Supplemental Material

Efficacy and Safety of Solriamfetol on Excessive Daytime Sleepiness Associated with Obstructive Sleep Apnea in China: A Phase 3, Multicenter, Double-Blind, Placebo-Controlled Randomized Clinical Trial

Running Title: Solriamfetol for EDS associated with OSA: A phase 3 RCT from China

Journal name: CNS Drugs

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Clinical Trial Protocol

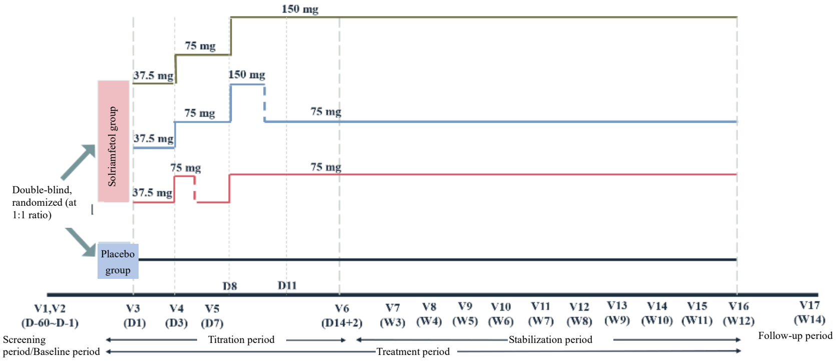
A Twelve-week, Double-blind, Placebo-controlled, Randomized, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Solriamfetol in the Treatment of Excessive Daytime Sleepiness (EDS) in Patients with Obstructive Sleep Apnea Syndrome (OSA)

Protocol Number:	IGN-B0301-03
Version No.:	V2.0
Version Date:	May 30, 2023

Ignis Therapeutics (Suzhou) Limited

Protocol Synopsis

Sponsor	Axsome Malta Ltd. Ignis Therapeutics (Suzhou) Limited (hereinafter referred to as "Ignis") Ignis is licensed to conduct clinical trials and regulatory affairs within China
Investigational Product	Solriamfetol
Title	A Twelve-week, Double-blind, Placebo-controlled, Randomized, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Solriamfetol in the Treatment of Excessive Daytime Sleepiness (EDS) in Patients with Obstructive Sleep Apnea Syndrome (OSA)
Protocol No.:	IGN-B0301-03
Phase:	III
Version No./Date:	V2.0/May 30, 2023
Participating Sites	Multicenter Study in China
Study Duration	The estimated study duration includes an up to 60-day screening/baseline period, a 12-week double-blind treatment period, and a 2-week safety follow-up period.
Study Objectives	● Primary objective: ➢ To evaluate the efficacy of solriamfetol in the treatment of EDS in adult patients with OSA. ● Secondary objectives: ➢ To evaluate the safety and tolerability of solriamfetol in the treatment of EDS in adult patients with OSA. ➢ To evaluate the pharmacokinetic (PK) profile of solriamfetol in adult OSA patients with EDS by sparse sampling.
Study Population	OSA patients with EDS, who are required to have a documented diagnosis of OSA and have sleepiness and an inability to stay awake as demonstrated by objective and subjective criteria.
Study Design	This study is a 12-week, randomized, double-blind, placebo-controlled, multicenter, parallel-design clinical trial to evaluate the efficacy and safety of solriamfetol in the treatment of EDS in adult patients with OSA. The study is comprised of three periods: the screening/baseline period, the double-blind treatment period, and the safety follow-up period. About 204 OSA patients with EDS are planned to be enrolled. In order to reflect the current treatment status of OSA in China and ensure generalizability of the study results, participants are eligible if they meet one of the following conditions: 1) participants who are currently using a primary OSA therapy at least once a week; 2) participants who have undergone a surgical intervention intended to treat the underlying airway obstruction; 3) participants who have previously used a primary OSA therapy for at least one month with at least one documented adjustment to the therapy; 4) a small proportion of participants who have never used and refuse to use a primary OSA therapy. The proportion of participants who meet the third and fourth conditions mentioned above will be maintained below 30%, ensuring that the study population enrolled is representative of patients with OSA in China.



Screening period (D-60 to D-8)/baseline period (D-7 to D-1)

All participants are required to complete screening examination, maintenance of wakefulness test (MWT), 24-hour ambulatory blood pressure monitoring, and relevant scale assessments. An overnight stay at the investigational site for nocturnal polysomnography (PSG) followed by a MWT on the next day will be required 1 week prior to randomization (D-7 to D-1). The inclusion and exclusion criteria will be verified in the screening/baseline visits. Following the successful completion of screening and baseline visits, eligible participants will be randomly assigned in a 1:1 ratio to solriamfetol or placebo treatment, respectively. Randomization will be stratified based on participants' primary OSA therapy usage (adherent to primary OSA therapy, nonadherent to primary OSA therapy, not using primary OSA therapy).

Treatment period (W1 to W12)

During the 12-week double-blind treatment period, the investigational drug will be administered once a day.

During the first two weeks of the treatment period, participants will be titrated to the maximum dose that is tolerated. Before each dose adjustment, the investigator is required to communicate with the participant, and the investigator will evaluate whether the dose can be titrated up or down according to the participant's condition. Down titration is only allowed once.

In the first week of the treatment period, participants will start at a once daily (QD) dose of 37.5 mg on Days 1 to 3 and then 75 mg QD from Days 4 to 7. For participants who could not tolerate, changes in dosing back to 37.5 mg QD are permitted at the discretion of the investigator. A safety visit will be scheduled at the end of the first week. Participants should be discontinued from the study if they could not tolerate 37.5 mg.

Study participants without dose reduction during the first week will receive 150 mg QD from the first day of the second week in the treatment period, after completing safety assessments at the end of the first week. Should a participant demonstrate intolerance to 150 mg QD, the investigator may decrease the dose to 75 mg QD following a telephone assessment and clinical evaluation. Any subsequent dose reduction will necessitate study discontinuation. Dosage must remain stable from Day 4 of the second week until the end of the double-blind treatment.

For study participants with dose reduction from 75 mg QD to 37.5 mg QD during the first week, they are required to complete safety assessment at the investigational site on the third day or later when 37.5 mg QD are taken (i.e., if down titration to 37.5 mg occurs on Day 6, then participants are required to complete safety assessment visit on Day 7 +1 or Day 7 +2; if down titration to 37.5 mg occurs on Day 7, then participants are required to complete safety assessment visit on Day 7 +2). Starting from the first day of the second week of the treatment period, these participants should receive 75 mg QD, and dosage must remain stable at 75 mg QD until the end of the double-blind treatment. Any subsequent dose reduction will necessitate study discontinuation.

During the treatment period, participants will return to investigational sites at the end of the first week for a safety assessment, and at the end of Weeks 2, 5, 8, and 12 for

	efficacy and safety assessments. An overnight stay at the investigational site for nocturnal PSG followed by a MWT and other assessments on the next day will be required for visits at Weeks 2, 5, and 12. The Week 8 visit will include 24-hour ambulatory blood pressure monitoring. Participants will take their final dose of investigational drug at the Week 12 visit prior to the Week 12 visit assessments. For study participants who receive at least one dose of investigational drug but withdraw prematurely from the study, an early termination clinic visit is required within 7 days of withdrawal. If participants are willing and able to take investigational drug until the day of early termination visit, an overnight stay at the investigational site for nocturnal PSG followed by a MWT and other assessments are required for the early termination visit. If participants do not return to the investigational sites immediately when discontinuing the investigational drug, or they are unwilling to take their final dose of investigation drug and complete a MWT, then PSG and MWT are not required for the early termination visit. <u>Safety follow-up period (2 weeks ± 3 days after the end of study treatment)</u> At the conclusion of the double-blind treatment period, participants will return to investigational sites for a safety follow-up assessments 2 weeks after the end of the study treatment. Unless there are any outstanding safety issues that require follow-up, participants will be discharged from the study. For participants who discontinue double-blind treatment prematurely, a safety follow-up visit will also be scheduled approximately 2 weeks after taking the final dose of investigational drug if possible. Six blood samples will be collected from each participant for PK evaluation. Blood samples collection is required at the following timepoints respectively: one sample will be collected on Day 1 within 1 hour before dosing, and one sample within 1-4 hours after dosing on Day 1; one sample will be collected on Week 2 (on Day 14) within 1 hour before dosing, and one sample within 1-4 hours after dosing on Day 14; one sample will be collected at Week 5 (on Day 35) within 1 hour before dosing, and one sample within 8-12 hours after dosing on Day 35. Safety will be assessed throughout the study. The safety assessment will be assessed by the incidence of treatment-emergent adverse events (TEAEs), and changes in vital signs, physical examination findings, 12-lead electrocardiogram (ECG), clinical laboratory tests (hematology, blood chemistry, urinalysis), 24-hour ambulatory blood pressure monitoring, and Columbia Suicide Severity Rating Scale (C-SSRS).
Sample Size	The calculation of sample size is based on a two-sample t-test with a two-sided significance level of 0.05. Based on the results of previous studies, a sample size of 86 participants per group (solriamfetol and placebo group) will provide at least 90% power to detect a difference of 6 minutes in the mean sleep latency as determined from the MWT (mean of the first four trials), with a common standard deviation of 12 minutes. A sample size of 86 participants per group will also provide at least 90% power to detect a difference of 2.5 points on the ESS changes from Baseline to Week 12 between solriamfetol and placebo treatment, with a common standard deviation of 5 points. Asuming a dropout rate of 15% for the two co-primary endpoints, approximately 102 participants per treatment group are required, thus approximately 204 participants are planned for enrollment.
Randomization and Blinding	This study implements competitive enrollment, with approximately 204 participants planned for enrollment. Randomization will be performed using a stratified design base on participants' primary OSA therapy situation (1. adherent to primary OSA therapy; 2. nonadherent to primary OSA therapy; 3. not using primary OSA therapy). A 1:1 ratio will be used to assign participants into solriamfetol and placebo treatment in each stratification. Each participant's primary OSA therapy usage situation will be reviewed and documented by the investigator in the CRF. Study participants will be assigned a randomization number through the interactive web response system (IWRS) in accordance with the randomization code generated by an authorized independent personnel using SAS 9.4 or the above version. All study participants, investigators, data analysts, and all other personnel involved in study

	assessment, data collection and monitoring should be blinded with respect to the participant's treatment assignment from randomization to the final database lock.
Investigational drug, and Dose	Solriamfetol will be supplied as 37.5 mg, 75 mg, 150 mg tablets that overencapsulated in an opaque gelatin capsule. Solriamfetol will be supplied by Ignis Therapeutics (Suzhou) Limited. Placebo: Placebo tablets will also be overencapsulated in the same opaque gelatin capsules that will be used for the active solriamfetol treatment. Placebo will be supplied by Ignis Therapeutics (Suzhou) Limited.
Treatment Administration	Participants will be instructed to take the investigational drug (either solriamfetol or matching placebo) on an empty stomach within 1 hour of awakening. Participants will also be instructed to abstain from eating or dringking (except for water) for 30 minutes after taking the investigational drug. If a participant fails to take the investigational drug within 1 hour of awakening, the participant should be instructed to take the investigational drug, if he/she is able to do so, at least 12 hours before his/her anticipated bedtime. If the participant cannot take the investigational drug at least 12 hours before his/her anticipated bedtime, the participant should not take the investigational drug for that day.
Inclusion Criteria	Participants must meet all of the following inclusion criteria to be enrolled in the study: 1. Male or female between 18 to 75 years of age, inclusive. 2. Diagnosis of OSA according to the International Classification of Sleep Disorders, 3rd edition (ICSD-3) criteria. 3. Patients with OSA may be considered for enrollment if they meet one of the following criteria: a) Use of a primary therapy for OSA (i.e., positive airway pressure (PAP), oral pressure therapy, oral appliance, or upper airway stimulator) on at least 1 night per week, or b) History of at least 1 month of an attempt to use one or more primary OSA therapies with at least one documented adjustment that was made in an attempt to optimize the primary OSA therapy, or participants who have never used and refuse to use a primary OSA therapy, or c) History of a surgical intervention intended to treat OSA symptoms. 4. A stable level of compliance with a primary OSA therapy for at least 1 month prior to the baseline visit as follows: a) A stable level of use of a primary OSA therapy, or b) A lack of use of a primary OSA therapy either following a history of attempted use, or have never used before, or c) A history of a surgical intervention intended to treat OSA symptoms. 5. Baseline ESS score no less than 10 points ($\geq$ 10 points). 6. Baseline MWT mean sleep latency < 30 minutes (documented by the mean of the first four 40-minute trials of the MWTs). 7. Usual nightly total sleep time of at least 6 hours ($\geq$ 6 hours). 8. Body mass index (BMI) from18 kg/m^2 to < 45 kg/m^2. 9. Female participants must have negative pregnancy test results at the screening and baseline visits; all participants must consent to use a medically acceptable method of contraception throughout the entire study period and for 30 days after the study is completed. 10. Willing and able to provide written informed consent, willing and able to comply with the study protocol (i.e., must be able to understand and complete the study

	questionnaires and scales, comply with the visit schedule and prescribed dosage regimens). 11. Determined by the investigator to be medically stable as assessed by medical history, physical examination, laboratory and electrocardiogram test results and review of concomitant medications.
Exclusion Criteria	Participants who demonstrate any of the following will be excluded from the study: 1. Female participants who are pregnant or lactating. 2. Usual bedtime later than 1 a.m. (01:00). 3. Occupation requiring nighttime shift work or variable shift work. 4. Any other clinically relevant medical, behavioral, or psychiatric disorders other than OSA that is associated with excessive sleepiness. 5. History or presence of bipolar disorder, bipolar related disorders, schizophrenia, schizophrenia spectrum disorder, or other psychotic disorders according to DSM-5 criteria, or presence of significant suicidality. 6. History or presence of any acutely unstable medical condition, behavioral or cognitive impairment, or any medical condition or surgical history that could affect the safety of the participant or interfere with study efficacy, safety and PK assessments, or the ability of the participant to complete the study per the judgment of the investigator. 7. History of the bariatric surgery within the past year or a history of any gastric bypass procedure. 8. Presence of renal impairment or calculated creatinine clearance less than 60 mL/min at screening, which is calculated using the following formula: CLcr (mL/min) = (140 - age [years]) x body weight (kg) x (0.85, if female))/(72 x serum creatinine value [mg/dL]), if serum creatinine is expressed in µmol/L, the value should be divided by 88.4 to convert µmol/L to mg/dL. 9. Clinically significant ECG abnormality in the opinion of the investigator would preclude participation in the study. 10. Presence of significant cardiovascular disease at screening, including but not limited to: myocardial infarction within the past year, unstable angina pectoris, symptomatic congestive heart failure [(American College of Cardiology/American Heart Association (ACC/AHA) Stage C or D)], revascularization procedures within the past year, ventricular cardiac arrhythmia requiring an automatic implantable cardioverter defibrillator (AICD) or medication therapy, uncontrolled hypertension, systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 95 mmHg (at Screening, or across Baseline measures according to protocol specifications), or any significant cardiovascular condition that in the investigator's opinion may jeopardize participant's safety in the study. 11. Laboratory value(s) outside the laboratory reference range that are considered to be clinically significant and may affect the safety of the participant per the judgment of the investigator (including clinical chemistry, hematology, and urinalysis) (Note: Screening labs may be repeated once). 12. Excessive caffeine use one week prior to the baseline assessments, or anticipated excess caffeine use during the study, defined as greater than 600 mg caffeine per day (>600 mg/day). 13. Use of any over-the-counter (OTC) or prescription medications that could affect the evaluation of excessive sleepiness within a time period prior to the baseline visit corresponding to at least five half-lives of the drug(s) or planned use of such drug(s) at some point throughout the duration of the study. Examples of excluded medications include OTC sleep aids or stimulants (e.g., pseudoephedrine), methylphenidate, amphetamines, modafinil, 2-acetamide, sodium oxybate,

	pemoline, trazodone, hypnotics, benzodiazepines, barbiturates, and opioids, and any traditional Chinese medicine that may affect sleep. Medications should be discontinued such that the participant has returned to his/her baseline level of daytime sleepiness at least 7 days prior to the baseline visit, in the opinion of the investigator. 14. Use of a monoamine oxidase inhibitor (MAOI) in the past 14 days or five half-lives (whichever is longer) prior to the baseline visit or plans to use an MAOI during the study. 15. Received an investigational drug or device in the past 30 days or five half-lives (whichever is longer) prior to the baseline visit, or plans to use an investigational drug (other than the investigational drug) or investigational medical devices during the study 16. Previous exposure to or participation in a clinical trial of solriamfetol. 17. Current or past (within the past 2 years prior to screening) diagnosis of a moderate or severe substance use disorders according to DSM-5 criteria or seeking treatment for a substance related disorder. 18. Nicotine dependence that has an effect on sleep (e.g., a participant who routinely awakened at night to smoke). 19. Urine drug screen positive for an illicit drug of abuse (including cannabinoids) at screening or at any point throughout the duration of the study, except for a prescriped drug (e.g., amphetamines) at screening. 20. History of phenylketonuria (PKU) or history of hypersensitivity to phenylalanine-derived products. 21. Vaccination within 31 days prior to the baseline visit or a plan for vaccination during the study. 22. Any other conditions that are not in line with the rights and interests of the participants or would preclude participation in the study as judged by the investigator. 23. Human Immunodeficiency Virus (HIV) or syphilis positive at screening
Criteria for removal of participants from the study	All participants are free to withdraw from the study at time for any reason, and without prejudice. At any time during the study, the investigator, sponsor or its designee may remove a participant from the study if any condition(s) of the participant preclude his/her participation in the study. If any of the criteria below are met during the study, the investigational drug administration must be stopped, and the participant should be discontinued from the study: • Suicide risk reported or assessed by C-SSRS. • 3-fold or greater elevation above the upper limit of normal (ULN) of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) accompanied by an elevation of serum total bilirubin greater than two times the ULN, and withdrawal is required as judged by the investigator • Liver enzyme (AST/ALT) value ≥ 5×ULN, and withdrawal is required as judged by the investigator. • Serum creatinine ≥ 2 mg/dL. • Positive pregnancy test. • Positive urine drug screen.

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<tr><td></td><td>Participant demonstrates a QTc value above 500 msec (determinations should be based on at least two ECG recordings performed on drug in close proximity), or QTcF prolongation that exceeds the baseline QTcF values by > 60 msec.
Any serious adverse event (SAE) considered to be related to the investigational drug or procedure and may preclude participation in the study as judged by the investigator.</td></tr>
<tr><td>Pharmacokinetic Assessment</td><td>Six blood samples will be collected from each participant for an assessment of solriamfetol PK parameters in Chinese participants using sparse sampling.

Blood samples collection is required at the following timepoints respectively: one sample will be collected on Day 1 within 1 hour before dosing, and one sample within 1-4 hours after dosing on Day 1; one sample will be collected on Week 2 (on Day 14) within 1 hour before dosing, and one sample within 1-4 hours after dosing on Day 14; one sample will be collected at Week 5 (on Day 35) within 1 hour before dosing, and one sample within 8-12 hours after dosing on Day 35.

Descriptive summary statistics will be performed for the obtained PK concentration data. If the data allow, population pharmacokinetics as well as pharmacokinetic and pharmacodynamic models, will be used to analyze the obtained PK data, pharmacodynamic data and safety data. The results of population pharmacokinetic analysis will not be included in the CSR of this study but will be presented in a specific population PK report.</td></tr>
<tr><td>Safety Evaluation</td><td>Safety and tolerability will be assessed by TEAEs, as well as changes in clinical laboratory tests (hematology, blood chemistry, urinalysis), vital signs, 24-hour ambulatory blood pressure monitoring, 12-lead ECG, physical examination, and C-SSRS assessment.</td></tr>
<tr><td>Analysis Populations</td><td>Randomized Set: Participants who receive a randomized treatment assignment.
Full Analysis Set (FAS): Following Intent-to-treat principle, participants who receive at least one dose of the investigational drug and have baseline and at least one post-baseline evaluation of efficacy data. This population will be the main analysis set for the efficacy endpoints.
Per-Protocol population: It is a subset of FAS, which consists of participants who completed the 12-week treatment without a major protocol violation that affect efficacy assessment, with evaluation data of co-primary efficacy endpoints at Week 12, with an investigational drug compliance ranged between 80% to 120% throughout 12-week treatment period. This population will be identified before unblinding the study and will only be used in a secondary analysis of the co-primary and key secondary endpoints.
Safety population: It includes all participants who received at least one dose of the investigational drug. This population will be analyzed for safety evaluation.
Pharmacokinetic Concentration Set (PKCS): It is a subset of the safety population, which consistes of participants who have at least one evaluable concentration data and without a major violation that affect pharmacokinetic analysis. Participants in the placebo group are excluded from PKCS.</td></tr>
<tr><td>Estimands</td><td>The estimands for this study in relation to the intercurrent events of early discontinuation and use of protocol-prohibited medications are defined as below. Please refer to Section 5.5 for list of protocol-prohibited medications,

<u>Primary Estimand</u><table><tr><th>Study Objectives</th><th>Estimands</th></tr></table></td></tr>
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	Primary Study Objective 1: To evaluate the effect of solriamfetol compared to placebo among patients with OSA in change from baseline to Week 12 in the mean MWT sleep latency (minutes, (determined from the first four 40-minute trials of the MWT)	**Primary Estimand 1:** **Treatment:** Randomly assigned treatment (see Section 5.4 for details) and possible concomitant treatments (see Section 5.5) **Population**: OSA patients with EDS, who are required to have a documented diagnosis of OSA and have sleepiness and an inability to stay awake as demonstrated by objective and subjective criteria. **Endpoint**: Change from baseline in mean MWT sleep latency (minutes, determined from the first four 40-minute trials of the MWT) to Week 12 **Intercurrent Events and Handling Strategies:** • For intercurrent events of early discontinuation and use of protocol-prohibited medications, a treatment policy strategy will be used, that is, the relevant measurements will be used and analyzed regardless of the occurrence of the event • For other intercurrent events, a treatment policy strategy will also be used, that is, the relevant measurements will be used and analyzed regardless of the occurrence of the event **Population-Level Summary**: The treatment difference versus placebo in LS mean from baseline to Week 12 will be analyzed using a mixed-effects model for repeated measures (MMRM)
		Supplementary Analysis of Primary Estimand 1: **Treatment**: Same as the primary estimand 1 **Population**: Same as the primary estimand 1 **Intercurrent Events and Handling Strategies:** • For intercurrent events of early discontinuation and use of protocol-prohibited medications, a hypothetical strategy will be used. Efficacy measurements after the intercurrent events will be replaced or imputed using the multiple imputation (MI) method • For other intercurrent events, a treatment policy strategy will be used, that is, the relevant measurements will be used and analyzed regardless of the occurrence of the event **Population-Level Summary**: Same as the primary estimand 1
	Primary Study Objective 2: To evaluate the effect of solriamfetol compared to placebo among patients with OSA in change from baseline to	**Primary Estimand 2:** **Treatment:** Randomly assigned treatment (see Section 5.4 for details) and possible concomitant treatments (see Section 5.5) **Population**: OSA patients with EDS, who are required to have a documented diagnosis of OSA and have sleepiness and an inability to stay awake as demonstrated by objective and subjective criteria. **Endpoint**: Change from baseline in ESS total score to Week 12 **Intercurrent Events and Handling Strategies:** • For intercurrent events of early discontinuation and use of protocol-prohibited medications, a treatment policy strategy will be used, that is, the relevant measurements will be used and analyzed regardless of the occurrence of the event

	Week 12 in ESS scores	• For other intercurrent events, a treatment policy strategy will also be used, that is, the relevant measurements will be used and analyzed regardless of the occurrence of the event **Population-Level Summary**: The treatment difference versus placebo in LS mean from baseline to Week 12 will be analyzed using a mixed-effects model for repeated measures (MMRM)
		Supplementary Analysis of Primary Estimand 2: **Treatment**: Same as the primary estimand 2 **Population**: Same as primary estimand 2 **Intercurrent Events and Handling Strategies:** • For intercurrent events of early discontinuation and use of protocol-prohibited medications, a hypothetical strategy will be used. Efficacy measurements after the intercurrent events will be replaced or imputed using the multiple imputation (MI) method • For other concomitant events, a treatment policy strategy will be used, that is, the relevant measurements will be used and analyzed regardless of the occurrence of the event **Population-Level Summary**: Same as the primary estimand 2

Key Secondary Estimand

Study Objectives	**Estimands**
Key Secondary Study Objective: To compare treatment with solriamfetol versus placebo on the percentage of participants reported as improved (minimally, much, very much) in PGIc at Week 12 among patients with OSA	**Key Secondary Estimand:** **Treatment:** Randomly assigned treatment (see Section 5.4 for details) and possible concomitant treatments (see Section 5.5) **Population**: OSA patients with EDS, who are required to have a documented diagnosis of OSA and have sleepiness and an inability to stay awake as demonstrated by objective and subjective criteria. **Endpoint**: Percentage of participants with improved PGIc at Week 12 **Intercurrent Events and Handling Strategies:** • For intercurrent events of early discontinuation and use of protocol-prohibited medications, a composite strategy will be used, and participant with the occurrence of the event is considered as not improved • For other intercurrent events, a treatment policy strategy will be used, that is, the relevant measurements will be used and analyzed regardless of the occurrence of the event **Population-Level Summary**: The rate difference in PGIc improvement at Week 12 will be analyzed using the CMH method

Other Secondary Estimands

Study Objectives	**Estimands**

	Other Secondary Study Objective 1: To evaluate the effect of solriamfetol compared to placebo among patients with OSA in change from baseline to Week 2 and Week 5 in the mean MWT sleep latency (minutes, determined from the first four 40-minute trials of the MWT)	**Other Secondary Estimand 1:** • Changes from baseline in MWT at the end of the Week 2 and Week 5 are defined as: mean sleep latency at the end of the Week 2 and Week 5 (determined from the first four 40-minute trials of the MWTs) minus the baseline measurement (minutes)
	Other Secondary Study Objective 2: To evaluate the effect of solriamfetol compared to placebo among patients with OSA in change from baseline to Week 2, 5 and 8 in ESS score	**Other Secondary Estimand 2:** • Changes from baseline in ESS scores at the end of Week 2, 5 and 8 are defined as: ESS total scores at the end of Week 2, 5 and 8 minus baseline values
	Other Secondary Study Objective 3: To compare treatment with solriamfetol versus placebo on the percentage of participants reported as improved (minimally, much, very much) in PGIc at Week 2, 5 and 8 among patients with OSA	**Other Secondary Estimand 3:** • The percentages of participants reported as improved (minimally, much, very much) in PGIc at Week 2, 5 and 8 are defined as the percentages calculated by dividing the number of participants reported as improved in PGIc by the total number of participants in the each treatment group at Week 2, 5 and 8
	Other Secondary Study Objective 4: To compare treatment with solriamfetol versus placebo on the percentage of participants rated as improved (minimally, much, very much) in CGIc at Week 12 among patients with OSA	**Other Secondary Estimand 4:** • The percentage of participants rated as improved (minimally, much, very much) in CGIc at the end of Week 12 is defined as the percentage calculated by dividing the number of participants who have achieve improvement (minimally, much, very much) in CGIc by the total number of participants in each treatment group at Week 12
	Other Secondary Study Objective 5: To compare treatment with solriamfetol versus placebo on the percentage of participants rated as improved (minimally, much, very much) in CGIc at Week 2, 5 and 8 among patients with OSA	**Other Secondary Estimand 5:** The percentage of participants rated as improved (minimally, much, very much) in CGIc at the end of Week 12 is defined as the percentage calculated by dividing the number of participants who have achieve improvement (minimally, much, very much) in CGIc by the total number of participants in each treatment group at Week 2, 5 and 8

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<td>
<table>
<tr><td>Other Secondary Study Objective 6:
To compare the efficacy of solriamfetol versus placebo throughout the day in sleep latency for each of the 5 MWT trials</td><td>Other Secondary Estimand 6:
Changes of the efficacy throughout the day in MWT: changes in sleep latency for each of the 5 MWTs (minutes)</td></tr>
</table>
<u>Functional Outcomes and Quality of Life Estimands</u>
<table>
<tr><th>Study Objectives</th><th>Estimands</th></tr>
<tr><td>Study Objective of Functional Outcomes:
To compare treatment with solriamfetol versus placebo on the changes from baseline in the total scores of the Functional Outcomes of Sleep Questionnaire (FOSQ-10) to the end of the Week 2, 5, 8, and 12 among adult OSA patients with EDS</td><td>Estimand of Functional Outcomes:
• The changes from baseline in the FOSQ-10 total scores at the end of the Week 2, 5, 8, and 12 are defined as: the FOSQ-10 total scores at the end of Week 2, 5, 8, and 12 minus the baseline FOSQ-10 total score</td></tr>
<tr><td>Study Objectives of Quality of Life:
To compare treatment with solriamfetol versus placebo on the changes from baseline in 36-Item Short Form Health Survey, 2nd edition (SF-36v2) total score and 8 domain scores, physical component summary score (PCS), and mental component summary score (MCS) to the end of Week 5, 8, and 12 among adult OSA patients with EDS</td><td>Estimand of Quality of Life:
• Changes from baseline in SF-36v2 total score, 8 domain scores, PCS, and MCS at the end of the Week 5, 8, and 12 are defined as: SF-36v2 total score, 8 domain scores, PCS, and MCS at the end of Week 5, 8, and 12 minus corresponding baseline scores</td></tr>
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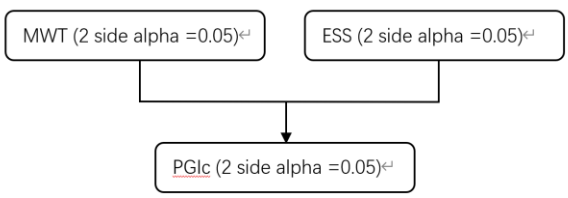
<tr>
<td>Statistical Methods</td>
<td>SAS 9.4 or above version will be used for statistical analysis in this study.

Primary Endpoint:

The primary endpoint is change from baseline to Week 12 in mean MWT sleep latency (determined from the first four 40-minute trials of the MWT) and ESS total score. Statistical analyses will be performed using the FAS and the Per Protocol population, with the FAS as the main analysis set and the Per Protocol population as the secondary analysis set. For the primary and supplementary analyses of the primary efficacy endpoints, a mixed-effects model for repeated measures (MMRM) will be used, with the baseline value of the efficacy endpoint as a covariate, treatment, visit, treatment-visit interaction, and randomization stratification factors (adherent to primary OSA therapy, nonadherent to primary OSA therapy, not using primary OSA therapy) as the fixed effects, and an unstructured covariance matrix will be used to model the correlation among repeated measures. The estimates of treatment difference versus placebo and their 95% confidence intervals will be presented.

MMRM will be carried out through the SAS procedure PROC MIXED, and all data collected under the estimand framework will be included for analysis.</td>
</tr>
</table>

	The primary analysis for the primary endpoints will be performed using data from the estimand framework handled with treatment policy strategy (intercurrent events of early discontinuation and use of protocol-prohibited medications, other intercurrent events). Supplementary analyses for the primary endpoints will be performed using data from the estimand framework handled with a hypothetical strategy (for intercurrent events of early discontinuation and use of protocol-prohibited medications) and a treatment policy strategy (other intercurrent events). A sensitivity analysis will be performed for primary endpoints using an analysis of covariance model (ANCOVA). This ANCOVA model will include change from baseline after treatment as the dependent variable, with the baseline value of the efficacy endpoint as a covariate, treatment and the randomization stratification factor (adherent to primary OSA therapy, nonadherent to primary OSA therapy, not using primary OSA therapy) as the fixed effects. The least-squares means, 95% confidence intervals and least-squares mean inter-group differences of the change from baseline to Week 12 in the MWT mean sleep latency and ESS total score will be presented. Key Secondary Endpoint: The key secondary endpoint is the improvement rate of PGIc at the end of the Week 12. The Cochran-Mantel-Haenszel method will be used for inter-group comparison, and the stratification factor is the use of primary OSA therapy at randomization (1. adherent to primary OSA therapy; 2. nonadherent to primary OSA therapy; 3. not using primary OSA therapy). Other Secondary Endpoints: For continuous variables of other secondary endpoints, the statistical analysis method is similar to the method used for the primary analysis of primary endpoints. For categorical variables, the CMH method will be used for inter-group comparison, and the stratification factor is the use of primary OSA therapy at randomization (1. adherent to primary OSA therapy; 2. nonadherent to primary OSA therapy; 3. not using primary OSA therapy). Multiplicity Adjustment: The primary endpoint of the study is the change from baseline to Week 12 in mean MWT sleep latency (determined from the first four 40-minute trials of the MWT) and ESS total score. The key secondary endpoint is percentage of participants with improved PGIc at Week 12. To address the multiplicity issue of multiple endpoints, the fixed hierarchical testing sequence will be used. Since they are co-primary endpoints, both have to be significant at the 0.05 level before the test can proceed to the key secondary endpoint. The testing sequence is outlined in below figure:  Statistical Analysis Plan: The detailed statistical analysis methods for this study are described in the Statistical Analysis Plan (SAP). The SAP includes details of statistical analysis plan, such as analysis populations, subgroup analysis, and summary of statistical strategies, etc..
End of Trial	The end of study is defined as the date of the last visit of the last participant unless the study is terminated due to any reason mentioned in the Section 4.5.1.

Schedule of Assessments and Events

Study period	Screening period	Baseline period	Treatment period [1]														Follow-up period [23-24]
			Titration period				Stabilization period										
Visit	V1[2-4]	V2	V3 [5]	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16/Early termination visit [22]	V17
Visit time (Week)		W-1	W1	W1	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W14
Visit time (Day)	D-60~D-8	D-7~D-1	D1	D3	D7	D14	D21	D28	D34&D35	D42	D49	D56	D63	D70	D77	D83&D84	D98
Visit window (days)	/	/	/	/	+2	+2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Clinic visit [6]	×	×	×		×	×			×			×				×	×
Phone contact				×			×	×		×	×		×	×	×		
Informed consent [7]	×																
Assignment of screening number	×																
Demographic and medical history (including OSA diagnosis and OSA therapy use) [8]	×	×															
Complete physical examination [9]	×															×	
Height (at screening only), weight	×	×				×			×			×				×	×
Vital signs [10]	×	×	×		×	×			×			×				×	×
12-lead ECG	×	×	×		×	×			×			×				×	×
Fasting blood chemistry	×	×				×			×			×				×	×
Urinalysis and hematology	×	×				×			×			×				×	×
Virus serology test [11]	×																

Study period	Screening period	Baseline period	Treatment period [1]														Follow-up period [23-24]
			Titration period				Stabilization period										
Visit	V1[2-4]	V2	V3 [5]	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16/Early termination visit [22]	V17
Visit time (Week)		W-1	W1	W1	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W14
Visit time (Day)	D-60~D-8	D-7~D-1	D1	D3	D7	D14	D21	D28	D34&D35	D42	D49	D56	D63	D70	D77	D83&D84	D98
Visit window (days)	/	/	/	/	+2	+2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Clinic visit [6]	×	×	×		×	×			×			×				×	×
Phone contact				×			×	×		×	×		×	×	×		
Urine drug screen [12]	×	×				×			×			×				×	
Blood/urine pregnancy test [13]	× (urine)	× (blood)														× (urine)	
Columbia Suicide Severity Rating Scale (C-SSRS)[14]	×	×			×	×			×			×				×	×

Study period		Screening period	Baseline period	Treatment period [1]														Follow-up period [23-24]
				Titration period				Stabilization period										
Visit		V1[2-4]	V2	V3[5]	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16/Early termination visit [22]	V17
Visit time (Week)			W-1	W1	W1	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W14
Visit time (Day)		D-60~D-8	D-7~D-1	D1	D3	D7	D14	D21	D28	D34&D35	D42	D49	D56	D63	D70	D77	D83&D84	D98
Visit window (days)		/	/	/	/	+2	+2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Clinic visit [6]		×	×	×		×	×			×			×				×	×
Phone contact					×			×	×		×	×		×	×	×		
24-hour ambulatory blood pressure [15]		×											×					
Efficacy Evaluation	Nocturnal polysomnography (PSG) [16] Maintenance of wakefulness test (MWT) [16]		×				×			×							×	
	Epworth Sleepiness Scale (ESS) [17]	×	×				×			×			×				×	
	Clinical Global Impression of Severity (CGIs) [18]		×															
	Patients' Global Impression of Change (PGIc) [18]						×			×			×				×	
	Clinical Global Impression of Change (CGIc) [18]						×			×			×				×	
	Functional Outcomes of Sleep Questionnaire (FOSQ-10) [19]		×				×			×			×				×	
	36-Item Short Form Health Survey, 2nd edition (SF-36v2) [19]		×							×			×				×	
Report and review of the use of primary OSA therapy		×	×			×	×	×	×	×	×	×	×	×	×	×	×	

Study period	Screening period	Baseline period	Treatment period [1]														Follow-up period [24-25]
			Titration period				Stabilization period										
Visit	V1[2-4]	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16/Early withdrawal visit [23]	V17
Visit time (Week) [5]		W-1	W1	W1	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W14
Visit time (Day) [6]	D-60~D-8	D-7~D-1	D1	D3	D7	D14	D21	D28	D34&D35	D42	D49	D56	D63	D70	D77	D83&D84	D98
Visit window (days)	/	/	/	/	+2	+2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Blood draws for PK [20]			×			×			×								
Evaluation of inclusion/exclusion criteria	×	×															
Randomization (assignment of randomization number)			×														
Dispense investigational drug and medication instructions [21]			×		×	×			×			×					
Return investigational drug/ compliance assessment					×	×			×			×				×	
Investigational drug administration prior to MWT						×			×							×	
Diary card distribution and filling instructions			×		×	×			×			×					
Diary return and review for completeness					×	×			×			×				×	
Adverse event [22]	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Concomitant medications and procedures	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Schedule next clinic visit or phone contact	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	
Light breakfast	×	×				×			×							×	
Light lunch		×				×			×							×	

Note:

1. The investigator may arrange unscheduled visits or tests based on the participant's condition.
2. The screening procedures can be completed at multiple visits; if a certain clinical laboratory test value is outside the laboratory reference range at screening, a re-test is allowed within 2 weeks, and the re-test results will be used as the basis for the evaluation of inclusion/exclusion criteria.
3. Participants may be allowed to rescreen if they have a likelihood of meeting the eligibility criteria as judged by the investigator and approved by the medical monitor. Participants who are approved for rescreening must be re-consented and reassigned a new participant number and must repeat all procedures at screening and baseline visits. A repeat PSG and MWT will not be required for certain participants being rescreened, if the results of previous PSG and MWT meet the current inclusion/exclusion criteria and there have been no changes to the medical history, concomitant medications, or primary OSA therapy that would likely affect the MWT, and the interval between the anticipated randomization date and the previous PSG/MWT assessment is less than 30 days.
4. A pre-existing medical condition/disease prior to the use of the investigational drug will be recorded as medical history. However, if the pre-existing medical condition worsens and meets the criteria for an adverse event (AE)/SAE after the use of the investigational drug, it should be recorded and reported as an AE/SAE.
5. The date of taking the first dose of investigational drug will be used as Day 1 to calculate the visit time point and window.
6. Participants should abstain from caffeine-containing foods or beverages and alcohol 10 hours prior to the clinic visit and ensure that blood samples for blood chemistry are collected under fasting condition.
7. Written informed consent must be obtained from the participant prior to the initiation of any study-related procedures.
8. Demographic information will include sex, age (date of birth [month-year]), and ethnic group. Demographic information will only be collected during the screening visit.

   The information for medical history will include prior medical conditions, prior medication and treatment procedures, concomitant medications and treatment procedures, allergies, tobacco/alcohol use, vaccination history, and reproductive status. Medical history should include documenting the diagnosis of OSA, any surgical intervention that was conducted in an attempt to treat OSA, and the frequency of use of a primary OSA therapy (positive airway pressure, oral pressure therapy, oral appliance, or upper airway stimulator), as well as any medications for the treatment of OSA symptoms. Medical history will be collected during screening visit, retrospective collection of prior medication (preferably covering 30 days prior to signing informed consent) is required. Any updates to the medical history will be assessed at the baseline visit (D-7 ~ D-1).
9. Complete physical examination will include a full examination of body systems covering general appearance, integument, lymph nodes, eyes, ears, nose and throat, head and neck, thoracic and lungs, heart, abdomen, back, spine and limbs, musculoskeletal and neurologic system, examination of genitourinary will not be required.
10. Vital signs will include blood pressure (systolic and diastolic), pulse rate, body temperature (it is recommended that the body temperature of the same participant be measured at the same measurement site), and respiratory rate. Vital signs will be obtained after the participant has been resting and seated for at least 5 minutes.
11. Virus serology test will be performed at screening visit and include testing of the following: hepatitis B virus surface antigen (HBsAg)/hepatitis B virus (HBV) DNA, hepatitis C virus (HCV) antibody/HCV RNA, human immunodeficiency virus antibody, treponema pallidum antibody. HBV DNA testing will be performed for any positive HBsAg test and HCV RNA testing will be performed for any positive HCV antibody test.
12. Urine drug screen for morphine, methamphetamine, ketamine, MDMA, tetrahydrocannabinolic acid will be performed at screening, baseline, Week 2, 5, 8, 12, or early termination visit.

13. Blood/urine pregnancy test will be performed for all female participants of childbearing potential. Pregnancy testing is not required for the following participants: female participants who have undergone surgical sterilization, who are postmenopausal (defined as aged greater than 50 years old with amenorrhoea of greater than 1 year), who have medically documented ovarian failure (defined as aged below 50 years old with serum estradiol and FSH levels within the institutional postmenopausal range and a negative serum or urine β-HCG). Blood samples will be collected for serum β-HCG testing at baseline, and urine samples should be collected for β-HCG testing at other visits. A confirmatory testing for serum beta-HCG should be performed on all positive urine beta-hCG testing.

14. C-SSRS is required to be assessed at screening, baseline, Week 1, 2, 5, 8, and 12 visits, and follow-up or early withdrawal visit.

15. Participants will undergo 24-hour ambulatory blood pressure monitoring at screening and Week 8 visit. At Week 8 visit, participant will undergo 24-hour ambulatory blood pressure monitoring after administration of the investigational drug, and blood pressure reading will be obtained over a 24-hour period till next day the same time.

16. A PSG followed by an MWT will be performed at baseline, Week 2, 5, and 12 visits (or at early termination visit if the participant is willing and able to take the investigational drug for the assessment). The PSG and MWT should be performed following procedures mentioned in Section 6. A repeat PSG and MWT will not be required for rescreened participants if fulfilling below criteria: previous PSG and MWT in the study meet the current inclusion/exclusion criteria and there have been no changes to the medical history, concomitant medications, or primary OSA therapy that would likely affect the MWT, and the interval between the anticipated randomization date and the previous PSG/MWT assessment is less than 30 days.

17. The ESS will be assessed at screening, baseline, Week 2, 5, 8 and 12 and early termination visit. At the baseline, Week 2, 5, and 12 visits, the ESS should be administered between the first and the second trial of the MWT.

18. The CGIs will be assessed by the investigator once at the baseline visit, between the first and the second trial of the MWT. The PGIc and CGIc will be assessed at Week 2, 5, 8, and 12 visits or the early termination visit. Thereinto, the PGIc and CGIc assessments at Week 2, 5, and 12 visits are required to be performed between the first and the second trial of the MWT.

19. The FOSQ-10 will be administered at baseline, Week 2, 5, 8, and 12 visits or early termination visit. Thereinto, the FOSQ-10 assessments at baseline, Week 2, 5, and 12 visits should be performed between the first and the second trial of the MWT. The SF-36v2 will be administered at baseline, Week 5, 8, 12 visits or early termination visit. Thereinto, the SF-36v2 assessments at baseline, Week 5 and 12 visit should be performed between the first and the second trial of the MWT.

20. Blood samples collection for PK assessment is required at the following timepoints respectively: one sample will be collected on Day 1 within 1 hour before dosing, and one sample within 1-4 hours after dosing on Day 1; one sample will be collected on Week 2 (on Day 14) within 1 hour before dosing, and one sample within 1-4 hours after dosing on Day 14; one sample will be collected at Week 5 (on Day 35) within 1 hour before dosing, and one sample within 8-12 hours after dosing on Day 35.

21. On Day 1 visit, participants will be instructed to take their investigational drug on that day (Day 1). For other visits, participants will be instructed not to begin taking their newly dispensed investigational drugs until the next day of the visits.

22. An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered related to study drug or procedure. All AEs whether observed by the investigator, reported by the study participants, determined from laboratory findings, ECG testing or other safety measures, will be recorded after signing ICF.

23. For study participants who receive at least one dose of investigational drug but withdraw prematurely from the study, an early termination clinic visit is required within 7 days of withdrawal. If participants are willing and able to take investigational drug until the day of early termination clinic visit, an overnight stay at the investigational site for nocturnal PSG followed by a MWT and other assessments are required for the early termination visit.

24. At the conclusion of the double-blind treatment period, participants will return to investigational sites for a safety follow-up assessments 2 weeks (± 3 days) after administration of the final dose of investigational drug.

25. For any untoward medical occurrences that are clinically significant as judged by the investigator, they should be followed to resolution or stabilization.

List of Supplemental Tables

Table S1. Analysis of Participants with MWT Mean Sleep Latency above the lower limit of Normal Range (FAS population)

Visit **Parameters**	**Placebo** **(N=100)**	**Solriamfetol** **(N=101)**
Baseline		
n (missing)	100 (0)	101 (0)
Participants with MWTSLAVG ≥ 19.4 min (percentage)	16 (16.0)	15 (14.9)
Week 2 (Observed Value)		
n (missing)	94 (6)	97 (4)
Participants with MWTSLAVG ≥ 19.4 min (percentage)	18 (19.1)	50 (51.5)
P value vs. Placebo		<.0001
Week 5 (Observed Value)		
n (missing)	95 (5)	99 (2)
Participants with MWTSLAVG ≥ 19.4 min (percentage)	12 (12.6)	50 (50.5)
P value vs. Placebo		<.0001
Week 12 (Observed Value)		
n (missing)	95 (5)	95 (6)
Participants with MWTSLAVG ≥ 19.4 min (percentage)	20 (21.1)	58 (61.1)
P value vs. Placebo		<.0001

Note：N = number of study participants within each group of analysis population; n = number of study participants with non-missing values within each group; MWT = Maintenance of Wakefulness Test.
MWT Mean Sleep Latency (MWTSLAVG): defined as the average of the first four MWT trial's measurements, if three or four of them are non-missing.
Percentage was calculated as numbers of participants with MWTSLAVG ≥19.4 min divided by n, then multiplied by 100%.
P value was tested by Chi-Square or Fisher Exact test.

Table S2. Analysis of Participants with ESS total score above the lower limit of Normal Range (FAS population)

Visit Parameters	Placebo (N=100)	Solriamfetol (N=101)
Baseline		
n (missing)	100 (0)	101 (0)
Participants with ESS Total Score ≤10 (percentage)	1 (1.0)	5 (5.0)
Week 2 (Observed Value)		
n (missing)	98 (2)	101 (0)
Participants with ESS Total Score ≤10 (percentage)	45 (45.9)	56 (55.4)
P value vs. Placebo		0.1790
Week 5 (Observed Value)		
n (missing)	96 (4)	99 (2)
Participants with ESS Total Score ≤10 (percentage)	59 (61.5)	68 (68.7)
P value vs. Placebo		0.2896
Week 8 (Observed Value)		
n (missing)	96 (4)	97 (4)
Participants with ESS Total Score ≤10 (percentage)	63 (65.6)	74 (76.3)
P value vs. Placebo		0.1027
Week 12 (Observed Value)		
n (missing)	96 (4)	97 (4)
Participants with ESS Total Score ≤10 (percentage)	69 (71.9)	78 (80.4)
P value vs. Placebo		0.1640

Note：N = number of study participants within each group of analysis population; n = number of study participants with non-missing values within each group; ESS=Epworth Sleepiness Scale.
Percentage was calculated as numbers of participants with ESS Total Score ≤10 divided by n, then multiplied by 100%.
P value was tested by Chi-Square or Fisher Exact test.

Table S3. Correlation analysis between MWT mean sleep latency and the ESS total score (FAS population)

Visit Treatment	Pearson correlation coefficient	*P* value
Baseline	-0.205	0.0034
Post-Baseline	-0.288	<.0001
Week 2		
Placebo	-0.227	0.0280
Solriamfetol	-0.247	0.0147
Week 5		
Placebo	-0.328	0.0012
Solriamfetol	-0.279	0.0052
Week 12		
Placebo	-0.254	0.0130
Solriamfetol	-0.330	0.0011

Table S4. Overview of supplementary analysis results of co-primary and key secondary efficacy endpoints at Week 12 based on "Per Protocol Population"

Visit	**Placebo (N = 89)**	**Solriamfetol (N = 86)**
MWT change from baseline to Week 12		
Number of cases (missing)	89 (0)	86 (0)
LS mean (SE)	-0.369 (1.04)	11.671 (1.06)
LS mean difference (95% CI)		12.040 (9.18, 14.90)
P value of comparison between groups		<0.0001
ESS change from baseline to Week 12		
Number of cases (missing)	89 (0)	86 (0)
LS mean (SE)	-5.8 (0.45)	-7.5 (0.46)
LS mean difference (95% CI)		-1.7 (-3.0, -0.5)
P value of comparison between groups		0.0067
PGI-C improvement rate at Week 12		
Nx	89	86
Improvement rate, n (%)[a]	71 (79.8)	80 (93.0)
Risk difference (95% CI) vs. Placebo[b]		15.4 (5.0, 25.7)
P value vs. Placebo[b]		.0112

CI, Confidence interval; ESS, Epworth Sleepiness Scale; MWT, Wakefulness maintenance test; LS, Least Square; Nx, the number of study participants with no missing values; PGI-C, Patient global impression of change; SE, standard error

[a] The percentage is calculated as n/Nx*100%.

[b] The comparison between the groups was based on the Cochran-Mantel-Haenszel method using randomization factor as the stratification factor, and the confidence intervals were calculated based on the Miettinen-Nurminen method.

Table S5. Overview of supplementary analysis results of co-primary and key secondary efficacy endpoints at Week 12 using data from the estimand framework handled with a hypothetical strategy and a treatment policy strategy[a] (FAS)

Visit	Placebo (N = 100)	Solriamfetol (N = 101)
MWT change from baseline to Week 12		
Number of cases	99	100
LS mean (SE)	-0.049 (1.01)	11.519 (1.00)
LS mean difference (95% CI)		11.568 (8.84, 14.29)
P value of comparison between groups		<0.0001
ESS change from baseline to Week 12		
Number of cases	100	101
LS mean (SE)	-6.0 (0.42)	-7.8 (0.42)
LS mean difference (95% CI)		-1.8 (-2.9, -0.7)
P value of comparison between groups		0.0019
PGI-C improvement rate at Week 12		
Nx	100	101
Improvement rate, n (%)[b]	79 (79.5)	94 (93.0)
Risk difference (95% CI) vs. Placebo[c]		15.1 (4.9, 25.2)
P value vs. Placebo[c]		.0133

CI, Confidence interval; ESS, Epworth Sleepiness Scale; FAS, Full analysis set; MWT, Wakefulness maintenance test; LS, Least Square; Nx, the number of study participants with no missing values; PGI-C, Patient global impression of change; SE, standard error

[a] Supplementary analyses were performed using data from the estimand framework handled with a hypothetical strategy (for intercurrent events of early discontinuation and use of protocol-prohibited medications) and a treatment policy strategy (other intercurrent events), missing data were imputed using multiple imputation approach.

[b] The percentage is calculated as n/Nx*100%.

[c] The comparison between the groups was based on the Cochran-Mantel-Haenszel method using randomization factor as the stratification factor, and the confidence intervals were calculated based on the Miettinen-Nurminen method.

Table S6. Overview of sensitivity analysis results of co-primary and key secondary efficacy endpoints at Week 12 (FAS)

Visit	Placebo (N = 100)	Solriamfetol (N = 101)
MWT change from baseline to Week 12[a]		
Number of cases	98	101
LS mean (SE)	0.084 (1.01)	11.778 (1.00)
LS mean difference (95% CI)		11.693 (8.98, 14.41)
P value of comparison between groups		<0.0001
ESS change from baseline to Week 12[a]		
Number of cases	100	101
LS mean (SE)	-5.9 (0.42)	-7.8 (0.42)
LS mean difference (95% CI)		-1.9 (-3.0, -0.8)
P value of comparison between groups		0.0012
PGI-C improvement rate at Week 12[b]		
Nx	100	101
Improvement rate, n (%)[c]	77 (77.0)	90 (89.1)
Risk difference (95% CI) vs. Placebo[d]		13.2 (2.7, 23.7)
P value vs. Placebo[d]		.0221

CI, Confidence interval; ESS, Epworth Sleepiness Scale; FAS, Full analysis set; MWT, Wakefulness maintenance test; LS, Least Square; Nx, the number of study participants with no missing values; PGI-C, Patient global impression of change; SE, standard error

[a] Sensitivity analyses for the co-primary endpoints were performed using an analysis of covariance (ANCOVA) model, with effect for treatment as a fixed effect and baseline value of the efficacy endpoint as the covariate. Missing data were imputed using last observation carried forward (LOCF).

[b] Sensitivity analysis for the key secondary endpint was performed using data from the estimand framework handled with a "composite variable strategy" (for intercurrent events of early discontinuation and use of protocol-prohibited medications) and a treatment policy strategy (other intercurrent events), missing data were imputed using multiple imputation approach.

[c] The percentage is calculated as n/Nx*100%.

[d] The comparison between the groups was based on the Cochran-Mantel-Haenszel method using randomization factor as the stratification factor, and the confidence intervals were calculated based on the Miettinen-Nurminen method.

Table S7. Summary of body weight from baseline to Week 12.

	Placebo (N = 102)	Solriamfetol (N = 102)
Baseline		
n (missing)	102 (0)	102 (0)
Mean (SD)	79.62 (13.87)	80.32 (12.51)
Week 2		
n (missing)	100 (2)	102 (0)
Mean (SD)	79.49 (14.00)	80.02 (12.56)
Week 5		
n (missing)	97 (5)	102 (0)
Mean (SD)	79.43 (14.17)	79.59 (12.50)
Week 8		
n (missing)	96 (6)	97 (5)
Mean (SD)	79.10 (14.07)	79.98 (12.42)
Week 12		
n (missing)	96 (6)	97 (5)
Mean (SD)	79.36 (14.07)	79.91 (12.47)

SD: Standard deviation

Table S8. Summary of regular vital sign measures at Baseline and Week 12 (Safety Population)

	Systolic Blood Pressure		Diasolic Blood Pressure		Pulse Rate	
	Placebo (N = 102)	**Solriamfetol (N = 102)**	**Placebo (N = 102)**	**Solriamfetol (N = 102)**	**Placebo (N = 102)**	**Solriamfetol (N = 102)**
Baseline						
n (missing)	102 (0)	102 (0)	102 (0)	102 (0)	102 (0)	102 (0)
Mean (SD)	120.7 (9.89)	120.8 (8.54)	80.5 (7.08)	80.5 (7.06)	75.2 (9.46)	76.9 (10.17)
Week 12						
n (missing)	96 (6)	97 (5)	96 (6)	97 (5)	96 (6)	97 (5)
Mean (SD)	120.9 (9.85)	123.5 (10.81)	79.3 (6.97)	79.9 (6.70)	79.7 (9.38)	81.8 (10.58)
Change from Baseline to Week 12						
n (missing)	96 (6)	97 (5)	96 (6)	97 (5)	96 (6)	97 (5)
Mean (SD)	0.1 (9.55)	2.7 (10.59)	-1.1 (7.54)	-0.6 (8.62)	4.0 (10.94)	5.3 (9.60)

SD: Standard deviation

Table S9. Summary of 24 Hours Ambulatory Blood Pressure Monitoring at Screening and Week 8 (Safety Population)

	Systolic Blood Pressure (mmHg)		Diasolic Blood Pressure (mmHg)		Pulse Rate (beats/min)	
	Placebo (N = 102)	Solriamfetol (N = 102)	Placebo (N = 102)	Solriamfetol (N = 102)	Placebo (N = 102)	Solriamfetol (N = 102)
Overall 24 hours						
Screening						
n (missing)	102 (0)	102 (0)	102 (0)	102 (0)	93 (9)	93 (9)
Mean (SD)	121.60 (10.44)	123.81 (10.81)	76.24 (7.73)	77.83 (6.96)	76.56 (9.61)	78.80 (10.81)
Week 8						
n (missing)	94 (8)	95 (7)	94 (8)	95 (7)	87 (15)	86 (16)
Mean (SD)	122.62 (10.83)	124.98 (11.70)	76.24 (7.20)	78.45 (7.58)	77.21 (8.36)	81.80 (10.05)
Change from Screening to Week 8						
n (missing)	94 (8)	95 (7)	94 (8)	95 (7)	86 (16)	84 (18)
Mean (SD)	1.06 (9.93)	1.03 (10.28)	0.09 (6.48)	0.54 (6.38)	0.42 (7.42)	2.91 (8.10)
Daytime period						
Screening						
n (missing)	102 (0)	102 (0)	102 (0)	102 (0)	89 (13)	87 (15)
Mean (SD)	125.49 (10.87)	127.33 (10.62)	79.24 (8.06)	80.48 (7.37)	79.92 (10.28)	82.86 (11.27)
Week 8						
n (missing)	94 (8)	95 (7)	94 (8)	95 (7)	84 (18)	84 (18)
Mean (SD)	126.13 (11.52)	128.94 (12.25)	79.17 (7.92)	81.48 (8.20)	80.65 (8.69)	86.25 (10.57)
Change from Screening to Week 8						
n (missing)	94 (8)	95 (7)	94 (8)	95 (7)	82 (20)	82 (20)
Mean (SD)	0.71 (11.71)	1.56 (11.30)	0.02 (7.27)	0.97 (7.43)	0.62 (7.86)	3.33 (8.81)
Nighttime period						
Screening						
n (missing)	102 (0)	102 (0)	102 (0)	102 (0)	89 (13)	87 (15)
Mean (SD)	113.73 (11.51)	116.31 (12.97)	69.89 (8.67)	72.08 (8.01)	67.92 (10.49)	68.32 (9.74)
Week 8						
n (missing)	94 (8)	95 (7)	94 (8)	95 (7)	84 (18)	82 (20)
Mean (SD)	114.79 (12.01)	117.68 (13.65)	70.45 (8.38)	72.58 (8.61)	68.99 (8.92)	70.78 (10.66)
Change from Screening to Week 8						
n (missing)	94 (8)	95 (7)	94 (8)	95 (7)	82 (20)	82 (20)
Mean (SD)	1.09 (10.75)	1.08 (12.51)	0.64 (7.70)	0.35 (7.82)	0.89 (9.75)	2.15 (9.58)

SD: Standard deviation

Table S10. Ethical approval numbers for each study site

Study site number	Ethical approval number for protocol V1	Ethical approval number for protocol V2
001	(2023) Ethics Review No. 22	(2023) Ethics Review No. 22-1
002	(Drug/Device) Ethics Review (2023) No. 35	(Drug/Device) Ethics Review (2023) No. X-52
004	SYL-2023-034-02	SYL-2023-034-03
005	2023177	2023230
006	KHLL-SOP/017/01.3	KHLL-SOP/017/01.4
007	2023-065-(1)	2023-065-(2)
008	YW2023-040-01	YW2023-040-02
010	2023 Clinical Review No. 655	2023 Clinical Review No. 655 Amendment 1
011	23Y135-001	23Y135-002
012	Clinical Drug Review [2023] No. 020	Clinical Drug Review [2023] No. 020-Amendment 1
013	[2023] Ethics Review Drug No. 016	[2023] Ethics Review Drug No. 016-1
015	[2023] YW No. 053	[2023] KS No. 115
016	HXSY-EC-2023032	HXSY-EC-2023032
017	EC-2023-046（YW)-02	EC-2023-046（YW)-03
019	Clinical Drug Review [2023] No. 50	Clinical Drug Review [2023] No. 50-01
020	Ethics Review 2023 Drug No. 023	Ethics Review 2023 Drug No. 023-YJ02
021	JD-LS2023035-I01	JD-LS2023035-A01
022	Ethics Review GCP No. 202305117	Ethics Review GCP No. 202305117-2
024	YW2023-030-02	YW2023-030-03
025	[2023] Ethics Review No. 70	[2023] Ethics Review No. K55
028	DXYEC-YWPJ-2023 No. 47	YWPJ-2023 No. 129
029	YW-2023-027-01	YW-2023-027-02
030	[2023] Clinical Review No. 567	[2023] Clinical Review No. 567-01
031	(2023) Ethics Review No. 228	(2023) Ethics Review No. 320
032	Drug (2023) Ethics Review No. 003	Drug (2023) Ethics Review No. 012
033	2023 Ethics Review (CY2023-086-01)	2023 Ethics Review (CY2023-086-03)