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Protocol Title: Solriamfetol's Effect on Cognitive Health in Apnea Participants During a Randomized Placebo-controlled Study (SHARP): a 5-Week Double-blind, Placebo-controlled, Randomized, Crossover, Multicenter Study of Solriamfetol in Improving Cognitive Function in Participants With Excessive Daytime Sleepiness Associated With Obstructive Sleep Apnea Plus Impaired Cognitive Function

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TITLE PAGE

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Protocol Number: JZP110-405

Amendment 1: Aug 12, 2022

Compound: Sunosi® (solriamfetol)

Brief Title: Solriamfetol's Effect on Cognitive Health in Apnea Participants During a Randomized Placebo-controlled Study (SHARP)

Study Phase: 4

[redacted]

[redacted]

[redacted]

APPROVAL SIGNATURES

PROTOCOL NUMBER: JZP110-405

PROTOCOL TITLE: Solriamfetol's Effect on Cognitive Health in Apnea Participants During a Randomized Placebo controlled Study (SHARP): a 5 Week Double blind, Placebo controlled, Randomized, Crossover, Multicenter Study of Solriamfetol in Improving Cognitive Function in Participants With Excessive Daytime Sleepiness Associated With Obstructive Sleep Apnea Plus Impaired Cognitive Function

PROTOCOL VERSION: Amendment 1 (V2.0)

PROTOCOL DATE: August 12, 2022

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

STUDY CONTACT AND DETAILS

SPONSORED BY: Axsome Therapeutics, Inc.

[redacted]

INVESTIGATOR: Multi-center. A list of sites will be housed in the Trial Master File.

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1.1. Synopsis

Protocol Title: Solriamfetol's Effect on Cognitive Health in Apnea Participants During a Randomized Placebo-controlled Study (SHARP): a 5-Week Double-blind, Placebo-controlled, Randomized, Crossover, Multicenter Study of Solriamfetol in Improving Cognitive Function in Participants With Excessive Daytime Sleepiness Associated With Obstructive Sleep Apnea Plus Impaired Cognitive Function

Brief Title: Solriamfetol's Effect on Cognitive Health in Apnea Participants During a Randomized Placebo-controlled Study (SHARP)

Rationale: The purpose of study JZP110-405 is to determine whether solriamfetol is effective at improving cognitive function in participants with excessive daytime sleepiness (EDS) associated with obstructive sleep apnea (OSA). The need for this proposed phase 4 study was identified following patient and physician input. An important element that patients consider when evaluating whether to start a treatment is how the treatment will affect their ability to work. The primary statistical hypothesis for this study is to show whether solriamfetol has a significantly improved effect versus placebo on the primary endpoint of changes in Digit Symbol Substitution Test (DSST) scores after 2 weeks of treatment. Demonstrating that solriamfetol improves both objective and subjective cognitive function would address a major unmet need for patients. In addition, characterizing the duration of effect across the 8-hour postdose period is also of interest.

Objectives and Endpoints:

Table 1: Objectives and Endpoints

Objectives	Estimands and Endpoints
Primary Objective	
To **evaluate the efficacy** of solriamfetol on cognitive function in adult participants with EDS associated with OSA plus impaired cognitive functioning	The primary estimand is defined by the following: • Population: Participants aged 18 to 65, with EDS associated with OSA and impaired cognitive function in the mITT set, defined as: all randomized participants with at least 1 dose of study drug and 1 postdose assessment of DSST RBANS • Variable: Change **from the average** of the DSST RBANS scores at Baseline (Visit 3) **to the average** of the postdose DSST RBANS scores (hours 2, 4, 6, and 8) at the end of each double-blind treatment period • Intercurrent events: – The participant's DSST RBANS data are not collected if the participant discontinued the treatment (while on treatment policy strategy) – Missing assessments after discontinuation of treatment due to AE, lack of efficacy, or any other reasons will not be imputed for primary analysis. • Population level summary: Difference in mean DSST RBANS **from the average** of the scores at Baseline (Visit 3) **to the average** of the postdose scores (at Visit 5 and Visit 8) between solriamfetol and placebo

Objectives	Estimands and Endpoints
Secondary Objectives	**Secondary Estimands**
To **further evaluate the efficacy** of solriamfetol on cognitive function in adult participants with EDS associated with OSA plus impaired cognitive functioning	<u>The first estimand for secondary objective evaluating efficacy is defined by the following:</u> • Population: Participants aged 18 to 65, with EDS associated with OSA and impaired cognitive function in the mITT analysis set, defined as: all randomized participants with at least 1 dose of study drug and 1 postdose assessment of DSST RBANS • Variable: Change from Baseline (Visit 3) to the end of each double-blind treatment period (Visit 5 and Visit 8) in overall score in BC-CCI • Intercurrent events: – The participant's British Columbia-Cognitive Complaints Inventory (BC-CCI) data are not collected if the participant discontinued the treatment (while on treatment policy strategy) – Missing assessments after discontinuation of treatment due to AE, lack of efficacy, or any other reasons will not be imputed • Population level summary: Difference in mean overall BC-CCI score from Baseline (Visit 3) to the end of double-blind treatment period (Visit 5 and Visit 8) between solriamfetol and placebo <u>The second estimand for secondary objective evaluating efficacy is defined by the following:</u> • Population: Participants aged 18 to 65, with EDS associated with OSA and impaired cognitive function in the mITT analysis set, defined as: all randomized participants with at least 1 dose of study drug and 1 postdose assessment of DSST RBANS • Variable: Categorical change from Baseline (Visit 3) to the end of each double-blind treatment period (Visit 5 and Visit 8) in each category of the BC-CCI • Intercurrent events: – The participant's BC-CCI data are not collected if the participant discontinued the treatment (while on treatment policy strategy) – Missing assessments after discontinuation of treatment due to AE, lack of efficacy, or any other reasons will not be imputed • Population level summary: Percentage of patients with an at least 1 category improvement in the BC-CCI score from Baseline (Visit 3) to the end of double-blind treatment period (Visit 5 and Visit 8) in each treatment group

Objectives	Estimands and Endpoints
To **evaluate the effect** of solriamfetol on cognitive function at individual post-dose timepoints in adult participants with EDS associated with OSA plus impaired cognitive functioning	The estimand for this secondary objective to evaluate the effect on cognitive function at individual post-dose timepoints is defined by the following: • Population: Participants aged 18 to 65, with EDS associated with OSA and impaired cognitive function in the mITT analysis set, defined as: all randomized participants with at least 1 dose of study drug and 1 postdose assessment of DSST RBANS • Variable(s): Change **from each** of the 2-, 4-, 6-, and 8-hour DSST RBANS sores at Baseline (Visit 3) **to each** of the corresponding 2-, 4-, 6-, and 8-hour postdose DSST RBANS scores at the end of each double-blind treatment period (Visit 5 and Visit 8) • Intercurrent events: – The participant's DSST RBANS data are not collected if the participant discontinued the treatment (while on treatment policy strategy) – Missing assessments after discontinuation of treatment due to AE, lack of efficacy, or any other reasons will not be imputed • Population level summary: Difference in mean DSST RBANS **from each** of the 2-, 4-, 6-, and 8-hour DSST RBANS scores at Baseline (Visit 3) **to each** of the corresponding 2-, 4-, 6-, and 8-hour postdose (at Visit 5 and Visit 8) DSST RBANS scores between solriamfetol and placebo

Objectives	Estimands and Endpoints
To **evaluate the efficacy** of solriamfetol on patient-reported global impression of concentration, memory, and thinking skills in adult participants with EDS associated with OSA plus impaired cognitive functioning	<u>The first estimand for this secondary objective evaluating efficacy is defined by the following:</u> • Population: Participants aged 18 to 65, with EDS associated with OSA and impaired cognitive function in the mITT analysis set, defined as: all randomized participants with at least 1 dose of study drug and 1 postdose assessment of DSST RBANS • Variable: Change from Baseline (Visit 3) to the end of each double-blind treatment period (Visit 5 and Visit 8) in Patient Global Impression of Severity (PGI-S) score • Intercurrent events: – The participant's PGI-S data are not collected if the participant discontinued the treatment (while on treatment policy strategy) – Missing assessments after discontinuation of treatment due to AE, lack of efficacy, or any other reasons will not be imputed • Population level summary: Difference in mean PGI-S score from Baseline (Visit 3) to the end of double-blind treatment period (Visit 5 and Visit 8) between solriamfetol and placebo <u>The second estimand for this secondary objective evaluating efficacy is defined by the following:</u> • Population: Participants aged 18 to 65, with EDS associated with OSA and impaired cognitive function in the mITT analysis set, defined as: all randomized participants with at least 1 dose of study drug and 1 postdose assessment of DSST RBANS • Variable: Categorical improvement from baseline on the PGI-S to the end of each double-blind treatment period (Visit 5 and Visit 8) • Intercurrent events: – The participant's PGI-S data are not collected if the participant discontinued the treatment (while on treatment policy strategy) – Missing assessments after discontinuation of treatment due to AE, lack of efficacy, or any other reasons will not be imputed • Population level summary: Percentage of participants reporting an at least 1 category improvement from baseline on the PGI-S to the end of each double-blind treatment period (Visit 5 and Visit 8) in each treatment group

Objectives	Estimands and Endpoints
To **evaluate the efficacy** of solriamfetol on improving EDS in adult participants with EDS associated with OSA plus impaired cognitive functioning	The estimand for this secondary objective evaluating efficacy is defined by the following: • Population: Participants aged 18 to 65, with EDS associated with OSA and impaired cognitive function in the mITT analysis set, defined as: all randomized participants with at least 1 dose of study drug and 1 postdose assessment of DSST RBANS • Variable: Change from Baseline (Visit 3) to the end of each double-blind treatment period (Visit 5 and Visit 8) in ESS score • Intercurrent events: – The participant's ESS data are not collected if the participant discontinued the treatment (while on treatment policy strategy) – Missing assessments after discontinuation of treatment due to AE, lack of efficacy, or any other reasons will not be imputed • Population level summary: Difference in mean ESS score from Baseline (Visit 3) to the end of double-blind treatment period (Visit 5 and Visit 8) between solriamfetol and placebo
To **evaluate the safety and tolerability** of solriamfetol administered once daily in adult participants with EDS associated with OSA plus impaired cognitive functioning	Safety and tolerability evaluations will be determined by the occurrence of and/or changes in: • Incidence and severity treatment emergent adverse events (TEAEs) • Vital signs • Columbia-Suicide Severity Rating Scale (C-SSRS)
Exploratory Objectives	**Exploratory Endpoints**
To **evaluate the association** between the improvement in EDS and improvement in cognitive function following solriamfetol treatment in adult participants with EDS associated with OSA plus impaired cognitive functioning	The exploratory endpoints for the exploratory objective of evaluating the association between the improvement in EDS and improvement in cognitive function are: • The correlation between the change from Baseline (Visit 3) at the end of each double-blind treatment period (Visit 5 and Visit 8) in ESS and DSST RBANS score • The correlation between the change from Baseline (Visit 3) at the end of each double-blind treatment period (Visit 5 and Visit 8) in ESS and BC-CCI score • The correlation between the change from Baseline (Visit 3) at the end of each double-blind treatment period (Visit 5 and Visit 8) in ESS and PGI-S

Abbreviations: AE = adverse event; BC-CCI = British Columbia-Cognitive Complaints Inventory; DSST RBANS = Digit Symbol Substitution Test Repeatable Battery for the Assessment of Neuropsychological Status; EDS = excessive daytime sleepiness; ESS = Epworth Sleepiness Scale; mITT = modified Intent-to-Treat; OSA = obstructive sleep apnea; PGI-S = Patients Global Impression of Severity; TEAE = treatment-emergent adverse event.

Brief Summary:

This is a prospective, multicenter, two-arm, randomized, double-blind, placebo-controlled interventional crossover study comparing solriamfetol 150 mg to placebo on tests of cognitive function in participants with EDS due to OSA. Participants will be in the study for approximately 8 weeks, including 2 weeks of solriamfetol treatment and 2 weeks of placebo treatment. Each participant will receive both double-blind treatment conditions, but will be randomized to undergo the conditions in a different sequence.

Cognitive function in this study will be assessed by the DSST (an objective test) and the British Columbia-Cognitive Complaints Inventory (BC-CCI) (a subjective test). The DSST has been used for decades to measure cognitive function. The BC-CCI was developed to measure cognitive complaints in individuals with major depressive disorder (MDD), but has also been used to measure cognitive deficits in individuals with poor sleep quality. Therefore, each test should be able to detect changes in cognitive function.

The primary endpoint is the change from the average of the DSST RBANS scores at Baseline to the average of the postdose DSST RBANS scores at the end of each double-blind treatment period. The secondary endpoints include: the change in overall score and categorical change from Baseline at the end of each double-blind treatment period in BC-CCI; the change from each of the 2-, 4-, 6-, and 8-hour DSST RBANS scores at Baseline to each of the corresponding 2-, 4-, 6-, and 8-hour postdose DSST RBANS scores at the end of each double-blind treatment period; change in overall score and categorical change from Baseline at the end of each double-blind treatment period in the PGI-S; and change in overall score from Baseline to the end of each double-blind treatment period in ESS.

Overall Design:

This is a phase 4, multicenter, randomized, double-blind, placebo-controlled, crossover study to evaluate the efficacy of solriamfetol in improving cognitive function in adult participants with EDS associated with OSA plus impaired cognitive function.

Table 2: Overall Study Design

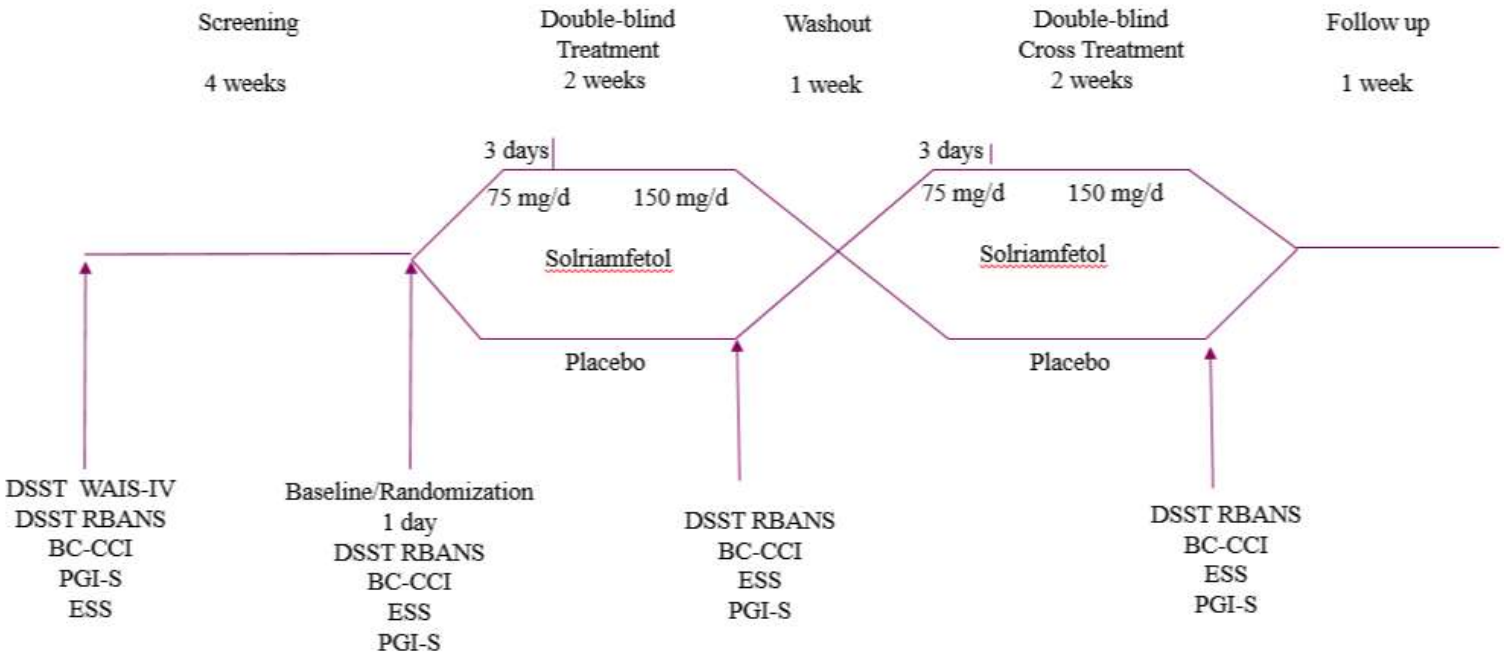
Overall Design	
Study Phase	4
Clinical Indication	EDS associated with OSA
Study Type	Interventional
Type of Design	Randomized, crossover, multicenter study
Type of Control	Placebo
Study Blinding	Double-blind
Population	Participants with a diagnosis of OSA according to the ICSD-3, with sleepiness as demonstrated by subjective criteria (ESS), and cognitive impairment based on a combination of subjective (BC-CCI) and objective (DSST WAIS) measures.

Overall Design	
	Participants must also meet 1 of the following criteria: 1) have stable, current use of a PAP machine with downloadable history as primary OSA therapy on at least 5 nights/week for 1 month prior to Baseline (with or without prior OSA surgery); 2) no current OSA therapy use for at least 1 month but with a history of prior PAP for at least 1 month with at least 1 documented adjustment attempting to optimize therapy (with or without prior OSA surgery); or 3) have undergone OSA surgery but continue to experience residual sleepiness (with or without current PAP use).
Number of Participants	Approximately 116 participants are planned for enrollment.
Duration of Participation	Each participant will participate in the study from the time they sign the ICF through the end of the study procedures. Each participant will be enrolled for approximately 8 weeks.
Number of Treatment Arms	2
Treatment Groups	1) Solriamfetol 2) Placebo
Treatment Sequences	1) Solriamfetol followed by placebo 2) Placebo followed by solriamfetol

Abbreviations: BC-CCI = British Columbia-Cognitive Complaints Inventory; DSST = Digit Symbol Substitution Test; EDS = excessive daytime sleepiness; ESS = Epworth Sleepiness Scale; ICF = informed consent form; ICSD-3 = International Classification of Sleep Disorders, Third Edition; OSA = obstructive sleep apnea; PAP = positive airway pressure; WAIS = Wechsler Adult Intelligence Scale.

1.2. Schema

Figure 1: Study Schema



Abbreviations: BC-CCI = British Columbia-Cognitive Complaints Inventory; d = day; DSST = Digit Symbol Substitution Test; ESS = Epworth Sleepiness Scale; PGI-S = Patients Global Impression of Severity; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; DSST WAIS-IV = Digit Symbol Substitution Test Wechsler Adult Intelligence Scale, Fourth Edition.

1.3. Schedule of Assessments

Table 3: Schedule of Assessments

Procedure	Screening		Baseline / Random-ization	Double-blind Treatment Period (Treatment Period 1)		Washout Period	Double-blind Crossover Treatment Period (Treatment Period 2) (First Dose Taken Day 21 to 24)		SFU or ED	Notes For ED participants, follow the SFU procedures. Participants will complete either SFU or ED.
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**The same procedures are conducted for SFU and ED visits.**
Study Days Relative to Randomization (Site Visits) or to Next Visit (Phone Calls)	**-28 to -14**	**3 days before Visit 3**	**0**	**3 days before Visit 5**	**13 to 16**	**20 to 23 (day before first dose of crossover period)**	**3 days before Visit 8**	**34 to 37**	**SFU: 4 to 10 days after last dose (Visit 8) ED: ≥4 days after last dose**	**Study visits can fall within the day ranges listed here, but all assessments must occur on the same day. Phone contact columns (for Visits 2, 4, 6, 7) are in gray.**
Site Visit	X		X		X			X	X	Visit 9 can be virtual or onsite based on local regulations and/or site preference.
Phone Contact		X		X		X	X		X	
Informed Consent	X									See Section 8.1.1 and Section 10.1.3
Review Inclusion/Exclusion Criteria	X		X							See Section 5
Demographics	X									
Height	X									See Section 8.4.1
Weight	X		X		X			X		BMI should be determined at Visits 1 and 3. Each calculation can use Screening height. See Section 8.4.1
Medical History	X		X							See Section 8.1.3
Adverse Events					X			X	X	See Section 8.5
Sleep Habits Assessment	X									See Section 8.3.1 [redacted]
Physical Examination	X									See Section 8.4.1
Caffeine and/or Nicotine Intake Assessment	X		X		X			X		Participants should be asked about their caffeine and/or nicotine intake the morning prior to arriving at study site See Section 5.3.1 and Section 8.3.4
Urine Drug Screen (dipstick)	X		X		X			X		See Section 8.4.6
Breath Alcohol Screen	X		X		X			X		See Section 8.4.6
Vital Signs	X		X		X			X		For BP, 3 readings are required. See Section 8.4.2
12-Lead ECG	X									See Section 8.4.3

Table 3: Schedule of Assessments (Continued)

Procedure	Screening		Baseline / Random-ization	Double-blind Treatment Period (Treatment Period 1)		Washout Period	Double-blind Crossover Treatment Period (Treatment Period 2) (First Dose Taken Day 21 to 24)		SFU or ED	Notes For ED participants, follow the SFU procedures. Participants will complete either SFU or ED.
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**The same procedures are conducted for SFU and ED visits.**
Study Days Relative to Randomization (Site Visits) or to Next Visit (Phone Calls)	**-28 to -14**	**3 days before Visit 3**	**0**	**3 days before Visit 5**	**13 to 16**	**20 to 23 (day before first dose of crossover period)**	**3 days before Visit 8**	**34 to 37**	**SFU: 4 to 10 days after last dose (Visit 8) ED: ≥4 days after last dose**	**Study visits can fall within the day ranges listed here, but all assessments must occur on the same day. Phone contact columns (for Visits 2, 4, 6, 7) are in gray.**
Serum Pregnancy Test	X									For women of child bearing potential only. Serum pregnancy test is required at Visit 9 only to confirm a positive urine test. See Section 8.4.5
Urine Pregnancy Test (dipstick)			X						X	For women of child bearing potential only. Serum testing may be required by local regulations. See Section 8.4.5
Chemistry, hematology and urinalysis (fasting)	X									See Section 8.4.4
Thyroid Panel	X									
OSA Therapy Adherence Check	X		X		X			X		See Section 8.3.3
C-SSRS (Baseline/Screen version)	X									See Section 8.4.7
C-SSRS (Since Last Visit Version)			X		X			X		See Section 8.4.7
Oversee study drug consumption at site					X			X		Document date and exact time of taking study intervention in the source documents.
Collect study drug/assess compliance					X			X	X	At the end of each treatment period, participants must return all remaining study intervention and containers (bottles and/or blister packs). Participants can return at the site visit or via shipment to the site.
DSST WAIS-IV	X									Confirm DSST WAIS-IV ACSS score ≤8 to verify eligibility.
DSST RBANS	X		X		X			X		Assess DSST RBANS 4 times at Screening if participant passes the DSST WAIS-IV. Assess DSST RBANS once for practice onsite visits, followed by 4 times at 2, 4, 6, and 8 hours postdose. See Section 8.2.1
BC-CCI	X		X		X			X		See Section 8.2.2

Procedure	Screening		Baseline / Random-ization	Double-blind Treatment Period (Treatment Period 1)		Washout Period	Double-blind Crossover Treatment Period (Treatment Period 2) (First Dose Taken Day 21 to 24)		SFU or ED	Notes For ED participants, follow the SFU procedures. Participants will complete either SFU or ED.
Visit Number	1	2	3	4	5	6	7	8	9	The same procedures are conducted for SFU and ED visits.
Study Days Relative to Randomization (Site Visits) or to Next Visit (Phone Calls)	-28 to -14	3 days before Visit 3	0	3 days before Visit 5	13 to 16	20 to 23 (day before first dose of crossover period)	3 days before Visit 8	34 to 37	SFU: 4 to 10 days after last dose (Visit 8) ED: ≥4 days after last dose	Study visits can fall within the day ranges listed here, but all assessments must occur on the same day. Phone contact columns (for Visits 2, 4, 6, 7) are in gray.
PGI-S	X		X		X			X		See Section 8.2.3

Table 3: Schedule of Assessments (Continued)

Procedure	Screening		Baseline / Random-ization	Double-blind Treatment Period (Treatment Period 1)		Washout Period	Double-blind Crossover Treatment Period (Treatment Period 2) (First Dose Taken Day 21 to 24)		SFU or ED	Notes For ED participants, follow the SFU procedures. Participants will complete either SFU or ED.
Visit Number	1	2	3	4	5	6	7	8	9	The same procedures are conducted for SFU and ED visits.
Study Days Relative to Randomization (Site Visits) or to Next Visit (Phone Calls)	-28 to -14	3 days before Visit 3	0	3 days before Visit 5	13 to 16	20 to 23 (day before first dose of crossover period)	3 days before Visit 8	34 to 37	SFU: 4 to 10 days after last dose (Visit 8) ED: ≥4 days after last dose	Study visits can fall within the day ranges listed here, but all assessments must occur on the same day. Phone contact columns (for Visits 2, 4, 6, 7) are in gray.
Dispense Sleep Diary	X		X		X					
Sleep Diary Review			X		X			X		See Section 8.3.2
Participant Reminder		X		X			X			See Section 8.1.7 for full list reminder items.
ESS	X		X		X			X		See Section 8.2.4
Concomitant Medications	X		X		X			X	X	See Section 6.8 and Section 8.1.4
Confirm study drug was not taken for 1 week and instruct taking study drug the next day						X				See Section 6.4
Randomization			X							

Procedure	Screening		Baseline / Random-ization	Double-blind Treatment Period (Treatment Period 1)		Washout Period	Double-blind Crossover Treatment Period (Treatment Period 2) (First Dose Taken Day 21 to 24)		SFU or ED	Notes For ED participants, follow the SFU procedures. Participants will complete either SFU or ED.
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**The same procedures are conducted for SFU and ED visits.**
Study Days Relative to Randomization (Site Visits) or to Next Visit (Phone Calls)	**-28 to -14**	**3 days before Visit 3**	**0**	**3 days before Visit 5**	**13 to 16**	**20 to 23 (day before first dose of crossover period)**	**3 days before Visit 8**	**34 to 37**	**SFU: 4 to 10 days after last dose (Visit 8) ED: ≥4 days after last dose**	**Study visits can fall within the day ranges listed here, but all assessments must occur on the same day. Phone contact columns (for Visits 2, 4, 6, 7) are in gray.**
Dispense study drug and remind participants to bring blister pack/bottle with them to next visit			X		X					See Section 6.1

Abbreviations: ACSS= age -corrected scaled score; BC-CCI=British Columbia-Cognitive Complaints Inventory; BMI=body mass index; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; DSST=Digit Symbol Substitution Test; ECG=electrocardiogram; ED=Early Discontinuation; ESS=Epworth Sleepiness Scale; OSA=obstructive sleep apnea; PGI-S=Patients Global Impression of Severity; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; SFU=Safety Follow-up; DSST WAIS-IV= Digit Symbol Substitution Test Wechsler Adult Intelligence Scale, Fourth Edition

2. INTRODUCTION

2.1. Study Rationale

The rationale for this phase 4 study was identified following patient and physician input. The study was designed to evaluate the impact of solriamfetol on cognitive outcome measures in participants with EDS associated with OSA plus impaired cognitive function.

An important element that patients consider when evaluating whether to start a treatment is how the treatment will affect their ability to work. Therefore demonstrating that solriamfetol not only improves cognitive function, but cognitive improvement is sustained throughout the day would address a major unmet need for patients. Further, this would differentiate solriamfetol from other treatment options that have not consistently demonstrated such an impact.

2.2. Background

Sunosi (henceforth referred to as solriamfetol; previously known as JZP-110, ADX-N05, R228060, and YKP10A) is a selective dopamine and norepinephrine reuptake inhibitor that has received marketing approval in the United States (US) for improving wakefulness in adult patients with EDS associated with narcolepsy or OSA. Solriamfetol also has received marketing approval in the European Union (EU) and the United Kingdom for improving wakefulness and reducing EDS in adults with narcolepsy (with or without cataplexy) and in adults with OSA whose EDS has not been satisfactorily treated by primary OSA therapy, such as continuous positive airway pressure. The recommended dose range for solriamfetol is 37.5 mg (OSA only) to 150 mg once daily.

Obstructive sleep apnea is a common disorder of breathing during sleep characterized by repeated obstruction of the upper airway (Bassiri and Guilleminault 2000). These obstructive events often lead to reduced blood oxygen saturation (hypoxia), resulting in increased respiratory effort and arousals from sleep to resume breathing (Ferguson 1995). A consequence of these repetitive obstructions and arousals is that normal sleep architecture is disturbed and sleep fragmented, particularly the time spent in rapid eye movement sleep and slow-wave sleep (stages N3/4), which are often decreased (Borak 1996).

Intermittent hypoxia is thought to contribute to cognitive dysfunction in OSA patients by impacting sleepiness, memory, and executive dysfunction (Naismith 2004; Beebe and Gozal 2002). Likewise, sleep fragmentation seen in OSA patients could result in cognitive impairment via its impact on attention (Verstraeten 2004). The basis of this argument is the strong similarity between cognitive deficits seen in OSA and those seen in healthy individuals who have been experimentally deprived of sleep (Verstraeten 2004). Additionally, sleep-deprived healthy individuals show reduced activity in the prefrontal and posterior parietal cortices and in the thalamus. These functional, central, neural changes have been associated with reductions in attention and vigilance (Verstraeten 2007).

The decrease in cognitive function seen in patients with OSA has implications for work performance and social functioning and increases the risk for occupational and motor vehicle accidents (Garbarino 2015; Garbarino 2016). In aggregate, about 40% of OSA patients (with or without positive airway pressure [PAP] use) complain of cognitive difficulties, and cognitive

difficulties are 1 of the top 5 symptoms that have a severe or moderate impact on patients' daily activities (American Sleep Apnea Association 2018). None of the treatments for EDS associated with OSA have consistently shown improvement in cognitive function despite how common complaints around cognitive function are in the disease (Wang 2020; Avellar 2016). Thus, there remains a large unmet need for therapies that can not only assist OSA patients with EDS but also improve their cognitive outcomes.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

Solriamfetol has a robust clinical safety database comprised of healthy adult participants and participants with OSA, narcolepsy, Parkinson's disease, and MDD with a consistent safety profile across conditions. Solriamfetol is approved in the US for the indication of improving wakefulness in adult patients with EDS associated with OSA or narcolepsy. Solriamfetol is approved in the EU for the indication of improving wakefulness and for reducing EDS in adults with narcolepsy (with or without cataplexy) or OSA, whose EDS has not been satisfactorily treated by primary OSA therapy. The risks to participants in this study are expected to be similar to those seen in prior clinical studies that evaluated the effects of 75 mg and 150 mg solriamfetol in OSA and narcolepsy participants, including those on concomitant antidepressants. Current information on the efficacy, pharmacokinetics (PK), and safety of solriamfetol is provided in the solriamfetol Investigator's Brochure (IB), the United States Package Insert (USPI) and the Summary of Product Characteristics (SmPC).

Underlying psychiatric comorbidities (ie, affective disorders and suicidal ideation), commonly seen in OSA and narcolepsy patients, could be exacerbated by the use of a stimulant or wake-promoting agent. In the solriamfetol clinical development program, serious psychiatric events occurred more commonly in the narcolepsy population than the OSA population. Further, although solriamfetol blocks dopamine and norepinephrine reuptake, nonclinical and clinical data show that the potential for abuse for solriamfetol is low.

Transient and dose-dependent increases in blood pressure (BP) and heart rate (HR) have been seen in clinical studies with OSA and narcolepsy participants. This population may be at risk for cardiovascular events due to certain intrinsic factors, such as increasing age, obesity, concurrent diabetes mellitus or cardiovascular disease, hyperlipidemia, and hypertension. In addition, the underlying disease pathophysiology may also predispose patients to cardiovascular disease. Based on the cardiovascular comorbidities in this population and depending on the cardiovascular risk profile, these events are anticipated to occur in this population.

In addition to the risks associated with the use of solriamfetol, participants with who enroll in this study may encounter study procedure-related risks, including risks and/or discomfort associated with blood collection, electrocardiogram (ECG), physical examination (PE), and completion of questionnaires and other assessments.

2.3.2. Benefit Assessment

Solriamfetol has demonstrated robust, clinically meaningful wake-promoting effects and reduced EDS in adult subjects with narcolepsy or OSA. The primary potential benefits of solriamfetol to

participants in this study is anticipated to be a significant improvement in cognitive function. However, not every participant on solriamfetol is anticipated to benefit.

Additional benefits to the participants include:

- Medical evaluations/assessments associated with this study's procedures (eg, comprehensive PE, clinical safety assessments, and laboratory testing).
- Close monitoring, advice, care, and support by a research team of doctors and other health care professionals who understand the disease or condition.
- The chance for the participant to play an active role in their own health care and gain a greater understanding of their disease or condition.
- The chance for the participant to help society by contributing to medical research. Even if the participant does not experience a direct benefit, the results of the clinical trial may help others and add to scientific knowledge.

2.3.3. Overall Benefit:Risk Conclusion

Previous clinical studies provide compelling evidence that solriamfetol has robust wake-promoting efficacy and a predictable safety profile that can be characterized, monitored and managed through routine clinical practice measures. Solriamfetol has a comprehensive clinical efficacy and safety database (including postmarketing experience) comprising healthy participants and those with EDS associated with OSA and narcolepsy, with a consistent safety profile across conditions. The benefit/risk profile is favorable in participants with OSA and narcolepsy, which supported the approval of doses up to 150 mg in each of these conditions. In the proposed trial, we will be targeting a final dose of 150 mg. This dose showed the highest level of improvement in wakefulness and reduction in sleepiness during the pivotal trials. The overall safety finding in participants taking the 150 mg dose was not significantly different from the 75 mg dose, and based on the titration schedule in clinical studies, the data from pivotal trials with solriamfetol (Studies 14-004 and 14-005) support the initiation of solriamfetol at 75 mg once daily.

Potential safety risks with the use of solriamfetol are serious psychiatric events, increases in BP and HR, and a potential for abuse. The risks to participants are expected to be similar to those seen in prior clinical studies, which are summarized in Section 2.3. Adverse events (AEs) following a single dose have generally been transient and mild to moderate.

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of solriamfetol may be found in the IB, USPI and SmPC.

3. OBJECTIVES AND ESTIMANDS AND ENDPOINTS

Objectives	Estimands and Endpoints
Primary	
To **evaluate the efficacy** of solriamfetol on cognitive function in adult participants with EDS associated with OSA plus impaired cognitive functioning	The primary estimand is defined by the following: • Population: Participants aged 18 to 65, with EDS associated with OSA and impaired cognitive function in the mITT set, defined as: all randomized participants with at least 1 dose of study drug and 1 postdose assessment of DSST RBANS • Variable: Change **from the average** of the DSST RBANS scores at Baseline (Visit 3) **to the average** of the postdose DSST RBANS scores (hours 2, 4, 6, and 8) at the end of each double-blind treatment period • Intercurrent events: – The participant's DSST RBANS data are not collected if the participant discontinued the treatment (while on treatment policy strategy) – Missing assessments after discontinuation of treatment due to AE, lack of efficacy, or any other reasons will not be imputed for primary analysis. • Population level summary: Difference in mean DSST RBANS **from the average** of the scores at Baseline (Visit 3) **to the average** of the postdose scores (at Visit 5 and Visit 8) between solriamfetol and placebo
Secondary Objectives	
To **further evaluate the efficacy** of solriamfetol on cognitive function in adult participants with EDS associated with OSA plus impaired cognitive functioning	The first estimand for the secondary objective of evaluating efficacy is defined by the following: • Population: Participants aged 18 to 65, with EDS associated with OSA and impaired cognitive function in the mITT analysis set, defined as: all randomized participants with at least 1 dose of study drug and 1 postdose assessment of DSST RBANS • Variable: Change from Baseline (Visit 3) to the end of each double-blind treatment period (Visit 5 and Visit 8) in overall score in BC-CCI • Intercurrent events: – The participant's BC-CCI data are not collected if the participant discontinued the treatment (while on treatment policy strategy) – Missing assessments after discontinuation of treatment due to AE, lack of efficacy, or any other reasons will not be imputed • Population level summary: Difference in mean overall BC-CCI score from Baseline (Visit 3) to the end of double-blind treatment period (Visit 5 and Visit 8) between solriamfetol and placebo

Objectives	Estimands and Endpoints
	The second estimand for secondary objective evaluating efficacy is defined by the following: • Population: Participants aged 18 to 65, with EDS associated with OSA and impaired cognitive function in the mITT analysis set, defined as: all randomized participants with at least 1 dose of study drug and 1 postdose assessment of DSST RBANS • Variable: Categorical change from Baseline (Visit 3) to the end of each double-blind treatment period (Visit 5 and Visit 8) in each category of the BC-CCI • Intercurrent events: – The participant's BC-CCI data are not collected if the participant discontinued the treatment (while on treatment policy strategy) – Missing assessments after discontinuation of treatment due to AE, lack of efficacy, or any other reasons will not be imputed • Population level summary: Percentage of patients with an at least 1 category improvement in the BC-CCI score from Baseline (Visit 3) to the end of double-blind treatment period (Visit 5 and Visit 8) in each treatment group
To **evaluate the effect** of solriamfetol on cognitive function at individual post-dose timepoints in adult participants with EDS associated with OSA plus impaired cognitive functioning	The estimand for this secondary objective to evaluate the effect on cognitive function at individual post-dose timepoints is defined by the following: • Population: Participants aged 18 to 65, with EDS associated with OSA and impaired cognitive function in the mITT analysis set, defined as: all randomized participants with at least 1 dose of study drug and 1 postdose assessment of DSST RBANS • Variable(s): Change **from each** of the 2-, 4-, 6-, and 8-hour DSST RBANS sores at Baseline (Visit 3) **to each** of the corresponding 2-, 4-, 6-, and 8-hour postdose DSST RBANS scores at the end of each double-blind treatment period (Visit 5 and Visit 8) • Intercurrent events: – The participant's DSST RBANS data are not collected if the participant discontinued the treatment (while on treatment policy strategy) – Missing assessments after discontinuation of treatment due to AE, lack of efficacy, or any other reasons will not be imputed • Population level summary: Difference in mean DSST RBANS **from each** of the 2-, 4-, 6-, and 8-hour DSST RBANS sores at Baseline (Visit 3) **to each** of the corresponding 2-, 4-, 6-, and 8-hour postdose (at Visit 5 and Visit 8) DSST RBANS scores between solriamfetol and placebo

Objectives	Estimands and Endpoints
To **evaluate the efficacy** of solriamfetol on patient-reported global impression of concentration, memory, and thinking skills in adult participants with EDS associated with OSA plus impaired cognitive functioning	The first estimand for this secondary objective evaluating efficacy is defined by the following: • Population: Participants aged 18 to 65, with EDS associated with OSA and impaired cognitive function in the mITT analysis set, defined as: all randomized participants with at least 1 dose of study drug and 1 postdose assessment of DSST RBANS • Variable: Change from Baseline (Visit 3) to the end of each double-blind treatment period (Visit 5 and Visit 8) in PGI-S score • Intercurrent events: – The participant's PGI-S data are not collected if the participant discontinued the treatment (while on treatment policy strategy) – Missing assessments after discontinuation of treatment due to AE, lack of efficacy, or any other reasons will not be imputed Population level summary: Difference in mean PGI-S score from Baseline (Visit 3) to the end of double-blind treatment period (Visit 5 and Visit 8) between solriamfetol and placebo The second estimand for this secondary objective evaluating efficacy is defined by the following: • Population: Participants aged 18 to 65, with EDS associated with OSA and impaired cognitive function in the mITT analysis set, defined as: all randomized participants with at least 1 dose of study drug and 1 postdose assessment of DSST RBANS • Variable: Categorical improvement from baseline on the PGI-S to the end of each double-blind treatment period (Visit 5 and Visit 8) • Intercurrent events: – The participant's PGI-S data are not collected if the participant discontinued the treatment (while on treatment policy strategy) – Missing assessments after discontinuation of treatment due to AE, lack of efficacy, or any other reasons will not be imputed Population level summary: Percentage of participants reporting an at least 1 category improvement from baseline on the PGI-S to the end of each double-blind treatment period (Visit 5 and Visit 8) in each treatment group

Objectives	Estimands and Endpoints
To **evaluate the efficacy** of solriamfetol on improving EDS in adult participants with EDS associated with OSA plus impaired cognitive functioning	The estimand for this secondary objective evaluating efficacy is defined by the following: • Population: Participants aged 18 to 65, with EDS associated with OSA and impaired cognitive function in the mITT analysis set, defined as: all randomized participants with at least 1 dose of study drug and 1 postdose assessment of DSST RBANS • Variable: Change from Baseline (Visit 3) to the end of each double-blind treatment period (Visit 5 and Visit 8) in ESS score • Intercurrent events: − The participant's ESS data are not collected if the participant discontinued the treatment (while on treatment policy strategy) − Missing assessments after discontinuation of treatment due to AE, lack of efficacy, or any other reasons will not be imputed Population level summary: Difference in mean ESS score from Baseline (Visit 3) to the end of double-blind treatment period (Visit 5 and Visit 8) between solriamfetol and placebo
To **evaluate the safety** and tolerability of solriamfetol administered once daily in adult participants with EDS associated with OSA plus impaired cognitive functioning	Safety and tolerability evaluations will be determined by the occurrence of and/or changes in: • Incidence and severity of TEAEs • Vital signs • C-SSRS
Exploratory	
To **evaluate the association** between the improvement in EDS and improvement in cognitive function following solriamfetol treatment in adult participants with EDS associated with OSA plus impaired cognitive functioning	The exploratory endpoints for the exploratory objective of evaluating the association between the improvement in EDS and improvement in cognitive function are: • The correlation between the change from Baseline (Visit 3) at the end of each double-blind treatment period (Visit 5 and Visit 8) in ESS and DSST RBANS score • The correlation between the change from Baseline (Visit 3) at the end of each double-blind treatment period (Visit 5 and Visit 8) in ESS and BC-CCI score • The correlation between the change from Baseline (Visit 3) at the end of each double-blind treatment period (Visit 5 and Visit 8) in ESS and PGI-S

Abbreviations: AE = adverse event; BC-CCI = British Columbia-Cognitive Complaints Inventory; C-SSRS = Columbia-Suicide Severity Rating Scale; DSST RBANS = Digit Symbol Substitution Test Repeatable Battery for the Assessment of Neuropsychological Status; EDS = excessive daytime sleepiness; ESS = Epworth Sleepiness Scale; mITT = modified Intent-to-Treat; OSA = obstructive sleep apnea; PGI-S = Patients Global Impression of Severity; RBANS = ; TEAE = treatment-emergent adverse event.

4. STUDY DESIGN

4.1. Overall Design

The study is designed as a prospective, multicenter, 2-arm, randomized, double-blind, placebo-controlled interventional crossover trial of solriamfetol (75 mg titrated to 150 mg after 3 days) or matched placebo, then continued for a 2 week period total before completing a 1-week washout followed by the crossover period. Study intervention will be administered in a balanced 2 × 2 Latin square design, where half of the participants will receive placebo first and half of the participants will receive solriamfetol first.

Cognitive function is assessed by an objective measure, the DSST (collected at 2, 4, 6 and 8 hours postdose), and a subjective measures, the BC-CCI and the Patients Global Impression of Severity (PGI-S) (both are collected at Baseline and at the end of each treatment period). The DSST has been frequently used in neuropsychological testing and dates back to the 1940s (Boake 2002). The DSST is a measure that requires attention, vigilance, processing speed and psychomotor speed, and it is sensitive to the effects of sleep deprivation and pharmacologic agents (Jaeger 2018). The DSST has previously been shown to be sensitive to pharmacologic alleviation of cognitive dysfunction in clinical studies of vortioxetine. Those findings are now included in the Trintellix™ (vortioxetine) product label (Trintellix 2013), and therefore warrant inclusion of the DSST in the current investigation of solriamfetol's ability to alleviate cognitive impairment linked to EDS associated with OSA. Similarly, the BC-CCI, originally developed to measure cognitive complaints in individuals with MDD (Iverson and Lam 2013), has been used successfully to measure the relationship between cognitive complaints and impaired sleep quality among individuals with chronic kidney disease (Zubair 2017) and chronic insomnia (Kyle 2020). The PGI-S is a 5-point Likert-type rating scale to evaluate the severity of illness and is a widely used measure to assess efficacy in clinical psychopharmacology trials (FDA 2018).

4.1.1. Screening Period

The Screening period will be 14 days (up to a maximum of 28 days) prior to Day 1 to minimize carry over learning effect of the DSST, and will serve to determine eligibility. During Screening, participants will provide informed consent and undergo a series of assessments to verify if they are eligible to participate in the study, as outlined in the Schedule of Assessments (SoA, Section 1.3).

4.1.2. Baseline and Randomization

The Baseline and Randomization visit will be used to confirm participant eligibility, and to assign participants to 1 of 2 treatment sequences: 1) solriamfetol in first double-blind treatment period (Treatment Period 1) followed by placebo in the second double-blind crossover treatment period (Treatment Period 2); or 2) placebo in first double-blind treatment period followed by solriamfetol in the second double-blind crossover treatment period. Participants will be randomly assigned to 1 of 2 treatment sequences in a 1:1 ratio, and each participant and will complete the assessments outlined in the SoA (Section 1.3). At the end of the Baseline and Randomization visit, participants will receive the double-blind study intervention for Treatment Period 1.

4.1.3. Double-blind Treatment Period (Treatment Period 1)

Throughout this protocol, the Double-blind Treatment Period will be referred to as Treatment Period 1. Treatment Period 1 begins the day after the Baseline and Randomization visit. Participants will take the first dose of study intervention at home upon waking the first day of the period. Participants will take study intervention at home until the next visit, but will be instructed by site staff to not take the final dose until after arrival at the study site, and to bring pill bottle/blister pack of study intervention to the site.

The last day of Treatment Period 1 is a site visit. Participants will turn in pill bottle/blister pack, take the final dose of study intervention for that treatment period in the presence of site staff, and undergo the assessments outlined in Section 1.3. At the end of the study site visit, participants will be provided with a supply of double-blind crossover study intervention for Treatment Period 2, but will be instructed to not to take any doses until after the 1-week washout. Site staff will then schedule the next visit to occur after the 1-week washout and 2-week double-blind crossover treatment periods are completed.

4.1.4. Washout Period

Participants will not take any study treatment during the 1-week washout period. At the end of the washout period, sites will call the participant to remind them to start taking the study intervention (see SoA, Section 1.3).

4.1.5. Double-blind Crossover Treatment Period (Treatment Period 2)

Throughout this protocol, the Double-blind Crossover Treatment Period will be referred to as Treatment Period 2. Treatment Period 2 begins after completion of the 7-day washout period. During Treatment Period 2, participants will take the study intervention once daily at home in the morning upon wakening. The last day of the Treatment Period 2 is a site visit. Participants will turn in pill bottle/blister pack, take the final dose of Treatment Period 2 intervention in the presence of site staff, and undergo the assessments outlined in Section 1.3.

4.1.6. Safety Follow-up or Early Discontinuation

Participants will complete either the Safety Follow-up (SFU) or the Early Discontinuation (ED) visit as outlined in the SoA (Section 1.3).

The same procedures will be administered during the SFU or ED visits. The SFU/ED visit can be virtual or onsite based on local regulations and/or site preference. The SFU visit will occur 4 to 10 days after the final dose of study intervention. The ED visit will occur $\geq$ 4 days after the last dose taken for participants who do not take all planned doses of either Treatment Period 1or Treatment Period 2.

4.2. Scientific Rationale for Study Design

A randomized, double-blind, placebo-controlled crossover study design has been selected for this study as it allows for an intra-participant comparison between solriamfetol and placebo in evaluating cognitive function. The crossover study design is appropriate in this study as the cognitive impairment and EDS associated with OSA are chronic and stable conditions, and the

treatment would not result in total cure but only alleviate the condition. This design also reduces the overall number of participants exposed to the test hypothesis required for evaluation.

Two-week treatment for each period is selected for the following reasons:

- Solriamfetol has a half-life of approximately 7 hours.
- Once daily solriamfetol dose of 150 mg reaches steady state within 3 days.
- Pivotal studies evaluating solriamfetol demonstrated that the effect of solriamfetol was seen as early as after 1-week treatment.

A 1-week washout period between the 2 double-blind treatment periods will minimize any potential carryover effect.

4.3. Justification for Dose

Results from the dose-dependent efficacy observed in the previous Studies 14-002 and 14-003 and in the open-label dosing periods in Studies 14-004 and 14-005, and supportive clinical pharmacology information (including population PK and exposure-response modeling data) suggest that the efficacious dose range for most participants is 75 mg to 300 mg once daily.

As the study is aimed to evaluate the efficacy of solriamfetol on cognitive function improvement and not to identify the optimal dose, solriamfetol dose of 150 mg per the prescribing label will be administered to participants. Based on the titration schedule in clinical studies in OSA (Studies 14-003, 14-004, 14-005), the data support the initiation of solriamfetol at 75 mg once daily. These data also show that solriamfetol may be increased by doubling the dose at intervals of 3 or more days. Starting the dose at 75 mg will shorten the duration of the titration period and maximize the duration of participant exposure to the prescribed dose of 150 mg. Hence, after starting solriamfetol at 75 mg for the first 3 days of the treatment period, the dose will then be titrated up to 150 mg for the remainder of the treatment period.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the SFU visit.

The end of study is defined as when all participants have completed the study, or have withdrawn or have been lost to follow-up.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex

1. Male or female between 18 (or the legal age of consent in the jurisdiction in which the study takes place) and 65 years of age, inclusive.

Type of Participant and Disease Characteristics

2. Diagnosis of OSA according to International Classification of Sleep Disorders, Third Edition criteria.
3. Participant report (with clinician concurrence) of at least 1 of the following primary OSA therapy criteria:
   - Consistent number of hours of primary PAP therapy use (with downloadable history) for OSA on at least 5 nights/week for at least 1 month prior to Baseline (with or without prior OSA surgical intervention), OR
   - No current use of PAP therapy for at least 1 month prior to Baseline but a history of at least 1 month of attempting to use PAP as the primary OSA therapy with at least 1 documented adjustment that was made in an attempt to optimize the therapy (with or without prior OSA surgical intervention), OR
   - History of a surgical intervention intended to treat OSA symptoms (with or without current PAP use as primary OSA therapy).
4. The participant has an age-corrected scaled score ≤ 8 on the DSST Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) at the Screening visit.
5. British Columbia-Cognitive Complaints Inventory ≥ 9 at Screening and Baseline.
6. Epworth Sleepiness Scale (ESS) score > 10 at Screening and Baseline.
7. Usual nightly total sleep time of ≥ 6 hours.

Weight

8. Body mass index from 18.5 to < 40 kg/m2.

Sex and Contraceptive/Barrier Requirements

9. Male and female Participants

   a. Male participants:

Male participants are eligible to participate if they agree to the following during the study intervention period and for at least 14 days after the last dose of study intervention:

- Refrain from donating sperm

PLUS, either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

  OR

- Must agree to use contraception/barrier as detailed below
- Agree to use a male condom with female partner use of an additional highly effective contraceptive method with a failure rate of < 1% per year as described in Appendix 5 Contraceptive and Barrier Requirements when having sexual intercourse with a women of childbearing potential (WOCBP) who is not currently pregnant.

b. Female participants:

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and 1 of the following conditions applies:
  - Is a woman of nonchildbearing potential (WONCBP) as defined in Appendix 5 Contraceptive and Barrier Guidance

    OR

  - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), as described in 0 Contraceptive and Barrier Guidance during the study intervention period and for at least 14 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within the Screening/Baseline period (once at the time of Screening for participation in the study and again at the time of the study Baseline assessment) before the first dose of study intervention, see Section 8.4.5 Pregnancy Testing.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.4.5.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

10. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants who demonstrate any of the following will be excluded from the study:

Medical and Sleep Conditions

1. Female participants who are pregnant, nursing, or lactating.
2. Usual bedtime later than 1 AM (0100 hours).
3. Occupation requiring nighttime or variable shift work.
4. Unable to understand or perform DSST test per investigator's judgement.
5. Use a PAP machine with no adherence data downloadable ability.
6. Diagnosis of another sleep disorder (other than OSA) including: circadian rhythm sleep disorders, narcolepsy, restless legs syndrome determined by participant sleep history.
7. Presence of acutely unstable major depression or current major depressive episode as based on the judgement of the investigator.
8. Participants with active clinically significant illness, including endocrine, neoplastic, gastrointestinal, hematological, hepatic, immunologic, metabolic, neurological, pulmonary, and/or renal disease, and/or surgical history which could interfere with the study efficacy, safety, conduct or the ability of the participant to complete the study based on the judgement of the investigator, or place the participant at risk during the trial or compromise the study objectives.
9. History or presence of any other clinically relevant medical, behavioral, or psychiatric disorder other than OSA that is associated with an impact on cognitive function; including history or presence of neurodegenerative condition (eg, mild cognitive impairment due to Alzheimer's), autism, vascular dementia, active suicidal ideation, that could affect the safety of the participant or interfere with study efficacy, safety, conduct or the ability of the participant to complete the trial based on the judgment of the investigator.
10. History or presence of bipolar disorder, bipolar related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria.
11. History of bariatric surgery within the past year or a history of any gastric bypass procedure.
12. Participants with movement or motor disorders such as Parkinson's disease, as they will not be able to complete the DSST.

Diagnostic Assessments

13. Presence of renal impairment or calculated creatinine clearance < 60 mL/minute.
14. Clinically significant ECG abnormality in the opinion of the investigator.
15. Presence of significant cardiovascular disease including but not limited to: myocardial infarction within the past year, unstable angina pectoris, symptomatic congestive heart failure (ACC/American Heart Association stage C or D), revascularization procedures within the past year, uncontrolled atrial fibrillation, ventricular cardiac arrhythmias requiring automatic implantable cardioverter defibrillator or medication therapy, uncontrolled hypertension (as defined by Centers for Disease Control and Prevention), systolic blood pressure ≥ 155 mmHg or diastolic blood pressure ≥ 95 mmHg (at Screening

or Baseline), or any history of cardiovascular disease or any significant cardiovascular condition that in the investigator's opinion may jeopardize participant safety in the study.

16. Laboratory value(s) outside the laboratory reference range that is considered to be clinically significant by the investigator (clinical chemistry, hematology, and urinalysis). NOTE: Screening labs may be repeated once.
17. Hypothyroidism or hyperthyroidism, unless stabilized by appropriate medication for at least 3 months prior to Screening (a normal thyroid-stimulating hormone is required prior to Randomization at Baseline).

Prior/Concomitant Therapy

18. Use of any over-the-counter (OTC) or prescription medications that could affect the evaluation of EDS within a time period prior to the Baseline visit corresponding to at least 5 half-lives of the drug(s) or planned use of such drug(s) at some point throughout the duration of the 5-week double-blind treatment period. Examples of excluded medications include OTC sleep aids, stimulants (eg methylphenidate, amphetamines, modafinil, and armodafinil), sodium oxybate, pemoline, pitolisant, bupropion, trazodone, vortioxetine, duloxetine, tricyclic antidepressants, hypnotics, benzodiazepines, pseudoephedrine, barbiturates, and opioids. Medications should be discontinued such that, in the opinion of the investigator, the participant has returned to his/her Baseline level of daytime sleepiness at least 7 days prior to the Baseline visit.
19. Current or recent (within the past 2 years) diagnosis of a moderate or severe substance use disorder (excluding caffeine) according to DSM-5 criteria, or seeking treatment for a substance-related disorder. Nicotine use disorder is excluded only if it has an effect on sleep (ie, a participant who routinely awakens at night to smoke).
20. Excessive caffeine use, defined as > 600 mg/day of caffeine (eg, more than 6 cups of brewed coffee, 15 cans of cola or 3 "energy shot" drinks), 1 week prior to Screening or anticipated excessive use during the study.
21. Urine drug screen positive for amphetamine, methamphetamine, tricyclic antidepressants, propoxyphene, benzodiazepines, barbiturates, cocaine, marijuana, morphine, ecstasy, oxycodone, buprenorphine, methadone, or phencyclidine at Screening or at any point throughout the duration of the study.
22. History of regular heavy use of tetrahydrocannabinol (THC) is excluded. Sporadic recreational users of THC can complete a repeat urine drug screen during the Screening period. If this is negative, the participant may be allowed to enter the study pending agreement to completely refrain from the use of THC during the course of the study.
23. Positive alcohol test at Screening.
24. Participants who binge drink, defined as 5 or more drinks in a day for men or 4 or more drinks in a day for women at least once in past month.
25. History of phenylketonuria or history of hypersensitivity to phenylalanine-derived products.
26. Currently receiving MAO inhibitors or having had received MAO inhibitors for 14 days prior to the Baseline visit.

Prior/Concurrent Clinical Study Experience

27. Previous exposure to solriamfetol (JZP-110, ADX-N05, R228060, or YKP-10A) in a clinical study or prescribed by a physician.
28. Received an investigational drug in the past 30 days or 5 half-lives (whichever is longer) prior to the Baseline visit, or plans to use an investigational drug (other than the study drug) during the study.
29. Is currently participating in another clinical study.

5.3. Lifestyle Considerations

Participants in this study will be asked to commit a good-faith effort to adhere to the study protocol.

5.3.1. Caffeine, Alcohol, and Tobacco

1. Participants will be allowed to drink a maximum of 200 mg of caffeine (eg, 2 cups of 8 oz coffee) the morning of the Baseline visit assessment session. During each subsequent visit, participants will be instructed to consume the same amount of caffeine as they did prior to the Baseline visit. No additional caffeine is allowed during the visit.
2. Participants who use tobacco products will be instructed to use the same amount of tobacco during each visit. Tobacco/nicotine products should not be consumed within 1 hour of performing the DSST assessment.
3. Participants will be asked to abstain from alcohol 24 hours prior to the start of each assessment visit. Participants will be screened (breath alcohol test) prior to each Test Session. Participant with positive breath alcohol tests will be permanently discontinued from the study and asked to complete an ED visit.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Participants may be allowed to repeat lab tests following resolution of transient exclusionary conditions or stabilization of conditions that were exclusionary and reversible (eg, unstable hypothyroidism, electrolyte abnormalities) and with the approval of the Medical Monitor. Participants who are approved for repeat labs must complete them within the 28-day Screening window. Rescreening for any purpose other than repeat laboratory testing will not be permitted.

5.5. Criteria for Temporarily Delaying Enrollment

Not applicable.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention/treatment is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s)/Treatment(s) Administered

The Sponsor will provide the clinical study unit with a supply of solriamfetol and placebo tablets as described in Table 4.

Table 4: Study Treatment/Intervention

Treatment Arm	Intervention/ Treatment Name	Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Use	Sourcing	Pkg	Labeling	Storage Conditions
1	Matching Placebo	Overencapsulated tablets	To match study intervention	N/A	Oral	Placebo	Sponsor	1 PBO Bottle & 1 Blister Card/PBO: 33 capsules in PBO/Bottle & 3 capsules in PBO/BC	Blinded	Do not store above 30°C/86°F. Do not refrigerate or freeze.
2	Solriamfetol	Overencapsulated tablets	75 mg, 150 mg	75 mg, 150 mg	Oral	Active	Sponsor	150 mg/1 Bottle & 75 mg 1 Blister Card 33 capsules in 150 mg/Bottle & 3 Capsules in 75 mg BC	Blinded	Do not store above 30°C/86°F. Do not refrigerate or freeze. Solriamfetol should be stored according to regulations for a DEA Schedule IV controlled substance in the US and according to any other regional regulations that apply.

Abbreviations: BC = blister card; DEA = Drug Enforcement Administration; PBO = placebo; Pkg = package; US = United States

6.2. Preparation/Handling/Storage/Accountability

1. Further guidance and information for the final disposition of unused study interventions are provided in the Investigator Trial Site Binder and the IMP Pharmacy Manual for sites to follow.
2. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
3. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
4. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants who sign the ICF will receive a participant number. The participant number identifies the participant for all study procedures that occur throughout the study. This number is unique and once assigned, cannot be reassigned to another study participant.

Treatment Randomization for this study will occur centrally through the use of an interactive response technology (IRT) system. Randomization numbers also cannot be reused. Participants cannot be rescreened, but may have repeat laboratory testing. The IRT will be programmed with blind-breaking instructions.

Emergency Unblinding

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and the IRT, as applicable.

Regulatory Reporting

The participant's treatment assignment may be unblinded for regulatory reporting purposes. Notification of the treatment assignment is only made known to those who require it for safety reporting and submission processes. All other individuals involved in the study, including the investigator, will remain blinded to treatment assignment. Participants for whom the blind is broken for this reason will not be withdrawn from the study.

6.4. Study Intervention/Treatment Compliance

Participants that are dosed at the site will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded. The dose of study intervention and study participant identification should be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

Sites will verify the participant's compliance with self-administered study intervention at each site visit. Compliance of the participant's self-administered study intervention at home will be assessed at each visit. Deviation(s) from the prescribed dosage regimen will be recorded.

A record of the quantity of placebo and solriamfetol dispensed to and administered to each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays, will be collected. For in-clinic dosing on test days, study site staff will verify the study intervention has been taken and ingested properly.

6.5. Dose Modification

For the solriamfetol treatment arm, participants will take 75 mg for the first 3 days and 150 mg for the remainder of the treatment period. For the placebo treatment arm, participants will take the placebo treatment for the entire period. There will be a washout period between the 2 treatment periods, during which no study intervention will be taken.

No dose adjustments or modifications (other than titration from 75 mg to 150 mg as described above) are allowed in this study. Participants who do not tolerate their assigned fixed dose of solriamfetol will be discontinued from the study intervention (see Section 7.1).

6.6. Continued Access to Study Intervention After the End of the Study

No extension study is planned. Upon completing the SFU/ED visit, participants should follow-up with their health care provider regarding the resumption of any medications that were discontinued prior to study participation.

6.7. Treatment of Overdose, Medication Errors, or Misuse

For this study, any dose of solriamfetol greater than 300 mg within a 24-hour period will be considered an overdose.

A specific reversal agent for solriamfetol is not available.

In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until solriamfetol can no longer be detected systemically (at least 2 days).
- Document the quantity of the excess dose as well as the duration of the overdose.

6.8. Prohibited Concomitant Therapy

The following concomitant medications are prohibited during the study:

- Use of any OTC or prescription medications that could affect the evaluation of EDS within a time period prior to the Baseline visit corresponding to at least 5 half-lives of the drug(s) or planned use of such drug(s) at some point throughout the duration of the 5-week double-blind treatment period. Refer to Section 5.2 exclusion criteria #18 for the list of prohibited OTC or prescription medications. Medications should be discontinued such that, in the opinion of the investigator, the participant has returned to his/her Baseline level of daytime sleepiness at least 7 days prior to the Baseline visit.
- Phenylketonuria or phenylalanine-derived products.
- Monoamine oxidase inhibitor (MAOI) in the past 14 days or 5 half-lives (whichever is longer) prior to the Baseline visit, or MAOI use during the study is also not allowed.

In addition to the prescription medications listed above, use of the following substances are prohibited:

- Nicotine use disorder which has an effect on sleep (ie, a participant who routinely awakens at night to smoke).
- Excessive caffeine use, defined as > 600 mg/day of caffeine (eg, more than 6 cups of brewed coffee, 15 cans of cola or 3 “energy shot” drinks), 1 week prior to Screening or anticipated excessive use during the study.
- Regular heavy use of THC.
- Binge drinking, defined as 5 or more drink in a day for men or 4 or more drinks in a day for women at least once a year.
- Participants must also refrain from any alcohol use during the 24 hours prior to each assessment visit.

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving within 30 days of Screening or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants may discontinue from study intervention at any time for any reason, or at the discretion of the investigator. In addition, a participant may be withdrawn from study intervention by the investigator or sponsor for safety, behavioral, compliance, and/or administrative reasons. For participants that discontinue study intervention, all effort should be made to complete the procedures listed in the SFU/ED visit (Section 1.3 and Section 4.1.1).

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for SFU/ED visit. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

A participant must be discontinued from study intervention for any of the following reasons:

- The participant or participant's legal representative requests to discontinue study intervention
- The participant has an AE that may compromise the participant's continued participation
- The participant has a positive serum pregnancy test (Section 1.3 and Section 8.4.5)
- The participant is noncompliant with study intervention or procedures
- The sponsor decides to terminate the study prior to completion.
- The investigator determines the participant should not continue on study intervention.

7.1.1. Temporary Discontinuation/Study Intervention Interruption

Temporary discontinuation or study intervention interruption are not allowed in this study, and participants who do not tolerate their assigned fixed dose of solriamfetol will be discontinued from the study intervention (see Section 6.5).

7.2. Participant Discontinuation/Withdrawal From the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. The participant will be permanently discontinued both from the study intervention and from the study at that time. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an ED visit should be conducted, as shown in the SoA (Section 1.3).
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study and lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of Study and Site Start and Closure Section 10.1.9.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3).

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator should maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for Screening failure, as applicable. The site is responsible for ensuring that reason for screen failure is entered into the IRT system.

Safety or laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded. The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 21 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. General Administrative Procedures

Planned time points for general administrative procedures are provided in the SoA (Section 1.3).

8.1.1. Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant/legal representative prior to participation in this study. A signed copy of the ICF should be given to the participant and the original should be placed in the participant's medical records.

8.1.2. Assignment of Participant Number

Each participant who signs the ICF will be assigned a unique number that will identify the participant throughout the study. Once a number has been assigned, it cannot be reassigned to another study participant.

8.1.3. Medical History

A medical history will be obtained by the investigator or a medically qualified designee (consistent with local regulations). All active conditions should be recorded and any condition that the investigator deems clinically significant and relevant to the study.

8.1.4. Medication Review (Prior and Concomitant Medications)

The investigator or medically qualified designee should review the participant's prior medication use within 30 days. Medication that is required to be washed out prior to the study should also be recorded. All medication currently taken by the participant should be recorded.

8.1.5. Inclusion and Exclusion Criteria Review

All inclusion and exclusion criteria should be reviewed by the investigator to ensure the participant qualifies for the study.

8.1.6. Timing of Study Intervention Dosing

Participants should take the study intervention dose once daily upon awakening (except for site visit days) and avoid administration within 9 hours of planned bedtime because of the potential to interfere with sleep. If the subject cannot take the study drug at least 9 hours before his/her anticipated bedtime, the subject should not take the study drug for that day.

For site visits, participants should not take their daily dose upon awakening. Instead, they should arrive at the study site 30 minutes prior to the time of drug administration (eg, 8:30 AM) for assessments so that they can take study intervention under site supervision promptly as scheduled (eg, 9:00 AM).

After the first Treatment Period 1 visit, participants will undergo a 1-week washout, where participants will not take any study intervention during this time.

8.1.7. Reminder Phone Calls

There will be several reminder phone calls made to participants throughout the study. If phone calls are not feasible, at their discretion sites can given participants the opportunity to "opt in" to an alternate, Health Insurance Portability and Accountability Act (HIPAA)-compliant method of contact; however, sites must record in source documents confirmation that notification was received.

The first phone contact is Visit 2, and should occur 3 days prior to Visit 3 (Baseline/Randomization). Participants will be reminded to:

- complete their sleep diary for 3 nights and bring the diary with them to site visit
- bring their PAP device
- not drink more than 200 mg of caffeine (eg, 2 cups of 8 oz coffee) the morning of the visit (see Section 5.3.1 for details)
- get the usual night's sleep the night before the site visit
- abstain from alcohol 24 hours before the site visit

The site will also confirm that the participant does not have plans to travel over the next 3 days and request the participant restrict any significant travel (eg, crossing time zone) before next visit.

The second phone contact is Visit 4, and should occur 3 days before Visit 5 (Treatment Period 1). Participants will be reminded to:

- complete their sleep diary for 3 nights and bring diary with them to site visit
- bring their PAP device
- bring all medications and medication bottles/blister packs
- not drink more than 200 mg of caffeine (eg, 2 cups of 8 oz coffee) the morning of the visit (see Section 5.3.1 for details)

- get the usual night's sleep the night before the site visit
- abstain from alcohol 24 hours before the site visit
- not to take study drug on day of the visit

The site will also confirm that the participant does not have plans to travel over the next 3 days and request the participant restrict any significant travel (eg, crossing time zone) before next visit.

The third phone contact is Visit 6, and should occur during the Washout Period 1 day before the first dose of Treatment Period 2 intervention. Participants will be reminded to begin taking crossover treatment next morning, and to continue taking it until the next site visit.

The fourth phone contact is Visit 7, and should occur 3 days before Visit 8 (Treatment Period 2). This reminder call is identical to the reminder phone call Visit 4.

8.2. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3).

8.2.1. Digit Symbol Substitution Test

The DSST is a measure that requires attention, vigilance, processing speed and psychomotor speed, and it is sensitive to the effects of sleep deprivation and pharmacologic agents (Jaeger 2018). The DSST generally requires matching of a list of symbols and digits to each other using a given digit symbol pairing key, as fast as possible within a given timeframe while remaining as accurate as possible. Two versions of the DSST will be administered in this study: 1) the DSST WAIS-IV at Screening, and 2) the DSST RBANS version for all other visits during the study.

8.2.1.1. Digit Symbol Substitution Test Wechsler Adult Intelligence Scale Fourth Edition

The DSST WAIS-IV will be used to determine eligibility. Participants will need an age-corrected score of ≤ 8 to be eligible for the study. To complete the WAIS-IV form, participants will receive a number and must match the symbol, as quickly and accurately as possible, within 120 seconds.

8.2.1.2. Digit Symbol Substitution Test Repeatable Battery for the Assessment of Neuropsychological Status Version

The DSST RBANS will serve as the primary efficacy endpoint. Although different staff can administer the DSST to a given participant, the participants should complete each of their DSSTs throughout the study in the same physical location at the study site.

To complete the RBANS form, participants will receive a symbol and must match the number, as quickly and accurately as possible, within 90 seconds. The number of correct symbol/number pairings determines the participants score.

[redacted]

8.2.2. British Columbia-Cognitive Complaints Inventory

The BC-CCI was developed to measure cognitive complaints in individuals with MDD (Iverson and Lam 2013). It is a 6-item self-report measure that asks respondents to rate problems with specific cognitive symptoms over the past 7 days. It takes less than 5 minutes to complete. A 4-point scale (0 "Not at all" to 3 "Very much") is used to rate each item. The total score (ranges from 0 to 18) that is generated assesses domains of memory, concentration, trouble expressing thoughts, word-finding, and problem solving. Higher scores indicate greater severity of cognitive impairment, with 4 established classification ranges for the BC-CCI total score: 0 to 4 = "broadly normal"; 5 to 8 = "mild" cognitive complaints; 9 to 14 = "moderate" cognitive complaints; and 15 to 18 = "severe" cognitive complaints. Three additional items that ask about how these symptoms impact work, relationships and social/recreational activities are also included to provide further information on the nature of functional impairment (however, those items are not included in the total score calculation).

Site personnel should ensure that the participant has completed the entire BC-CCI according to the instructions in the BC-CCI training manual.

8.2.3. Patient Global Impression of Severity

The PGI-S is a 5-point Likert-type rating scale and a widely used assessment in clinical psychopharmacology trials to assess severity of illness (FDA 2018). Participants will be asked to rate the level of severity of their problems with concentration, memory, and thinking skills during the past 7 days. The responses of this participant-completed scale range from "none" (0) to "very

severe" (4). Participants will rate their impression of the severity of their current condition at Screening, and at each site visit as shown in the SoA (Section 1.3).

8.2.4. Epworth Sleepiness Scale

The ESS is a self-administered questionnaire with 8 questions (Johns 1991). Respondents rate on a 4-point scale (0 to 3) their usual chances of dozing off or falling asleep while engaged in 8 different activities. Most people engage in those activities at least occasionally, although not necessarily every day. The ESS total score (the sum of 8 item scores, 0 to 3) can range from 0 to 24. Higher ESS total scores are associated with higher sleep propensity in daily life, also referred to as 'daytime sleepiness'.

Site personnel should ensure that the participant completes the entire ESS, and should be scored on the Screening and Baseline visits to ensure a score > 10 to confirm eligibility.

8.3. Other Assessments

8.3.1. Sleep Habits Assessment

The participant's responses to the Sleep Habits Assessment questions at Screening will be collected to have information on their typical sleep habits and to determine study participation eligibility [redacted]

Based on the sleep habits assessment, participants will be excluded if they meet either criteria:

- Usual bedtime later than 1 AM (0100 hours)
- Usual nightly total sleep time is < 6 hours [redacted]

8.3.2. Sleep Diary

The Sleep Diary [redacted] is a self-administered questionnaire that participants will complete on 3 consecutive mornings prior to Visits 3, 5 and 8 (2 mornings leading up to the day of the site visit and the morning of the site visit). Study site staff will review the sleep diary at Visits 3, 5 and 8 as listed the SoA (Section 1.3). [redacted]

[redacted]

Each participant's diary will be collected (if available) and stored with other source documents. If a diary is missing or incomplete, site staff should ask the participant about their sleep during the last 3 nights and recent travel to evaluate whether the visit should be rescheduled due to insufficient sleep or travel.

For any study site visits that are rescheduled due to insufficient sleep (ie, < 4 hours on any of the 3 prior nights) prior to the visit or significant travel (ie, crossing a time zone), the visit window will be extended without being considered a protocol violation.

8.3.3. Obstructive Sleep Apnea Therapy Adherence

Study site personnel should collect and record participants' OSA therapy adherence information; data will be recorded but will not be used to discontinue/early discontinue any participants. Typically, this will consist of downloading data from the PAP machine. Participants who have undergone surgery and are not currently using PAP therapy will not require documented adherence. During the Screening and Baseline visits, adherence will be reviewed to assess inclusion/exclusion criteria. Adherence will be recorded according to the SoA (Section 1.3).

8.3.4. Caffeine and/or Nicotine Intake Check

Sites should ask about caffeine and/or nicotine intake as described in the SoA (Section 1.3). Specifically, sites should verify that participants are complying with the caffeine/nicotine restrictions outlined Section 6.8 before, and during site visits. Sites should record in the source documents any noncompliance, and determine if participants should be rescheduled or terminated as deemed appropriate by the investigator.

8.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.4.1. Physical Examinations

- A complete PE will include, at a minimum, assessment of the cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded. At Screening and Baseline/Randomization visits, sites must calculate body mass index in order to verify eligibility.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
  - Any abnormalities identified at the Screening PE should be recorded as medical history.
  - Any clinically significant abnormalities identified after initiating study intervention should be recorded as AEs.

8.4.2. Vital Signs

Vital signs will be collected prior to study intervention administration for Visit 5 and Visit 8.

- Oral temperature, pulse rate, respiratory rate, and BP will be assessed.

- Blood pressure and pulse measurements will be assessed in the sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 BP measurements (3 consecutive BP readings will be recorded at intervals of at least 1 minute). The average of the 3 BP readings will be recorded.
- For clinically significant abnormal vital signs results, sites should document them in the medical history (Screening and Randomization) or as AEs (after initiating study intervention).

8.4.3. Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and corrected QT interval (QTc) intervals. Any abnormal safety assessments including ECG readings considered clinically significant in the medical and scientific judgment of the investigator should be reported as an AE (Appendix 4). The investigator should review the ECG and document that review in the source documents.
- For clinically significant abnormal ECG results, sites should document them in the medical history (Screening results) or as AEs (after initiating study intervention).

8.4.4. Clinical Safety Laboratory Assessments

- See Appendix 3 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE (after initiation study intervention). The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with abnormal values considered clinically significant during participation in the study or within 14 days after the last dose of study intervention (and considered by the investigator to be related to study drug) should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the investigator or medical monitor.
  - If clinically significant values do not return to normal/Baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

- All protocol-required laboratory tests, as defined in Appendix 3, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

8.4.5. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at Screening, and at Baseline visits.
- Pregnancy testing (urine or serum as required by local regulations) should also be conducted at the end of relevant systemic exposure (SFU/ED visit).
  - If the SFU/ED visit is conducted remotely, the site will provide and ship the urine pregnancy test kit and facilitate the remote testing with the participant to document the test results.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during participation in the study.

8.4.6. Alcohol and Drug Screen

Breath alcohol and urine drug screen tests will be performed at the study site. Test results will be recorded and any participants who are noncompliant should be discontinued early from the study.

8.4.7. Suicidal Ideation and Behavior Risk Monitoring

Participants in this study should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of intervention, or at the time of dose changes, either increases or decreases. As the study is blinded, this will require site staff to monitor such signs throughout the duration of the study. Participants who experience signs of suicidal ideation or behavior should undergo a risk assessment. All factors contributing to suicidal ideation and behavior should be evaluated and consideration should be given to discontinuation of the study intervention.

When informed consent has been given, families and caregivers of participants being treated with solriamfetol should be alerted about the need to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior and to report such symptoms immediately to the study investigator.

Baseline assessment of suicidal ideation and behavior/ intervention emergent suicidal ideation and behavior will be monitored during the study using Columbia-Suicide Severity Rating Scale (C-SSRS).

Active suicidal ideation (e.g., a positive response to Question 4 or 5 on the C-SSRS or behavior; or a positive response to any suicidal behavior question on the C-SSRS) must be recorded as an AE and reported to the sponsor or designee within 24 hours of first knowledge of the event by study personnel. Please refer to Appendix 4 for details on reporting OREs.

At the Screening Visit, the C-SSRS will be administered by appropriately trained personnel to participants to exclude any individuals with active suicidal ideation or behavior. Suicidal ideation will be assessed for lifetime and over the past 12 months, and suicidal behavior will be assessed

for lifetime and over the past 5 years with the Baseline/Screening Version of the C-SSRS. The C-SSRS (since last visit version) will be administered to participants at subsequent times as indicated in the Schedule of Events (Section 1.3).

8.5. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 4.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs (see Appendix 4).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

8.5.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Events Information

All AEs and SAEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA (Section 1.3).

Note: All SAEs that occur after the consent form is signed but before study intervention/treatment must be reported by the investigator if they cause the participant to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure**.**

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and within 24 hours of first knowledge of the event by study personnel, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator should promptly notify the sponsor.

8.5.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.5.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is

otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 4.

8.5.4. Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports will be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary. The Reference Safety Information for the determination of expectedness of solriamfetol can be found in the IB.

8.5.5. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 14 days after the last dose of the study intervention.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant (or the participant's pregnant female partner) will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant (or the participant's pregnant female partner) and the neonate, and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.5.4. While the investigator is not obligated to actively seek this information

in former study participants (or the participant's pregnant female partner), he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.5.6. Overdose, Medication Errors, and Misuse

Overdose (defined as any dose administered or received that was higher than the intended dose), medication errors (defined as any unintentional error in the dispensing or administration of the study drug), and misuse of the study drug are considered reportable experiences. The method for completing and transmitting reports of these experiences are provided in Appendix 4.

If any overdose, medication error, or misuse of the study drug results in an AE, this must be recorded. If the AE is serious, it must also be reported as described in Appendix 4.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.6. Pharmacokinetics

Pharmacokinetics will not be evaluated in this study.

8.7. Genetics

Genetics will not be evaluated in this study.

8.8. Biomarkers

Biomarkers will not be evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are not applicable to this study.

8.10. Health Economics

Health economics will not be evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

9.1.1. Primary Hypothesis

The primary statistical hypothesis for this study is to show whether solriamfetol has a significantly improved effect versus placebo on the primary endpoint of the changes in average DSST scores (average of the postdose DSST scores [hour 2, 4, 6, and 8] versus average of the Baseline DSST scores) after 2 weeks of treatment (H_1: $\mu_{sol} - \mu_{pl} > 0$) using a 1-sided significance level of 0.025. The statistical null hypothesis is that solriamfetol does not improve versus placebo on the change in DSST scores after 2 weeks of treatment (H_0: $\mu_{sol} - \mu_{pl} \leq 0$).

9.2. Sample Size Determination

A sample size of 49 participants per treatment sequence for a total sample size of 98 will provide 90% power to detect a difference of 3 points in means for the change from Baseline to Week 2 on DSST RBANS scores between solriamfetol and placebo, assuming a standard deviation of 9 points in the change in DSST (the cross over analysis of variance [ANOVA] root mean squared error (RMSE) is 6.36). The sample size estimates are based on the results from Trintellix randomized parallel placebo-controlled trials (McIntyre 2014; Mahableshwarkar 2015). The change from Baseline to Week 8 resulted in an estimated delta on DSST performance score of 1.8 ~ 4.3 (average 3.4) and SD of 6.6 ~ 8.6. Another reference is a crossover study with 5 dosages of MK-0249, modafinil 200 mg, and placebo and each period is 2 weeks, the RMSEs are estimated from 4.4 ~ 5.7 (Herring 2013). It is increased to 6.36 to account for uncertainty in sample size assumptions. A 1-sided significance level of 0.025 using a 2 group t-test (crossover ANOVA) is used in the sample size calculation. Assuming a correlation of 0.5 between periods on DSST, a delta of 3, a standard deviation of 9, and a 15% dropout rate, a total of 116 (58 participants per treatment sequence) will be randomized.

Note: "Randomized" means a participant who consented to the study and was assigned to a randomized treatment group and received at least 1 dose of study intervention.

9.3. Analysis Populations

Population	Description
Safety	All randomized participants who receive at least 1 dose of study intervention. This analysis set will be used for safety analyses and participants should be summarized according to actual treatment. This population will be analyzed for safety evaluations and will be presented in the tables and listings of safety data.
ITT	All randomized participants.
mITT	All participants who were randomized, received at least 1 dose of study medication, have Baseline and at least 1 postdose evaluation of DSST. If a participant in the mITT population does not have an assessment for a particular endpoint, it will be excluded in the analysis of that endpoint. The primary efficacy analyses will be based on the mITT population.

Abbreviations: DSST = Digit Symbol Substitution Test; ITT = Intent-to-Treat; mITT = modified ITT

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to the database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and secondary endpoints.

9.4.1. General Considerations

All study data will be summarized using descriptive statistics. Categorical variables (eg, race, ethnicity) will be reported as frequency and percent. Continuous variables will be reported as number of participants, mean, SD, median, minimum, and maximum (eg, age, weight). All summaries, statistical analyses, and individual participant data listings described below will be completed using the SAS Statistical Analysis System (SAS Institute, Inc.; Cary, NC)

9.4.1.2. Definition of Study Periods for Analysis

There are 2 periods, treatment period and crossover treatment period. Efficacy will be analyzed and summarized based on the modified Intent-to-Treat analysis set. Safety will be summarized based on the Safety Population.

9.4.1.3. Intercurrent Event Strategies

The following are intercurrent events that may occur during the study:

- Study treatment discontinuation due to AEs, lack of efficacy or use of other (prohibited) concomitant medications, etc.
- Withdrawal from the study

- Lost to follow-up

Participant's DSST data will not be collected if the participant discontinues the treatment (while on treatment policy strategy). Missing assessments after discontinuation of treatment due to AE, lack of efficacy, or any other reasons will not be imputed for primary analysis.

9.4.1.4. Pooling of Investigational Centers

Data from all investigational centers will be pooled for primary and secondary endpoints analyses. Data may also be pooled by region as appropriate for exploratory analyses.

9.4.1.5. Dropouts and Missing Data

Missing data will not be imputed. For the primary endpoint, if any of the 2-, 4-, 6-, or 8-hour DSST RBANS are missing, the average of the nonmissing assessments be used. If all assessments are missing then it will be considered missing.

9.4.2. Primary Endpoints

The primary estimand is described in Section 3. The primary outcome measure is the change from the average of the DSST RBANS scores at Baseline to the average of the postdose DSST RBANS scores at the end of each double-blind treatment period. This will be analyzed using a Mixed Model with Repeated Measures (MMRM). The model will include sequence, participant within sequence, treatment (solriamfetol and placebo), period as fixed effects, and the baseline average of the DSST RBANS scores as the covariate. The unstructured covariance for the repeated measurements will be assumed. The treatment effects, the 2 sided 95% confidence interval (CI) of treatment difference (solriamfetol - placebo) will be presented.

9.4.3. Secondary Endpoints

The secondary estimands are described in Section 3. The same methods used for primary efficacy analysis will be used for the secondary endpoints. .

9.4.4. Exploratory Endpoint(s)

The exploratory endpoints are the correlations between the change from Baseline at the end of each double-blind study treatment period in ESS and DSST RBANS score, BC-CCI, and PGI-S. Nominal p-values will be provided with appropriate 95% CIs for the exploratory endpoints.

9.4.5. Safety Analyses

Safety analyses will be performed for the Safety Population. No formal statistical testing will be performed.

9.4.6. Other Analyses

There are no other analysis (eg, subgroups of interest) planned for this study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC, before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require regulatory authority approval as applicable according to local regulations prior to initiation, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Safety Committee Structure

The Sponsor recognizes the importance of ongoing review of the accumulating safety and efficacy data. The Sponsor will perform periodic safety data monitoring regularly by data listing review. In addition, safety data from the study will be reviewed on an ongoing basis as part of routine pharmacovigilance and safety surveillance activities. Reports of safety findings (from either single events or based on aggregate review) that suggest a significant risk to humans will be distributed to all participating Investigators and to the relevant regulatory authorities and IRBs/IECs.

10.1.6. Dissemination of Clinical Study Data

The sponsor of the study is solely responsible for disclosing results on ClinicalTrials.gov, EudraCT, and other public registries in accordance with applicable global laws and regulations. By signing this protocol, the investigator acknowledges that all posting requirements are solely the

responsibility of the sponsor, and agrees not to submit any information about the study or its results.

10.1.7. Data Quality Assurance

- Investigators and site staff will be trained on protocol procedures and electronic case report form (eCRF) completion prior to enrolling participants in the study.
- All participant data relating to the study, will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the case report form (CRF).
- Guidance on completion of CRFs will be provided in the CRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues, and monitoring techniques (central, remote, or onsite monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organization [CRO]).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator or institution/site as applicable, for the period of time established in the clinical study agreement entered into by the investigator's study site unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the eCRF Completion Guidelines.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

10.1.9.1. First Act of Recruitment

The study start date is the date on which the first participant has the first visit.

10.1.9.2. Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

Details on the Publication Policy for this study are provided in the Clinical Trial Agreement.

APPENDIX 1. ABBREVIATIONS AND DEFINTIONS

Abbreviation	Description
AE	adverse event
BC-CCI	British Columbia-Cognitive Complaints Inventory
BP	blood pressure
CFR	Code of Federal Regulations
CI	confidence interval
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CRO	Contract Research Organization
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSST	Digit Symbol Substitution Test
ECG	electrocardiogram
ED	early discontinuation
EDS	excessive daytime sleepiness
eCRF	electronic case report form
ESS	Epworth Sleepiness Scale
EU	European Union
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	interactive response technology
MAOI	monoamine oxidase inhibitor
MDD	major depressive disorder
MMRM	Mixed Model of Repeat Measures

Abbreviation	Description
OREs	other reportable events
OSA	obstructive sleep apnea
OTC	over-the-counter
PAP	positive airway pressure
PE	physical examination
PGI-S	Patients Global Impression of Severity
PK	pharmacokinetic(s)
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
SAE	serious adverse event
SFU	Safety Follow-up
SmPC	Summary of Product Characteristics
SoA	Schedule of Assessments
solriamfetol	Also known as Sunosi, JZP-110, ADX-N05, R228060, and YKP10A
THC	tetrahydrocannabinol
US	United States
USPI	United States Package Insert
WAIS	Wechsler Adult Intelligence Scale
WONCBP	woman of nonchildbearing potential

APPENDIX 2. REFERENCES

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APPENDIX 3. CLINICAL LABORATORY TESTS

- The tests detailed in Table 6 will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 6: Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters			
Hematology (fasting)	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[a] (fasting)	BUN	Potassium	AST/SGOT	Total and direct bilirubin
	Creatinine	Sodium	ALT/SGPT	Total Protein
				Thyroid panel
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal)			
Pregnancy testing	A highly sensitive serum human chorionic gonadotropin pregnancy test will be administered at Screening and analyzed by the central laboratory. A urine pregnancy test will be administered at the clinic site during the Baseline/Randomization visit, and the SFU/ED visit.[1]			
Other Screening Tests	All study-required laboratory tests as outlined above will be performed by a central laboratory, with the exception of the urine drug Screening test, which will be performed at the site with kits supplied by a central laboratory. Urine drug screen (dipstick [to include at minimum: amphetamine, methamphetamine, tricyclic antidepressants, propoxyphene, benzodiazepines, barbituates, cocaine, marijuana, morphine, ecstasy, oxycodone, buprenorphine, methadone, or phencyclidine]) Breath alcohol screen will also be performed onsite using a breathalyzer.			

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ED = early discontinuation; IRB/EC = Institutional Review Board/ Ethics Committee; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; RBC = red blood cell; SFU = Safety Follow-up; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cell.

[a] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

APPENDIX 4. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of Adverse Events

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of Unsolicited and Solicited AE
• An unsolicited AE is an AE that was not solicited using a Participant Diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs. • Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The participant will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records • Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during interview with the participant and by review of available medical records at the next visit • Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence SAE that, at any dose:
Results in death
Is life-threatening • The term "life-threatening" in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a preexisting condition that did not worsen from Baseline is not considered an AE.
Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Is a suspected transmission of any infectious agent via an authorized medicinal product

An SAE is defined as any untoward medical occurrence SAE that, at any dose:

Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

Recording and Follow-up of Adverse Events and/or Serious Adverse Events

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or its designee in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or its designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or its designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:
  - Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only
  - Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
  - Severe: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. An AE/SAE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
  - Life-threatening: life-threatening consequences; urgent intervention indicated.
  - Fatal: death related to AE
- When the severity of an AE increases over time, the increase in the severity will be recorded as a new AE and the original AE will stop when the new AE starts.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor or its designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or its designee. • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor (or designee) to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or its designee with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to the sponsor or its designee within 24 hours of receipt of the information.

Reporting of Serious Adverse Events

SAE Reporting to the Sponsor or its designee

- SAEs must be reported to the sponsor (or designee) using an SAE Reporting Form within 24 hours of first knowledge of the event by study personnel.
- The site will also enter the SAE data into the case report form (CRF) as soon as it becomes available.
- The form, instructions on completion, and contact information can be found in the Investigator trial binder.
- The SAE Reporting Form should be completed as much as possible before transmittal.
- Contacts for SAE reporting can be found in the Investigator trial binder.

Reporting of Other Reportable Experiences

- Other reportable experiences (OREs) must be reported to the sponsor or its designee using an ORE Reporting Form within 24 hours of first knowledge of the event by study personnel.
- The form, instructions on completion, and contact information can be found in the Investigator trial binder.
- The ORE Reporting Form should be completed as much as possible before transmittal.
- Contacts for ORE reporting can be found in the Investigator trial binder.

APPENDIX 5. CONTRACEPTIVE AND BARRIER GUIDANCE

Definitions

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to 1 of the following:
   a. Documented hysterectomy
   b. Documented bilateral salpingectomy
   c. Documented bilateral oophorectomy
   d. For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal female
   a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
      - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
      - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of < 1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device
• Intrauterine hormone-releasing system[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

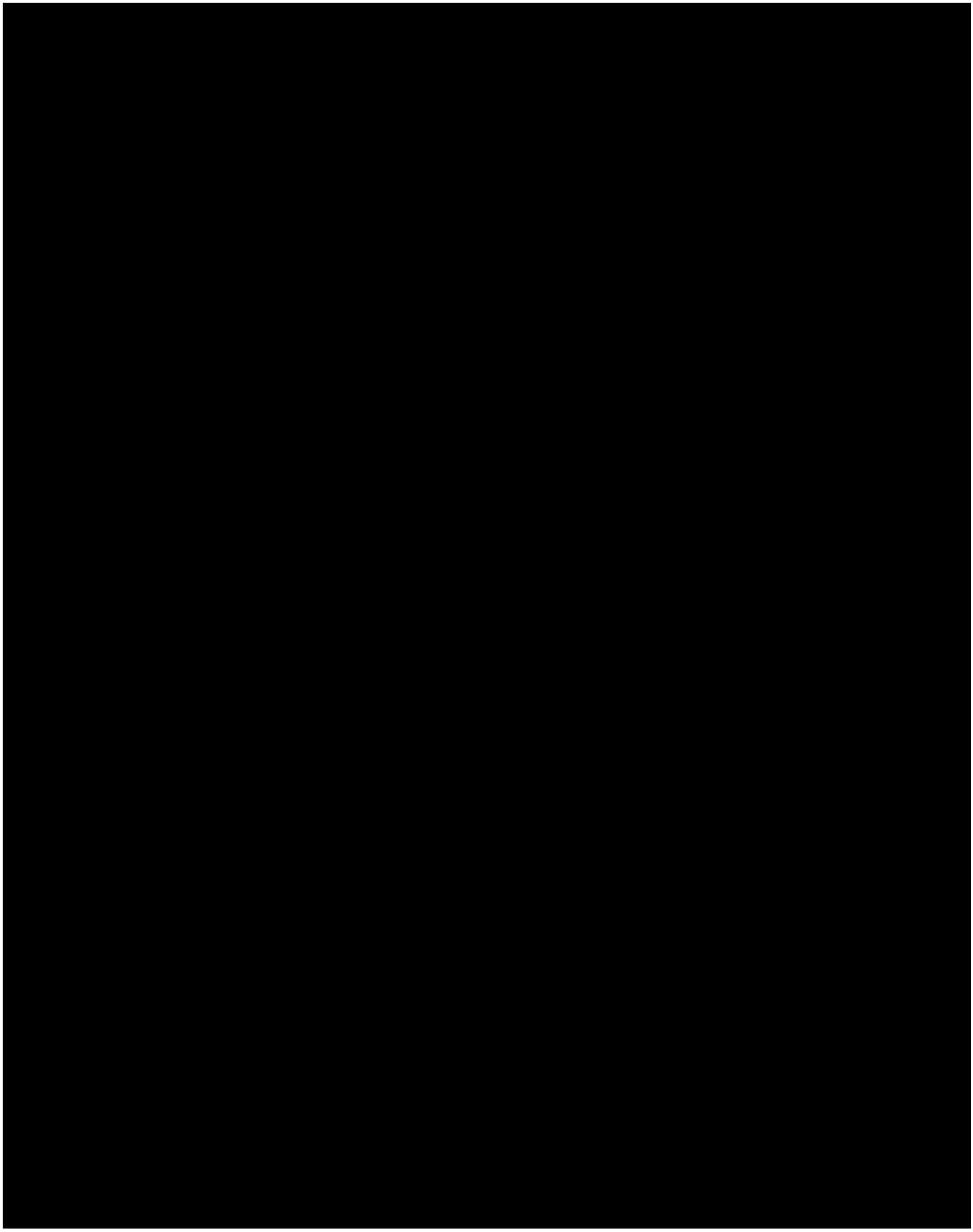
CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

[b] Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[c] If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together due to risk of failure from friction.



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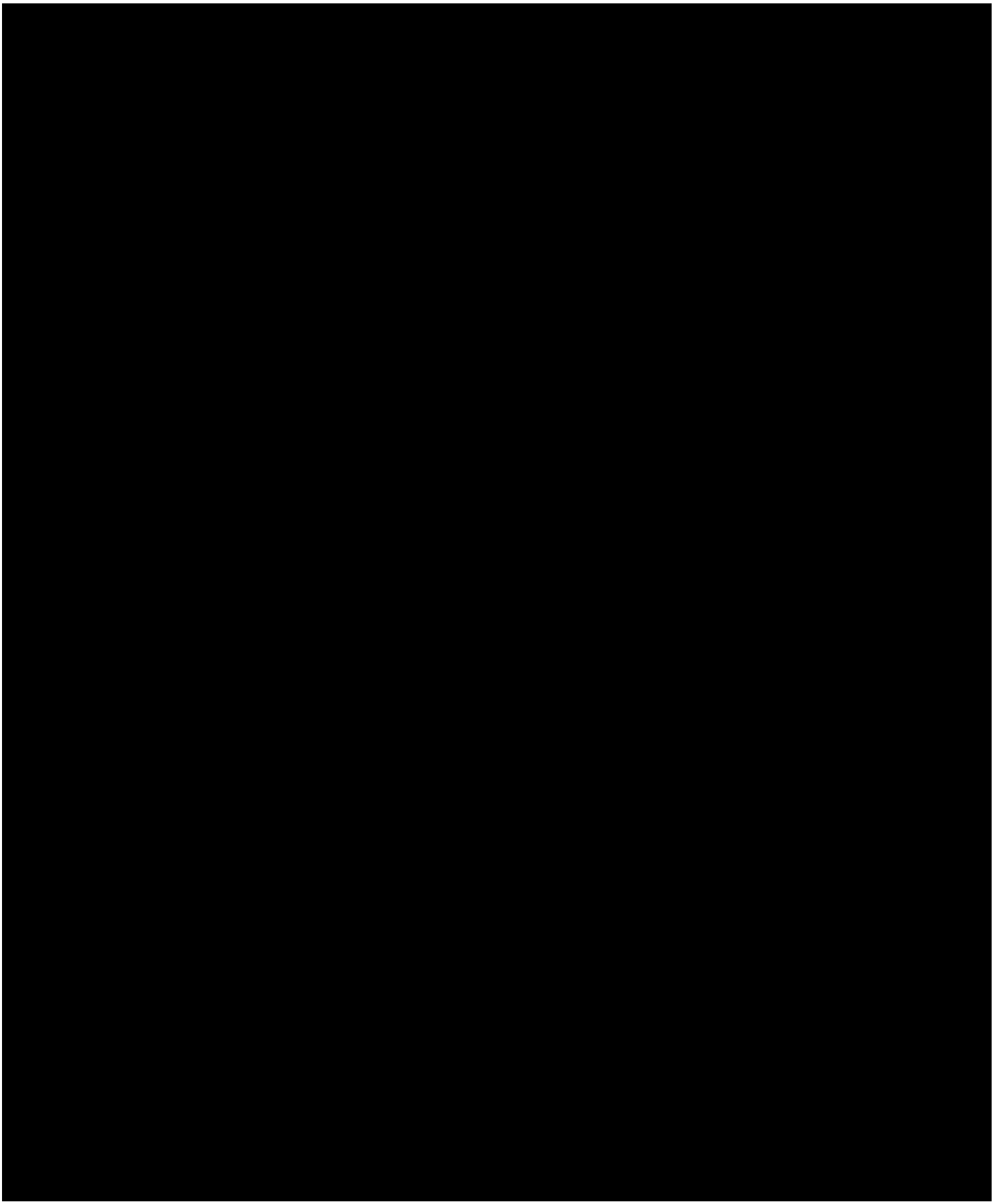

APPENDIX 9. SIGNATURE OF INVESTIGATOR'S AGREEMENT

PROTOCOL NUMBER:	JZP110-405
PROTOCOL TITLE:	Solriamfetol's Effect on Cognitive Health in Apnea Participants During a Randomized Placebo controlled Study (SHARP): a 5 Week Double blind, Placebo controlled, Randomized, Crossover, Multicenter Study of Solriamfetol in Improving Cognitive Function in Participants With Excessive Daytime Sleepiness Associated With Obstructive Sleep Apnea Plus Impaired Cognitive Function
PROTOCOL	Amendment 1: 12Aug2022

I have read this protocol and the Investigator's Brochure and agree to conduct this clinical study as outlined herein. I will ensure that all sub-investigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with Axsome and its designated vendors during the study. I carry out the study in accordance with the revised Declaration of Helsinki 1996. I will adhere to all applicable regulations and guidelines regarding clinical studies on a study drug during and after study completion.

Having considered fully all the available information, I consider it is ethically justifiable to give the study drug to selected participants in my care according to the study protocol. I:

- Agree to use the study material, including the study drug, only as specified in the protocol and understand that changes cannot be made to the protocol without prior written approval from Axsome Therapeutics.
- Understand that any violation of the protocol may lead to early termination of the study.
- Agree to report any serious AE, whether or not considered related to administration of the study drug, to Axsome Therapeutics within the required timeframe.
- Agree to comply with Axsome Therapeutics and regulatory requirements for the monitoring and auditing of this study.

I, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

Investigator's site name and address:

_____

_____

_____