STUDY PROTOCOL

Title: Effects of Lemborexant vs placebo on total daytime sleep in shift workers: A randomized controlled trial

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PROTOCOL SYNOPSIS

TITLE	Effects of Lemborexant vs placebo on total daytime sleep in shift workers: A randomized controlled trial
SPONSOR	Eisai Co, Ltd
FUNDING ORGANIZATION	Eisai Co, Ltd
NUMBER OF SITES	1
RATIONALE	*Insomnia and daytime sleepiness are common among shift workers, and there is a lack of available treatments. Lemborexant, which is a hypocretin/orexin antagonist, is a plausible treatment to improve sleep in shift workers*
STUDY DESIGN	*This is a randomized, double-blind, placebo-controlled phase 4 study.*
PRIMARY OBJECTIVE	Test the effect of Lemborexant on daytime total sleep time (measured via sleep diary) compared to placebo
NUMBER OF SUBJECTS	45 night shift workers enrolled; accounting for attrition, we expect 30 completers
SUBJECT SELECTION CRITERIA	Inclusion Criteria: • 20 to 60 years old; • Full-time night shift work (at least 6 hours per shift, 4 days per week or 32 hours per week); • Employed as a night shift worker for at least 3 months; • Self-reported difficulty sleeping during the daytime (Insomnia Severity Index>8). Exclusion Criteria: • Pregnancy (verified by urine pregnancy test) or plan to become pregnant in the next 3 months; • Currently breastfeeding; • Inadequate opportunity for sleep during the daytime (< 7 hours opportunity) after overnight shift. • Extreme circadian preference (based on Horne & Ostberg Morningness-Eveningness Questionnaire); • Severe depressive symptoms (>25 on CES-D); • Unwillingness to discontinue sleep aids (prescription or non-prescription) during the study period; • Presence of sleep disordered breathing (verified by Z-machine); • Self-reported diagnosis of narcolepsy, restless legs syndrome;

	• Intake of >600mg of caffeine per night shift or use of stimulants during night shift, rotational, or irregular shifts; • Unstable or untreated medical or psychiatric condition based on clinical interview. • Severe hepatic or renal impairment (based on chemistry panel); • Self-reported use of digoxin or strong or moderate cytochrome P450 3A4 isozyme inhibitors or cytochrome P450 3A4 isozyme inducers for 6 months prior to or during the study
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	*Product Lemborexant at 5mg dose (titration up to 10mg based on participants perceived benefit)* *Lemborexant will be administered immediately prior to daytime sleep attempt over the course of 3 weeks. The first week will constitute the titration week. Two-week treatment phase begins following titration week.*
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	*Placebo* *Placebo will be administered immediately prior to daytime sleep attempt over the course of 3 weeks. The first week will constitute ehte titration week. Two-week treatment phase begins following titration week.*
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	*Subjects will be on study for up to 6 weeks* ***Screening:*** *1 day* ***Medication tapering (if needed)****: up to 1 week* ***Baseline sleep assessment****: 2 weeks* ***Titration phase:*** *1 week* ***Treatment phase:*** *2 weeks* *The total duration of the study is expected to be 12-months.*
EFFICACY EVALUATIONS	
PRIMARY ENDPOINT	• Primary Outcome: Daytime total sleep time (sleep diary) averaged over 2-week treatment period. Participants will be asked to take their medication immediately prior to their daytime sleep attempt
SECONDARY ENDPOINTS	• Daytime total sleep time (actigraphy) averaged over 2-week treatment period
OTHER EVALUATIONS	
SAFETY EVALUATIONS	Adverse event assessment, by history, at post-intervention follow-up.
PLANNED INTERIM ANALYSES	None

STATISTICS **Primary Analysis Plan**	We will compare within-person changes in daytime total sleep time (primary: diary, secondary: actigraphy) averaged over a two-week baseline and treatment period between groups (Lemborexant vs. placebo) using linear mixed effects models (repeated measures of outcomes, with time, treatment group, and time by group interactions as predictors, as well as potentially random intercepts, and random slopes to accommodate between subject differences in rates of change). We will calculate 95% confidence intervals for the time by group interaction to provide a range of differences in change that are consistent with the data and test interactions using likelihood ratio tests. Linear mixed models will also be carried out to test the other proposed study outcomes. This will accommodate an intent to treat analysis.
Rationale for Number of Subjects	We will recruit 45 nightshift workers, accounting for 30% attrition, to randomize 30 participants who will first carry out 2 weeks of sleep diaries and wrist actigraphy and then be randomized to 1 week of Lemborexant (5mg) or placebo during which time they will undergo a titration period. After the week, participants will discuss with the researcher whether they would like to increase their dose to 10mg. Participants will then either take Lemborexant (5 mg-10mg) or placebo for 2 weeks within 60 minutes of attempting daytime sleep. Sample size was calculated based on previously published study demonstrating a robust improvement in diary based daytime total sleep time vs placebo (d=1.39) in response to treatment with 20 mg Suvorexant[6]. Based on these data, we would require 12 participants in each condition to detect a large effect size with 90% power. However, to be conservative and ensure that we are adequately powered, we will randomize 15 participants per condition.

BACKGROUND

Lemborexant is a hypocretin/orexin antagonist FDA approved to treat Insomnia Disorder. Prior studies support its efficacy in improve an individual's ability to fall and stay asleep; however, its efficacy has not been tested in shiftworkers.

STUDY RATIONALE

Insomnia and daytime sleepiness are common complaints among night shift workers[1,2]. A meta-analysis on sleep in shift workers indicates that fixed night shift workers sleep, on average, 0.4 hours less than fixed day shift workers, while rotating shift workers sleep on average 1 hour less than fixed day shift workers[3]. While there may be several reasons for sleep difficulties and sleep loss among shift workers, the misalignment of one's sleep preference (i.e., goal of sleeping during the day) and one's circadian rhythm (i.e., endogenous rhythm that signals the body to be awake during the day) is thought to be a primary cause. Insufficient sleep among night shift and rotating shift workers is linked with significant health consequences, including elevated risk for cardiovascular disease and cancer[4,5]. Effective sleep treatments in shift workers are lacking. However, a recent randomized study of Suvorexant (20mg), a hypocretin/orexin receptor antagonist, produced a significant improvement in daytime total sleep time compared to placebo[6]. Available evidence suggests that the reason suvorexant is effective is because it blocks the hypocretin/orexin receptors that mediate signaling from the biological clock (suprachiasmatic nucleus of the hypothalamus) attempting to maintain sustained wakefulness during the biological day[7]. As Lemborexant is also a hypocretin/orexin antagonist, it would also be expected to improve daytime sleep in shift workers but would have the advantage over suvorexant of being highly effective in the dosages available for clinical use. As such, Lemborexant may be effective and important treatment of sleep problems in shift workers.

The aim of this Phase IV double-blind, placebo-controlled, randomized study is to test whether a dual orexin antagonist, Lemborexant (5mg or 10mg), which would be expected to block the clock-driven orexin-mediated wakefulness during the day, will increase daytime sleep time in shift workers who complain of difficulty sleeping during the daytime compared to placebo.

STUDY OBJECTIVES

Primary Objective

The primary objective is to assess the clinical efficacy, as measured by sleep diary total sleep time during daytime sleep attempts over a 2-week period.

STUDY DESIGN

Study Overview

This will be a 5-week double blinded placebo controlled trial (2 weeks of baseline assessment followed a 1 week titration of 5mg Lemborexant/placebo, followed by agreed upon dose (5mg or 10 mg) or placebo for 2-weeks). The trial design is based on a recent successful study of the treatment of sleep problems in shift workers with a hypocretin/orexin receptor antagonist. Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study.

The following treatment regimens will be used:

Experimental treatment Lemborexant at either 5mg or 10mg

Placebo control

Total duration of subject participation will be 5 weeks.

Criteria for evaluation

Primary Efficacy Endpoint

- Daytime total sleep time (sleep diary) averaged over 2-week treatment period. Participants will be asked to take their medication immediately prior to their daytime sleep attempt

Secondary Efficacy Endpoints

- Daytime total sleep time (actigraphy) averaged over 2-week treatment period

SUBJECT SELECTION

Study Population

Subjects who are shift workers and report difficulty sleeping during the daytime and who meet the inclusion and exclusion criteria will be eligible for participation in this study.

Inclusion Criteria

1. 20 to 60 years old;
2. Full-time night shift work (at least 6 hours per shift, 4 days per week or 32 hours per week);
3. Employed as a night shift worker for at least 3 months;
4. Self-reported difficulty sleeping during the daytime (Insomnia Severity Index>8).
5. Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.

Exclusion Criteria

1. Pregnancy (verified by urine pregnancy test) or plan to become pregnant in the next 3 months;
2. Currently breastfeeding;
3. Inadequate opportunity for sleep during the daytime (< 7 hours opportunity) after overnight shift.
4. Extreme circadian preference (based on Horne & Ostberg Morningness-Eveningness Questionnaire);
5. Severe depressive symptoms (>25 on CES-D);

6. Unwillingness to discontinue sleep aids (prescription or non-prescription) during the study period;
7. Presence of sleep disordered breathing (verified by Apnea link);
8. Self-reported diagnosis of narcolepsy, restless legs syndrome;
9. Intake of >600mg of caffeine per night shift or use of stimulants during night shift, rotational, or irregular shifts;
10. Unstable or untreated medical or psychiatric condition based on clinical interview.
11. Severe hepatic or renal impairment (based on chemistry panel);
12. Self-reported use of digoxin or strong or moderate cytochrome P450 3A4 isozyme inhibitors or cytochrome P450 3A4 isozyme inducers for 6 months prior to or during the study
13. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.

Concurrent Medications

Study participants will be required to be free from prescription and non-prescription sleep aids and stimulants during the study. To be eligible, participants will need to undergo a washout period prior to baseline assessment of at least 5 half-lives of any drug with a significant effect on sleep/wake function.

STUDY TREATMENTS

Method of Assigning Subjects to Treatment Groups

Up to 45 eligible patients will be randomly assigned to Lemborexant (5mg) or placebo treatment groups in a 1:1 ratio using a pre-generated randomization scheme developed by the study data management provider.

Blinding

Due to the objectives of the study, the identity of test and control treatments will not be known to investigators, research staff, or patients. The following study procedures will be in place to ensure double-blind administration of study treatments.

Access to the randomization code will be strictly controlled.

Packaging and labeling of test and control treatments will be identical to maintain the blind.

The study blind will be broken on completion of the clinical study and after the study database has been locked.

During the study, the blind may be broken **only** in emergencies when knowledge of the patient's treatment group is necessary for further patient management. When possible, the Investigator should discuss the emergency with the Medical Monitor prior to unblinding.

Formulation of Test and Control Products

The study drug, Lemborexant (5mg) and placebo will be provided by the sponsor, Eisai Co, Ltd.

Supply of Study Drug at the Site

The Sponsor will ship Study Drug to the investigational site. The initial study drug shipment will be shipped after site activation (i.e., all required regulatory documentation has been received by the Sponsor and a contract has been executed). Subsequent study drug shipments will be made after site request for resupply.

Dosage/Dosage Regimen

Following the baseline assessment, participants will be randomized to either drug or placebo. Those in the drug condition will be provided 5mg Lemborexant and re-evaluated one week later as part of the titration period. Those who wish to increase their dose to 10mg may do so for the 2-week drug period. The same option will be provided to the placebo condition.

Dispensing

The drug will be dispensed by the study physician, Dr Andrew Krystal, MD, who is Co-PI on this study.

Storage of drug

Study drug should be stored by the study site at controlled room temperature, 15 to 30ºC (59 to 86ºF). If the temperature of study drug storage in the clinic/pharmacy exceeds or falls below this range, this should be reported to the Sponsor or designee and captured as a deviation. Subjects will be instructed to store the medication in original packaging (foil pouch and protected from light) at room temperature according to the instructions outlined on the Drug Administration Instructions.

Measures of Treatment Compliance

Medication adherence will be monitored using electronic pill caps (Mems caps) which monitor each time the pill bottle is opened.

STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject or subject's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

Clinical Assessments

Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Baseline/Screening, and at early termination when applicable. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

Demographics

Demographic information (date of birth, gender, race) will be recorded at Screening.

Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at Screening.

Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded.

Clinical Laboratory Measurements

Blood Chemistry Profile

Blood will be obtained and clinical chemistry lab for determination of serum sodium, potassium, chloride, bicarbonate, random glucose, BUN, creatinine, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), albumin and LDH.

Pregnancy Test

A urine pregnancy test will be obtained from female subjects who are of childbearing age prior to their participation in the study.

EVALUATIONS BY VISIT

Visit 1

1. Confirm eligibility (self-report)
2. Medical history interview
3. Medication assessment
4. Psychiatric clinical interview
5. Sleep disorder clinical interview
6. Review the study with the subject (subject's legal representative) and obtain written informed consent and HIPAA authorization and assent, if appropriate.
7. Questionnaires.
8. Blood draw for blood chemistry

Baseline sleep assessment (2-weeks in duration)

1. Wrist actigraphy
2. Sleep diary
3. Obstructive sleep apnea evaluation (Z-machine, 1night)

Visit 2

1. Medication assessment

2. Pregnancy test (if applicable)
3. Record any Adverse Experiences and/or Review subject diary for adverse experiences and dosing compliance.
4. Randomization
5. Patient global impression/clinician global impression completed.

Visit 3

1. Record any Adverse Experiences and/or Review subject diary for adverse experiences and dosing compliance.
2. Medication assessment
3. Patient global impression/clinician global impression completed.
4. Decision made on medication dose based on PGI.

Treatment sleep assessment (2-weeks)

1. Wrist actigraphy
2. Sleep diary

Visit 4

1. Record any Adverse Experiences and/or Review subject diary for adverse experiences and exclusionary medication use.
2. Medication assessment
3. Patient global impression/clinician global impression completed.
4. Questionnaires
5. Collect unused medication.

Open-label (if opt in; 2-weeks).

1. Record any Adverse Experiences.

ADVERSE Experience REPORTING AND DOCUMENTATION

Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents.

Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.

Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

Include appropriate wording here

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

DISCONTINUATION And Replacement of subjects

Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

Subject withdrawal of consent (or assent)

Subject is not compliant with study procedures

Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment

Protocol violation requiring discontinuation of study treatment

Lost to follow-up

Sponsor request for early termination of study

Positive pregnancy test (females)

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents Refer to Section 10 for early termination procedures.

Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to Visit 2) should have an early discontinuation visit.

STATISTICAL METHODS AND CONSIDERATIONS

We will analyze data from all participants who undergo randomization.

Analysis of Primary Endpoint

We will compare within-person changes in daytime total sleep time (primary: diary, secondary: actigraphy) averaged over a two-week baseline and treatment period between groups (Lemborexant vs. placebo) using linear mixed effects models (repeated measures of outcomes, with time, treatment group, and time by group interactions as predictors, as well as potentially random intercepts, and random slopes to accommodate between subject differences in rates of change). We will calculate 95% confidence intervals for the time by group interaction to provide a range of differences in change that are consistent with the data and test interactions using likelihood ratio tests. Linear mixed models will also be carried out to test the other proposed study outcomes. This will accommodate an intent to treat analysis. Covariates, such as number of sleep entries (i.e., number of available diary/actigraphy daytime sleep attempts), will be included is analyses if needed.

Sample Size and Randomization

We will recruit 45 nightshift workers, accounting for 30% attrition, to randomize 30 participants who will first carry out 2 weeks of sleep diaries and wrist actigraphy and then be randomized to 1 week of Lemborexant (5mg) or placebo during which time they will undergo a titration period. After the week, participants will discuss with the researcher whether they would like to increase their dose to 10mg. Participants will then either take Lemborexant (5 mg-10mg) or placebo for 2 weeks within 60 minutes of attempting daytime sleep. Sample size was calculated based on previously published study demonstrating a robust improvement in diary based daytime total sleep time vs placebo (d=1.39) in response to treatment with 20 mg Suvorexant[6]. Based on these data, we would require 12 participants in each condition to detect a large effect size with 90% power. However, to be conservative and ensure that we are adequately powered, we will randomize 15 participants per condition.

APPENDIX 1.

Screening	• Computer assessed eligibility
Visit #1	• Eligibility confirmed • Medical history interview • Medication assessment • Psychiatric clinical interview • Sleep disorder clinical interview (SCISD) • Informed consent • Blood chemistry • Questionnaires
Medication tapering (if needed)	• Tapering protocol (supervised by Dr. Krystal; washout period prior of at least 5 half-lives of any drug with a significant effect on sleep/wake function)
Baseline Sleep Assessment (2-weeks)	• Wrist actigraphy • Sleep diary • OSA evaluation (Z-machine, 1-night)
Visit #2	• Eligibility confirmed • Medication assessment • Adverse Event form • Pregnancy test • Randomization (5mg Lemborexant/placebo) - 15 participants (Lemborexant, 5mg) - 15 participants (placebo) • Drug/Placebo distribution (MemsCaps) • Patient global impression • Clinician global impression
Titration (1-week)	• Wrist actigraphy • Sleep diary

Visit #3	• Adverse event form • Medication assessment • Patient global impression • Clinician global impression • Drug/Placebo distribution (MemsCaps)
Treatment (2-weeks)	• Wrist actigraphy • Sleep diary
Visit #4	• Adverse event assessment • Medication assessment • Patient global impression • Clinician global impression • Questionnaires