CENTRAL UNIVERSITY RESEARCH ETHICS COMMITTEE (CUREC)

Ethics Application

Application: An investigation of the effects of dual orexin antagonism on emotional processing and learning in healthy individuals
ID: 582356

Risk:	High
Submitted:	21 Feb 2026, 00:30
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Applicant:	Daniela Almeida Borges
Submitter:	Daniela Almeida Borges
Principal Investigator:	Professor Catherine Harmer
Org Unit:	Department of Psychiatry
Project Title:	An investigation of the effects of dual orexin antagonism on emotional processing and learning in healthy individuals
Project Duration:	09 Sep 2025 – 08 Mar 2027
Funder:	WT
Project Description:	This project is exploring how a brain system called the orexin system affects human behaviour and brain activity, especially in ways that may help us better understand and treat mental health conditions like depression. Orexin is a chemical in the brain that's best known for helping regulate sleep and wakefulness. But scientists have also found that it plays a role in other important functions, like stress, emotion, reward, motivation, and thinking. Problems with these functions are common in mental health disorders. Previous studies in animals suggest that turning down orexin activity might help reduce stress and make people less sensitive to negative emotions. However, it has been difficult to study orexin in people—until now—because we haven't had the right tools. That's changing thanks to a new medication called daridorexant, which was recently approved for treating insomnia. This drug blocks orexin across the brain and gives researchers a new way to study how orexin affects behaviour in humans. In this study, healthy volunteers will be randomly given either a single dose of daridorexant or a placebo (a dummy pill), without knowing which one they've received. Then, they'll complete tasks that test how they process emotions, learn from rewards, and use thinking skills. By comparing the two groups, the study aims to shed light on how the orexin system works in the human brain. The results could help us understand how orexin contributes to emotional and cognitive problems seen in depression, anxiety, and bipolar disorder—and whether targeting this system could lead to new treatments. This study is part of a larger research program funded by the Wellcome Trust. The results will be shared in a student thesis and may also be published in scientific journals or presented at conferences. All data will be anonymised, and the study will follow ethical guidelines, including being officially preregistered before it begins.
Student Project:	Yes - Masters by Research
Supervisor:	Catherine Harmer

SCOPE

Is this research:	Yes
Not research:	
Human Participant Involvement:	Yes
Research does not involve participants, tissue or personal data:	
Researcher division:	Other
Taught student module:	
SSH Minimal Risk:	
Any secondary data:	No
Secondary data only:	
Anonymised secondary Data:	
External ethics review required:	No
Identify NHS staff involvement:	No
Biological samples:	Yes
Biological samples yes:	ONLY samples taken as part of this research
Drug or medicine:	Yes
Foodstuffs or supplements:	No
Medical device:	No
OxTREC Scope:	No
OxTREC minimal risk:	No

RESEARCH TEAM

Principal Investigator: Professor Catherine Harmer

Student Researchers:

Student name	Degree Programme	Department/Institute
Dr Daniela Almeida Borges	Ms by Research in Psychiatry	Department of Psychiatry

Researchers and Training:

Researcher title and name	Depart./ Institute Name	Role in research	Research Integrity Course*	Research Integrity Refresher*	Supplementary Module	Information Security Training	Other (please specify)
Dr Daniela Almeida Borges	Department of Psychiatry - PERL	Involved in all aspects of the study	26/11/24	N/A	Research involving human participants (26/11/24)	08/12/2025	NIHR GCP (03/12/24) Human Tissue Act training (26/11/24)
Dr Michael Colwell	Department of Psychiatry - PERL	Involved in all aspects of the study	N/A	30/11/24	Research Involving Human Participants (30/11/24)	01/12/2025	Human Tissue Act training (MRC) - 20/05/2025; Good Research Practice (MRC) - 07/12/21
Georgia Feltham	Department of Psychiatry - PERL	Research Assistant Overseeing day-to-day management of project (including set-up, recruitment, data collection and analysis).	10/01/24	N/A	Research involving human participants (19/01/24)	24/04/2025	Human Tissue Act training (12/01/24)
Professor Simon Kyle	Sir Jules Thorn Sleep and Circadian Neuroscience Institute	Involved in study design, data interpretation and write up	N/A	March 2025	Research involving human participants (March 2025)	March 2025	Good Clinical Practice – January 2024
Professor Catherine Harmer	Department of Psychiatry - PERL	Principal Investigator	N/A	30/07/2024	Research involving human participants (30/07/2024)	02/12/2025	Good Clinical Practice – 20/06/24

External collaborator: No

Medically qualified collaborator details:

Name	Medical Qualification	Contact Details	Institutional affiliation
Professor Phil Cowen	MD, FRCPsych, FMedSci	phil.cowen@psych.ox.ac.uk +44 (0)1865 618311	University of Oxford; Oxford Health NHS Foundation Trust
Dr Daniela Borges	MD (Univ. of Coimbra, Portugal), MRCPsych	daniela.almeidaborges@psych.ox.ac.uk	Oxford University Hospitals NHS Foundation Trust; Oxford Health NHS Foundation Trust; Psychological Medicine, Kings College London

Conflict of Interest: No

METHODOLOGY

Short title: Dual ORexin antagonism and Emotion and Affective processing (DOREA) study

Research Summary: This experimental medicine study aims to understand the role of the orexin system in human behaviour and neural activity. The study utilises a double-blind, randomised, placebo-controlled, between-subjects trial design. The neuropsychological effects of single-dose daridorexant (50mg) versus placebo will be explored using a battery of tasks and questionnaires in healthy volunteers (18 to 40 years). The target sample size is 62 participants, with 31 participants per allocation group (daridorexant and placebo).

The primary outcomes of this study are:
1. The Pavlovian reinforcement learning task (PALT) - choices, response time and computational parameters (derived from models fit to choice behaviour)
2. The Emotional Go/No-Go task (EGNGT) - accuracy and response

Secondary outcomes are :
1) Pupillometry changes (pupil diameter) during a) the PALT and the b) the EGNGT.
2) Salivary alpha-amylase (SAA) level changes
3) Probabilistic Instrumental reinforcement learning task (PILT) - choices, response time and computational parameters (derived from models fit to choice behaviour)
4) Change Detection task (CDT) - accuracy and response time
5) Facial Expression Recognition Task (FERT) - Accuracy
6) Emotional Classification Task (ECAT) - Accuracy
7) Emotional Recall Task (EREC) - Accuracy

The study involves three screening steps (a 15-minute online screening questionnaire, a 45-minutes screening videocall and in-person eligibility checks at the start of the first study visit as described in the human participants section), two in-person study visits (lasting 2.5 and 5 hours respectively) at the Department of Psychiatry and a 15-minute online follow-up questionnaire the day after.

During the study visit 1, participants will complete the baseline questionnaires - Consensus Sleep Diary for previous night (CSD), Morningness and Eveningness questionnaire reduced version (MEQr), Patient Health questionnaire (PHQ-9), State-Trait Anxiety Inventory (STAI), Perceived Deficits Questionnaire (PDQ), Positive and Negative Affect Schedule (PANAS), Visual analogue scale (VAS); the digit-span test (to assess baseline cognitive ability); and three of the computer tasks (PALT, EGNGT and CDT) to optimise the computational model validation and fit.

Eligible participants will then be randomly assigned to treatment or placebo using the variance minimisation algorithm to ensure an even distribution of key covariates (gender and chronotype / MEQr score) between the groups. An independent researcher will generate the randomisation code following the procedure described by Sella, Raz, and Cohen Kadosh (2021), record the allocation on a Randomisation log, as well as identify and prepare the correct envelope with the drug or placebo by writing the participant ID on it.

The study visit 2 will take place in the morning and within four weeks of study visit 1. Participants will be advised to avoid alcohol, recreational drugs, or grapefruit juice 24 hours before and after the study visit; as well as not to carry out activities requiring full alertness (e.g. driving) until the morning after drug administration. They will be asked to avoid smoking before the study visit, have a maximum of a cup of coffee (or equivalent) up to 90

minutes before the visit time and have a light breakfast (e.g. 2 toasts of bread or yogurt with cereal). They will be advised to avoid attending the department by car or bicycle and will be provided with transport (if required) home after the study visit.

In the study visit, eligibility is re-confirmed. If still eligible, participants will be asked to complete the CSD and a battery of questionnaires (PDQ, VAS, PANAS, STAI), which they will repeat after the administration of the drug. The Karolinska Sleepiness Scale will be completed just before drug administration and hourly until the end of the visit.

Participants will then take a single tablet of daridorexant or placebo under supervision by a researcher. The following hour, they will be asked to remain within the Department of Psychiatry and avoid eating food, having non-caffeinated drinks or smoking until the end of the visit.

After one hour, they will complete a series of computerised tasks with a researcher, which are expected to take about 3 hours.
- The PALT involves predicting if a stimulus will lead to a tolerable electrical shock (via surface electrode attached to the back of the hand using adhesive strips); the level of pain is calibrated with the participant before the task takes place. During this task, participants will collect 3 saliva samples (before, during and 10 minutes after the task) using Salivette synthetic swabs to measure SAA levels (marker of sympathetic activity).
- The PILT involves choosing between shapes which may result in monetary win or loss. Earnings from this task can be between £0-£10.
- The emotional processing tasks (FERT, ECAT, EREC) involve correctly classifying emotional stimuli (i.e., words or faces) into their respective category (e.g., if a face shows an angry expression, pressing the 'Anger' button).
- The EGNGT involves responding to an image which will either require one to inhibit a response ('no-go') or submit a response ('go'), while emotional distractors also appear on the screen (e.g., fearful face).
- The CDT is a visuo-spatial working memory task where individuals will need to identify subtle changes of colour in an array of ‘items’ (e.g. coloured blocks) previously visualised.

During the PALT and EGNGT, participants’ eye movements will be tracked alongside the degree of dilatation of their pupils using an eye-tracking equipment (EyeLink 1000 Plus). It is a safe and non-invasive way to measure by proxy the influence of neurochemicals (as noradrenaline) that interact with orexin while processing negative information (Sears, 2013).

Before the visit concludes, participants will be asked to repeat some questionnaires (as above). Participants will then be reminded of the safety advice, provided with the contact of the study medic for concerns over the next 24 hours, and organised transport home (if required).

The day after, participants will be contacted via email asking them to complete a final online questionnaire on Qualtrics. This will include the CSD for the previous night, the side effects questionnaire and a question to guess if they took placebo or daridorexant.

Lastly, participants will be asked for their bank details so they can be reimbursed for time and travel expenses by bank transfer.

Location: Neurosciences Building, Department of Psychiatry, University of Oxford, Warneford Hospital, Warneford Lane, Oxford, OX3 7JX

Location Permission:	No
CUREC Approved Procedure(s) yes:	AP02 Studies involving administration of interviews and/or questionnaires on sensitive and/or medical topics, for testing and/or recruitment of participants AP18 Psychophysiological methods with adults AP19 Experimentally induced pain AP24 Taking urine, saliva, stool and/or venous blood samples
CUREC Best Practice Guidance:	
International Risky Travel?:	No
Hazardous Substances:	No
Researcher Distress Potential?:	No
Lone Working?:	No
Non-public Visit?:	No
GMO Involved?:	No
Oversight:	The study team will meet fortnightly to discuss the study, including potential adverse events and to check procedures are being followed (Approved Procedures and Best Practice Guidance). The Principal Investigator and named researchers will be present in these meetings. Student researchers will receive regular supervision/line management from the Principal Investigator.
Research-specific ethical considerations:	1. Incidental findings Participants will be explicitly informed that their urine samples will be tested for pregnancy and recreational drug use, in both study visits, and informed of their right to withdraw from the study. They will also be told in advance that if the drug screen returns positive results, they will be excluded from the study. If participants consent to providing a urine sample for the pregnancy test and the test result is positive, the researcher will act in accordance with the pregnancy urine test SOP, wherein they will feed the result back to the medic covering

the visit or a member of the research team, before communicating the result to the participant and providing any relevant advice. Results of the screening will remain confidential within the study team and participants will be informed of this.
If a researcher has concerns that a volunteer may have an undiagnosed psychiatric condition that is causing distress (identified during the online screening videocall or following review of the mood-related questionnaires), CUREC Best practice guidance 08 on Handling distress in participants will be followed. The researcher will seek advice from the Principal Investigator and /or study medic who may discuss the symptoms in greater detail with the volunteer and/or offer the opportunity to speak with a senior clinical researcher. If the volunteer indicates that they are not currently receiving support and it is felt necessary, they will be encouraged to contact their General Practitioner.

2. Serious adverse events
A serious adverse event (SAE) occurring to a participant should be reported to the Medical Sciences IDREC where, in the opinion of the Principal Investigator, the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' (the type of event is not listed in the protocol as an expected occurrence). Reports of related and unexpected SAEs should be submitted within 15 days of the Principal Investigator becoming aware of the event. For fatal and life-threatening SUSARs, this will be done no later than 7 calendar days after PI is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report.

3. Data breach
Potential data breaches will be reported immediately to the departmental Information Systems & Governance Officer and the university's Information Compliance Team (ICT). The ICT will determine whether the data breach needs to be reported.

4. Physical/verbal abuse and/or psychological distress from study participants
There is a low risk of physical or verbal abuse from study participants. The study sample will be healthy young individuals without psychiatric conditions which is not typically considered a high risk sample. Screening (including psychiatric assessment) procedures will take place in a screening videocall and at the in-person study visits in the Neurosciences Building. In each instance, researchers will undertake assessments and data collection in a respectful, calm and compassionate manner. In the event that participants become distressed or physically/verbally abusive, researchers will not put themselves at unnecessary risk, per Best Practice Guidelines on researcher safety (BPG01) and participant psychological distress (BPG08).

5. Complications of handling of biological specimen
There is a risk of transmission of infectious disease or hazardous substances through the handling of urine and saliva samples. Researchers will be required to handle specimens during the participant screening process. Researchers will adhere to best practice/CUREC guidelines (AP024) during this process, including the donning of disposable aprons and gloves, handwashing before and after handling samples, and the safe and sterile disposal of samples, containers and drug tests using clinical waste systems. The collection of the samples will be completed by the participant.

6. Safety incident
In the unlikely event of a participant being involved in any safety incident at the Department of Psychiatry, their details (name) may be shared with safety officers, without any further personal information being shared.

HUMAN PARTICIPANTS

Participants Description:	We are aiming to recruit 62 participants aged 18-40 years. Half (31 participants) will be randomly allocated to the daridorexant group and the other half (31 participants) to the placebo group.
Sample size justification:	A priori power calculations (80% power, 1 - β error probability) estimate a required sample of N = 58 (29 per group) for detecting group-level differences (two-tailed) in the primary outcomes (e.g., aversive learning behaviour) based on an expected standardised effect size/Cohen's d of 0.75 from previous experimental medicine work (Colwell et al., 2024). An additional four participants will be recruited to mitigate potential data quality or participant attrition issues from randomised participants, summating to a final required sample size of N=62.
Participant Inclusion Criteria:	- Adult participant, aged 18 to 40 years - Willing and able to give informed consent for participation in the trial - Able to follow study procedures as laid out in the participant information sheet - Able to read and understand English - Willing to avoid drinking alcohol, using recreational drugs, drinking grapefruit juice 24 hours before and after the study visit - Willing to avoid driving or engaging in any activities requiring full alertness (e.g. cycling or operating heavy machinery) until the morning after the study visit day. - Able to complete computer tasks without eye glasses even if uses correction regularly
Participant Exclusion Criteria:	1. History of, receiving or seeking treatment for any sleep or circadian rhythm disorder or positive in screening questionnaires. 2. History of, receiving or seeking treatment for any clinically significant mental health condition (including but not limited to schizophrenia, psychosis, bipolar affective disorder, major depressive disorder, obsessive compulsive disorder, post-traumatic stress disorder) or positive in screening questionnaires. 3. History of, or current medical condition(s) which might increase the risk of oral administration of daridorexant, including: - ADHD requiring treatment with stimulants or other centrally-acting drugs - Neurological problems, including traumatic brain injury, epilepsy, Central Nervous System tumours or other severe neurological problems (e.g. Parkinson's disease; blackouts requiring hospitalisation) - Current Asthma, Chronic Obstructive Pulmonary Disease, emphysema or any medical condition that affects the lungs or breathing - Mild to severe hepatic impairment (Child-Pugh class A-C) - Severe renal disease - Severe gastrointestinal problems - History of, or current medical condition(s) which, in the opinion of the Investigator may interfere with the safety of the participant or the scientific integrity of the study 4. Pregnancy (as determined by urine pregnancy test taken during first study visit), intention to become pregnant or breastfeeding during the study or over the following six months. 5. Body mass index (BMI) below 18 or above 30kg/m2. 6. Current or past history of drug or alcohol dependency. 7. Regular alcohol consumption of more than 21 units per week or use of recreational drugs or performance-enhancing drugs (e.g. cannabis, cocaine, amphetamines) within past three months. 8. Excessive caffeine consumption, i.e., consumption higher than 400mg a day of caffeine. This corresponds to more than 4 cups of brewed coffee, 6 espressos or filtered coffees, 9 cups of black tea, 10 cans of cola, or two "energy shot" drinks.

9. Smoking more than 5 cigarettes per day (or other nicotine replacement equivalent, including vaping on average more than 50 puffs a day).
10. Current or recent (past two months) use of any medication or medical devices (e.g. implanted neurostimulator) that affect brain function for the exception of contraceptives (pill, the Depo-Provera injection or the progesterone implant). This includes drugs that cause sedation (e.g. benzodiazepines, opioids, tricyclic antidepressants or sedative antipsychotics) or antihistamines.
11. Current use of any medications at risk of interaction with daridorexant; in particular:
- strong or moderate CYP3A inhibitors (e.g. strong inhibitors - itraconazole, clarithromycin, ritonavir, grapefruit juice; moderate inhibitors - fluconazole, verapamil, diltiazem, erythromycin, ciprofloxacin, cyclosporine)
- strong or moderate CYP3A inducers (e.g. of strong inducers - rifampicin, carbamazepine, St. John's wort; moderate inducers - bosentan, efavirenz, etravirine, modafinil)
- Gastric pH-modifiers (e.g. famotidine and proton pump inhibitors such as omeprazole)
- P-gp transporters (e.g. dabigatran, digoxin)
12. Inability to ingest up to 95mg of lactose.
13. Previous participation in any other drug study or sleep intervention study in the last three months.
14. Previous participation in any other study by the Psychopharmacology and Emotion Research lab (Department of Psychiatry, University of Oxford) or which uses the same computer tasks in the last 6 months
15. Participant is unlikely to comply with the clinical study protocol or is unsuitable for any other reason, in the opinion of the Investigator.

Participant Protected Characteristics:

In this study we will select participants of a certain age group (18 to 40 years) to minimise the variation of outcome results that could be influenced by having a mixture of different ages in the sample population. We have excluded from participation people with current or past diagnosis of mental illness (which can in some cases be considered a disability under the Equality Act 2010) to minimise initially the risk of using psychoactive drugs in clinical populations for an experimental medicine study design.
Furthermore, pregnancy is an exclusion criterion as daridorexant is contraindicated in pregnancy.

Participant Identification:

Potential participants will be identified only through community advertisements (see below approaching participants section) and be given a link / QR code on our recruitment materials which will take them to the study online screening questionnaire where more information will be available.

Vulnerable Participants:

No

Approaching participants

Participants will be recruited by word of mouth, emails to departmental and college mailing lists (sent by the list holder on request of the researchers), posters in University and community spaces, local magazines, social media posts (Instagram, X, TikTok, Bluesky), NIHR Be Part of Research Volunteer Service registry (more information below), as well as through websites (e.g. Daily Info, Call for Participants, and MQ research website).
The adverts (available in documents) will contain brief information about the inclusion criteria for the study and participant involvement, as well as contact details for the study email and link/ QR code to the study online screening questionnaire. We have also prepared Reels for social media promotion. All promotion text templates are included in a document attached.
Participants may also be recruited via advertisements targeting Oxford Brookes University, following approval from Oxford Brookes Research Ethics Committee. Oxford Brookes will be made aware that the study drug is not licensed in the UK as part of this approval process. Any advertisements for Oxford Brookes students and staff will contain

this additional statement: “Oxford Brookes University has knowledge of this study and has permitted recruitment at the University. In the event of any questions about the study, please contact the researchers in the first instance. Should you need to contact anyone at Oxford Brookes about this further, please email: ethics@brookes.ac.uk”.
We will also contact other adult learning organisations (universities and colleges) to request their authorisation and cooperation to send email promotion or display posters about the study. This might require sharing of approved texts, study methodology and ethic submission documents and favourable opinion letters for review by the organisation ethics committee.

We have agreed an email template (attached in documents) with the Be Part of Research Volunteer Service (BPORVS) team to be sent to registered study volunteers criteria. We will provide monthly updates to the team about the number of people that have registered to take part in the study through this service. No participant details will be shared. The purpose of the BPORVS is to allow members of the public to become volunteers by creating an account, specifying the areas of research that they are interested in and give consent to be contacted by the Be Part of Research team. Those who consent will receive information about BPORVS, in particular to alert them to specific BPORVS registered studies that they may be interested in, based on their volunteered details and study specific eligibility criteria, using an online self-registration service. The register is open to those that live in the UK, are over 18 and have an email address. At the time of registration, volunteers are made aware that they are not signing up to take part in a specific health study when they join this register and that they will only be signposted to studies that have NIHR funding or are listed on the NIHR RDN Portfolio. If the volunteer is interested in the study there will be a link in the email to take them to the study team (e.g. website, pre-screener) where they will move into the study team’s screening process and consenting process if they take part in the study. The Be Part of Research Volunteer Service is funded by the Department of Health and Social Care and delivered by the National Institute for Health and Care Research (NIHR) in conjunction with Public Health Agency, Research & Development, Northern Ireland, NHS Scotland and Health and Care Research Wales. Further information on the Be Part of Research Volunteer Service is available here: https://bepartofresearch.nihr.ac.uk/volunteer-service/researchers

Investigator Influence or Authority: No

Participant Investigator Relationship: N/A

Participant Recruit Information:

1. Potential participants will be identified through community advertisements (see above approaching participants section) and be given a link / QR code on our recruitment materials which will take them to our study online screening questionnaire where the Participant Information Sheet (PIS; available in documents) will be available. Prospective participants can contact the named researchers via the study email for further information at any point.

2. Then, prospective participants will be asked to complete the online screening questionnaire (on Qualtrics; available copy in documents) . They will firstly be presented with a link to the PIS and a copy of the study summary advert. Then, interested participants will be asked to tick a box to confirm they consent to complete the screening questionnaire to check if they meet the inclusion and exclusion criteria for the study.

If they meet the eligibility criteria and are interested to take part in the study, participants will be asked to provide an email address. At this point, a screening ID number will be assigned to the participant. If researchers notice that one of the participants responses to the questionnaire might indicate they would not be eligible for the study, they will contact the participant via email to inform them of this.
Otherwise, the contact details will not be asked, they will be thanked for their interest, signposted to the Department of Psychiatry (https://www.psych.ox.ac.uk/getinvolved) and Psychopharmacology and Emotion Research Laboratory (https://perloxford.com/) current studies webpages. There will be no further contact from the research team.

3. If eligible after filling in the online screening questionnaire, participants will be contacted via email within 10 days to arrange a 45-minutes videocall screening session on MS Teams. We will offer screening session slots using the Bookings app of the University Nexus 365 for business account, which will collect their name and email address for the booking. Participants can also request to complete the session over telephone call.

At the beginning of this online screening videocall, one of the named researchers will explain the study to the participant, confirm they read the PIS, and answer any questions that they might have. The researcher will then ask the participant to complete an online informed consent form on Qualtrics (available in documents). The participant must personally sign by typing their name and date the form before any study specific procedures are performed. The signatures of the researcher who presented and obtained the Informed Consent will be on the form. A copy of the completed online Informed Consent (in pdf) will be sent to the participant via email and another copy will be saved in the electronic TMF.

The online screening videocall will then include the following screening procedures (case record form available in documents):
- Personal contact details collection (separately recorded)
- Demographic data including ethnicity, gender, age, years in full-time education
- Medical history screening and details of current and past medication (including confirmation of exclusion criteria)
- Selected sections of the Structured Clinical Interview for DSM-5 (SCID-5), which probes for past or current psychiatric illness (exclusion criteria)
- Relevant screening questions for insomnia disorder (screen negative for insomnia symptoms on the Sleep Condition Indicator) and other sleep or circadian rhythm disorders (based on screening questions for other disorders identified by Wilson et al)

If the participant does not meet the eligibility criteria for the study, the researcher will sensitively inform the participant they are ineligible and the screening process will end. If there are any questions about the participant's suitability to take part in the study, the researcher will ask a study medic after the online screening videocall to check the information collected. The medical doctor might need to discuss the study with the participant and perform a medical examination, if deemed necessary. Participants will be informed of this and that they will be contacted with an outcome. If the outcome of the online screening videocall indicates that the participant meets all of the study eligibility criteria, the participant will be invited to the in-person first study visit and the date and time for this will be booked during the call.

4. The study visit 1 at the Neurosciences building (Department of Psychiatry, Warneford Hospital) is expected to last 2.5 hours. It will start with checking if the participant has any

questions about the study. Then the researcher will take a written consent from the participant using the latest approved version of the Informed Consent form in an iPad document or in paper (available in documents). The participant must personally sign and date the form, as well as the researcher who presented and obtained the Informed Consent. A copy of the completed Informed Consent form will be given to the participant either in paper or via email in PDF format. Another copy will be saved in the electronic TMF or on the TMF paper folder. This will then be followed by the final eligibility checks:
- Review if any new medical problems or medications;
- Weight and height measurement, for calculation of Body Mass Index (BMI)
- Blood pressure and pulse recording at rest
- Urine drug screening test for amphetamine, barbiturates, benzodiazepines, buprenorphine, cocaine, marijuana, methadone, methamphetamine, methylenedioxymethamphetamine (MDMA), morphine, methaqualone, opiates, phencyclidine, propoxyphene, tricyclic antidepressants, tramadol, ketamine, oxycodone, cotinine, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), fentanyl, synthetic marijuana, 6-mono-acetyl-morphine (6-MAM).
- Urine pregnancy test (for female at birth)

If the outcomes of the eligibility checks indicate:
a) the participant meets all of the study eligibility criteria, the participant will be enrolled in the study and assigned a participant ID number. They will be asked to complete a battery of baseline questionnaires, the digit-span test and three of the computer tasks (as described in research methodology section) at this visit.
b) the participant does not meet the eligibility criteria for the study, the researcher will sensitively inform the participant they are ineligible and the screening process will end.
c) any questions about the participant's suitability to take part in the study, the participant will still complete the baseline questionnaires and tasks. The researcher will ask a study medic during or after the study visit to check the information collected. The medical doctor might need to discuss the study with the participant and perform a medical examination, if deemed necessary. Participants will be informed of this and that they will be contacted with an outcome, if this is not completed at the visit.

If during recruitment or screening procedures, a participant considers to take part in another research study that would meet the exclusion criteria for the DOREA study (any other drug study or sleep intervention study; any other study which uses the same computer tasks), they will be asked to make a decision independently about which study to participate in.

Participant Decision Duration: The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. This is only conditioned by the end of study which is the date of the last visit of the last participant. Written informed consent will then be obtained as described in the next question.

Participants Informed Consent: Yes

Participants Informed Consent More Info: Prospective participants will be able to access the latest version of the Participant Information Sheet (PIS) by selecting the link provided on all study adverts that will direct them to the study website, or receiving a copy through email after request.

Prospective participants will be asked to complete the online screening questionnaire through a link available on the study website (as above) and will firstly be presented with

a link to the PIS. Then, interested participants will be asked to tick a box to confirm their consent to complete the screening questionnaire to check if they meet the inclusion and exclusion criteria for the study. If the prospective participant is eligible and interested to take part in the study, they will be asked to share their contact details and will be be invited to book a videocall screening session within 10 days.

Following this, at the online screening videocall, one of the named researchers will explain the study to the participant, confirm they read the PIS, and answer any questions that they might have about the study. Written and verbal versions of the PIS and Informed Consent form will be presented to the participants. This will detail the exact practical demands of the research, written from the participant's perspective and in simple lay language. It will describe when and where they will be required to attend, what procedures are involved and for how long, how data will be collected and offer brief justification of the intervention. It will also contain information about any possible risks and benefits of taking part in the research, such as side effects of the study drug. Prospective participants will be allowed as much time as they wish to consider the information and will have the opportunity to ask questions of the Investigator/research team or other independent parties. It will be clearly stated that the participant is free to withdraw from the research until a month after their second study visit for any reason and with no obligation to give the reason for withdrawal.

The researcher will then take written consent from the participant using the latest approved version of the Online Informed Consent form (available in documents) on Qualtrics. The researcher who obtained the consent will be suitable trained and experienced, and have been authorised to do so by the Principal Investigator. The participant must sign the form by typing their name and date the form before any study specific procedures are performed. The signatures of the researcher who presented and obtained the Informed Consent will be on the form. A copy of the signed consent form (in pdf) will be sent to the participant via email and another copy will be saved in the electronic TMF.

At the start of first study visit (1) at the Neurosciences building (Department of Psychiatry, Warneford Hospital), the researcher will again take a written consent from the participant using the latest approved version of the Informed Consent form in an iPad (using a pdf version of the document) or in paper (available in documents). The participant must personally sign and date the form, as well as the researcher who presented and obtained the Informed Consent. A copy of the completed Informed Consent will be provided to the participant either in paper or via email in PDF format. Another copy will be retained in the electronic TMF or at the study site in the paper TMF folder.

Any feedback: Yes

Participant Feedback: Participants will be debriefed and have an opportunity to ask questions more detailed/complete descriptions about the study procedure/purpose after all data has been collected. Participants (and researchers) will not be aware of group allocation given the double-blind design, therefore this will not be included in the debriefing process.

Withdrawal Arrangements: Each participant has the right to withdraw from the study at any time. Participants can also request for their data to be withdrawn until a month after their second in-person study visit. They will have to communicate this in writing to the study email.

In addition, the Investigator may discontinue a participant from the research at any time if the Investigator considers it necessary for any reason including:

•Pregnancy

•Ineligibility (either arising during the research or retrospectively having been overlooked at screening)
•Significant protocol deviation
•Significant non-compliance with treatment regimen or research requirements
•Withdrawal of Consent
•Loss to follow up

If a participant withdraws/is withdrawn from the study no further procedures or observations will continue to be required.
In the case of withdrawal from the study prior to randomisation, all the participant data will be securely removed and not analysed. However, if the participant has been randomised and has received the study drug/placebo, their data from the tasks may be analysed if they withdraw one month after their second in-person study visit. Withdrawn participants will be replaced. The reason for withdrawal if given will be recorded in the Participant Log of the Trial Master File.

Withdrawal More Information: Each participant has the right to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

If a participant withdraws from the study prior to randomisation, all their data (personal, screening and research data) will be securely removed and not analysed, only keeping the screening ID, consent form, and reason for withdrawal if provided. In the case of an exclusion due to a positive drug test, this will be linked only with a screening ID number and all personal identifiers and information will be destroyed.

If the participant has been randomised and has received the study drug/placebo, their data from the tasks may be analysed if they withdraw one month after their second in-person study visit. Otherwise, we will remove their data and it will not be analysed.

Participants will still be reimbursed pro-rata from the start of attending the first study visit to the point they participated in.

In the case of a withdrawal, the type of withdrawal and reason for withdrawal will be recorded in the Participant log.

Any participants that drop out without completing the study will be replaced.

Participant Deception: No

CUREC Approved Procedure 07: No

Social Media: No

Sensitive Topics: Yes

Sensitive Topics More Info: In the screening procedures, we will enquire about participants medical and psychiatric history (please find in the supporting documents copies of the online screening questionnaire, the online screening videocall interview and first study visit eligibility checks). In the screening visit, participants will also undertake a standardised psychiatric interview (SCID-5) which enquires about an individual's current and past psychological wellbeing (including questions about past traumatic experiences, substance abuse etc.). This might be uncomfortable for participants or reveal current psychological distress. This information is required to ensure that participants do not fulfil exclusion criteria including current or past psychiatric disorder, sleep disorders and some medical conditions.

Illegal Behaviour: No

Awareness Disclosure Harm: Yes

Awareness Disclosure Harm More Info: In the screening procedures, participants will undertake a standardised psychiatric interview (SCID-5) in which participants will be asked directly by researchers about suicidal ideation. During the interview, they might also have questions that indirectly prompt for disclosure of current or past experiences of harm to themselves and others, abuse or neglect. To mitigate the risk associated with psychiatric interviewing, participants will be informed about the nature of the interview before their participation in the screening.

All researchers involved in participant facing work will be provided training on the delivery of psychiatric interviews and required to read the best practice guidelines on researcher safety (BPG 01) and on handling distress in participants (BPG 08); as well as CUREC approved procedure on studies involving administration of interviews and/or questionnaires on sensitive and/or medical topics, for testing and/or recruitment of participants. Screening procedures (including psychiatric assessment) will take place in a screening videocall and at the in-person study visits in the Neurosciences Building..

Should there be a participant disclosure of a past or current intent to harm themselves or another, abuse or neglect, CUREC Best practice guidance on handling distress in participants (BPG 08) will be followed. The researcher will seek advice from the Principal Investigator and /or qualified medical doctor covering the visit who may discuss the symptoms in greater detail with the participant and/or offer the opportunity to speak with a senior clinical researcher. If the participant, indicates that they are not currently receiving support and it is felt necessary, they will be encouraged to contact their General Practitioner. In urgent situations, in which participants express thoughts of harming themselves imminently, they will be strongly advised to attend the local emergency department.

The information collected about the participant during the course of the research is kept confidential. In the context of the above disclosures, confidentiality would only be breached in the very rare circumstance that is judged that the participant or someone else is at immediate risk of serious harm. In these circumstances, only information necessary to ensure immediate safety would be released and this would be discussed with the Principal Investigator and /or qualified medical doctor covering the visit. The only other circumstance in which information would be released is if it was requested by an order of a court of law.

Risk of Injury: Yes

Risk of Injury More Information: - Risk of psychological distress: As part of their eligibility screening, participants will undertake a standardised psychiatric interview (SCID-5) in order to ensure that they do not fulfil criteria for any current or past psychiatric disorder. Psychiatric interview questions enquire about an individual's current and past psychological wellbeing (including questions about past traumatic experiences, substance abuse etc.). This might be uncomfortable for participants or reveal current psychological distress. There is a lower likelihood of this happening as prospective participants will be asked directly in the online screening questionnaire if they have been previously diagnosed with any significant mental health conditions as this would be an exclusion criteria for this study.

- Risk of incidental findings: There is a risk of incidental findings being identified when doing the urine drug screen, the urine pregnancy test or identifying some signs/symptoms of an undiagnosed psychiatric condition that is causing distress to the participant.

- Risk of side effects: side effects and adverse reactions to daridorexant administration have been described in drugs/substance section.

- Risk of pain inducing task: One of the experimental behaviour tasks will involve the use of experimentally induced pain (individually tailored electrical stimulation) which have been used in previous studies (Browning 2015; Lawson 2014). It will be delivered via a surface electrode attached to the back of the non-dominant hand using adhesive strips following an established protocol (Approved Procedure 19). Beyond the risk of pain, the electrical pain stimuli by electrode may lead to a skin reaction which should clear within 2 hours of completing the task.

- Risk of using an eye-tracking and pupillometry device: Eye-tracking and pupillometry are non-invasive methods that pose no direct health risks to participants. In this study, an Eyelink 1000Plus (manufactured by SR Technologies) will be used to continuously measure pupil diameter and pupillary response dynamics under controlled lighting conditions. Participants will complete cognitive tasks on a specialized screen while resting their chin on a headrest, allowing the eye tracker to collect physiological data in a non-invasive manner. The collected data will include pupil diameter (mm), pupil constriction velocity (mm/s), minimum diameter (mm), time to minimum diameter (s), relaxation velocity (mm/s), and final diameter (mm) (Connelly et al., 2014). Although most participants typically experience no discomfort during pupillometry studies, remaining in a fixed position (up to 20 minutes at a time) could feel uncomfortable for some. Eye-tracking records saccadic eye movements through Reflective Differencing of Infra-Red (IR) light emitted by IR emitters mounted on the Head Mounted Transducer. Prolonged exposure to IR light can pose a small risk of triggering seizures in individuals with photosensitive epilepsy (3–5% of people with epilepsy).

Risk of Injury Mitigation:

- Risk of psychological distress: To mitigate the risk associated with psychiatric interviewing, participants will be informed about the nature of the interview before their participation in the screening.
- Risk of incidental findings: These will be addressed as described in the methodology section.

- Risk of side effects: In order to minimise the risks, all participants will be screened for physical or psychological risk factors before enrolment in the study. In addition, a qualified medical doctor will always be available for phone advice and within 30 minutes of the Neurosciences building during the study procedures involving drug administration and all participants will receive detailed instructions on how to behave within 24h of intervention (e.g. avoid grapefruit juice, drugs, alcohol, sedative medication , driving, cycling, or operating heavy machinery) and what to do if they experience any problems following their participation. All participants will be provided with contact details of a research team member whom they can contact.

- Risk of pain inducing task: There will be a calibration process prior to the experiment to guarantee that the current is well within the personally tolerable range of what the participants report as painful. In the calibration, the participant will be seated in a comfortable position and we will gradually turn up the magnitude of the current while explaining to the participant what to expect (i.e. painful stimulation). We will try to confirm the pain sensitivity threshold for the participant with small increments in the current. The subjective pain will be assessed by a 10-point scale on which 1 was defined as “minimal pain”, 10 as “worst possible pain”. The highest magnitude stimuli in the experiment will be equated to 8 on this scale.

	- Risk of using an eye-tracking and pupillometry device: Discomfort during the pupillometry study will be mitigated by providing supportive padding and ensuring a comfortable position. Participants will also be able to take breaks between blocks of cognitive tasks and may withdraw from the study at any time if they wish. To minimize the risk of seizure due to prolonged exposure of infra-red light, individuals with a history or diagnosis of epilepsy are excluded from the study. In the rare event that participants experience sensations or auras that may signal an impending seizure, they will be advised to avert their gaze from the eye tracker and should stop the task.
Invasive Procedures:	No
DBS Check:	Yes
Participant Compensation:	Yes
Compensation Details:	Participants will be paid by bank transfer up to £135 for full participation in the whole study. This is based on a rate of £15 per hour and with an expected 9-hour involvement in study activities. Additionally, participants can win up to an extra £10 depending on their performance in the cognitive tasks administered during the study visit. We will reimburse participants with a pro-rata amount if they withdraw before completing the whole study. If a participant attends the videocall screening session but is deemed ineligible to take part in the study, we will reimburse them with a pro-rata amount of £10. If a participant physically comes in to the first study visit but is deemed ineligible to take part in the study in the initial eligibility checks, we will reimburse them with a pro-rata amount of £15. If an eligible participant drops out after completing the baseline research activities in the first study visit, after daridorexant or placebo administration or has to be excluded before completing all research activities, they will be given a pro-rata amount to recompense the time they spent in the study based on £15 per hour rate and not exceeding the £135 . Reasonable travel expenses (up to £20 per visit; more if previously agreed) for any visits will be re-imbursed on production of receipts, or a mileage allowance provided as appropriate. On the second study visit, after drug administration, we will organise a taxi and/or public transport from the Warneford Hospital to the local accommodation, unless the participant has an equivalent transport arrangement (e.g. someone to drive them by car) already organised.
Undue Incentives:	No
Compensation After Withdrawal:	If participants do not complete the study, they will be given a pro-rata amount to recompense the time they did spend in the study as described above.

SECURITY

Security More Information: N/A

Security Risk Mitigation: N/A

Prevent duty: No

ENVIRONMENTAL IMPACT

Environmental Impact: The research project will not produce waste that will outright impact local ecology, hydrology, and the community. This study will require the use of printed materials and computer equipment which may produce some minor impact to the environment. There is also the impact of participant transport, particularly the necessity of a taxi or car drive home after the study visit. Motor vehicles have a significant environmental impact on air pollution (from exhaust emissions), greenhouse gas emissions, increased traffic congestion, resource consumption and noise pollution. We will try to minimise the environmental impact of the study by implementing some preventative measures (as described below).

Environmental Impact Monitored: To minimise the environmental impact of our study, we will:

1) Print materials only when necessary; questionnaires and most data collection will be collected using digital equipment to avoid paper waste, and we will have an electronic trial master file.

2) Encourage participants to use less polluting means of transportation (as cycling, walking or use public transport) for visits, with the exception of the journey home from the study visit; this is due to the risk of side effects after daridorexant administration and the safety measure of the participant being driven home.

3) Testing equipment throughout the study will be powered off when not in operation and include a charging limit. Lights in study testing rooms will be switched off when not in use.

4) We will be mindful how long experimental tasks last (e.g., using computers) with consideration how much power they draw.

5) Where appropriate, an effort will be made to recycle all waste produced during the study (e.g., cardboard boxes).

DATA MANAGEMENT

Data Type:

Firstly, we will collect screening documents. This includes data from the online screening questionnaire on Qualtrics (see in documents the Online Screening questionnaire) which will check for essential inclusion and exclusion criteria for the study; and data collected in the online screening videocall and study visit 1 (see in documents the case record forms) which will be associated to a screening ID. This includes:

- Demographic data (including ethnicity, gender, age, years in full-time education);
- Information about the health of the participant (including past medical history, medication history and structured clinical interviews to identify current or past history of psychiatric disorders or sleep and circadian rhythm disorders);
- Physiological measurements (weight, height, BMI calculation, blood pressure, pulse) and urine samples (for urine drug screening and urine pregnancy test for females at birth that will be recorded only as positive or negative)

During screening, we will collect contact details for the purpose of this research only. If eligible in the online screening questionnaire, the prospective participant will be asked to provide an email contact after completing an online screening consent for this. When invited by email to book the online screening videocall, prospective participants will be asked to select a slot using Microsoft Bookings app of the university Nexus 365 for business account which collects their name and email address. In the video call screening session, they will also be asked for their personal contact details.

Online consent forms will be collected electronically (on Qualtrics and exported as pdf). In-person consent forms will be collected on PDF format (using an iPad pencil for signature) or paper form and will include participants' names.

Questionnaire responses and task results will be collected in the screening and study visits. Further questionnaire responses will be collected the day after study visit on an online questionnaire on Qualtrics.

During one of the computer tasks at the study visit, three saliva samples will be collected by participants for salivary alpha-amylase analysis.

Participant bank details will be collected for sharing with the finance team via electronic format for reimbursement of participants.

Data Access Control?:

No

Data Storage Location:

We will use an electronic trial master file (TMF) which will be stored in a University Nexus 365 One drive folder and given access only to researchers working in the study through their password protected university accounts. The University Nexus 365 One drive uses Microsoft 365 for business which guarantees encryption of data. The pseudonymised data associated only to a screening and participant identification (ID) numbers will be stored in a separate research data folder in the University Nexus 365 One drive. These will be shared with some members of the research team for the study. Some TMF folders and documents will be either stored separately (in digital or paper format) or will have a separate password for access as described below.

The Microsoft Bookings app of the university Nexus 365 for business account will have an account linked to the study email and primary researchers accounts that will collect the participants name and email address for the purpose of booking the video call screening session. The in-person study visits bookings will also be sent to participants email using

Microsoft Bookings app. This will not collect any other personal data and will not have the screening or participant ID numbers.

The online screening questionnaire will be conducted and stored on Qualtrics and no IP addresses will be collected. The only information that will be collected will be the personal contacts to book the online screening videocall.

Paper consent forms will be stored securely in a locked filing cabinet in a room in the Neurosciences Building (Department of Psychiatry). PDF consent forms will be stored in the respective eTMF folder accessible only by critical members of the research team.

A participant enrolment log will link participants' personal details to their unique (screening and participant) ID numbers. This document will be stored digitally in the respective folder of the TMF but with a separate password accessible only by critical members of the research team and separate from all research data.

At the online screening videocall, personal/sensitive information (i.e., date of birth, name, address, contact number) will be stored separately to non-identifiable screening data (e.g., age, gender, educational level etc). The former will be stored digitally on a password protected document (Personal contacts) of the electronic TMF linked to a screening ID. While the latter screening data, will be stored digitally on the OneDrive research data folder. It will be linked to personal identifiers via the linkage code (Screening ID).

The randomisation log and associated documents of the variance minimisation process will be stored in a separate folder in password-protected documents and will be linked to personal identifiers via the linkage code (Participant ID). These documents will only be accessible by Professor Cowen (or delegated to another study medic in his absence) and the independent researcher(s) that will manage the randomisation process.

Saliva samples will be rendered acellular by centrifugation within 7 days and then samples will be stored in the Neurosciences Building (Department of Psychiatry) in a pseudo-anonymised form at -20oC. Access to the samples will be by the research team and the samples will be held in the custody of the primary researcher who will hold the code linking the samples to a particular individual.

Questionnaire and cognitive task data will be recorded on a digital format on the password-protected OneDrive research data folder, de-identified and linked via linkage codes (screening and participant ID). Equally, the results of salivary alpha-amylase analyses will be stored in an electronic data sheet, using only the unique participant ID. Some data will be collected electronically using Qualtrics software and this data will be downloaded from Qualtrics and stored directly on the research data folder. All participant data will be stored under their screening or participant ID numbers. The cognitive task data will be backed up to a usb stick allocated to the project in a locked cabinet in a room in the Neurosciences Building (Department of Psychiatry). All research data storage will adhere to best practice guidance BPG09 'data security'.

Participant bank details will be collected on an electronic document and shared with colleagues from the finance team via electronic format for bank transfer.

Data Storage Period: Consent forms will be kept securely on paper or PDF for 10 years after the end of the study.

Participants' bank details will be sent electronically to the finance team and kept by them for 7 years before being deleted.

Personal/sensitive information stored in the electronic TMF, data from screening online questionnaires and the participant log that links participants' personal details to their unique ID numbers will be destroyed after the study has concluded, and the results have been written up and published.

The anonymised online screening responses of people that are not eligible to participate in the study and do not provide an email contact will be deleted from Qualtrics monthly.

Other non-identifiable screening and research data, as well as the randomisation log will be archived and stored safely for 5 years after the final publication. Of note, this data will also be made available to the public and research community on data repository in line with Open Science Principles as described in the next question. The cognitive task data will be backed up to a usb stick allocated to the project in a locked cabinet in a room in the Neurosciences Building until the research data is processed, analysed and published.

Any saliva samples labelled with the code linking the samples to a particular individual will be disposed of within six months according to HTA guidelines. The results of the salivary alpha-amylase analyses linked to the participant ID in an electronic data sheet will be deleted alongside other non-identifiable screening and research data 5 years after the final publication.

Data Retention Reuse:

In line with Open Science principles, this study will be preregistered on the Open Science Framework (https://osf.io/k6gmd/) and on the NIH Clinical Trials registry (https://clinicaltrials.gov/).

On completion of full data analysis and manuscript submission we will make deidentified task and questionnaire data, along with relevant processing scripts, available to the public and research community on a data repository (Zenodo/GitHub) in line with Open Science Principles. This will ensure long-term archiving and permit dataset accessibility/ discovery via common internet search engines. A Digital Object Identifier (DOI) link will be created for the dataset, enabling coupling to related publications. At no point will any of the data used for potential publication or presentation, or open science be linked to any personally identifiable information.

Data which has been de-identified may be shared with other academic and commercial organisations in the future, including those outside of the UK and the EU. Participants will be informed of this and specific consent to this is obtained within the Informed Consent Form.

For promotion in the Be Part of Research (BPoR) registry, we are required to provide monthly the information about how many participants heard about the study using BPoR. We will collect this data using one question on the online screening questionnaire that enquires about how they heard about the study. We will not provide any participant details to BPoR, except the frequency of cases that confirmed hearing about the study using the BPoR registry.

Data Destruction:

Once the study has concluded, the data has been analysed and the results have been written up and published , personal/sensitive information stored in the electronic TMF, data from screening online questionnaires on Qualtrics and the participant log that links

participants' personal details to their unique ID numbers will be destroyed by safely deleting the files.

Any saliva samples labelled with the code linking the samples to a particular individual will be disposed of within six months on ending the study.

Consent forms will be shredded or deleted 10 years after the end of the study.

Participants' bank details will be deleted by the finance team 7 years after the end of the study.

The anonymised online screening responses of people that are not eligible to participate in the study and do not provide an email contact will be deleted from Qualtrics monthly.

Other non-identifiable screening and research data, as well as the randomisation log will be safely deleted 5 years after the final publication.

Data Access: Data stored physically will be kept in the physical trial folder, which alongside cognitive task data backed up to a project usb stick will be locked and secure in a filing cabinet located in a room which is locked when not in use (room located in the Neurosciences Building, Department of Psychiatry) and card-accessed.

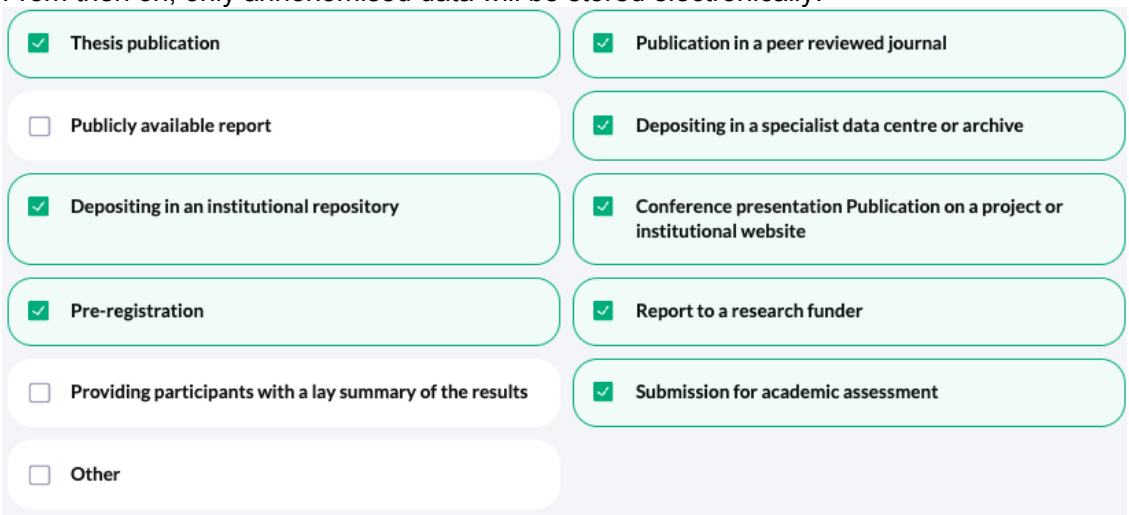
The electronic TMF folder and research data folder (with de-identified information linked to a unique ID number) on One drive will be shared with the research team for the study. However, some documents and folders in the TMF will have a separate password and access restrictions:

- A participant enrolment log that links participants' personal details to their unique ID numbers (screening and participant ID) will be stored under a separate password and accessible only by critical members of the research team, separate from all research data.
- The Personal contacts log in the electronic TMF is a document with personal/sensitive information (i.e., date of birth, name, address, contact number and email address) and will have a separate password and will be accessible only by critical members of the research team.
- The consent forms in PDF format are saved in a specific folder in the electronic TMF and will be accessible only by critical members of the research team.
- The randomisation log and associated documents of the variance minimisation process will be stored separate in a folder only accessible to Professor Cowen (or delegated to another study medic in his absence) and the independent researcher(s) that will manage the randomisation process. The documents will be password-protected and will be linked to personal identifiers via the linkage code (Participant ID). These independent researchers will be provided with the participant ID and essential anonymised data (gender and chronotype MEQr score) for the randomisation process.

The study email and the Microsoft Bookings app (part of the university Nexus 365 for business account) is linked to the primary researchers university accounts which require a password and a two-factor authenticator process to be accessed.

In the unlikely event of a participant being involved in any safety incident at the Department of Psychiatry, their details (name) may be shared with safety officers, without any further personal information being shared.

Organisation Data: No

Recording:	No
Participant Data Confidentiality:	The study will comply with the UK General Data Protection Regulation which requires data to be anonymised as soon as it is practical to do so. All participants details shared in screening questionnaire or visits will be treated as confidential by the research team and will be recorded as electronic data without name or address and assigned a study ID. A linking file will enable identification by matching the study ID to the participant name; this file will be stored securely and separately from the coded research data. All documents will be stored securely and only accessible by study staff and authorised personnel.
Participant Data Anonymity:	No
Participant Data Pseudoanon:	Yes
Participant Data Pseudoanon More Info:	Each participant will be assigned a unique study number at screening following informed consent to participate is confirmed. During the study, a key will link participants' personal details to their unique study number in a document that will be stored separately from all research data. Both screening and study data will be stored pseudoanonymously (using study specific identifier - screening and participant ID) and will be retained for 5 years after publication and then destroyed, in line with Oxford University policy on the management of research data and records. Once the data has been analysed and the results have been published, the online screening data, contact information, participant enrolment log with the linking key will be destroyed. From then on, only annonomised data will be stored electronically.
Publication:	

HUMAN TISSUE

Training:

Researcher name	Title of course	Date of completion
Dr Daniela Almeida Borges	Human Tissue Act training (MRC)	26/11/2024
Dr Michael Colwell	Human Tissue Act training (MRC)	20/05/2025
Georgia Feltham	Human Tissue Act training (MRC)	12/01/2024
Professor Catherine Harmer	Human Tissue Act training (MRC)	06/08/2024

What samples: Urine; Saliva

Samples previously collected and anonymised: No

Amount collected (new samples): Urine – 30ml (Volume to be collected per participant)
Saliva samples using Sarstedt salivettes - about 4.5ml in total (3 samples of 1.5ml per participant)

Relevant material: Yes

Relevant material (yes): A license is not required.
Urine is considered a relevant material under the Human Tissue Act. This study on healthy volunteers only includes the use of urine samples for baseline testing (for drug use and pregnancy) to confirm some of the exclusion criteria. It will only require the collection and immediate dipstick testing of the urine sample, with no storage, and the sample being destroyed on the day taken. As per Guidance on the registration of samples under an HTA licence at the University of Oxford (point 2.4.a on page 3), an HTA licence is only required if the samples are stored.
Saliva is also considered a relevant material under the Human Tissue Act. However, the saliva samples will be rendered acellular by centrifugation within 7 days. Published work has shown that centrifugation at standard speeds (around 1,000–1,600 × g) is widely used to obtain cell-free saliva, and that further high-speed centrifugation can remove nearly all residual extracellular DNA and cell debris (Štibinger et al., 2019, Biomolecules). As our study deals with saliva samples rather than blood, that are collected in a synthetic swab, the protocols for rendering plasma acellular are not relevant in this context. We have also considered the salivettes manufacture guidance for the sample processing. Hence, we will complete centrifugation of the salivettes (1000xg for 2 minutes) within 4 hours of collection; transferring the supernatant to another tube and freeze it at -20o C; and finally dispose of the salivette collection tube (with the residue at the bottom) and the insert with synthetic swab in a hazardous biological waste container. Otherwise, the samples will be placed in the fridge and the centrifugation will take place within 7 days following the same steps. In these cases, the samples are viewed as acellular non-HTA relevant samples and a licence is not required, provided that the processing takes a matter of hours or days and no longer than a week.

Is transfer required: No

DNA: No

Is storage required: Yes

Storage required (yes)	Saliva samples will be de-identified and be assigned a linkage code to link participants with their respective samples. The samples will be rendered acellular by centrifugation within 7 days and then frozen. The salivette will be removed and destroyed after centrifugation. Prior to salivary alpha-amylase assay, the samples will be stored in the Neurosciences Building (Department of Psychiatry) in de-identified form at -20oC. The assays will be carried out in the Neurosciences Building. Access to the samples will be by the research team and the samples will be held in the custody of Professor Harmer. The primary researcher will hold the code linking the samples to a particular individual. Any excess acellular supernatant of saliva remaining at the end of the study will be disposed of within six months according to HTA guidelines.
End of research:	Disposal in accordance with the Human Tissue Act 2004

DRUGS/SUBSTANCES

CTIMP: No

CTIMP no: In this trial we will use the dual orexin receptor antagonist daridorexant which is an oral medication licensed for the treatment of insomnia in adults in the UK (August 2022). This drug was developed and is currently marketed by Idorsia Pharmaceuticals Limited Company. Daridorexant's efficacy for insomnia treatment was investigated in two multicentre, randomised, double-blind, placebo-controlled, parallel-group, Phase 3 studies, as well as its safety profile (Mignot, 2022).

This study will assess daridorexant's non-clinical effects, i.e. reaction times or performance on emotional, reward and cognitive processing tasks in healthy subjects. Daridorexant is being used as a pharmacological tool to examine the effects of dual orexin receptor antagonism on emotion processing and cognition. The study is not a clinical trial under the scope of SI 1031. It will not investigate the efficacy and/or safety profile of daridorexant. Furthermore, it is not designed to discover, verify/compare the daridorexant's clinical effects; to discover or verify/compare its pharmacological effects (e.g. pharmacodynamics); to identify or verify/compare its adverse reactions; or to study or verify/compare its absorption, distribution, metabolism or excretion as described by the MHRA.

Local licence: Yes

Local licence details: Daridorexant has a license as an oral medication for the treatment of insomnia in adults. We will be using this medication in healthy adult participants to assess non-clinical effects of a dual orexin receptor antagonist.

DSMB: No

DSMB no: A Data and Safety monitoring board will not be required as this research study is not a Clinical Trial of an Investigative Medicinal Product. Furthermore, this study will not include vulnerable patients, will be delivered in a single centre with a low-risk intervention. This study will follow a simple study design of a double-blind randomised controlled trial of daridorexant or placebo used once in the study location by healthy volunteers. As a research team, we will monitor data quality and safety as described in the methodology section.

Sponsor: Does not apply.

Drug detail:

Name of drug/substance to be used	Daridorexant	Lactose and/or sucrose
Purpose of use in this research	For neuropsychological effects testing	Placebo
Adverse reactions and side effects posing a particular risk	Common: Somnolence, Dizziness, Fatigue, headache and nausea. Uncommon: Hypersensitivity (including rash, urticaria); Hallucinations (Hypnagogic and hypnopompic); Abnormal dreams, nightmares; Somnambulism; Sleep paralysis	N/A (placebo)
Formulation	Film-coated tablet will be encapsulated in opaque capsules	Tablet (max dose of lactose 95mg) tablet will be encapsulated in opaque capsules
Dose and route of administration for research	50mg tablet for oral administration	1 tablet for oral administration

Duration of treatment for research	Single dose	Single dose
Licence status where the research is taking place	Licensed for use in the UK by MHRA	N/A (inactive substance)
Usual Indication	Insomnia disorder in adults	N/A (placebo)
Usual Dose	25 – 50 mg per day	N/A (placebo)
Dose to be used in research	50mg	1 tablet
Usual duration of treatment	Short-term, with review within 3 months and periodically thereafter. Clinical data are available for up to 12 months of continuous treatment.	N/A (placebo)
Duration of treatment in this research	Single dose	Single dose
Source of drug/substance (name and address of manufacturer and/or supplier)	Idorsia Pharmaceuticals Uk Limited	Homeopathic Supply Company (HSC), UK

Storage: The Daridorexant and placebo tablets will be stored at room temperature in a locked storage cupboard in the Neurosciences building.

Dispensing: Daridorexant and placebo tablets will be dispensed from the Neurosciences building by a study medic.

Preparation: Daridorexant and placebo will be over-encapsulated by study investigators and department staff by using the lab standard operating procedure (SOP).

Each time a participant is assessed in screening processes as eligible, they will be randomly assigned to treatment or placebo using the variance minimisation algorithm to ensure an even distribution of key covariates (gender and chronotype / MEQr score) between the groups. An independent researcher(s) will generate the randomisation code following the procedure described by Sella, Raz, and Cohen Kadosh (2021). They will then record the allocation on the Randomisation log, identify the correct envelope with the drug or placebo (previously encapsulated) and write the participant's ID on it. This will then be ready for study researchers to collect and give to the respective participant in the study visit.

Baseline safety: When participants express an interest in taking part in the study, they will be asked to complete an online consent for eligibility screening questionnaire to check for inclusion and exclusion criteria. The exclusion criteria were defined to mitigate the risk of daridorexant or placebo use in healthy adult volunteers. In particular, we considered to exclude participants with:

1. Any sleep or circadian rhythm disorders (covered in in screening procedures); in particular narcolepsy for which daridorexant is contraindicated, as well as the risk of developing different sleep bheaviours, sedation and respiratory depression that might worsen sleep conditions.
2. History of, receiving or seeking treatment for any mental health condition (covered in screening procedures); in particular due to risk worsening depression and suicidal ideation with daridorexant.
3. History of, or current medical condition(s) which might increase the risk of oral administration of daridorexant:

- ADHD requiring treatment with stimulants or other centrally-acting drugs
- Neurological problems, including traumatic brain injury, epilepsy, Central Nervous System tumours or other severe neurological problems (e.g. Parkinson's disease; blackouts requiring hospitalisation)
- Current Asthma, Chronic Obstructive Pulmonary Disease, emphysema or any medical condition that affects the lungs or breathing
- Mild to severe hepatic impairment (Child-Pugh class A-C)
- Severe renal disease
- Severe gastrointestinal problems
- History of, or current medical condition(s) which, in the opinion of the Investigator may interfere with the safety of the participant or the scientific integrity of the study
4. Pregnancy, intention to become pregnant or breastfeeding during the study, as this would be a contraindicated use of daridorexant.
5. Body mass index (BMI) below 18 or above 30kg/m2, to ensure an appropriate pharmacokinetic profile for daridorexant is achieved.
6. Current or past history of drug or alcohol dependency, and inability to withhold from alcohol within 24 hours of study visit as concomitant use with daridorexant increases postural instability and memory issues caused by alcohol.
7. Regular alcohol consumption of more than 21 units per week or use of recreational drugs or performance-enhancing drugs (e.g. cannabis, cocaine, amphetamines) within past three months, and inability to withhold from alcohol within 24 hours of study visit as it might interact with daridorexant.
8. Excessive caffeine consumption (above 400mg a day) as it could affect the sleep-wake cycle influenced by daridorexant.
9. Current or recent (past two months) use of any psychoactive medications, antihistamines, or medical device (e.g. implanted neurostimulator) that can cause sedation due similar effect profile of daridorexant and cumulative risk of sedation.
10. Current use of any medications or substances at risk of interaction with daridorexant; in particular:
- strong or moderate CYP3A inhibitors (e.g. strong inhibitors - itraconazole, clarithromycin, ritonavir, grapefruit juice; moderate inhibitors - fluconazole, verapamil, diltiazem, erythromycin, ciprofloxacin, cyclosporine) as these would increase risk of daridorexant side effects
- strong or moderate CYP3A inducers (e.g. of strong inducers - rifampicin, carbamazepine, St. John's wort; moderate inducers - bosentan, efavirenz, etravirine, modafinil) as these would reduce exposure to daridorexant.
- Gastric pH-modifiers (e.g. famotidine and proton pump inhibitors) can decrease daridorexant maximum concentration
- P-gp transporters (dabigatran, digoxin) as daridorexant can reduce effect of P-gp transporter drugs.
11. Inability to ingest up to 95mg of lactose due to the potential use of placebo tablets.
12. Previous participation in any other drug study or sleep intervention study in the last three months

Participants that meet the eligibility screening criteria in the online screening questionnaire will be invited to the online screening videocall to continue the screening process. At the visit, they will first discuss and sign the consent form for study participation. Then, they will complete the required baseline screening interview, including:
- Personal contact details collection

- Demographic data including ethnicity, gender, age, years in full-time education
- Medical history screening and details of current and past medication (including confirmation of exclusion criteria)
- Selected sections of the Structured Clinical Interview for DSM-5 (SCID-5), which probes for past or current psychiatric illness (exclusion criteria)
- Relevant screening questions for insomnia disorder (screen negative for insomnia symptoms on the Sleep Condition Indicator) and other sleep or circadian rhythm disorders (based on screening questions for other disorders identified by Wilson et al)

At the first study visit (1), they will complete all measurements and investigations to confirm their eligibility for the study, including:
- Weight and height measurement, for calculation of Body Mass Index (BMI)
- Blood pressure and pulse recording at rest
- Urine drug screening test
- Urine pregnancy test (for female at birth)

If they do not meet the eligibility criteria for the study at any of the screening procedures, the researcher will sensitively inform the participant they are ineligible and the screening process will end.
If the outcomes of all screening procedures indicate the participant meets all of the study eligibility criteria, the participant will be enrolled in the study and assigned a participant ID.
If screening or eligibility checks raise any questions about the participant's suitability to take part in the study, the participant will still complete the baseline questionnaires and tasks at the screening visit. The researcher will ask a study medic during or after the screening videocall or study visit 1 to check information collected. The medical doctor might need to discuss the study with the participant and perform a medical examination, if deemed necessary. Participants will be informed of this and that they will be contacted with an outcome, if this is not completed at the screening visit.

Safety Monitoring:

If participants are eligible for the study, they will be invited for the second visit (Study visit 2) at the Neurosciences Building in the Department of Psychiatry and previously randomised to take daridorexant or placebo. A study medic will be available for phone advice and within 30-minute of the research site throughout the study visit period. A maximum of four weeks is allowed between the online screening videocall and the first Study Visit, as well as between the first and second study visits. If this duration is exceeded, another screening will be performed to ensure eligibility.

We have considered the risk of sedation with daytime administration of daridorexant. Hence, we will organise the study visit in the morning as non-clinical evidence suggests that the risk of sedation with daridorexant is reduced in the first few hours after waking up (Roch et al., 2021). We will also ask participants to avoid certain substances that might interact with daridorexant or cause sedation (alcohol, recreational drugs, or grapefruit juice) 24 hours before the study visit. They will be asked to avoid smoking before the study visit, have a maximum of a cup of coffee (or equivalent) up to 90 minutes before the visit time and have a light breakfast (e.g. 2 toasts of bread or yogurt with cereal). They will be asked to arrive via walking, being driven to, by public transport or taxi. They will otherwise be advised to complete their normal morning routine before study attendance.

Before the study visit starts, we will check if participants still do not meet the exclusion criteria. Once they are administered the daridorexant or placebo tablets, they will be asked to stay at the Neurosciences building in a separate room and will be checked every 30 mins. They will only start cognitive tests 1 hour after administration. After administration and until the end of the study, participants will be asked to not eat food, drink caffeinated drinks or smoke. They will be encouraged to take comfort breaks. This is based on pharmacokinetics of Daridorexant (Muehlan et al., 2018; Boof et al., 2019; Muehlan et al., 2020; Berger et al., 2021).

Their sleepiness state will be monitored using a validated one-item scale (Karolinska Sleepiness Scale) during the study visit. This will be checked before administration of daridorexant or placebo and hourly thereafter. Once the tasks are completed, they will be asked to continue to avoid driving or engaging in any activities requiring full alertness (e.g. cycling or operating heavy machinery) until the next morning. They will be advised that they should expect feeling completely back to normal the following day. However, if it happens that they feel drowsy, they will be advised not to carry out activities requiring full alertness. We will organise a taxi and/or public transport from the Warneford Hospital to their local accommodation, unless the participant has an equivalent transport arrangement (e.g. someone to drive them by car) already organised. If the Karolinska Sleepiness Scale is above 7 at the end of the study visit, we will organise a taxi. All participants will receive a phone number for calling the study medical doctor (Dr Borges) in case they need medical advice related to the study after the visit has taken place. We will also send a follow up questionnaire the next day to check on effects experienced and impact on sleep using the consensus sleep diary.

The randomisation code will be broken if a participant requires treatment for a new medical condition or experiences serious adverse reactions, and either of these situations make it clinically important to know what medication they took. In order to unblind the participant, Professor Cowen or one of the independent researchers will access the randomisation log and will unblind the allocation if deemed necessary after discussion of the case. If breaking the code is necessary then only that individual's code will be broken. Data from unblinded participants will not be admitted to analysis. If unblinding occurs, the researcher will record the reason and result of the unblinding, as well as the date and time of the event.

Medical Cover: A medical doctor who is part of the research team will review the screening and make a final judgment about including participants in the study. A qualified medical doctor will be contacted if a participant expresses concern to a named researcher regarding side effects or health status changes during the course of the study.

GP notification: No

GP further info: Participants' GPs will not be informed about their participation in the study. A one-off dose of daridorexant is not regarded as a clinically significant intervention and is not expected to have any impact on participants' health or wellbeing.