Daridorexant (insomnia)

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 *Daridorexant (Insomnie) – 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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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 one person.

IQWiG thanks the respondent and the Chronische Schlafstörungen Selbsthilfe (self help group for chronic sleep disorder) for participating in the written exchange and for their support. The respondent and the Chronische Schlafstörungen Selbsthilfe were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CBT	cognitive behavioural therapy
CBT-I	cognitive behavioural therapy for insomnia
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
PSG	polysomnography
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) 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 daridorexant. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 March 2024.

Research question

The aim of the present report is to assess the added benefit of daridorexant compared with best supportive care (BSC) as appropriate comparator therapy (ACT) in adult patients with insomnia characterized by symptoms present for at least 3 months and considerable impact on daytime functioning.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of daridorexant

Therapeutic indication	**ACT**[a]
Adults with insomnia characterized by symptoms present for at least 3 months and considerable impact on daytime functioning[b, c]	BSC[d, e]

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the requirements of the Pharmaceutical Directive Appendix III on daridorexant must be taken into account. The G-BA pointed out that according to the Pharmaceutical Directive, it must be checked before prescribing drugs whether non-drug treatments can be considered instead. According to the G-BA, it is assumed in the present therapeutic indication that CBT-I was carried out before the start of drug treatment and that the patient did not respond sufficiently, or that CBT-I could not be carried out. It must be documented whether CBT-I was carried out or could not be carried out.
c. The G-BA assumed both adults with concomitant diseases and adults without concomitant diseases to be comprised by the intended therapeutic indication. It is assumed that patients receive optimal treatment of any underlying/accompanying diseases (e.g. depression).
d. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
e. According to the G-BA, it is assumed that sleep hygiene measures are implemented in both the comparator arm and the intervention arm. In addition, short-term drug therapy (maximum 4 weeks) with short-acting benzodiazepines or non-benzodiazepine receptor agonists may be indicated for patients during the course of long-term therapy. For implementation in a study, a selection of these treatment options should be available to these patients. A CBT-I should not be discontinued solely for reasons of study inclusion. If indicated, it should be examined whether patients can be offered CBT-I in both the intervention and the comparator arm.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; CBT-I: cognitive behavioural therapy for insomnia

While the company claimed to have followed the ACT specified by the G-BA, it deviated from the G-BA's specification by stating that BSC corresponded to optimized non-drug care at the physician's discretion and in accordance with availability.

The present benefit assessment was implemented in comparison with the ACT specified by the G-BA. In addition, 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 study duration of 24 weeks were used for deriving any added benefit.

Results

The check of completeness of the study pool did not reveal any relevant study for assessing the added benefit of daridorexant in comparison with the ACT. The company, in contrast, identified Studies 301 and 303, which compared different dosages of daridorexant with placebo, and used them in its assessment.

Data presented by the company

Study 301

Study 301 is a double-blind RCT comparing daridorexant at doses of 25 mg and 50 mg against placebo. It included adult patients with chronic sleep disorder of at least moderate severity (Insomnia Severity Index [ISI] value ≥ 15). In addition, patients had to have insufficient sleep quantity, meeting the following criteria on at least 3 nights per week and for at least 3 months prior to study start in their self-reported history: ≥ 30 minutes to fall asleep, total wake time after sleep onset ≥ 30 minutes, and total sleep time ≤ 6.5 hours. Before randomization, these criteria had to be confirmed by the patient in a placebo-treated run-in phase as part of the screening on at least 3 nights out of 7 nights. In addition, the criteria for sleep quantity (latency to persistent sleep, wake time, and total duration of sleep) were further verified during the run-in phase using polysomnography (PSG) on 2 nights. Patients who had started cognitive behavioural therapy (CBT) within 1 month prior to study start were excluded from the study.

The study comprises a screening phase of 1 month maximum, including a 13 to 24-day placebo-treated run-in phase, a 12-week double-blind treatment phase, a 7-day single-blind placebo-treated run-out phase, and a further 23-day follow-up observation. This means that the patients had no knowledge of the type of their study medication from the beginning of the run-in phase until the end of the run-out phase, while the randomized study phase was double-blind.

In Study 301, a total of 930 patients were randomly allocated in a 1:1:1 ratio to treatment with daridorexant (25 mg [N = 310]), 50 mg (N = 310), or placebo (N = 310).

Treatment with daridorexant in the 50 mg arm, but not in the 25 mg arm, was in compliance with the dosage recommendations in the Summary of Product Characteristics (SPC).

Coprimary outcomes of the study were the total duration of wake after sleep onset and the latency to persistent sleep. Patient-relevant secondary outcomes were outcomes on morbidity and adverse events (AEs).

Study 303

Study 303 is an extension study of Studies 301 and 302. Patients who had completed the double-blind treatment phase and the placebo-treated run-out phase of Studies 301 and 302 had the option to participate in Study 303. Study 302 is a double-blind RCT comparing daridorexant at doses of 10 mg and 25 mg against placebo. In Study 302, daridorexant was not administered in compliance with the SPC.

Study 303 comprised a 40-week double-blind treatment phase, a 7-day single-blind placebo-treated run-out phase, and a further 23-day follow-up observation.

A total of 804 patients were enrolled in Study 303. The study had 5 arms. Three arms were the continuation of the respective daridorexant arms of Studies 301 and 302 (10 mg, 25 mg and 50 mg). Patients who had received placebo in Studies 301 and 302 were re-randomized at the start of Study 303 in a 1:1 ratio to placebo or daridorexant at a dose of 25 mg.

AEs were the primary outcome of the study. Patient-relevant secondary outcomes were outcomes on morbidity.

Approach of the company

For its assessment of the added benefit of daridorexant, the company used the results of Studies 301 and 303, which compared daridorexant at a dose of 50 mg with placebo. For all outcomes except AEs, it considered Studies 301 and 303 as one continuous study (described by the company as a “continuous study with a total duration of 52 weeks”). In addition to the data of the patients in Study 301, these analyses also include the data of those patients in Study 303 who received 50 mg daridorexant (N = 137) or placebo (N = 57) in Study 301 and Extension Study 303. The company analysed the data from Studies 301 and 303 separately for the outcomes on side effects. For its assessment, it additionally used the results of Study 301 for the outcomes that were only recorded in Study 301.

The company assumed the ACT BSC to be implemented in the placebo arms of Studies 301 and 303.

Assessment of the data presented by the company

Studies 301 and 303 are unsuitable for assessing any added benefit of daridorexant versus the ACT. This is mainly because the ACT was not implemented in the studies, and because the patient population in the studies does not correspond to the present research question.

Patient population of Study 301 (and Extension Study 303) does not correspond to the research question

According to guidelines, CBT-I is the first treatment option in the treatment of insomnia. Correspondingly, the G-BA pointed out in its notes on the ACT that according to the Pharmaceutical Directive, it must be checked before prescribing drugs whether non-drug treatments can be considered instead. According to the G-BA, it is assumed in the present therapeutic indication that CBT-I was carried out before the start of drug treatment and that the patient did not respond sufficiently, or that CBT-I could not be carried out.

In Study 301, patients were asked at screening, whether they were currently receiving CBT and also about any reasons for not receiving CBT. Only 2 patients in the potentially relevant study arms (50 mg daridorexant or placebo) were receiving CBT at baseline. Almost 90% of patients stated that they did not know that CBT existed or that they had never been offered CBT (269 patients [86.8%] in the 50 mg daridorexant arm and 271 patients [87.4%] in the placebo arm). Other reasons for not using CBT were costs or lack of reimbursement (n [%]: 24 [7.7] versus 20 [6.5]), previous treatment failure (7 [2.3] each), no local access/no therapist available (5 [1.6] versus 4 [1.3]), and other reasons (4 [1.3] versus 7 [2.3]). Overall, around 90% of the patients in Study 301 thus do not correspond to the present research question, as they were never offered CBT.

Appropriate comparator therapy not implemented in Study 301 (and Extension Study 303)

The G-BA specified BSC as ACT for the present therapeutic indication. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. The G-BA further specified the implementation of BSC in its additional notes. According to these notes, it is assumed that sleep hygiene measures are implemented in both the comparator arm and the intervention arm. In addition, short-term drug therapy (maximum 4 weeks) with short-acting benzodiazepines or non-benzodiazepine receptor agonists may be indicated for patients during the course of long-term therapy. For implementation in a study, a selection of these treatment options should be available to these patients. Besides, a CBT-I should not be discontinued solely for reasons of study inclusion. If indicated, it should be examined whether patients can be offered CBT-I in both the intervention and the comparator arm.

Study 301 used placebo in the comparator arm. According to the study protocol, concomitant medication was preferably not changed and initiation of new medication was discouraged. Potential short-term medication with short-acting benzodiazepines or non-benzodiazepine receptor agonists in accordance with the notes on the ACT was also not possible. There is also no information in the study protocol that sleep hygiene measures were applied at the start of the study or during the course of the study. At the time of screening, only 2 patients were receiving CBT, which was to be continued during the course of the study according to the

protocol. However, initiation of CBT at the beginning or during the course of the study was not allowed, although about 90% of the patients had never been offered CBT. Overall, the ACT was therefore not implemented in Study 301, as the patients, with the exception of 2 patients with CBT in the comparator arm, did not receive any measures in the sense of the ACT in addition to placebo. Extension Study 303 had analogous restrictions regarding concomitant medications to those in Study 301 mentioned above.

Analyses of Studies 301 and 303 as one continuous study not suitable

For the majority of outcomes, the company's dossier presented analyses that considered Studies 301 and 303 as one continuous study with a treatment duration of 52 weeks. All patients who had completed the double-blind study phase and the single-blind placebo-treated run-out phase of Study 301 had the option to participate in Study 303. Of 284 patients who had completed the run-out phase in the 50 mg daridorexant arm of Study 301, only 137 patients (48.2%) entered Extension Study 303 (based on all randomized patients in Study 301 [N = 310]: 44.2%). Of 557 patients who had completed the run-out phase in the respective placebo arms of Study 301 (n = 278) and Study 302 (n = 279), only 255 patients (45.8%) entered Extension Study 303 (isolated data for Study 301 are not available). The reasons why the majority of patients did not transfer to Study 303 were not recorded. Overall, the intention-to-treat principle is thus violated to such an extent that the data of Extension Study 303 cannot be used, making the analyses of the company to consider Studies 301 and 303 as one continuous study unsuitable as well. Analyses that only consider Study 301 are only available for selected outcomes in the dossier. Irrespective of this, with a study duration of 12 weeks, Study 301 alone is too short.

Results on added benefit

There are no suitable data available for the benefit assessment of daridorexant compared with the ACT in adult patients with insomnia characterized by symptoms present for at least 3 months and considerable impact on daytime functioning. There is no hint of an added benefit of daridorexant in comparison with the ACT; an added benefit is therefore not proven.

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

Table 3 shows a summary of probability and extent of the added benefit of daridorexant.

Table 3: Daridorexant – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with insomnia characterized by symptoms present for at least 3 months and considerable impact on daytime functioning[b, c]	BSC[d, e]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the requirements of the Pharmaceutical Directive Appendix III on daridorexant must be taken into account. The G-BA pointed out that according to the Pharmaceutical Directive, it must be checked before prescribing drugs whether non-drug treatments can be considered instead. According to the G-BA, it is assumed in the present therapeutic indication that CBT-I was carried out before the start of drug treatment and that the patient did not respond sufficiently, or that CBT-I could not be carried out. It must be documented whether CBT-I was carried out or could not be carried out.
c. The G-BA assumed both adults with concomitant diseases and adults without concomitant diseases to be comprised by the intended therapeutic indication. It is assumed that patients receive optimal treatment of any underlying/accompanying diseases (e.g. depression).
d. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
e. According to the G-BA, it is assumed that sleep hygiene measures are implemented in both the comparator arm and the intervention arm. In addition, short-term drug therapy (maximum 4 weeks) with short-acting benzodiazepines or non-benzodiazepine receptor agonists may be indicated for patients during the course of long-term therapy. For implementation in a study, a selection of these treatment options should be available to these patients. A CBT-I should not be discontinued solely for reasons of study inclusion. If indicated, it should be examined whether patients can be offered CBT-I in both the intervention and the comparator arm.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; CBT-I: cognitive behavioural therapy for insomnia

The G-BA decides on the added benefit.

[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].

I 2 Research question

The aim of the present report is to assess the added benefit of daridorexant compared with BSC as ACT in adult patients with insomnia characterized by symptoms present for at least 3 months and considerable impact on daytime functioning.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of daridorexant

Therapeutic indication	**ACT[a]**
Adults with insomnia characterized by symptoms present for at least 3 months and considerable impact on daytime functioning[b, c]	BSC[d, e]

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the requirements of the Pharmaceutical Directive Appendix III on daridorexant must be taken into account. The G-BA pointed out that according to the Pharmaceutical Directive, it must be checked before prescribing drugs whether non-drug treatments can be considered instead. According to the G-BA, it is assumed in the present therapeutic indication that CBT-I was carried out before the start of drug treatment and that the patient did not respond sufficiently, or that CBT-I could not be carried out. It must be documented whether CBT-I was carried out or could not be carried out.
c. The G-BA assumed both adults with concomitant diseases and adults without concomitant diseases to be comprised by the intended therapeutic indication. It is assumed that patients receive optimal treatment of any underlying/accompanying diseases (e.g. depression).
d. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
e. According to the G-BA, it is assumed that sleep hygiene measures are implemented in both the comparator arm and the intervention arm. In addition, short-term drug therapy (maximum 4 weeks) with short-acting benzodiazepines or non-benzodiazepine receptor agonists may be indicated for patients during the course of long-term therapy. For implementation in a study, a selection of these treatment options should be available to these patients. A CBT-I should not be discontinued solely for reasons of study inclusion. If indicated, it should be examined whether patients can be offered CBT-I in both the intervention and the comparator arm.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; CBT-I: cognitive behavioural therapy for insomnia

While the company claimed to have followed the ACT specified by the G-BA, it deviated from the G-BA's specification by stating that BSC corresponded to optimized non-drug care at the physician's discretion and in accordance with availability. The company did not consider short-term drug therapy to be part of the ACT, as this was not indicated for chronic insomnia and also did not correspond to the health care context. According to the company, the use of CBT-I or short-term drug therapy would additionally lead to a bias in the study results, and the ACT could be operationalized as placebo due to the existing supply deficit in the area of psychotherapy.

The company's deviation from the G-BA's ACT is not appropriate. The ACT, including the notes by the G-BA, corresponds to guideline recommendations, according to which CBT-I including

sleep hygiene measures as the first treatment option, and short-term drug therapy are indicated for chronic insomnia [3,4].

The present benefit assessment was implemented in comparison with the ACT specified by the G-BA. In addition, 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 study duration of 24 weeks were used for deriving any added benefit. This deviates from the company's inclusion criteria, which did not define a minimum study duration.

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on daridorexant (status: 31 January 2024)
- bibliographical literature search on daridorexant (last search on 4 December 2023)
- search in trial registries/trial results databases for studies on daridorexant (last search on 5 December 2023)
- search on the G-BA website for daridorexant (last search on 5 December 2023)

To check the completeness of the study pool:

- search in trial registries for studies on daridorexant (last search on 8 March 2024); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any relevant studies for assessing the added benefit of daridorexant in comparison with the ACT.

The company, in contrast, identified the studies ID-078A301 (hereinafter referred to as Study 301) [5-8] and ID-078A303 (hereinafter referred to as Study 303) [9-12], which compared different dosages of daridorexant with placebo, and used them in its assessment.

I 3.1 Data presented by the company

Below, Study 301 and Extension Study 303 as well as the data presented by the company are described first. Thereafter (Section I 3.2), the reasons why the studies are not suitable for assessing the added benefit of daridorexant compared with the ACT will be explained.

Study 301

Study and intervention characteristics of Study 301 are presented in I Appendix B (Table 6 and Table 7) of the full dossier assessment. Study 301 is a double-blind RCT comparing daridorexant at doses of 25 mg and 50 mg against placebo. The study included adult patients with chronic sleep disorder according to Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria, of at least moderate severity (Insomnia Severity Index [ISI] score ≥ 15). In addition, patients had to have insufficient sleep quantity, meeting the following criteria on at least 3 nights per week and for at least 3 months prior to study start in their self-reported history: ≥ 30 minutes to fall asleep, total wake time after sleep onset ≥ 30 minutes, and total sleep time ≤ 6.5 hours. Before randomization, these criteria had to be confirmed by the patient in a placebo-treated run-in phase as part of the screening on at least 3 nights out of 7 nights. In addition, the criteria for sleep quantity (latency to persistent sleep,

wake time, and total duration of sleep) were further verified during the run-in phase using PSG on 2 nights. Patients with acute or unstable psychiatric conditions (including but not restricted to anxiety disorder, depression, bipolar disorder, schizophrenia, obsessive compulsive disorder) that are diagnosed or that require pharmacological treatment were excluded from the study. Patients who had started CBT within 1 month prior to study start were excluded from the study.

The study comprises a screening phase of 1 month maximum, including a 13 to 24-day single-blind placebo-treated run-in phase, a 12-week double-blind treatment phase, a 7-day single-blind placebo-treated run-out phase, and a further 23-day follow-up observation (for information on the study design of Study 301, see Figure 1 in I Appendix C of the full dossier assessment). This means that the patients had no knowledge of the type of their study medication from the beginning of the run-in phase until the end of the run-out phase, while the randomized study phase was double-blind. Patients who had completed the double-blind treatment phase and the 7-day placebo-treated run-out phase had the option to participate in an extension study (Study 303, see next section).

In Study 301, a total of 930 patients were randomly allocated in a 1:1:1 ratio to treatment with daridorexant (25 mg [N = 310]), 50 mg (N = 310), or placebo (N = 310). Randomization was stratified by age (< 65 and ≥ 65 years).

In the 50 mg arm, treatment with daridorexant was in compliance with the dosage recommendations in the SPC [13]. In the 25 mg arm, however, treatment with daridorexant was not in compliance with the dosage recommendations in the SPC. The SPC recommends a dose of 25 mg daridorexant in patients with moderate hepatic impairment or using moderate CYP3A4 inhibitors [13], but such patients were not included in the study population. Dose adjustments were not allowed. Contrary to the SPC, according to which treatment with daridorexant should be as short as possible, and appropriateness of continued treatment should be assessed within 3 months and periodically thereafter [13], treatment with daridorexant in Study 301 was set for a predetermined period of 12 weeks.

Coprimary outcomes of the study were the total duration of wake after sleep onset and the latency to persistent sleep. Patient-relevant secondary outcomes were outcomes on morbidity and AEs.

Study 303

Study and intervention characteristics of Study 303 are presented in I Appendix B (Table 6 and Table 7) of the full dossier assessment. Study 303 is an extension study of Studies 301 and 302 [5]. Patients who had completed the double-blind treatment phase and the placebo-treated run-out phase of Studies 301 and 302 had the option to participate in Study 303. Study 302 is a double-blind RCT comparing daridorexant at doses of 10 mg and 25 mg against placebo. In

Study 302, daridorexant was not administered in compliance with the SPC. Therefore, the company did not include Study 302 and did not consider the corresponding data of the patients who transferred from Study 302 to Study 303 in its analyses (see the following section on the company's approach).

Study 303 comprised a 40-week double-blind treatment phase, a 7-day single-blind placebo-treated run-out phase, and a further 23-day follow-up observation.

A total of 804 patients were enrolled in Study 303. The study had 5 arms. Three arms were the continuation of the respective daridorexant arms of Studies 301 and 302:

- 10 mg daridorexant (continuation from Study 302); N = 142
- 25 mg daridorexant (continuation from Studies 301 and 302); N = 270
- 50 mg daridorexant (continuation from Study 301); N = 137

Patients who had received placebo in Studies 301 and 302 were re-randomized at the start of Study 303 in a 1:1 ratio to placebo or daridorexant at a dose of 25 mg, stratified by age (< 65 and ≥ 65 years):

- placebo (continuation of placebo from Studies 301 and 302); N = 128, including N = 57 from Study 301
- 25 mg daridorexant (placebo in Studies 301 and 302, switch to daridorexant in Study 303); N = 127

In addition to the data of the patients in Study 301 (50 mg daridorexant or placebo arm), the company's dossier considered the data of patients who transferred from Study 301 to Study 303 and continued to receive daridorexant at a dose of 50 mg (N = 137) or placebo (N = 57) in this study (see the following section on the company's approach).

Contrary to the SPC, there is no information in the study documents that the appropriateness of continued treatment was assessed at the transition to Study 303 and during Study 303 within 3 months and periodically thereafter. Instead, the duration of treatment with daridorexant in Study 303 was set over a predetermined period (40 weeks), as in Study 301.

AEs were the primary outcome of the study. Patient-relevant secondary outcomes were outcomes on morbidity.

Approach of the company

For its assessment of the added benefit of daridorexant, the company used the results of Studies 301 and 303, which compared daridorexant at a dose of 50 mg with placebo. For all outcomes except AEs, it considered Studies 301 and 303 as one continuous study (described

by the company as a “continuous study with a total duration of 52 weeks”). In addition to the data of all patients in Study 301 (N = 310 in the 50 mg daridorexant arm and N = 310 in the placebo arm), these analyses also include the data of those patients in Study 303 who received 50 mg daridorexant (N = 137) or placebo (N = 57) in Study 301 and Extension Study 303. For the usability of the analyses that consider Studies 301 and 303 as one continuous study, see Section I 3.2. For the side effect outcomes, the company analysed the data from Study 301 (N = 310 patients each) and Study 303 (N = 137 versus N = 57 patients) separately. For its assessment, it additionally used the results of Study 301 for the outcomes that were only recorded in Study 301 (but not in Study 303).

The company assumed the ACT BSC to be implemented in the placebo arms of Studies 301 and 303.

The company derived an added benefit on the basis of the data of both studies.

I 3.2 Assessment of the data presented by the company

The data presented by the company are unsuitable for the benefit assessment of daridorexant in comparison with the ACT. This is explained below.

Patient population of Study 301 (and Extension Study 303) does not correspond to the research question

According to guidelines, including the German S3 guideline on insomnia in adults, which is currently being revised, CBT-I is the first treatment option for the treatment of insomnia [3,4]. Correspondingly, the G-BA pointed out in its notes on the ACT that according to the Pharmaceutical Directive, it must be checked before prescribing drugs whether non-drug treatments can be considered instead. According to the G-BA, it is assumed in the present therapeutic indication that CBT-I was carried out before the start of drug treatment and that the patient did not respond sufficiently, or that CBT-I could not be carried out.

In Study 301, patients were asked at screening, whether they were currently receiving CBT and also about any reasons for not receiving CBT. Only 2 patients in the potentially relevant study arms (50 mg daridorexant or placebo) were receiving CBT at baseline. Almost 90% of patients stated that they did not know that CBT existed or that they had never been offered CBT (269 patients [86.8%] in the 50 mg daridorexant arm and 271 patients [87.4%] in the placebo arm). Other reasons for not using CBT were costs or lack of reimbursement (n [%]: 24 [7.7] versus 20 [6.5]), previous treatment failure (7 [2.3] each), no local access/no therapist available (5 [1.6] versus 4 [1.3]), and other reasons (4 [1.3] versus 7 [2.3]). Overall, around 90% of the patients in Study 301 thus do not correspond to the present research question, as they were never offered CBT.

Appropriate comparator therapy not implemented in Study 301 (and Extension Study 303)

The G-BA specified BSC as ACT for the present therapeutic indication. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. The G-BA further specified the implementation of BSC in its additional notes. According to these notes, it is assumed that sleep hygiene measures are implemented in both the comparator arm and the intervention arm. In addition, short-term drug therapy (maximum 4 weeks) with short-acting benzodiazepines or non-benzodiazepine receptor agonists may be indicated for patients during the course of long-term therapy. For implementation in a study, a selection of these treatment options should be available to these patients. Besides, a CBT-I should not be discontinued solely for reasons of study inclusion. If indicated, it should be examined whether patients can be offered CBT-I in both the intervention and the comparator arm.

Study 301 used placebo in the comparator arm. According to the study protocol, concomitant medication was preferably not changed and initiation of new medication was discouraged. Central nervous system-active drugs, including stimulants, antidepressants, antipsychotics, anxiolytics, hypnotics (incl. zolpidem), and anticonvulsants (incl. benzodiazepines), were prohibited for 5 half-lives of the respective drug (but at least for 2 weeks) prior to study start until the end of the study. Thus, potential short-term medication with short-acting benzodiazepines or non-benzodiazepine receptor agonists in accordance with the notes on the ACT was also not possible. There is also no information in the study protocol that sleep hygiene measures (e.g. in the form of a training) were applied at the start of the study or during the course of the study. At the time of screening, only 2 patients were receiving CBT, which was to be continued during the course of the study according to the protocol. However, initiation of CBT at the beginning or during the course of the study was not allowed, although about 90% of the patients had never been offered CBT. Overall, the ACT was therefore not implemented in Study 301, as the patients, with the exception of 2 patients with CBT in the comparator arm, did not receive any measures in the sense of the ACT in addition to placebo. Extension Study 303 had analogous restrictions regarding concomitant medications to those in Study 301 mentioned above.

Analyses of Studies 301 and 303 as one continuous study not suitable

For the majority of outcomes, the company's dossier presented analyses that considered Studies 301 and 303 as one continuous study (see Section I 3.1) with a treatment duration of 52 weeks. All patients who had completed the double-blind study phase and the single-blind placebo-treated run-out phase of Study 301 had the option to participate in Study 303. Of 284 patients who had completed the run-out phase in the 50 mg daridorexant arm of Study 301, only 137 patients (48.2%) entered Extension Study 303 (based on all randomized patients in Study 301 [N = 310]: 44.2%). Of 557 patients who had completed the run-out phase in the respective placebo arms of Study 301 (n = 278) and Study 302 (n = 279), only

255 patients (45.8%) entered Extension Study 303 (isolated data for Study 301 are not available). Of these 255 patients, 128 patients (57 from Study 301 and 71 from Study 302) were randomized to placebo. Of 278 patients who had completed the run-out phase in the placebo arm of Study 301, only 57 patients (20.5%) in total entered the placebo arm of Study 303 (based on all randomized patients in Study 301 [N = 310]: 18.4%). The reasons why the majority of patients did not transfer to Study 303 were not recorded. Overall, the intention-to-treat principle is thus violated to such an extent that the data of Extension Study 303 cannot be used, making the analyses of the company to consider Studies 301 and 303 as one continuous study unsuitable as well. Analyses that only consider Study 301 are only available for selected outcomes in the dossier.

Irrespective of this, with a study duration of 12 weeks, Study 301 alone is too short. Since the present therapeutic indication is a chronic disease, a minimum study duration of 24 weeks is considered appropriate (as described in Section I 2). This is also supported by the patients' disease duration: in Study 301, the patients in the 2 relevant study arms had already had sleep disturbances for an average of 11 years before inclusion in the study.

Further notes on the data presented by the company

Exclusion of patients at the start of the study in the placebo-treated run-in phase

In the beginning of the study, patients in Study 301 were diagnosed during screening based on self-reported information regarding their insomnia: Patients had to report sleep disturbances on ≥ 3 nights/week for ≥ 3 months prior to the start of the screening phase based on quantitative criteria (≥ 30 minutes to fall asleep, wake time during sleep ≥ 30 minutes, total sleep time ≤ 6.5 hours). Before randomization, the same subjective criteria had to be confirmed in a single-blind placebo-treated run-in phase of 13 to 24 days on at least 3 nights out of 7 nights. In addition, further objective quantitative sleep criteria were recorded as inclusion criteria using PSG. According to the study protocol, the goal of the placebo run-in phase was to increase the proportion of patients who would benefit from active treatment, by reducing the placebo effect during the double-blind treatment phase of the study. It also aimed to confirm a stable diagnosis of insomnia.

Of the 3326 patients initially enrolled, 2022 patients took part in the placebo-treated run-in phase. The main reason for exclusion were unfulfilled inclusion and exclusion criteria. Of these 2022 patients, a further 1004 patients (49.7% of the 2022 patients in the run-in phase) were excluded after the run-in phase and before randomization due to unfulfilled inclusion and exclusion criteria. The company's dossier does not provide any information on how many patients were excluded during the run-in phase due to not fulfilling the sleep criteria for insomnia. These patients had potentially responded to the administration of placebo and their exclusion before randomization may lead to a reduction in the placebo effect. The approval documents list the most common reasons for excluding patients during the initial screening

and the placebo run-in phase. Accordingly, it can be assumed that at least 23% of patients (based on all 3326 initially enrolled patients) were excluded due to unmet sleep criteria under placebo in the run-in phase. In relation to the patients who took part in the run-in phase (n = 2022), the proportion is therefore about 38%. Overall, a relevant proportion of patients who potentially respond to placebo were excluded, which means that the effect estimates for patient-relevant outcomes of Study 301 have to be interpreted against the background of a reduction in the placebo effect.

Baseline under single-blind placebo treatment

In Study 301, baseline values for the analyses of all recorded outcomes were defined at the time when patients were already receiving single-blind placebo treatment as part of the run-in phase. Patients were not allowed to be informed about the change in medication (randomization to daridorexant or placebo) even after the run-in phase. The baseline values were thus defined at a time when the patients already assumed that they were receiving the study medication or placebo. The effect regarding the bias of the results of Study 301 is unclear.

Conclusion

Studies 301 and 303 are unsuitable for assessing any added benefit of daridorexant versus the ACT for the following reasons:

- The patient population of Study 301 (and of Extension Study 303) does not correspond to the research question.
- The ACT in Study 301 (and Extension Study 303) was not implemented.
- The study duration of Study 301 was too short at 12 weeks, and the intention-to-treat principle was violated to such an extent that the data from Extension Study 303 cannot be used.

I 4 Results on added benefit

There are no suitable data available for the benefit assessment of daridorexant compared with the ACT in adult patients with insomnia characterized by symptoms present for at least 3 months and considerable impact on daytime functioning. There is no hint of an added benefit of daridorexant in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of the added benefit of daridorexant in comparison with the ACT.

Table 5: Daridorexant – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with insomnia characterized by symptoms present for at least 3 months and considerable impact on daytime functioning[b, c]	BSC[d, e]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, the requirements of the Pharmaceutical Directive Appendix III on daridorexant must be taken into account. The G-BA pointed out that according to the Pharmaceutical Directive, it must be checked before prescribing drugs whether non-drug treatments can be considered instead. According to the G-BA, it is assumed in the present therapeutic indication that CBT-I was carried out before the start of drug treatment and that the patient did not respond sufficiently, or that CBT-I could not be carried out. It must be documented whether CBT-I was carried out or could not be carried out.
c. The G-BA assumed both adults with concomitant diseases and adults without concomitant diseases to be comprised by the intended therapeutic indication. It is assumed that patients receive optimal treatment of any underlying/accompanying diseases (e.g. depression).
d. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
e. According to the G-BA, it is assumed that sleep hygiene measures are implemented in both the comparator arm and the intervention arm. In addition, short-term drug therapy (maximum 4 weeks) with short-acting benzodiazepines or non-benzodiazepine receptor agonists may be indicated for patients during the course of long-term therapy. For implementation in a study, a selection of these treatment options should be available to these patients. A CBT-I should not be discontinued solely for reasons of study inclusion. If indicated, it should be examined whether patients can be offered CBT-I in both the intervention and the comparator arm.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; CBT-I: cognitive behavioural therapy for insomnia

The assessment described above deviates from that by the company, which derived an indication of considerable added benefit based on Studies 301 and 303.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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