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Efficacy and safety of Lemborexant in combination with Escitalopram in treating major depressive disorder with comorbid insomnia: study protocol for a multicenter, randomized, double-blind, placebo-controlled trial

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Efficacy and safety of Lemborexant in combination with Escitalopram in treating major depressive disorder with comorbid insomnia: study protocol for a multicenter, randomized, double-blind, placebo-controlled trial

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Abstract

Background Insomnia is a common clinical symptom of major depressive disorder (MDD) and an independent risk factor for the subsequent onset and recurrence of MDD. The short- and long-term efficacy and safety of Lemborexant (LEM), a dual orexin receptor antagonist (DORA), for the treatment of primary insomnia have been well established. However, no randomized controlled trial (RCT) has evaluated its efficacy and safety in patients with MDD and comorbid insomnia. This RCT aims to assess the efficacy and safety of LEM combined with Escitalopram (ESC) for patients with MDD and comorbid insomnia.

Methods In this multicenter, double-blind RCT, 286 adult patients with newly diagnosed or recurrent MDD and comorbid insomnia who have not received standard antidepressant therapy during the current depressive episode will be enrolled and randomized in a 1:1 ratio to receive ESC plus LEM or ESC plus placebo (PBO) for 6 weeks. The primary endpoint is the between-group difference in the change from baseline in subjective total sleep time, as measured using a sleep diary, at the end of 6 weeks of treatment. The secondary endpoints include between-group comparisons of changes from baseline in other subjective sleep parameters, objective sleep parameters assessed by polysomnography, the Insomnia Severity Index, and the 17-item Hamilton Depression Rating Scale score, excluding sleep-related items. Adverse events (AEs), treatment-emergent AEs, and serious AEs will be recorded.

Discussion This study aims to explore a potentially safer and more effective treatment option than conventional benzodiazepine receptor agonists for patients with MDD and comorbid insomnia. Furthermore, it aims to investigate the potential role of LEM as an adjunctive treatment for MDD, and to provide preliminary evidence as to whether DORAs may confer benefits beyond sleep improvement in this population.

Chinese Clinical Trial registry (ChiCTR) registration: ChiCTR2600119476 (Date of registration: February 27, 2026)

Keywords: Major depressive disorder, insomnia, Lemborexant, Escitalopram, dual orexin receptor antagonist, randomized controlled trial

Introduction

Sleep disturbance is a prevalent symptom of major depressive disorder (MDD), affecting approximately 90% of patients[1-4]. Insomnia, a common form of sleep disturbance, is characterized by difficulty initiating or maintaining sleep, as well as early-morning awakening[2]. In addition to being a common comorbidity of MDD, insomnia is an independent risk factor for the future onset and recurrence of MDD[1]. Residual sleep disturbance in patients with MDD is associated with a 4.8-fold higher risk of recurrence than in those without sleep disturbance[3]. Improving sleep may alleviate depressive symptoms and contribute to a better prognosis. Therefore, in patients with MDD and comorbid insomnia, addressing insomnia is as important as treating depressive symptoms to achieve favorable outcomes[1].

Benzodiazepine receptor agonists (BZRAs), including benzodiazepines (BZDs) and non-BZDs (Z-drugs), are the most commonly prescribed hypnotic medications and are often used in combination with antidepressants to treat patients with MDD and comorbid insomnia[5, 6]. Maruki et al.'s meta-analysis found that, compared with antidepressant monotherapy, adjunctive treatment with one or more Z-drugs was associated with a higher rate of depression remission and greater short-term improvements in insomnia and depressive symptoms, with benefits observed for up to 12 weeks.[6]. However, as agonists at the gamma-aminobutyric acid type A receptor, BZRAs induce sleep through widespread inhibition of central nervous system (CNS) activity [5]. Consequently, BZRAs are associated with a wide range of adverse events (AEs), including next-morning residual effects, cognitive impairment, and an increased risk of falls and motor vehicle accidents[5-8]. Furthermore, long-term BZRA use is associated with diminished efficacy, dependence and abuse, and withdrawal effects upon discontinuation[5]. Moreover, BZRA use has been linked to an increased risk of suicide among psychiatric patients and an increased risk of

depressive symptoms among older adults[7, 8]. Accordingly, BZRAs should be used only for the short-term treatment of insomnia (≤4 weeks)[5]. Therefore, there is an urgent need to explore effective and safe alternatives to BZRAs for patients with MDD and comorbid insomnia.

Lemborexant (LEM) is a dual orexin receptor antagonist (DORA) approved for the treatment of insomnia and recommended as a first-line treatment option for insomnia in countries including China and Japan[9, 10]. By competitively and reversibly binding to both orexin receptor types 1 and 2 (OX1R and OX2R) and exhibiting rapid dissociation kinetics, LEM induces sleep by inhibiting the wake-promoting activity of orexin neuropeptides[5]. Two pivotal phase 3 randomized controlled trials (RCTs), SUNRISE 1 and SUNRISE 2, demonstrated the short- and long-term efficacy and safety of once-nightly LEM at doses of 5 mg and 10 mg in adults with insomnia[11-13]. In the 1-month SUNRISE 1 study, compared with both placebo and zolpidem tartrate extended-release (ZOL-ER), LEM produced significantly greater improvements in sleep onset and sleep maintenance on nights 1, 2, 29, and 30, as assessed by objective polysomnography (PSG) and subjective sleep diary[11]. The SUNRISE 2 study evaluated changes in subjective sleep parameters using sleep diaries in adults treated with LEM. At 6 months, LEM was associated with an approximately 70-minute increase in subjective total sleep time (sTST) and significant improvements in other subjective sleep parameters; these benefits were maintained through 12 months of treatment[12, 13].

Unlike BZRAs, LEM induces sleep in a manner consistent with normal sleep and without disrupting normal sleep architecture, and may ameliorate age-related alterations in sleep architecture among older adults with insomnia[5][14]. Notably, in the SUNRISE 1 study, LEM improved rapid eye movement (REM) sleep and REM sleep latency while maintaining both measures within the normal range for adults aged ≥55 years[14]. This feature may be particularly

relevant for patients with MDD, who commonly exhibit sleep abnormalities such as increased REM sleep during the first REM period and shortened REM latency. These findings suggest that LEM is unlikely to exacerbate these sleep abnormalities in patients with MDD [15].

Beyond its efficacy in treating insomnia, LEM has demonstrated a favorable safety profile, with minimal next-day residual effects and limited impairment of daytime functioning, including cognition and driving performance. LEM is also associated with a significantly lower risk of dizziness than BZRAs and has not been associated with rebound insomnia or withdrawal symptoms after discontinuation[5]. Furthermore, in the 12-month SUNRISE 2 study, long-term LEM treatment was not associated with an increased risk of suicide[13].

Although the short- and long-term efficacy and safety of LEM for primary insomnia have been established[11-13], evidence regarding its efficacy and safety in patients with MDD and comorbid insomnia remains limited. Most available data are derived from small prospective or retrospective observational studies with potential confounding factors[12, 16-18]. A post hoc analysis of the SUNRISE 2 study found that, after 6 months of treatment, LEM improved subjective sleep parameters, including sTST and subjective wake after sleep onset (sWASO), in participants with and without a history of depression[12]. However, this analysis did not establish the efficacy of LEM in patients with active MDD and comorbid insomnia. In addition, a 12-week, open-label pilot intervention study included 83 patients with insomnia comorbid with MDD or bipolar disorder (BD) whose depressive symptoms had not remitted despite stable treatment for depression. LEM significantly improved Insomnia Severity Index (ISI) scores in both diagnostic groups[18]. The study also reported significant improvements in 17-item Hamilton Depression Rating Scale (HAMD-17) scores after 12 weeks; mean HAMD-17 scores in the three cohorts (MDD monotherapy, MDD add-on therapy, and BD monotherapy) decreased to below 7[18]. Importantly,

improvement in total HAMD-17 scores was maintained after the exclusion of sleep-related items, suggesting that LEM may exert antidepressant effects[18]. However, this study did not evaluate LEM in patients with MDD and comorbid insomnia who had not received standard antidepressant treatment during the current depressive episode[18].

To date, no RCT has evaluated the efficacy and safety of LEM for MDD with comorbid insomnia. This multicenter, double-blind RCT aims to compare LEM plus escitalopram (ESC) with ESC plus placebo (PBO) as initial treatment for improving insomnia and depressive symptoms in patients with first-episode or recurrent MDD and comorbid insomnia who have not received standard antidepressant treatment during the current depressive episode. The primary objective is to compare the effects of LEM and PBO on sleep diary-derived sTST after 6 weeks of treatment. Secondary objectives include comparisons of LEM and PBO with respect to additional subjective and objective sleep parameters; ISI; the Epworth Sleepiness Scale (ESS); the Fatigue Severity Scale (FSS); the Patient Global Impression of Improvement (PGI-I); HAMD-17 and Hamilton Anxiety Scale (HAMA) scores, excluding sleep-related items; and the Clinical Global Impression-Improvement scale (CGI-I). Safety objectives are to evaluate the safety and tolerability of LEM in this population.

We hypothesize that LEM combined with ESC will improve insomnia symptoms in patients with MDD and comorbid insomnia, while also improving mood and daytime functioning, with favorable safety and tolerability and without increasing suicide risk. Accordingly, this study seeks to evaluate LEM as a potentially safer and more effective alternative to conventional hypnotics, such as BZRAs, for patients with MDD and comorbid insomnia.

Methods

Study design

This is a multicenter, prospective, double-blind RCT in which 286 eligible patients with MDD and comorbid insomnia will be randomized in a 1:1 ratio to receive either LEM plus ESC (the LEM group) (n=143) or ESC plus placebo (the PBO group) (n=143). Assuming a 50% screening failure rate, approximately 572 patients will need to be screened. The patient screening and recruitment start date is May 1, 2026, and its expected completion date is June 30, 2027. This protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT 2025) guidelines[19].

Study setting

The trial is conducted at 12 hospitals in China, and eligible patients will be recruited through the following channels: 1) recruitment information published by the research center's official WeChat account; 2) recruitment advertisements posted on the research center's patient recruitment platform; 3) retractable banner posters placed in the outpatient clinics of the department responsible for the research in the participating hospitals; and 4) patient enrollment by psychiatrists during their routine clinical practice.

Patients

Eligible patients who meet the following inclusion criteria and do not meeting the following exclusion criteria will be enrolled in the study prior to randomization. Inclusion criteria: 1) are male or female adult patients aged ≥18 years and <65 years at the time of signing the informed consent form; 2) diagnosed with first-episode or recurrent MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); 3) have a HAMD-17 total score >17, with a subscore of ≥3 on the sleep-related items; 4) have chronic insomnia according to

the DSM-5, with symptoms of insomnia occurring on ≥3 nights per week over the past three months, defined as sTST<6 hours, sWASO ≥60 minutes, with or without subjective sleep onset latency (sSOL) ≥30 minutes; 5) an ISI total score ≥15, with a subscore of ≥2 on item 2 (daytime functioning); and 6) are able to maintain a bedtime duration of ≥7 hours per night.

Exclusion criteria: 1) have other mental disorders according to the DSM-5 as judged by the investigators, including schizophrenia spectrum and other psychotic disorders, bipolar and related disorders, obsessive-compulsive and related disorders, and somatic symptom disorders; 2) have MDD with psychotic symptoms according to the DSM-5; 3) risk of suicide, or had a score of ≥3 on Item 3 (Suicide) of the HAMD-17, or a "Yes" response to Items 3, 4, or 5 (suicidal ideation) of the Columbia-Suicide Severity Rating Scale (C-SSRS) within 6 months prior to enrollment, or have a history of suicidal behavior within one year prior to enrollment; 4) have treatment-resistant depression (previously or currently no or minimal response to adequate treatment with two or more antidepressants of different chemical classes at the maximum label-recommended dose for ≥4 weeks); 5) contraindications to LEM, such as narcolepsy; 6) have other comorbid sleep disorders such as sleep apnea, periodic limb movement disorder, and restless legs syndrome; 7) have severe or unstable cardiovascular, hepatic, renal, hematological, endocrine, neurological, or other systemic or organic diseases as judged by the investigators, such as asthma/chronic obstructive pulmonary disease (COPD), chronic pain, thyroid disease, diabetes, and hypertension; 8) have received ESC treatment for ≥2 weeks or other antidepressant treatment during the current depressive episode; 9) Inability to discontinue the use of sedative-hypnotic medications (Appendix 1) and medications known to significantly affect sleep during the treatment period, or unable to complete a washout period of ≥5 half-lives before initiating the study drug; 10) Inability to discontinue psychotherapy such as cognitive behavioral therapy (CBT), during the treatment

period; 11) habitual bedtime earlier than 21:00 or later than 01:00, or habitual wake time later than 09:00 more than twice per week; 12) history of alcohol abuse within 6 months before enrollment (daily alcohol consumption >2 standard units or weekly consumption >14 standard units [1 standard unit is equivalent to 360ml of beer, 45ml of 40% alcohol spirit, or 150ml of wine]); 13) Current or planned use of moderate or strong inducers or inhibitors of CYP3A4 during the study (Appendix 1); 14) pregnant or breastfeeding; 15) severe hypersensitivity, or allergy to ≥2 classes of drugs, or known allergy to the ingredients or excipients of the study drug; 16) any conditions that make the subject unsuitable for the trial, or may increase the risk to the subject or interfere with the clinical trial, as judged by the investigator.

Withdrawal criteria: All subjects have the right to withdraw from the trial at any time: 1) Withdrawal of consent by the subject for any reason; 2) subject-initiated request to withdraw from the study due to an adverse event (AE); 3) subject-initiated request to withdraw from the trial due to lack of efficacy; 4) loss to follow-up; 5) subject-initiated request to withdraw from the study due to other reasons. Furthermore, subjects may be withdrawn from the study at the discretion of the investigator under the following circumstances: 1) Increased suicidal ideation due to their deteriorated condition (a score ≥3 on item 3 [Suicide] of the HAMD-17), or a "Yes" response to Items 3, 4, or 5 of the C-SSRS since initiation of the study medication, or a history of suicidal behavior within one year prior to enrollment, or the need for hospitalization; 2) pregnancy or suspected pregnancy; 3) any AEs, allergic reactions, abnormal laboratory findings, illnesses or other abnormal conditions discovered during the trial, which make the subject unsuitable to continue in this trial as judged by the investigator; 4) occurrence a major protocol violation or other reasons that make it difficult to assess efficacy and safety; 5) use of prohibited medications or treatments during the trial, which may significantly affect the safety and efficacy of the trial,

making the subject unsuitable for continued participation as judged by the investigator; 6) unblinding; 7) upon post-randomization discovery that the subjects seriously violates the inclusion/exclusion criteria; the investigator may determine whether to withdraw the subject based on the specific circumstances; 8) withdrawal from the trial is in the best interest of the subject or is necessary out of ethical considerations as judged by the investigator; 9) other reasons that make it necessary for the subject to withdraw from the study as judged by the investigator.

The investigators will advise patients who withdraw from the study to choose alternative treatment options based on their condition and treatments, including other pharmacological and non-pharmacological treatments.

Study procedure

The study flowchart is presented in Figure 1. This multicenter, double-blind RCT consists of an eligibility screening period (Week [W]-4 to -2), a run-in period (W-2 to 0), a baseline assessment (W0), a 6-week double-blind treatment period (W0-6), and a 1-week observation period after drug discontinuation (W7).

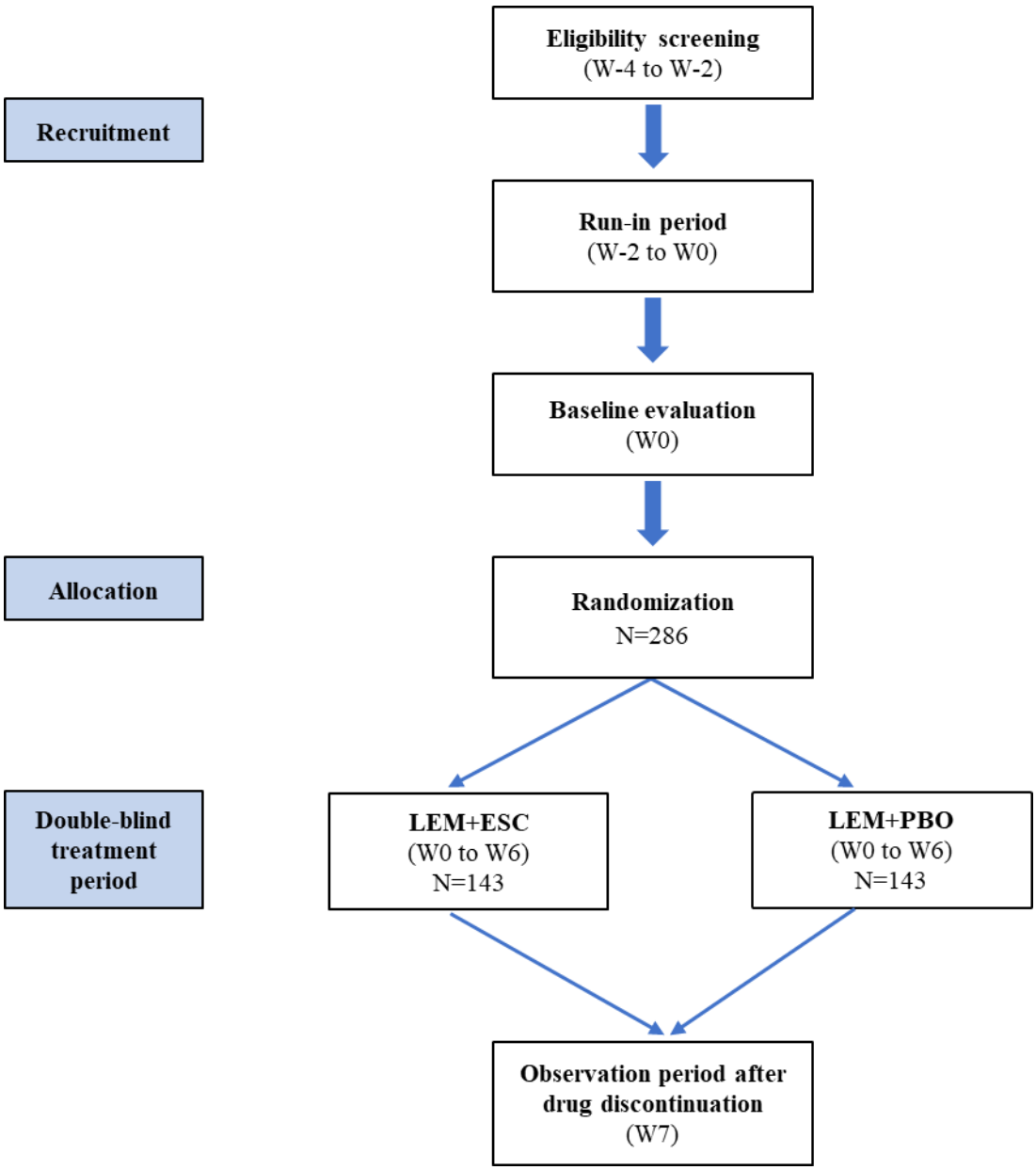


Figure 1 Study flowchart

The screening period

During the ≤2-week screening period, patients will sign the informed consent form, and their demographic and clinical information will be collected and recorded. At this visit (Visit 1), they will be assessed for the inclusion/exclusion criteria. Their sTST, sWASO, and sSOL will be obtained based on their chief complaint and medical history. They will be asked to complete the ISI, ESS, and FSS, and the study investigator will administer HAMD-17, HAMA, CGI-S, and C-

SSRS. Patients who are taking or have recently taken any medications prohibited by the study protocol will enter a washout period to guarantee a ≥5-half-life interval between the last dose of the prohibited medication and the start of the run-in period (Table 1).

Table 1 Schedule of enrollment, intervention and assessment

	Screening	Lead-in period	Baseline	Double-blind treatment period			Observation period after drug discontinuation	Early discontinuation of study drug	Unscheduled visits
Visit	**V1**	**-**	**V2**	**V3**	**V4**	**V5**	**V6**		
Week	**W-4~W-2**	**W-2~W0**	**W0**	**W2**	**W4**	**W6**	**W7**		
Day	**-28~-14**	**-14~0 ±2**	**0**	**14 ±2**	**28 ±2**	**42 ±2**	**49±2**		
General information									
Informed consent[1]	×								
Demographics[2]	×								
Inclusion/exclusion criteria	×		×						
Vital signs[3]			×			×			×
Diagnosis and assessment of scales									
DSM-5 diagnostic criteria	×								
Sleep diary (sTST, sSOL, sWASO and sSE)		×	×	×	×	×	×	×	×
PSG (taken by 50% of the enrolled patients)			×			×			
ISI	×		×	×	×	×	×	×	×

ESS	×		×	×	×	×		×	×
FSS	×		×	×	×	×		×	×
PGI-I				×	×	×		×	×
HAMD-17	×		×	×	×	×	×	×	×
HAMA	×		×	×	×	×	×	×	×
CGI-S	×		×	×	×	×	×	×	×
CGI-I				×	×	×		×	×
C-SSRS	×		×	×	×	×		×	×
BWSQ							×		
Laboratory testings and ECG									
CBC[4]			×			×			×
Blood biochemistry tests[5]			×			×			×
Urinalysis[6]			×			×			×
Urine pregnancy test[7]			×			×			×
Thyroid function tests[8]			×						×
ECG[9]			×			×			×
Other assessments and intervention									
Randomization			×						
Dispensing of LEM or PBO[10]	×		×	×	×				
Return of LEM or PBO packaging			×	×	×	×		×	
Dispensing of ESC[11]	×		×	×	×	×			
Return of ESC and its packaging			×	×	×	×	×	×	
AEs[12]			×	×	×	×	×	×	×

Concomitant medications[1] [3]	×		×	×	×	×	×	×	×

[1] Informed Consent: The subject or their legally acceptable representative must sign the written informed consent form before the initiation of any trial-related activities;
[2] Information collected during screening: Demographics (age, sex, ethnicity, height, and weight); medical history (MDD: diagnosis date, prior/current treatments; other history: prior illnesses/medications, surgery/transfusion, allergies, substance-induced mental disorders, smoking, and alcohol use);
[2] Vital signs include body temperature, pulse, systolic/diastolic blood pressure, and respiratory rate;
[4] CBC include red blood cell count, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count, and hemoglobin;
[5] Blood biochemistry tests include total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), creatine kinase (CK), creatine kinase-MB (CK-MB), total protein, albumin, blood urea nitrogen (BUN)/urea, creatinine, calcium, phosphorus, iron, magnesium, blood glucose, total cholesterol, high-density lipoprotein (HDL), triglycerides, and low-density lipoprotein (LDL);
[6] Urinalysis includes urine protein, urine glucose, microscopic examination of red blood cells and white blood cells, and urine ketones;
[7] A urine pregnancy test will be performed at baseline to obtain the results prior to the first dose of study drug;
[8] Thyroid function tests include thyroid-stimulating hormone (TSH), free thyroxine (free T4), thyroxine (T4), triiodothyronine (T3), and free triiodothyronine (free T3);
[9] ECG parameters include heart rate, PR interval, QRS duration, QT interval, and QTcF;
[10] Dispensing of LEM or PBO: During screening, PBO will be dispensed to all subjects who meet the inclusion criteria and do not meet any exclusion criteria. At all other visits, subjects will be dispensed with LEM or PBO will be dispensed to the subjects according to the randomization schedule;
[11] At Visit 5, ESC will be dispensed only to those subjects who have voluntarily discontinued LEM or PBO after the double-blind treatment period and have entered the observation period after drug discontinuation;
[12] AEs must be monitored and recorded from the start of the study treatment until the subject discontinues the study treatment or completes the termination visit. All AEs should be followed until they resolve, return to levels meeting the inclusion/exclusion criteria, or are clinically stable as judged by the investigator at two consecutive visits, or until the subject is lost to follow-up. All observed AEs must be recorded at each visit.
[13] Except for the management of AEs or treatment of sudden illnesses, no medications or treatments that may affect the efficacy or safety of the study drug are allowed during the trial. If a subject needs non-study medications/treatments during the trial, the investigator will decide whether the subject may continue to remain in the study. If concomitant medication/treatment is used, detailed information must be recorded, including start and end dates, dosage, route of administration, frequency, and reason for use. All concomitant medications/treatments used during the study must be recorded from the signing of the informed consent until the subject completes the study or withdraws from the study.

Abbreviations: C-SSRS, the Columbia-Suicide Severity Rating Scale; ISI, Insomnia Severity Index; sTST, subjective total sleep time; sSOL, subjective sleep onset latency; sWASO, subjective wake after sleep onset; sSE, subjective sleep efficiency; PSG, polysomnography; ESS, Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; PGI-I, Patient Global Impression of Improvement; HAMD-17, Hamilton Depression Rating Scale-17; HAMA, Hamilton Anxiety Rating Scale; CGI-S, Clinical Global Impression of Severity; CGI-I, Clinical Global Impression of Severity; BWSQ, Benzodiazepine Withdrawal Symptom Questionnaire; ECG, electrocardiogram; CBC, complete blood count; LEM, lemborexant; PBO, placebo; ESC, AEs, adverse events; ESC, escitalopram.

The run-in period

Patients who meet the inclusion criteria and do not meet the exclusion criteria will enter the 1- to 2-week run-in period. The run-in period for patients who have not taken any antidepressants during the current episode will be 2 weeks. These patients will start taking ESC 10mg/day at the beginning of Week 1 and continue for 2 weeks, and they will also start taking LEM-matching PBO 5mg/day at the beginning of Week 2 and continue for 1 week. For patients who are taking ESC before entering the run-in period, the run-in period will be 1 week, during which they will take ESC 10mg/day combined with LEM-matching PBO 5mg/day.

Each morning during the run-in period, patients are instructed to complete the sleep diary about the previous night using an electronic Patient-Reported Outcome (ePRO) system. They will be trained on how to complete it before the formal recording begins and will be repeatedly reminded about the importance of maintaining it. At the end of the run-in period, the sleep diaries will be reviewed to assess eligibility. In addition, AEs, serious AEs (SAEs), concomitant medications, and treatment compliance will be documented.

Patients who meet any of the following criteria during the run-in period will be withdrawn from the study: 1) Intolerance to ESC 10mg/day; 2) a sleep diary completion rate of <80%; 3) worsened depressive symptoms at the end of the run-in period, defined as a ≥25% increase in the HAMD-17 score compared with that at the screening visit (Visit 1); 4) significant insomnia remission at the end of the run-in period, defined not meeting the following criterion: sTST <6 hours and sWASO ⩾60 minutes *with or without sSOL ⩾30 minutes) on at least 3 of the most recent 7 nights; 5) an ISI score of <15; 6) failure to guarantee adequate time in bed, i.e. >2 nights with <7 or >10 hours in bed.

Baseline assessments

At the baseline visit (Visit 2), eligible patients will be reconfirmed for the inclusion/exclusion criteria. The sleep diaries from the run-in period will be reviewed, and the average values of sTST, sSOL, sWASO, and sSE over the past week will be calculated. In addition, study investigators will administer the ISI, ESS, FSS, HAMD-17, HAMA, CGI-S, and C-SSRS. Vital signs, laboratory tests (complete blood count [CBC], blood biochemistry, urinalysis, urine pregnancy test, and thyroid function), and an electrocardiogram (ECG) (heart rate, PR interval, QRS duration, QT, and QTcF) will be performed. Finally, to aid in differential diagnosis of other sleep disorders and to assess the quality of the subjective sleep diary recordings, PSG monitoring will be performed in 50% of the patients at qualified centers to measure TST, LPS, WASO, and SE (Table 1).

Double-blind treatment period

During the 6-week double-blind treatment period, enrolled patients will be randomized 1:1 in a double-blind manner to receive ESC combined with LEM (the LEM group) or ESC combined with PBO (the PBO group). During the first 2 weeks, patients will receive LEM or PBO 5mg qn in combination with ESC 10mg/day. At the beginning of the third week, the doses of LEM and PBO will be increased to 10mg qn for all patients, combined with ESC 10mg/day, and this regimen is maintained for the remaining 4 weeks.

The 10mg/day dose of LEM may be reduced to 5mg/day if the investigator judges that an intolerable study drug-related AE occurs. The uniform criteria for intolerance are as follows: persistent Grade ≥2 drug-related AEs according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (including, but not limited, to daytime somnolence, dizziness, headache, fatigue, gait abnormality) despite symptomatic treatment that are intolerable to the subject; or a Grade 1 AE that significantly affects the patient's daytime functioning and prevents

him/her from keeping the 10mg/day dose. LEM dose reduction is allowed only once, after reduction to 5 mg/day, the dose must be maintained until the end of the treatment period and may not be increased again. All dose adjustments must be fully recorded in the source records and in the electronic case report form (eCRF), with a clear record of the reason for adjustment, time of assessment, adjusted dose, and outcomes of the AEs.

The ESC starting dose is 10mg/day. After 2 weeks of treatment, if the reduction in a patient's HAMD-17 score from the screening visit is <50% of that score, the dose will be increased to 20mg/day.

Patients will be asked to record the previous night's sleep diary each morning using the ePRO system. Study visits are scheduled at the end of Weeks 2, 4, and 6 (Visits 3-5) to assess mean sTST, sSOL, sWASO, and sSE over the past week, and to evaluate ISI, ESS, FSS, and PGI-I via ePRO. The study investigator will administer HAMD-17, HAMA, CGI-S, CGI-I, and C-SSRS. AEs, SAEs, concomitant medications, and treatment compliance will be recorded. At the end of Week 6, vital signs and laboratory testing will be repeated. Patients who underwent PSG at baseline will be asked to repeat PSG assessments for TST, LPS, WASO, and SE at the end of Week 6 (Visit 5) (Table 1).

Observation period after drug discontinuation

Patients who complete the double-blind treatment period and are willing to discontinue LEM or PBO will enter a 1-week observation period, during which time they will discontinue LEM or PBO but continue taking ESC at the dose maintained during the treatment period. These patients will still be required to record the previous night's sleep diary each morning using the ePRO system. A withdrawal observation visit (Visit 6) will be conducted 1 week after discontinuation, and mean sTST, sSOL, sWASO, and sSE over the past week will be assessed; the ISI will be evaluated; and

the study investigator will administer the HAMD-17, HAMA, CGI-S, and the Benzodiazepine Withdrawal Symptoms Scale (BWSQ). Finally, AEs and SAEs will be recorded.

For patients who continue taking the study medication after the treatment period, the investigator will determine appropriate treatment based on the patient's clinical condition.

Early discontinuation of the study drug

Patients who discontinue the study drug before the end of the treatment period will be asked to return to the hospital as soon as possible to complete the early termination visit. At the visit, subjective sleep parameters from the sleep diary over the past week will be assessed, the ISI, ESS, FSS, and PGI-I will be recorded, and the study investigator will administer the HAMD-17, HAMA, CGI-S, CGI-I, and C-SSRS. AEs, SAEs, concomitant medications, and treatment compliance will be documented. Patients who discontinue the study drug due to an AE must complete the early termination visit, and all AEs must be recorded, regardless of their relationship to the study drug. All AEs must be followed up until 28 days after the last dose of study drug or until their resolution, whichever occurs first. Patients who withdraw from the study will be advised by the investigator to consider other treatment options based on their clinical condition.

Unscheduled visits

The study investigator may increase the number and frequency of follow-up visits for a patient who experiences an AE, abnormal laboratory findings, or any other discomfort, for safety reasons. The investigator must accurately record each unscheduled visit in the source records. The assessments performed at the unscheduled visit are determined by the investigator based on the patient's condition and may include any or all assessments performed during the scheduled visits.

Randomization

Enrolled patients will be randomly assigned in a 1:1 ratio to the treatment group (LEM) or the control group (PBO). A centralized stratified block randomization method will be used, and randomization of patients and the study drugs will be performed using an Interactive Web Response System (IWRS), with competitive enrollment across participating centers. The stratification factors in this trial are study center and whether PSG monitoring will be conducted.

The schedules for patient randomization and of drug randomization will be separately generated by the unblinded statistician using SAS version 9.4 or higher (SAS Institute, Cary, NC, USA) and then imported into the IWRS by the system engineer. The patient randomization schedule includes the patient randomization number and the corresponding treatment group; the drug randomization schedule includes the drug randomization number and its corresponding drug name.

After a patient is successfully screened and enrolled, the investigator at each participating center will log into the IWRS to obtain the patients randomization number. When dispensing medication during visits, the investigator logs into the IWRS to obtain the drug number and dispense the study medication accordingly.

Double-blinding design

All study personnel will remain blinded to treatment assignments until the study is unblinded. The LEM tablets and the LEM-matching PBO tablets have identical appearances and packaging.

Personnel not involved in the trial will perform the drug blinding according to the drug randomization schedule generated by the unblinded statistician. The process of blinding will be documented in a blinding record, in which the randomization schedule becomes the blind code. After drug blinding is completed, the blind code will be electronically stored by the unblinded statistician, and a paper copy will be kept at the leading participating site. The randomization code,

the selected block length, the random number seed, and other parameters are all treated as confidential data and sealed in the blind code.

When a SAE or other emergency occurs and the patient's treatment assignment is needed for proper treatment of the patient, emergency unblinding to obtain information on the patient's treatment assignment may be performed by an authorized investigator via the emergency unblinding module of the IWRS. If possible, the authorized investigator shall notify the principal investigator as well as the relevant sponsor prior to unblinding. If the principal investigator and sponsor cannot be reached before emergency blinding, the authorized investigator must contact them within 24 hours after the unblinding. The date, reason, and the unblinding procedure must be documented in the source document, and the patient must be withdrawn from the trial as a dropout after unblinding.

A single-step unblinding is planned the trial. The unblinding will occur after the statistical analysis plan and data review report are finalized and the database is locked, and it will then reveal the group assignment corresponding to each randomization number so that group-based statistical analyses of all data can be performed.

When a Suspected Unexpected Serious Adverse Reaction (SUSAR) occurs, the submitter of the SUSAR report may request temporary unblinding. Upon approval by the investigator, temporary unblinding may be executed via the central randomization system, and access to the disclosed information regarding the blind code will be limited to the submitter.

Study medications and concomitant medications

Before dispensing study medications, it must be ensured that the patient has not taken any prohibited medications for this study, or that there is a ≥5-half-life interval between the last dose

of a prohibited medication and the first dose of the study medication. Patients will receive the study medication according to the drug number at Weeks 0, 2, and 4 of the trial (Visits 2, 3, and 4). At Weeks 2, 4, and 6 (Visits 3, 4, and 5), the previously dispensed medication will be collected from the patients and counted to evaluate treatment compliance.

The study medications in the trial are LEM (trade name: Dayvigo®, Eisai Manufacturing Ltd., Tokyo, Japan), PBO (Guangdong Wasing Pharmaceutical Ltd., Guangzhou, China), and ESC (trade name: Lexapro®, H. Lundbeck A/S, Copenhagen, Denmark),. The LEM tablets and the LEM-matching PBO tablets have identical appearances and packaging.

During the trial, concomitant use of medications for somatic diseases based on the patient's medical needs and the investigator's judgment is permitted, so long as it does not affect the assessment of the study drug's efficacy.

Prohibited concomitant medications and treatments are listed in Appendix 1.

Efficacy endpoints

The primary endpoint is the comparison of changes in sTST from baseline, as measured via sleep diary, between the LEM and PBO groups after 6 weeks of treatment. The secondary endpoints include comparisons of changes from baseline in the following parameters between the LEM group and the PBO group after 2, 4, and 6 weeks of treatment: 1) sSOL, sWASO, and sSE, measured via sleep diary; 2) TST, LPS, WASO, and SE, measured via PSG in the 50% of enrolled patients who underwent PSG monitoring; 3) the ISI total score and the Item 3 score; 4) the ESS, FSS, and PGI-I scores; 5) the HAMD-17 scores (excluding sleep-related items); 6) the HAMA scores (excluding sleep-related items); and 7) the CGI-S scores. Additional secondary endpoints include comparisons between the two treatment groups of the following parameters after 2, 4, and

6 weeks of treatment: 1) insomnia remission rates (the proportion of patients with an ISI score <8 [indicating no clinically significant insomnia]) and response rates (the proportion of patients who have a ⩾7-point reduction in their ISI total score from baseline); 2) MDD remission rate (the proportion of patients with a HAMD-17 score [excluding sleep-related items] ⩽7) and MDD responder rates (the proportion of patients who have a ⩾50% reduction in their HAMD-17 scores [excluding sleep-related items] from baseline); and 3) the effective rate according to the CGI-I, defined as a CGI-I of 1 or 2. Finally, rebound insomnia in subjective sleep parameters assessed via sleep diary during the week following treatment discontinuation will also be compared between the two groups.

Safety

Safety assessments will be conducted at every follow-up visit and at the end of the trial (Visits 3-6). The incidence of AEs, treatment-emergent adverse events (TEAEs) and SAEs will be calculated. In addition, changes from baseline in the C-SSRS will be assessed and compared between the two treatment groups. All AEs must be recorded, described, and actively managed with appropriate treatment. When inquiring about AEs, the investigators shall ask the patients open-ended and non-leading verbal questions to minimize bias, and they should determine the date of onset, severity, intervention, as well as causality between the AE and the study medication.

Severity of AE will be graded according to the CTCAE. A SAE is defined as an AE that, following study medication administration, leads to death, is life-threatening, causes persistent or significant disability/incapacity, requires or prolongs inpatient hospitalization, or results in a congenital anomaly/birth defect. When becoming aware of a SAE, the investigator shall submit a written initial report followed by timely detailed written reports. A report on death submitted to

the ethics committee shall include any additional required documents such as the autopsy report and final medical report.

Sample size calculation

This RCT is designed to assess whether ESC combined with LEM increases sTST compared with ESC combined with PBO. In the Phase 3 SUNRISE 1 study that compared the efficacy and safety of LEM vs ZOL-ER in treating patients with insomnia who were at least 55 years old, LEM was significantly superior to ZOL-ER after one month of treatment[11]. To date, no published studies have assessed the effects of DORAs on TST in patients with MDD and comorbid insomnia.

Based on data from an RCT that assessed ZOL-ER combined with ESC in patients with MDD and comorbid insomnia and a post-hoc analysis of the phase 3 SUNRISE 2 LEM study in patients with a history of MDD, the following parameters were set: power = 80%, a one-sided t-test significance level $\alpha = 0.025$, a mean between-groups difference of 27 minutes in the change in TST from baseline after 6 weeks of treatment, and an SD of 67 minutes for both treatment groups[18, 20]. It was thus estimated that 100 patients per treatment group would be needed. Assuming an expected dropout rate of 30% during the study, 143 patients per group were needed, resulting in 286 randomized patients. With an estimated 50% screening failure rate, about 572 patients would need to be screened.

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Data management

An electronic data capture (EDC) system will be used for data management for this trial. The eCRF will be developed by the data manager according to the study protocol and the sample case

report forms, with edit-check programs embedded during construction, and the database will be launched after it passes the User Acceptance Testing (UAT).

User access to the EDC is dually controlled by roles and permissions. For role definition, the table of role and permission definition will be set up in the EDC by the system administrator after it is confirmed and approved by the investigator and before the database's official release for formal study data collection. For user management, before accessing the EDC, all users must complete an application form for user account, which is subsequently confirmed and approved by the investigator or by an entity delegated by the investigator. A project administrator account will be created by the system administrator, and the account will grant permission to the project administrator. The project administrator may then apply to create accounts for investigators, Clinical Research Coordinators (CRCs), monitors, auditors, and data managers, and grant them different role-based permissions to access the EDC. For example, investigators at each center can only access data from their own center and have rights to modify data from their center. Meanwhile, monitors can view EDC data from all centers with no modification rights, though they may raise questions.

Statistical analysis

All statistical analyses will be conducted using SAS version 9.4 or later. All tests will be two-sided, with statistical significance defined as $P < 0.05$. Continuous variables will be summarized using the number of non-missing observations, mean, standard deviation (SD), median, minimum, and maximum. Categorical and ordinal variables will be summarized using frequencies and percentages. Unless otherwise specified, percentages will be calculated using non-missing observations as the denominator.

Between-group comparisons of demographic and baseline clinical characteristics will be performed using appropriate statistical methods. Continuous variables will be compared using the independent-samples t-test for normally distributed data and the Wilcoxon rank-sum test for non-normally distributed data. Within-group changes from baseline will be assessed using the paired t-test or Wilcoxon signed-rank test, as appropriate. Categorical variables will be analyzed using the chi-square test or Fisher's exact test when the expected frequency in any cell is less than 5.

The primary efficacy analysis will be conducted in the full analysis set (FAS), defined as all randomized patients who provided written informed consent and had at least one post-dose efficacy assessment, and in the per-protocol set (PPS), defined as all patients who met the eligibility criteria, completed the study without major protocol deviations, and were evaluable for efficacy. The primary endpoint, change from baseline in sleep diary-derived sTST after 6 weeks of treatment, will be analyzed using a mixed model for repeated measures (MMRM). Changes from baseline at Weeks 2, 4, and 6 will be modeled as the dependent variable, with baseline sTST as a covariate and study center, treatment group, visit, and treatment-by-visit interaction as fixed effects. Missing data will not be imputed. Adjusted mean changes from baseline at Week 6, between-group differences in adjusted means, and corresponding 95% confidence intervals (CIs) will be estimated from the model.

A sensitivity analysis will be performed in the FAS using the last observation carried forward (LOCF) method to impute missing Week 6 data. An analysis of covariance (ANCOVA) model will be used, with change from baseline in sTST at Week 6 as the dependent variable, treatment group and study center as fixed effects, and baseline sTST as a covariate. Secondary efficacy analyses will be performed in the FAS and PPS. At each follow-up visit, observed values and changes from baseline in subjective sleep parameters, including sTST, sSOL, sWASO, and sSE;

objective polysomnography parameters, including TST, LPS, WASO, and SE; ISI, ESS, and FSS scores; PGI-I; HAMD-17 and HAMA scores excluding sleep-related items; and CGI-I will be summarized by treatment group using descriptive statistics. Between-group differences and changes over time will be analyzed using MMRM, as appropriate. Responder and remission rates based on the ISI, HAMD-17, and CGI-I will be summarized by treatment group at each visit. The corresponding 95% CIs for rates and between-group differences will be calculated using the normal approximation method. Between-group comparisons will be performed using the chi-square test or Fisher's exact test, as appropriate.

Safety analyses will be performed in the safety set (SS), defined as all randomized patients who had at least one post-dose safety assessment. The number and incidence of AEs, treatment-related AEs, SAEs, treatment-related SAEs, and AEs leading to study withdrawal will be summarized by treatment group. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by System Organ Class (SOC), Preferred Term (PT), and severity. The number of events and affected patients, together with their incidence, will be presented for each category. Changes from baseline in C-SSRS scores will be summarized descriptively. Laboratory test results and ECG findings, including changes from baseline, will be summarized by treatment group using descriptive statistics. Cross-tabulations of pre- and post-treatment categories will also be provided to describe changes in laboratory and ECG findings.

Confidentiality

The investigator shall protect and safeguard the privacy rights of all subjects. During the trial, a subject's source data may be linked to the trial database or other trial files only through a unique identification code. To the extent permitted by applicable laws and regulations, limited subject

characteristics, such as sex, age, or date of birth, and the subject's initials may be used to verify the subject's identity and the accuracy of the unique identification code. Any copies of a subject's source documents provided to the investigator must be redacted to remove personally identifiable information, including, but not limited to, the subject's name, address, and any other identifying information not entered in the EDC system.

Discussion

Sleep disturbance, particularly insomnia, affects most patients with MDD, and a complex, bidirectional relationship exists between MDD and insomnia[1-4]. Therefore, to improve treatment outcomes and prognosis, it is important to address both depression and insomnia in patients with MDD and comorbid insomnia[1]. However, BZRAs, the commonly used sedative-hypnotics for treating insomnia in patients with MDD, carry a wide range of AEs, particularly in psychiatric patients, in whom BZRA use is associated with increased suicide risk[5-8].Hence, there is an urgent need to explore alternative therapeutics to achieve safer and more effective treatment outcomes in these patients.

The short- and long-term efficacy and safety of LEM for primary insomnia are well established[11, 13]. As a DORA, it has a more favorable safety profile than BZRAs[5]. Importantly, its long-term use does not increase suicide risk, which is particularly relevant for patients with MDD[13]. However, whether LEM improves insomnia symptoms in patients with MDD and comorbid insomnia, and whether it can serve as an adjunct to antidepressants with antidepressant effects independent sleep improvement, remain to be fully investigated. To date, no high-level evidence on this subject from large-sample, double-blind RCTs is available for this specific population. As the first multicenter, double-blind, placebo-controlled RCT in China that assesses

LEM combined with antidepressants for MDD and comorbid insomnia, this study aims to fill this evidence gap.

The study is designed to balance clinical relevance with methodological rigor. First, ESC, a selective serotonin reuptake inhibitor (SSRI), was chosen as the background antidepressant in the study. Numerous studies and treatment guidelines have indicated that SSRI treatment is the first-line treatment for severe depression, and ESC is a commonly used SSRI drug[21-23]. It is widely used as a background antidepressant in RCTs assessing sedative-hypnotics (e.g., zolpidem and eszopiclone) for insomnia in patients with depression and insomnia[24, 25]. Thus, using ESC as the background antidepressant enhances good clinical comparability and generalizability of findings. Second, the 2-week run-in period is designed to screen for subjects with good adherence and tolerance to ESC and to exclude those whose insomnia resolves spontaneously, thereby increasing the study's power, and the 6-8 week treatment period (including the run-in period) covers the acute-phase antidepressant treatment window as well as aligns with the commonly adopted observational period for assessing short-term efficacy of an insomnia treatment[26, 27]. Third, sTST assessed using a sleep diary was selected as the primary endpoint of the study, because short sleep time is a core clinical complaint its improvement correlates with patient satisfaction. Furthermore, as a classic assessment tool, a sleep diary has high validity and closely reflects patients' daily perception of their sleep quality. Fourth, secondary endpoints of the study include objective sleep parameters from PSG, additional subjective sleep parameters from the sleep diary, insomnia severity, scores of depression and anxiety scales that exclude sleep-related items, daytime functioning, and rebound insomnia, among other multidimensional outcome measures. Such a design enables objective sleep parameters to cross-validate subjective endpoints, while also exploring LEM's

effects on patients' overall functioning and assessing its potential independent antidepressant effects.

This study protocol has several limitations. First, the 6-week treatment duration does not allow for assessing long-term efficacy and safety of LEM combined with ESC. However, this limitation could be addressed in future extension studies. Second, since only ESC is used as the background antidepressant, whether findings from the study can be generalized to other antidepressants needs further investigations. Third, the primary endpoint is based on patient-reported sleep diaries and therefore carries inherent self-report bias. To mitigate this bias, objective PSG sleep parameters are included as key secondary endpoints, as cross-validation between subjective and objective measures can minimize the impact of such bias on the results. Fourth, due to resource and operational constraints, only 50% of the enrolled subjects underwent PSG monitoring. To minimize its potential confounding effects, a stratified randomization design is adopted to ensure that baseline characteristics were well balanced between the two treatment groups of subjects who underwent PSG assessments. Fifth, the study excludes patients with treatment-resistant depression, severe physical illnesses, or other sleep disorders. Therefore, caution should be exercised when extrapolating findings from the study to the broader population with one or more of these excluded conditions.

In conclusion, this study employs a rigorous multicenter, double-blind, placebo-controlled design to systematically evaluate the efficacy and safety of LEM combined with ESC for treating MDD with comorbid insomnia. If the study yields positive results, it will offer these patients a safer alternative to BZRAs, and help reduce the risks associated with benzodiazepine exposure in clinical practice. Furthermore, it will provide preliminary evidence for the use of orexin receptor

antagonists as an adjunctive treatment for depressive disorders, thereby offering evidence-based support for future studies and clinical practice.

Abbreviations

5-HT	5-hydroxytryptamine
AEs	Adverse events
ANCOVA	Analysis of Covariance
BD	Bipolar disorder
BWSQ	Benzodiazepine Withdrawal Symptom Questionnaire
BZDs	Benzodiazepines
BZRAs	Benzodiazepine receptor agonists
CACTE	Common Terminology Criteria for Adverse Events
CBT	Cognitive behavioral therapy
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CIs	Confidence intervals
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CRC	Clinical Research Coordinator
CSF	Cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DORA	Dual orexin receptor antagonist
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
eCRF	Electronic case report form
EDC	Electronic data capture system
ePRO	Electronic Patient-Reported Outcome

ESC	Escitalopram
ESS	Epworth Sleepiness Scale
FAS	Full analysis set
FSS	Fatigue Severity Scale
HAMA	Hamilton Anxiety Rating Scale
HAMD-17	Hamilton Depression Rating Scale-17
ISI	Insomnia Severity Index
IWRS	Interactive Web Response System
LEM	Lemborexant
LOCF	Last Observation Carried Forward
GWAS	Genome-wide association study
LPS	Latency to persistent sleep
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
NMPA	The National Medical Products Administration
NREM	Non-rapid eye movement
OX1R	Orexin receptor types 1
OX2R	Orexin receptor types 2
PBO	Placebo
PGI-I	Patient Global Impression of Improvement
PPS	Per protocol set
PSG	Polysomnography

PT	Preferred term
qn	Once every night
RCT	Randomized, controlled trial
REM	Rapid eye movement
SAEs	Serious adverse events
SD	Standard deviation
SE	Sleep efficiency
SERT	Serotonin transporter
SNRI	Serotonin-noradrenaline reuptake inhibitors
SOC	System Organ Class
SS	Safety set
SSRI	Selective serotonin reuptake inhibitor
sSOL	Subjective sleep onset latency
sTST	Subjective total sleep time
sSE	Subjective sleep efficiency
SUSAR	Suspected Unexpected Serious Adverse Reaction
sWASO	Subjective wake after sleep onset
TEAEs	Treatment emergent adverse events
TST	Total sleep time
UAT	User Acceptance Testing
WASO	Wake after sleep onset
WHO	World Health Organization
ZOL-ER	Zolpidem extended-release

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Authors' contributions

ZW, WM, XL, and LL contributed to the study conception and design, and drafted the manuscript. YZ, HJ, XZ, YS, TL, YC, GW, HL, YX, ZS, YF, YL, JZ, YaL, HuanL, SS, YW, LH, ZL, XinL, XT, and YS contributed substantially to the implementation of the experimental protocol, data analysis, and interpretation. All authors critically reviewed and approved the final manuscript and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data availability

No datasets were generated or analysed during the current study.

Ethics approval and consent to participate

The protocol has been approved by the Medical Ethics Committee of the Peking University Sixth Hospital (Peking University Institute of Mental Health) (Approval number: X2025-11-19-2-1) and registered at the Chinese Clinical Trial registry (ChiCTR) (registration number: ChiCTR2600119476) on February 27, 2026. The investigators obtain written informed consent from all subjects prior to any trial-related activities. The study is conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice (ICH GCP), This protocol is Version 3.0 (January 23, 2026).

Consent for publication

Not applicable.

Competing interests

The authors report no conflicts of interest in this work.

References

[1]Fang H, Tu S, Sheng J, et al. Depression in sleep disturbance: A review on a bidirectional relationship, mechanisms and treatment [J]. Journal of Cellular and Molecular Medicine, 2019, 23(4):2324-2332.

[2]Ye Y, Wang C, Lan X, et al. Abnormal amygdala functional connectivity in MDD patients with insomnia complaints [J]. Psychiatry Research: Neuroimaging, 2022, 328 :111578.

[3]Kishi T, Koebis M, Sugawara M, et al. Orexin receptor antagonists in the treatment of insomnia associated with psychiatric disorders: a systematic review [J]. Translational Psychiatry, 2024, 14(1):374.

[4]Lin YS, Wang CC, Chen CY. GWAS Meta-Analysis Reveals Shared Genes and Biological Pathways Between Major Depressive Disorder and Insomnia [J]. Genes (Basel), 12(10):1506.

[5]Kim WJ, Kim HS. Emerging and upcoming therapies in insomnia [J]. Transl Clin Pharmacol, 2024, 32(1):1-17.

[6]Maruki T, Takeshima M, Yoshizawa K, et al. Efficacy and safety of each class of sleep medication for major depressive disorder with insomnia symptoms: A systematic review and meta-analysis of double-blind randomized controlled trials [J]. Psychiatry Clin Neurosci, 2025, 79(6):306-318.

[7]Cato V, Holländare F, Nordenskjöld A, et al. Association between benzodiazepines and suicide risk: a matched case-control study [J]. BMC Psychiatry, 2019, 19(1):317.

[8]Van Vliet P, Van Der Mast RC, Van Den Broek M, et al. Use of benzodiazepines, depressive symptoms and cognitive function in old age [J]. Int J Geriatr Psychiatry, 2009, 24(5):500-508.

[9][Guidelines for the diagnosis and treatment of insomnia disorder (2025 edition)] [J]. Zhonghua Yi Xue Za Zhi, 2025, 105(34):2960-2981.

[10]Takaesu Y, Sakurai H, Aoki Y, et al. Treatment strategy for insomnia disorder: Japanese expert consensus [J]. Front Psychiatry, 2023, 14:1168100.

[11]Rosenberg R, Murphy P, Zammit G, et al. Comparison of Lemborexant With Placebo and Zolpidem Tartrate Extended Release for the Treatment of Older Adults With Insomnia Disorder: A Phase 3 Randomized Clinical Trial [J]. JAMA Netw Open, 2019, 2(12):e1918254.

[12]Kärppä M, Yardley J, Pinner K, et al. Long-term efficacy and tolerability of lemborexant compared with placebo in adults with insomnia disorder: results from the phase 3 randomized clinical trial SUNRISE 2 [J]. Sleep, 2020, 43(9):zsaa123.

[13]Yardley J, Inoue Y, Pinner K, et al. Efficacy and safety of lemborexant in subjects previously treated with placebo for 6 months in a randomized phase 3 study [J]. Sleep Med, 2023, 110:111-119.

[14]Moline M, Zammit G, Cheng JY, et al. Comparison of the effect of lemborexant with placebo and zolpidem tartrate extended release on sleep architecture in older adults with insomnia disorder [J]. J Clin Sleep Med, 2021, 17(6):1167-1174.

[15]Rosenblum Y, Nakagawa J, Van Hattem T, et al. Sleep Neurophysiology in Depression [J]. Biol Psychiatry, 2025, 98(11):842-853.

[16]Kishi T, Koebis M, Sugawara M, et al. Orexin receptor antagonists in the treatment of insomnia associated with psychiatric disorders: a systematic review [J]. Transl Psychiatry, 2024, 14(1):374.
[17]Krystal A, Blier P, Culpepper L, et al. Efficacy and safety of lemborexant in subjects with insomnia disorder receiving medications for depression or anxiety symptoms [J]. Neuropsychopharmacol Rep, 2025, 45(1):e12509.
[18]Takaesu Y, Muraoka H, Takeshima M, et al. A 12-Week, Open-Label, Multicenter Pilot Study to Evaluate the Efficacy and Safety of Lemborexant in Patients with Insomnia Comorbid with Depressive Episodes (SELENADE) [J]. CNS Drugs, 2026, 40(3):467-480.
[19]Chan AW, Boutron I, Hopewell S, et al. SPIRIT 2025 statement: updated guideline for protocols of randomised trials [J]. BMJ, 2025, 389:e081477.
[20]Mishima K, Fujimoto K, Endo A, et al. Safety and Efficacy of Lemborexant in Insomnia Patients: Results of a Postmarketing Observational Study of Dayvigo(®) Tablets [J]. Drugs R D, 2024, 24(2):211-226.
[21]Montgomery SA, Huusom AKT, Bothmer J. Escitalopram is a new and highly efficacious SSRI in the treatment of major depressive disorder [J]. European Neuropsychopharmacology, 2002, 12:254-255.
[22]Hemels ME, Kasper S, Walter E, et al. Cost-effectiveness analysis of escitalopram: a new SSRI in the first-line treatment of major depressive disorder in Austria [J]. Curr Med Res Opin, 2004, 20(6):869-878.
[23]Nordström G, Danchenko N, Despiegel N, et al. Cost-effectiveness evaluation in Sweden of escitalopram compared with venlafaxine extended-release as first-line treatment in major depressive disorder [J]. Value Health, 2012, 15(2):231-239.
[24]Maurizio F, Asnis GM, Shrivastava RK, et al. Improved insomnia symptoms and sleep-related next-day functioning in patients with comorbid major depressive disorder and insomnia following concomitant zolpidem extended-release 12.5 mg and escitalopram treatment: a randomized controlled trial [J]. Journal of Clinical Psychiatry, 2011, 72(7):914-928.
[25]Chen H, Zeng G, Wu S, et al. Efficacy and Safety of Escitalopram Combined with Tandospirone Citrate in Treating Patients with Vascular Depression and Chronic Insomnia: A Randomized Controlled Trial [J]. CNS Drugs, 2025, 39(7):669-683.
[26]Ghaemi SN, Whitham EA, Vohringer PA, et al. Citalopram for Acute and Preventive Efficacy in Bipolar Depression (CAPE-BD): A Randomized, Double-Blind, Placebo-Controlled Trial [J]. The Journal of Clinical Psychiatry, 2021, 82(1) :19m13136.
[27]Unruh M, Cukor D, Rue T, et al. Sleep-HD trial: short and long-term effectiveness of existing insomnia therapies for patients undergoing hemodialysis [J]. BMC Nephrology, 2020, 21(1):443.

Figure legends

Figure 1 Study flowchart. W, week; LEM, Lemborexant; ESC, Escitalopram; PBO, placebo.

Legends for the appendix

Appendix 1 Prohibited concomitant medications and treatments.

Supplementary Files

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