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ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness Analysis of Daridorexant for the Pharmacological Treatment of Chronic Insomnia Disorder in Adults

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Abstract

Objective Daridorexant 50 mg is recommended for treating chronic insomnia in England, Wales (NICE, 2023) and Scotland (Scottish Medicines Consortium, 2024). This study examines the model and cost-effectiveness profile that led to these positive reimbursements.

Methods The cost-effectiveness model integrated data from daridorexant 50 mg phase III trials (studies 301 and 303) and the National Health and Wellness Survey (NHWS). Clinical parameters were the Insomnia Severity Index (ISI) score and adverse events. Using the NHWS, ISI data were mapped to utility, healthcare resource use, and work productivity. Daridorexant 50 mg was priced at £1.40/day. The base-case time horizon was 1 year. A lifetime model explored long-term effects. Parameters, data inputs, structural uncertainty, and alternative scenarios are all presented.

Results In the 12-months model compared with placebo, daridorexant was estimated to have an incremental cost of £389 and generate an additional 0.024 quality-adjusted life-years (QALYs), resulting in an incremental cost-effectiveness ratio (ICER) of £16,300 per additional QALY from a health service perspective. Due to selective attrition, the ICER improved to £9580 per QALY for those continuing treatment for >12 months. Adopting a societal productivity perspective, daridorexant was estimated to offer £596 (£330–£896) total productivity savings versus £411/year in treatment costs, leading to a situation of dominance. Lifetime modeling improved the long-term cost effectiveness of daridorexant under the assumption that any waning of treatment effect led to further dropout.

Conclusion Daridorexant 50 mg is estimated to be a cost-effective pharmacological treatment for chronic insomnia disorder in adult patients.

Key Points for Decision Makers

In the first year of treatment, daridorexant was cost effective compared with placebo for treating adults with chronic insomnia disorder.

Over a lifetime, the cost effectiveness of daridorexant increased further.

When productivity costs were integrated, daridorexant became a dominant option compared with no treatment, as productivity cost savings outweighed treatment costs.

1 Introduction

Insomnia, a prevalent sleep disorder characterized by difficulty in falling asleep or staying asleep with associated daytime impairments, has emerged as a substantial public health concern with profound implications for individual wellbeing and societal productivity. Chronic insomnia, also known as chronic insomnia disorder, is defined as symptoms occurring for ≥3 nights per week for ≥3 months, together with daytime impairments [1].

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Patients with insomnia have both nighttime symptoms and daytime functioning impairments, affecting subjective and objective dimensions of health [2]. The burden of insomnia extends beyond its immediate impact on sleep quality and duration and may give rise to a cascade of negative consequences, including impaired cognitive function, diminished quality of life, and an increased risk of psychiatric and somatic comorbidities [3–6]. The economic ramifications of insomnia are also far-reaching, encompassing healthcare expenditure, workplace absenteeism, reduced productivity, and accidents related to impaired alertness [3, 7–14]. As healthcare systems strive to allocate resources judiciously whilst optimizing patient outcomes, the cost effectiveness of emerging therapeutic interventions becomes a critical consideration.

Pharmacologic treatment of chronic insomnia disorder in adults commonly includes hypnotic agents (e.g., benzodiazepines and non-benzodiazepine receptor agonists), although the therapeutic benefit of these drugs is disadvantaged by a relatively high incidence of treatment-emergent adverse events (AEs), such as tolerance, dependency, rebound, withdrawal, and residual daytime sedation [15–18]. In recent years, the search for innovative pharmacological solutions to address the multifaceted nature of insomnia led to the development of dual orexin receptor antagonists (DORAs), including suvorexant, lemborexant, and daridorexant. While all three are approved for the treatment of insomnia in adults in the United States of America, only daridorexant is authorized for use in the European Union [19].

Daridorexant selectively targets the orexin system, which plays a pivotal role in regulating wakefulness and sleep [20]. By antagonizing orexin receptors, daridorexant modulates the delicate balance between the two states, offering a unique pharmacological approach to insomnia treatment and the potential to deliver clinical efficacy while mitigating the adverse effects commonly associated with traditional hypnotic agents (e.g. daytime drowsiness, cognitive impairment, dependency, and rebound insomnia). Therefore, understanding the economic implications of introducing daridorexant into the therapeutic insomnia landscape is paramount for healthcare decision makers, patients, and other stakeholders.

This paper aims to analyze the cost effectiveness of daridorexant within the UK health system in the context of chronic insomnia management by evaluating its clinical effectiveness, direct medical costs, and costs related to productivity (absenteeism and presenteeism). By highlighting the potential economic advantages of daridorexant in the UK health system and the wider economy, this study seeks to inform healthcare policies, clinical decision making, and resource allocation strategies in the evolving landscape of insomnia management.

We review key evidence on the safety and effectiveness of daridorexant from its clinical trial program, as well as additional evidence linking clinical outcomes to generic health-related quality of life (HRQoL) outcomes and resource consequences of insomnia needed to construct a cost-effectiveness model of chronic insomnia and its treatment.

2 Materials and Methods

In this study, the decision problem was to investigate the cost effectiveness of daridorexant according to its indication and treatment positioning. Cognitive behavioral therapies for insomnia (CBT-I) are the only first-line therapy recommended for the management of chronic insomnia, while existing sedatives (e.g., benzodiazepines and non-benzodiazepines) are only recommended for short-term use (<1 month). Daridorexant is the first DORA and pharmacological treatment recommended in the UK [21] and Europe [19] for the treatment of chronic insomnia. The positioning for daridorexant in primary and secondary care for long-term insomnia is as follows:

1. For treatment-experienced patients who have already completed standard of care including pharmacotherapy, daridorexant can be an alternative option.
2. For treatment-naïve patients who failed to respond to digital or face-to-face CBT-I, daridorexant may be administered as a second-line treatment.
3. Where digital or face-to-face CBT-I is inaccessible, or where a patient is unable to follow CBT-I steps, or refuses CBT-I, daridorexant may be administered as an alternative first-line treatment.
4. When longer-term management of insomnia symptoms (i.e., beyond 4 weeks) is required, daridorexant may be administered as maintenance treatment.
5. When a patient is awaiting access to CBT-I or referral to a sleep specialist, daridorexant may be administered to provide rapid symptom relief.

Given its positioning and indication, the relevant model comparator for daridorexant in this decision problem was placebo (a proxy for 'no treatment') in agreement with the National Institute for Health and Care Excellence (NICE) technology appraisal final scope [21]. This model comparator was also reinforced by the fact that the daridorexant 12-months clinical trial program was based on a direct comparison with placebo only. Key model features are summarized in Table 1 and further detailed throughout the Materials and Methods section.

2.1 Key Clinical Parameter

The clinical outcome driving the model is the Insomnia Severity Index (ISI) [22, 23], a well-established, patient-reported outcome measure and an exploratory endpoint in the daridorexant phase III clinical trials. The ISI captures both patient-perceived insomnia severity and impact on daytime functioning and has been validated as a treatment response metric for insomnia patients [22, 24]. It consists of seven questions on a 0–4 response scale that reflect current (i.e., the last month) insomnia problems. The total score reflects the severity of insomnia, where a score of 0–7 indicates no clinically significant insomnia, 8–14 subthreshold insomnia, 15–21 clinical insomnia (moderate severity), and 22–28 clinical insomnia (severe).

2.2 Data Sources

Two principal data sources were used to develop the model: the daridorexant 50 mg clinical trials consisting of a 12-week phase III registration study (study 301: ClinicalTrials.gov identifier NCT03545191) [25, 26] and its 40-week treatment period, double-blind, extension study (study 303: NCT03679884) [27], and a complementary observational data set from the National Health and Wellness Survey (NHWS) [28].

Table 1 Overview of the cost-effectiveness model of chronic insomnia

Parameter	Description
Type of health economic analysis	Cost-effectiveness analysis
Population	Adults with CID in the UK in primary and secondary care
Intervention	Daridorexant 50 mg (one pill every night before sleep, £1.40 per pill)
Comparator	Placebo
Perspective	Healthcare perspective
Data source	• One multi-center, randomized, double-blind, placebo-controlled, 3-month phase III study (study 301) • One extension-study, multi-center, randomized, double-blind, placebo-controlled, 40-week phase III study (study 303) • A secondary database to source the pharmacoeconomic outcomes: the NHWS (the largest international self-reported patient, cross-sectional annual survey in the healthcare industry)
Time horizon	The time horizon for the base case is 1 year. This corresponds to the length of the combined double-blind periods in study 301 and study 303 A scenario analysis with a lifetime time horizon has also been explored
Discounting	3.5% for both QALYs and costs (for the lifetime scenario only)
Cost-effectiveness analysis outcomes	• Cost of treatment • Direct and indirect costs • QALYs • ICER • NMB
Model structure	A *de novo* pathway model based on trial data
Efficacy	ISI total score
Safety	All TEAEs occurring in >2% in any treatment arm were included in the model
Utility values	EQ-5D-3L
Health care resource use	• Number of emergency room visits • Number of hospitalizations • Number of GPs visits
Productivity	• Work Productivity and Activity Impairment Questionnaire: o Absenteeism o Presenteeism • A scenario analysis using the Sheehan Disability Scale
Sensitivity analysis	• Scenario analysis • DSA • PSA
Software	Microsoft 365 MSO (Version 2111 Build 16.0.14701.20254)

CID chronic insomnia disorder, *DSA* deterministic sensitivity analysis, *EQ-5D-3L* EuroQoL 5-dimensions 3-levels, *GP* general practitioner, *ICER* incremental cost-effectiveness ratio, *ISI* Insomnia Severity Index, *NHWS* National Health and Wellness Survey, *NMB* net monetary benefit, *PSA* probabilistic sensitivity analysis, *QALY* quality-adjusted life-year, *TEAE* treatment-emergent adverse event, *UK* United Kingdom

2.2.1 Daridorexant Clinical Trial Program

2.2.1.1 Phase III Confirmatory Trial (Study 301) Study 301 was a multi-center, randomized, double-blind, placebo-controlled, parallel-group phase III trial [25, 26, 29]. Adult subjects (aged ≥18 years) with insomnia disorder but without insomnia-related comorbidities were randomized in a 1:1:1 ratio to daridorexant 25 mg, 50 mg, or placebo taken once daily in the evening for 12 weeks (84 ± 2 days) followed by a 7 ± 2 days, single-blind, placebo run-out period. The primary endpoints were the change from baseline in wake time after sleep onset (WASO) and latency to persistent sleep (LPS) by polysomnography at months 1 and 3. The secondary endpoints were the change from baseline in self-reported total sleep time (TST) and the sleepiness domain score of the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) at months 1 and 3.

The ISI [22, 23] was an exploratory endpoint measured at baseline, day 28 (week 4), and day 84 (the end of the double-blind 12-week period).

The Sheehan Disability Scale (SDS) [30], a generic measure of disability and functional impairment (see Sect. 2.4.4), was also measured at baseline, day 28, and day 84.

Of note, study 302 (NCT03575104), an identically designed contemporaneous study that assessed daridorexant 10 mg and 25 mg [25, 26, 31], was not considered in this cost-effectiveness analysis beyond its contribution to recruitment for study 303 because the recommended dose of daridorexant is 50 mg.

2.2.1.2 40-Week Extension Study (Study 303) Study 303 was a multi-center, double-blind, parallel-group, randomized, placebo-controlled, extension of studies 301 and 302. Subjects who had completed the 12-week double-blind treatment plus the placebo run-out and were willing to participate were eligible to enroll. Subjects who had received daridorexant in study 301 or 302 were assigned the same dose (i.e., 10 mg, 25 mg, or 50 mg), whereas subjects who were originally randomized to placebo were re-randomized to placebo or daridorexant 25 mg in a 1:1 ratio [27, 32]. The treatment phase ran from informed consent (Visit 1) to week 40 (Visit 5), followed by a 30-day safety follow-up period, which included a 7-day, single-blind, placebo run-out. Visit 1 was performed on the same day as the end of treatment of the 301 or 302 study, after the placebo run-out assessments had been completed (7 ± 2 days), or as an independent visit within a maximum of 7 days after treatment end. The primary objective was to assess the long-term safety and tolerability of daridorexant. Along with safety parameters, ISI and SDS instruments for each subject were assessed at weeks 14, 27, and 40.

2.2.2 National Health and Wellness Survey

The NHWS is a large, nationally representative, cross-sectional, self-administered, internet-based questionnaire of adults (aged ≥18 years) in the US, UK, France, Germany, Italy, Spain, and Japan [28]. It is designed to reflect the general population of each country surveyed, with potential respondents recruited through an existing, general-purpose, web-based consumer panel. All subjects completed the generic HRQoL instrument (EQ-5D), the Work Productivity and Activity Index (WPAI) [33], and answered questions on their health care resource use (HCRU) (i.e., general practitioner [GP] visits, emergency room [ER] attendances, and hospital inpatient [IP] stays). The WPAI captures two components of work productivity: absenteeism and presenteeism. Absenteeism refers to unplanned absences at work (here due to insomnia). Presenteeism, or working while sick, is the act of employees continuing to work despite having reduced productivity levels. Subjects self-reporting insomnia were administered insomnia-specific questions, including the ISI, thereby creating a data source that would allow mapping between the ISI and other measures of interest for the economic model.

2.3 Cost-Effectiveness Model Overview

The model structure is illustrated as pathways in Fig. 1 and shows that clinical trial data was used for the direct estimation of treatment (daridorexant 50 mg or placebo) effect on ISI, AEs, and productivity losses (SDS). This provided an estimate of the number of days on treatment at a cost of £1.40 per day. The impact of treatment on EQ-5D, WPAI, and HCRU was captured indirectly via ISI using the external data source, NHWS.

The pathways from treatment to SDS (measured directly) or WPAI (estimated indirectly via ISI) to cost effectiveness are shown as a dotted line in Fig. 1, as the incorporation of productivity losses in the calculation of cost effectiveness is controversial, and guidance on this varies by jurisdiction. For example, in the UK, the NICE reference case excludes productivity costs [34].

As the daridorexant clinical trial program was based on a 12-week confirmatory trial (301) and its 40-week extension study (303), we chose a 12-month timeframe for the base case rather than extrapolating to patient lifetimes. We consider this as an appropriate time horizon for several reasons. First, no mortality effects for insomnia treatment are assumed; therefore, the only impact is on HRQoL (as measured by the EQ-5D). Second, daridorexant has a quick onset and short half-life, suggesting that treatment effect is gained (and lost) within a short period of time [35, 36]. This statement is also supported by the significant sleep improvement seen after days 1 and 2 in the phase II trial [35, 36]

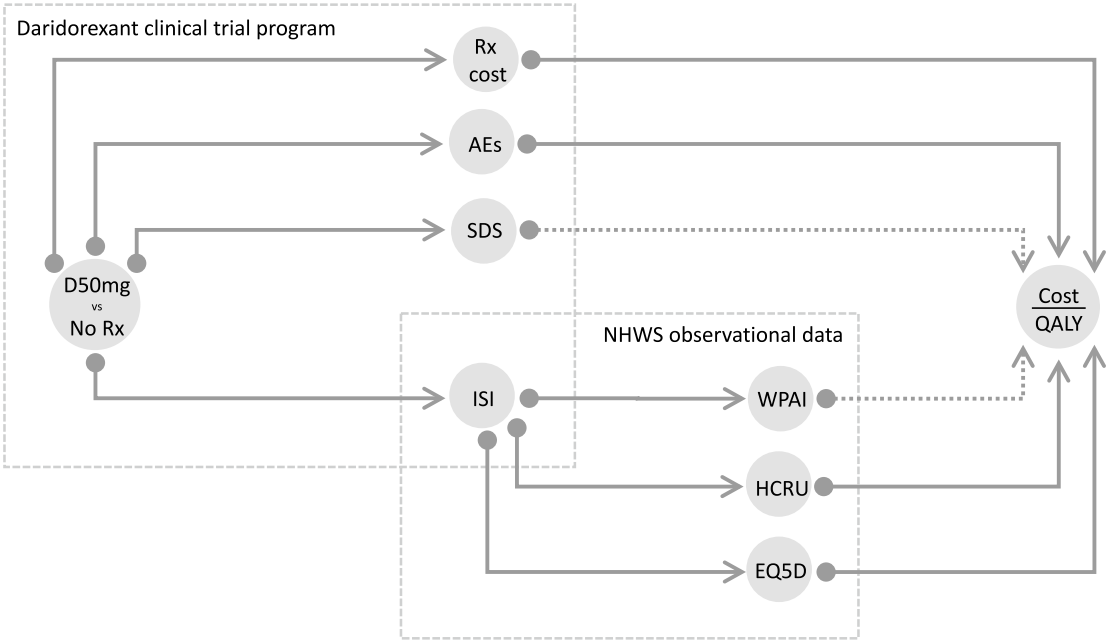

Fig. 1 Schematic of the structure of the 12-month model for daridorexant. *AEs* adverse events, *D* daridorexant, *EQ-5D* EuroQoL 5-dimensions, *ISI* Insomnia Severity Index, *HCRU* health care resource use, *NHWS* National Health and Wellness Survey, *QALY* quality-adjusted life-year, *Rx* treatment, *SDS* Sheehan Disability Scale, *WPAI* Work Productivity and Activity Index

and the rapid loss of efficacy seen during the placebo run-out period of study 301 [25, 26]. Lastly, the labeling for daridorexant suggests that the appropriateness of continued treatment should be assessed within 3 months and periodically thereafter.

Adopting a 12-months timeframe allows the model to capture important aspects of treatment discontinuation, which can have both negative (dropout unrelated to outcome) and positive (dropout among subjects with less treatment benefit or safety problems) consequences for the estimated cost effectiveness. However, given indirect evidence linking insomnia to long-term problems, a lifetime timeframe could be explored on the potential long-term benefits of daridorexant on overall mortality through a reduction in road traffic accidents, cardiovascular stress, neurodegenerative diseases (e.g., Alzheimer's disease), mental health disorders (e.g., anxiety and depression), and falls [37–49]. Since there is some indirect epidemiological evidence for these long-term effects, we examine separate scenarios exploring the potential long-term cost effectiveness of daridorexant when the long-term impact on general mortality is included (see Sect. 2.7).

2.4 Daridorexant Clinical Trial Program Evidence

2.4.1 Impact of Daridorexant on Insomnia Severity Index (ISI) Score

The relationship between ISI scores at weeks 4 and 12 (study 301) was modeled using seemingly unrelated regression (SUREG) [50]. Although seemingly unrelated, the correlation structure between the regression for each time point is captured, and a joint covariance matrix is provided for all coefficients, which provides the necessary information for the probabilistic sensitivity analysis. For study 303, the aggregate data on ISI from the Clinical Study Report (CSR) [32] were used.

In addition to this ISI analysis submitted to NICE and the Scottish Medicines Consortium, an alternative mixed effects model, fitting data from both studies, was performed. This model is reported in full in the Supplementary Materials (see electronic supplementary material [ESM]) but did not form part of the submission to UK reimbursement authorities.

2.4.2 Treatment Discontinuation

Treatment discontinuation was based on the discontinuation rates observed in the clinical trial program. Among the 1684 subjects who completed study 301 and were given the option to continue (or not) into the extension study, 880 (52.3%)

decided to do so. However, the reasons for non-participation were not reported. The proportion of subjects who discontinued was higher in the 303-extension study than in the phase III 301 study, where discontinuation rates were low (see table in Fig. 2).

For the 804 subjects who entered study 303, the proportion of subjects who completed the double-blind treatment period was higher in the daridorexant 50-mg arm (67.9%) compared with the placebo arm (60.9%). As the reasons for treatment discontinuation were recorded, we know that twice as many people dropped their treatment due to lack of efficacy in the placebo arm (22.7%) compared with the daridorexant 50-mg arm (9.5%) (Table S1 details reasons for premature study treatment discontinuation during the double-blind period of study 303, see ESM). These data show a differential drop-out in favor of daridorexant versus placebo, which would be due mainly to the lack of placebo efficacy.

2.4.3 Adverse Events of Daridorexant

The safety of daridorexant was evaluated in the clinical trial program [19]. The label for daridorexant 50 mg identifies headache and somnolence as potential side effects of treatment and notes that these were not significantly more frequent than placebo in the registration trials.

To assess the potential impact of AEs on the cost effectiveness of daridorexant, we included an indication of the likely cost and HRQoL impact of all AEs reported in either study 301 or 303 that occurred with >2% frequency (the arbitrary cut-off adopted in the clinical study report).

2.4.4 Impact of Daridorexant on the Sheehan Disability Scale (SDS)

The SDS [30] is a validated 5-item patient-reported outcome measure. It assesses functional impairment in work/school (item 1), social life (item 2), and family life/home responsibilities (item 3), measured visually as a horizontal line marked with numbers (0–10) and verbal anchors (0 = not at all; 1–3 = mildly; 4–6 = moderately; 7–9 = markedly; 10 = extremely). It also records the number of days of work/school missed in the past week (item 4) and the number of days underproductive in the past week (item 5). A measure of absenteeism comes directly from item 4, and an equivalent number of days lost due to presenteeism can be obtained from (item 1)/(10*(item 5)) [51] since (item 5) gives the number of days unproductive and (item 1)/10 gives a weight to the level of productivity on those days such that a score of 0 on item 1 would give 0 unproductive days and a score of 10 on item 1 would weight all days in item 5 as completely unproductive.

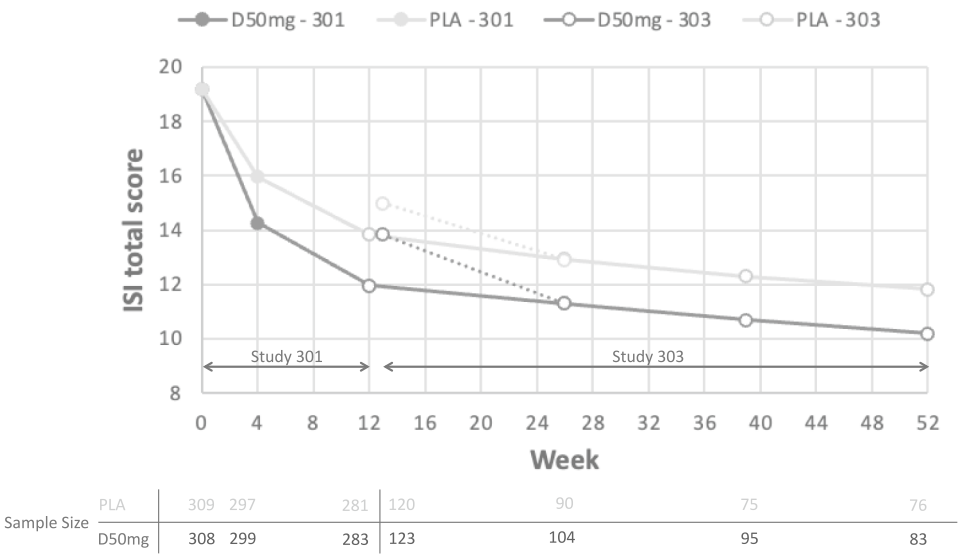

Fig. 2 Total Insomnia Severity Index (ISI) scores in subjects treated with daridorexant 50 mg (D) or placebo (PLA) from the clinical trial program (studies 301 and 303). The modeled profile is represented by the *solid lines* connecting the studies. The *dashed lines* show the total ISI scores at week 13 in subjects who progressed to study 303 after the 1-week placebo run-out. The sample size contributing to each data point at weeks 0, 4, 12, 13, 26, 39, and 52 are listed in the table. The treatment effect of daridorexant on ISI is highly significant both at 1-month and final (3-month) follow-up in study 301 (Table S3 of the electronic supplementary material). The PLA group in study 303 comprises subjects from study 301 and 302

2.5 National Health and Wellness Survey (NHWS) Evidence

2.5.1 Impact of ISI on Utility

A novel mapping algorithm [52] was used to derive EQ-5D-3L utilities converting EQ-5D-5L questionnaires using the Hernández-Alava et al. 2022 crosswalk algorithm [53] from ISI scores based on the NHWS cross-sectional survey. This new mapping, developed according to ISPOR task force guidance [54], not only draws its strengths from the use of a large international dataset but also incorporates adjustment variables (including sociodemographic and general health characteristics) to reduce the effects of confounders. In the base case, a generalized linear model (GLM) was used to create the mapping function. This base case model was compared with an alternative Adjusted Limited Dependent Variable Mixture Model (ALDVMM) [55] in a scenario analysis. Although the ALDVMM approach had a slightly better fit to the data, it was less parsimonious, involving five times as many parameters as the GLM used in the base case [52].

2.5.2 Impact of ISI on Health Care Resource Use

The association between direct HCRU categories (GP visits, ER attendances, IP stays) and ISI was calculated from the NHWS data using the GLM, with a negative binomial distribution family and a log link. Unit costs (base year of costing 2020/21) of £39.23 for a GP visit [56], £184.62 for an ER attendance [57], and £996.29 for an IP day [57] were applied to predicted resource counts to estimate the total health service cost.

As the NHWS data did not include two main categories of HCRU (outpatient [OP] visits and concomitant medications), a simple inflation factor was introduced to the model. In an analysis of health care costs of insomnia in the US, Wickwire and colleagues found that OP visits and prescription costs made up 27% of total health service costs [58]. In order to adjust for these missing costs in the NHWS data, the total predicted costs were inflated by $1/(1-0.27)\times100\%$.

2.5.3 Impact of ISI on Work Productivity and Activity Index (WPAI)

As the NHWS dataset included the administration of the WPAI, we examined the effect of insomnia on work productivity. The WPAI consists of six questions relating to (1) current employment; (2) hours missed due to health problems; (3) hours missed for other reasons; (4) hours worked; (5) the degree to which health problems affected productivity while working (on a 1–10 VAS scale); and (6) the degree to which health problems affected productivity for unpaid activities (on a 1–10 VAS scale) [33, 59]. Percentage absenteeism was calculated from the following formula (where Q# relates to the question number given above) as $Q2/(Q2+Q4)\times100\%$ for subjects who were currently employed, and percentage presenteeism was calculated as $Q5/10\times100\%$ for subjects who were currently employed and had worked in the past 7 days.

In separate models, the percentage of absenteeism and presenteeism formed the response variable in a binomial family, log-link GLM, with ISI as an explanatory variable. Percentage absenteeism as a function of ISI was then costed utilizing the median annual wage rate of £25,971 [60]. Percentage presenteeism was applied as a weighting to the percentage of time that subjects were present at work (i.e., to the 1 − percentage absenteeism) and was also costed using the median annual wage rate.

2.6 Cost Effectiveness, Parameter Estimation, and Uncertainty Analysis

Point estimates for all model parameters were included in the model to estimate the incremental cost effectiveness of daridorexant 50 mg compared with standard of care (sleep hygiene) plus placebo. Incremental costs and incremental quality-adjusted life-years (QALYs) are presented separately from incremental cost-effectiveness ratios (ICERs). Uncertainty estimates for modeled quantities were obtained by propagating input parameter uncertainty through the model using Monte Carlo simulation (probabilistic sensitivity analysis).

Where input parameters are estimated statistically from either of the two datasets, expected values and standard errors are used for the point estimates and uncertainty, respectively. Further, where these parameters are jointly estimated from a statistical GLM, the correlation between input parameters is captured through the covariance matrix for the model and the resulting Cholesky decomposition matrix [61]. For unit costs, the standard error for probabilistic analysis was assumed to be 10% of the point estimate. Uncertainty in output parameters is illustrated on the cost-effectiveness plane and as confidence intervals.

ESM Table S2 contains a full set of input parameters for the 12-month model and information on the distributions used for probabilistic analysis. Probabilistic analyses were based on 1000 simulations.

2.7 Exploratory Lifetime Model

Although the justification for using a 12-month model was made in Sect. 2.3, we also noted the possible long-term impacts of improving sleep. Since it is possible that patients may stay on daridorexant for more than 12 months, we produced an illustrative lifetime model that allows extrapolation of treatment to a lifetime time horizon. In doing so, we included the following additional elements for the long-term

model: potential mortality effects of better sleep estimated from the epidemiological literature [48]; an additional yearly dropout rate parameter; the inclusion of a 'waning' parameter to explore what happens if the effectiveness of treatment diminishes over time; inclusion of an additional GP visit in the long-term model to 'challenge' long-term treatment with the associated assumption that patients for whom treatment effect has waned will not restart treatment; and discount rates for costs and effects occurring beyond 12 months (both 3.5%) (see ESM Table S2 for additional lifetime model parameters). According to the labeling, 'challenge' was defined as a periodical review by the treating physician to assess the appropriateness of pursuing the long-term use of daridorexant 50 mg. Note that our longer-term model does not model the separate impacts of the possible impacts of insomnia identified in Sect. 2.3. Rather, we assume that the mortality impacts identified in the literature [48] are an amalgam of the individual-specific effects on mortality. Of course, this means that we are neglecting the non-fatal event impacts on HRQoL in the long term.

3 Results

3.1 Daridorexant Clinical Trials

3.1.1 Impact of 12 Months of Treatment on ISI

The SUREG model estimated for 551 subjects in study 301 (ESM Tables S3 and S4) was combined with aggregate study 303 data for 804 subjects to give the estimated 12-month ISI profile shown in Fig. 2. The SUREG model on study 301 shows that the treatment effect of daridorexant on ISI is highly significant both at 1 month and at the final (3-month) follow-up. This profile shows a greater decrease (improvement) in ISI total scores for subjects treated with daridorexant compared with placebo. Over the study period, a decrease in ISI total scores was observed from week 0 to week 12 in both treatment groups and continued, albeit gradually, through to week 52.

3.1.2 Selective Attrition

For the 804 subjects who entered study 303, the potential for selective attrition to impact the cost-effectiveness results was considered. Selective attrition occurs when the ISI scores for subjects who do not finish the study are shown to be markedly different from those of subjects motivated to continue taking treatment.

Figure 3, which further stratified subjects as completers or non-completers, suggests that subjects who dropped off from treatment had lower ISI improvements than those who stayed on treatment. The hypothesis being that subjects for whom treatment has a beneficial effect have a higher tendency to continue treatment. This phenomenon is called selective attrition. It is defined as the selective dropout of some participants who systematically differ from those who remain in the study.

In the case of study 303, the selective attrition bias penalized the daridorexant treatment arm. This is because a higher proportion of subjects drop out from placebo due to lack of efficacy. This artificially increases (improves) the average change from baseline in ISI for those who continued placebo, compared with the daridorexant arm. Performing

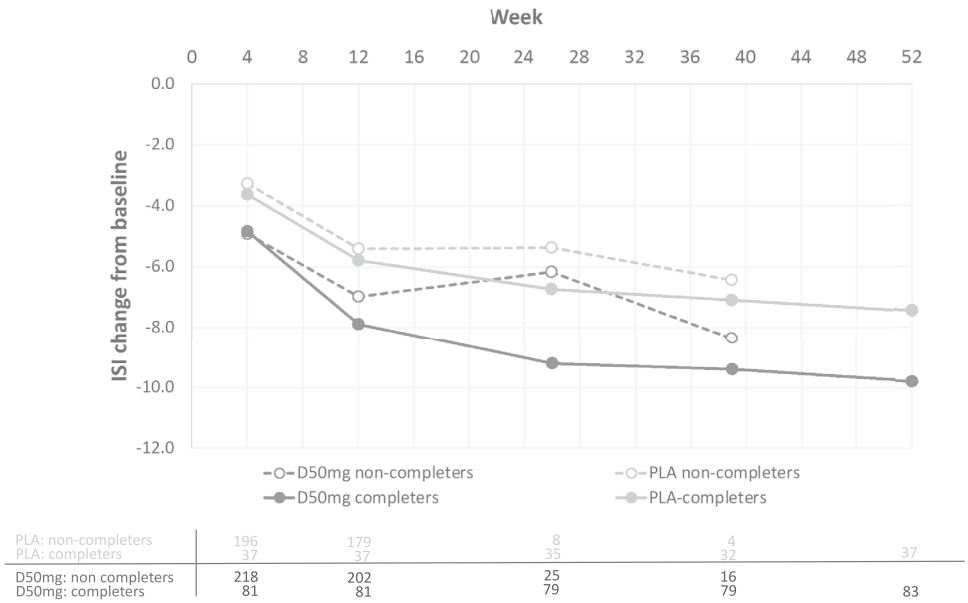

Fig. 3 Evidence of selective attrition based on the change in Insomnia Severity Index (ISI) score from baseline in subjects who discontinued treatment with daridorexant 50 mg (D) or placebo (PLA). The active treatment and placebo groups were further stratified into subjects who completed the 52-week study period (*solid lines*) and those who failed to complete the full 52 weeks (*dotted lines*). The 'non-completer' group, shown as *dashed lines*, comprises all individuals for whom the last observed measure occurred before week 52. In contrast to Fig. 2, the placebo group shown here are subjects that started in study 301 and, therefore, exclude subjects recruited from study 302

the analyses in the full analysis set (FAS) does not solve the problem, as it would necessitate complete follow-up of all randomized subjects for study outcomes. Alternatively, the ISI outcome was missing for most of the subjects who dropped out.

Selective attrition bias has important implications for how 'no active treatment' is modeled in the base case.

A substantial placebo effect was apparent in Fig. 2, as seen by the change from baseline in ISI total scores in placebo-treated subjects. In subjects who progressed to study 303 after the placebo run-out, ISI total scores increased at week 13 in both treatment groups (dashed lines in Fig. 2), although a subsequent decrease in ISI total scores was observed after the reinstatement of treatment in study 303. Selective attrition bias was shown to be responsible for continued improvement in ISI total scores in study 303 in both treatment groups. Selective attrition bias favors the placebo arm, and as the placebo is a proxy for 'no treatment,' we could argue that neither the selective attrition bias nor the placebo effect will be observed in real life. Therefore, we constructed one base case and two scenario analyses for the no-treatment comparator group: (1) placebo correction based on study 301 only (base case and solid line); (2) placebo correction based on study 301 and study 303 (dotted line); and (3) no placebo correction (dashed line). These are illustrated as potential comparators to active treatment in the cost-effectiveness model in Fig. 4. So as not to clutter the figure, confidence intervals are not presented, but Table S5 of the ESM shows the uncertainty associated with each data point in Fig. 4 together with the difference between daridorexant 50 mg and the selective attrition/full placebo correction.

Our base-case assumption was that after the 301 study, no-treatment subjects would continue at the same ISI achieved at the end of study 301. In the real world, patients without treatment would not be expected to improve relative to their stable baseline ISI scores since, in the real world, no placebo would be given, and no placebo effect would be apparent. Therefore, we model, as a more optimistic scenario, that the full change from baseline score is attributable to treatment (dashed line in Fig. 4). A more pessimistic scenario would be to continue to placebo adjust into the period of the 303-extension study, as shown by the dotted line in Fig. 4.

3.1.3 Adverse Events Results

An analysis of potential AEs (see ESM Tables S7–S9) showed an estimated incremental cost associated with AEs of £6.21 per patient and an associated loss of 0.2 incremental quality-adjusted life days or 0.0005 QALYs. In the probabilistic analysis, we assumed the standard error (SE) would be half these expected values, which is equivalent to making these results borderline statistically significant in the model (despite a lack of evidence of difference in AEs in the label).

3.1.4 Treatment Impact on the SDS

The impact of treatment on productivity losses, measured across study 301 and study 303, is presented in Fig. 5. Productivity losses are lower for daridorexant than placebo at all time points after baseline for absenteeism and presenteeism. The difference between daridorexant and placebo in absenteeism and presenteeism is shown below the axis and can be interpreted as the productivity savings attributable to active

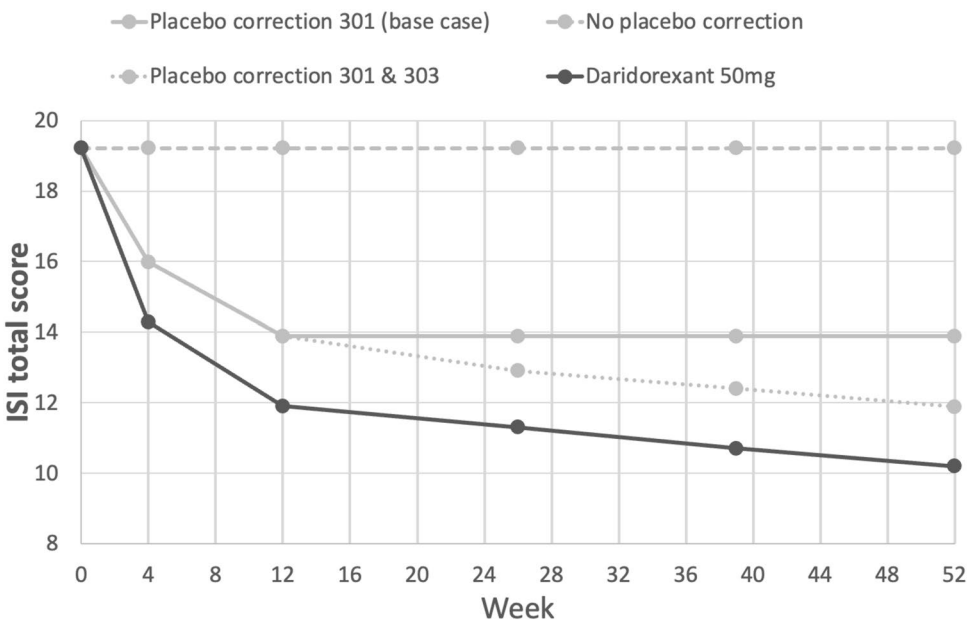

Fig. 4 Modeled trajectory of Insomnia Severity Index (ISI) total scores from the phase III study 301 (week 0 to 12) and the 303-extension study (week 13 to 52) showing active treatment (daridorexant 50 mg) and no-treatment comparator consisting of base case (placebo correction 301), optimistic (no placebo correction), and pessimistic (placebo correction 301 and 303) scenarios regarding placebo adjustment

treatment. Accumulating these productivity savings over the 12 months of the cost-effectiveness model gives an estimated £252 (confidence interval [CI] from the probabilistic sensitivity analysis: 5–503) absenteeism savings plus £344 (CI: 203–503) presenteeism savings, for a total of £596 (CI: 330–896) total productivity savings, which is higher than the yearly cost of treatment at £411 (adjusted for dropout).

3.2 Mapping Results Based on the NHWS Dataset

3.2.1 ISI to EQ-5D Utility

The GLM of disutility described in Sect. 2.5.1 generated a mean (SE) constant term of −1.865 (0.024) and a coefficient on ISI score of 0.047 (0.018). ISI scores in Fig. 4 mapped to EQ-5D utility using the GLM algorithm results in the QALY profiles are presented in Fig. 6. This shows that, as in Fig. 4, the base-case scenario is closer to the placebo correction from baseline (dotted line) than the scenario with no placebo correction (dashed line). Furthermore, the linear interpolation between the estimated EQ5D at each timepoint facilitates the use of the trapezium rule to estimate the area under the utility curve to estimate QALYs and QALY gains.

3.2.2 ISI to Health Care Costs and WPAI Productivity Losses

The total health care cost for all resource categories (GP visits, ER attendances, IP stays, OP visits, concomitant medications), presented as a function of the ISI total score, increased with increasing insomnia severity (Fig. 7). Similarly, annual productivity losses due to absenteeism and presenteeism by ISI score also increased with increasing insomnia severity (Fig. 8).

3.3 Modelled Cost-Effectiveness Results

3.3.1 12-Month Model

In the 12-month cost-effectiveness model (Table 2), the 12-month health service costs and QALYs were higher for the daridorexant treatment arm than the standard of care plus placebo arm. This corresponded to an incremental cost (QALY) of £478 (0.033) and a resulting ICER of £14,287, with all participants assumed to be taking active treatment for the full year. When adjusted for the impact of dropout rates (observed in studies 301 and 303), the ICER increased to £16,282, as subjects who drop out of treatment still incur treatment costs over 12 months but do not experience treatment benefits. In the estimated cost effectiveness for subjects who remain on treatment at 12 months, the ICER improved

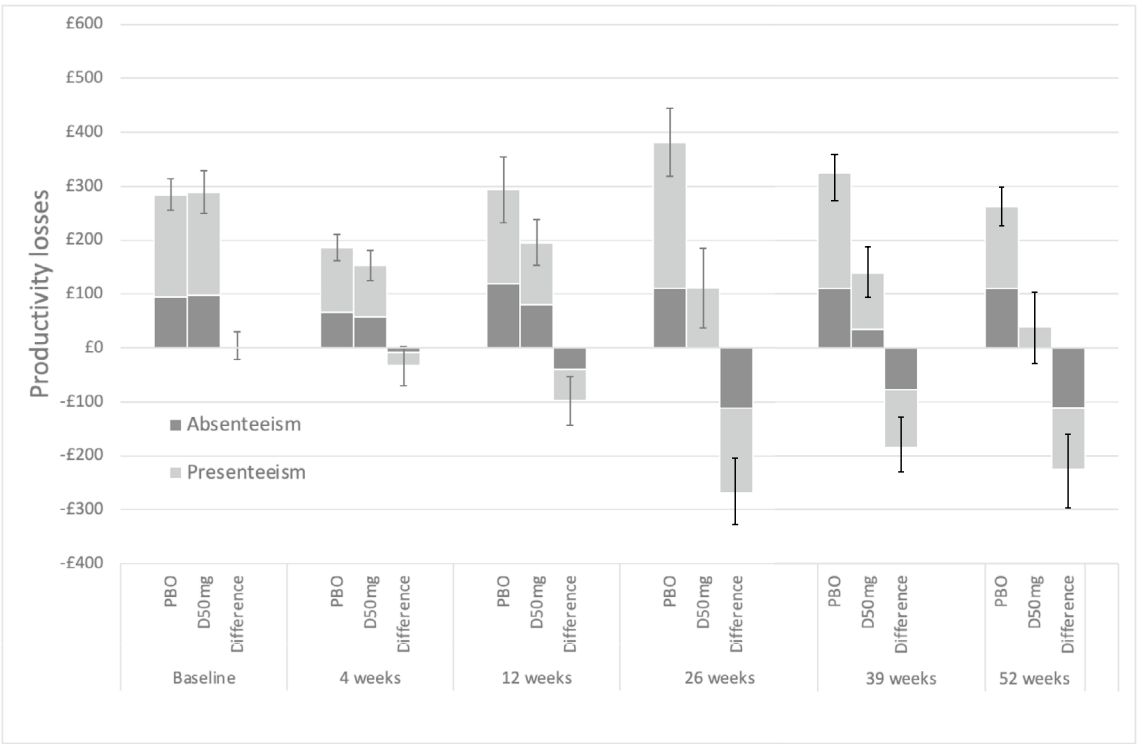

Fig. 5 Treatment impact on productivity losses (£) based on the Sheehan Disability Scale (SDS) [30], and measured across studies 301 and 303 by time point in the cost-effectiveness model. *D* daridorexant, *PBO* placebo

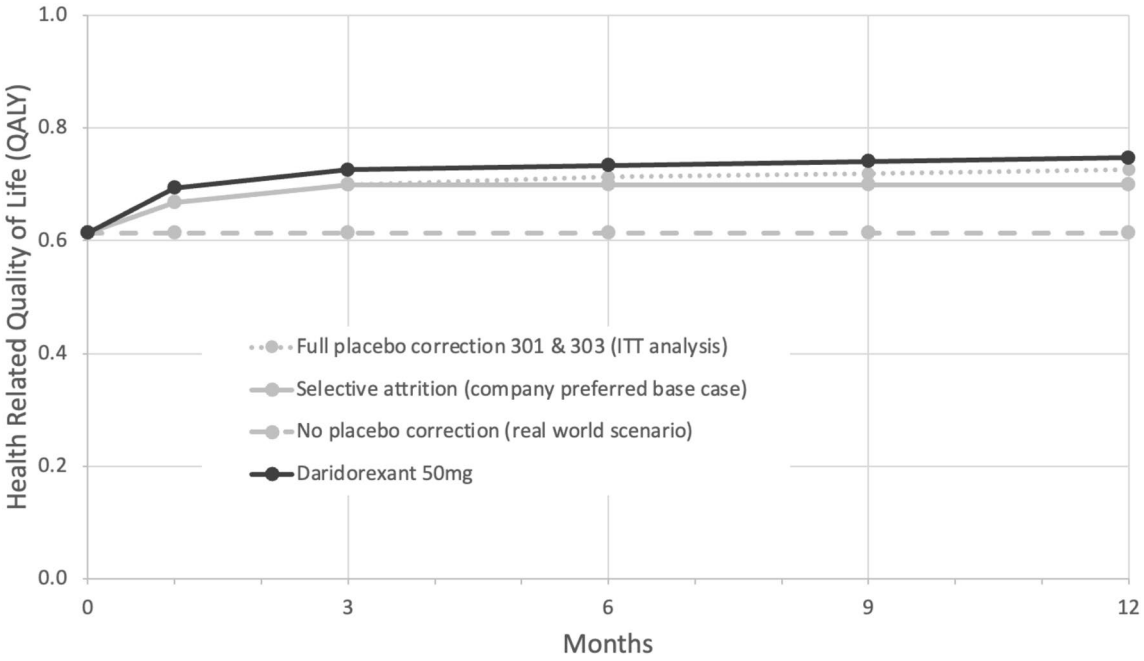

Fig. 6 Health-related quality of life utility profile of EQ-5D mapped from the Insomnia Severity Index (ISI). *ITT* intent to treat, *QALY* quality-adjusted life-year

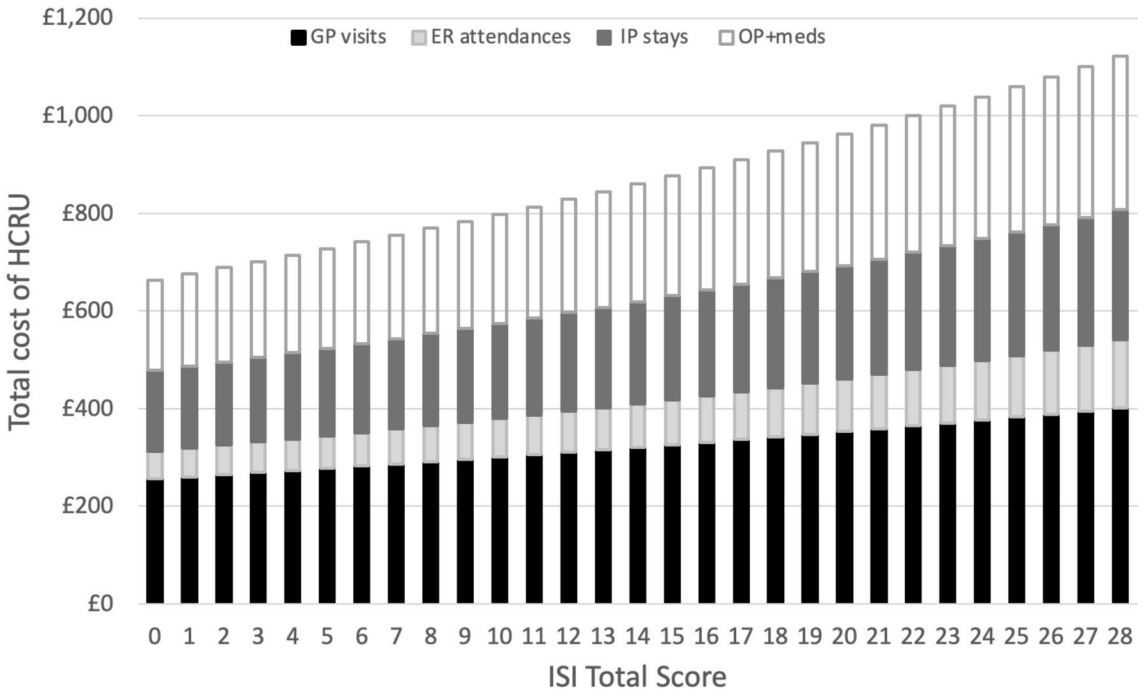

Fig. 7 Total health care costs by resource use category mapped to the Insomnia Severity Index (ISI) total score. *ER* emergency room, *GP* general practitioner, *HCRU* health care resource use, *IP* inpatient, *meds* concomitant medications, *OP* outpatient visits

(£9580), as these subjects are shown to get greater benefit from treatment (on average) than those who drop out from treatment (the selective attrition effect).

Uncertainty for the base-case results of the 12-month dropout-adjusted results are shown on the cost-effectiveness plane in Fig. 9. The estimated ICER in the base case was £16,300 (£11,300–£30,300) per QALY and the decision

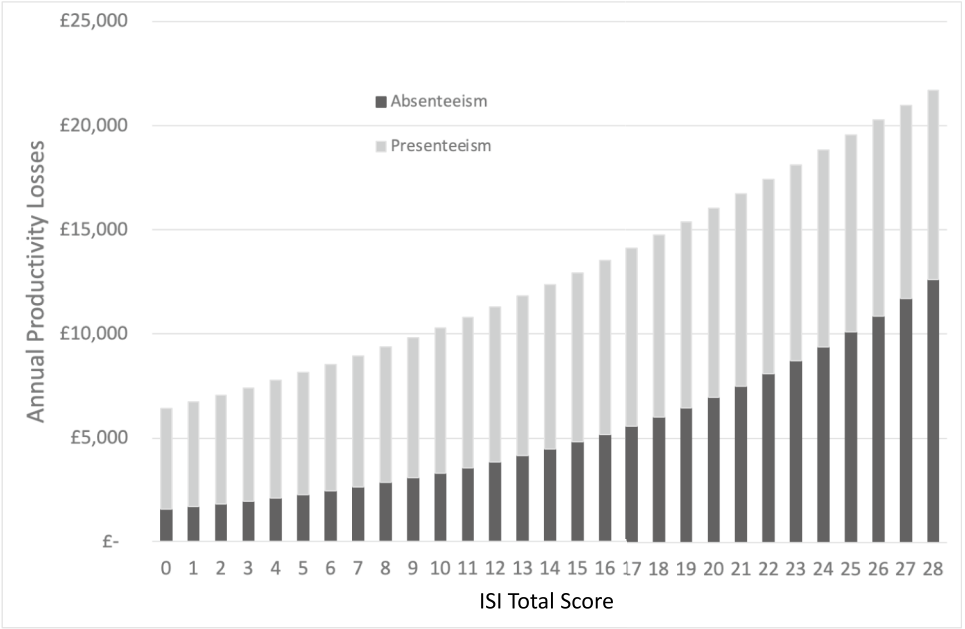

Fig. 8 Annual productivity losses by Insomnia Severity Index (ISI) total score

Table 2 The 12-month model cost-effectiveness results showing the 12-month cost and quality-adjusted life-years (QALYs) for the placebo and daridorexant treatment arms, together with the incremental costs and the incremental cost-effectiveness ratios (ICERs)

Technology	Cost	QALY
Full compliance model[a]		
No treatment	£866	0.692
Daridorexant	£1344	0.725
Incremental cost	£478	0.033
ICER	£14,287	
Impact of dropout rates (observed in studies 301 and 303)		
Incremental cost (over 1 year)[b]	£389	0.024
ICER (over 1 year)[b]	£16,282	
Estimated cost effectiveness for subjects who stay on treatment		
Incremental cost (at 1 year)	£458	0.048
ICER (at 1 year)	£9580	

[a]All participants are assumed to be taking active treatment for the full year

[b]Adjusted for dropout

thresholds in Fig. 9 show that the simulations supported the cost effectiveness of daridorexant in 76% and 98% of cases for decision thresholds of £20,000 and £30,000 per QALY, respectively.

3.3.2 Lifetime Model Scenarios

In Europe, daridorexant is the only licensed pharmacological therapy for chronic insomnia disorder in adults with evidence of efficacy for a duration of 12 months of treatment. In principle, treatment could be continued for longer than 12 months if required. As shown in Table 2, the cost effectiveness during the first year of the model is not as favorable as the cost effectiveness for subjects that continue with treatment during the entire 12 months (ICER of £14,287 vs £9580).

A lifetime analysis of daridorexant therapy was modeled using additional parameters and assumptions about the potential long-term benefits of improved sleep on all-cause mortality. Although there was no evidence from the clinical trial data that the effectiveness of daridorexant waned over the 12 months of treatment (and indeed, the evidence is to the contrary), there is no guarantee that the efficacy would be maintained with long-term use. For this reason, a treatment 'waning' parameter was introduced, and the use of an annual challenge was modeled. The annual challenge involved an additional consultation with the GP whereby treatment was withdrawn and only restarted in subjects with a loss of efficacy.

Lifetime cost effectiveness for four scenarios is shown in Fig. 10. The first shows the cost effectiveness over the lifetime where no waning of treatment effect is assumed. In this scenario, an initial improvement in cost effectiveness is observed over time from the 12-months base-case cost-effectiveness (i.e., £16,300) towards the cost effectiveness in subsequent years where an additional benefit is the (modest) reduction in mortality associated with improved sleep patterns.

When a 5% waning of the effect parameter is introduced, the cost effectiveness improves initially but returns to approximate the base-case cost effectiveness over time (Fig. 10). If a 10% waning parameter is introduced, cost effectiveness improves initially but rapidly increases above

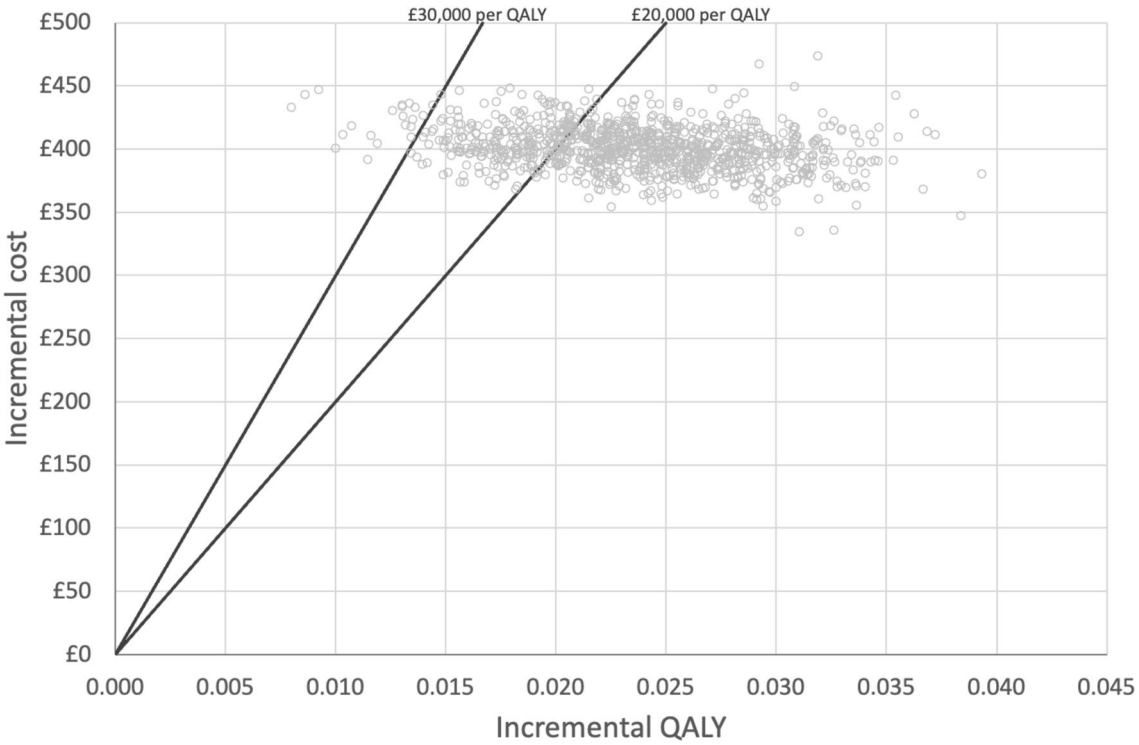

Fig. 9 Results of the probabilistic sensitivity analysis on the cost-effectiveness plane. *QALY* quality-adjusted life-year

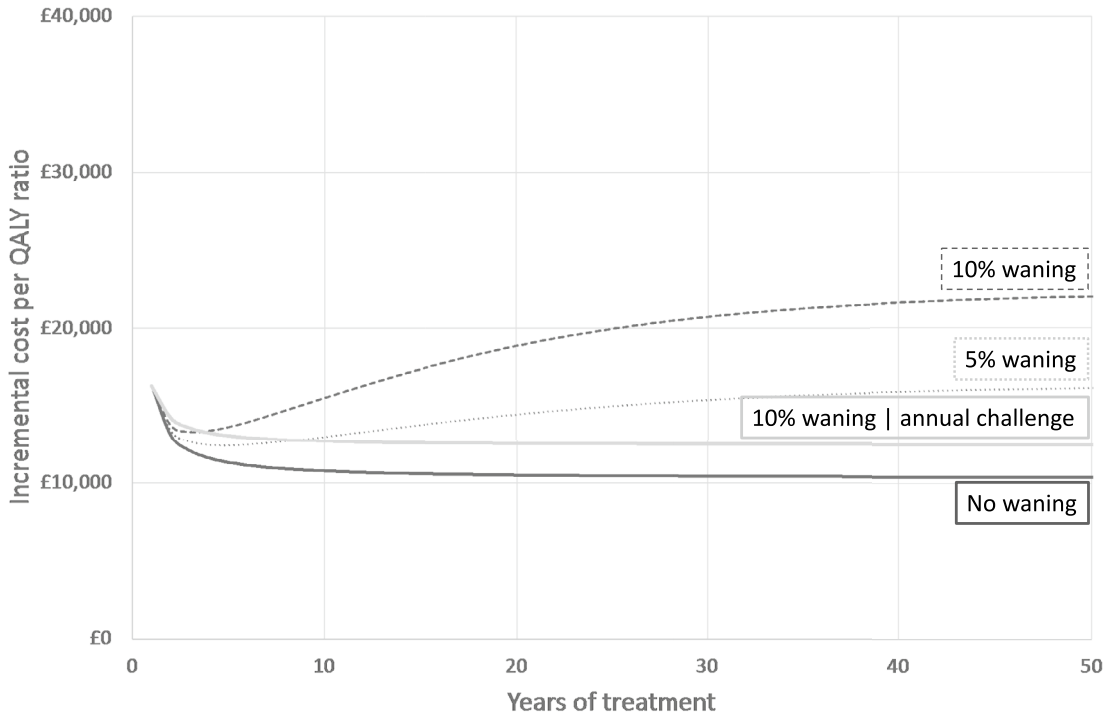

Fig. 10 Lifetime cost effectiveness of daridorexant under different assumptions. *QALY* quality-adjusted life-year

the base-case cost effectiveness. However, if a 10% waning effect plus an annual challenge is assumed, the risk of treatment waning is mitigated, and the long-term cost effectiveness remains below the base-case cost effectiveness (Fig. 10).

3.4 Additional Uncertainty and Scenario Analyses

Several different scenarios were tested to explore uncertainty related to analytic assumptions, each with a nested probabilistic analysis (Fig. 11). By assuming the full placebo correction only (thereby ignoring the selective attrition evidence), the ICER becomes less favorable than the base-case results. All other assumptions improve the ICER, including the lifetime scenario, which includes 10% waning with an annual challenge (Fig. 11). The real-world scenario, whereby daridorexant is not compared with placebo but with the baseline ISI score without treatment, shows a large reduction in the ICER and the underlying uncertainty, as shown by the narrow CI bars from the probabilistic sensitivity analysis. Although the CI bars widen for the scenarios with productivity costs included, the overall decision in uncertainty is reduced. This is because, whether productivity losses are estimated directly from the SDS instrument in the clinical trial or indirectly by mapping ISI to WPAI, productivity losses dominate the cost of treatment such that the model predicts that there are cost savings to society. The resulting ICERs are negative (dominant strategies).

As noted in Sect. 2.4.1, an additional mixed model analysis was performed based on individual patient data for study 301 patients that proceeded to study 303. These results are reported in ESM Tables S10 and S11, with replication of Fig. 4 using the mixed model in ESM Fig. S1. The mixed model produced very similar results to the SUREG model for 301 with aggregate 303 data that formed the basis of the submissions to UK reimbursement authorities.

4 Discussion

In this manuscript, we describe a UK cost-effectiveness analysis on the use of daridorexant to treat chronic insomnia disorder. This analysis formed the basis of a submission to NICE (England and Wales) and the Scottish Medicines Consortium. As part of the submission process, several issues were raised that merit further discussion.

4.1 Cost Effectiveness of Daridorexant

Within its positioning, daridorexant is the only pharmacological treatment demonstrating cost effectiveness in the treatment of chronic insomnia disorder. NICE

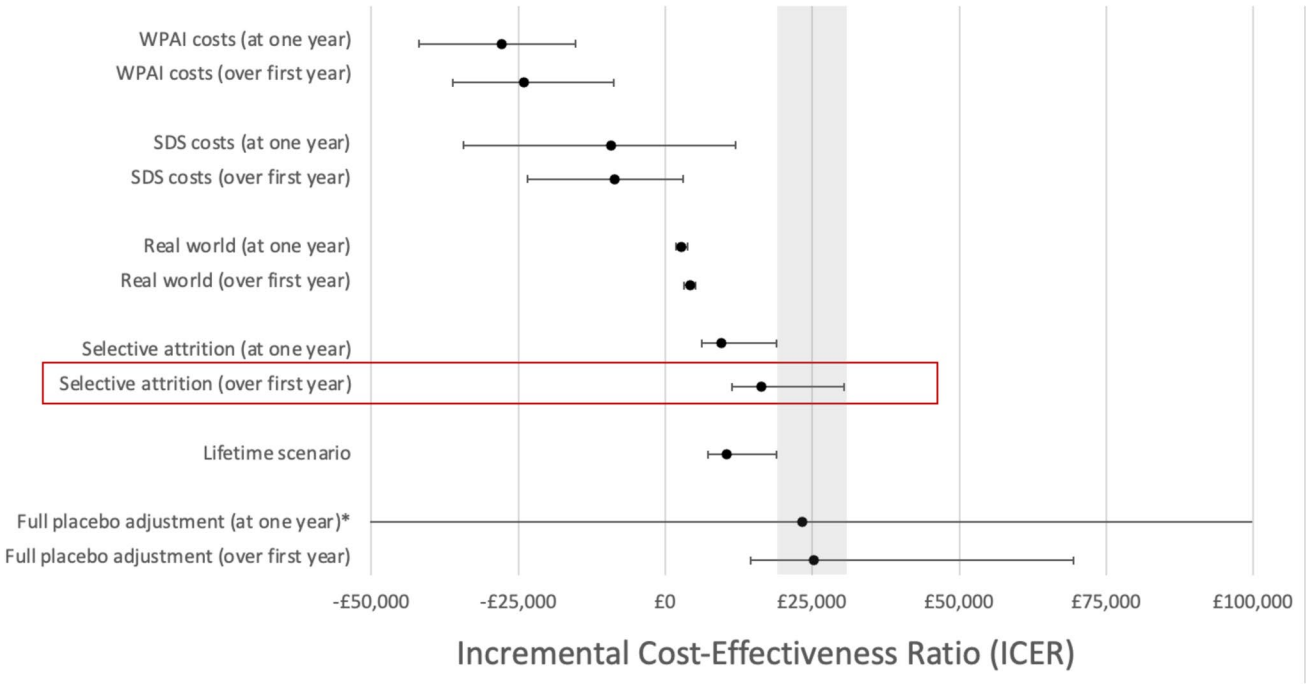

Fig. 11 Comprehensive scenario analysis with nested probabilistic uncertainty analysis. The base-case analysis is highlighted by the box. *Upper limit of confidence interval is truncated for this scenario – extends to £194,000. *SDS* Sheehan Disability Scale, *WPAI* Work Productivity and Activity Index

recommended daridorexant for routine use (according to the prescribing information) in the National Health Service (NHS) in England and Wales, based on its preferred ICER with full placebo correction (daridorexant £1.40 per pill) of £25,383 per QALY. It is worth mentioning that all other most plausible scenarios (i.e., productivity costs, no selective attrition, no placebo correction, lifetime model) led to a lower ICER or dominant (negative) ICER. Payers valuing the societal productivity perspective (e.g., employers, private payers, or Health Technology Assessment) can expect that treating a patient with daridorexant 50 mg compared with placebo could save an estimated total of £596 (£330–£896) in productivity costs, an amount which is higher than the estimated daridorexant annual treatment cost of £411 (after adjusting for treatment discontinuation).

4.2 Appropriate Comparators

At the scoping stage of the UK NICE submission and during the subsequent exchanges during the submission process there was an acknowledgement that subjects with chronic insomnia disorder may take a variety of treatments in real life to combat their insomnia. This could include using hypnotics (benzodiazepines or Z-drugs) for a greater duration than their 1-month licensed indication. The extent of this use is not well understood, but even if real-world evidence on the prevalence of off-label use of hypnotics and other treatments were available, no evidence exists on the long-term off-label use of these products. For example, the most comprehensive meta-analysis of insomnia treatments found no evidence for the long-term use of hypnotics beyond their licensed indication of 1 month [15]. Recognizing the potential harmful effects of long-term hypnotic use as well as the risk of dependency, NICE's own work has suggested that CBT treatment, together with tapering, is a cost-effective strategy to reduce long-term hypnotic use [34]. This suggests that any model to compare daridorexant with an off-label comparator of hypnotic use would improve the cost effectiveness for daridorexant due to the avoidance of long-term harm. Of course, not all subjects with chronic insomnia disorder resort to long-term, off-label hypnotic use, but the same problem exists that, in the real world, it is difficult to estimate precisely what the effect of unproven self-medication for insomnia is. For these reasons, NICE accepted the 'no treatment' comparator as represented in our model.

4.3 Placebo Correction versus Selective Attrition in Study 303

The most important issue from the perspective of the estimated cost-effectiveness ratio was the extent of placebo correction in the base-case model. The preferred base case is presented in this manuscript and illustrated in Fig. 4 (ISI total score) and Fig. 6 (mapping to EQ-5D). This is based on full placebo correction of the phase III 301 study but with no further placebo correction in the 303 extension study based on the argument that the full benefit of treatment is achieved by 3 months and that any further improvement in ISI scores seen in the 303 study was the result of selective attrition, whereby subjects remaining in the study had higher ISI scores than those who dropped out before the end of the extension study (Fig. 3).

NICE, in its final appraisal determination [21], preferred to adopt a more cautious approach that employed a full placebo correction across both studies. Although the NICE committee appeared to acknowledge the selective attrition issues, they ultimately preferred to use the intent-to-treat (ITT) results. Use of the ITT results as the base case has a modest impact on the point estimate of the ICER, which remains below £20,000, but does have a more dramatic impact on the estimated confidence interval with an upper limit above £30,000 per QALY, suggesting increased uncertainty over whether daridorexant is cost effective at conventional decision-making thresholds.

4.4 12-Month versus Lifetime Models

The analysis presented here has a 12-month model as its base case and reflects (i) the 12-month maximum duration of the evidence base; (ii) the fact that no mortality benefit was expected or claimed from daridorexant; and (iii) that daridorexant effects are expected to occur quickly when taking the drug and to be lost quickly when treatment is removed. It was considered inappropriate to present a lifetime model of treatment given that this introduces many unknown factors that go beyond the evidence for the drug (increasing uncertainty). In addition, the label for daridorexant advises that subjects use daridorexant for as short a period as possible and that the appropriateness of long-term use should be periodically reviewed by the treating physician.

Nevertheless, this decision proved to be somewhat controversial. The online manual for NICE health technology evaluations [34] includes four paragraphs on the appropriate time horizon for studies. Paragraph 4.2.23 states: *"Many technologies have effects on costs and outcomes over a patient's lifetime. In these circumstances, a lifetime time horizon is usually appropriate. A lifetime time horizon is needed when alternative technologies lead to differences in survival or benefits that last for the remainder of a person's*

life." and paragraph 4.2.25 suggests: *"A time horizon shorter than a patient's lifetime could be justified if there is no differential mortality effect between technologies and the differences in costs and clinical outcomes relate to a relatively short period."* Our interpretation of these paragraphs is that without a mortality benefit and with a fast-occurring and short treatment effect that needs to be taken every day to be effective, the information provided by the 12-month clinical trials is sufficient to capture all the expected differences in costs and clinical outcomes. The alternative interpretation that was put to us was that because treatment could be chronic, and that a subject might take treatment for the rest of their life, a lifetime model was appropriate. The compromise was that a 12-month model was accepted as base case by NICE, and a lifetime model was presented as a possible scenario. As Fig. 10 shows, as soon as additional parameters—particularly the idea of treatment waning—are introduced, the uncertainty over long-term cost effectiveness increases. However, we show that this risk can be mitigated by a regular (annual) challenge to long-term use, as is stated on the product label. On balance, we contend that it is inappropriate for a short-acting daily treatment like daridorexant to be subjected to a lifetime analysis that could jeopardize its perceived cost effectiveness when it is possible to show, based on strong clinical evidence, that short-term cost effectiveness has already been achieved.

4.5 Societal Productivity versus Health Care Perspective

That insomnia can impact productivity at work is not only intuitive but is supported by increasingly strong evidence—not least in the daridorexant clinical trial program presented here. Additionally, the scale of burden is potentially huge at the societal level. A recent RAND study found that: *"Chronic insomnia is … associated with an average loss in workplace productivity of 45–54 days, resulting in estimated annual losses in national gross-domestic product ranging from 0.64 to 1.31%, or in terms of cost, approximately $4,195 to $19,350 per capita (2019 USD)."* [9].

In the UK, the NICE reference case clearly states that it will only consider a National Health Service (NHS) and personal social services perspective: *"Productivity costs should not be included"* (Paragraph 4.2.9) [34]. However, NICE's methods guidance appears to allow non-reference case analyses to be presented separately when there are substantial benefits that go beyond the reference case perspective: "*These issues should be identified during the scoping phase of an evaluation*". (Paragraph 4.2.10) [34]. Since productivity losses due to chronic insomnia were not in the original NICE scope, their inclusion—even as a scenario analysis—was not considered by the committee. Despite NICE's insistence on excluding productivity gains from its reference case, it is nonetheless clear that, at the listed price of daridorexant, the potential productivity benefits alone could justify its use.

4.6 Does EQ-5D Capture All the Insomnia Burden?

The daridorexant clinical trial program did not include the EQ-5D instrument. Therefore, to estimate QALYs for the NICE reference case, we developed the de novo mapping algorithm summarized here and reported in full by Chalet and colleagues [52]. However, despite the success in generating a mapping algorithm, the authors identified concerns that the EQ-5D itself may fail to capture important HRQoL impacts of chronic insomnia. Perneger and Courvoisier [62] identified 'Sleep' and 'Fatigue/energy' as two of five possible dimensions missing from the EQ-5D, both of which are directly impacted by insomnia. As Chalet and colleagues state, "*If the EQ-5D itself fails to capture important dimensions of QoL related to sleep deprivation, then no mapping, however statistically accurate, will be able to account for this deficiency and the QALY burden of insomnia will inevitably be underestimated."* [52]. This implies that the ICERs presented here might be considered conservative.

5 Conclusions

We present here a UK cost-effectiveness analysis that formed the basis of a successful submission to NICE, with daridorexant recommended by NICE for treating chronic insomnia disorder in adults in England and Wales in November 2023 and the Scottish Medicines Consortium following suit in March 2024. Our study highlights several methodological challenges that may merit further attention when methods guidance is updated. These include whether placebo correction is always appropriate; when short-term analyses can be employed over lifetime models; whether current restrictions to a public-sector-only reference are too strict in the face of substantial societal benefit (i.e., the importance of considering productivity in economic assessments for insomnia products); and whether the EQ-5D instrument, which is widely used to generate QALYs, can sometimes miss important dimensions of HRQoL. Addressing these complexities in future methods guidance is crucial for advancing rigorous and comprehensive health economic evaluations.

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Declarations

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Conflicts of Interest AB, AW and BG have received consultancy payments from Idorsia Pharmaceuticals in relation to the work reported here. F-XC and PG were employees of Idorsia Pharmaceuticals at the time of conducting the work. JC is an employee of Avalon Health Economics which was compensated by Idorsia Pharmaceuticals for completion of this work. SP has received a personal honorarium payment from Idorsia Pharmaceuticals for participation in a related advisory board meeting. PM has no conflicts of interest to declare. CMM received research grants from Eisai, Idorsia, and Lallemand Health and served as consultant for Idorsia and Haleon. He received royalties from Mapi Research Trust.

Data Availability In addition to Idorsia's existing clinical trial disclosure activities, the company is committed to implementing the Principles for Responsible Clinical Trial Data Sharing jointly issued by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). Requests for data sharing of any level can be directed to clinical-trials-disclosure@idorsia.com for medical and scientific evaluation. The NHWS is a commercial dataset. Access to the dataset used in this present paper must be requested to Cerner Enviza via the following link: https://www.cernerenviza.com/contact-us. Data access conditions will be detailed by the responsible team.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Code Availability The model that forms the basis of this manuscript is available through the GitHub repository: https://github.com/Akadeem/Dari under Creative Commons License: Attribution-NonCommercial-ShareAlike 4.0 International.

Author Contributions The underlying model reported in this manuscript was conceived and developed by AB, FXC, JC, and PG. SP, PM, AW, and BG critical evaluated the model's design. AB drafted the first version of the manuscript, which was reviewed and edited by all authors for scientific content. All authors approved the final version, each of whom has met the requirements for authorship.

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