Daridorexant for treating insomnia disorder [ID3774]

For committee – contains Redacted AIC information Post FAC

Technology appraisal committee B [06 July 2023]

Chair: Charles Crawley

Lead team: Gabriel Rogers and Tony Wootton

Evidence assessment group: Kleijnen Systematic Reviews

Technical team: Anuja Chatterjee, Claire Hawksworth, Richard Diaz

Company: Idorsia Pharmaceuticals

Draft guidance recommendation

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.

Background

Causes of insomnia: disruption of normal sleep-wake cycle caused by interplay of molecular, genetic, neurological and psychological factors. It presents as either acute or chronic (insomnia disorder)

Epidemiology: About 9.3 million adults (1 in 5) in England experience insomnia symptoms, and 3.3 million meet criteria for insomnia disorder

Symptoms and prognosis:

- Difficulty getting to or maintaining sleep, early wakening, or non-restorative sleep despite adequate opportunity; poor concentration, mood disturbance, fatigue during day
- Impaired daytime functioning negatively impacts social life, relationships, family life
- If untreated, insomnia can increase risk of depression, anxiety, and, in long term, diabetes and cardiovascular disease

Diagnosis and classification of insomnia disorder: persistent with symptoms occurring for ≥ (more than or equal to) 3 nights per week for ≥3 months (as per DSM-5® criteria)

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

Technology details

Technology and Marketing authorisation (MA)	• Daridorexant (Quviviq, Idorsia): MHRA MA approved August 2022 for "treatment of adult patients with insomnia characterised by symptoms present for at least 3 months and considerable impact on daytime functioning"
Mechanism of action	• Selective and potent dual orexin receptor antagonist, acting as an equipotent orthosteric antagonist at both orexin 1 and orexin 2 receptors
Administration	• One oral tablet: 50 mg once per night • Some people may be offered 25 mg once per night (for example, people with moderate hepatic impairment or when used with moderate CYP3A4 inhibitors) • Treatment duration - short as possible. Continued treatment assessed within 3 months and periodically thereafter. No formal stopping rule
Price	• List price per pack for 50mg or 25mg: £2.12/day; Annual cost of £773.80. Patient access scheme not applicable (daridorexant to be used mainly in primary care)
Comparator	• Established clinical management (including sleep hygiene advice) without daridorexant

MHRA, Medicines and Healthcare Products Regulatory Agency

Clinical effectiveness recap

Key clinical trials

	Study 301 (N=930)	Study 303 (N=804)
Design	Double-blind randomised controlled trial (RCT)	Double-blind RCT, extension study of Study 301 and 302
Population	Adult (18-64 years, ≥65 years) with insomnia disorder according to Diagnostic and Statistical Manual of Mental Disorders (DSM-5®) criteria	Adult (18-64 years, ≥65 years) with insomnia disorder according to DSM-5® criteria
Intervention	Daridorexant (25 mg and 50 mg)	Daridorexant (10 mg, 25 mg and 50mg)
Comparator	Placebo	Placebo
Treatment Duration	12 weeks	40 weeks
Primary outcomes	Wake after sleep onset (WASO), Latency to persistent sleep	Treatment-emergent adverse events
Key secondary outcomes*	Subjective total sleep time (sTST), Insomnia Daytime Symptoms and Impacts Questionnaire	Subjective WASO and sTST *Insomnia severity index was an exploratory endpoint in 301 and 303

Cost effectiveness recap

Company's model overview and key outcome drivers

Company: multiple regression models at months 1, 3, 6, 9 and 12

Model type / structure	Described as a 'mediated analysis'. Company not aware of "any formal terminology has entered the lexicon" to describe model form. Company 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). **Company**: ISI used because lack of data sources to estimate a mapping function for other trial outcomes
Time horizon	12 months (lifetime considered as scenario analysis)
Discounting	Not applicable given 12-month time horizon (discount rates of 3.5% for both effects and costs were used in lifetime model scenario)
Technology modelled to affect:	
Costs	Treatment costs, health care costs, productivity loss (in scenario analyses)
QALYs	Study 301 and Study 303 ISI scores and ISI to EQ-5D mapping algorithm

*ISI assesses insomnia based on criteria from the International Classification of Sleep Disorders, Third Edition and is currently one of the most used insomnia-specific Patient Reported Outcome questionnaires.

ISI, insomnia severity index; PSS, Personal Social Services; QALY, quality-adjusted life year

How company incorporated evidence into model

Input	Assumption and evidence source
Intervention efficacy	Observed ISI scores from months 0, 1, 3,6, 9 and 12 (from study 301 and study 303).
Comparator efficacy	Observed ISI scores from months 0, 1, 3 from (study 301) Assumption that people in 'no treatment'* arm would continue at same ISI achieved by end of study 301.
Utilities	Novel mapping algorithm applied to derive EQ-5D utilities from ISI scores
Resource use	Association between direct healthcare resource use (related to GP visits, emergency room attendances, and inpatient care) and ISI score were calculated from NHWS data using a generalised linear model with a negative binomial distribution family and a log link.
Costs	Calculated by combining estimated resource use with unit costs from PSSRU 2021 (GP visits) and NHS England 2019/2020 costs (emergency room and inpatient costs), inflated to 2021 costs using CPI index 06: Health
Adverse events	Not included in model
Treatment discontinuation	Observed discontinuation rates from study 301 and study 303 Assumptions: (1) discontinuation occurred at midpoint of studied periods; (2) treatment costs were incurred for full period assuming that prescriptions would be filled at start of period before discontinuation occurs. Company considered dropout rates from study 303 [redacted] clinical practice more accurately → explored as scenario analysis

* Placebo arm from the trial referred to as 'no treatment' arm in the model

CPI, consumer price index; ISI, insomnia severity index; NHWS, National Health and Wellness Survey; PSSRU, Personal Social Services Research Unit

Committee conclusions

Key clinical issues discussed at ACM1

Issue	Committee conclusion
Generalisability of trial population and clinical evidence to decision problem	Trial inclusion criteria narrower than anticipated treatment population: 1) Exclusion of people with mental health conditions 2) Different ethnicities between the trial and anticipated UK practice → adds uncertainty to the generalisability of the evidence
Concomitant treatments	If recommended, daridorexant could be used at the same time as other treatments available in practice (for example sleep hygiene measures)
Omission of clinical study	Committee concluded that Study 201 (Dauvilliers et al. 2020: multi-center, double-blind, randomised, placebo-controlled dose response study assessing 25 mg and 50 mg daridorexant doses) should be included.

Key cost-effectiveness issues discussed at ACM1

Issue	Committee conclusion
Longer term benefits for daridorexant	Uncertainty in daridorexant's long-term treatment effect, treatment effect waning and stopping rule scenarios requested
Exclusion of 25mg dose from economic model	Committee requested to see evidence on the treatment effect of the daridorexant 25 mg dose from study 302 (RCT with 10mg, 25mg and placebo arms) as part of its decision making
Exclusion of AEs in economic model	Adverse event costs and associated disutility to be included
Modelling of placebo effect	Preferred EAG approach: using the ISI scores from both study 301 and study 303 to inform the ISI for the no treatment group. Selective attrition possible but company should provide more evidence
Mapping of ISI scores to EQ-5D	Utility values appropriate for decision making but uncertainties in mapping noted and considered in decision making
Costs in economic model	Model should include costs incurred by the NHS, including support and training for GP practices

ACM1, Appraisal committee meeting 1; ISI, insomnia severity index; RCT, Randomised controlled trial

Draft guidance consultation comments

DG consultation responses

Company, clinical expert and members of the public responded

Stakeholder/consultee	Details
Company	Idorsia Pharmaceuticals
Experts	1 clinical expert
Web comments	5 commentators

Company provided:

- ✓ Evidence as requested by the committee in the draft guidance
- ✓ Additional evidence provided by company on inclusion of productivity costs in the model

Clinical expert - DG consultation comments

- **Concerns with prescribing longer-term medication**: Long-term insomnia mimics other types of sleep disorders → challenging to diagnose. There are concerns with prescribing longer-term medication → leaves other conditions undiagnosed for longer (for example, obstructive sleep apnoea)
- **Clinical expert opinion on differences between daridorexant and other treatments needs to be elaborated on in certain sections of the draft guidance:** Whilst daridorexant has a better safety profile than other treatments, some are considered equally safe.
- **People have access to free digital CBTi/NICE recommended tools/IAPT services**: Both knowledge of CBTi within primary care and a range of ways to access therapy is available
- **Experts may have a limited knowledge of IDSIQ**: It is a new measure published in March 2021, designed by company employees and shareholders

CBTi, Cognitive behavioural therapy for insomnia; DG, draft guidance; IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; IAPT, improving access to psychological therapies

Web comments - DG consultation comments

- **Attrition in IAPT services is also high:** Patient attrition/relapse data for CBTi should be compared with daridorexant
- **Generalisability of evidence base is sufficient:** Under representation of ethnic groups not unique to daridorexant and not everyone with mental health comorbidities (for example depression) can access psychological treatments in primary care
- **Wider societal impact not included**: Productivity loss not considered (for example, impact on professional drivers/shift workers) (RAND 2023 report)
- **Community pharmacies represent '1st line'**: Antihistamines used as first-line treatment off label and are psychologically addictive. CBTi not widely available and high unmet need. Pharmacies should be trained to supply daridorexant
- **Impractical to advise GPs to explore issues with accessing CBTi**: Current burden on primary care → not practical for GPs to explore unavailability of CBTi.
- **No stopping rule should not be barrier to treatment:** Daridorexant encourages a clinical review at 3 months. Stopping rules for current unlicensed treatments are also based on clinical judgement.

CBTi, Cognitive behavioural therapy for insomnia; DG, draft guidance; IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; IAPT, improving access to psychological therapies

Company’s response to consultation

New evidence from company in response to committee requests

Committee requests at ACM1	Company evidence submitted
Treatment effect evidence of daridorexant 25mg and 50mg from study 201; 25mg from study 302	✓ Scenario provided using study 201 (Dauvilliers 2020) and study 302 (Mignot 2022, randomised controlled trial daridorexant 25mg compared with placebo)
Cost-effectiveness of daridorexant 25mg dose	✓ Cost-effectiveness analysis provided using safety and efficacy outcomes from study 301 and 303
Supportive evidence/data for selective attrition assumption	✓ Data from study 303 and additional evidence supporting the assumption provided
Treatment effect waning and stopping treatment in lifetime horizon model	✓ Treatment effect waning (5% and 10% applied to health-related quality of life and mortality benefit) and “annual challenge” modelled
Impact of AEs on costs and QALYs	✓ Any treatment-emergent adverse events occurring in more than 2% (either arm) included
Costs for support and training for GPs	✓ UK data on treated or untreated insomnia and GP survey data included. Per patient cost of £10.90 modelled.

Outstanding issues for ACM2

Three key remaining issues for discussion

Issue	Resolved?	ICER impact
Application of placebo effect	No – Company submitted additional evidence as requested by committee for discussion	Large
Treatment effect waning in lifetime horizon model (scenario)	No – Company scenario for discussion as requested by committee	Large
Excluding 25mg dose from economic model	No – Company submitted evidence and scenarios as requested by committee for discussion	Large

Key issue: Application of placebo effect

Background: Company believe placebo arm has inflated ISI scores as people with poorer outcomes dropped out (selective attrition) which underestimated the treatment effect- people in 'no treatment' arm would continue at same ISI achieved by end of study 301. EAG's disagrees that bias occurs and prefers to apply full placebo effect from study 301 and 303 in placebo arm for the full 40 weeks.

Company: Subjects who dropped out (study 303) had worse outcomes compared with those who completed the study

- ISI [redacted] could be attributed to selective attrition
- Treatment discontinuations [redacted]
  Discontinued because of lack of efficacy: placebo group [redacted] twice as high compared with daridorexant 50mg group ([redacted]).

ISI, insomnia severity index

Key issue: Application of placebo effect

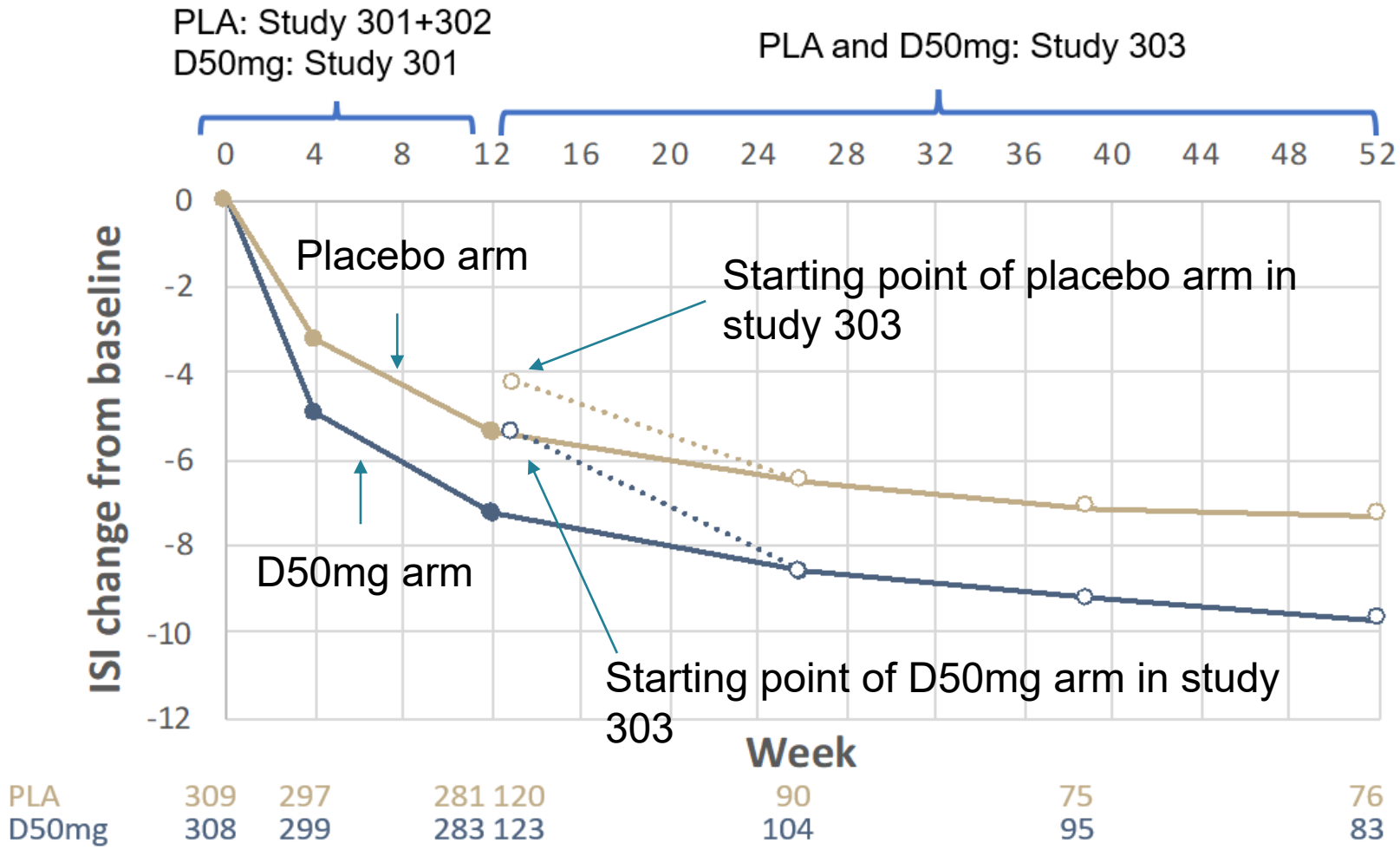
EAG comments:

- 'loss to follow up' causes selective attrition bias
- Differences in outcomes between completers and non-completers does not prove selective attrition bias.
- Dropout is XXXXXXX in both arms, and non-completers have poorer outcomes than completers in both arms. Doesn't support argument that those with poorer ISI scores drop out of placebo alone- true for daridorexant arm too
- For month 3 onwards: Company uses month 3 ISI scores from study 301 placebo arm to model no-treatment arm, but Study 303 ISI scores for daridorexant arm in the model
- An ITT approach should be taken to minimise attrition bias as per Cochrane.org
- If selective attrition bias adjustment is applied in the model, it should be applied to both placebo and daridorexant arms and not only to placebo arm.
- Using Study 303 ISI scores for the no treatment arm is the only way to 'cancel out' selective attrition in both arms in the model
- Full placebo effect should be applied- argument for lack of treatment effect not coherent

ISI, insomnia severity index

Changes in ISI scores from baseline to end of extension study

Figure A: Changes in ISI scores from Study 301 and 303 all subjects included (ITT analysis)



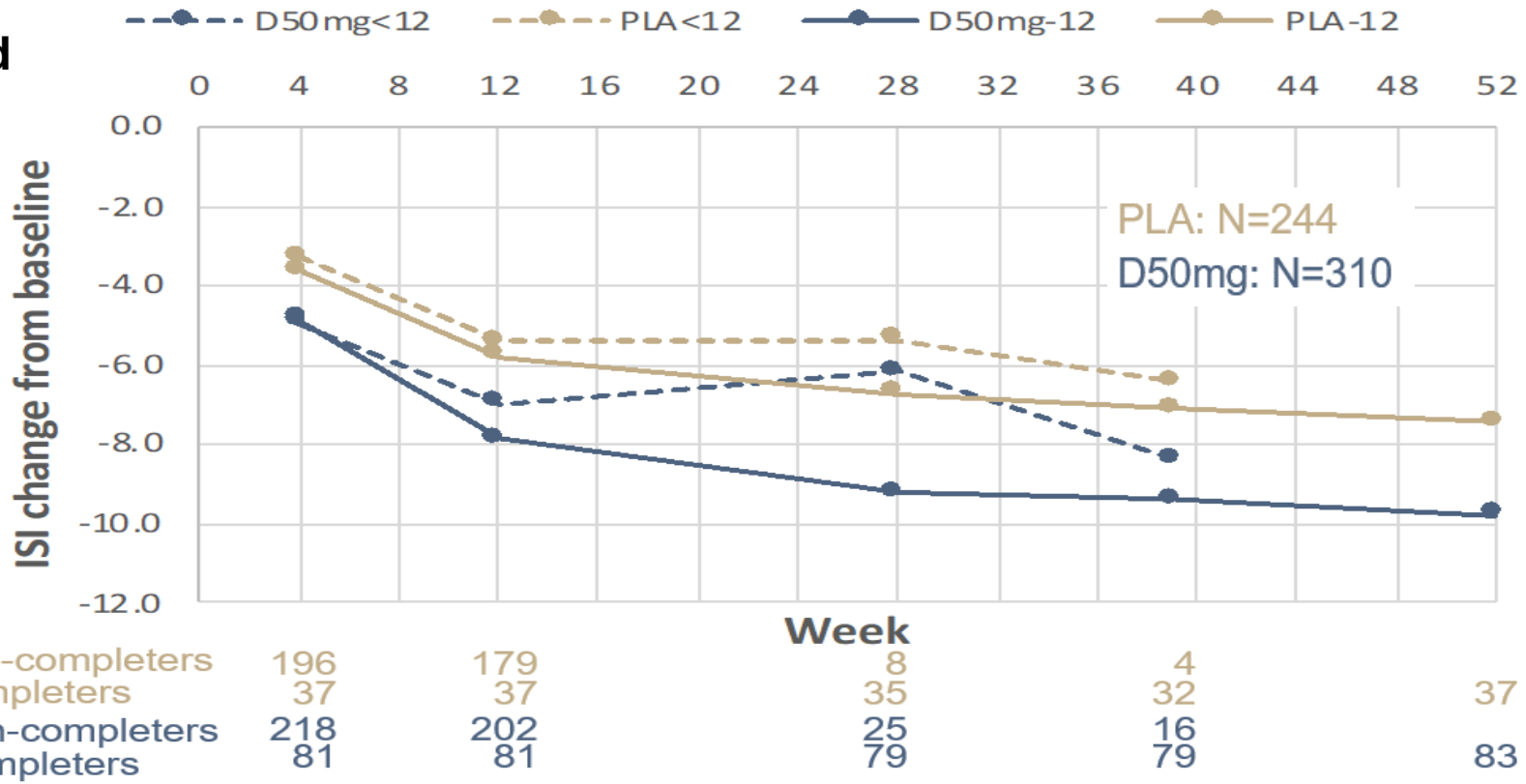
- Dotted lines show the starting ISI scores for placebo and D50mg group from study 303 →both decreased between end of study 301 and start of study 303

D50mg: daridorexant 50mg; ISI, insomnia severity index

Changes in ISI scores from baseline to end of extension study

Figure B: Study 301 and 303 stratified by study completion status

- Solid lines - Completers: subjects who completed both 301 and 303 studies (full 12 months follow up).
- Dotted lines - Non-completers: subjects who dropped out at any point before the end of either study (less than 12 months follow up).



Company: Continued improvement in ISI difference from baseline as study 303 progresses is selective attrition as subjects with no improvement would have dropped out after study 301 and not continued into study 303. The ISI scores at 12 weeks in study 303 are improved compared with 12 weeks into study 301.

1. Do we believe there is selective attrition bias?
2. Is this disproportionately higher for placebo compared with daridorexant arm?
3. How should the placebo effect be included?

Key issue: Treatment effect waning in lifetime horizon model

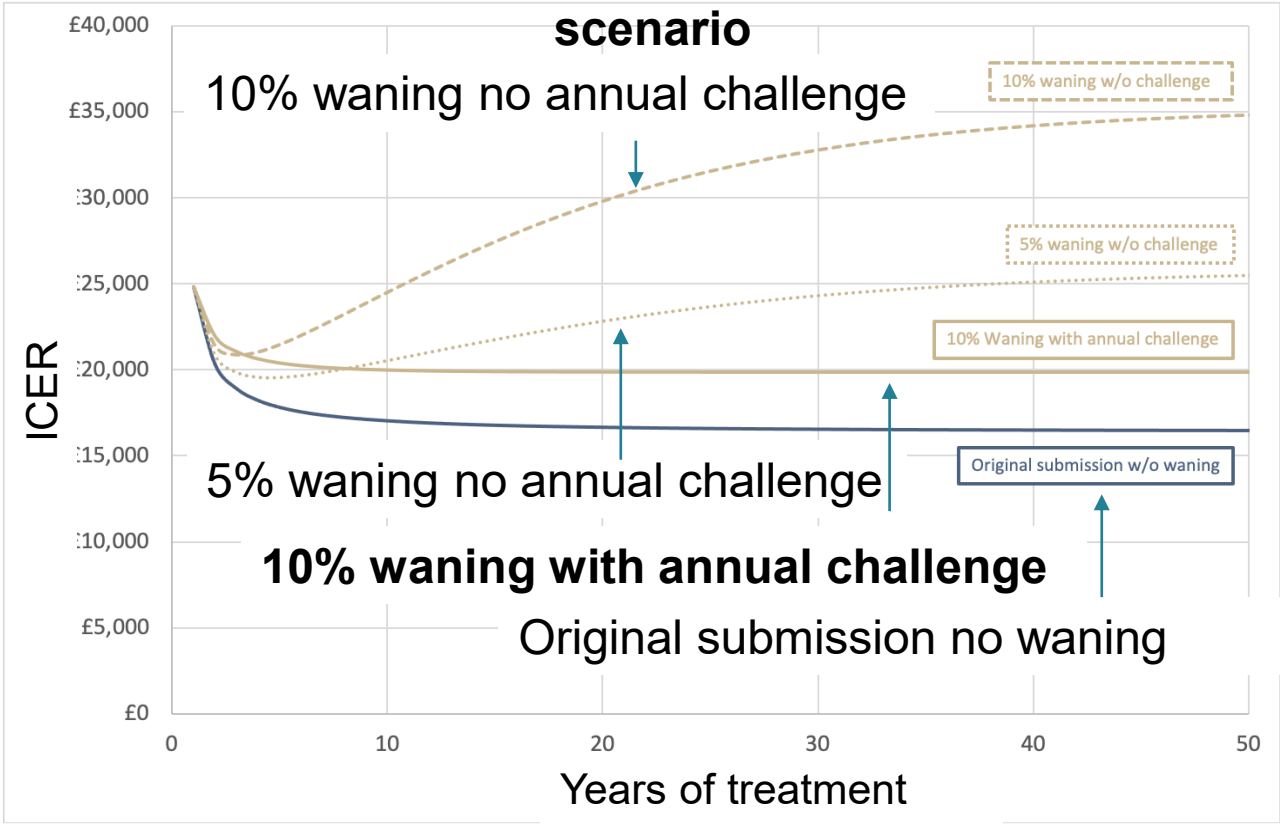
Background

- Daridorexant's SmPC does not include a stopping rule. No trial data on daridorexant's treatment effect beyond 12 months. Long-term treatment effect is uncertain.
- Committee requested analyses exploring treatment effect waning and stopping rule in the company's lifetime time horizon scenario.

Company

- Scenarios with annual 5% or 10% treatment effect waning applied to short term HRQoL and long-term mortality benefit. No change to costs.
- "annual challenge" scenario (in lieu of stopping rule) where treatment is withdrawn at annual review to assess if treatment effect is lost: →10% treatment effect waning, 20% discontinue treatment every year after review, cost of yearly GP review modelled

Figure: Treatment effect waning and annual challenge scenario



Is it appropriate to assume mortality benefit in the lifetime horizon model?

Key issue: Excluding 25mg dose from economic model

Company: General use of 25mg dose is not evidence based and contradicts the SmPC

Background

- Daridorexant marketing authorisation includes 25mg and 50mg dose
- ACM1: committee requested treatment effect evidence on 25mg dose

Company

- Provided 25mg results from Study 301, 302 and 201. Prefer trial data from 301 and 303 for 25mg (to align with 50mg base case). Scenario with 301 and 302 trial data.
- 25 mg dose showed efficacy on some sleep variables but not daytime functioning
- EMA: questionable clinical relevance of 25mg dose
- SmPC: 25mg recommended for moderate liver impairment or on a concomitant moderate CYP3A4 inhibitor. 50mg recommended for everyone else.

EAG comments

- Limited evidence to show 25mg has poorer outcomes than 50mg
- Study 201: larger point estimates for outcomes in 50mg group vs placebo compared with 25 mg but differences were small. Only 30-day treatment period, AEs comparable.
- Study 303: 50mg sTST outcomes better than 25mg, other measures show limited differences.
- Apart from greater costs of 50 mg dose, little evidence to prohibit use of a 25 mg dose

AE, Adverse eventEAG, Evidence Assessment Group, EMA, European Medicines Agency; SmPC, Summary of Product Characteristic ; sTST, Subjective total sleep time

Dose-response meta-analysis for day-time variables

Figure AIC and is redacted

Company: Analyses of study 301, 302 and 201 demonstrates dose-response and superiority of daridorexant 50 mg

IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire

Please see back up slides for an overview of the night-time variable outcomes

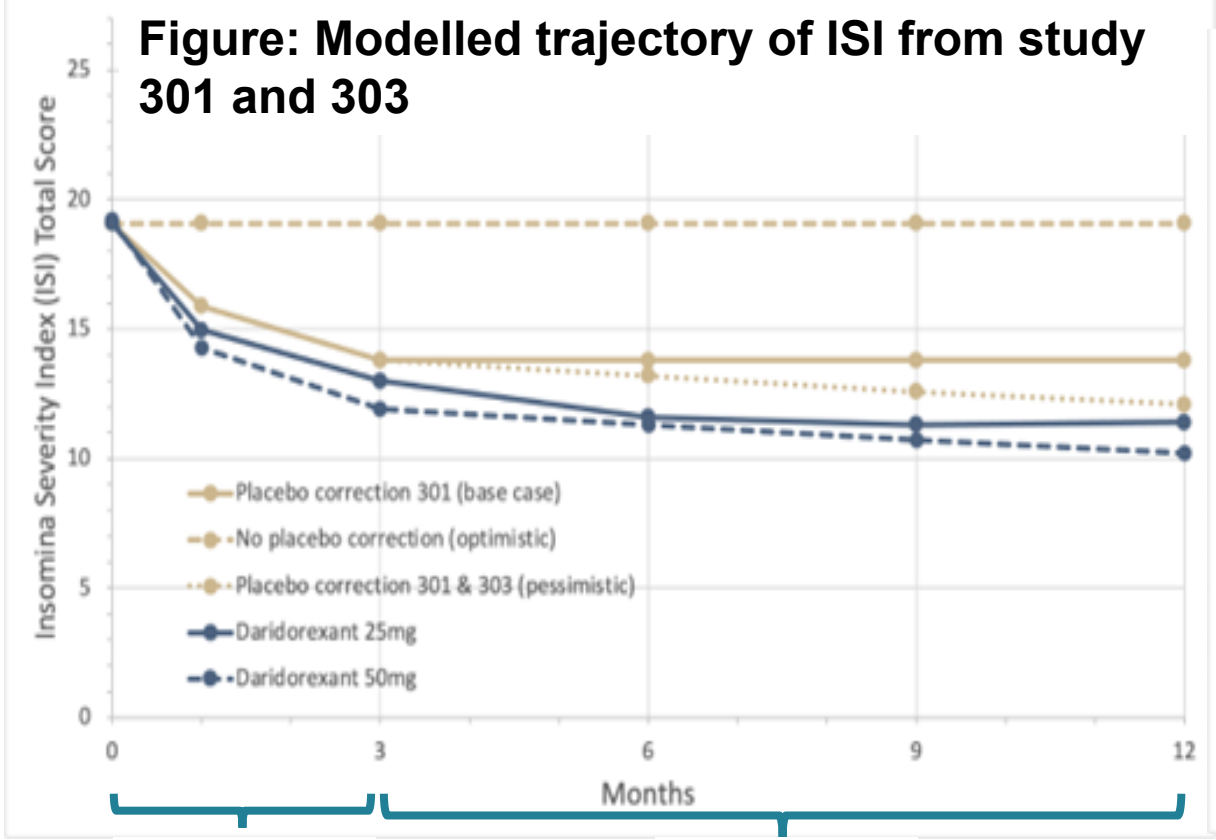
Mean observed sTST improvement from baseline by 4-weekly intervals during the 40-week treatment in study 303, by treatment group

Figure AIC and is redacted

sTST, Subjective total sleep time

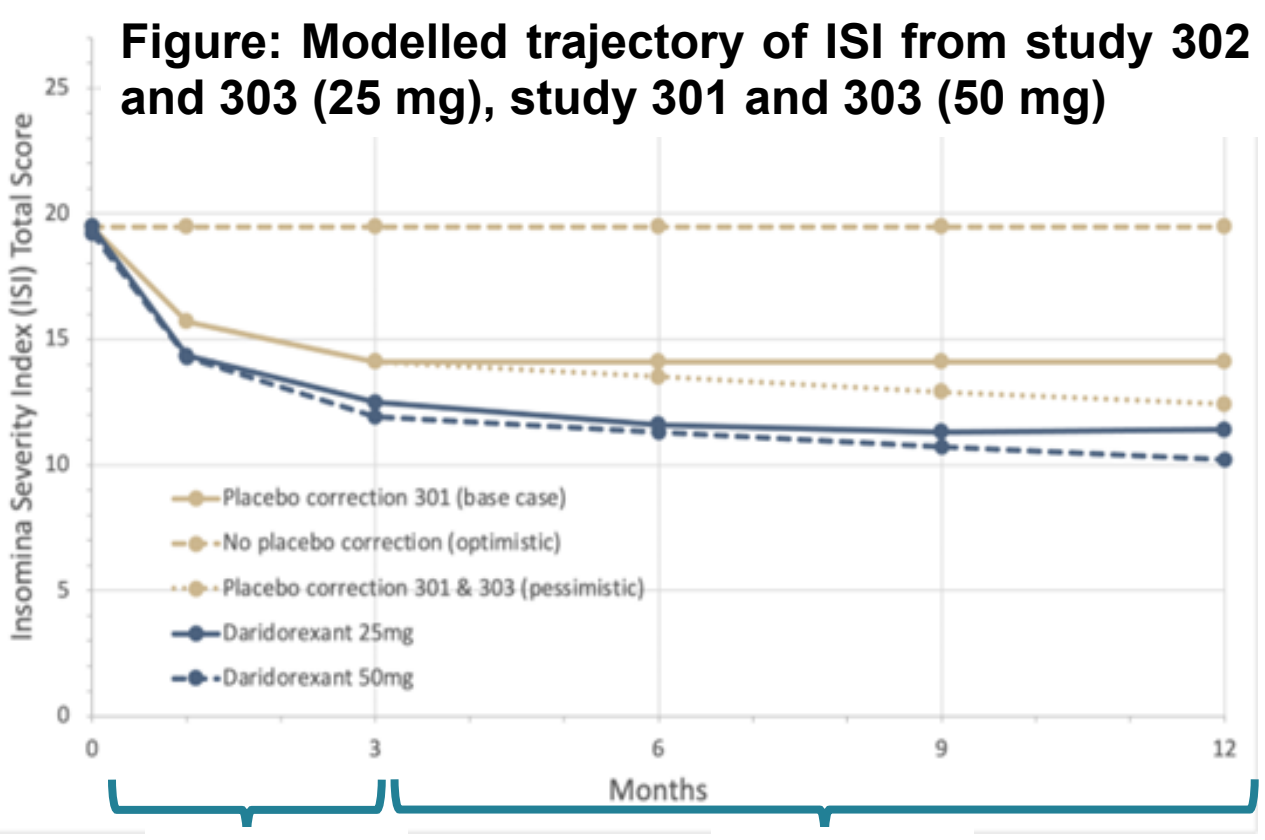
Comparison of 50mg and 25mg modelled ISI outcomes

Figure: Modelled trajectory of ISI from study 301 and 303



Company preferred: study 301 25mg ISI data (N=301) for first 3 months + study 303 25mg ISI data (N=270) from 3 months to up to a year.

Figure: Modelled trajectory of ISI from study 302 and 303 (25 mg), study 301 and 303 (50 mg)



Scenario: study 302 25mg ISI data (N=309) for first 3 months + study 303 25mg ISI data (N=270) from 3 months to up to a year.

Are committee reassured on the clinical and cost-effectiveness evidence for the 25mg dose?

Other changes requested by committee

Request	Included ?	Details	Change to base case ICERs
Additional GP training	☑	Per patient cost: £10.90	ICER increases slightly. →EAG notes that training costs should be considered
Prescription and outpatient visit cost	☑	Inflation factor of 1/0.72 = 1.39 applied to direct health costs (Wickwire 2019: inpatient stays & ER attendances 72% of direct health care costs)	ICER reduces slightly
Adverse event costs	☑	Used QALY data for nasopharyngitis, headache, influenza. Assumed prescription, GP and A&E visit costs	ICER increases slightly

HRQoL, Health related quality of life; ICERs, Incremental cost-effectiveness analysis; QALY, Quality adjusted life years

12-month model: key cost-effectiveness assumptions

Key difference between company's and EAG's base-case is approach for placebo adjustment

Assumption / parameter	Company base case or scenario	EAG base case and comments	ICER impact	Status	Committee preference
Placebo effect	☑ Base case (end of study 301 ISI score persists for no-treatment arm)	☑ Base case with placebo adjustment for full 40 weeks (study 301 and 303 ISI score used for no-treatment arm)	Large	Unresolved	To be discussed
Costs	☑ Scenario GP training, prescription and outpatient visit, adverse events	GP training costs should be included ☒ new costs not included	Small	Committee requested additional costs included at ACM1	To be discussed
Utility mapping function model	☑ Base case ALDVMM model	☑ Base case with Gamma-log GLM	Small	Resolved	Company's mapping was appropriate
Dose	☑ Base case - 50 mg ☑ Scenario – 25 mg	☑Base case - 50 mg ☒Base case/scenario with 25mg not provided	Large	Unresolved	To be discussed

ALDVMM, adjusted limited dependent variable mixture models

Lifetime model (scenario): key cost-effectiveness assumptions

Assumption / parameter	Company base case or scenario	EAG base case and comments	ICER impact	Status
Treatment effect waning (waning)	☑ Scenarios 5% waning and 10% waning modelled separately	Waning may increase the ICER	Large	Updated scenarios at committee request
Stopping rule	☑ Scenario Annual challenge: 10% waning, 20% per annum discontinue after review, cost of annual GP review	Did not comment	Large	Updated scenarios at committee request
Placebo effect / costs / utility mapping function	Same as 12-month model			
Dose	Only modelled for 50mg dose			

Which model is the final decision-making model? 12-month or lifetime horizon model?

Other considerations – societal perspective

Company states daridorexant has additional societal value through improved productivity not currently captured. Company provided the following evidence post ACM1:

- RAND reports the socioeconomic impact of long-term insomnia which include:
    - 44 to 54 days of overall productivity loss annually
    - 1.31% UK GDP lost in terms of working days lost per year
- Two scenarios previously provided shows introduction of daridorexant is:
    - Cost neutral → Using Sheehan disability scale from clinical trial scenario
    - Cost saving → Using WPAI questionnaire from NHWS scenario

NICE Tech team comments - Manual section 4.2.7-4.2.10: 'For the reference case, perspective adopted on costs should be that of the NHS and PSS. Productivity costs should not be included. Evaluations that consider benefits to the government outside of the NHS and PSS will be agreed with the Department of Health and Social Care and other relevant government bodies as appropriate. They will be detailed in the remit from the Department of Health and Social Care and the final scope.'

GDP, Gross Domestic Product; NHWS, National health and wealth survey; PSS, Personal social services ; WPAI, Work Productivity and Activity Impairment

Cost-effectiveness results

12 month, 50 mg dose model

New company base case- 12-month model, 50mg dose with NHS costs and AEs but no GP training

Company ACM1 base case and ACM2 scenario analyses (deterministic*):

	ICER (Deterministic)	Change in ICER
Company preferred base case ACM1 (12 month, 50mg dose model, end of study 301 ISI score persists for no-treatment arm and ALDVMM ISI-EQ-5D utility mapping algorithm)	£24,832	
Company one-way changes- included costs		
Prescription and outpatient visit cost inclusion (a)	£24,504	-328
Adverse event costs inclusion (b)	£25,573	+741
Revised company base case (a) + (b)	£25,239	+ £407
Additional training of 2 hours per annum per GP (c)	£25,282	+450
All cost changes combined: a+b+c	£25,698	+866

☒ Company revised base case does not include additional GP training costs

*Please see back up slides for company's rationale on presenting deterministic analysis results instead of probabilistic analysis

ALDVMM, adjusted limited dependent variable mixture models; ISI Insomnia severity index; ICER, incremental cost-effectiveness ratio

Scenarios- placebo adjustment, 12-month model, 50mg dose

Company have not provided an updated scenarios post ACM1. These were provided at company submission but are illustrative

Company ACM1 scenario analyses (probabilistic):

No.	Scenario	ICER (£)	
		Adjusted for dropout	**No dropout adjustment (100% persistence)**
Company base case (at company submission)		£24,891	-
1	Full placebo adjustment (assumes effect from study 301 and into study 303- EAG preferred)	£36,554	£34,257
2	No placebo adjustment (assumes baseline ISI score from study 301 persists)	£6,843	£6,126

☒ Does not include additional NHS costs, AEs or GP training costs

ICER, incremental cost-effectiveness ratio; Inc, incremental; QALY, quality-adjusted life year

Scenarios- productivity losses, 12-month model, 50mg dose

Company ACM1 base case and scenario analyses:

	ICER*	Change in ICER
Company ACM1 preferred base case (12 month, 50mg dose)	£24,832	
Scenarios		
Productivity loss directly estimated from SDS in clinical trial	215	-24,617
Productivity loss indirectly estimated from mapping WPAI to ISI in NHWS database	Dominant	

✓ End of study 301 ISI score persists for no-treatment arm
☒ Does not include additional NHS costs, AEs or GP training costs

*Company have not stated whether these ICERs are deterministic or probabilisitic

SDS, Sheehan disability scale

EAG ACM1 base case results

*EAG's preferred base case remains the same

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k /QALY)	NHB (£30k /QALY)
Daridorexant	£1,222	0.720				-	-
No-treatment	£614	0.703	£608	0.017	£36,554	-0.013	-0.003

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k /QALY)	NHB (£30k /QALY)
Daridorexant	£1,231	0.720				-	-
No-treatment	£622	0.703	£609	0.017	£36,562	-0.013	-0.003

✓ Full 40 week placebo adjustment
✓ Gamma-log GLM utility mapping algorithm
☒ Does not include additional NHS costs, AEs or GP training costs

NICE

ALDVMM, adjusted limited dependent variable mixture models; CS, company submission; EAG, evidence assessment group, GLM, generalised linear model; ISI Insomnia severity index; PSA, probabilistic sensitivity analysis; TE, technical engagement

Comparison of EAG and company results for ACM2

Deterministic incremental cost effectiveness ratio (cost per QALY) results

	Recap company preference end of study 301 ISI score persists for no-treatment arm	EAG preference full placebo adjustment for 40 weeks
Company preferred base case (12 month, 50mg dose model, ALDVMM ISI-EQ-5D utility mapping algorithm)	£24,832	£36,741
One-way changes - included costs		
Prescription and outpatient visit cost inclusion (a)	£24,504	£36,411
Adverse event costs inclusion (b)	£25,573	£38,175
Revised company base case (a) + (b)	**£25,239**	**£37,836**
Additional training of 2 hours per annum per GP (c)	£25,282	£37,399
All cost changes combined: a+b+c	£25,698	£38,513

- With EAG's preferred full placebo adjustment all ICERs are above the £30,000 cost per QALY willingness to pay threshold

12 month, 25 mg dose model

Scenarios- 12-month model, 25mg dose results

Company ACM2 scenario analyses (probabilistic):

	ICER (Probabilistic)*
25mg dose model includes all cost changes (GP training/Prescription and outpatient/AE) requested by committee combined	
Company base case: Daridorexant 25 mg versus no treatment • Trial data: study 301 and 303 • Placebo adjustment: study 301 only (end of study 301 ISI score persists for no-treatment arm)**	£37,551
Company scenario with Study 302 data: Daridorexant 25 mg versus no treatment • Trial data: study 302 and 303 • Placebo adjustment: study 301 only**	£28,863

✓ End of study 301 ISI score persists for no-treatment arm
~~✓ ALDVMM ISI-EQ-5D utility mapping algorithm~~
✓ All cost changes requested by committee

*Assumed these are probabilistic because 95% confidence interval has been reported in company evidence document

ACM2: Appraisal committee meeting 2; ALDVMM, adjusted limited dependent variable mixture models; ISI Insomnia severity index; ICER, incremental cost-effectiveness ratio

Lifetime horizon, 50 mg dose model

Lifetime horizon model, 50mg dose model with treatment effect waning and stopping rule

Company ACM1 base case and ACM2 scenario analyses:

	ICER	Change in ICER
Company lifetime model (probabilistic analysis results) at ACM1	£16,234	
*Lifetime model: Treatment effect waning inclusion 5%	£25,500	+9,266
*Lifetime model: Treatment effect waning inclusion 10%	£36,500	+20,266
*Lifetime model: Treatment effect waning (10%) and annual challenge (20% dropout)	£19,900	+3,666

*Scenarios are deterministic

- ✓ End of study 301 ISI score persists for no-treatment arm
- ✓ ALDVMM ISI-EQ-5D utility mapping algorithm
- ~~✓ All cost changes requested by committee~~

ACM1 /ACM2: Appraisal committee meeting 1 /2; ALDVMM, adjusted limited dependent variable mixture models; ISI Insomnia severity index; ICER, incremental cost-effectiveness ratio

End of Part 1

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Back up slides

Details of Study 201

Phase 2, randomised, double-blind, placebo-controlled, and active controlled dose-response study. Conducted at 38 sites across 6 countries (Germany, Hungary, Israel, Spain, Sweden, and the USA).

Primary efficacy endpoint: Objective sleep maintenance

Key secondary efficacy endpoints: Subjective sleep maintenance, objective sleep initiation, subjective sleep initiation

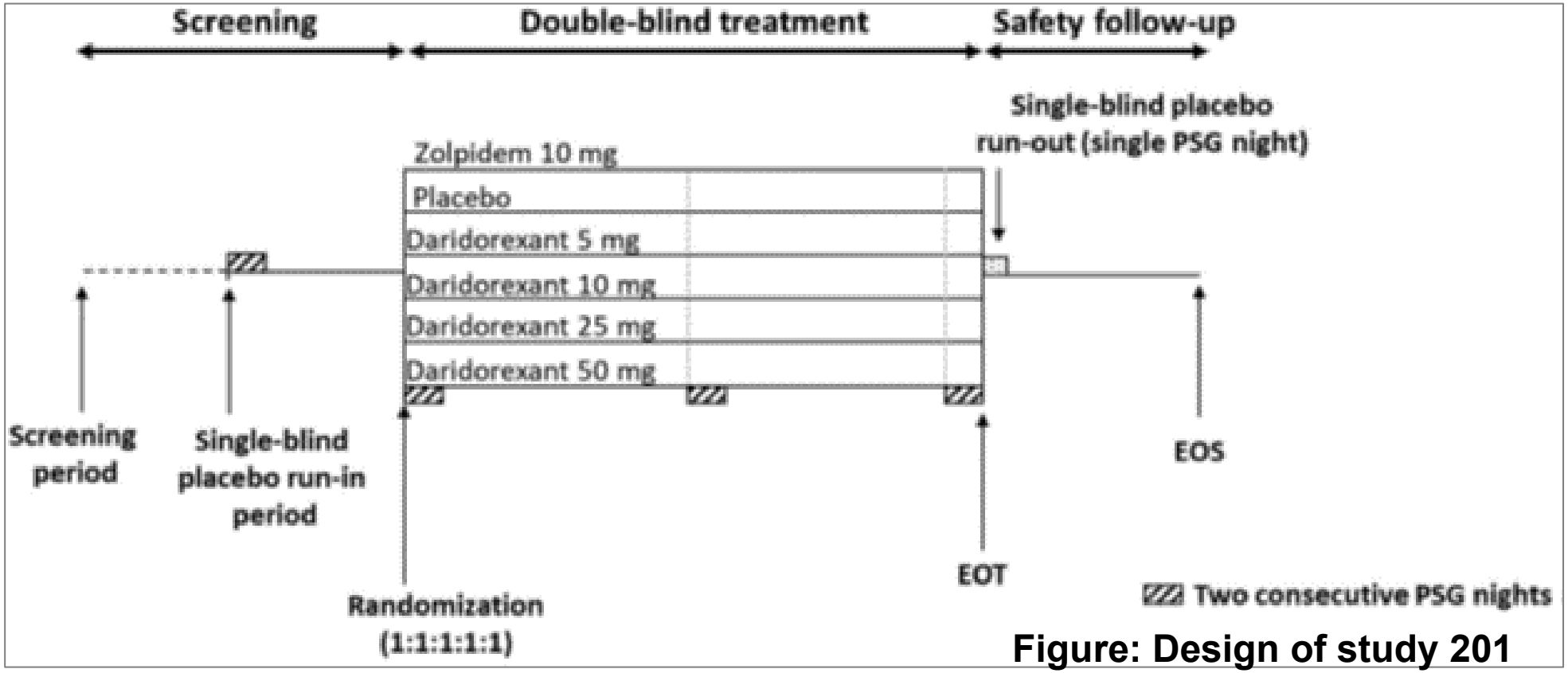

Figure: Design of study 201

EOS, End of study; EOT, End of treatment; PSG, Polysomnography

Details of Study 302

Design, eligibility criteria, pre-specified endpoints and statistical methods identical to that of study 301

924 subjects randomly assigned to receive daridorexant 10 mg (n=307), daridorexant 25 mg (n=309), or placebo (n=308)

Primary efficacy endpoint:
Wake after sleep onset
Latency to persistent sleep

Key secondary efficacy endpoint:

- Subjective total sleep time
- Insomnia daytime symptoms and impacts questionnaire
- Subjective Wake after sleep onset
- Subjective latency to sleep onset
- Total sleep time

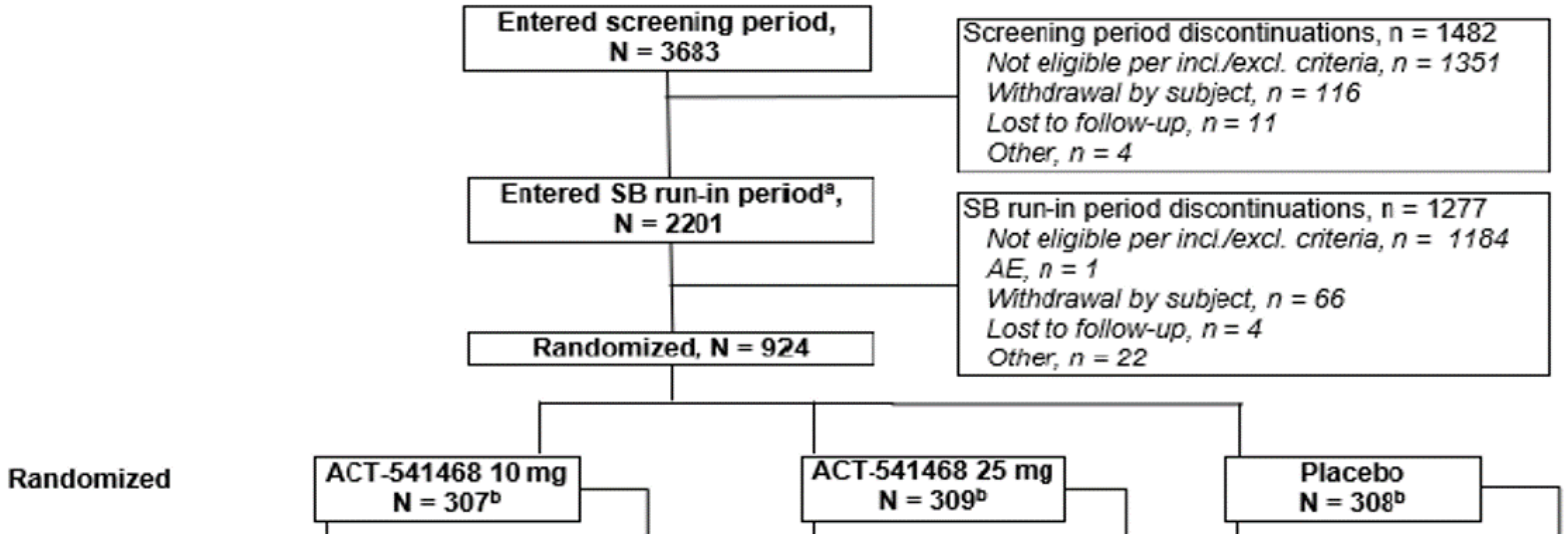

Figure: Design of study 302

AE, Adverse event; SB, Single blind

Dose-response meta-analysis for night-time variables (1/2)

Figure: Observed mean difference in wake after sleep onset (WASO)

Figure: Observed mean difference in latency to persistent sleep (LPS)

Figures are AIC and redacted

- Dose-response meta-analysis based on the comparable population and endpoints of study 301 and 302. Study 201, conducted in similar populations, with the same sleep endpoints
- Descriptive statistics with observed values are graphically represented across studies and doses. Please refer to company response for statistical modelling based outcomes.

Dose-response meta-analysis for night-time variables (2/2)

Figure: Observed mean difference in subjective total sleep time (sTST)

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Company rationale for deterministic analysis (1/2)

- In response to the EAGs request to use the best fitting (ALDVMM) mapping model for utility, we duly included the ALDVMM model. Unfortunately, the estimated covariance matrix for the ALDVMM model was not positive-definite which means it was not possible to derive the Cholesky decomposition matrix and include the uncertainty in the ALDVMM model in the probabilistic analysis. For this reason, the results presented in the response to the ACD were deterministic in nature since we thought it better not to include a probabilistic assessment with a key part missing. Nevertheless, in the original company submission a probabilistic analysis was presented alongside the deterministic analysis and shown to give very similar results. This is because the core part of the model (the impact of treatment on ISI) is a linear model (since it is estimated using a linear regression model). There are some non-linearities in subsequent parts of the model in terms of the relationship between ISI and NHS costs and the mapping from ISIS to utility. Nevertheless it is possible to show (see Table) that these non-linearities have minimal impact on the estimated ICER showing that the model remains approximately linear and that the deterministic point estimates are a good approximation for the mean of the probabilistic analyses as expected when models are linear.

Company rationale for deterministic analysis (2/2)

- The table shows results for both the ALDVMM analysis (where uncertainty in the mapping function is not included in the probabilistic analysis) and the GLM analysis (where it is possible to include uncertainty in the mapping function in the probabilistic analysis). Results are presented for incremental cost, incremental QALY and the estimated ICER. The first row of the table shows the base case analysis is very similar between the ALDVMM and GLM models (£24,832 and £24,731 respectively for the cost per QALY). The next 10 rows show the mean results for 10 separate probabilistic analyses of the models where each probabilistic analysis is based on 1,000 Monte Carlo simulations. The mean across these ten trials closely corresponds the deterministic results (£24,839 and £24,802 per QALY for the ALDVMM and GLM mapping functions respectively) and the standard deviation between the means on the probabilistic analysis is low (relative to the standard deviation across the 1,000 simulations within each probabilistic analysis which represents uncertainty in the estimated quantities.)

	ALDVMM			GLM		
	inc Cost	inc QALY	ICER	inc Cost	inc QALY	ICER
deterministic	£ 601.57	0.0242	£ 24,832	£ 601.57	0.0243	£ 24,731
Probabilistic:						
1	£ 601.46	0.0239	£ 25,118	£ 601.55	0.0243	£ 24,769
2	£ 602.11	0.0243	£ 24,825	£ 601.63	0.0241	£ 24,962
3	£ 601.20	0.0242	£ 24,793	£ 601.34	0.0243	£ 24,746
4	£ 601.66	0.0243	£ 24,795	£ 602.09	0.0241	£ 24,942
5	£ 601.81	0.0243	£ 24,787	£ 600.96	0.0241	£ 24,941
6	£ 602.15	0.0242	£ 24,837	£ 601.88	0.0242	£ 24,863
7	£ 601.31	0.0243	£ 24,717	£ 600.79	0.0244	£ 24,610
8	£ 600.38	0.0242	£ 24,860	£ 602.19	0.0244	£ 24,729
9	£ 601.80	0.0242	£ 24,821	£ 601.79	0.0243	£ 24,740
10	£ 601.33	0.0242	£ 24,839	£ 601.00	0.0243	£ 24,722
mean	£ 602	0.0242	£ 24,839	£ 602	0.0243	£ 24,802
SD	£ 1	0.0001	£ 106	£ 1	0.0001	£ 118