in study 201



Absoluter Wert +/- 95% Konfidenz-Intervall = Absolute value +/- 95% confidence interval; Woche = Week

Figure 8: Mean values of observations with corresponding 95% confidence intervals over time for the supplementary outcome of patient-reported total sleep time by treatment arm in study 201