Single Technology Appraisal

Daridorexant for treating insomnia [ID3774]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

1. **Draft Guidance Document (DG)** as issued to consultees and commentators

2. **Consultee and commentator comments on the Draft Guidance Document** from:
   a. Idorsia Pharmaceuticals Ltd

3. **Comments on the Draft Guidance Document from experts:**
   a. Clinical Expert, nominated by British Sleep Society

4. **Comments on the Draft Guidance Document received through the NICE website**

5. **External Academic Group critique of company response to the DG**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Daridorexant for treating long-term insomnia

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using daridorexant in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using daridorexant in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 27 April 2023
- Second evaluation committee meeting: 4th May 2023
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Daridorexant is not recommended, within its marketing authorisation, for treating insomnia in adults with symptoms for at least 3 months and a considerable effect on daytime functioning.

1.2 This recommendation is not intended to affect treatment with daridorexant that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Cognitive behavioural therapy for insomnia (CBTi) is currently the standard first-line treatment for people with long-term insomnia after sleep hygiene advice is offered. But access to CBTi varies across the UK, sometimes it does not work, and sometimes it is unsuitable. Daridorexant may be another option for these people.

Clinical trial evidence shows that daridorexant improves symptoms of insomnia compared with placebo at 12 months. But the effects if it's taken for longer than this are unknown. There are also uncertainties in the economic model. The most likely cost-effectiveness estimate is above what NICE normally considers an acceptable use of NHS resources. So, daridorexant is not recommended.

2 Information about daridorexant

Marketing authorisation indication

2.1 Daridorexant (QUVIVIQ, Idorsia) is indicated for 'the treatment of adult patients with insomnia characterised by symptoms present for at least 3 months and considerable impact on daytime functioning'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for daridorexant.

Price

2.3 The list price of daridorexant has not yet been approved. The company have provided an anticipated list price, which is considered confidential until it has been approved.

3 Committee discussion

The evaluation committee considered evidence submitted by Idorsia, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of the condition

3.1 Long-term insomnia, also known as chronic insomnia or insomnia disorder, is defined as dissatisfaction with quantity or quality of sleep for 3 nights or above per week for at least 3 months with an effect on daytime functioning. Long-term insomnia has both night-time symptoms and an effect on daytime functioning. This affects subjective and objective dimensions of health. The patient expert described how insomnia negatively affects mental and physical health and emotional wellbeing. They explained that insomnia is more than struggling to sleep, it also affects daytime functioning and social relationships. The patient expert explained that people with insomnia may have different care depending on where they live. They said that people with the condition would benefit from a longer-term treatment option, because current medicines can only be used for a short time. The committee concluded that long-term insomnia can substantially affect people's quality of life, and there is an unmet need for longer-term treatment options.

Treatment pathway

First-line standard treatment is CBTi

3.2 The company explained that insomnia is often treated in primary care. For short-term insomnia, sleep hygiene advice is offered. After this, medicines such as benzodiazepines, zopiclone, zolpidem and melatonin are used for a short time (less than 4 weeks or less than 13 weeks for melatonin; although some people take them for longer than this). The company highlighted the difference between treatments for short-term insomnia and long-term insomnia. It stated that sleep hygiene advice is also offered for long-term insomnia. Then, cognitive behavioural therapy for insomnia (CBTi) is the recommended first-line treatment. However, currently access to CBTi varies across the country. The clinical experts also noted that there are difficulties accessing CBTi. They explained that there is no data on the use of CBTi in the NHS nationally, but research done in London showed that access to CBTi was very poor. Even when CBTi was available, people with insomnia were often not aware of it. The clinical experts added that CBTi has a 70% to 80% response rate and roughly 50% of people whose condition responds to it experience long-term remission. They also noted that recently, NICE's medical technologies guidance recommended Sleepio, a self-help digital sleep improvement programme based on CBTi for insomnia and insomnia symptoms. But some people may struggle with online CBTi and some people do not have access to it. The committee understood that CBTi is currently the standard first-line treatment for people with long-term insomnia but access to it varies.

Company's proposed positioning of daridorexant

3.3 The company proposed that daridorexant would be used in primary care for long-term insomnia as:

- a second-line treatment option when digital or face-to-face CBTi has been tried but not worked, or as maintenance treatment for managing longer-term symptoms

- a first-line treatment option when CBTi is not available or unsuitable.

The committee's discussion focused on the company's positioning of daridorexant as a first-line treatment option when CBTi is not available or unsuitable. The committee was aware that access to CBTi varies across the country (see section 3.2) and treatment effects may also vary. It understood that this may also be related to the lack of resources to either referral or signposting to CBTi by GPs. One of the clinical experts emphasised that when possible, GPs should be encouraged to explore reasons why CBTi is not available during diagnosis and signpost people to have CBTi treatment first. The committee agreed with the clinical expert. The committee concluded that the company's positioning of daridorexant as a second-line treatment option for long-term insomnia, when digital or face-to-face CBTi has been tried but not worked, or as maintenance treatment for managing longer-term symptoms, was appropriate. It also concluded that positioning daridorexant as a first-line treatment option when CBTi is not available or unsuitable was acceptable. But when available and suitable, CBTi should always be offered first before daridorexant.

Comparator

3.4 The company provided evidence on daridorexant compared with placebo (see section 3.7). Because CBTi should be the first-line treatment when available and if suitable, the committee agreed it was not an appropriate comparator. So it agreed that placebo was the appropriate comparator for decision making.

Diagnosis of long-term insomnia

3.5 The committee noted that daridorexant would be used mainly in primary care by GPs. It discussed how long-term insomnia would be diagnosed by GPs and how this tied in with the population enrolled in the pivotal trial for daridorexant, study 301 (see section 3.7). The clinical experts explained that there are criteria for diagnosis of long-term insomnia, but in practice it

would also be based on patient experience. GPs would assess perception of sleep quality, sleep quantity and any daytime symptoms. The clinical experts also explained that the natural history of insomnia varies across people. Acute insomnia may be resolved in the short term. But once becoming chronic and lasting for more than 6 months, it may last for years and be difficult to resolve. The committee, comprised partly of GPs, discussed the lack of guidance on insomnia in the UK and highlighted the importance of considering differential diagnoses before prescribing medicine for long-term insomnia. The committee understood that the time constraint of a GP appointment can be a barrier to this. The clinical experts also noted that if recommended, daridorexant would be new to primary care. They explained that it would be good to have a longer-term treatment option in primary care. But GPs may not be confident or may be reluctant to start medicines for longer-term use. So, the clinical experts highlighted that, if daridorexant were recommended, support to and training of GPs would be key for its implementation in practice. The committee understood that although there are criteria for diagnosing insomnia, GPs also assess people's experience of the condition, which is subjective. So there may be uncertainties or variations in diagnosis. It also recognised that, if daridorexant were to be recommended, further support and training for GPs about diagnosing long-term insomnia and the available treatment options would be important. This is because daridorexant, if recommended, would be the first medicine available to GPs for the longer-term treatment of long-term insomnia.

Concomitant treatments

3.6 The EAG highlighted that people could have other treatments at the same time as the randomised treatments (concomitant) in the company's pivotal trials, study 301 and study 303. CBTi was allowed if it had been started 4 or more weeks before baseline and continued throughout the studies. Non-prohibited medicines that were part of people's normal care were also allowed. People in both arms did sleep hygiene measures during the study. The committee discussed whether daridorexant, if recommended,

could be used alongside other medicines and non-medicine treatments in practice. The clinical experts explained that adherence to sleep hygiene measures are still important when having medicine. They reiterated that sleep hygiene measures and behavioural changes for people with insomnia are essential to maximise the treatment effect of daridorexant. They also explained that other treatments for insomnia work in a different way to daridorexant, in that they help with falling asleep. Daridorexant, in comparison, also helps with staying asleep. The committee understood that if daridorexant were recommended, ongoing reinforcement of behavioural changes or sleep hygiene would still be necessary and important. It considered that the comparative effectiveness evidence from the trials was appropriate for decision making. The committee concluded that, if recommended, daridorexant could be used at the same time as other medicines or non-medicine treatments available in practice.

Clinical evidence

Clinical effectiveness evidence

3.7 The clinical effectiveness evidence was from study 301 and its extension study, study 303. Study 301 was a phase 3 double-blind randomised controlled trial with 930 people with long-term insomnia randomly assigned to have daridorexant 25 mg (n=310), daridorexant 50 mg (n=310) or placebo (n=310) for 12 weeks. The company only presented evidence for the 50 mg dose of daridorexant compared with placebo in its submission. The double-blind treatment period was followed by a placebo run-out period in which people had once daily single-blind placebo treatment, and then an unblinded safety follow-up period. Key inclusion criteria for study 301 and study 303 were:

- a diagnosis of insomnia disorder (referred to as long-term insomnia in this guidance) according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria and

- An insomnia severity index (ISI) score of at least 15.

Key exclusion criteria included:

- concomitant CBTi unless started at least 1 month before visit 3 (baseline timepoint) and continued throughout the study
- mental health conditions diagnosed by the Mini International Neuropsychiatric Interview as 'acute or unstable'
- concomitant CYP3A4 inhibitors.

The primary efficacy endpoints in study 301 were change in:

- wake after sleep onset (WASO) from baseline to month 1 and month 3, respectively
- latency to persistent sleep (LPS) from baseline to month 1 and month 3, respectively.

Study 303 was primarily a comparative safety study, but it included placebo-controlled subjective outcomes to assess the long-term maintenance effect of daridorexant. People who had daridorexant 50 mg in study 301 or study 302 (another phase 3 study double-blind randomised controlled trial) continued having the same dose in study 303 (n=137). Those assigned to placebo in study 301 or study 302 were re-randomised to have either placebo (n=128) or daridorexant 25 mg in study 303. The treatment period lasted 40 weeks in study 303 (total follow-up time from study 301 and study 303 was 12 months). The primary outcome measure for study 303 was the total number of people with at least 1 treatment-emergent adverse event. The committee noted that evidence from study 302, in which 924 people with long-term insomnia were randomly assigned to have daridorexant 10 mg (n=307), daridorexant 25 mg (n=309) or placebo (n=308) for 12 weeks, was not presented. This is because the company only considered evidence for the 50 mg dose of daridorexant relevant for the submission.

Clinical effectiveness results

WASO and LPS

3.8 There were greater reductions from baseline in WASO and LPS for daridorexant 50 mg compared with placebo at both month 1 and month 3 in study 301. For WASO, at month 1 and month 3, daridorexant 50 mg was associated with less wake time after sleep onset from baseline compared with placebo (least squares mean [LSM] difference 22.78 minutes [p<0.0001] and 18.30 minutes [p<0.0001], respectively). Similarly, for LPS, at month 1 and month 3, daridorexant 50 mg was associated with a shorter delay to persistent sleep from baseline compared with placebo (LSM difference 11.35 minutes (p<0.0001) and 11.67 minutes (p<0.0001), respectively. The company explained that these objective measures were used as the primary outcomes for regulatory approval. The clinical experts explained that daridorexant is a medicine for sleep maintenance. They noted that the differences in WASO and LPS can be considered clinically meaningful but emphasised that in practice, subjective improvements in sleep quality, sleep quantity and daytime symptoms are more important than measures such as WASO and LPS.

ISI score

3.9 The ISI score was an exploratory outcome in study 301 and study 303 and was the only efficacy outcome the company used to inform its economic modelling. The ISI has 7 questions and the total score, ranging from 0 to 28, is the sum of the scores for each of the questions. Higher scores indicate a higher severity of insomnia. Reductions from baseline in ISI were greater for daridorexant 50 mg compared with placebo at both month 1 and month 3. At month 1, the reduction from baseline in mean ISI was 4.9 (standard deviation [SD] 5.5) and 3.1 (SD 4.7) for daridorexant and placebo, respectively. At month 3, the reduction from baseline in mean ISI was 7.2 (SD 6.5) and 5.4 (SD 5.7) for daridorexant and placebo, respectively. The EAG did a between-arm analysis for ISI at 3 months,

which showed a mean difference of -1.8 (95% confidence interval - 2.74 to -0.85). The clinical experts commented that a difference of at least 4 in a between-arm analysis for ISI would be considered clinically meaningful but noted that the placebo effect in this case was substantial. They also noted that in clinical practice only people who benefit from treatment would continue, so it can be expected that a larger reduction would be seen in clinical practice. The ISI results from study 303 are considered confidential and cannot be reported here. The committee concluded that daridorexant may be associated with a greater reduction in ISI scores compared with placebo. But there was uncertainty about whether the difference between the 2 arms was clinically meaningful.

Exploratory outcomes

3.10 Some other exploratory outcomes were assessed in study 301 and study 303, including total sleep time, Insomnia Daytime Symptoms and Impacts Questionnaire, Patient Global Assessment of Disease Severity score, Patient Global Impression of Change score and sleep efficiency (%). Between-arm analyses were done for the outcomes by the company and EAG. That is, the mean difference of change from baseline in outcome on daridorexant minus the mean difference of change from baseline on placebo. For most outcomes, daridorexant showed a statistically significant reduction in insomnia compared with placebo at 3 months. But the EAG noted that the benefits of daridorexant compared with placebo at 3 months follow up did not appear to persist at 12 months for some outcomes. The exact outcomes are considered confidential and cannot be reported here. The committee noted that there was no clinical data beyond 12 months. The clinical experts stated that it was difficult to predict long-term treatment effect without data beyond 12 months, but noted that people would stop treatment if they were no longer benefitting. The committee concluded that daridorexant was largely effective in improving symptoms related to long-term insomnia at 12-month follow up, but there are uncertainties about the duration and extent of benefit of treatment beyond 12 months.

Safety results

3.11 In study 301, during the double-blind study period, treatment-emergent adverse events were reported in 37.7% (116 out of 308) and 34.0% (105 out of 309) of people in the daridorexant 50 mg arm and placebo arm, respectively. Treatment-emergent serious adverse events were reported in 1.0% (3 out of 308) and 2.3% (7 out of 309) of people in the daridorexant 50 mg arm and placebo arm, respectively. In study 303, during the double-blind study period, there were treatment-emergent adverse events in 38.0% (52 out of 137) and 33.6% (43 out of 128) of people in the daridorexant 50 mg arm and placebo arm, respectively. Treatment-emergent serious adverse events were reported in 5.1% (7 out of 137) and 1.6% (2 out of 128) of people in the daridorexant 50 mg arm and placebo arm, respectively. The clinical experts commented that the safety effect profile of daridorexant indicates that it is better tolerated than other medicines used for treating insomnia.

Uncertainty in longer-term treatment effect

3.12 The committee was aware that evidence from study 301 and study 303 indicated that daridorexant's treatment effect compared with placebo at 3 months did not appear to persist at 12 months for some outcomes (see section 3.10). There was also no trial evidence on daridorexant's treatment effect beyond 12 months. It questioned whether it could be possible for the treatment effect to taper but still provide some marginal benefit. The clinical experts explained that it is unknown because of the lack of evidence. People would stop treatment if there is no benefit but may still continue if there is some benefit. The clinical experts also explained that some people may neglect sleep hygiene measures while taking medicine, which could affect the treatment effect. But there is a lack of opportunity to find out what behaviours offset the effect of medicines. A clinical expert continued that a 'drug holiday' may also be possible in practice, and some people may continue benefitting from treatment after stopping. The committee agreed that it is important for GPs to reinforce sleep hygiene advice alongside use of medicines in practice. It concluded

that the long-term treatment effect of daridorexant is uncertain and took this into account in its decision making.

Generalisability of evidence to NHS population

Selective enrolment criteria of trials

3.13 The committee understood that the DSM-5 criteria of insomnia disorder was one of the criteria used to enrol people in study 301 and study 303. According to the DSM-5 criteria, insomnia disorder is defined as dissatisfaction with sleep quantity or quality associated with:

- difficulty falling asleep or maintaining sleep
- waking up early without being able to return to sleep
- significant social or functional distress or impairment because of sleep disturbance. Sleep difficulty occurs at least 3 nights a week and happens for at least 3 months despite adequate opportunities for sleep.

The EAG noted that the trial inclusion criteria for study 301 contained specific details on top of the DSM-5 criteria. For example, an ISI score of at least 15, at least 30 minutes to fall asleep, and wake time during sleep of at least 30 minutes. The EAG further added that this could make the trial population narrower than those seen in the NHS. The committee recalled that clinical experts stated that diagnosis of long-term insomnia in practice would also be based on people's experience, which could be subjective. GPs would assess perception of sleep quality, sleep quantity and any daytime symptoms (see section 3.5). The clinical experts added that ISI is not a screening tool so should not be used in clinical practice to diagnose insomnia. The committee concluded that the inclusion criteria for the trial may result in a narrower trial population than the anticipated treatment population, which adds uncertainty to the generalisability of the evidence. It took this into account in its decision making.

Excluding mental health conditions

3.14 Study 301 excluded people with 'acute and unstable' mental health conditions. The company explained that 'acute and unstable' was defined in the trial as any mental health condition needing psychoactive medicine. The committee considered this to be very broad and included many chronic conditions. The EAG noted that insomnia frequently occurs alongside mental health conditions. So excluding people with mental health conditions also results in uncertainty about the generalisability of treatment effect to the anticipated treatment population. The company acknowledged that people with comorbid mental health conditions who need medicine were not included in the trials. This was because it may be challenging to separate the benefits of daridorexant from treatments for mental health conditions. The company added that medicines for mental health conditions are known to affect sleep, have been associated with insomnia and also modulate neurotransmitters involved in the regulation of the sleep-wake cycle. The clinical experts explained that medicines for insomnia can be offered to people with mental health conditions. So they would expect that daridorexant would also be offered to people with mental health conditions. The committee noted the importance of differential diagnoses including chronic, stable and comorbid psychiatric diagnoses. It also noted that people with mental health conditions would likely follow the treatment pathway for their condition first before daridorexant would be considered as a treatment option for long-term insomnia. The committee understood the company's reason for excluding people with mental health conditions from the trials. It noted that daridorexant may be offered to people with mental health conditions in practice. It concluded that excluding people with mental health conditions from trials resulted in uncertainty about the generalisability of the clinical evidence. The committee took this into account in its decision making.

Ethnicity

3.15 Study 301 (n=930) reported ethnic groups as follows: 1% Asian, 9.5% Black and 89.5% White. Study 303 reported ethnic groups as follows: 1%

Asian, 8.5% Black and 89.5% White. The EAG highlighted that there was a possible difference in the proportions of ethnic groups in the UK population of people with long-term insomnia, and the clinical trial populations. The proportions of ethnic groups in the UK population with long-term insomnia do not appear to be available in the literature. So there is uncertainty about whether proportions of ethnicities in the trial are representative of the UK target population. The EAG commented that if ethnicity is a treatment effect modifier for daridorexant, differences in ethnicity proportions between study 301 and study 303, and the UK target population, could potentially affect applicability. Study 301 did not subgroup for ethnicity. Also, while study 303 did not find evidence that ethnicity was an effect modifier, analyses were only presented for 2 outcomes. The company explained that published literature suggested that differences in metabolism between ethnic groups are not clinically significant, so it expects that the treatment effect is not affected by ethnicity. The clinical experts stated that in their experience, response to insomnia medicine is not affected by ethnicity. But study 301 and study 303 did not include people from the UK. A clinical expert stated that behaviours affecting sleep quality could differ between the UK and other European counties. The committee understood that currently there is a lack of evidence on whether ethnicity would modify the treatment effect of daridorexant. It concluded that the difference in the proportions of ethnic groups between the UK population with long-term insomnia and the clinical trial populations adds further uncertainty to the generalisability of the evidence. The committee took this into account in its decision making.

Additional clinical study and evidence on 25 mg dosage

3.16 The EAG was concerned that Dauvilliers et al. (2020), a study comparing daridorexant (5 mg, 10 mg, 25 mg or 50 mg) with placebo was not included in the company's clinical effectiveness results. The company explained that this study assessed the dose–response relationship, so was not designed to evaluate efficacy and safety of daridorexant compared with placebo because of the small sample size. It added that

outcomes were assessed on days 1 and 2 only and not deemed relevant to long-term treatment of long-term insomnia. A clinical expert noted that daridorexant is a new medicine with limited evidence. So, they would consider this study relevant despite the limitations with follow-up time and sample size because it would increase the evidence base. The committee recalled clinical expert opinion that in clinical practice, GPs are likely to start from the lower 25 mg dose and titrate up to the 50 mg dose if needed (see section 3.18). The committee also recalled that study 302 included the 25 mg dose of daridorexant (see section 3.7). The committee concluded that it would like to see evidence on the treatment effect of the daridorexant 25 mg and 50 mg doses from the Dauvilliers et al. (2020) study. It further concluded it would also like to see evidence on the treatment effect of the daridorexant 25 mg dose from study 302 as part of its decision making.

Economic model

Company's modelling approach

3.17 The company presented a de novo economic model and stated that it was not aware of any formal terminology to describe the model form. It used multiple regression models to estimate costs and effects for months 1, 3, 6, 9 and 12 based on observed ISI scores from study 301 and study 303. The company explained that it chose ISI to inform the model because there is a lack of data sources to inform the mapping to EQ-5D for other trial outcomes. The time horizon in the company's base-case model was 12 months. The company also presented a lifetime time horizon scenario analysis which explored the epidemiological relationship between poor sleep and poor long-term health outcomes. This included a mortality benefit for daridorexant and improved cost effectiveness compared with the base case. The company explained that a 12-month time horizon was chosen for the base case because this timeframe corresponds to the combined period of study 301 and study 303. Extrapolating beyond the available data would be based on assumptions, which would add uncertainty. It further stated that the

benefits of daridorexant would apply within hours of starting treatment and are lost within hours of stopping treatment. So a 12-month time horizon is sufficient and appropriate to estimate cost effectiveness while allowing for including dropout rates. The committee understood that long-term insomnia is a chronic condition but the model assessed symptoms related to it as measured by ISI. The committee also understood that there was no evidence on daridorexant's long-term treatment effect (see section 3.10). So the committee accepted a 12-month time horizon for the base-case analysis.

Dosage

3.18 The committee noted that the marketing authorisation for daridorexant includes the 25 mg and 50 mg doses. But the company submission focused on the clinical effectiveness of the 50 mg dose (see section 3.7), and the model included only the 50 mg dose. The company explained that the 25 mg dose is indicated for a subgroup of people with liver problems or who are having CYP3A4 inhibitors. It added that for this subgroup, the 25 mg dose is to achieve '50 mg equivalent' daridorexant plasma levels and that the cost effectiveness is expected to be the same for both doses. The EAG considered that omitting the 25 mg dose presented a problem for population applicability because the results from the trial are not applicable to people with conditions for which the 25 mg dose is indicated (see section 2.2). A clinical expert added that in clinical practice, GPs are likely to start from the lower 25 mg dose and titrate up to the 50 mg dose if needed. The committee acknowledged that the trial data for the 25 mg dose is not applicable to the population for which summary of product characteristics recommends the 25 mg dose. But based on clinical expert opinion, the committee considered that people without liver problems or not having CYP3A4 inhibitors may still start on the 25 mg dose. The committee concluded that it would like to see a scenario analysis for the cost effectiveness of the 25 mg dose.

Model comparators

3.19 The decision problem comparator is established clinical management (ECM). The comparator used by the company in the economic modelling was 'no treatment', with the placebo arm of the trial serving as a proxy for no treatment based on the analysis of study 301 (see section 3.7). The company stated that none of the currently approved medicines are recommended for long-term use. It explained that daridorexant is indicated for long-term insomnia with symptoms for at least 3 months, as per the clinical trial. The company reiterated that the proposed positioning for daridorexant is at second line after CBTi has been tried and not worked, or as a maintenance treatment option for longer-term management of symptoms, or at first line when CBTi is not available or unsuitable. So medicines or CBTi cannot be considered ECM or appropriate comparators. The committee recalled that it considered the company's positioning of daridorexant appropriate (see section 3.3). Based on the company's proposed positioning of daridorexant in the treatment pathway, after CBTi unless CBTi was inaccessible or unsuitable, the committee concluded that 'no treatment' is the appropriate comparator in the model.

Placebo effect

3.20 The ISI scores for both the daridorexant and the placebo arm decreased at each timepoint in study 301 and study 303. The company's base-case analysis only accounted for the placebo effect for the first 3 months. Specifically, it assumed that the no treatment group would continue at the same ISI achieved by the end of study 301 (that is, month 3). The company considered this assumption conservative (compared with ISI scores for the no treatment group dropping to baseline). It also considered that the increasing improvement in ISI scores over time in study 303 could be attributed to selective attrition (the selective dropout of some people who systematically differ from those who remain in the study) in both treatment groups. The company added that the trial data showed that people who dropped out of study 303 before the week 40 visit had smaller

changes in ISI scores compared with those who completed the study, which supported the selective attrition argument. The EAG explained that the company's approach of accounting for placebo effect for the first 3 months was not necessarily conservative and there was uncertainty. The EAG commented that it was unclear whether the improvement in ISI scores over time could be attributed to natural improvement of symptoms, regression to the mean, or the placebo effect. It added that despite a rebound effect between the end of study 301 and beginning of study 303, study 303 continued for 40 weeks more and scores could have improved naturally, especially given that insomnia is highly related to lifestyle factors. In its base case, the EAG preferred to include placebo adjustment for the time horizon of 12 months based on ISI scores in both study 301 and study 303. The committee considered that selective attrition might be a possible explanation for the improvement in ISI scores. But it was not presented with evidence supporting this argument. The committee understood that the EAG considered that the improvement in ISI score could also be caused by natural improvement of symptoms, regression to the mean or the placebo effect. Given the uncertainties, the committee concluded that it preferred the EAG's base-case assumption, which used the ISI scores from both study 301 and study 303 to inform the ISI for the no treatment group. It acknowledged that selective attrition might be possible, but it would like to see additional data or evidence to support this argument.

Stopping treatment

3.21 The committee noted that the summary of product characteristics for daridorexant does not include a stopping rule. However, it states that treatment duration should be as short as possible, with check-ups within 3 months and periodically after. The committee noted that study 303 reported that about less than 10% (the exact data is considered confidential so not reported here) of people on daridorexant 50 mg stopped because of lack of treatment effect. It also noted that in the company's analysis based on patient level data from the trials, a relatively

large proportion of people (the data is considered confidential so not reported here) dropped out from the daridorexant arm at 12 months. The committee recalled the discussion about daridorexant's longer treatment effect (see section 3.12) and the uncertainties related to it. The committee was also aware that there are not many secondary care sleep services in many parts of the UK. Given this lack and the uncertainty in daridorexant's long-term treatment effect, the committee considered that exploring stopping daridorexant, which will be mainly used in a primary care setting, would be important. The committee concluded that it would prefer to see analyses exploring treatment effect waning, as well as a stopping rule in the company's lifetime time horizon scenario.

Adverse events

3.22 The company's economic model did not include adverse events. This was based on the company's opinion that adverse events were not expected to significantly affect health-related quality of life and costs. The EAG stated that it did not expect a large impact on cost-effectiveness results but would prefer all adverse events from study 301 and study 303 to be included in the cost-effectiveness analysis. The committee concluded that the effect of including adverse events in the model is likely to be minor. But it would prefer the estimated impact of adverse events on costs and quality-adjusted life years (QALYs) to be included in the economic model.

Utility values

3.23 The company developed a novel mapping algorithm based on the National Health and Wellness Survey (NHWS) dataset to map ISI data from study 301 and study 303 to EQ-5D values. The company stated that ISI was used because there were no available data sources to estimate a mapping function for other trial outcomes. The company's base-case model used an adjusted limited dependent variable mixture model to create the mapping function. This model narrowly out-performed a generalised linear model with a gamma distribution family and log link function based on model fitting performance and predictive validity. The

EAG was concerned with the lack of a conceptual overlap between ISI and EQ-5D instruments, and the subsequent suitability of the mapping algorithm to estimate health-related quality of life in insomnia. The EAG also had concerns that the population used for developing the mapping algorithm (from the NHWS survey) was broader than the trial population. The company responded that ISI correlates with EQ-5D and was suitable to estimate QALYs. It added that it is very plausible that the EQ-5D does not fully capture the effect of long-term insomnia on health-related quality of life, so QALY benefits may be underestimated. Regarding the comparability of populations for developing the mapping algorithm, the company stated that the broader range of severity from the NHWS survey than in the clinical trial could be argued as a positive attribute. This is because a broader range of ISI and EQ-5D values should result in a more robust mapping algorithm. The committee concluded that the utility values presented by the company were appropriate for decision making but noted the uncertainties in mapping. It took this into account of its decision making.

Costs

3.24 The company's economic model included treatment costs and medical costs (GP visits, emergency room attendances and inpatient care). To estimate the resource use for medical costs, the association between direct healthcare resource use (GP visits, emergency room attendances and inpatient care) and ISI scores were calculated from the NHWS data. This was done using a generalised linear model with a negative binomial distribution family and a log link. The EAG stated that it would prefer all relevant costs to the NHS and personal social services to be included in the economic model. For example, the company did not include concurrent medication costs and outpatient care costs. The committee agreed that including only costs related to GP visits, emergency room attendances and impatient care was a conservative assumption. Further, the committee recalled the discussion (see section 3.5) that, if daridorexant were recommended, further support and training for GPs

would be needed for diagnosing long-term insomnia in primary care. The committee also recalled that reinforcement about currently available treatment options would be important to ensure daridorexant's effective use in primary care. So, the committee concluded that it would prefer all costs incurred by the NHS, including providing support and training for GP practices, to be included in the economic model.

Cost-effectiveness estimates

Uncertainties in evidence and model assumptions

3.25 The committee noted the high level of uncertainty in the company's clinical evidence and model assumptions, specifically the:

- uncertainty in whether the difference from baseline in ISI scores between the 2 arms was clinically meaningful (see section 3.9)
- lack of evidence about daridorexant's longer-term treatment effect, including uncertainties in treatment duration as well as extent of benefit of treatment beyond 12 months (see section 3.12 and section 3.21)
- trial populations being narrower than the anticipated treatment population (see section 3.13)
- generalisability of evidence from study 301 and study 303 to UK practice in terms of excluding people with mental health conditions and non-UK based trial locations (see sections 3.14 and 3.15)
- uncertainty about whether ethnicity is a treatment effect modifier for daridorexant, and the proportion of ethnic groups in trials not representing that of the UK population with insomnia (see section 3.15)
- omission of study results from Dauvilliers et al. (2020) and evidence on the clinical effectiveness of daridorexant 25 mg not presented (see section 3.16)
- 25 mg dose of daridorexant not assessed in the economic model (see section 3.18)
- uncertainty about whether the improvement in ISI in the placebo arm of study 303 was a result of selective attrition, natural improvement of

symptoms, regression to the mean or the placebo effect (see section 3.20)

- adverse events not being included in the economic analyses (see section 3.22)
- uncertainty associated with the mapping of ISI to EQ-5D (see section 3.23)
- not all relevant costs to the NHS and personal social services being included in the model, for example, costs to provide support and training for GP practices (see section 3.24).

Uncertainty in cost effectiveness and more analyses needed

3.26 NICE's manual for health technology evaluations notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the incremental cost-effectiveness ratio (ICER). The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. Because the list price of daridorexant is not yet approved, the ICERs are commercial in confidence and cannot be reported here. But the committee noted that the cost-effectiveness estimates including some of its preferred assumptions were above the range NICE normally considers to be an acceptable use of NHS resources. Neither the company nor the EAG's base cases or scenario analyses included all the committee's preferred assumptions. The committee considered that further analyses are needed. It requested:

- including the evidence on the treatment effect of daridorexant 25 mg from study 302; and evidence on the treatment effect of daridorexant 25 mg and 50 mg from the Dauvilliers et al. (2020) study (see section 3.16)
- estimating the cost effectiveness of the 25 mg dose of daridorexant in the economic analysis (see section 3.18)
- providing additional evidence or data that supports the argument of selective attrition (see section 3.20)

- exploring treatment effect waning and stopping treatment in the lifetime horizon scenario analysis (see section 3.21)
- including the impact of adverse events on costs and QALYs in the model (see section 3.22)
- all costs that would occur in the NHS in the model, including the costs to provide support and training for GPs (see section 3.24).

Other factors

Equality issues

3.27 The company noted that that CBTi is recommended as first-line treatment for long-term insomnia but may not be suitable for or accessible to all people. The committee recognised this and understood that care varied, with people having different standards of care for long-term insomnia depending on where they live in the country. But the committee noted that access to treatments is an implementation issue that cannot be addressed by a NICE technology appraisal recommendation. No other equality or social value issues were identified.

Innovation

3.28 The company considered that daridorexant is innovative. This is because the current medicines are recommended only for short-term use, and daridorexant is a longer-term option. Also, daridorexant is the first dual orexin receptor antagonist approved in the UK and Europe for treating long-term insomnia. The company also explained that there may be uncaptured benefits in its base-case analysis, because daridorexant may reduce the risk of cardiovascular disease and mortality in people with insomnia in the longer term. The committee concluded that there might be additional benefits with daridorexant. But, given the uncertainties in the evidence and in the model (see section 3.24), it was unclear whether there were any not captured in the cost-effectiveness analysis.

Conclusion

Recommendation

3.29 The committee considered the most plausible ICER available and took into account the degree of certainty around the ICER. The most plausible ICER was above the range NICE normally considers cost effective. It concluded that it was not possible to recommend daridorexant for treating long-term insomnia in adults.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Charles Crawley

Chair, technology appraisal committee B

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Dilan Savani

Technical lead

Yelan Guo

Technical adviser

Daniel Davies

Project manager

ISBN: [to be added at publication]

Daridorexant for treating long-term insomnia [ID3774]

Company response to draft guidance

1. Executive summary

We welcome the opportunity to comment and provide the additional analyses requested by the committee in the Appraisal Consultation Document (ACD) on the use of daridorexant to treat long-term insomnia.

Idorsia is disappointed that daridorexant is not currently recommended for NHS use in England. It is however encouraging that the committee recognises that long-term insomnia can substantially impact people's quality of life and that there is a significant unmet need for additional treatment options in this therapeutic area. It is also helpful that the committee has been pragmatic in acknowledging the access challenges with both face-to-face and digital cognitive behavioural therapy for insomnia (CBTi).

Although we believe we have shown daridorexant to be cost-effective in the base case model of the company submission (CS), we understand the committee has some concerns around the degree of certainty in some parameters and the impact this may have on the incremental cost-effectiveness ratio (ICER). In this response we have addressed each point raised by the committee and as a result have reduced uncertainty and strengthened the overall cost-effectiveness proposition for daridorexant.

Critically, on selective attrition we provide evidence to show the effect is real and justifies the lack of placebo correction in study 303, as per the company base case. Three important considerations of study 303 were used for the analysis: First, academic / commercial in confidence information removed. Second, academic / commercial in confidence information removed. Third, analysis of the efficacy endpoints of study 303 (i.e., sTST, Insomnia Daytime Symptoms and Impacts Questionnaire [IDSIQ] sleepiness domain and Insomnia Severity Index© [ISI©]) showed that academic / commercial in confidence information removed.

We also address concerns around treatment waning in lifetime horizon scenario analysis and demonstrate how this can be mitigated by an annual treatment challenge, keeping the long-term ICER below the lower end of the NICE threshold (Table 1).

Table 1: Cost-effectiveness results for adding treatment waning to the company's lifetime horizon scenario

	ICER
Company lifetime horizon scenario	£16,500
Add waning @ 10% with annual challenge (20% drop out)	£19,900

On the remaining cost-effectiveness issues identified by the committee (adverse events, NHS costs, general practitioner [GP] training) we have considered an updated cost-effectiveness model where we have included these concerns and it is evident that they have a negligible effect on the ICER (Table 2). We note the committee has commented on potential additional costs for GP support and training which may be associated with the introduction of daridorexant. We have addressed this with specific comments and additional information; however we wish to highlight that the relative priority of the condition and the required training and support for long-term insomnia are longstanding issues and not exclusive to daridorexant, or likely to be cost additive. The changes requested by the committee are summarised in the tables below.

Table 2: Cost-effectiveness results for the concerns identified by the committee (NHS costs, adverse events, and GP training costs)

	ICER
Company preferred base case	**£24,832**
Add missing NHS costs	£24,504
Add Adverse event (AE) impacts	£25,573
Add GP training costs	£25,282
Combine all three changes	**£26,032**

AE=Adverse event; NHS=National health service.

While daridorexant is shown to be cost-effective in the base case model of the CS, given the acknowledgement in the ACD of the negative impact long-term insomnia has on daytime functioning, we believe consideration of productivity is important to fully represent its value. We note that the productivity scenarios were not considered in the ACM1 from NICE's comment "the results from the productivity scenarios were deemed to have limited applicability for decision making". We acknowledge this may have been driven by

uncertainties and are now addressed in this ACD response. We have also provided additional justifications and evidence in section 8. Consideration of productivity costs in the assessment of the cost-effectiveness of daridorexantand would encourage the committee to fully explore and consider the cost-effectiveness of daridorexant taking productivity scenarios into account (as per the revised methods guide introduced January 2022). We contend that recognition of the positive effect on productivity can significantly mitigate any remaining uncertainty the committee may have. The summary results including productivity from the CS are as below (Table 3).

Table 3: Cost-effectiveness analysis of productivity estimated from Sheehan disability scale© (SDS©)

	ICER
Directly estimated from SDS in clinical trial	£215
Indirectly estimated from mapping WPAI to ISI in NHWS database	Dominant

ISI=Insomnia severity index; NHWS=Cerner Enviza National Health and Wellness Survey; WPAI= Work Productivity and Activity Impairment;

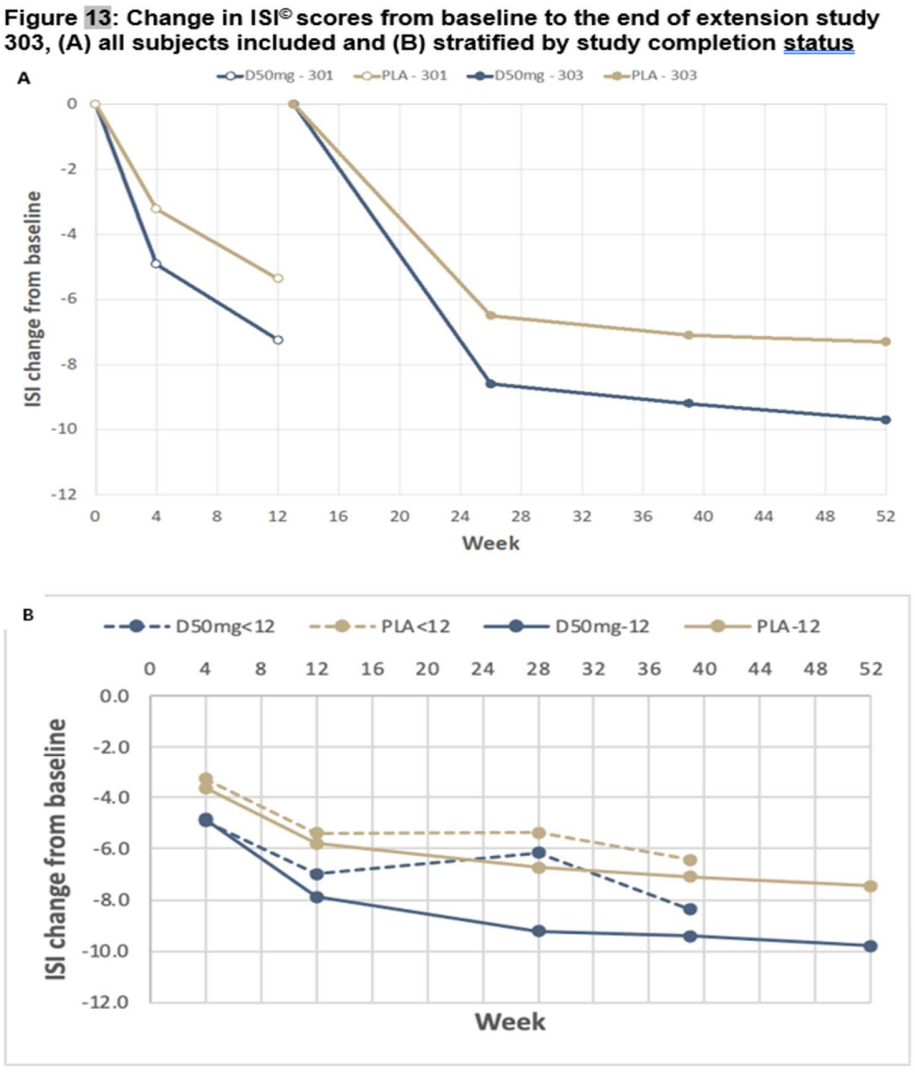
It is clear from the ACD that the committee wishes to see detailed results from the perceived missing data on 25mg from study 302, and on 25mg and 50mg from study 201. A cost-effectiveness analysis was also requested on 25mg. This information with supporting narrative, plus an additional dose-response analysis is provided in Appendix 1. Daridorexant has been assessed by the MHRA under the European Commission Decision Reliance Procedure and was found to be efficacious for long-term insomnia at the 50mg dose. The EPAR states that “50 mg dose can be validated as clearly efficient dose. The 25 mg dose used in both phase 3 trials failed to demonstrate consistent and robust efficacy results from a statistical point of view on primary efficacy parameters”. We would like to highlight that the 25 mg dose is only indicated in patients with moderate liver impairment or who are on concomitant moderate cytochrome P450 3A4 (CYP3A4) inhibitors, per the summary of product characteristics (SmPC). Any recommendation for general use of the 25 mg dose, based on anecdotal evidence that GPs would regard this as an initiating dose and titrating upwards to 50 mg based on response, is not evidence based and contrary to the SmPC.

The specific analyses requested, with accompanying commentary, follow in the subsequent sections. We also provide additional comments on the ACD in section 10. Additional comments on ACD.

2. Selective attrition in study 303

We note the comment in section 3.20 of p.19 of the ACD on selective attrition where the committee specifies that it was “not presented with evidence supporting this argument”. A critical piece of evidence from the CS was previously provided in document B (B2.9.2, Figure 13). The committee slides included Figure 13A but not Figure 13B which clearly demonstrated the effect of selective attrition. As this is a crucial point, we highlighted this prior to the committee meeting, however the relevant figure was not shown. This is replicated below (Figure 1).

Figure 1: Figure 13 from the CS to support selective attrition



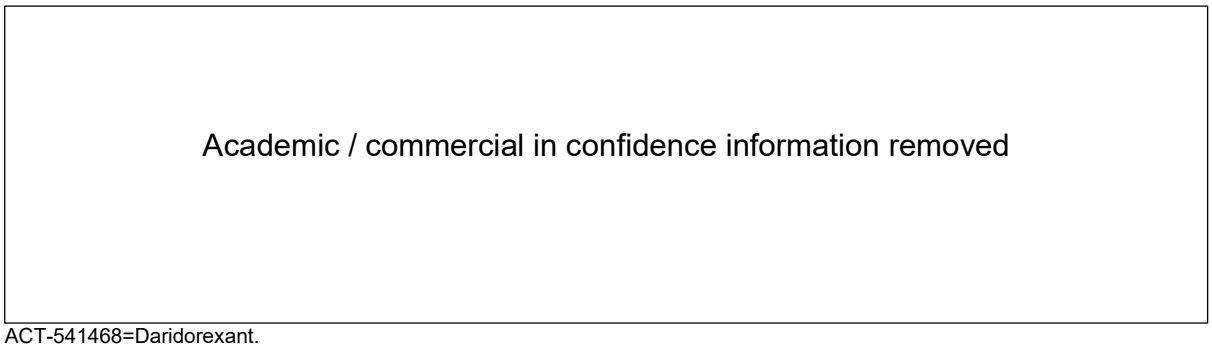
This illustrates the change in ISI© scores from baseline of study 301 to the end of extension study 303 with patients staying in the study shown by the solid line and the mean values for patients not completing the full 52 week treatment period shown in by the dashed lines. In both treatment groups, subjects who dropped out at any point had smaller changes in ISI© scores compared to those who completed the study. Visual inspection of the week 28, week 39 and week 52 change scores of subjects who completed the study showed a plateau after week 28. In the CS we proposed the increasing improvement in ISI© scores

over time observed in extension study 303 (Table 36 of the CS) could be attributed to selective attrition.

In addition we have provided further analysis that supports the CS position on selective attrition. An element of selective attrition was already suggested at the transition from 301/302 to 303. The European public assessment report (EPAR) reads "*In the placebo arm, patients were already on placebo in phase 3 study. As these patients accepted to continue the treatment in study 303, they can be considered as good responders under placebo...*"

Although the effect of daridorexant was maintained during the 40 weeks of treatment, as expected in long-term studies, premature study discontinuation was observed in extension study 303. From the 804 patients who entered study 303 (801 received treatment), 550 patients (68.4%) completed 40 weeks of double-blind treatment. Academic / commercial in confidence information removed. Figure 2 Academic / commercial in confidence information removed. This illustrates selective attrition, which in turn impacts the estimate of long-term outcome and consequently cost-effectiveness.

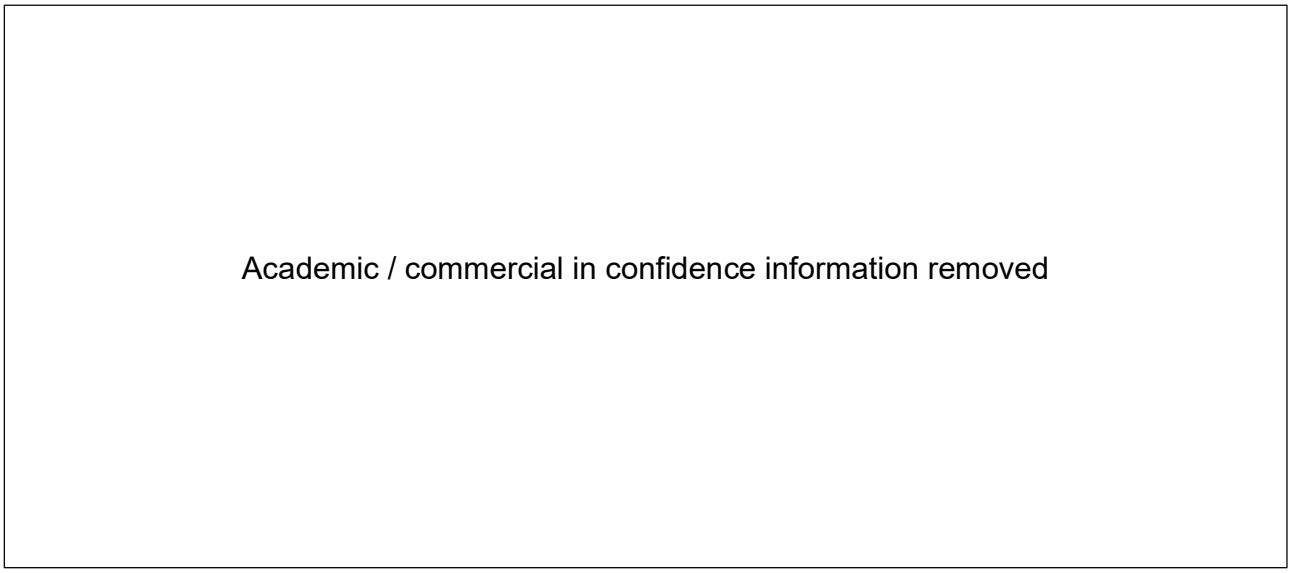
Figure 2: Proportion of subjects completing treatment or discontinuing treatment prematurely by treatment group and by reason for premature discontinuation



ACT-541468=Daridorexant.

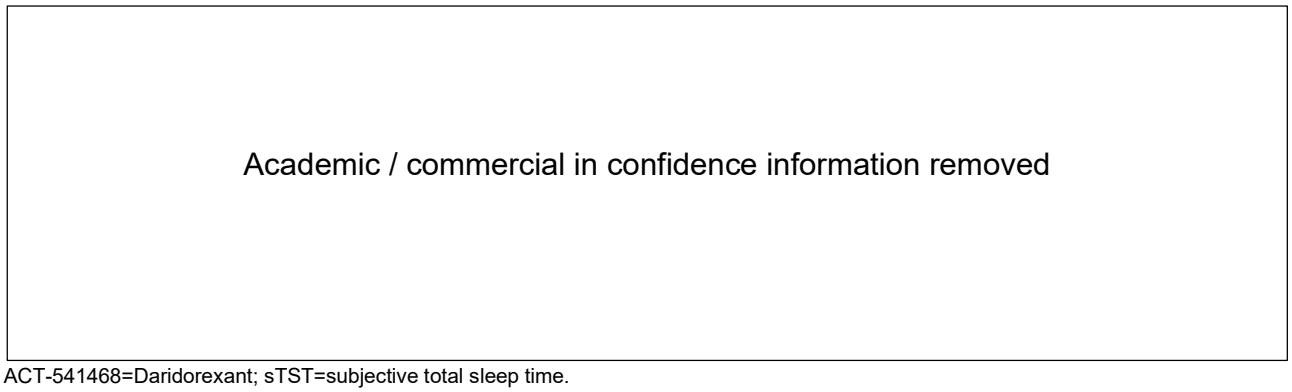
Figure 3 illustrates the observed mean sTST improvement from baseline during the 40-week extension, by treatment group. It shows that the academic / commercial in confidence information removed. For example, in the academic / commercial in confidence information removed.

Figure 3: Mean observed sTST improvement from baseline by 4-weekly intervals during the 40-week treatment in study 303, by treatment group



To further evaluate the impact of selective attrition, the mean change from baseline in sTST was calculated according to the completion status at the end of the treatment period (i.e., all patients and patients who completed the treatment), at each timepoint and in each treatment group. academic / commercial in confidence information removed.

Figure 4: Mean observed sTST improvement from baseline over time, by treatment group, and according to the completion status

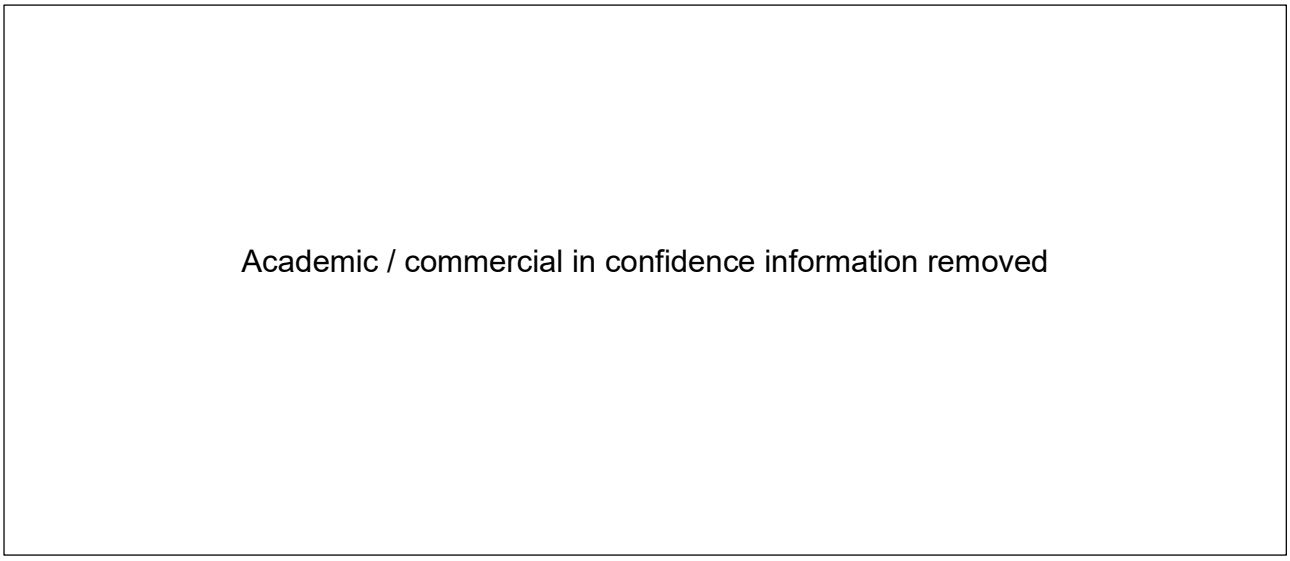


ACT-541468=Daridorexant; sTST=subjective total sleep time.

Finally, the last observed value was computed for completed subjects (value at the end of the double-blind treatment period), and for prematurely discontinued subjects (the last value measured in the double-blind treatment period). academic / commercial in confidence information removed (Figure 5). Furthermore, when comparing the sTST of

the patients who dropped out in the different groups, the mean values academic / commercial in confidence information removed, thus highlighting that the selective attrition is more pronounced for placebo.

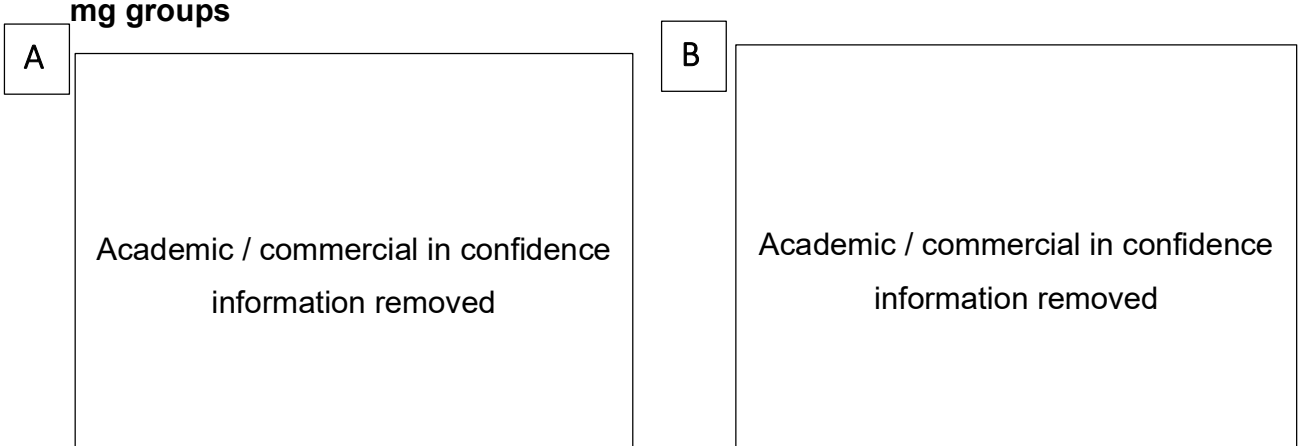
Figure 5: Last values (mean and SEM) observed in treatment period for completed participants (red) and subjects prematurely discontinuing treatment (blue).



ACT-541468=Daridorexant; sTST=subjective total sleep time.

The same analysis was conducted for IDSIQ sleepiness domain scores and for the ISI© scores, academic / commercial in confidence information removed. Figure 6 illustrates the results in the relevant groups of daridorexant 50 mg and placebo.

Figure 6: A: IDSIQ sleepiness domain; B: ISI©; top panels: mean (SEM) last values for completers and premature discontinuation, in the placebo and daridorexant 50 mg groups



ACT-541468=Daridorexant; IDSIQ= Insomnia Daytime Symptoms and Impacts Questionnaire.

In conclusion, selective attrition leading to bias against daridorexant is observed in the extension study 303. The additional evidence presented further supports our base case assumptions in the economic model of daridorexant 50 mg in the CS. Specifically, due to selective attrition, placebo effect was applied to the no treatment group using study 301 and the same rate was extrapolated to the entire duration of the model. As explained in Document B of the CS (B.3.3.2), it was assumed that the no treatment group would continue at the same ISI© achieved by the end of study 301 (i.e., the 3rd month). In the CS, we proposed selective attrition as the explanation for the improving ISI© score in study 303 beyond the third month of treatment. This argument is now further strengthened with the additional analysis presented, where differential dropout was observed between the daridorexant and placebo groups, and selective attrition was also seen in other endpoints such as sTST and IDSIQ sleepiness domain in study 303, resulting in a possible artificial increase in placebo efficacy.

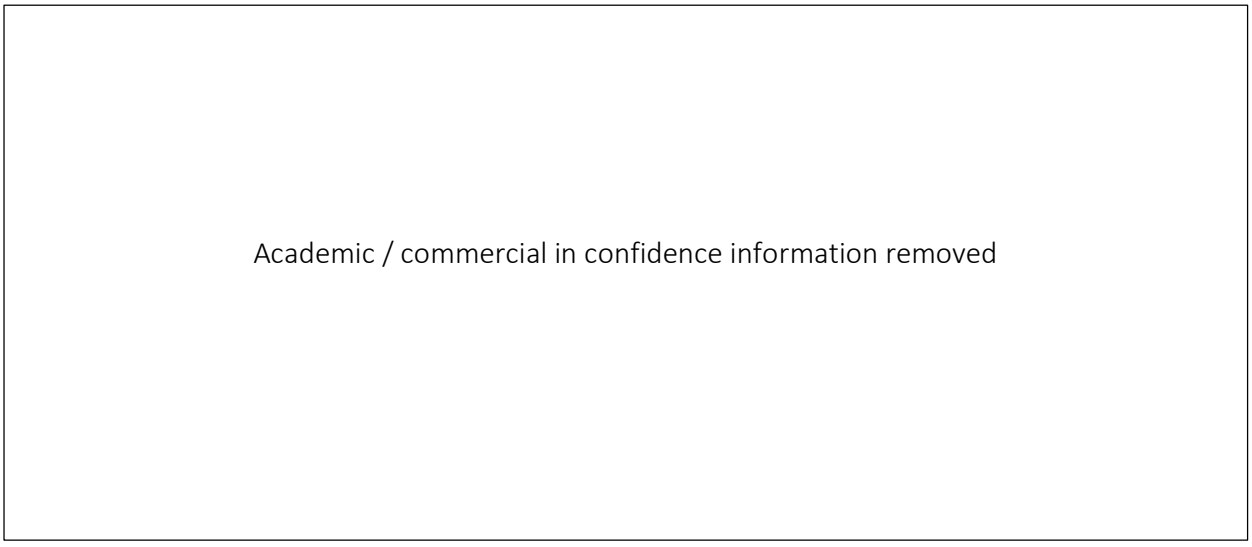
3. Impact of stopping daridorexant treatment

As per the SmPC, we acknowledge that the treatment duration with daridorexant should be as short as possible, and the appropriateness of continued treatment should be re-assessed within 3 months. The EPAR makes a very explicit statement that “as there is no risk of withdrawal or rebound effect, treatment can be stopped without specific stopping rules”. Prescribers can be confident of stopping daridorexant to assess whether there is still a need to continue, and if insomnia returns that the beneficial effects of daridorexant will resume upon treatment re-initiation.

In study 301, the 3-month treatment period was followed by a placebo period of 1 week during which sleep parameters and daytime symptoms were collected. The results show that the treatment effect of daridorexant is rapidly lost, with return to approximately the placebo level, with no rebound insomnia. Upon treatment re-initiation in patients transitioning to study 303, the beneficial effect is quickly resumed. This is illustrated in Figure 7.

At the timepoint academic / commercial in confidence information removed. At the timepoint academic / commercial in confidence information removed.

Figure 7: Concatenated mean sTST over time on daridorexant 50 mg, 25 mg and placebo in the subgroup of patients from study 301 transitioning to study 303



sTST=Subjective total sleep time.

At the end of study 303, the treatment period was also followed by a 1-week placebo period. Results similar to the placebo run-out period in 301 were observed. As shown in Table 4, when daridorexant was stopped and patients received placebo for 1 week, academic / commercial in confidence information removed.

Table 4: Impact of stopping treatment on sTST.

Treatment	Mean (SD) change from baseline at week 40 (min)	Mean (SD) change from baseline at run-out (min)	Mean (SD) difference run-out minus week 40 (min)
Daridorexant 25 (n=114)			
Daridorexant 50 (n=66)			
Placebo (n=45)			

Academic / commercial in confidence information removed

Min=minutes; SD=Standard deviation; sTST=Subjective total sleep time.

In both study 301 and 303, no signs of rebound insomnia and no withdrawal symptoms were observed after stopping treatment. These results indicate that the treatment effect was maintained during the entire treatment period of 12 months across study 301 and 303, and discontinuing the treatment had no negative consequences beyond an anticipated return of long-term insomnia. The SmPC notes "*Treatment can be stopped without down-titration*", with further explanation in the EPAR "*Also, as there is no risk of withdrawal or rebound effect, treatment can be stopped without specific stopping rules."*

The totality of clinical trial data and subsequent analyses presented indicates that the wording of the SmPC is appropriate: "The appropriateness of continued treatment should be assessed within 3 months and periodically thereafter". Therefore, prescribers can be confident of stopping daridorexant to assess whether there is still a need to continue, and if insomnia returns that the beneficial effects of daridorexant will resume upon treatment re-initiation. In response to the NICE committee's request, we have proposed an "annual challenge" instead of a stopping rule in the lifetime model, where treatment is withdrawn from patients to assess whether treatment effect has been lost and we assume that those who no longer receive a benefit from the treatment discontinue. Details of this approach and the corresponding results are presented in section 4. Adding treatment waning to the cost-effectiveness model

4. Adding treatment waning to the cost-effectiveness model

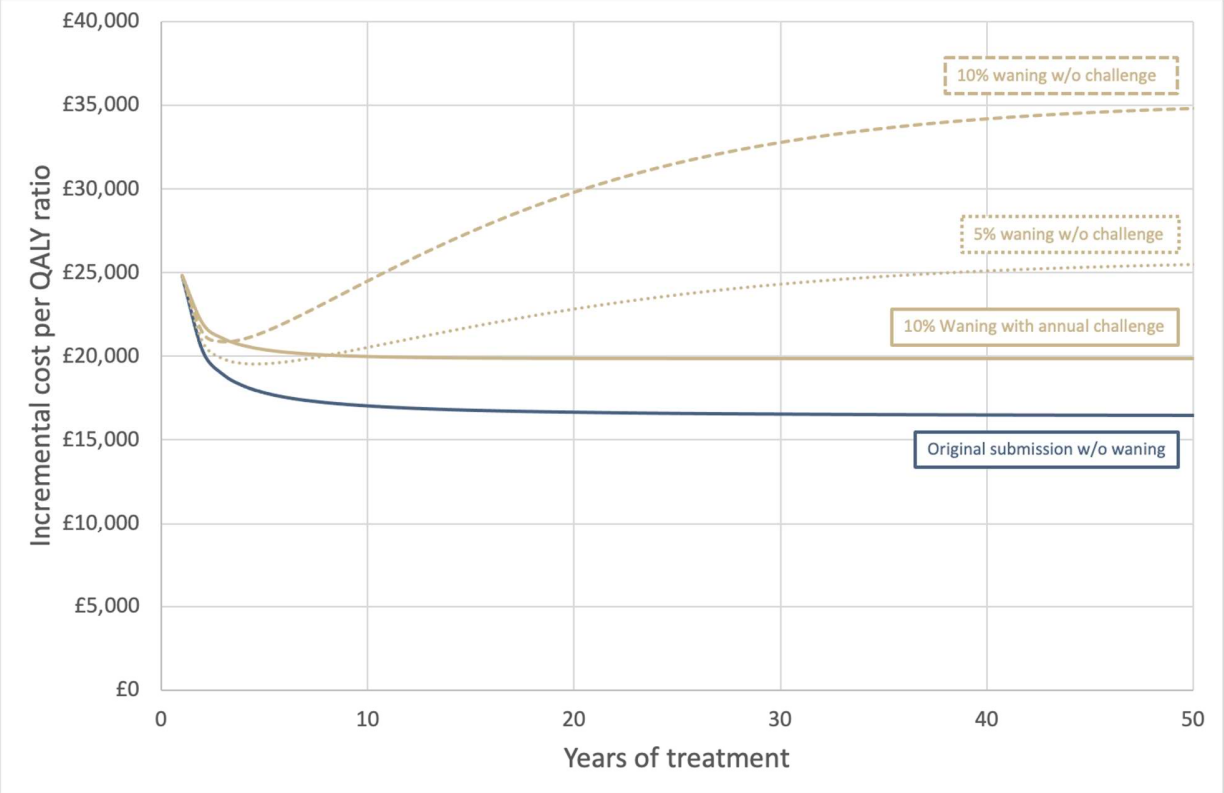
As requested, we have explored hypothetical treatment waning alongside an annual challenge and demonstrated that cost-effectiveness continues to improve even when treatment waning is included in the model. The original cost-effectiveness model submitted to NICE was based on a one-year treatment model. During the first year, 45% of subjects initiating treatment subsequently discontinued, majorly for lack of efficacy. This resulted in a first year base case estimate of cost-effectiveness of £24,832 per Quality-Adjusted Life Year (QALY), compared to an estimated £15,600 in subsequent years for subjects continuing treatment.

The CS also included a lifetime scenario that projected the effectiveness of treatment for those continuing beyond the first year and modelled potential insomnia impact on all-

cause mortality. A 5% annual discontinuation rate was assumed subsequent to the first year discontinuation of 45%. The lifetime cost-effectiveness in this scenario was estimated as £16,500 per QALY gained.

The NICE committee noted that the lifetime scenario, while incorporating further treatment dropout did not incorporate the potential for treatment to wane over time. The model has now been adapted to include a treatment waning parameter and the results of the lifetime modelling are reported in Figure 8 below.

Figure 8: Lifetime cost-effectiveness of daridorexant 50 mg with treatment waning



QALY=quality-adjusted life year; w/o=without.

Note that the first year cost-effectiveness remains the same for all modelled scenarios at just under £25,000 per QALY. In all scenarios, the cost-effectiveness initially improves reflecting the fact that subsequent effectiveness beyond the first year is higher for those remaining on treatment than in the first year. Without any treatment waning, the cost-effectiveness continues to improve over the lifetime of the model leading to the original estimated lifetime cost-effectiveness of £16,500 per QALY. Introducing an annual waning of 10% of the treatment effect (applied to both short term health-related quality of life

(HRQoL) improvement and long-term mortality benefit) means that the initial reduction in cost-effectiveness is reversed and the lifetime cost-effectiveness will rise to £36,500 per QALY. If the waning parameter is set to 5% per year, then the lifetime cost-effectiveness returns to approximately the same value as the first year cost-effectiveness (£25,500 per QALY).

However, both these scenarios apply the waning parameter independently from the discontinuation parameter. We have been asked to explore a stopping rule. It is clear from the data provided (section 3. Impact of stopping daridorexant treatment) that a clinician can stop treatment at any point to assess efficacy and need for continuation; however for the purposes of cost-effectiveness we propose an "annual challenge". If we assume an 'annual challenge' such that treatment is withdrawn from patients in order to see whether treatment effect has been lost and we assume that those who no longer receive a benefit from treatment discontinue, the cost-effectiveness continues to improve even when treatment waning is included in the model, although the lifetime cost-effectiveness rises to £19,900 per QALY for a 10% waning effect (which includes a cost of an additional annual GP visit to review treatment and assumes an increased dropout rate of 20% per annum).

5. Inclusion of training and additional costs for the NHS in the economic model

The committee requested an exploration of NHS costs and those to provide support and training for GPs. We have now taken this into the model with a marginal increase in the ICER from the base case.

According to the Cerner Enviza NHWS UK data (N=10,034) year 2020, respondents with treated or untreated insomnia reported a higher frequency of GP visits (6.82 and 6.00 visits, respectively) in the past 6 months compared to adults in the general population (2.39 visits).[1] Patients prescribed daridorexant should be reviewed at least every 3 months to assess appropriateness of continued treatment per the SmPC. Therefore, introducing daridorexant is not expected to result in additional monitoring/GP visits other than those required for the routine care of long-term insomnia. As such, we do not anticipate

additional costs to the NHS associated with the introduction of daridorexant, other than those that are included in the economic model.

In a subsequent section we have provided data from several recent GP surveys and a primary care advisory board to provide further clarity on the current situation in primary care (section 9. GP training and support). This suggests that GPs are comfortable diagnosing long-term insomnia but have limited confidence in treating, primarily driven by limited treatment options. Lack of access to CBTi, lack of a clear patient pathway with limited, if any referral option, and lack of medications were identified as the main challenges as opposed to diagnosis. The introduction of daridorexant would provide another option to improve the management of long-term insomnia in primary care. We do not believe that this represents a significant additional training need. Notwithstanding this, we have incorporated an element of GP training into the economic model, as requested. In addition, as a new stakeholder in insomnia, Idorsia will provide training resources in the formats most preferred and accessed by GPs.

If we assume that additional training of 2 hours per annum per GP on the use of daridorexant then this would have an opportunity cost of 120 minutes divided by 9 minutes average consultation time at £39.23 per consultation = £523. From the company's own survey of GPs it is estimated that 12 new long-term insomnia patients present every three months = 48 patients per annum.[2] The per patient cost of GP training could therefore be expected to add £523 / 48 = £10.90 to the incremental cost of treatment. This takes the base case ICER from £24,832/QALY to £25,282/QALY.

6. Inflation for missing outpatient visits and prescriptions

The original submitted model estimates only inpatient costs, emergency room attendances and GP visits. The EAG pointed out that prescription costs and outpatient visits were missing. In order to adapt the model, we have applied an inflation factor based on a study by Wickwire and colleagues (2019) that found that inpatient stays & ER attendances made up 72% of direct health care costs that included prescription costs and outpatient visits.[3] Therefore, an inflation factor of 1/0.72 = 1.39 was applied to the direct

health care costs estimated as a function of ISI from the NHWS database. Applying this inflation factor reduced the base case ICER from £24,832/QALY to £24,504/QALY.

7. Including adverse events on costs and QALYs in the economic model

All TEAEs occurring >2% in any treatment arm were included in the model. The two most common AEs are nasopharyngitis and headache. For nasopharyngitis we made the conservative assumption that this could be as bad as influenza using a previously published pooled estimate of the QALY impact of influenza being 0.01 QALYs per episode.[4] Similarly, for headache we used a conservative estimate that this could be as bad as migraine which has been estimated to reduce HRQoL (as measured by the EQ-5D) by 0.13.[5] We further assumed that this effect would resolve after four days leading to a QALY impact of 0.0014. For all infections (upper respiratory tract infection, urinary tract infection, tonsillitis & pneumonia), we used the influenza estimate. Similarly, for other symptom-related AEs (fatigue, dizziness, nausea, somnolence, cough, back pain, myalgia, sinusitis), we assumed the same QALY deficit as for headache. For accidental overdose and hepatic enzyme increase, we assumed no HRQoL/QALY impact since these events were clinically defined. The majority of falls recorded did not result in injury, but approximately 20% resulted in fracture for which we assumed a 0.04 HRQoL impact based on a wrist fracture in the literature.[6]

For health service costs, we assumed that all AEs would require a GP visit except for the 20% of falls that resulted in fracture which would require an emergency department visit. For infections, we assumed a £6.21 prescription of antibiotics would be also required based on the average cost of an antibiotic prescription in the ONS Prescription Cost Analysis database.[7]

The cost and QALY impacts of the abovementioned AEs are summarised in Table 22. These impacts are combined with the frequencies of the AEs for each study to give the incremental QALY and cost impacts between daridorexant 50 mg and placebo (no treatment).

Table 5: Impact of adverse events on QALY and cost

	Impact estimates				
Adverse event	**QoL impact***	**Duration* (days)**	**QALY**	**Cost**	**Source**
Nasopharyngitis			0.0100	£39.23	Jit et al 2010 (influenza)
Headache	0.13	4	0.0014	£39.23	Domitrz et al 2022 (migraine)
Accidental overdose	0	1	0.0000	£39.23	Assumption
Fatigue	0.13	4	0.0014	£39.23	Assumption (as for headache)
Dizziness	0.13	4	0.0014	£39.23	Assumption (as for headache)
Nausea	0.13	4	0.0014	£43.23	Assumption (as for headache)
Somnolence	0.13	4	0.0014	£39.23	Assumption (as for headache)
Fall	0.04	90	0.0020	£68.31	Si et al 2014 (wrist fracture) x 20%
URTI	1	1	0.0100	£45.44	Assumption (as for influenza)
Cough	0.13	4	0.0014	£39.23	Assumption (as for headache)
Pneumonia			0.0100	£39.23	Assumption (as for influenza)
Back pain	0.13	4	0.0014	£39.23	Assumption (as for headache)
Tonsilitis			0.0100	£45.44	Assumption (as for influenza)
UTI			0.0100	£45.44	Assumption (as for influenza)
Myalgia	0.13	4	0.0014	£39.23	Assumption (as for headache)
Sinusitis	0.13	4	0.0014	£39.23	Assumption (as for headache)
Hepatic enzyme increased	0	1	0.0000	£39.23	Assumption

QALY=Quality-adjusted life years; QoL=Quality of life. *Note that blank cells are intentional where the QALY decrement is taken from the published source rather than being calculated as the product of the QoL decrement and the duration.

Overall adjusting for AE results in an addition of £6.21 to the incremental cost and a reduction in 0.0005 QALYs from the incremental effect. This means the base case ICER changes from £24,832 to £25,573.

8. Consideration of productivity costs in the assessment of the cost-effectiveness of daridorexant

In a separate clarification question related to the ACD we asked if the productivity scenarios submitted by Idorsia, based both on clinical trial and the NHWS data, were

considered by the committee. There is no mention of this in the ACD. The response was that due to other issues to be discussed the productivity scenarios were not included in the committee meeting slides, and that "the results from the productivity scenarios were deemed to have limited applicability for decision making". We find this surprising as NICE's manual for health technology evaluations notes that productivity scenarios "can be presented separately, as additional information for the committee, if such costs may be a critical component of the value of the technology". In the CS, we provided one scenario derived directly from measures in the clinical trial (SDS©) and then supported with a second scenario to reduce uncertainty by utilising the WPAI questionnaire from the NHWS. In the SDS© scenario, the introduction of daridorexant was cost neutral and in the NHWS scenario it was cost saving.

Table 6: Cost-effectiveness analysis of productivity estimated from SDS©

	ICER
Directly estimated from SDS in clinical trial	£215
Indirectly estimated from mapping WPAI to ISI in NHWS database	Dominant

Data to support the SDS© analysis is provided in the CS and a pre-submission manuscript is added in Appendix 2 – SDS pre-submission manuscript of this document. The key results are highlighted below.

The productivity costs savings were estimated by multiplying the productivity results by the median hourly wage in 2022 (£14.77) (Office for National Statistics), assuming 255 working days per year and 8 hours of work per day. The area under the curve was calculated using the trapezoidal rule starting from £0 at day 0 (Figure 9 and Appendix 2 – SDS pre-submission manuscript).

Figure 9: Cumulative productivity costs savings with daridorexant versus placebo

academic / commercial in confidence information removed

We also supplied additional evidence from the recently published RAND report "The societal and economic burden of insomnia in adults" which does not seem to have been considered by the committee. The objective of RAND Europe's study was to identify and quantify the societal burden of long-term insomnia and its resultant impacts, both in terms of indirect economic costs (i.e., non-healthcare related costs) and intangible costs (i.e., costs that are not directly observed through economic transactions but nonetheless have impacts on an individual's health or wellbeing).

The report findings reveal the indirect and intangible costs that long-term insomnia place on the UK economy. Key findings show that:

- Long-term insomnia is associated with approximately 11 to 18 days of absence from work, 39 to 45 days of working while sick, and 44 to 54 days of overall productivity loss annually;
- Working days lost to long-term insomnia result in an overall cost to UK Gross Domestic Product (GDP) of 1.31% in lost productivity per year;
- According to RAND Europe's macroeconomic modelling, if long-term insomnia was treated effectively and comprehensively across the working age population it would increase the GDP in the UK by as much as £34 billion per year;
- Using the "WELLBY"* approach RAND Europe found that people suffering from insomnia, including long-term insomnia, would be willing to trade on average an estimated 14% of their annual per-capita household income to recuperate the wellbeing loss associated with the condition;
- When extrapolated across the UK population, RAND Europe estimates the total wellbeing costs of insomnia in the UK could be close to £17.7 billion.

**WELLBY (Wellbeing-adjusted Life Year) is a simple measure of wellbeing, defined as a one-point change in life satisfaction for an individual for one-year as measured on a Likert scale between 0 to 10. WELLBY closely relates to a QALY but expands the idea of a QALY to the whole of life, not just health*

The results from the RAND report are compelling with regards to the socioeconomic impact of long-term insomnia. Therefore, we would encourage the committee to fully

explore and consider the cost-effectiveness of daridorexant taking this into account, as per the NICE manual.

9. GP training and support

As highlighted in section 1. Executive summary, the committee had concerns about GP support and training associated with the introduction of daridorexant. We have commented that training and support around long-term insomnia and the relative priority of the condition are longstanding issues and not exclusive to daridorexant, or likely to be cost additive.

We explored this in a recent survey (250 UK GPs), of GP learning needs.[8] Figure 10 below demonstrates academic / commercial in confidence information removed. Exploring this further in a primary care advisory board, it seemed that lack of access to CBTi, lack of a clear patient pathway, and lack of medications were identified as the main challenges as opposed to diagnosis of insomnia.[9]

Figure 10: General practitioners' confidence in diagnosing, treating and referring chronic insomnia[8]

academic / commercial in confidence information removed

In the larger 1,000 GP survey it was noted that an average UK GP treats/consults [redacted] This survey also highlighted that [redacted].[2] The primary care advisory board confirmed as per the CS, [redacted].[9] Many of these tools are easily available

and validated for use in primary care. There is also a specific NHS Self-Assessment which can be used by patients and GPs.

Consequently, the most important learning needs identified were around treatment options, referral pathways, and new treatments (Figure 11**Error! Reference source not found.**).[8]

Figure 11: General practitioners' most important learning needs in the diagnosis and management of insomnia[8]

academic / commercial in confidence information removed

As highlighted in the CS and the EPAR, daridorexant is a treatment which is easy to start, monitor, and stop. It has a good safety profile and no evidence of tolerance, withdrawal or addictive effects. As with any new treatment education will be required in understanding the evidence, the mode of action, appropriate patient selection, and how to use. We do not believe, however, that this represents a significant additional training need. We note from the educational GP survey that [redacted].[8] We are also aware there is already a requirement for 50 hours per year of continuing professional development, which could incorporate training on long-term insomnia and its treatment options. Notwithstanding this, we have incorporated an element of GP training into the economic model, as requested.

There is a broader issue regarding the fact that CBTi access is poor and that many parts of the UK have limited or no access to referral pathways. For digital CBTi, Sleepio® is already approved by NICE and should be available in all localities. However, many areas do not commission it, nor do they commission face-to-face CBTi which limits its access. From our 1,000 GP survey we can see that academic / commercial in confidence information remove of GPs are able to "prescribe" CBTi. Thus, it is important to improve the access to CBTi across all regions of the UK.[2]

On entering the insomnia market, Idorsia would provide additional education around long-term insomnia and the appropriate use of all therapies, as per the prevailing guidance and positioning agreed with NICE. We have already invested in understanding educational needs and the channels and preferences for clinicians to access such training. In our commitment to long-term insomnia care, we are planning to support educational programmes on sleep, and have already provided educational support to activities associated with the British Association of Psychopharmacology, the Royal Society of Medicine's Sleep Medicine Section and are finalising an agreement on a project with the Royal College of General Practitioners to support general sleep education.

10. Additional comments on ACD

10.1 Section 3.3 p.6

Idorsia recognises CBTi as the preferred first line treatment option and this will be clear in any interactions with healthcare professionals (HCPs) and the NHS. We agree that it would be helpful for GPs to explore why this is often unavailable. It is a consistent theme in our system research that, in many parts of the country neither face-to-face nor digital CBTi is commissioned (despite Sleepio being NICE approved in May 2022) It is also a consistent theme that in many parts of the country there are no referral options for long-term insomnia. These are longstanding issues that we would urge the NHS to address. As a stakeholder in long-term insomnia Idorsia will provide additional support and education to prescribers, and is keen to work with the NHS to help improve outcomes for patients suffering with this debilitating condition.

10.2 Section 3.5 p.7

It is perhaps misleading to say there is a lack of guidance on insomnia in the UK. Guidelines do exist, in the form of the NICE CKS and the British Association for Psychopharmacology consensus statement on evidence based treatment of insomnia, parasomnias and circadian rhythm disorders. In terms of diagnosis, the diagnostic criteria are set out with guidance for clinicians. It also includes the following statement: "Like depression, anxiety or pain, there is no objective test for insomnia, and in practice it is evaluated clinically. Diagnosis, therefore, is through appraisal against diagnostic criteria,

clinical observations and the use of validated rating scales. There are a number of ways in which sleep can be assessed. The simplest is by asking the patient about their sleep. Are they having difficulty getting to sleep and/ or staying asleep? Is this occurring most nights? Is this persistent and affecting how they feel during the day? An extension of this interview enquiry is to administer a clinical rating scale". This is consistent with comments in the CS. There are a wide variety of validated tools that could be used, of which several are in use across the UK. It may be helpful for the NHS to endorse a more uniform approach and Idorsia would be happy to support communication and implementation of this.

10.3 Section 3.7 p.9

As requested, we have now provided additional data on 25mg. We would however restate the regulator's comment that "from the efficacy perspective, the clinical development adequately supports the proposed indication at 50mg". The 25mg dose is indicated in specific circumstances set out in the daridorexant SmPC and to make any recommendation beyond this would, in our view, be endorsing inappropriate as well as off-label prescribing. The detailed results from study 302 (for 25 mg) and 201 (for 25 mg and 50 mg) are presented in Appendix 1.

10.4 Section 3.9 p.11

We note the comments on a substantial placebo effect. A high placebo response is particularly prominent in insomnia trials. We have previously provided the Jiang meta-analysis of placebo response in insomnia demonstrating that maximum placebo effect appears in the initial phase of treatment and then stabilises around week 9-12 further supporting no additional placebo correction beyond 12-weeks.[10]

10.5 Section 3.10 p.11

We note the comment on uncertainties beyond 12 months but would highlight that there are very few studies evaluating long-term treatment of insomnia and that the data on daridorexant is some of the longest available.

10.6 Section 3.13 p.13

We note the comments on additional inclusion criteria however would classify these as confirmatory rather than narrowing the population. For example, an ISI score of <15 confirms either absence of insomnia (0-7) or sub-threshold insomnia (8-14). It is also worth noting that the diagnostic criteria was DSM-5 and ISI© was administered to assess the nature, severity, and impact of insomnia.[11]

10.7 Section 3.16 p.16 and Section 3.18 p.17

We note the comment “GPs are likely to start from the lower 25mg dose and titrate up to the 50 mg dose if needed”. Neither Idorsia nor the regulators (EMA / MHRA) support this approach. It is clear in the EPAR comments that the recommended treatment dose is 50 mg, with 25 mg only to be utilised in circumstances set out in the SmPC. As requested, we have supplied a package of data and analyses that confirm this position (Appendix 1).

We hope that our responses address the concerns raised by committee.

Appendix 1

1.1 Treatment effect of daridorexant 25 mg

In 3.26 of the ACD, the committee requested for the company to include the evidence on the treatment effect of daridorexant 25 mg from study 302; and evidence on the treatment effect of daridorexant 25 mg and 50 mg from the Dauvilliers et al. (2020) study. The requested information is presented below. In addition, the company has provided a commentary on the treatment effect of daridorexant 25 mg from study 201 and 302. All information presented are adapted from the clinical study reports, Dauvilliers (2020) for study 201, and Mignot (2022) for study 302.[12-15]

1.1.1 Study 302

The design, eligibility criteria, pre-specified endpoints and statistical methods of study 302 are identical to that of study 301 presented in the CS. In terms of study treatment, patients in study 302 were randomised in a 1:1:1 ratio to daridorexant 10 mg, daridorexant 25 mg or placebo. The results of daridorexant 10 mg are excluded since it is not licensed in the UK and therefore not relevant for decision making.

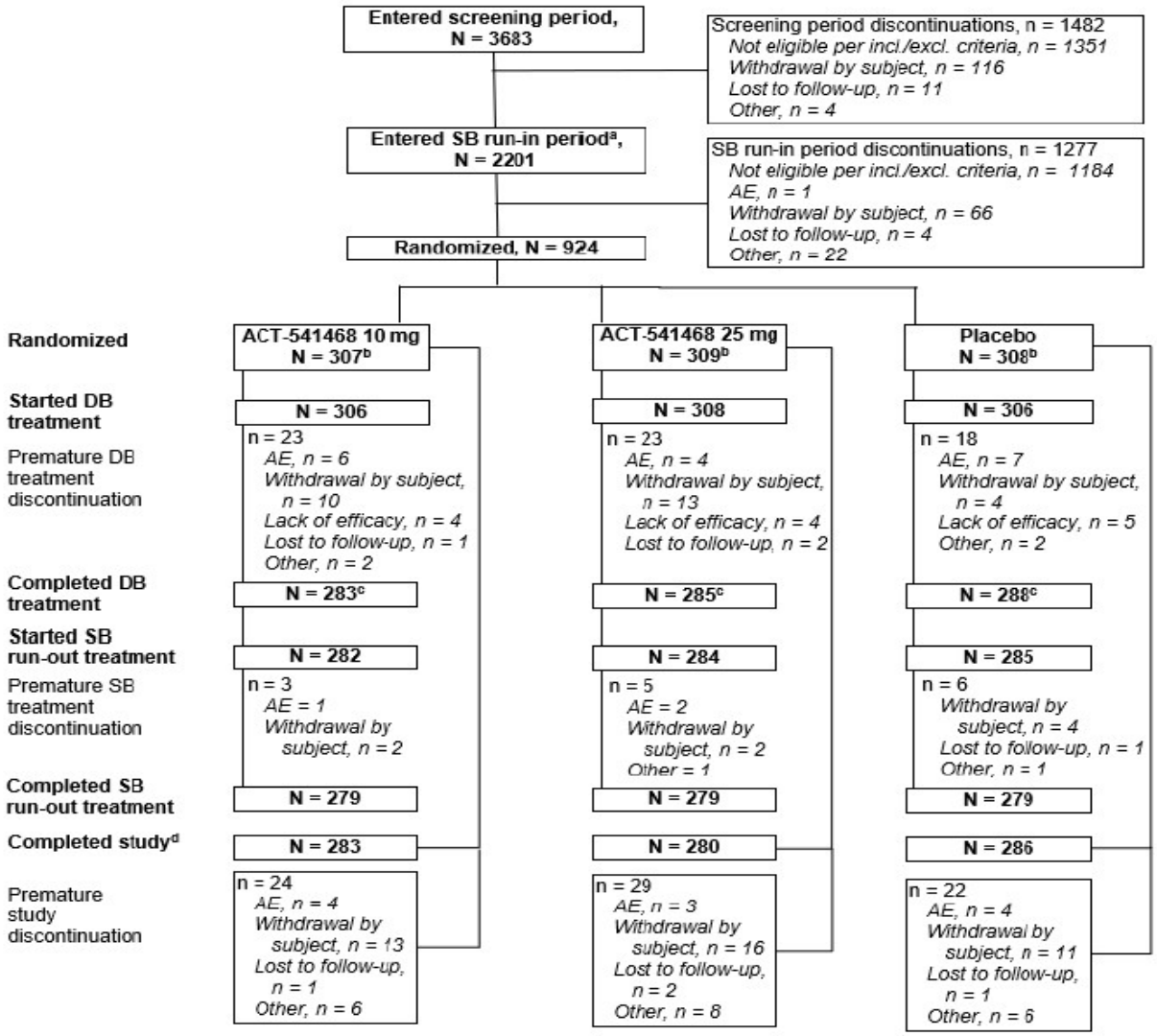
1.1.1.1 Participant flow

Between 29th May 2018 and 14th May 2020, 3,683 participants were screened for inclusion in study 302, of whom 924 were randomly assigned to receive daridorexant 10 mg (n=307), daridorexant 25 mg (n=309), or placebo (n=308) and were included in the full analysis set. The most common reasons for screening failure were either a high apnoea or hypopnoea index (≥15 events per hour) or an event associated with blood oxygen saturation of less than 80%, or that the participant did not meet subjective sleep criteria (assessed by the eDiary) or objective sleep variable criteria (assessed by polysomnography during the run-in). Of the 924 participants randomly assigned in study 302, 856 (93%) completed double-blind treatment. Among the subjects who completed double-blind treatment (n=856), 5 subjects (1 in daridorexant 10 mg, 1 in daridorexant 25 mg, and 3 in placebo) did not start placebo run-out treatment. Of the 851 subjects (282, 284, and 285 subjects in the daridorexant 10 mg, 25 mg, and placebo groups,

respectively) who started placebo run-out treatment, 837 (98.4%) completed the treatment.

No randomised subjects were being treated with cognitive behavioural therapy for insomnia (CBTi) at screening. Previous treatment failure with CBTi was reported by 9 subjects (1.0%; 2, 4, and 3 subjects [daridorexant 10 mg, 25 mg, and placebo, respectively]). 761 subjects (82.4%; 258, 250, and 253 subjects, respectively) did not know CBTi existed or were never offered CBTi as a treatment option. An overview of the disposition of subjects is shown in Figure 12.

Figure 12: Disposition of subjects in study 302



AE = adverse event; DB = double-blind; excl. = exclusion; incl. = inclusion; SB = single-blind.
Subjects are displayed by randomised treatment group.

[a] Subject received at least one dose of SB run-in treatment.
[b] 4 randomised subjects did not receive DB treatment and discontinued from the study
[c] 5 subjects completed DB study treatment but did not start run-out treatment
[d] Subject completed the 30-day follow-up telephone call.

1.1.1.2 Baseline characteristics and demographics

Demographic characteristics of subjects in the full analysis set were balanced across the treatment groups (Table 7). The majority of subjects were female (69.0%) and White (87.8%). The median age of study subjects at screening was 59 years (range 19–85 years), with elderly subjects (aged ≥ 65 years) comprising 39.3% of the study population. The majority of elderly subjects were aged 65 to <75 years (33.2% of the study population); subjects aged 75 to <85 years comprised 6.0% of the study population, and 1 subject (0.1%) was ≥85 years. The mean (standard deviation [SD]) body mass index (BMI) was 26.1 (4.3) kg/m^2; the majority of subjects were above normal weight, being either overweight (BMI 25.0 to ≤30.0, 38.2%) or obese (BMI > 30.0, 16.8%).

Table 7: Demographic characteristics, full analysis set

Variable Statistic	Daridorexant 25 mg N = 309	Placebo N = 308
Age at screening (years)		
Mean (SD)	56.3 (14.4)	56.7 (14.1)
Median (Min, Max)	59 (22, 84)	59 (20, 85)
Sex [n (%)]		
Male	91 (29.4)	103 (33.4)
Female	218 (70.6)	205 (66.6)
Race [n (%)]		
Black or African American	26 (8.4)	29 (9.4)
American Indian or Alaska Native	0	0
Native Hawaiian or other Pacific Islander	1 (0.3)	1 (0.3)
Asian	11 (3.6)	10 (3.2)
White	271 (87.7)	267 (86.7)
Not permitted as per legislation/regulation	0	1 (0.3)
Other	0	0
Ethnicity [n (%)]		
Hispanic or Latino	14 (4.5)	51 (16.5)
Not Hispanic or Latino	295 (95.5)	259 (83.5)
Unknown	0	1 (0.3)
Not permitted as per legislation/regulation	0	1 (0.3)
BMI (kg/m^2) at screening		

Variable Statistic	Daridorexant 25 mg N = 309	Placebo N = 308
Mean (SD)	26.105 (4.209)	26.229 (4.320)
Median (Min, Max)	25.72 (18.03, 39.02)	25.69 (18.56, 39.67)
Region [n (%)]		
United States (US)	108 (35.0)	114 (37.0)
Other (non-US)	201 (65.0)	194 (63.0)

SD = standard deviation; BMI = body mass index

Dissatisfaction with sleep quantity or quality, and sleep disturbance causing significant distress or impairment in daytime functioning were reported by all subjects in the full analysis set. Time since insomnia diagnosis at randomisation was balanced across treatment groups, with a median (Q1, Q3) of 8.2 years (3.3, 15.7) for the daridorexant 25 mg group, and 7.4 years (2.7, 15.0) for the placebo group. Baseline values for the primary and secondary endpoints, and for ISI©) score, were balanced across treatment groups (Table 8).

Table 8: Baseline values for Wake after sleep onset (WASO), Latency to persistent sleep (LPS), sTST, IDSIQ sleepiness domain score, and ISI© score, full analysis set

	Daridorexant 25 mg N = 309	Placebo N = 308
WASO (min)		
n	309	308
Mean (SD)	106.031 (49.103)	108.073 (48.713)
LPS (min)		
n	309	308
Mean (SD)	68.877 (40.545)	71.815 (46.089)
sTST (min)		
n	309	308
Mean (SD)	308.489 (52.849)	307.570 (51.521)
IDSIQ sleepiness domain score		
n	308	307
Mean (SD)	22.242 (6.193)	22.571 (5.757)
ISI© score		
n	308	306
Mean (SD)	19.5 (4.0)	19.6 (4.1)

Higher IDSIQ sleepiness domain score represents greater burden of illness.
IDSIQ = Insomnia Daytime Symptoms and Impacts Questionnaire; ISI© = Insomnia Severity Index©; LPS = latency to persistent sleep; SD = standard deviation; sTST = subjective total sleep time; WASO = wake after sleep onset.

1.1.1.3 Primary efficacy endpoints

1.1.1.3.1 WASO

At month 1 and month 3, mean and median reductions (improvements) from baseline were observed in both treatment groups (Figure 13A). Numerically, observed reductions from baseline were greater for daridorexant 25 mg than placebo. In the linear mixed effects model, adjusted mean reductions (improvements) from baseline in WASO were observed in both treatment groups. Reductions from baseline were greater for daridorexant 25 mg than for placebo, with differences to placebo statistically significant at both month 1 and month 3 (two-sided p-values 0.0001 and 0.0028, respectively) (Table 9).

1.1.1.3.2 LPS

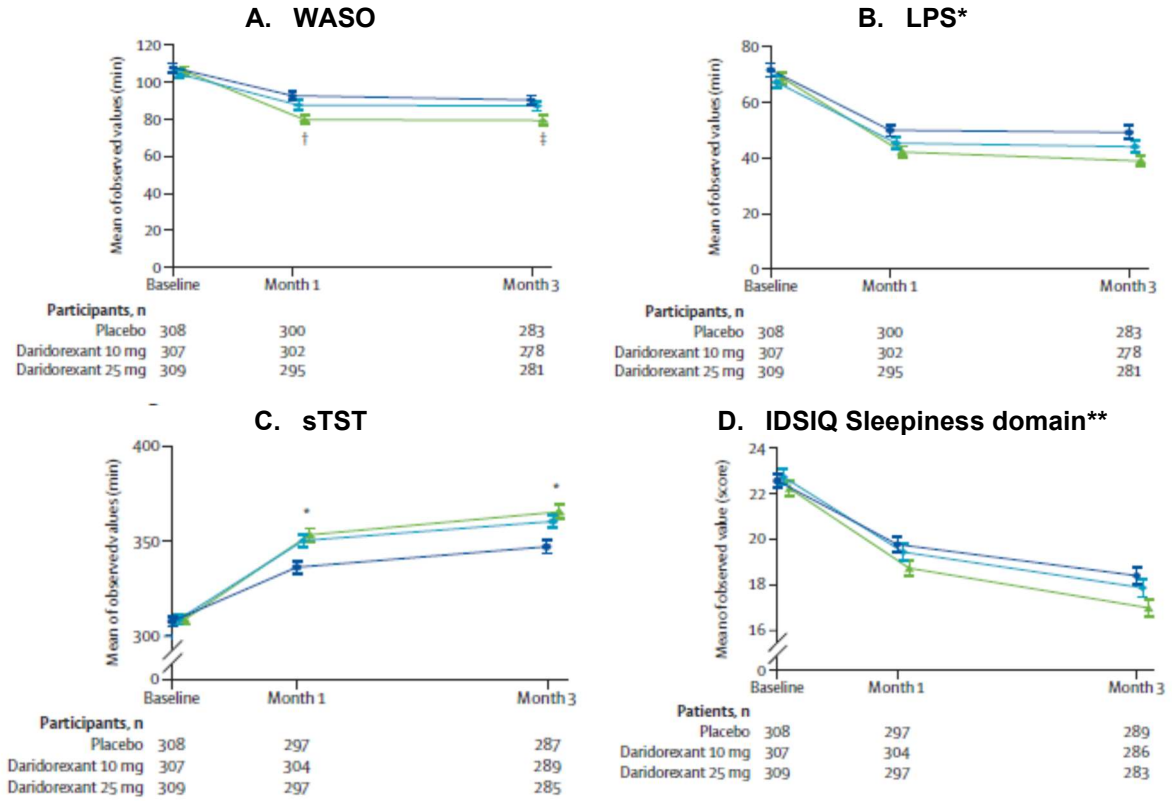
At month 1 and month 3, mean and median reductions (improvements) from baseline were observed in both treatment groups (Figure 13B). Numerically, observed reductions from baseline were greater for daridorexant 25 mg than for placebo. In the linear mixed effects model, adjusted mean reductions (improvements) from baseline in LPS were observed in both treatment groups, with numerically greater reductions from baseline observed for daridorexant 25 mg than for placebo. Differences to placebo were not statistically significant at both month 1 and month 3 (two-sided p-values 0.0303 and 0.0053 [thresholds for significance are 0.025 and 0.00313] respectively) (Table 9).

Table 9: WASO and LPS – Between treatment analysis for change from baseline to month 1 and month 3, full analysis set

Variable [outcome category] Treatment group	n	LSM	SE	95% CL	Difference to placebo			
					LSM	SE	95% CL	p-value (two-sided)
Between treatment analysis for change from baseline in WASO (min) to month 1 and month 3 [improvement of night-time symptoms of insomnia]								
Change from baseline to Month 1								
Daridorexant 25 mg (N=309)	295	-24.19	2.180	-28.466, -19.911	-11.62	3.050	-17.604, -5.633	0.0001
Placebo (N=308)	300	-12.57	2.164	-16.817, -8.323	-	-	-	-
Change from baseline to Month 3								
Daridorexant 25 mg (N=309)	281	-24.25	2.432	-29.021, -19.474	-10.25	3.414	-16.950, -3.548	0.0028
Placebo (N=308)	283	-14.00	2.424	-18.756, -9.241	-	-	-	-
Between treatment analysis for change from baseline in LPS (min) to month 1 and month 3 [improvement of night-time symptoms of insomnia]								
Change from baseline to Month 1								
Daridorexant 25 mg (N=309)	295	-26.46	2.123	-30.626, -22.292	-6.45	2.973	-12.282, -0.614	0.0303*
Placebo (N=308)	300	-20.01	2.108	-24.148, -15.875	-	-	-	-
Change from baseline to Month 3								
Daridorexant 25 mg (N=309)	281	-28.91	2.296	-33.413, -24.399	-9.01	3.224	-15.339, -2.684	0.0053**
Placebo (N=308)	283	-19.89	2.287	-24.384, -15.405	-	-	-	-

CL = confidence limit; LPS = latency to persistent sleep; LSM = least squares mean; SE = standard error; WASO = wake after sleep onset.
Non-significant p-values (threshold for significance is *0.025 and **0.00313)

Figure 13: Night-time efficacy endpoints and IDSIQ sleepiness domain score



Two-sided p-values shown are versus placebo, calculated using the linear mixed effects model for repeated measures. LPS = latency to persistent sleep. sTST = subjective total sleep time. WASO = wake time after sleep onset. IDSIQ = Insomnia Daytime Symptoms and Impacts Questionnaire *p<0·0001. †p=0·0001. ‡p=0·0028.
Non-significant p-values [threshold for significance for LPS: *0.025 (month 1) and *0.00313 (month 2); for IDSIQ sleepiness domain: **0.00625 (month 1) and **0.00391 (month 3)]

1.1.1.4 Secondary and other efficacy endpoints

The results of the between treatment analyses of secondary and other efficacy endpoints of study 302 are presented in

Table 10. For the secondary endpoint of subjective total sleep time (sTST), adjusted mean increases (improvements) from baseline were observed in both treatment groups (Figure 13C). Differences to placebo were statistically significant for daridorexant 25 mg both at month 1 and month 3 (both two-sided p-values <0.0001). For the secondary endpoint of IDSIQ sleepiness domain score, adjusted mean reductions (improvements) from baseline were observed in both treatment groups (Figure 13D). Differences to placebo for were not statistically significant for daridorexant 25 mg at Month 1 or Month 3 (two-sided p-values 0.0733 and 0.0120 [thresholds for significance are 0.00625 and 0.00391]).

Results for the other efficacy endpoints academic / commercial in confidence information removed, and IDSIQ total score, alert/cognition domain score, and mood domain score) supported the findings from the primary and secondary efficacy endpoints (

Table 10). For all the endpoints, academic / commercial in confidence information removed.

1.1.1.5 Subgroup analyses

Pre-specified subgroup analysis was performed to evaluate the consistency of treatment effect across the following demographic subgroups:

- Age: <65, ≥ 65years
- Sex: Male, female
- Region: US, other (non-US)

The effect of daridorexant 25 mg on the primary and secondary efficacy endpoints was largely consistent across the above subgroups.

Table 10: Secondary and other efficacy endpoints – Between treatment analysis for change from baseline to month 1 and month 3, full analysis set

Variable [outcome category] Treatment group	n	LSM	SE	95% CL	Difference to placebo			
					LSM	SE	95% CL	p-value (two-sided)
Between treatment analysis for change from baseline in sTST (min) to month 1 and month 3 [improvement of night-time symptoms of insomnia]								
Change from baseline to Month 1								
Daridorexant 25 mg (N=309)	297	43.77	2.873	38.136, 49.412	16.13	4.028	8.224, 24.035	<0.0001
Placebo (N=308)	297	27.64	2.868	22.015, 33.274	-	-	-	-
Change from baseline to Month 3								
Daridorexant 25 mg (N=309)	285	56.18	3.244	49.812, 62.547	19.06	4.552	10.125, 27.994	<0.0001
Placebo (N=308)	287	37.12	3.232	30.776, 43.464	-	-	-	-
Between treatment analysis for change from baseline in IDSIQ sleepiness domain score to month 1 and month 3 [daytime functioning]								
Change from baseline to Month 1								
Daridorexant 25 mg (N=309)	297	-3.51	0.300	-4.096, -2.917	-0.75	0.421	-1.581, 0.071	0.0733
Placebo (N=308)	297	-2.75	0.300	-3.340, -2.163	-	-	-	-
Change from baseline to Month 3								
Daridorexant 25 mg (N=309)	283	-5.27	0.355	-5.964, -4.569	-1.25	0.498	-2.230, -0.276	0.0120
Placebo (N=308)	289	-4.01	0.352	-4.705, -3.322	-	-	-	-
Between treatment analysis for change from baseline in TST (min) to month 1 and month 3 [changes in sleep architecture and sleep efficiency]								
Change from baseline to Month 1								
Daridorexant 25 mg (N=309)	academic / commercial in confidence information removed							
Placebo (N=308)								
Change from baseline to Month 3								
Daridorexant 25 mg (N=309)	academic / commercial in confidence information removed							
Placebo (N=308)								

Variable [outcome category] Treatment group	n	LSM	SE	95% CL	Difference to placebo			
					LSM	SE	95% CL	p-value (two-sided)
Between treatment analysis for change from baseline in sWASO (min) to month 1 and month 3 [improvement of night-time symptoms of insomnia]								
Change from baseline to Month 1								
Daridorexant 25 mg (N=309)	academic / commercial in confidence information removed							
Placebo (N=308)								
Change from baseline to Month 3								
Daridorexant 25 mg (N=309)	academic / commercial in confidence information removed							
Placebo (N=308)								
Between treatment analysis for change from baseline in sLSO (min) to month 1 and month 3 [changes in quality of sleep, depth of sleep, daytime alertness and daily ability to function]								
Change from baseline to Month 1								
Daridorexant 25 mg (N=309)	academic / commercial in confidence information removed							
Placebo (N=308)								
Change from baseline to Month 3								
Daridorexant 25 mg (N=309)	academic / commercial in confidence information removed							
Placebo (N=308)								
Between treatment analysis for change from baseline in IDSIQ total score to month 1 and month 3 [daytime functioning]								
Change from baseline to Month 1								
Daridorexant 25 mg (N=309)	297	-11.90	0.982	-13.824, -9.971	-3.11	1.375	-5.807, -0.412	0.0239
Placebo (N=308)	297	-8.79	0.979	-10.708, -6.867	-	-	-	-
Change from baseline to Month 3								
Daridorexant 25 mg (N=309)	283	-17.30	1.181	-19.620, -14.985	-4.23	1.654	-7.477, -0.986	0.0107
Placebo (N=308)	289	-13.07	1.171	-15.370, -10.773	-	-	-	-
Between treatment analysis for change from baseline in IDSIQ alert/cognition domain score to month 1 and month 3 [daytime functioning]								
Change from baseline to Month 1								
Daridorexant 25 mg (N=309)	297	-4.88	0.425	-5.718, -4.049	-1.12	0.596	-2.289, 0.048	0.0602

Variable [outcome category] Treatment group	n	LSM	SE	95% CL	Difference to placebo			
					LSM	SE	95% CL	p-value (two-sided)
Placebo (N=308)	297	-3.76	0.424	-4.595, -2.931	-	-	-	-
Change from baseline to Month 3								
Daridorexant 25 mg (N=309)	283	-7.25	0.512	-8.251, -6.241	-1.66	0.717	-3.068, -0.253	0.0208
Placebo (N=308)	289	-5.59	0.508	-6.582, -4.589	-	-	-	-
Between treatment analysis for change from baseline in IDSIQ mood domain score to month 1 and month 3 [daytime functioning]								
Change from baseline to Month 1								
Daridorexant 25 mg (N=309)	297	-3.54	0.312	-4.152, -2.929	-1.25	0.437	-2.111, -0.397	0.0042
Placebo (N=308)	297	-2.29	0.311	-2.897, -1.676	-	-	-	-
Change from baseline to Month 3								
Daridorexant 25 mg (N=309)	283	-4.83	0.370	-5.554, -4.100	-1.34	0.519	-2.354, -0.318	0.0102
Placebo (N=308)	289	-3.49	0.367	-4.212, -2.770	-	-	-	-

CL = confidence limit; IDSIQ = Insomnia Daytime Symptoms and Impacts Questionnaire; LSM = least squares mean; SE = standard error; sTST = subjective total sleep time; sWASO = subjective wake after sleep onset; sLSO = subjective latency to sleep onset; TST = total sleep time

1.1.1.6 Exploratory endpoints

1.1.1.6.1 ISI© scores

The baseline mean (SD) ISI© scores were comparable between daridorexant 25 mg and placebo (19.5 [4.0] and 19.6 [4.1], respectively). Numerically, daridorexant 25 mg demonstrated greater reduction in mean (SD) ISI© scores from baseline to both month 1 and month 3 compared with placebo (month 1: -5.1 [5.2] versus -3.8 [4.6]; month 3: - 6.9 [6.0] versus -5.4 [5.5]) (

Table 11).

1.1.1.6.2 Other exploratory endpoints

The results of other exploratory endpoints that are relevant to the decision problem per outcome category are summarised in

Table 11. The results showed that subjects benefited from treatment with daridorexant 25 mg based on subjective assessments of sleep severity and quality: changes from baseline in visual analogue scale (VAS) scores from the Sleep Disorders Questionnaire (SDQ) (quality and depth of sleep, daytime alertness, ability to function) were greater for daridorexant 25 mg than for placebo.

Table 11: Exploratory endpoints (patient-reported symptoms and impacts of insomnia - Observed value and change from baseline to month 1 and month 3, full analysis set

Variable [outcome category] Treatment group	Baseline		Month 1		Month 3		Change from baseline to	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	Month 1, mean (SD)	Month 3, mean (SD)
ISI© scores [improvement of night-time symptoms of insomnia]								
Daridorexant 25 mg	308	19.5 (4.0)	287	14.4 (5.8)	280	12.5 (6.0)	-5.1 (5.2)	-6.9 (6.0)
Placebo	306	19.6 (4.1)	294	15 (0, 28)	277	14.1 (5.9)	-3.8 (4.6)	-5.4 (5.5)
VAS quality of sleep (mm) [improvement of night-time symptoms of insomnia]								
Daridorexant 25 mg	309	37.94 (15.02)	297	49.38 (18.13)	285	55.76 (20.05)	11.20 (15.55)	17.77 (18.55)
Placebo	308	36.91 (14.77)	297	46.32 (17.46)	287	50.34 (19.51)	9.41 (14.44)	13.18 (17.33)
VAS daytime alertness (mm) [improvement of night-time symptoms of insomnia]								
Daridorexant 25 mg	308	40.16 (17.20)	297	49.86 (18.85)	283	55.95 (20.87)	9.51 (16.00)	15.80 (19.54)
Placebo	307	38.83 (16.63)	297	46.75 (18.47)	289	51.61 (20.13)	8.03 (13.72)	12.51 (18.08)
VAS Ability to function (mm) [improvement of night-time symptoms of insomnia]								
Daridorexant 25 mg	308	41.70 (16.82)	297	50.46 (18.73)	283	56.18 (20.45)	8.56 (15.16)	14.42 (18.88)
Placebo	307	40.37 (16.53)	297	47.86 (18.35)	289	51.94 (20.08)	7.57 (14.15)	11.40 (17.80)
PGA-S (daytime symptoms) [improvement of night-time symptoms of insomnia]								
Daridorexant 25 mg	academic / commercial in confidence information removed							
Placebo								
PGI-C (daytime symptoms) [improvement of night-time symptoms of insomnia]								
Daridorexant 25 mg	academic / commercial in confidence information removed							
Placebo								
PGI-S (night-time symptoms) [improvement of night-time symptoms of insomnia]								
Daridorexant 25 mg	academic / commercial in confidence information removed							
Placebo								

Variable [outcome category] Treatment group	Baseline		Month 1		Month 3		Change from baseline to	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	Month 1, mean (SD)	Month 3, mean (SD)
PGI-C (night-time symptoms) [improvement of night-time symptoms of insomnia]								
Daridorexant 25 mg	academic / commercial in confidence information removed							
Placebo								
Latency from LPS to REM [sleep architecture and sleep efficiency]								
Daridorexant 25 mg	academic / commercial in confidence information removed							
Placebo								
Latency (min) from sleep onset to REM [sleep architecture and sleep efficiency]								
Daridorexant 25 mg	academic / commercial in confidence information removed							
Placebo								
Sleep efficiency (%) [sleep architecture and sleep efficiency]								
Daridorexant 25 mg	academic / commercial in confidence information removed							
Placebo								
Sleep onset latency (min) [sleep architecture and sleep efficiency]								
Daridorexant 25 mg	academic / commercial in confidence information removed							
Placebo								

ISI© = Insomnia severity index©; LPS = latency to persistent sleep; min = minute; PGA-S = Patient Global Assessment of Disease Severity; PGI-C = Patient Global Impression of Change; REM = rapid eye movement; SD = standard deviation; VAS = visual analogue scale

1.1.1.7 Safety

1.1.1.7.1 Treatment-emergent adverse events (TEAEs)

During the double-blind study period, 39.3% and 32.7% of subjects reported TEAEs in the daridorexant 25 mg group and placebo group, respectively. Most of the events were of mild or moderate intensity. The most commonly reported AEs were nasopharyngitis (4.2% [daridorexant 25 mg] and 5.2% [placebo]) and headache (4.9% [daridorexant 25 mg] and 3.6% [placebo]). TEAEs with an incidence of ≥2% in any treatment group are shown in Table 12. Of these, TEAEs reported more frequently for daridorexant than placebo (≥1%) were headache, nasopharyngitis (see above); fatigue (3.6%, and 0.7%), and somnolence (3.2%, and 1.3%). All AEs of fatigue and somnolence were of mild and moderate intensity, and most were considered related to study treatment by the investigator. TEAEs during the double-blind study period considered related to study treatment by the investigator were reported for 37 subjects (12.0%), and 25 subjects (8.2%) in the daridorexant 25 mg, and placebo groups, respectively.

Table 12: TEAEs during the double-blind study period reported for ≥2% in any treatment group, by preferred term, safety set

Treatment-emergent adverse event*, by preferred term	Daridorexant 25 mg N = 308 n (%)	Placebo N = 306 n (%)
Subjects with at least one event**	121 (39.3)	100 (32.7)
Headache	15 (4.9)	11 (3.6)
Nasopharyngitis	13 (4.2)	16 (5.2)
Fatigue	11 (3.6)	2 (0.7)
Somnolence	10 (3.2)	4 (1.3)
Upper respiratory tract infection	3 (1.0)	6 (2.0)

* Includes TEAEs occurring (i.e., that started or worsened) during the double-blind study period.
**Total number of subjects per treatment group with at least one event. Table is truncated to show only those AEs reported for at least 2% in any treatment group.
Percentages are based on the treatment group N; n = number of subjects with at least one row event; Subjects may be counted in more than one row.
Preferred terms are based on MedDRA dictionary version 22.1.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

TEAEs occurring during the double-blind study period were analysed by the subgroups of age (<65, ≥65 years) and BMI (<25, 25–30, >30 kg/m^2). Overall, although there were some numerical differences between subgroups regarding the incidence of individual TEAEs, none of these differences were considered of medical significance, there was no clear dose dependence, and overall no consistent differences between both dose groups and placebo, including in the subgroup of ≥65 years subjects.

1.1.1.7.2 Treatment-emergent serious adverse events (SAEs)

Treatment-emergent SAEs were reported for 7 subjects: 3 (1.0%), and 4 (1.3%) in the daridorexant 25 mg and placebo groups, respectively. Apart from an SAE of appendicitis, which occurred during the safety follow-up period, all treatment-emergent SAEs occurred during the double-blind study period. All SAEs were assessed as not related to study treatment by the investigator.

Table 13: Treatment-emergent SAEs by preferred term, safety set

Treatment-emergent SAE, by preferred term	Daridorexant 25 mg N = 308 n (%)	Placebo N = 306 n (%)
Subjects with at least one event	3 (1.0)	4 (1.3)
Haemoptysis	1 (0.3)	0
Lumbar radiculopathy	1 (0.3)	0
Schizophrenia	1 (0.3)	0
Hypertensive crisis	0	1 (0.3)
Joint dislocation	0	1 (0.3)
Meniscus injury	0	1 (0.3)
Rotator cuff syndrome	0	1 (0.3)

Percentages are based on the treatment group N; n = number of subjects with at least one row event; Subjects may be counted in more than one row.
Preferred terms are based on MedDRA dictionary version 22.1.
Includes all SAEs occurring from start of double-blind study treatment up to the earlier of 30 days after the end of double-blind study treatment or enrolment in the extension study 303.
MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event

1.1.1.7.3 Rebound insomnia

Analyses of rebound insomnia using sleep measures assessed during the placebo run-out period are presented in Table 14. Mean and median observed values for WASO and LPS at visit 9 (the first night on single-blind placebo run-out treatment) were lower than at baseline (i.e., improved) in both treatment groups. Mean and median observed values for sTST during the placebo run-out period (mean value after visit 9) were higher than baseline (i.e., improved). The results indicate absence of rebound insomnia, though no statistical comparisons were done.

Table 14: Rebound insomnia – Observed value and change from baseline to placebo run-out period, treatment withdrawal set

Treatment group	Baseline		Placebo run-out period		Change from baseline to placebo run-out period	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Change from baseline in WASO (min) to placebo run-out period						
Daridorexant 25 mg (N=284)	284	106.864 (48.795)	276	99.364 (64.616)	276	-5.092 (57.901)
Placebo (N=285)	285	108.328 (49.141)	275	80.791 (55.055)	275	-26.175 (53.536)
Change from baseline in LPS (min) to placebo run-out period						
Daridorexant 25 mg (N=284)	284	67.518 (39.845)	277	55.760 (68.555)	277	-10.264 (67.287)
Placebo (N=285)	285	71.614 (44.495)	276	52.842 (63.526)	276	-18.278 (63.785)
Change from baseline in sTST (min) to placebo run-out period						
Daridorexant 25 mg (N=284)	284	309.691 (51.567)	279	356.116 (66.626)	279	46.750 (55.356)
Placebo (N=285)	285	308.749 (51.501)	279	351.566 (63.674)	279	42.299 (53.788)

Values for placebo run-out were calculated only for subjects who had a baseline value.
LPS = latency to persistent sleep; SD = standard deviation; sTST = subjective total sleep time; WASO = wake after sleep onset

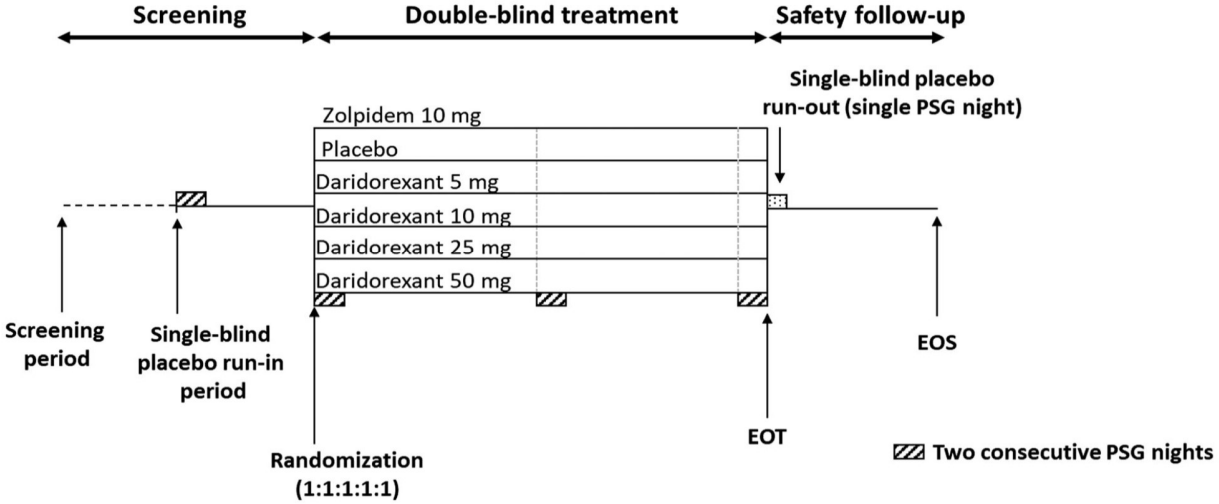
1.2.1 Study 201

1.2.1.1 Study design

This was a phase 2, randomised, double-blind, placebo-controlled, and active controlled dose-response study. Eligible subjects were men and women of 18 to 64 years of age who met the criteria of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) for insomnia disorder. Subjects were required to have a self-reported history of ≥30 minutes LSO, ≥30 minutes WASO, a TST ≤ 6.5 hours on at least 3 of 7 consecutive nights, and a bedtime between 21:30 and 00:30 hours.

The overall study design is illustrated in Figure 14. The study comprised a screening period (including a single-blind placebo run-in phase), followed by a treatment phase, a single-blind placebo run-out period, and a safety follow-up period.

Figure 14: Design of study 201



EOS=End of study; EOT=End of treatment; PSG: Polysomnography.

The study comprised of a screening period of 14 to 28 days, followed by a 30-day double-blind treatment period, a single-blind placebo run-out for 1 day, and a 30-day safety follow-up period. The screening period included a single-blind placebo run-in phase; during the screening phase, subjects completed a daily sleep diary for at least 7 consecutive days to assess baseline sleep characteristics. Polysomnography (PSG) was recorded during 2 consecutive, single-blind, placebo-treated nights. Subjects were required to meet the PSG criteria for randomisation: mean of 2 nights WASO ≥ 30

minutes, LPS ≥ 30 minutes, and TST < 420 minutes. Subjects had to have an ISI©) score of at least 15.

1.2.1.2 Study sites

Study 201 was conducted at 38 sites across 6 countries (Germany, Hungary, Israel, Spain, Sweden, and the USA).

1.2.1.3 Study eligibility criteria

For inclusion in the study, eligible subjects were required to have fulfilled all of the following inclusion criteria (Table 15).

Table 15: Inclusion and exclusion criteria of study 201

Inclusion criteria	• Signed informed consent prior to any study-mandated procedure.
	• Male or female aged 18–64 years (inclusive).
	• A woman of childbearing potential was required to provide:
	  ○ Negative serum pregnancy test (V1);
	  ○ Negative urine pregnancy test (V3);
	  ○ Agreement to undertake pregnancy tests up to 30 days after EOT;
	  ○ Agreement to use the contraception scheme from screening up to at least 30 days after EOT.
	• BMI: 18.5 ≤ BMI (kg/m^2) < 32.0.
	• Insomnia disorder according to DSM-5 criteria.
	• Self-reported history of all of the following on at least 3 nights per week and for at least 3 months prior to screening period:
	  ○ ≥ 30 minutes to fall asleep;
	  ○ Wake time during sleep ≥ 30 minutes;
	  ○ TST ≤ 6.5 h.
	• ISI© score ≥ 15.
	• Willing to comply with all aspects of the study protocol.
	• Ability to communicate well with the investigator, to understand the study requirements and judged by the investigator to be alert and orientated to person, place, time and situation.
	• Meeting the following sleep parameters on at least 3 nights out of 7 consecutive nights on the sleep diary completed at home between screening and placebo run-in period:
	  ○ ≥ 30 minutes to fall asleep;
	  ○ Wake time during sleep ≥ 30 minutes;
	  ○ TST ≤ 6.5 h.
	• Usual bedtime between 21:30 and 00:30 as reported on sleep diary completed between screening and placebo run-in period.
	• Regular time in bed between 6 and 9 hours as reported on sleep diary between screening and placebo run-in period.
	• Meeting the following sleep parameters on the 2 PSG nights:
	  ○ Mean LPS ≥ 20 min (with none of the 2 nights < 15 min), and
	  ○ Mean WASO ≥ 30 min (with none of the 2 nights < 20 min), and
	  ○ Mean TST < 420 minutes.

BMI=Body mass index; DSM-5=Diagnostic and Statistical Manual of Mental Disorders; EOT=End of treatment; ISI= Insomnia Severity Index; LPS=Latency to persistent sleep; PSG=Polysomnography; TST=Total sleep time; V1=visit 1 (screening period); V3=Randomisation (treatment phase); WASO=Wake after sleep onset.

Subjects with lifetime suicidal behaviour, suicidal ideation, unstable medical condition, or significant medical disorder (i.e., depression and anxiety) assessed by clinical judgement that could interfere with safety, treatment compliance, and study assessments were excluded. Other exclusion criteria included ongoing sleep disorders other than insomnia, treatment with a central nervous system-active drug, and cognitive behaviour therapy for insomnia within 1 month prior to study start. Subjects were excluded before randomisation based on occurrence of an apnoea or hypopnea event above 10 per hour.

1.2.1.4 Study treatment, prior and concomitant medications

Eligible subjects were randomised in a 1:1:1:1:1:1 ratio to 1 of the 6 treatment arms: placebo (0mg), 5, 10, 25, 50mg daridorexant, or 10mg zolpidem. Study treatment comprised 2 capsules for each intake: daridorexant, placebo capsules matching daridorexant, over encapsulated zolpidem, or placebo capsules matching over encapsulated zolpidem.

1.2.1.5 Pre-specified study endpoints

The pre-specified efficacy and safety endpoints of study 201 are presented in Table 16

Table 16: Primary, secondary and exploratory endpoints of study 201

Primary efficacy endpoints	**Definition**
Objective sleep maintenance	Absolute change from baseline[a] to Days 1 and 2[b] in WASO (min) as determined by PSG.
Secondary efficacy endpoints	**Definition**
Subjective sleep maintenance	Absolute change from baseline[c] to Week 4[d] in mean sWASO.
Objective sleep initiation	Absolute change from baseline[a] to Days 1 and 2[b] in mean LPS.
Subjective sleep initiation	Absolute change from baseline[c] to Week 4[d] in mean sLSO.

Other efficacy endpoints	Definition

Other endpoints were related to various objective (as determined by PSG) and/or subjective (as self-reported in the sleep diary) assessments of sleep maintenance, sleep onset, TST, sleep quality, sleep architecture, sleep continuity, sleep efficiency and next-day performance	• Objective and subjective sleep maintenance:
	  • WASO over time (by hour and by quarter of the night);
	  • sWASO
	• Objective and subjective sleep onset:
	  • LPS;
	  • sLSO.
	• Objective and subjective TST:
	  • TST
	  • sTST
	• Sleep quality, as determined by scores on the VAS, mm).
	• Sleep architecture:
	  • Duration and percentage of TST in each sleep stage (S1, S2, SWS and REM);
	  • Latency to each sleep stage.
	• Objective and subjective sleep continuity:
	  • Number of shifts from S2, SWS or REM to S1 or awake;
	  • Wake time during sleep
	  • Number of awakenings
	  • Self-reported number of awakenings.
	• Sleep efficiency
	• Insomnia severity:
	  • ISI© scores.
	• Next-day performance.
	  • Morning sleepiness, daytime alertness and daytime ability to function, as determined by scores on the VAS (mm).

Safety endpoints	Definition

Safety endpoints	• Treatment-emergent AEs and SAEs (i.e., occurring from day of first dose of double-blind study treatment to EOS)
	• AEs leading to premature discontinuation of the double-blind study treatment.
	• TEAEs of special interest (AESIs) after adjudication by ISB:
	  • Narcolepsy-like events (e.g., excessive daytime sleepiness, cataplexy);
	  • Complex sleep behaviours events;
	  • Suicidal thoughts and/or behaviours.
	• Change from baseline (mean of the 2 PSG nights at run-in period, run-in period) to the last value on double-blind study treatment in vital signs (SBP, DBP, pulse rate and body temperature)
	• Change from baseline (screening period) to the last value on double-blind study treatment in body weight.
	• Marked electrocardiogram (ECG) abnormalities during the double-blind treatment period
	• Change from baseline (run-in period) to the last value on double-blind study treatment in ECG parameters.
	• Treatment-emergent marked laboratory abnormalities
	• Change from baseline (run-in period) to the last value in the double-blind period in laboratory variables
	• Rebound insomnia:
	  • Change from baseline (worst value of either PSG night at run-in period) to the morning of run-out period in WASO, TST and LPS.
	• Withdrawal symptoms:
	  • Change from third visit (2nd morning) to run-out (morning) in the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) scores
	  • AEs and ECG abnormalities during the withdrawal period (between third visit and run-out period)
	• Change from baseline (mean of the 2 PSG nights at run-in period) to mean of the two PSG nights of randomisation (Days 1 & 2), second and third visit ([Days 15 & 16] and [Days 28 & 29]) in:
	  • Digit Symbol Substitution Test© (DSST©) performed in the morning, 30–60 minutes after lights on;
	  • SDS© performed in the morning, 30–60 minutes after lights on;
	  • Karolinska Sleepiness Scale (KSS) performed in the morning, 30–60 minutes after lights on.
	• Change from baseline (run-in period, second morning) to the worst value on double-blind study treatment in C-SSRS©

[a]Baseline was the mean value of the 2 PSG nights during the run-in period
[b]Days 1&2 was the mean value of the corresponding two PSG treatment nights
[c]Baseline was the mean value in the screening sleep diary entries at home between run-in period and randomisation across 7 consecutive days.
[d]Week 4 was the mean value based on the sleep diary entries at home across the 7 consecutive days immediately prior to the PSG at third visit.
AEs=Adverse events; AESI= Adverse event of special interest; BWSQ= Benzodiazepine Withdrawal Symptom Questionnaire; C-SSRS©= Columbia Suicide Severity Rating Scale©; ECG= electrocardiogram; IDSIQ=Insomnia Daytime Symptoms and Impacts Questionnaire; ISB=independent safety board; ISI©=Insomnia severity index©; LPS=latency to persistent sleep; PGA-S=Patient Global Assessment of Disease Severity; PGI-C=Patient Global Impression of Change; PGI-S=Patient Global Impression of Severity PICO=population, intervention, comparator and outcome; PSG=polysomnography; REM=rapid eye movement; S1, S2, S3= sleep stage 1, 2 and 3; SAE=Serious AEs; SDS= Sheehan Disability Scale©; sLSO=subjective latency to sleep onset; sTST=subjective total sleep time; sWASO=subjective wake after sleep onset; SWS= slow-wave sleep; TEAEs= Treatment-emergent AEs; TST= total sleep time; VAS=visual analogue scale; WASO=wake after sleep onset.

1.2.1.6 Statistical methods and analysis sets

Assuming the maximum mean reduction in WASO from baseline to days 1 and 2 (primary endpoint) with a daridorexant dose was 25 minutes longer than with placebo (SD = 40 minutes), with values from 8% of subjects not available for analysis, a total sample size of approximately 250 (i.e., 50 subjects per arm) would provide between 89 and 92% power (power of 90% when averaged over all dose-response models) to reject the null hypothesis (absence of a dose-response relationship) with a 2-sided 5% type I error.

The primary endpoint was analysed using the modified full analysis set (FAS). This comprised all subjects from the FAS (all randomised subjects who received at least 1 dose of double-blind study treatment) who had at least 1 WASO assessment at baseline and at days 1 and 2. All subjects who received at least 1 dose of double-blind study treatment were included in the safety set. Analyses of rebound insomnia and withdrawal symptoms were performed on the subset of subjects who received the 1 dose of single-blind placebo treatment in the run-out period.

The absolute change in WASO was analysed using the MCP-Mod approach. This approach combines a Multiple Comparison Procedure (MCP) to assess the efficacy of ACT-541468 versus placebo followed by a modelling (Mod) step to characterise the dose-response relationship and to identify a dose (or dose range) that has shown signs of a clinically relevant effect.

The analysis of the secondary and other efficacy endpoints was performed on the FAS. Questionnaire data based on the nights in the sleep laboratory (i.e., the mornings following any PSG night) were excluded from the calculation of the weekly averages.

For objective endpoints, subjects were required to have at least one value at a given time point (e.g., Days 1&2) to calculate a mean. For subjective endpoints, at least 3 days of data during each week were required to calculate a weekly mean. Otherwise, the mean value was considered missing for that time point or week.

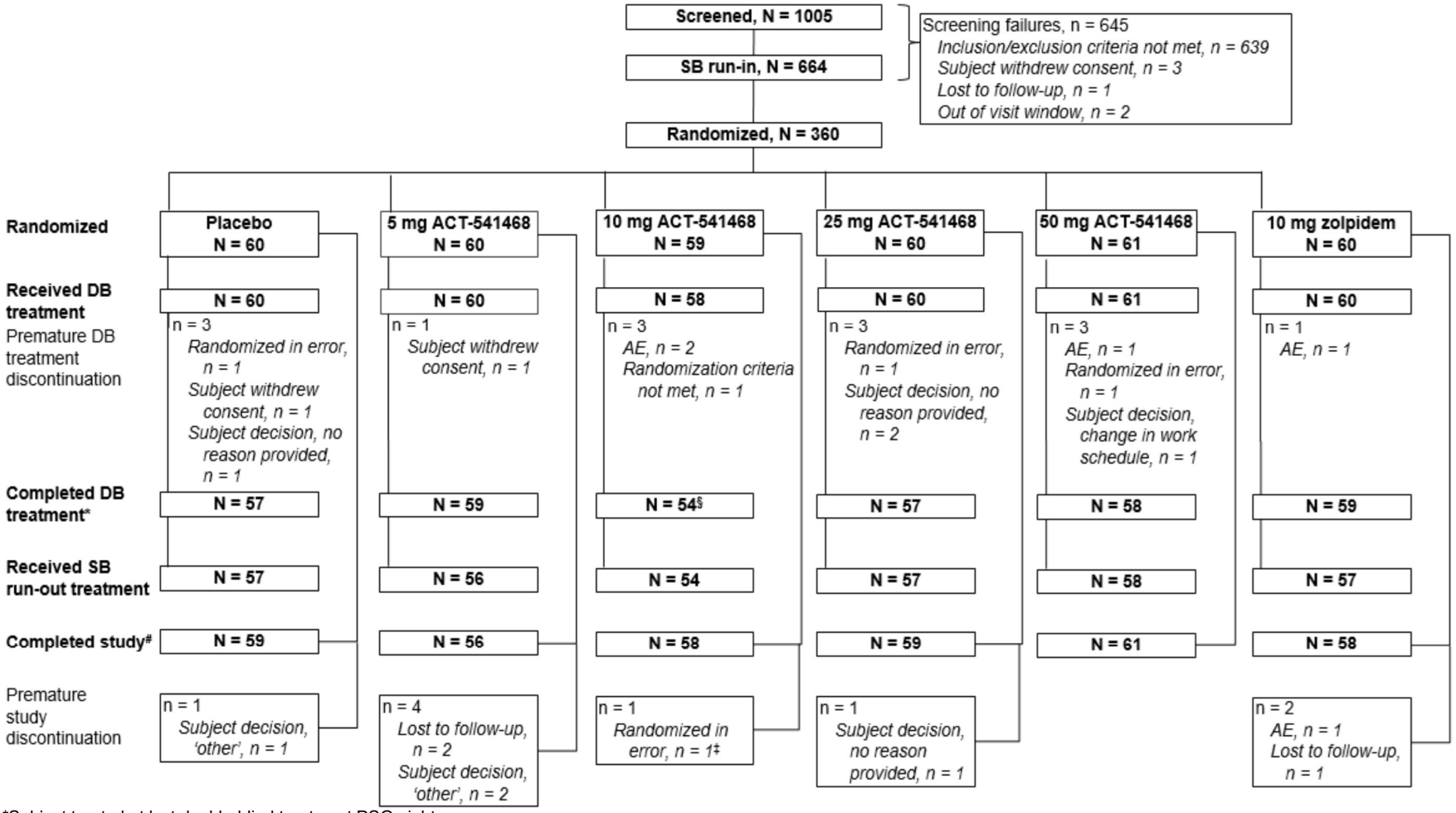
Descriptive statistics were provided for all exploratory variables either as frequency and percentage for categorical variables or using descriptive statistics for continuous variables. Occurrences of AEs and serious AEs (SAEs) and change in laboratory

markers, questionnaires, VAS, ECG, and vital signs were summarised using descriptive statistics.

1.2.1.7 Participant flow

Between October 4, 2016, and June 20, 2017, a total of 1,005 subjects were screened. Of 360 randomised subjects, 359 received at least 1 dose of double-blind study treatment (Figure 15). Most subjects (94%) completed the 30-day treatment period and received the single-blind placebo run-out treatment. Treatment discontinuation was not related to dose or treatment group.

Figure 15: Disposition of subjects in study 201



*Subject treated at last double-blind treatment PSG nights.
§1 subject did not return to site for the last double-blind treatment PSG nights.
#Subject competed the 30-day follow-up telephone call.
±Subject discontinued from the study prior to receiving DB treatment
DB=double-blind; SB=single-blind.

1.2.1.8 Baseline characteristics and demographics

The baseline characteristics and results of daridorexant 5 mg and 10 mg are excluded since these doses are not licensed in the UK and therefore not relevant for decision making.

Demographic characteristics of subjects were comparable across the treatment groups (Table 17). The majority of subjects were female (n = 230, 64%), and Caucasian (n = 321, 89%). The median age at screening was 44.7 years (range: 18–64 years), and mean BMI (± SD) was 25.17 ± 3.28 kg/m^2. Baseline sleep parameters were similar across the treatment groups (Table 17).

Table 17: Demographic characteristics, FAS

Characteristic	Placebo (N=60)	Daridorexant 25 mg (N=60)	Daridorexant 50 mg (N=61)	Zolpidem 10 mg (N=60)	Total (N=359)
Gender [n (%)]					
Male	22 (37)	21 (35)	22 (36)	22 (37)	129 (36)
Female	38 (63)	39 (65)	39 (64)	38 (63)	230 (64)
Mean age (SD)	45.7 (10.4)	46.4 (11.9)	45.0 (11.5)	45.0 (11.5)	44.7 (11.3)
Mean BMI (SD, kg/m^2)	25.4 (3.3)	24.9 (3.3)	24.5 (2.9)	26.0 (3.5)	25.2 (3.3)
Ethnicity (%)					
Caucasian	52 (87)	56 (93)	56 (92)	54 (90)	321 (89)
Black or African American	7 (12)	4 (7)	5 (8)	6 (10)	35 (10)
Asian	1 (2)	0 (0)	0 (0)	0 (0)	1 (0.3)
Native Hawaiian/other Pacific Islander	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)
Other	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)
Objective sleep parameters, mean min (SD)					
WASO	95.8 (34.7)	99.6 (40.9)	94.0 (31.9)	99.2 (38.8)	97.5 (38.6)
LPS	74.3 (39.3)	74.3 (43.5)	69.6 (30.2)	73.4 (34.8)	71.8 (39.3)
TST	317.7 (53.9)	313.7 (57.1)	323.3 (45.6)	315.8 (54.9)	318.45 (26.6)

Subjective sleep parameters, mean (SD)					
sWASO	79.4 (37.2)	77.6 (43.7)	78.1 (46.7)	76.2 (41.1)	80.4 (43.0)
sLSO	55.0 (22.6)	53.9 (24.5)	58.5 (30.5)	51.7 (24.9)	55.9 (27.1)
sTST	322.3 (55.1)	317.2 (54.9)	315.0 (48.7)	322.1 (52.6)	316.8 (52.6)
ISI©	21.3 (2.7)	21.3 (2.7)	21.1 (2.7)	21.3 (2.9)	21.2 (2.8)

BMI = body mass index; ISI = Insomnia Severity Index; LPS = latency to persistent sleep; M = male; SD = standard deviation; sLSO = subjective latency to sleep onset; sTST = subjective TST; sWASO = subjective WASO; TST = total sleep time; WASO = wake after sleep onset.
Note: 5 mg and 10 mg doses of daridorexant are excluded since they are not licensed in the UK and therefore not relevant for decision making.

1.2.1.9 Efficacy endpoints

Mean reductions (improvements) from baseline were observed for objective efficacy measures of WASO (primary endpoint) and LPS (secondary endpoint) in all treatment groups on days 1 and 2 (Table 18). These improvements were sustained on days 28 and 29 (Table 19). The mean reductions (improvements) in subjective sleep parameters of sWASO and sTST, while not statistically significant compared to placebo, were consistent with the objective measures of WASO and LPS. Zolpidem 10 mg was included as an active control in study 201; it improved sleep latency parameters (LPS and sLSO) but had no significant effect on WASO (Table 18 and Table 19).

TST increased from baseline on days 1 and 2 and showed sustained effects at days 15 and 16 and days 28 and 29 (Table 19). Sleep duration over the whole night and by quarter of the night increased with daridorexant treatment for all sleep stages. In terms of ISI© scores, the absolute change from baseline to day 30 was similar between placebo and daridorexant, and smaller than the active control arm of zolpidem 10 mg (Table 19). VAS data were consistent with the sleep quality subjectively experienced by subjects in the zolpidem group (Table 19). Sleep quality was judged to be better at week 4 than week 2 in all groups. All findings were generally observed at the first time point and sustained across the double-blind treatment period (Table 19); no differences in treatment effect were noted between male and female subjects. No effects of daridorexant were apparent for the remaining endpoints of self-reported sleep.

Table 18: Between treatment analysis for change from baseline in primary and secondary efficacy endpoints

Visit Treatment group [Outcome category]	n	LSM	SE	95% CL	Difference to placebo			
					LSM	SE	95% CL	p-value (two-sided)
Change from baseline to Days 1&2 in WASO (min), Modified FAS [Improvement of night-time symptoms of insomnia]								
Daridorexant 25 mg	60	-37.7	4.25	-46.0, -29.3	-16.2	5.95	-27.9, -4.5	0.007
Daridorexant 50 mg	61	-47.1	4.21	-55.3, -38.8	-25.6	5.92	-37.3, -13.9	<0.001
Placebo	60	-21.4	4.24	-29.8, -13.1	-	-	-	-
Zolpidem 10 mg*	60	-29.9	4.30	-38.4, -21.4	-8.5	5.97	-20.4, 3.3	0.155
Placebo*	60	-21.4	4.24	-29.8, -13.1	-	-	-	-
Change from baseline to Days 1&2 in LPS (min), FAS [Improvement of night-time symptoms of insomnia]								
Daridorexant 25 mg	60	-34.2	3.82	-41.7, -26.7	-14.1	5.34	-24.6, -3.6	0.009
Daridorexant 50 mg	61	-37.2	3.78	-44.6, -29.7	-17.0	5.33	-27.5, -6.6	0.002
Placebo	60	-20.1	3.81	-27.6, -12.6	-	-	-	-
Zolpidem 10 mg*	60	-44.0	4.72	-53.4, -34.6	-23.6	6.55	-36.5, -10.6	<0.001
Placebo*	60	-20.4	4.73	-29.8, -11.1	-	-	-	-
Change from baseline to Week 4 in sWASO (min), FAS [Improvement of night-time symptoms of insomnia]								
Daridorexant 25 mg	53	-32.9	4.11	-41.0, -24.8	-7.6	5.81	-19.1, 3.8	0.190
Daridorexant 50 mg	49	-36.8	4.27	-45.2, -28.4	-11.5	5.93	-23.2, 0.2	0.053
Placebo	50	-25.2	4.20	-33.5, -17.0	-	-	-	-
Zolpidem 10 mg*	48	-30.2	3.87	-37.9, -22.5	-6.2	5.31	-16.7, 4.4	0.248
Placebo*	50	-24.0	3.77	-31.5, -16.5	-	-	-	-
Change from baseline to Week 4 in sLSO (min), FAS [Changes in quality of sleep, depth of sleep, daytime alertness and daily ability to function]								
Daridorexant 25 mg	56	-17.9	2.99	-23.7, -12.0	-0.3	4.16	-8.5, 7.9	0.939
Daridorexant 50 mg	57	-23.5	2.95	-29.3, -17.7	-5.9	4.14	-14.1, 2.2	0.152
Placebo	57	-17.5	2.96	-23.4, -11.7	-	-	-	-

Visit Treatment group [Outcome category]	n	LSM	SE	95% CL	Difference to placebo			
					LSM	SE	95% CL	p-value (two-sided)
Zolpidem 10 mg*	59	-20.9	2.01	-24.9, -16.9	-5.5	2.83	-11.1, 0.1	0.055
Placebo*	57	-15.4	2.06	-19.5, -11.4	-	-	-	-

Note: 5 mg and 10 mg doses of daridorexant are excluded since they are not licensed in the UK and therefore, not relevant for decision making.
*Separate Analysis of covariance (ANCOVA) model
CL=confidence level; LSM=Least squares mean; LPS=Latency to persistent sleep; SE=standard error; sWASO=subjective wake after sleep onset; sLSO=subjective latency to sleep onset; WASO=wake after sleep onset.

Table 19: Between treatment analysis for change from baseline in other efficacy endpoints

Efficacy endpoints	Timepoint	Placebo, 0 mg, n=60	Daridorexant		Zolpidem 10 mg (n=60)
			25 mg (n=60)	50 mg (n=61)	
Objective sleep parameters, mean min (SD)					
WASO	Days 1 and 2	−21.4 (4.2)	−37.7 (4.3)	−47.1 (4.2)	−29.9 (4.3)
	Days 28 and 29	−33.8 (4.2)	−38.9 (4.2)	−48.0 (4.1)	−36.5 (4.4)
LPS	Days 1 and 2	−20.1 (3.8)	−34.2 (3.8)	−37.2 (3.8)	−44.0 (4.7)
	Days 28 and 29	−28.4 (4.3)	−37.9 (4.3)	−35.8 (4.3)	−45.1 (3.3)
TST	Days 1 and 2	38.2 (5.6)	69.7 (5.6)	81.4 (5.6)	68.8 (6.3)
	Days 28 and 29	60.0 (5.6)	75.1 (5.6)	81.6 (5.5)	78.0 (5.1)
Subjective sleep parameters					
sTST, mean min (SD)	Week 2	41.4 (45.0)	48.9 (54.7)	57.0 (41.9)	44.7 (36.0)
	Week 4	52.7 (50.3)	56.2 (51.5)	77.4 (58.7)	53.2 (35.5)
ISI©, mean (SD)	Day 30	−7.7 (5.4)	−7.9 (5.9)	−8.5 (6.3)	−9.0 (5.0)
Self-reported VAS scores, mean mm (SD)					
Sleep quality	Week 2	12.8 (14.7)	16.1 (17.2)	14.3 (14.6)	15.4 (13.7)
	Week 4	19.0 (18.0)	21.3 (19.2)	20.9 (17.7)	19.3 (15.6)
Morning sleepiness	Week 2	11.1 (13.5)	12.5 (15.7)	11.9 (13.3)	12.3 (13.1)
	Week 4	17.4 (16.7)	17.4 (18.1)	17.0 (17.6)	16.2 (15.8)
Daytime alertness	Week 2	10.2 (14.7)	11.2 (15.2)	11.5 (12.6)	12.7 (17.0)
	Week 4	15.7 (17.9)	17.0 (19.4)	16.0 (15.9)	17.3 (17.9)

Efficacy endpoints	Timepoint	Placebo, 0 mg, n=60	Daridorexant		Zolpidem 10 mg (n=60)
			25 mg (n=60)	50 mg (n=61)	
Daytime ability to function	Week 2	10.4 (15.2)	11.2 (15.0)	12.4 (14.0)	13.0 (15.9)
	Week 4	16.2 (17.7)	16.1 (19.2)	17.1 (16.6)	16.6 (17.3)
Sleep efficiency					
%, mean (SD)	Days 1 & 2	8.6 (13.1)	15.3 (9.8)	16.5 (8.8)	14.9 (9.9)
	Days 28 & 29	12.5 (9.6)	15.9 (9.6)	16.8 (11.1)	16.5 (11.1)

Data are least squares mean (standard error of the mean), unless otherwise specified.
ISI = Insomnia Severity Index; LPS = latency to persistent sleep; SD = standard deviation; sLSO = subjective latency to sleep onset; sTST = subjective TST; sWASO = subjective WASO; TST = total sleep time; VAS = visual analogue scale; WASO = wake after sleep onset.
Note: Note: 5 mg and 10 mg doses of daridorexant are excluded since they are not licensed in the UK and therefore, not relevant for decision making.

1.2.1.10 Safety endpoints

Overall, daridorexant demonstrated a favourable safety and tolerability profile. The incidence of TEAEs was 38%, and 34% in subjects treated with 25, and 50 mg daridorexant, respectively, compared with 30% in subjects on placebo, and 40% in the 10 mg zolpidem-treated group (Table 20). The most frequent TEAEs in subjects treated with daridorexant were headache (up to 10%), somnolence (up to 7%), diarrhoea (up to 5%), and fatigue (up to 5%) (Table 20). At least 1 treatment-emergent SAE was reported for 3 subjects, but none was considered to be related to treatment (one subject on daridorexant 50 mg had angioedema, one subject on daridorexant 10 mg reported myocardial infarction, and another on daridorexant 10 mg had two SAEs: accident at work and craniocerebral injury).

TEAEs leading to premature discontinuation of double-blind treatment were reported for 2 subjects: angioedema (1 subject on 50mg daridorexant); and anxiety (1 subject on 10mg zolpidem) (Table 20). No deaths were reported.

Table 20: TEAEs by treatment group

Treatment-emergent adverse event	Placebo, 0mg, n=60	Daridorexant		Zolpidem, 10mg, n=60
		25mg, n=60	50mg, n=61	
Subjects with at least 1 TEAE	18 (30)	23 (38)	21 (34)	24 (40)
Subjects with at least 1 serious TEAE	0	0	1 (1.6)	0
Angioedema	0	0	1 (1.6)	0
Subjects with at least 1 TEAE leading to treatment discontinuation	0	0	1 (1.6)	1 (1.7)
Angioedema	0	0	1 (1.6)	0
Anxiety	0	0	0	1 (1.7)
TEAE occurring in >1 subject in any group				
Abdominal pain upper	1 (1.7)	0	1 (1.6)	4 (6.7)
Alanine aminotransferase increased	0	2 (3.3)	1 (1.6)	0
Blood calcium decreased	2 (3.3)	0	0	0
Blood creatine phosphokinase increased	1 (1.7)	1 (1.7)	1 (1.6)	0
Diarrhoea	2 (3.3)	3 (5.0)	0	1 (1.7)
Dizziness	1 (1.7)	0	0	4 (6.7)
Fatigue	2 (3.3)	3 (5.0)	0	1 (1.7)

Treatment-emergent adverse event	Placebo, 0mg, n=60	Daridorexant		Zolpidem, 10mg, n=60
		25mg, n=60	50mg, n=61	
Gait disturbance	1 (1.7)	0	0	2 (3.3)
Gamma-glutamyl transferase increased	0	0	2 (3.3)	0
Headache	1 (1.7)	5 (8.3)	5 (8.2)	6 (10.0)
Nasopharyngitis	4 (6.7)	0	2 (3.3)	5 (8.3)
Nausea	0	2 (3.3)	1 (1.6)	4 (6.7)
Pruritus	0	0	2 (3.3)	0
Somnolence	3 (5.0)	4 (6.7)	4 (6.6)	3 (5.0)

TEAE = treatment-emergent adverse event.

No drug-related effects were observed on blood pressure, body weight, ECG, or clinical laboratory assessments. There was no evidence of TEAEs suggesting drug abuse, rebound insomnia, or drug withdrawal syndrome. The assessment of morning sleepiness with VAS showed no difference between any dose of daridorexant and placebo in terms of sleepiness the following day. The placebo run-out period included as part of the study design assessed the potential for rebound insomnia or occurrence of drug withdrawal syndrome; however, no such effects were observed with daridorexant on subjective or objective parameters during the withdrawal period. Mean and median changes in WASO/LPS showed a academic / commercial in confidence information removed in all dose groups, however for WASO the academic / commercial in confidence information removed on the higher doses of daridorexant (Table 21). Mean and median changes in TST academic / commercial in confidence information removed in all dose groups (Table 21).

Table 21: Change in WASO, TST and LPS from worst baseline value to first value after double-blind treatment, Withdrawal set

Treatment group	Change from worst baseline value to first value after double-blind treatment (V6)	
	n	Mean (SD), min
WASO		
Daridorexant 25 mg	academic / commercial in confidence information removed	
Daridorexant 50 mg		
Zolpidem 10 mg		
Placebo		

Treatment group	Change from worst baseline value to first value after double-blind treatment (V6)	
	n	Mean (SD), min
TST		
Daridorexant 25 mg	academic / commercial in confidence information removed	
Daridorexant 50 mg		
Zolpidem 10 mg		
Placebo		
LPS		
Daridorexant 25 mg	academic / commercial in confidence information removed	
Daridorexant 50 mg		
Zolpidem 10 mg		
Placebo		

Min=Minute; SD=Standard deviation.

1.3 Interpretation of clinical effectiveness and safety evidence

The results from study 302 and study 201 demonstrated that, unlike daridorexant 50 mg which demonstrated consistent efficacy across night-time and daytime variables, treatment with daridorexant 25 mg in patients with long-term insomnia led to improvements only in some of the night-time variables. The results for the 25 mg dose also lacked consistency across studies.

- In study 302, treatment with daridorexant 25 mg led to a clinically and statistically significant reduction (improvement) from baseline for the primary endpoint of WASO (least squares mean [LSM] difference: -11.62 minutes [p=0.0001] and -10.25 minutes [p=0.0028], respectively) and the secondary endpoint of sTST (LSM difference: 16.13 minutes [p<0.0001] and 19.06 minutes [p<0.0001], respectively) at months 1 and 3, compared to placebo. While there were numerical improvements in the primary endpoint of LPS (LSM difference: -6.45 minutes [p=0.0303] and -9.01 minutes [p=0.0053], respectively) and secondary endpoint of IDSIQ sleepiness domain (LSM difference: -0.75 [p=0.0733] and -1.25 [p=0.0120], respectively) compared to placebo, these differences were not statistically significant at months 1 and 3.
- In study 201, treatment with daridorexant 25 mg led to a reduction (improvement) from baseline for the primary endpoint of WASO and secondary endpoint of LPS were observed on days 1 and 2 (LSM difference: WASO -16.2 minutes [p=0.007] and LPS -14.1 minutes [p=0.009]), compared to placebo. There were numerical improvements

in the subjective secondary endpoints of sWASO (LSM difference: -7.6 minutes [p=0.190]) and sLSO (LSM difference: -0.3 minutes [p=0.939]) compared to placebo at week 4. However, as presented in the CS, study 201 was a dose-response study, and therefore these endpoints were not statistically powered to draw conclusions on the efficacy of daridorexant 25 mg.

The findings are consistent with those of the daridorexant 25 mg arm in study 301 (see clinical study report of study 301 in the evidence package of the CS), indicating that, unlike daridorexant 50 mg which demonstrated efficacy across night-time and daytime variables, the 25 mg dose demonstrated efficacy only on certain sleep variables, but not daytime functioning. In the ACD, the clinical experts emphasised the greater importance of subjective improvements in sleep quality, sleep quantity and daytime symptoms over measures such as WASO and LPS (see section 3.8). This aligns with the company's view, that a major unmet medical need in long-term insomnia is impaired daytime function, which existing pharmacotherapies do not adequately address (see section B.2.15 of CS). While daridorexant 25 mg can improve some sleep variables, the magnitude of improvement is less than that of the 50 mg dose and lacks clinical relevance, as supported by the evidence presented in section 1.2.1 Study 201 and the dose-response analysis in section 1.2 Additional analyses of dose-response across all studies. This is mentioned in the EPAR (section 2.6.6), which states that “With regard to the assumed difference compared to placebo in the mean change from baseline for WASO (-15 min) and LPS (-15 min), …the clinical relevance of the 25 mg dose is questionable.”, and “With regard to the assumed difference compared to placebo in the mean change from baseline for sTST (-20 min), …the clinical relevance of the 25 mg dose is questionable”. Moreover, the benefit of the 25 mg dose on daytime functioning was not shown in both study 302 and study 301.

The analysis of ISI© scores in study 302 showed greater reductions from baseline for daridorexant 25 mg compared to placebo at both month 1 and month 3. However, the magnitude of the between treatment differences in ISI© scores was less with the 25 mg dose (-1.5) than with the 50 mg dose (-1.8) at month 3. This finding is consistent with the 25 mg arm of study 301, as well as in the extension study 303, and supports the

company's view that daridorexant 25 mg is not as efficacious as the 50 mg dose in improving subjective sleep quality, sleep quantity and daytime symptoms.

In terms of safety, daridorexant 25 mg was well tolerated and revealed no safety concern at either dose, neither in the adult nor the elderly population. There were no safety signals, manifesting as TEAEs, or any indications of a dose-related effect on safety. The relatively short half-life of daridorexant may have also resulted in fewer residual effects and improved quality of sleep that may contribute to absence of next-morning residual effects. In addition, no signs of rebound insomnia or withdrawal upon treatment discontinuation were observed in the study. The findings are consistent with the 25 mg arms of study 301 and 303, with no prominent dose-response adverse effects when compared with the 50 mg dose.

From the ACD, there is some discussion around the possibility of clinicians starting patients on 25 mg and then increasing this to 50 mg (sections 3.16 and 3.18). However, given the clinical data presented for the 25 mg dose in study 302 and 201, it is anticipated that most patients will require the 50 mg dose, unless they meet the criteria specified in the SmPC – moderate liver impairment or on a concomitant moderate CYP3A4 inhibitor. Therefore, any recommendation for general use of the 25 mg dose, based on anecdotal evidence that GPs would regard this as an initiating dose and titrating upwards to 50 mg based on response, is not evidence based and contrary to the SmPC of daridorexant.

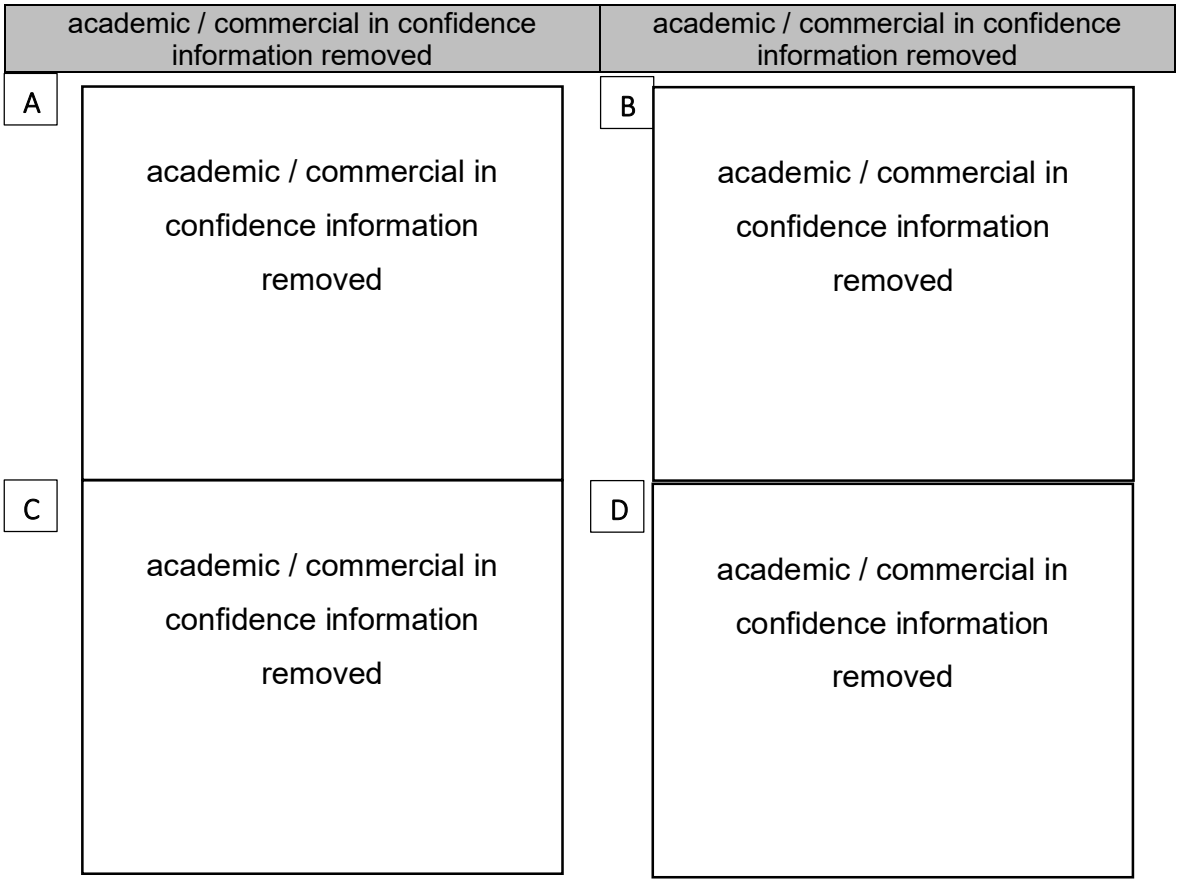
1.2 Additional analyses of dose-response across all studies

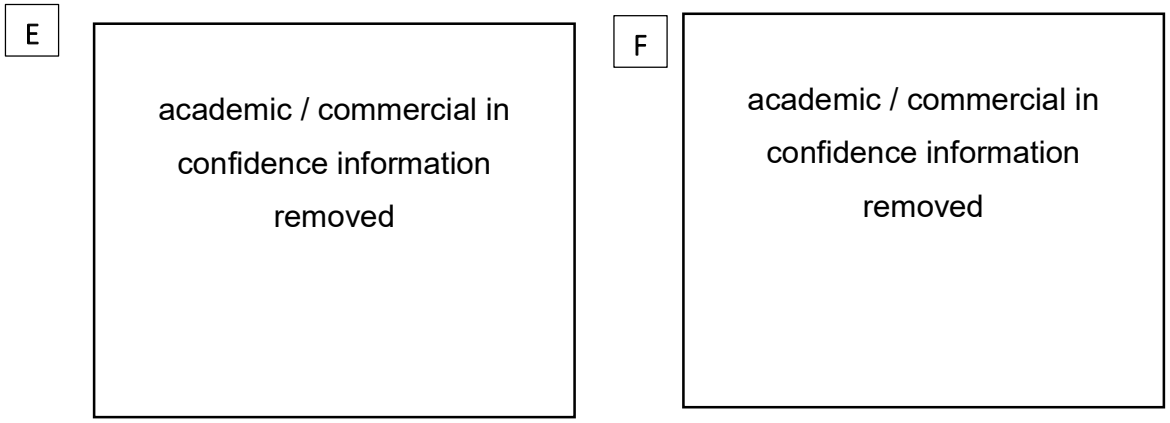
1.2.1 Analyses of study 301, 302 and 201 demonstrating dose-response and superiority of daridorexant 50 mg

1.2.1.1 Night-time variables (WASO, LPS and sTST)

We conducted a dose-response meta-analysis based on the comparable population and endpoints of study 301 and 302. Study 201, conducted in similar patients, with the same sleep endpoints, and 4 dose levels of daridorexant (i.e., 5, 10, 25 and 50 mg) was also included in this meta-analysis. Two approaches were utilised. In the first approach, descriptive statistics with observed values are graphically represented across studies and doses (Figure 16A, C and E). The second approach involved a more sophisticated statistical modelling (Crippa and Orsini. BMC Medical Research Methodology (2016) 16:91) that estimated the dose-response taking the totality of the data from the three studies into account (Figure 16B, D and F).[16] The dose-response was academic / commercial in confidence information removed.

Figure 16: Dose-response analysis of daridorexant after 1 month of treatment – night-time variables in study 301, 302 and 201



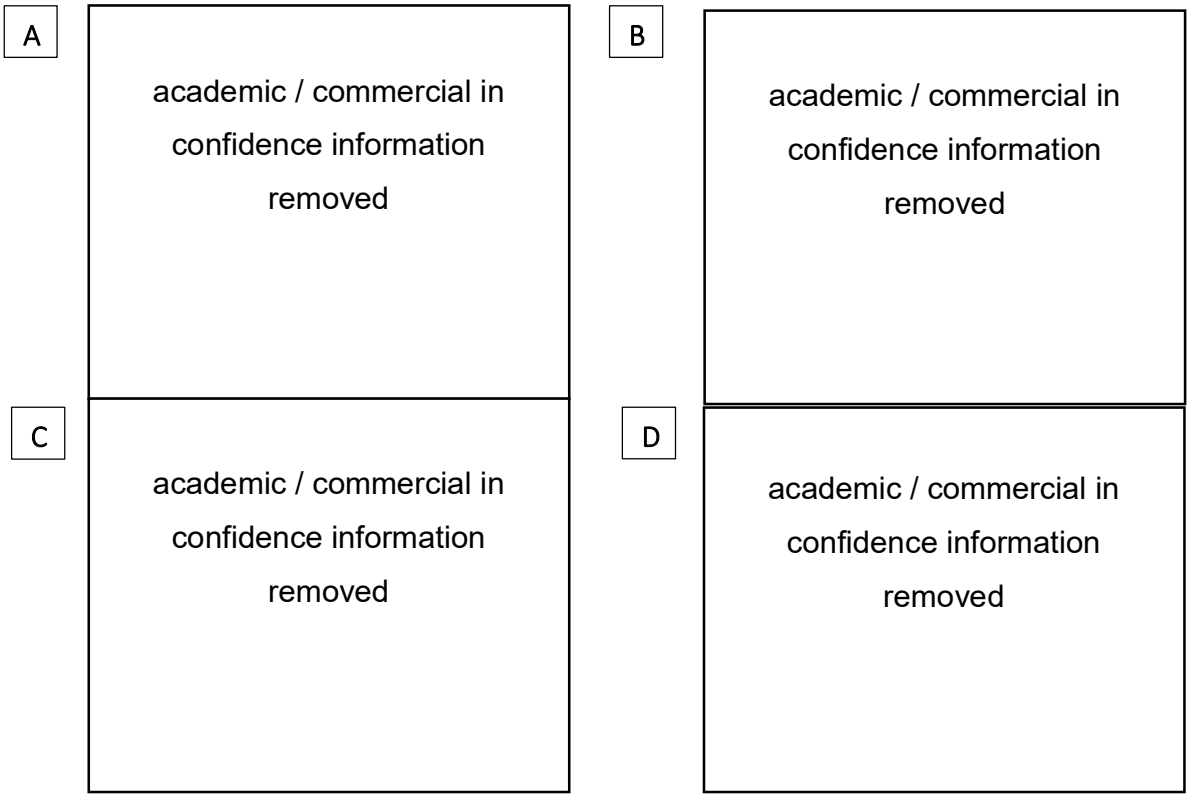


academic / commercial in confidence information removed

1.2.1.2 Daytime function variables (IDSIQ)

For daytime symptoms assessed using IDSIQ, only study 301 and 302 could be included as IDSIQ was not an endpoint of study 201. The results of the meta-analysis for the sleepiness domain and other scores (i.e., IDSIQ total, alert/cognition and mood scores) showed a academic / commercial in confidence information removed.

Figure 17: Dose-response analysis of daridorexant from baseline to 1 month – IDSIQ in study 301 and 302



academic / commercial in confidence information removed

1.2.1.3 Interpretation of dose-response analysis

Based on the above findings, it can be concluded that academic / commercial in confidence information removed of long-term insomnia. academic / commercial in confidence information removed. However, academic / commercial in confidence information removed, supporting the final choice of the 50 mg dose, which was then approved as such in the regulatory submissions. As described in the EPAR, a small increase in AEs were observed for daridorexant compared to placebo, regardless of the dose. Daridorexant reduced morning sleepiness as assessed by VAS which contributed to reduced tendency for next-morning residual effects. This could be further attributed to improved sleep quality and other aspects of sleep improvement (depth of sleep, duration of sleep, sleep architecture). Furthermore, irrespective of dosage, no evidence of withdrawal syndrome or rebound insomnia were observed after discontinuation of daridorexant. The advantage of the 50 mg dose is well recognised by the posology recommendation in the SmPC, which limits the place of 25 mg dose to subjects with moderate liver impairment or concurrently treated with moderate CYP3A4 inhibitors.

In conclusion, based on the totality of the efficacy results that showed academic / commercial in confidence information removed and safety results academic / commercial in confidence information removed, the 50 mg dose of daridorexant is the most appropriate dose. There is less benefit and no safety advantage of a lower dose which is reserved for patients with moderate liver impairment or using moderate CYP3A4 inhibitors. Consistent with the clinical evidence for daridorexant 25 mg presented in section 1.1 Treatment effect of daridorexant 25 mg, there is no clinical rationale to start treating with a lower dose of 25 mg and no evidence to support an up-titration to 50 mg.

1.3 Cost-effectiveness analysis of daridorexant 25 mg

The cost-effectiveness analysis of daridorexant 25 mg was assessed using the same economic model structure and underlying assumptions as for daridorexant 50 mg, except for the trial data as detailed below

1.3.1 Key model parameters

1.3.1.1 Efficacy (ISI©)

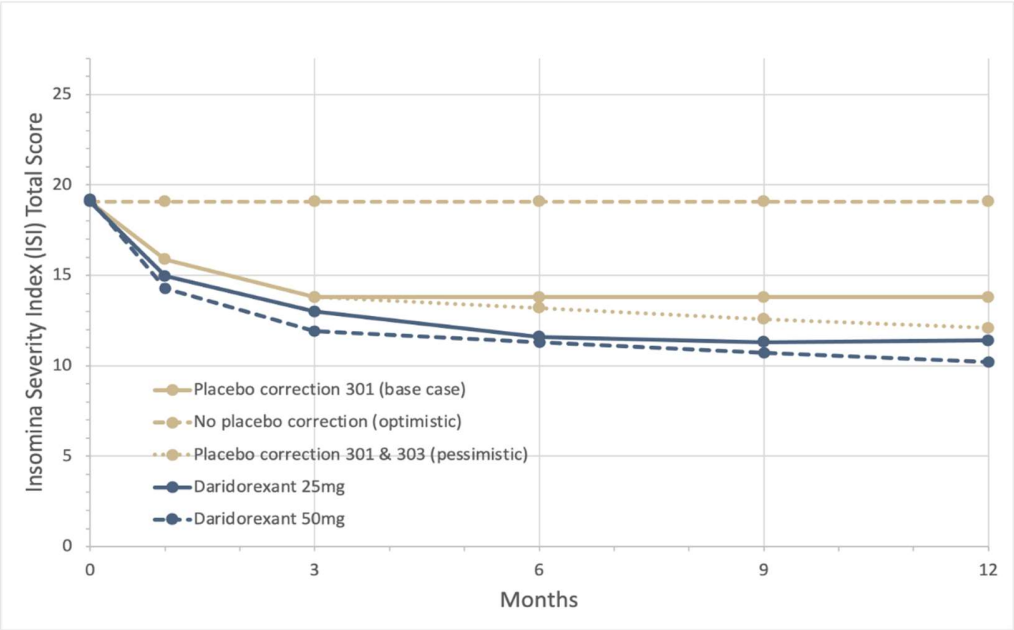
The ISI© data from study 301 (N=301) was used to model the treatment effect of daridorexant 25 mg over the first 3 months. In a scenario analysis, we also assessed the cost-effectiveness of daridorexant 25 mg using the ISI© data of the daridorexant 25 mg arm (N=309) from study 302. ISI© data from study 301 were preferred in base case analysis because both daridorexant 25 mg and 50 mg doses were investigated, while daridorexant 10 mg and 25 mg were investigated in study 302. Therefore, study 301 allowed for more appropriate comparison between the two doses.

ISI© data in the first 3 months of daridorexant treatment was modelled using seemingly unrelated regressions. These equations allowed for the usual estimation of treatment effect that adjusted for both baseline ISI© and placebo, while further allowing the correlation between month 1 and month 3 observations to be captured for use in the probabilistic sensitivity analysis (PSA).

We used the ISI© data of daridorexant 25 mg arm (N=270) from the 40-week extension study 303 to model treatment effect beyond 3 months to up to a year. It is worth noting that daridorexant 25 mg arm in study 303 re-randomised patients from study 301 and study 302 already treated with daridorexant 25 mg and had decided to continue in the extension study. This led to a larger sample size than that of the daridorexant 50 mg arm (N=137). After 3 months, we used the mean (SD) post-baseline ISI© data without any baseline or placebo adjustment.

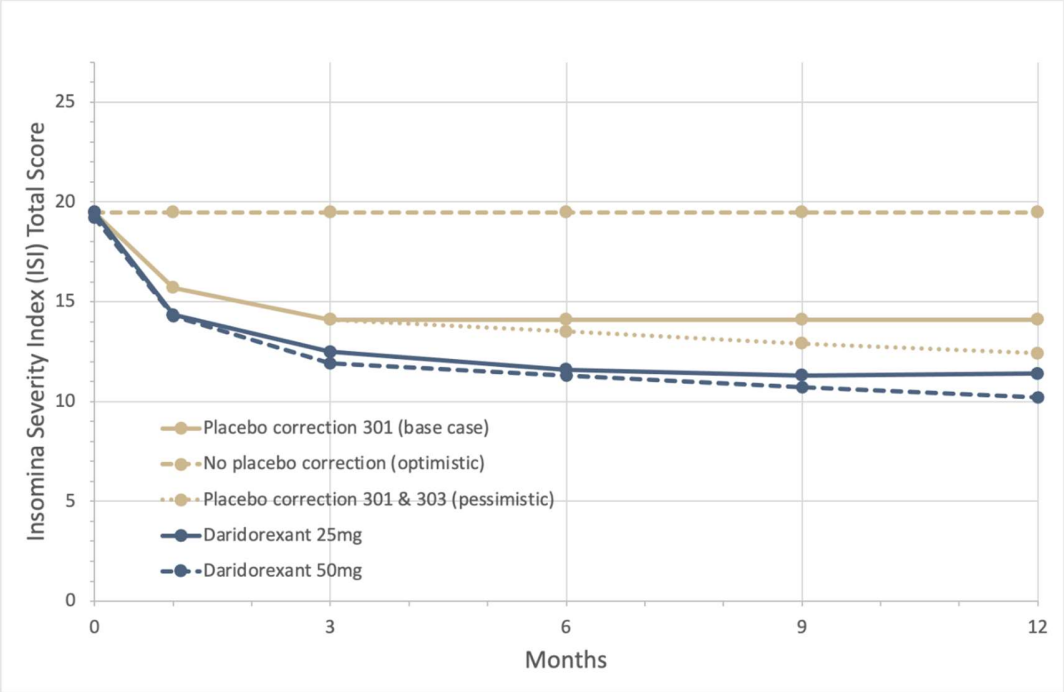
The mean ISI© of daridorexant 25 mg across all time points from study 301 (month 1 and 3) and study 303 (month 6, 9 and 12) are depicted in Figure 18, alongside daridorexant 50 mg. Figure 19 illustrates the modelled ISI© trajectory using data from study 301, 302 and 303. Both trajectories show that the ISI© treatment effect of daridorexant 50 mg are lower than that of daridorexant 25 mg across all modelled time points. This is consistent with the better efficacy of daridorexant 50 mg compared to 25 mg as presented in section 1.2 Additional analyses of dose-response across all studies.

Figure 18. Modelled trajectory of ISI© from study 301 and 303



Note: in base case, we assumed a placebo effect and correction over the first 3 months and then a constant placebo effect (see solid golden line). The base case assumption relies on selective attrition phenomenon. In the optimistic scenario, we assumed no placebo effect and correction over the 12 months period given the "no treatment" comparator (see long dash golden line). Finally, in the pessimistic scenario, we assumed a full placebo effect and correction over the 12 months period (see dotted golden line).

Figure 19. Modelled trajectory of ISI© from study 301 (daridorexant 50 mg), study 302 (daridorexant 25 mg) and 303



Note: in base case, we assumed a placebo effect and correction over the first 3 months and then a constant placebo effect (see solid golden line). The base case assumption relies on selective attrition phenomenon. In the optimistic scenario, we assumed no placebo

effect and correction over the 12 months period given the "no treatment" comparator (see long dash golden line). Finally, in the pessimistic scenario, we assumed a full placebo effect and correction over the 12 months period (see dotted golden line).

1.3.1.2 Safety

All TEAEs occurring >2% in any treatment arm were included in the model. The two most common AEs are nasopharyngitis and headache. For nasopharyngitis we made the conservative assumption that this could be as bad as influenza using a previously published pooled estimate of the QALY impact of influenza being 0.01 QALYs per episode.[4] Similarly, for headache we used a conservative estimate that this could be as bad as migraine which has been estimated to reduce HRQoL (as measured by the EQ-5D) by 0.13.[5] We further assumed that this effect would resolve after four days leading to a QALY impact of 0.0014. For all infections (upper respiratory tract infection, urinary tract infection, tonsillitis & pneumonia), we used the influenza estimate. Similarly, for other symptom-related AEs (fatigue, dizziness, nausea, somnolence, cough, back pain, myalgia, sinusitis), we assumed the same QALY deficit as for headache. For accidental overdose and hepatic enzyme increase, we assumed no HRQoL/QALY impact since these events were clinically defined. The majority of falls recorded did not result in injury, but approximately 20% resulted in fracture for which we assumed a 0.04 HRQoL impact based on a wrist fracture in the literature.[6]

For health service costs, we assumed that all AEs would require a GP visit except for the 20% of falls that resulted in fracture which would require an emergency department visit. For infections, we assumed a £6.21 prescription of antibiotics would be also required based on the average cost of an antibiotic prescription in the ONS Prescription Cost Analysis database.[7]

The cost and QALY impacts of the abovementioned AEs are summarised in Table 22.

Table 22: Impact of adverse events on QALY and cost

	Impact estimates				
Adverse event	**QoL impact**	**Duration (days)**	**QALY**	**Cost***	**Source**
Nasopharyngitis			0.0100	£39.23	Jit et al 2010 (influenza)
Headache	0.13	4	0.0014	£39.23	Domitrz et al 2022 (migraine)
Accidental overdose	0	1	0.0000	£39.23	Assumption

	Impact estimates				
Adverse event	**QoL impact**	**Duration (days)**	**QALY**	**Cost***	**Source**
Fatigue	0.13	4	0.0014	£39.23	Assumption (as for headache)
Dizziness	0.13	4	0.0014	£39.23	Assumption (as for headache)
Nausea	0.13	4	0.0014	£43.23	Assumption (as for headache)
Somnolence	0.13	4	0.0014	£39.23	Assumption (as for headache)
Fall	0.04	90	0.0020	£68.31	Si et al 2014 (wrist fracture) x 20%
URTI	1	1	0.0100	£45.44	Assumption (as for influenza)
Cough	0.13	4	0.0014	£39.23	Assumption (as for headache)
Pneumonia			0.0100	£39.23	Assumption (as for influenza)
Back pain	0.13	4	0.0014	£39.23	Assumption (as for headache)
Tonsilitis			0.0100	£45.44	Assumption (as for influenza)
UTI			0.0100	£45.44	Assumption (as for influenza)
Myalgia	0.13	4	0.0014	£39.23	Assumption (as for headache)
Sinusitis	0.13	4	0.0014	£39.23	Assumption (as for headache)
Hepatic enzyme increased	0	1	0.0000	£39.23	Assumption

QALY=Quality-adjusted life years; QoL=Quality of life.

1.3.2 Other model parameters

The same model parameters from the cost-effectiveness analysis of daridorexant 50 mg were used:

- The cost of daridorexant is assumed to be £2.12 per day;
- Use of the discontinuation rates observed in the clinical trial programme;
- Use of conservative half cycle correction for utilities, costs (direct and indirect) and discontinuation rates between time points; but not for the treatment cost (i.e., the cost of treatment is applied at the start of the period for the full period, whether or not a patient discontinued);
- Use of a novel mapping algorithm based on the NHWS dataset to map ISI© data from study 301 and study 303 to EQ-5D values.[17] This new mapping, unlike Gu et al. (2014), used a larger sample size; included other geographies like France, Germany,

Italy, Spain, and the United-Kingdom in addition to the US; and adjusted for a large list of potential confounders such as age, gender, and comorbidities.[18] The chosen mapping algorithm was the adjusted limited dependent variable mixture model slightly outperforming the generalised linear model (GLM) with a gamma distribution family and log link;

- Use of several mapping algorithms, GLM models with a negative binomial distribution family and a log link, based on from the NHWS dataset to map ISI© data from study 301 and study 303 to the health care resource use (i.e., general practitioner [GP] visit, emergency department visit and hospitalisation); and productivity losses (i.e., absenteeism and presenteeism).

In addition, we have included additional parameters/scenarios as requested by the NICE committee:

- The treatment-related adverse event costs and QALYs (section 3.22 of ACD),
- All the relevant costs to the NHS and personal social services (section 3.24 of ACD),
- The base case scenario around the improvement in ISI© in the placebo group of study 303
    - The base case assumption assumed that the placebo effect in the "no treatment" patients would reach its peak at month 3, and that for 303 study, the ISI© would be the same than the one achieved by the end of study 301. This base case assumption is based on the selective attrition argument described in section 2. Selective attrition in study 303.

1.3.3 Cost-effectiveness analyses

We performed two analyses to assess daridorexant 25 mg cost-effectiveness as listed in Table 23. The base case analysis assessed daridorexant 25 mg cost-effectiveness over 12-months. We also assessed daridorexant 25 mg cost-effectiveness using the ISI©, SDS© and TEAE data from study 302.

Table 23: Scenario analyses performed for the cost-effectiveness analysis of daridorexant 25 mg

Scenario	Description
Base case	Time horizon: 12 months Trial data: study 301 and 303 Placebo adjustment: study 301 only
302 data	Time horizon: 12 months Trial data: study 302 and 303 Placebo adjustment: study 301 only

Sensitivity analyses (PSA) were performed only for the base case scenario. Nonetheless, the user can perform sensitivity analyses using the Microsoft® Excel model that accompanies this submission.

1.3.4 Results

1.3.4.1 Base case

The base case results of the cost-effectiveness of daridorexant 25 mg compared to no treatment are presented in Table 24. The persistence adjusted ICER (95% CI) was £37,881 (£27,811 to £ 55,541).

Since the one-year cost-effectiveness is above the thresholds of £20,000 per QALY and £30,000 per QALY in both scenarios, we see a negative net-health-benefit at the lower threshold and at the higher threshold.

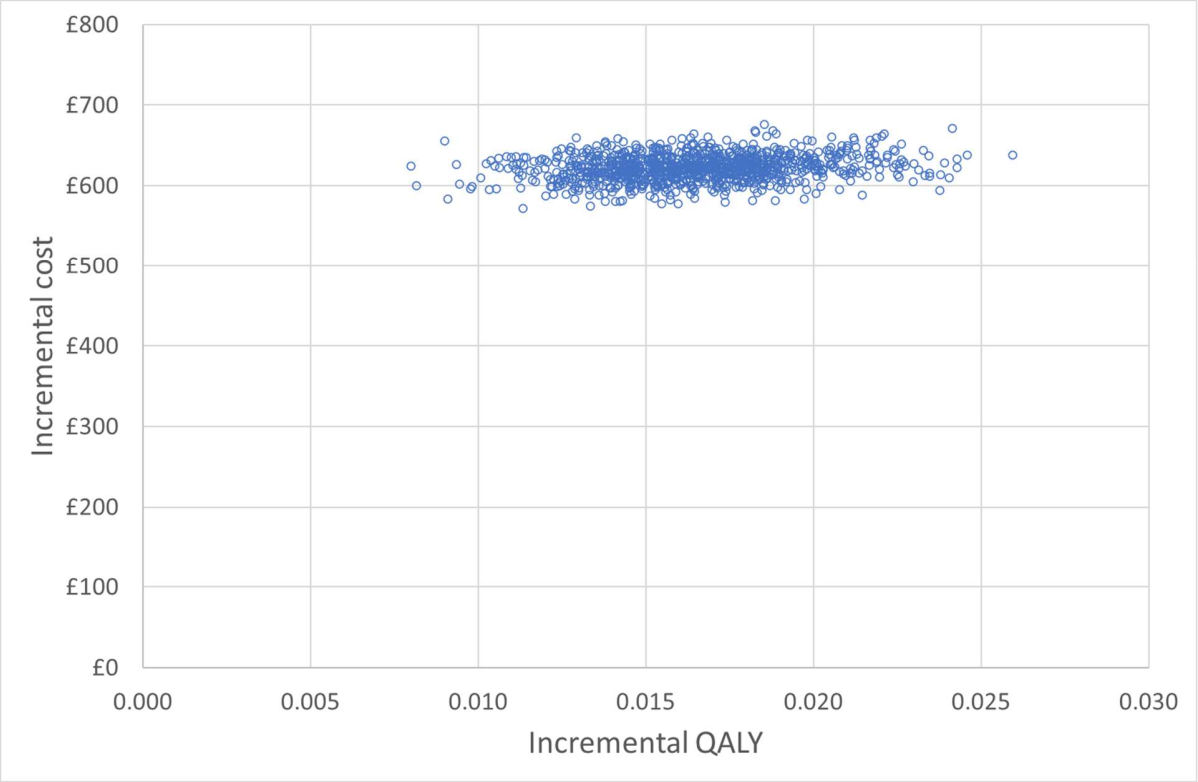
Table 24: Base case cost-effectiveness results for the 12-month model

Technology	Cost	QALY
No Treatment	£623	0.688
Daridorexant 25 mg	£1'390	0.711
Increment	£754	0.024
ICER	£31,991	
Increment*	£622	0.017
ICER* (95% CI)	£37,881 (£27,811 to £ 55,541)**	
NHB (20k)* (95% CI)	-0.1079 (-0.116to -0.100)**	
NHB (30k)* (95% CI)	-0.0665 (-0.073 to -0.060)**	

*Adjusted for persistence; **95% uncertainty intervals from the probabilistic analysis

In Figure 20, the ICER is influenced by the QALY dimension mapped to the ISI© data.

Figure 20: Probabilistic results for the base case cost-effectiveness analysis presented on the cost-effectiveness plane



1.3.4.2 Scenario analysis

1.3.4.2.1 302 data scenario

The 302 data scenario results of the cost-effectiveness model are presented in Table 25. In this scenario, the better efficacy data of daridorexant 25 mg in study 302 led to a lower persistence adjusted ICER (95% CI) of £29'188 (£23’654 to £38’103) (Table 25).

Table 25: 302 data scenario cost-effectiveness results for the 12-month model

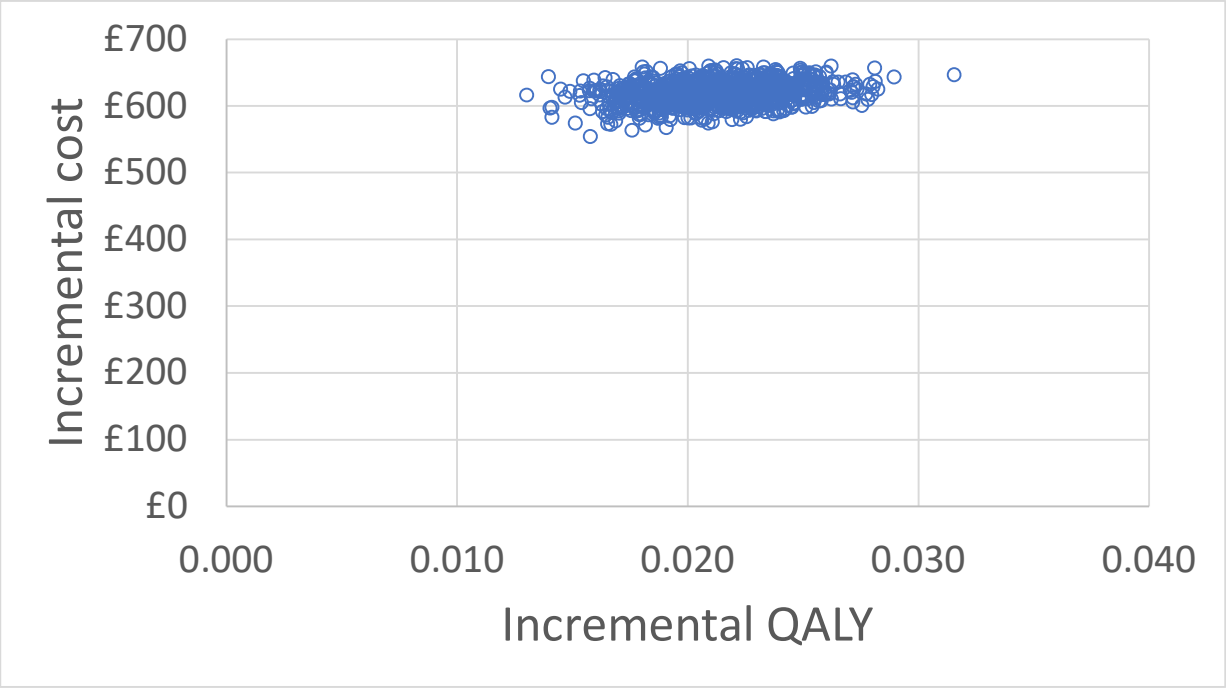
Technology	Cost	QALY
No Treatment	£626	0.684
Daridorexant 25 mg	£1'390	0.714
Increment	£749	0.0296
ICER	£25,305	
Increment*	£619	0.0212
ICER* (95% CI)	£29'188 (£23’654 to £38’103)	

NHB (20k)* (95% CI)	-0.1026 (-0.110 to -0.095)
NHB (30k)* (95% CI)	-0.0613 (-0.067 to -0.055)

*Adjusted for persistence; **95% uncertainty intervals from the probabilistic analysis

In Figure 21, the ICER is influenced by the QALY dimension mapped to the ISI© data.

Figure 21: Probabilistic results for the base case cost-effectiveness analysis presented on the cost-effectiveness plane



Appendix 2 – SDS pre-submission manuscript

Exploratory analysis of the effect of daridorexant on productivity

1. Data source

Academic / commercial in confidence information removed

2. Results

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Figure 22. Academic / commercial in confidence information removed

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Figure 24. *academic / commercial in confidence information removed*

3. academic / commercial in confidence information removed

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Reference (for the pre-submission manuscript)

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NICE National Institute for Health and Care Excellence

Daridorexant for treating insomnia [ID3774]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 27 April 2023. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[Insert organisation name]

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Daridorexant for treating insomnia [ID3774]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 27 April 2023. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	As previously stated - funding to attend an educational event hosted by Idorsia in 2022. Attendance at day case conferences at the Sleep medicine section of the Royal Society of Medicine where Idorsia was one of four sponsors but did not influence academic content.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Within section 3.5 - page 6 of 26 and later on page 7 - "The clinical experts explained that there are criteria for diagnosis of long-term insomnia" I feel this section does not emphasise how common other sleep disorders (sleep apnoea, restless legs) are as mimics, reflecting the difficulty faced by a GP. This is a concern when prescribing a longer rather than shorter term medication, for example leaving someone with undiagnosed obstructive sleep apnoea for a prolonged period.
2	page 8 of 26 - "They also explained that other treatments for insomnia work in a different way to daridorexant, in that they help with falling asleep. Daridorexant, in comparison, also helps with staying asleep." Dadidorexant has a long half life and therefore has less effect on sleep onset but more effect on sleep maintenance (staying asleep). Other sleeping tablets are shown to help both sleep onset and maintenance eg temazepam
3	3.11 The clinical experts commented that the safety effect profile of daridorexant indicates that it is better tolerated than other medicines used for treating insomnia. Melatonin is very safe with no potential for dependence or tolerance and would be considered equally safe with very few adverse

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Daridorexant for treating insomnia [ID3774]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 27 April 2023. Please submit via NICE Docs.

	events. I agree that other tablets have a higher side effect profile and more adverse events reported.
4	Lack of access to CBTi is quoted throughout the document - however there are freely available digital CBTi therapies (https://sleepful.me) as well as the recent NICE recommendation for Sleepio and a number of IAPT services that provide this already as a group therapy and an understanding of insomnia is within the IAPT curriculum. I accept that patients may well prefer a more immediate therapy but within the North East of England, both knowledge of CBTi within primary care and a range of ways to access therapy is available
5	3.10 - outcome measures include the IDSIQ - it should be noted that this is a new measure designed by employees and shareholders in the company, only published in March 2021 - this is a new measure for the experts to evaluate and therefore knowledge may be more limited
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Single Technology Appraisal

Daridorexant for treating insomnia disorder [ID3774]

Comments on the draft guidance received through the NICE website

User	Consultation Name	Document Name	Chapter Name	Section Header	Section Number	Selected Text	Comment
Commentator 1	Draft guidance	Draft guidance consultation	committee-discussion	Treatment pathway	3.1		While CBTi is the 'recognised' first-line standard treatment for short-term insomnia, the reality is that OTC sleep aids (currently first generation antihistamines being used off label for their sedative effect) are first line. In future we will see cannabinoids in the OTC space too. The community pharmacist and team are the first line healthcare professsionals consulted. They are often pressured into supply of such first generation antihistamines (sometimes by illicit drug users) as there are in reality no valid alternatives. Access to CBTi is a postcode lottery and does not suit everybody. In my personal view alternatives to OTC sleep aids (and the lack of access to CBTI) are desperately needed. As such community pharmacy (when appropriately sleep trained) should be empowered to supply daridorexant in defined circumstances. Restricting daridorexant to GPs in the face of a pandemic of insomnia is not an enlightened position.

Commentator 1	Draft guidance	Draft guidance consultation	committee-discussion	Treatment pathway	3.1		I am astonished that the committee have apparently not walked around a community pharmacy to see with that COMMUNITY PHARMACY is the first component of the treatment pathway. Sleep hygiene advice is typically delivered in a trivialising way. Sufferers need viable alternatives and primary care (in particular community pharmacy) needs insomnia education and viable alternatives to OTC sleep aids and Z drugs. It would appear that daridorexant offers an alternative.
Commentator 1	Draft guidance	Draft guidance consultation	committee-discussion	First-line standard treatment is CBTi	3.1		First generation antihistamines that are psychologically addictive ARE in reality the first-line treatment. CBTi is not widely available. And you cannot access it privately.

Commentator 2	Draft guidance	Draft guidance consultation	id3774-daridorexant-for-insomnia-disorder-final-draft-guidance-to-pm-for-consultation-noacicdocx				Many thanks for providing me with an opportunity to comment on this comprehensive draft guidance report. It is very encouraging to read the committee's appreciation of the burden and negative sequelae of Chronic Insomnia Disorder for both the individual and society; as well as their understanding of the barriers in accessing appropriate treatment in the UK. The latter not only refers to CBT-I (Cognitive Behavioural Treatment for Insomnia), but also to accessing appropriate medical treatment, the lack of which clearly disadvantages UK patients and society (e.g. we currently have no access to 'top' evidence-based hypnotics - https://www.thelancet.com/article/S0140-6736(22)00878-9/fulltext)) From my reading of the draft consultation, there are 4 areas where I wish to comment (in no particular order): 1. 12-months as the longest study period for Daridorexant. To my mind, this is in keeping with other licensed medications for Chronic Insomnia Disorder. For example, the longest study with Circadin (prolonged release melatonin) was for 6 months, and as the committee rightly acknowledge, even though it is licensed in the UK for a maximum use of 13-weeks, it is often used clinically for a lot longer (https://bmcmedicine.biomedcentral.com/articles/10.1186/1741-7015-8-51) In the history of hypnotics, to my knowledge, the longest clinical trial has just been 12 months (i.e. for Eszopiclone; https://pubmed.ncbi.nlm.nih.gov/16230048/).

							2. Concerns over a placebo effect A hypnotic placebo effect is well-recognised in sleep medicine, and is probably most reflective of an individual's belief and expectation (https://pubmed.ncbi.nlm.nih.gov/31504091/; https://www.sciencedirect.com/science/article/abs/pii/S1087079205000419; https://link.springer.com/article/10.1007/s10865-014-9590-5), which eases anxiety and/or reduces arousal, thereby permitting sleep. I think one should be wary of clinically dismissing the placebo effect, as a clinical response to any medical treatment will involve both a true drug and a placebo effect. For example, for Z-drugs (e.g. Zolpidem; licensed for insomnia), both a true drug effect and placebo response have been demonstrated to be small and of questionable clinical importance. However, when both the Z-drug and placebo effect are added together, they lead to a reasonably large clinical response (https://www.bmj.com/content/345/bmj.e8343). 3. Lack of sleep medicine knowledge in primary care. I agree, and think the committee make this point very well. Indeed, I would argue that there is a paucity of sleep medicine education right across the board in the NHS. Thankfully, there is a growing awareness of this need*, with many interested professional/educational bodies increasing sleep medicine education (e.g. work of the Sleep Medicine Section at the Royal Society of Medicine, who run specific training days for GPs**). However, I am uncertain if this can be Daridorexant's i.e. a medications' responsibility ?

							What may be helpful here, are the development of clear local treatment pathways; appropriate use of 'Advice and Guidance' (A&G) services where there is clinical doubt; as well as local training events. Encouragingly, Daridorexant does not require any specialist monitoring. *https://nshcs.hee.nhs.uk/programmes/respiratory-and-sleep-training-programmes/about-the-pg-cert-sleep-medicine/ **https://www.rsm.ac.uk/events/sleep-medicine/2022-23/slr01/ 4. No end point for stopping the medication. I do not opine that this should be a barrier. Many of the unlicensed medications that we already use in Chronic Insomnia Disorder (such as the sedating anti-depressants and anti-psychotics) equally have no defined/regulated treatment endpoint (indeed, primary care often favour long-term low-dose Amitriptyline use); and ultimately, one relies on their clinical judgement in consultation with the patient, whilst practicing 'good prescribing' https://acnr.co.uk/articles/the-misprescribing-of-z-drugs-for-insomnia/) . It is encouraging that Daridorexant already encourages a clinical review at 3 months. Moreover, as the committee rightly points out, even though other licensed insomnia medications, such as Circadin and the Z-drugs have defined end-points, they are often prescribed for a lot longer than their license states.

Commentator 3	Draft guidance	Draft guidance consultation					This comment is from Professor David Baldwin, current President of the British Association for Psychopharmacology (BAP), on behalf of that organisation. The BAP has previously published guidelines on the management of patients with sleep disturbance (Wilson et al., 2010; Wilson et al., 2019) which have become widely used in clinical practice. The BAP agrees with the Committee conclusion that the proposed positioning of daridorexant as a second-line treatment option for long-term insomnia, when digital or face-to-face CBTi has been tried but not worked, or as maintenance treatment for managing longer-term symptoms, was appropriate. The BAP also supports the conclusion that positioning daridorexant as a first-line treatment option when CBTi is not available or unsuitable is acceptable. The BAP disagrees with one of the clinical experts and the wider committee, who emphasised that when possible, GPs should be encouraged to explore reasons why CBTi is not available during diagnosis and signpost people to have CBTi treatment first. The BAP believes that this is an impractical recommendation, given the current overwhelming burden on primary care practitioners: it would simply not be feasible to do this in practice. We believe that the committee's concerns relating to cost-effectiveness are rather unhelpful. For example, whilst noting that patients with comorbid conditions were excluded from study 301 and study 303, the Commitee should also acknowledge that patients with comorbid conditions such as depression are frequently disbarred from receiving CBTi. Similarly, whilst the proportions within the trial populations are not fully representative of the ethnic groups within the UK, the Committee should acknowledge that similar criticisms apply to access to psychological treatments in primary care (such as CBTi).

							The BAP supports the Committee in asking for the further analyses described in Section 3.26. For the sake of balance, the BAP recommends that similar data relating to patient attrition during CBTi are sought (attrition in IAPT services is known to be high), and also recommends that data on relapse of symptoms during CBTi is sought (as this would provide useful comparative data when considering the potential enduring effect of daridorexant). We agree that consideration of adverse events is an important aspect of cost-effectiveness calculations, and so recommend that adverse patients experiences of CBTi are also considered in this judgement.

Commentator 4	Draft guidance	Draft guidance consultation	id3774-daridorexant-for-insomnia-disorder-final-draft-guidance-to-pm-for-consultation-noacicdocx	ID3774 daridorexant for insomnia disorder final draft guidance to PM for consultation [NoACIC].docx		Has all of the relevant evidence been taken into account?	The APPG for Sleep has been considering the impact of insomnia at a societal and personal level. The key findings from the research we have undertaken around the impact of insomnia do not appear to have been taken into proper account by NICE. Specifically there does not appear to be consideration of the impact on the individual or on society. There appears to be no real discussion or thoughts on the impact of insomnia on productivity. Treatment is currently dominated by medication, which can have unpleasant or harmful side effects. Last year, more than 12 million prescriptions were written to deal with insomnia, at a cost to the NHS of £72m. GPs have been placed in the position where off-label prescribing is commonplace, which is not ideal for patients. RAND Europe, in its 2016 report "Why Sleep Matters", estimated that the UK loses some 200,000 working days a year because of insomnia and poor sleep. Sleep is affected by physical and mental health and environmental and social factors. Short-term sleep disruptions increase the risk of workplace and driving accidents, while long-term sleep disruptions are associated with a range of poor health outcomes, including increased accidents and falls among the elderly. The RAND report in 2016 on chronic adult insomnia found that:

							• Insufficient sleep increases mortality risk by up to 13 per cent • Up to $680 billion are lost each year across five OECD countries due to insufficient sleep • Workers who sleep less than six hours per day report on average about a 2.4 % higher productivity loss due to absenteeism or presenteeism than workers sleeping between seven to nine hours a day • Insufficient sleep is costly for employers by reducing workplace productivity The updated RAND report from 2023 found that: • In productivity terms, chronic insomnia costs a substantial amount to the UK - 1.3% of GDP each year, or $41.4bn • Adults in the UK with insomnia had on average, lower self-rated life-satisfaction scores compared to those without insomnia The impact of insomnia is felt across the whole of society: • Chronic insomnia is associated with a range of medical and psychiatric complications and comorbidities • Insomnia is strongly associated with mood disorders, with daytime symptoms putting patients at particularly high risk for developing anxiety, depression and suicidal ideation • Daytime symptoms of insomnia have a considerable negative impact on functioning and daily life, such as working and driving, and insomnia increases the risk of accidents • Insomnia has a heavy impact on the health and workplace performance of shift workers -shift work was associated with 67% increased risk of reporting poor subjective health and 183% increased risk in reporting disturbed sleep • Insomnia is associated with significantly higher rates of work impairment vs. healthy people and a substantial healthcare

							resource burden • It has a cause-and-effect relationship with a range of medical and psychiatric conditions, including mental health disorders such as depression and anxiety and is also a risk factor for several cardiac conditions • Patients with insomnia have an increased risk of home, work, and motor vehicle accidents and accidents in public places • Daytime insomnia symptoms increase the risk of falls and injuries in elderly patients The APPG believes that proper consideration needs to be taken on the wider societal impact and on productivity.

Commentator 4	Draft guidance	Draft guidance consultation	id3774-daridorexant-for-insomnia-disorder-final-draft-guidance-to-pm-for-consultation-noacicdocx	ID3774 daridorexant for insomnia disorder final draft guidance to PM for consultation [NoACIC].docx		Are the recommendations sound and a suitable basis for guidance to the NHS?	Not in our opinion. We have heard evidence that there are no effective treatments for clinicians at primary care level for patients, other than CBT-i and that this is patchy across the country with poor uptake. We believe that if there is a clinically proven alternative treatment then we would strongly support clinician choice in offering the treatment they consider necessary after first line treatment.

Commentator 5	Draft guidance	Draft guidance consultation					1. Has all of the relevant evidence been taken into account? No, I feel it didn't take into account key issues like productivity. There are a lot of data about that, I am including below a couple of examples. Driver fatigue | Brake The road safety charity Brake has published a page on their site related to Driver Fatigue. In it, they claim Tired drivers have slower reaction times and suffer from reduced attention, awareness, and ability to control their vehicles Research suggests driving tired can be as dangerous as drink-driving 10–20% of all crashes are estimated to be caused by driver fatigue Drivers are 20 times more likely to fall asleep at the wheel at 6 am than at 10 pm 1 in 8 drivers admit falling asleep at the wheel However, there is no break down within the statistics to differentiate fatigue from insomnia. RoSPA Road Safety Factsheet 2020 Driver Fatigue Factsheet 0220 (rospa.com) Findings It is not possible to calculate the exact number of sleep related accidents, but research shows that driver fatigue may be a contributory factor in up to 20% of road accidents and up to one quarter of fatal and serious accidents These types of crashes are about 50% more likely to result in death or serious injury Crashes caused by tired drivers are most likely to happen:

							on long journeys on monotonous roads, such as motorways between 2 am and 6 am between 2 pm and 4 pm (especially after eating or having even one alcoholic drink) after having less sleep than normal after drinking alcohol if taking medicines that cause drowsiness after long working hours or on journeys home after long shifts, especially night shifts The factsheet states that young male drivers, truck drivers, company car drivers and shift workers are most at risk of falling asleep while driving. Many professional drivers, especially HGV drivers, report increased levels of sleepiness and are involved in a disproportionately high number of fatigue-related accidents, with around 40% of sleep-related accidents involving commercial drivers. 3. Are the recommendations sound and a suitable basis for guidance to the NHS? No. It doesn't take into account key issues like productivity.

Daridorexant for treating long-term insomnia [ID3774]

EAG comments on the company response to draft guidance

The EAG has read the company's response to the draft guidance, and would like to make the following comments.

Comments on section 2: selective attrition in study 303

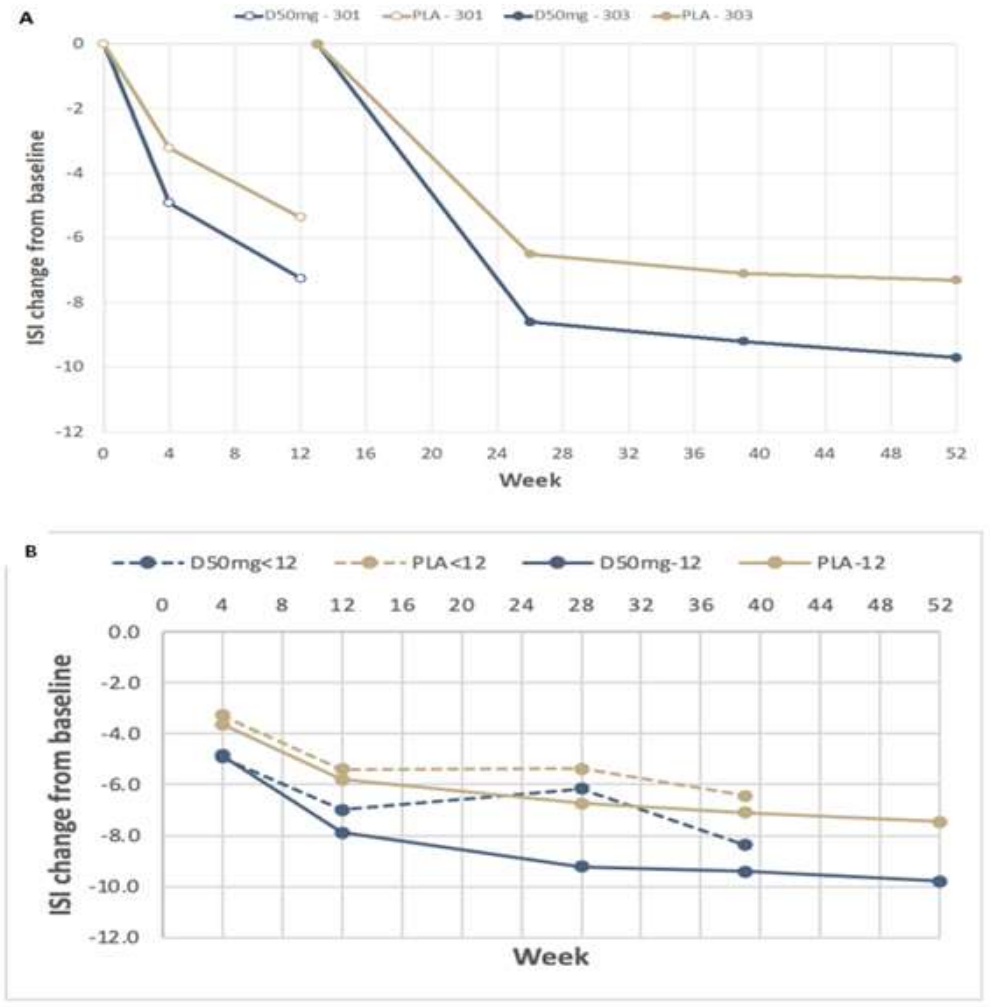
The company have tried to explain the smaller than expected effect size for daridorexant in study 303 by appealing to 'selective attrition'. In summary, the company argue that the difference between daridorexant and placebo was reduced by attrition bias that favoured the placebo group. This initially sounds plausible but it doesn't appear to stand up to scrutiny.

Attrition bias may express itself if one group loses more participants to analysis than the other due to poor responses to treatment or adverse effects. The underlying concept is that if a patient is not responding to the intervention or having bad adverse effects, they will not only drop out of treatment, but will also not tend to attend outcome measurements at the end of the study (and therefore be lost to follow up). Being lost to follow up is where the bias occurs. If a group loses its worst responders from analysis, then that group will end up looking much better than it would otherwise have done had those people somehow been kept in the analysis. It's the equivalent of a school expelling all its worst students just before the A level exams so the school can have a greater proportion of its students getting A star grades. Thus, a group that has greater attrition in terms of numbers lost to follow up is likely to derive a spurious advantage.

However, this does not appear to be the same 'attrition' bias that the company is talking about. The company first direct us to the Figure 1 below. In part B of the Figure, the company draw our attention to the stratified analysis. The continuous lines are data for people who attended all treatments and the dotted lines are data for people who, at some point, dropped out of treatment. Importantly, outcome data are available for all of these people, both completers and treatment drop-outs (which is obvious, since the outcome data for both the completers and non-completers are shown on the graph). The values given for the treatment non-completers are not estimates, but real, measured values. This is the crux of the problem – the attrition that the company draw attention to appears to be treatment discontinuation, which is not necessarily the same as being *lost to follow up*, and has a different effect on the direction of bias. As we have argued, if a group suffers a loss of people to *follow up*, then (assuming those lost participants would have had worse outcomes) this will spuriously improve the overall outcome measured in that group because the bad responders are not included. On the other hand, if a group has

a proportion of people not attending for treatment, but all attend for follow up, then the fact that those people didn't have the intervention or placebo (which will mean the loss of the treatment effect + placebo effect for the intervention group and the loss of the placebo effect for the placebo group) will mean that group actually fares *worse* than it would otherwise have done.[i]

Therefore, the way that attrition is defined is very important, as this will affect the direction of any alteration in the study outcome. For Figure 1, the company certainly seem to be describing attrition as withdrawal from treatment, rather than loss to follow up (as everyone on that Figure was followed up). However, they also appear to be assuming that the greater attrition from the placebo group will lead to a spurious *improvement* for that group. For example, the company emphasise that the degree of treatment drop-out due to lack of efficacy was greatest in the placebo group, which they then imply would have led to the placebo group receiving a spurious advantage. However, spurious improvement for the placebo group would only happen if the attrition were in terms of loss to follow up. Given that the attrition in the placebo group is withdrawal from treatment, such greater attrition in that group would have actually led to a *disadvantage*, because the poorer outcomes of many of these treatment drop-outs would still have remained in the analyses. Therefore, this does not support the company hypothesis of attrition leading to an unfair *advantage* to the placebo group.



D50mg=daridorexant 50mg, PLA=placebo, D50mg<12=on daridorexant for less than 12 months; D50mg-12=on daridorexant for 12 months; PLA<12=on placebo for less than 12 months; PLA-12=on placebo for 12 months; ISI©=Insomnia severity index.

Figure 1. Change in ISI scores from baseline to the end of the extension study 303, (A) all participants included and (B) stratified by study completion status

In addition to the company's incorrect understanding about the mechanisms of attrition bias, there are other flaws in their argument. In Figure 2 below (Figure 3 in the company document), the company describe

[redacted]

Figure 2. Figure 3 from the company document

Likewise, in Figure 3 below (Figure 4 in the document) the argument is made that [redacted].

Figure 3. Figure 4 from the company document

Similarly, in Figure 4 (Figure 5 in the company document) the company argue that [redacted]

[redacted] Given that data were available for these drop outs (this is clear, as the drop-out data are displayed in the graph) and that these data would have been part of the ITT analysis, then the fact that [redacted].

Figure 4. Figure 5 from the company document

Overall, therefore, the company's 'selective attrition' explanation for the lack of significant difference between daridorexant and placebo in study 303 is neither coherent nor convincing.

Comments on section 10: Incorporating placebo effect in health economic analyses

Whether or not selective attrition might be more pronounced in for the placebo group than for the daridorexant group is not relevant for the decision to incorporate the placebo effect (or not) in the health economic analyses. Patients discontinuing treatment due to lack of effectiveness, is a common phenomenon and that is likely also present in clinical practice. To avoid bias that can arise from, for instance selective attrition, it is recommended to perform analyses according to the intention to treat (ITT) principle.[1] ITT analyses is often recommended as the least biased way to estimate intervention effects in randomized trials.[2] Consistently, according to the Cochrane handbook, the effect of assignment to intervention should be estimated by an ITT analysis that includes all randomized participants. Accordingly, the placebo effect should be included in the cost-effectiveness modelling.

Comments on scenario analyses provided by the company

The company performed scenario analyses incorporating alternative assumptions regarding:

1. Inclusions of waning of treatment effect
2. Inclusion of costs related to support and training for GP's
3. Inclusion of inflated prescription costs and outpatient visits
4. Inclusion of impact of adverse events on costs and QALYs
5. Inclusion of 25 mg dose for daridorexant

Including waning of treatment effect might have a substantial impact on the estimated ICER (see CS addendum Figure 8). Including costs related to support and training for GP's, inflated prescription costs and outpatient visits and the impact of adverse events on costs and QALYs altered the company's base-case ICER by approximately +£500, -£300 and +£700 respectively. Additionally, the base-case ICER for daridorexant 25 mg versus no treatment was estimated to be £37,881 per QALY gained (CS addendum Table 24).

Comments on Appendix 1 – 25 mg dose

The committee proposed that a 25 mg dose would be useful as a starting dose. Studies 302 and 201 both include data for 25 mg daridorexant. The 302 study appears to be free from systematic selection bias, with arms that compare well for all of the important baseline variables. The same is true for study 201.

The company's interpretation is that 25 mg led to smaller and less consistent benefits than 50 mg, and that it should not be used as a general dose. However, comparing the 25 mg data from study 302 to the 50 mg data from the main CS data (study 301), there is not much evidence that 25 mg is inferior. For example, although the effect (versus placebo) for WASO at 3 months is slightly better for 50 mg [50 mg: -18.3 (-23.95,-12.66); 25 mg: -10.25 (-16.95, -3.55)], there is little difference between the doses for sTST [50 mg: 19.77 (10.62,28.92); 25 mg: 19.06 (10.13, 27.99)], IDSIQ sleepiness [50 mg: -1.9 (-2.91,-0.905); 25 mg: -1.25 (-2.23, -0.276)], sWASO [50 mg: -4.78(-11.9,2.362); 25 mg: -5.05 (-11.28, 1.171)] and sLSO [50 mg: -8.29(-12.95,-3.6); 25 mg: -6.49 (-11.55, -1.423)]. There is, of course the risk that differences in populations may confound the dose comparison. However, in the direct head-to-head analysis of study 201, although there is some evidence of larger point estimates (versus placebo) in the 50 mg group compared to the 25 mg group, the differences are again small [WASO: 25 mg v placebo -7.6 (-19.1,3.8), 50 mg v placebo -11.5 (-23.2, 0.2); sLSO: 25 mg v placebo -0.3(-8.5,7.9), 50 mg v placebo -5.9(-14.1, 12.2)] and it should be noted that these results were based on a short 30-day treatment period. In terms of adverse events, the 50 mg dose does not appear to wield any greater safety concerns than 25 mg.

It should be noted that both studies 301 and 303 included 25 mg daridorexant as a comparator, thus providing further direct comparison between 25 mg and 50 mg. However, data for the 25 mg dose was not included in the CS, nor the CS appendices. The CSR for study 303 was available in the company

reference file, and demonstrates that whilst sTST (12 months change from baseline) was better at 50 mg than 25 mg in terms of the difference versus placebo, there were minimal differences between 50 mg and 25 mg for IDSIQ sleepiness (12 months change from baseline), sLSO (12 months change from baseline) and sWASO (12 months change from baseline). The CSR from 301 did not appear to be available in the references sent by the company and so it was not possible to confirm the company's statement that "unlike daridorexant 50 mg which demonstrated efficacy across night-time and daytime variables, the 25 mg dose demonstrated efficacy only on certain sleep variables, but not daytime functioning". Therefore, overall, given the likely greater costs of the 50 mg dose, there appears to be little solid evidence to prohibit the use of a 25 mg dose.

Comments on section 9: GP training and support

The company claims that the introduction of daridorexant will not lead to additional needs for GP support and training. This is based on the following evidence:

Figure 5: General practitioners' confidence in diagnosing, treating and referring chronic insomnia

From this graph, [redacted] of GPs have a confidence score of [redacted] for treating insomnia. It would therefore be reasonable to interpret this to mean that [redacted] of GPs are not very confident of treating insomnia. The introduction of a new treatment will probably not increase this low level of confidence, and it is therefore reasonable for the committee to have concerns about a possible training and support burden.

References

[1] Negida A. Attrition bias in randomized controlled trials [Internet]. Cochrane, 2017 [accessed 16.5.23]. Available from: https://s4be.cochrane.org/blog/2017/02/13/attrition-bias-randomized-controlled-trials/

[2] Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. Int J Epidemiol 1992; 21(5):837-41

[i] In reality, of course, it is likely that some of those not attending for treatment would also have not attended follow up, and the so the true situation would not be quite as simple as this. As shown by the n values in Figure 2, there was clearly a large loss from follow up as well. However, the fact remains that data were available for many of the treatment drop outs (as the outcomes from these treatment drop-outs are freely displayed on the company's graphs).