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Are you participating in any other research studies? _____ Yes _____No

PURPOSE OF RESEARCH

You are invited to participate in a research study on Delayed Sleep Phase Syndrome (DSPS). In this 2-year study, we will examine if Lemborexant administered 5-10 mg nightly taken at desired bedtime (at least 2 hours prior to self-reported sleep onset time) can improve the symptoms of Delayed Sleep Phase Syndrome. Lemborexant is an FDA-approved drug for insomnia. Because this is a placebo-controlled study, there is a 50% chance that you may receive a placebo and a 50% chance that you may receive the active drug. You were selected as a possible participant in this study because you have been diagnosed with Delayed Sleep Phase Syndrome.

If you decide to terminate your participation in this study, you should notify Mila Trabanino at (650) 497-8690.

This research study is looking for 45 participants with Delayed Sleep Phase Syndrome (DSPS) to complete the study at Stanford University. 60 participants will complete the study across all sites.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately 2 years in total. Your participation in the study will last ~2 months from first contact, involve 2-3 initial phone calls/virtual meetings for prescreening, 4 visits (2 of them with the sleep medicine physician), 4 blood draws, 3 ECGs, 2 urine collections and 1 at-home DLMO exam.

PROCEDURES

Prescreening and inclusion:
If your doctor feels that you would be a good match for this study and could be eligible, he/she will discuss the study with you. Afterward, they would set up a

phone call for you and a study coordinator to discuss the study, including time commitment, etc. During the first phone call/virtual meeting, a coordinator will inform you of the study, check that you have a desired bedtime at least 2 hours earlier than your current bedtime, and that you are a good potential subject. The desired bedtime will be noted, and you will also be asked to complete the Alliance Sleep Questionnaire (ASQ) (online) if not already completed. The ASQ will then be used to exclude potential confounders and to confirm a potential diagnosis of DSPS based on the International Classification of Sleep Disorders 3rd Edition (ICSD3) criteria:

a) Sleep is delayed by two hours or more beyond what is considered an acceptable or conventional bedtime for you (your desired bedtime).
b) Not able to fall asleep if trying to sleep before the later bedtime;
c) This is interfering with your wishes/having social impact.

At the end of the screening phase, you will be invited to attend the screening visit, one day before starting the baseline phase. At this visit, the study coordinator will give some questionnaires, collect your vital signals and deliver the actigraphy watch and the sleep logs to you. In addition, an ECG, a pregnancy test (for women of childbearing potential), an alcohol and drug screening test and a blood collection will be performed to ensure that you do not have any clinical condition that would exclude you from the study.

Baseline and inclusion

Following a successful final screening visit, you will enter the baseline portion of the trial. At this phase, you will be asked to complete a daily log noting lights off/bedtime lights on/wake time and to wear the high resolution (>25Hz) actigraphy watch for 2 weeks or more at baseline, prior to randomization. At the end of the 2-week baseline period, you will be asked to come to the clinic again for a final inclusion. Logs/actigraphy recordings will be collected and used to check if you meet inclusion criteria prior to randomization (>2 hr. difference between sleep onset/actual bedtime and desired bedtime). This will be done by estimating sleep onset with actigraphy and logs in comparison to desired bed/sleep onset time.

Treatment and withdrawal phase

This second visit will be followed by a 2-week post randomization/treatment phase when you will take placebo or the study drug (titrate for one week) while going to bed at your desired bedtime. Additionally, there will be a 2-week post-treatment observation phase, following treatment cessation, with the instruction of still trying to sleep at your desired bedtime as when taking the drug/placebo.

Visits

In-person visits will occur 1) one day before the beginning of the baseline phase; 2) at the end of the baseline phase; 3) at the end of the treatment period (a short 1 hr visit); and 4) 2 weeks following the end of treatment. During visits, patients will not receive any information regarding light control, to avoid performance bias. For this reason, only on the last visit, the research staff will explain to the patient about the ideal light regimen.

During the first visit, the screening visit, patients will be asked to complete 4 questionnaires (PHQ-9, GAD-7, KSS, and ESS). The study staff also will administer the CSS and check the participant clinical symptoms. An ECG test will be done, and the participant will give urine to run the alcohol and drug screening test and the pregnancy test (if applicable). A blood sample (around 4ml) will also be collected to check the patient liver function (AST/ALT). At this visit, we will also provide the actigraphy watches and sleep logs to participants.

During the second visit, the randomization and allocation visit, the patients will be asked to complete 2 questionnaires (KSS and ESS) and the study staff will administer the CSS. A sleep medicine physician will also collect the medical history and perform a physical exam. An ECG test will be done, and the participant will give urine to run the alcohol and drug screening test and the pregnancy test (if applicable). A blood sample (around 4 ml), will also be collected to run liver enzymes (AST/ALT). We will check if the logs have been completed and if actigraphy watches are collecting data correctly. All the data collected from the actigraphy should be downloaded and the sleep log data transcribed in our encrypted database. The DLMO kits will also be provided during this visit along with the instructions to collect the saliva samples.

On the night of this second visit, we will conduct an at-home salivary dim light melatonin onset (DLMO) study (starting 7 hours before usual bedtime and continuing one-hour past bedtime). Patients can contact the study coordinator during this test in case they have any questions. All the saliva samples should be kept frozen until the next morning, when the participant will ship them back to the study site (according to the at-home DLMO Participant Instructions).

In the third visit, the end-of-therapy visit, the participant will be asked to complete 2 questionnaires (KSS and ESS) and the study staff will administer the CSS. A sleep medicine physician will also collect the medical history and perform a physical exam. An ECG test will be done as well. A blood sample (around 4ml) will also be collected to check the patient liver function (AST/ALT). We will also check that the logs have been completed and that the actigraphy watch has

been working. All the data collected from the actigraphy will be downloaded and the sleep log data transcribed in our encrypted database.

In the fourth visit, the post-treatment visit, the patients will be asked to complete 2 questionnaires (KSS and ESS) and the study staff will administer the CSS. We will also check that the logs have been completed and that the actigraphy watch has been working. All the data collected from the actigraphy will be downloaded and the sleep log data transcribed in our encrypted database. The participants will also return the actigraphy watch and the logs.

In total, the study will last ~2 months from first contact, involve 2-3 initial phone calls/virtual meetings for prescreening, 4 visits (2 of them with the sleep medicine physician), 3 blood draws, 3 ECGs, 2 urine collections and 1 at-home DLMO exam.

Women of Childbearing Potential

If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently breastfeeding, you may not participate in this study. You understand that if you are pregnant, if you become pregnant, or if you are breastfeeding during this study, you or your child may be exposed to an unknown risk.

To confirm to the extent medically possible that you are not pregnant, you agree to have a urine pregnancy test done before beginning this research study.

Future Use of Private Information and/or Specimens

Research using private information and/or specimens is an important way to try to understand human disease. You are being given this information because the investigators want to save private information and/or specimens for future research.

Your specimens will be stored using your unique subject code in a locked lab.

Because your specimens will not be linked to your name after they are stored, you cannot withdraw your consent to the use of the specimens after they are taken.

Identifiers might be removed from identifiable private information and/or identifiable specimens and, after such removal, the information and/or specimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you.

Genetic Testing and Future Research

As part of the analysis on your specimens, the investigators may do genetic testing. Genetic research is research that studies genes, including gene characteristics and gene versions that are transmitted by parents to children. Genetic research may include looking at information, such as personal appearance and biochemistry, gene sequences, genetic landmarks, individual and family medical histories, reactions to medications and responses to treatment. Genetic research raises certain questions about informing you of any results. Possible risks of knowing results include: anxiety; other psychological distress; and the possibility of insurance and job discrimination. A possible risk of not knowing includes being unaware of the need for treatment. These risks can change depending on the results of the research and whether there is a treatment or cure for a particular disease.

Sometimes patients have been required to furnish information from genetic testing for health insurance, life insurance, and/or a job. A Federal law, the Genetic Information Nondiscrimination Act of 2008 (GINA), generally makes it illegal for health insurance companies, group health plans, and employers with 15 or more employees to discriminate against you based on your genetic information.

This research might include whole genome sequencing.

The results of the study of your specimens from this project will be used for research purposes only, and you will not be told the results of the tests.

Regarding informing you of the test results, you should understand the following:

- The information may be too limited to give you particular details or consequences;
- You may be determined to carry a gene for a particular disease that can be treated;
- You may be determined to carry a gene for a particular disease for which there is no current treatment;
- You carry a gene for a disease and might consider informing relatives that they, too, might carry the gene.

You have the right to refuse to answer particular questions.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

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- Follow Stanford COVID 19 Police.
- Follow the instructions of the Protocol Director and study staff.
- Take the study drug as instructed.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Tell the Protocol Director or research staff if you believe you might be pregnant or gotten your partner pregnant.
- Keep the study drug in a safe place, away from children and for your use only.
- Fill out your diaries as instructed.
- Complete your questionnaires as instructed.
- Wear your actigraphy watch as instructed.
- Perform the at-home DLMO as per protocol.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify Dr. Emmanuel Mignot at 650-723-5879.

If you withdraw from the study, or the study medication is stopped for any reason, you must return all study related supplies including unused study drug.

The Protocol Director may also withdraw you from the study and the study medication may be stopped, without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.
- Pregnancy.
- You need treatment not allowed in the study.

- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

Blood draws
The most common side effects of drawing blood seen in humans or animals are pain, bruising and, rarely, infection, at the site where blood is drawn. It is also possible that patients may feel lightheaded or faint. Please tell the study doctor or study staff if you do not feel well after having your blood drawn.

Lemborexant
Some potential adverse events that have been found from the use of 5 mg Lemborexant are: headache, somnolence, upper respiratory tract infection, arthralgia, back pain, dizziness, fatigue, fall, and nausea. In the 10 mg group, the most common AEs were somnolence, influenza, urinary tract infection, fatigue and back pain.

The use of Lemborexant is also associated with the following symptoms/events:

a. CNS depressant effects and daytime impairment: Lemborexant is a central nervous system (CNS) depressant that can impair daytime wakefulness even when used as prescribed. CNS depressant effects may persist in some patients for up to several days after discontinuing the drug. Nextday somnolence can occur. Driving ability can be impaired in some subjects taking Lemborexant 10 mg. The risk of daytime impairment is increased if Lemborexant is taken with less than a full night of sleep remaining or if a higher than recommended dose is taken- in these circumstances, patients should be cautioned against driving and other activities requiring complete mental alertness. Co-administration with other CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants, alcohol) increases the risk of CNS depression, which can cause daytime impairment. The use of Lemborexant with other drugs to treat insomnia is not recommended. Do not to consume alcohol in combination with Lemborexant because of additive effects. Because Lemborexant can cause drowsiness, patients, particularly the elderly, are at a higher risk of falls.

b. Sleep Paralysis, Hypnogogic/Hypnopompic Hallucinations, and Cataplexy-like Symptoms: Sleep paralysis, an inability to move or speak for up to several minutes during sleep-wake transitions, and hypnagogic/hypnopompic hallucinations, including vivid and disturbing perceptions, can occur with the use of Lemborexant. Symptoms similar to mild cataplexy can occur with Lemborexant, like periods of leg weakness lasting from seconds to a few minutes.

c. Complex Sleep Behaviors: Complex sleep behaviors, including sleep-walking, sleep-driving, and engaging in other activities while not fully awake (e.g., preparing and eating food, making phone calls, having sex), have been reported to occur with the use of hypnotics such Lemborexant. These events can occur in hypnoticnaïve as well as in hypnotic-experienced persons. Patients usually do not remember these events. Complex sleep behaviors may occur following the first or any subsequent use of Lemborexant, with or without the concomitant use of alcohol and other CNS depressants.

d. Possible impairment of respiratory function: The effect of Lemborexant on respiratory function should be considered if prescribed to patients with compromised respiratory function, since its effect has not been studied in patients with moderate to severe obstructive sleep apnea (OSA) or in patients with chronic obstructive pulmonary disease (COPD).

e. Worsening of depression/suicidal ideation: In clinical studies of Lemborexant in patients with insomnia, the incidence of suicidal ideation or any suicidal behavior, as assessed by questionnaire, was higher in patients receiving Lemborexant than in those receiving placebo (0.3% for Lemborexant 10 mg, 0.4% for Lemborexant 5 mg, and 0.2% for placebo). In primarily depressed patients treated with hypnotics, worsening of depression and suicidal thoughts and actions (including completed suicides) have been reported. Suicidal tendencies may be present in such patients and protective measures may be required.

At-home DLMO

Some people may find it uncomfortable to collect 2 ml of saliva every 1 hour, making a total of 9 samples after 8 hours. The participant may also experience some degree of somnolence at the end of the exam, as they will have to stay awake until 1 hour after their usual bedtime.

ECG: An ECG measures how you heart is beating. The test takes a few minutes and is not painful. The study staff will put electrodes (sticky patches) on your skin

for the ECG. The patches might cause irritation, redness, and/or itchiness. To make the patches stick, you may have to have some of the hair shaved off of your skin, for example, in your chest area. Females may be required to remove their bra.

Questionnaires
The questions asked in the questionnaires may cause discomfort in some patients.

POTENTIAL BENEFITS

We cannot and do not guarantee or promise that you will receive any benefits from this study.

ALTERNATIVES

The alternative would be to not participate in the study and to resume with treatment that your physician recommends (i.e. light therapy, melatonin use).

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

ClinicalTrials.gov

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONFIDENTIALITY

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law**.** However, there is always some risk that even de-identified information might be re-identified.

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Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

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Authorization To Use Your Health Information For Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?
The purpose of this study is to examine if Lemborexant administered 5-10 mg nightly taken at desired bedtime (at least 2 hours prior to self-reported sleep onset time) can improve the symptoms of Delayed Sleep Phase Syndrome. Your personal health information will be utilized by the study team but will not be shared outside of our secured system. Any information that gets shared will be under a unique subject with all identifiers removed.

Do I have to sign this authorization form?
You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study including receiving any research-related treatment. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?
If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your

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authorization for the research use or disclosure of your health information in this study, you must write to: Dr. Emmanuel Mignot at 3165 Porter Drive Palo Alto CA 94304.

What Personal Information Will Be Obtained, Used or Disclosed?

Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to,

- Medical records (from any doctor, hospital or other healthcare provider)
- Name
- Demographics (age, sex, ethnicity, and race)
- Medical History
- Information from physical examinations
- Vital signs
- Results of 12-lead ECGs
- Information from assessments
- Information from laboratory blood and urine tests
- Information from pregnancy tests
- Information from drug and alcohol screens
- Information created or collected during the research. This could include medical history, and dates or results from any physical exams, laboratory tests, or other tests.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director, Dr. Emmanuel Mignot
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff

Who May Receive or Use the Information?

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The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S.
- FDA
- Department of Health and Human Services
- Eisai

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?
Your authorization for the use and/or disclosure of your health information will end on December 31, 2045 or when the research project ends, whichever is earlier.

Will access to my medical record be limited during the study?
To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

FINANCIAL CONSIDERATIONS

Payment/Reimbursement
In total, the study will last ~2 months from first contact, involve 2-3 initial phone calls/virtual meetings for prescreening, 4 visits (2 of them with the sleep medicine physician), 4 blood draws, 3 ECGs, 2 urine collections and 1 at-home DLMO exam.

You will be compensated up to $1280.00 for your participation if you complete the entire study. Should you elect to stop the study, your compensation will be pro-rated by the number of visits ($320 per visit). You will not receive payment until all samples are collected and the study equipment (goggles, actigraphy watch, special bulbs, and night lights) are returned.

Payments may only be made to U.S. citizens, legal resident aliens, and those who have a work eligible visa. You may need to provide your social security number to receive payment.

Sponsor
Eisai is providing financial support and/or material for this study.

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.
You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or

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alternative courses of treatment, you should ask the Protocol Director, Dr. Emmanuel Mignot. You should also contact him at any time if you feel you have been hurt by being a part of this study. You may contact him now or later at 650-723-5879.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

Alternate Contact: If you cannot reach the Protocol Director, please contact Mila Trabanino at (650) 497-8690.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

May we contact you about future studies that may be of interest to you?

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____ Yes ____ No

Signing your name means you agree to be in this study and that you will receive a copy of this signed and dated consent form.

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

_____ _____
Signature of Person Obtaining Consent Date

_____
Print Name of Person Obtaining Consent