INFORMATION AND CONSENT FORM

Title of the research project:	Double Blind Clinical Trial of Daridorexant for Alzheimer Disease Prevention
Principal investigator:	Dr Sylvia Villeneuve
Co-researcher(s) :	Dr Simon Ducharme. MD – study physician Dr Judes Poirier, PhD Dr Maiya Geddes, MD Dr Thien Thanh Dang-Vu, MD Dr Andrée-Ann Baril, PhD Dr Andrew Lim, MD Dr Mohamed Badawy, MD
Member(s) of research staff:	Jennifer Tremblay-Mercier, MSc Nolan-Patrick Cunningham, BA
Sponsor **Granting agency:**	Douglas Mental Health University Institute Research Centre- StoP-Alzheimer Centre Weston Family Foundation
Protocol number:	*REB: [2025-1180]* *HC: DARAD2025*

1. Introduction

We invite you to participate in a research project. However, before agreeing to participate in this project and signing this information and consent form, please take the time to read, understand, and carefully consider the following information.

This form may contain words you do not understand. We invite you to ask any questions that you may have to the researcher in charge of this project or to a member of its research staff and to ask them to explain anything that is not clear.

2. Nature and objectives of the research project

Alzheimer's disease (AD) is characterized by the accumulation of proteins in the brain (amyloid and tau), leading to cognitive decline and memory loss. There are many factors contributing to

AD, and the role of sleep is increasingly recognized as a crucial factor in both the development and progression of AD. The quality of sleep decreases as we age, and objective disruption of sleep quantity (excessive or reduced number of hours sleeping in a day) and sleep architecture (the structure and organization of sleep during the various stages and cycles that occur throughout the night) are known risk factors for AD. Importantly, disruptions in sleep can occur in individuals **who do not self-report insomnia symptoms**. This means they may not complain about having trouble sleeping, yet objective assessments like polysomnography might reveal issues with sleep duration, efficiency, or stage architecture. Finally, the glymphatic system which has as a main function to clear the brain of protein waste products such as amyloid and tau, is mainly active during sleep. Improving sleep, even in individuals who would have no sleep impairment might therefore still reduce the accumulation of amyloid and tau by facilitating their clearance from the brain.

Sleep quality can be improved using medication:

Increasing evidence from human and rodents' studies suggest that Dual Orexin Receptor Antagonist (DORA) medications, a class of treatments prescribed to treat chronic insomnia, may help clear early forms of amyloid and tau proteins from the brain. Interestingly, the study performed with human included participants aged 45 to 65 years with no cognitive impairments, suggesting that DORA medication might work as a preventive treatment for AD, in individuals that do not yet have cognitive impairments and/or advanced AD pathology.

We want to investigate, in individuals with no diagnosis of AD, if a DORA medication (Daridorexant), can help clear amyloid and tau proteins and improve cognition. Our hypothesis is that Daridorexant will have a protective effect toward the development of AD by slowing down amyloid and tau accumulation over time and that this effect will not be restricted to individuals with insomnia.

For the realization of this clinical trial, we plan to recruit up to 240 participants with or without insomnia, aged from 50 to 90 years old. We are asking people to join this clinical trial to compare the effects of Daridorexant (50 mg once per day) against a sugar pill (placebo). People in the trial are asked to take a study medicine (either Daridorexant or placebo) once a day for 1 year. You won't know if you are taking the active medication (Daridorexant) or the placebo and the research team won't know either until the end of the trial. Trials often use this kind of "double-blind" design to keep personal opinions from influencing the results.

3. Conduct of the research project

3.1 Location of the research project, duration and number of visits

This trial is one of the studies performed in the PREVENT-AD research program at the StoP-AD Centre. The StoP-Alzheimer Centre is located at the Perry Pavilion - Douglas Mental Health University Institute and your participation in this project will last 12 months and will include 4 visits at the Center and 2 remote visits (telephone or videoconference).

3.2 Nature of your participation

Pre-screening: Before coming to the first eligibility visit at the Centre, we will ask you to answer a few questions to start evaluating your eligibility to the project. These questions can be answered online via a link (electronic consent through a system called REDcap), or by phone (verbal consent). The questions will serve to evaluate the main inclusion/exclusion criteria such as age, level of education, pharmacological profile, and medical history including a questionnaire about obstructive sleep apnea. We will also ask you if you have someone in your entourage who could act as a 'study partner'. A study partner is an individual who is close to you and familiar with your daily life, such as a close friend, life partner, or relative. During the cognitive evaluation at the eligibility visit, a study partner may be needed to answer brief questions about you, providing insights based on their knowledge of your everyday activities and behaviors. This helps ensure a comprehensive understanding of your cognitive function in real-world settings.

Screening visit: If you are still interested and seem eligible, we will invite you to come to the Centre for a formal screening visit. We will ask you a few more questions regarding your intake of medication, your sleep habits, and your general health status and history. We will perform a cognitive test with you and we will also have questions for your study partner, if required. A blood draw will be taken for the evaluation of your general health.

Pre- and Post-intervention tests: If you are eligible and if you agree to participate, you will perform various tests before the beginning of the intervention and the exact same tests after 1 year of intervention. We call them the 'Pre-intervention' and 'Post-intervention' tests. These include the following: cognitive tests (about 1.5 hours), self-reported questionnaires related to your psychological well-being and your sleep habits (about 30 min), and a health assessment including vital signs and a few medical questions. Blood samples (3 tubes of 10 milliliters – 2 tablespoons) will be taken, prepared, and frozen for future analysis to examine proteins and biochemicals that are related to brain health. The total duration of these visits will be around 3.5 hours.

You will be also be asked to wear a device that will measure your sleep quality and sleep architecture. This device is a headband (Muse S. system) that you will need to wear at night, for 1 week, before and after the intervention. You will also be asked to write in a sleep journal each morning after you have slept with the headband (1 week). The type of information requested in the journal will include wake up time, bed time, level of fatigue during the day, intake of caffein, alcohol, medication, and number of awakenings during the night. This headband will track your brain activity via EEG (electroencephalogram) recordings and will measure the time you spend in different sleep phases, the quantity and intensity of deep sleep phases, etc. You will have to transfer the data on a server every morning by following a simple procedure. A staff member will explain the data transferring procedure to you, make sure you have all the material needed to transfer the data, and will provide all of the instructions to you on paper.

Lumbar puncture (optional): As part of the pre- and post-intervention evaluations, we are also interested in measuring biochemical compounds related with brain health in the cerebrospinal fluid (CSF). Hence, a lumbar puncture (LP) will be proposed to you, as an option, before and after the year of treatment. The LP is usually not performed at the same time as the rest of the

pre- and post-intervention evaluations; instead, it is usually done fasted, a few days later. If you have done a lumbar puncture as part of the PREVENT-AD cohort evaluations within 1 year from the start of your study medication, it could be considered as the 'pre-intervention' LP and you would not have to do another one, but we will ask you if you want to do another one at the end of the 1-year treatment phase. If you are interested, let the research team know, and they will give you additional information. There is a separate consent form for this procedure.

Study drug: After all the pre-intervention procedures, we will give you your first supply of study medicine (3-month supply). There is a 50% chance that this medicine will be Daridorexant 50 mg and 50% that it will be an inert placebo. You will be asked to take one pill every day about 30 minutes before going to bed at night. We will tell you how to keep track of your use of the medicine and we will evaluate your compliance and adherence to the treatment regularly.

Safety visits: We will ask you to come back at the Center after 3 and 6 months for a health assessment and to perform a blood draw. The visit will last about 45 minutes. During these visits, we will give you your medication supplies (a 3-month supply and a final 6-month supply).

After 2 weeks and 9 months, we will call you by phone or via a videoconferencing software (Zoom or Teams) to check on your well being and ask you some questions about any experienced side effects from the study drug, if you are forgetting to take the tablets, or have any problems with the compliance to the treatment.

For this clinical trial, the analysis will use data on sleep, cognition, and the biological markers of Alzheimer's disease measured in your blood. However, we might want to analyze additional complementary data. If you are a PREVENT-AD participant with regular annual visits, we will potentially use data from the PREVENT-AD evaluations such as the magnetic resonance imaging (MRI) or positron emissions tomography (PET) scans in secondary and exploratory analyses.

Early termination visit: If you want to withdraw completely from the study before the end of the expected schedule of events (before your planned 1-year post-intervention visit), we will propose a quick follow-up with you in person or remotely by video call. We would want to do a brief assessment to accurately complete our research information with regards to your safety (adverse events, compliance, and medication count). If you agree to come in person, we will use the occasion to perform a blood draw which will serve as the final measurement of the trial.

1 week-post treatment safety call: 1 week after the end of the 12-month treatment period or after the discontinuation of the study drug, we will call you to inquire about any residual side effects of the study medication and we will follow-up on any ongoing side effects until they are resolved. We will also propose to you an optional blood draw 1 month after the end of the trial that will allow us to test if the effect of Daridorexant lasts beyond the termination of the medication.

4. Risks and disadvantages associated with the research project

There are small but real risks involved in joining this trial.

Some people may feel uncomfortable if they are asked questions they find difficult. Our staff members are trained to recognize these feelings, and they will do what they can to help you and avoid discouragement or distress.

Sometimes people get a bruise on their arm from the blood draw. Occasionally people may feel faint or dizzy after their blood sample is taken. Infection at the site of the blood draw is possible, but rare.

Although it is light and comfortable, you might grow tired of wearing the EEG headband device every night for 1 week.

Risks and disadvantages related with the optional lumbar puncture are explained in a separate consent form (cerebrospinal fluid collection via lumbar puncture).

Despite all our efforts to protect your confidentiality there a small risk of a confidentiality breach (see confidentiality section).

Adverse reactions related with the intake of Daridorexant: Many medications can cause side effects or adverse reactions. A side effect is an unwanted response to a medication when taken in normal doses. The side effects listed below are not experienced by everyone who takes this medication. The side effects in people without insomnia are not expected to differ from those observed in people with insomnia. They might be equal, more frequent, or stronger, an aspect that will be carefully monitored. *Some people may want to talk with their regular doctor before they decide whether or not to join the trial or to continue taking the study medicine. You should always feel free to do this.*

<u>List of most common side effects:</u>

- Daytime sleepiness (2%)
- Headache (6%)
- Fatigue (2%)
- Nausea (2%)
- Dizziness (2%)

Other reported side effects:

Most of the side effects listed below do not occur very often, but you should consult with a professional and/or our research team if they happen to you:

- Sleep paralysis (a feeling of being conscious but unable to move (0.3%)) cataplexy-like symptoms (a sudden muscle weakness, commonly in the legs, that can last a few

seconds to a few minutes) or hallucinations (seeing or hearing things that are not there while falling asleep or when you wake up.)
- Complex sleep-related disorder (sleepwalking with object manipulation and sleep-related eating disorders, and inappropriate sexual behavior)
- Sleep-related psychiatric symptoms such as nightmare and abnormal dreams.
- Emotional perturbation (depressive symptoms, agitation, suicidal ideation).

Alcohol and other medications that may cause drowsiness: You should not combine Daridorexant with alcohol or other medications (e.g., antidepressants, sleeping pills, anxiolytics) that cause drowsiness, as taking Daridorexant at the same time as other medications that cause drowsiness increases the likelihood of being sleepy or less alert during the day.

You should allow for at least 7 hours of time in bed for sleeping. Should you not be able to achieve 7 hours or more of sleep, there is a risk of the study drug (Daridorexant) affecting your daytime wakefulness. Don't drive, use machines, or do other activities requiring vigilance or focus until you are fully alert and you know how the drug affects you. You're more likely to feel drowsy if you sleep less than 7 hours or take other medicines that cause sleepiness.

We will inquire about the apparition of any adverse reactions over the course of the study and the study physician will advise you as needed. We encourage you, your family members, and your study partner to monitor and report any signs of depression or any suicidal thoughts as it has been previously reported for some people who were taking Daridorexant. Sometimes, the study medication can be interrupted temporarily, or simply discontinued. If the study medication is discontinued after the first 3 months of the trial, we will still ask you to come to all of the planned visits and continue the project until the end, if this is possible for you. Note that even after the cessation of the study drug (Daridorexant), depressant effects in the central nervous system may persist in some individuals for up to several days upon discontinuation. As mentioned above, our research team will contact you 1 month after the end of your treatment period to follow-up on your condition and you can call the Centre at any time if you wish to speak with our research team.

5. Benefits associated with the research project

We hope the results obtained will contribute to the advancement of scientific knowledge on the importance of sleep for the prevention of Alzheimer Disease. While we cannot assure you of that, you may be getting a personal benefit from your participation in this research project by reducing your risk of AD (by improving the clearance of amyloid and tau) and/or by improving your sleep.

6. Voluntary participation and possibility of withdrawal

Your participation in this research study is voluntary. Therefore, you may refuse to participate. You may also withdraw at any time, without giving any reasons, by informing the doctor or the researcher in charge of this research study or a member of the research team.

Before you sign up for the study or at any time thereafter, you may wish to consult with another doctor who is not part of this study. You are by no means obligated to participate in whatever study is offered to you.

The researcher in charge of this research study, the Research Ethics Board, or the funding agency may put an end to your participation without your consent. This may happen if new findings or information indicate that participation in this research study is no longer in your best interests, if you do not follow study instructions, or if there are administrative reasons to terminate the study.

However, as mentioned in the 'early termination section', if you withdraw from the study, we suggest that you take part in a final evaluation, for safety reasons.

You have the right to modulate your withdrawal from the study at any time, by:

- Stopping the study drug
- Withdrawing from the clinical trial completely

If you withdraw or are withdrawn from the clinical trial, no further data or samples will be collected. However, the information and biological material, blood and cerebrospinal fluid samples, audio recordings, test and questionnaire results already collected for the clinical trial will be stored, analyzed and used to ensure the integrity of the study, as described in this document.

Any new findings acquired during the course of the study that could influence your decision to continue your participation will be shared with you quickly.

7. Confidentiality

During your participation in this study, the researcher in charge of the study and the research team will collect, in a study file, the information about you needed to meet the scientific objectives of the study. The study file may include information including your identity, such as your name, gender, date of birth, ethnicity, past and present health status, lifestyle, and the results of all tests, exams, and procedures that will be performed during this research study. Upon the daily transfer of the tracking data from the EEG device to a secured cloud space, the research team will then be transferring copies of the data to the secured computer network of the StoP-AD Centre. All the coded research data collected in this trial will be entered in LORIS, a secure centralized database used at the StoP-AD Center for all the PREVENT-AD research program datasets (preventad.loris.ca). All data related to this clinical trial will also be added to the same separate subproject dedicated solely to this trial in our LORIS database.

All study data collected during this research study (including personal information and samples) will remain confidential to the extent provided by law. You will be identified by a code number

only. The key to the code linking your name to your study file will be kept by the researcher and the research team in charge of this study.

A document indicating your participation in this clinical trial, for example a copy of the informed consent form or a data information sheet, could be sent to your family doctor to be put in your medical chart, if requested. The results of certain tests conducted as part of the research may be included as well, if you request it. As a result, any person or company to whom you give access to your medical chart will have access to this information. In addition, relevant information about your participation in this study and the study drug(s) may be forwarded to your community pharmacy for your safety.

The researcher in charge of this research study or a member of the research team could forward your coded data to the funding agency or research partners.

Secondary use of data:

The principal investigator may use and share your data collected during the study to answer questions beyond those of this study. This could advance science in many areas. Your data will be protected in a number of ways. For example, your data will be coded. This means it will not contain your name or any other information that directly identifies you. However, this data may be combined with other data of yours that was not collected for this study. This could allow some people to identify you even if your data does not contain your name. This is called re-identification. The principal investigator undertakes to prohibit any attempt to re-identify you by persons/organizations with whom it shares your data. Methods are in place to prevent accidental re-identification. If the principal investigator discovers accidental re-identification, it will notify the institution if possible.

Your data may be used to:

- Confirm the results of this study
- Produce more information on the study drug and how similar drugs work
- Develop tests to understand how a drug works
- Learn more about sleep, healthy aging, the prevention of dementia, or neurosciences in general
- Create new studies
- Develop new ways to review and use scientific data more effectively
- Develop and provide access to new drugs, medical devices, and healthcare solutions

To take part in this study you must also consent that your coded information will be available on the Canadian Open Neuroscience Platform (CONP). CONP does not itself perform research. Instead, it is a resource made available on the internet to researchers for the conduct of projects that advance neuroscience research and its clinical applications.

The data will be made available on CONP only to qualified researchers who will register with CONP and make a commitment to follow ethical standards when examining and analyzing the data (“Registered Access”). This level of access will reduce the risk of re-identification of the

data (that people find out it is about you) and any potential misuse of the data, but we cannot guarantee that this will never occur. If your data were re-identified and fell into the wrong hands, people might misuse information about you and your family's health, including data on your health, details about your family history of Alzheimer Disease, or demographic data about your personal situation, profession, etc. As an additional precaution, your coded information will be re-coded a second time with a new "CONP code", which won't be associated with your identity.

Except for our research partners and through our data sharing initiatives, we will not release your identifiable information to anyone else unless we are required to do so by law. In all cases, we will comply with all laws that protect your confidentiality.

Any partners outside of Quebec are required to respect confidentiality rules equivalent to those in effect in Quebec and Canada, regardless of the country to which your data may be transferred.

Study data will be stored for 15 years following the end of the study (or less depending on resources availabilities) by the researcher in charge of this research study and the funding agency. After the 15 years storage period (or when we no longer have the human resources), your original data will be destroyed by the researcher.

The study data may be published or shared at scientific meetings. In such instances, at the time of publication in a scientific journal, the publisher might request to share individual coded data used in the publication to a repository that could be accessible by the larger scientific community. Again, methods are in place to prevent accidental re-identification.

For monitoring, control, safety, security, and approval of the study drug by regulatory agencies, your study file as well as your medical charts may be examined by a person mandated by Canadian or international regulatory authorities, such as Health Canada, as well as by authorized representatives of the principal investigator, the institution, or the Research Ethics Board. All these individuals and organizations will have access to your personal data, but they adhere to a confidentiality policy.

You have the right to consult your study file in order to verify the information gathered, and to have it corrected if necessary. However, to protect the scientific integrity of this study, you may have to withdraw from the study if you access certain information before the study ends.

The use of Zoom or Teams for the safety visits or the sleep advice component may require that you consent to the platform's Terms and Conditions and/or Privacy Policy, which may include information that differ from the information provided in this Informed Consent Form. Please carefully read these online documents before agreeing to download and/or use Zoom or Teams. Due to the potentially identifying nature of online interviews, there is a small risk of re-identification and breach of confidentiality. However, measures are in place to minimize these risks.

8. Possibility of commercialization

The researchers do not intend to create commercial products as a result of this study. Muse (the company providing the EEG device) might however use some of the sleep recording data combined with other research data (such as your subjective sleep reports and your cognitive performance) to improve their devices. Muse will only have access to a limited number of information and they will not have access to information that could identify you.

9. Financing of the research project

The researcher responsible for this research project received funding from Weston Family Foundation to carry out this research project.

10. Compensation

You will receive an amount of $110 for the visit pre-intervention and 110$ for the visit post-intervention to cover the costs of travel, parking, and other expenses from participating in this study. (Participants living outside a 50 km radius of the Douglas Institute will receive an additional 50 ¢ per additional kilometer traveled to a maximum of $500 per visit). You will receive 50$ for the visit at the Centre at 3 months and another 50$ for the visit at 6 months. If you do the optional lumbar punctures, as mentioned in the related consent form, you will receive 200$ per procedures.

The research drug (Daridorexant or placebo) will be offered to you free of charge for the duration of this research study.

11. Should you suffer any harm

Should you suffer harm of any kind following administration of the study drug or any other procedure related to this research study, you will receive all the care and services required by your state of health. By agreeing to participate in this research study, you are not waiving any of your rights nor discharging the researcher in charge of the study, the funding agency, or the institution of their civil and professional responsibilities.

12. Contact information

If you have any questions or if you have a problem you believe may be related to your participation in this research study, or if you would like to withdraw, you may communicate with the study physician or the researcher in charge of this research study or with someone on the research team at the following number: 514-761-6131 ext.: 3329

13. Complaints

For any questions regarding your rights as a research participant in this study, or if you have comments or wish to file a complaint, you may communicate with: Commissioner for Complaints and Quality Services CIUSSS de l'Ouest-de-l'Île-de-Montréal at 1-844-630-5125 or by email at commissariat.plaintes.comtl@ssss.gouv.qc.ca.

14. Declaration of interests

The principal investigator (SV) states that they have no personal interest in the Idorsia company (fabricating the study drug) or the study drug that could conflict with their role as a researcher.

15. Monitoring of the ethical aspects of the research project

The Research Ethics Board of CIUSSS de l'Ouest-de-l'île-de-Montréal has given ethics approval to this research study and is responsible for monitoring the study.

Additional consent options:

Audio recording

Do you accept to be audio recorded during your cognitive testing? The audio recordings (stored in digital files) will be included in your research file and be kept for a maximum period of 15 years after the end of the study (or when we no longer have the human resources) by the researcher responsible for this research project. Content of the recordings will be used to ease the scoring of the cognitive tests (as some participants might speak fast or are harder to understand in real-time). This is to insure a proper scoring and a high-quality dataset. We will also to extract some additional data such as flow of words, the number of pauses, and other kinds of measurements.

☐ **Yes** ☐ **No**

Transmission to attending physician

Do you authorize the researcher or their team to inform your attending physician of your participation in this project and to transmit to them any relevant information?

☐ **Yes** ☐ **No**

Re-contact for participation in other studies

Do you agree to be contacted in the future to be invited to participate in other research projects? These other research projects will then be presented to you and project-specific free and informed consent will be sought. Only projects that have obtained ethics approval will be presented to you.

☐ **Yes** ☐ **No**

Indicate your coordinates for re-contact: _____
_____
_____

Declaration of Consent

Title of research project: Double Blind Clinical Trial of Daridorexant for Alzheimer Disease Prevention

Signature of participant

I have reviewed the Informed Consent Form. Both the research study and the Informed Consent Form were explained to me. My questions were answered, and I was given sufficient time to decide. After reflection, I consent to participate in this research study in accordance with the conditions stated above, including the use of all personal data and samples collected.

I authorize the study team to access my medical chart.

I acknowledge that in order to ensure my safety, information about my participation in this study and the study drug(s) may be forwarded to my community pharmacy.

Name and signature of participant Date

Signature of the person obtaining consent

I have explained the research study and the terms of this Informed Consent Form to the research participant, and have answered all questions asked.

Name and signature of the person obtaining consent Date

Commitment of the Principal Investigator

I certify that this Informed Consent Form was explained to the research participant, and that the participant's questions were answered.

I undertake, together with the research team, to respect what was agreed upon in the Informed Consent Form, and to give a signed and dated copy of this form to the research participant.

Name and signature of the Principal Investigator Date