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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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STATISTICAL ANALYSIS PLAN

VERSION: 1.00
DATE: AUGUST 17, 2022

STUDY DRUG:

JZP-110 (solriamfetol)

PROTOCOL NUMBER:

JZP110-405

STUDY 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 (SHARP)

SPONSOR:

Axsome Therapeutics

[redacted]

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

SIGNATURE PAGE

TABLE OF CONTENTS

LIST OF TABLES

1. DOCUMENT HISTORY

Version	Date	Changes made since previous version
1.00	August 17, 2022	Original

2. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Definition
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 Conference 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
OREs	other reportable events
OSA	obstructive sleep apnea
OTC	over-the-counter
PAP	positive airway pressure

PE	physical examination
PGI-S	Participants 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

3. INTRODUCTION

This statistical analysis plan (SAP) is based on Protocol JZP110-405 Amendment 1.

The purpose of this document is to provide details on study populations and on how the variables will be derived, how missing data will be handled, as well as details on statistical methodologies to be used to analyze the safety and efficacy data from the study.

The document may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. However, the final SAP must be finalized, approved by the Sponsor, and placed on file before the database is locked and treatment codes are unblinded. The approved plan will be used to carry out all analyses for the Clinical Study Report. Deviations, if any, from the approved plan will be noted in the Clinical Study Report.

4. STUDY DESIGN

4.1. Study Objectives and Endpoints

The table below summarizes the objectives and endpoints for the study:

Objectives	Estimands and Endpoints
Primary Objective	
To **evaluate the efficacy** of solriamfetol on cognitive function in adult participants with excessive daytime sleepiness (EDS) associated with OSA (obstructive sleep apnea) 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 modified Intent-to-Treat (mITT) set, defined as: all randomized participants with at least 1 dose of study drug and 1 postdose assessment of Digit Symbol Substitution Test (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 adverse event (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	**Secondary Estimands**
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 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 overall score in British Columbia-Cognitive Complaints Inventory

Objectives	Estimands and Endpoints
	(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
To **further evaluate the efficacy** of solriamfetol on cognitive function in adult participants with EDS associated with OSA plus impaired cognitive functioning	<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 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: 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	<u>The estimand for this secondary objective to evaluate the effect on cognition at individual post-dose timepoints 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

Objectives	Estimands and Endpoints
	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
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
To **evaluate the efficacy** of solriamfetol on patient-reported global impression of concentration,	<u>The second estimand for this secondary objective evaluating efficacy is defined by the following:</u>

Objectives	Estimands and Endpoints
memory, and thinking skills in adult participants with EDS associated with OSA plus impaired cognitive functioning	• 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
To **evaluate the efficacy** of solriamfetol on improving EDS in adult participants with EDS associated with OSA plus impaired cognitive functioning	<u>The 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 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

Objectives	Estimands and Endpoints
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 = Participants Global Impression of Severity; TEAE = treatment emergent adverse event.

4.2. Study Treatments

The active treatment in this study is Sunosi® (solriamfetol) and the matching control is placebo. In this 2-way crossover study, participants in Sequence 1 will receive active treatment in Period 1 and placebo in Period 2, while participants in Sequence 2 will receive placebo in Period 1 and active in Period 2. During the active treatment, participants will receive 75 mg for the first 3 days and 150 mg for the remaining days.

4.3. Study Design

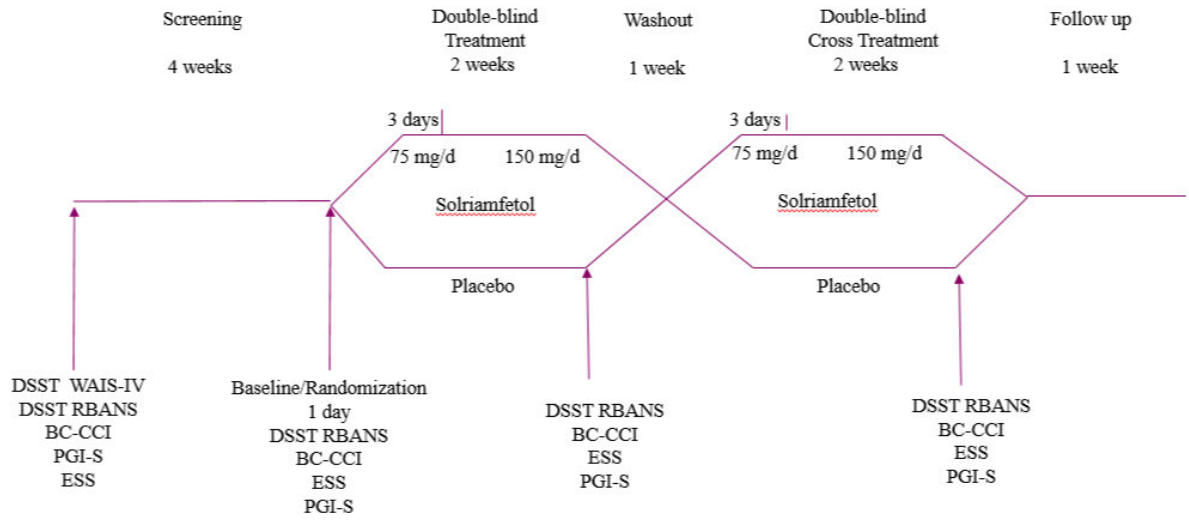
4.3.1. Summary

This is a phase 4, multicenter, randomized, double-blind, placebo-controlled, 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 RBANS (an objective test) and the British Columbia Cognitive Complaints Inventory (BC-CCI) (a subjective test). The DSST RBANS 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) and has also been used to measure cognitive deficits in individuals with poor sleep quality.

The primary endpoint is the change from the average of the DSST RBANS scores at Baseline to the average of the postdose (2-, 4-, 6-, and 8-hours) 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 PGI-S; and change in overall score from Baseline to the end of each double-blind treatment period in ESS.

Figure 1: Study Schema



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

Table 2: 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
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
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**
Site Visit	X		X		X			X	X
Phone Contact		X		X		X	X		X
Informed Consent	X								
Review Inclusion/Exclusion Criteria	X		X						
Demographics	X								
Height	X								
Weight	X		X		X			X	
Medical History	X		X						
Adverse Events					X			X	X
Sleep Habits Assessment	X								
Physical Examination	X								
Caffeine and/or Nicotine Intake Assessment	X		X		X			X	
Urine Drug Screen (dipstick)	X		X		X			X	
Breath Alcohol Screen	X		X		X			X	
Vital Signs	X		X		X			X	
12-Lead ECG	X								
Serum Pregnancy Test	X								
Urine Pregnancy Test (dipstick)			X						X
Chemistry, hematology and urinalysis (fasting)	X								
Thyroid Panel	X								
OSA Therapy Adherence Check	X		X		X			X	
C-SSRS (Baseline/Screen version)	X								
C-SSRS (Since Last Visit Version)			X		X			X	
Oversee study drug consumption at site					X			X	
Collect study drug/assess compliance					X			X	X
DSST WAIS-IV	X								
DSST RBANS	X		X		X			X	
BC-CCI	X		X		X			X	
PGI-S	X		X		X			X	
Dispense Sleep Diary	X		X		X				
Sleep Diary Review			X		X			X	
Participant Reminder		X		X			X		
ESS	X		X		X			X	
Concomitant Medications	X		X		X			X	X
Confirm study drug was not taken for 1 week and instruct taking study drug the next day						X			
Randomization			X						
Dispense study drug and remind participants to bring blister pack/bottle with them to next visit			X		X				

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 RBANS =Digit Symbol Substitution Test Repeatable Battery for the Assessment of Neuropsychological Status; ECG=electrocardiogram; ED=Early Discontinuation; ESS=Epworth Sleepiness Scale; OSA=obstructive sleep apnea; PGI-S=Patients Global Impression of Severity; SFU=Safety Follow-up; DSST WAIS-IV= Digit Symbol Substitution Test Wechsler Adult Intelligence Scale, Fourth Edition.

4.3.2. Randomization and Blinding

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 will complete the assessments outlined in the Schedule of Assessments. At the end of the Baseline and Randomization visit, participants will receive the double-blind study intervention for Treatment Period 1.

Unblinding procedures can be found in Section 6.3 of the protocol.

5. EFFICACY ASSESSMENTS

5.1. 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.

5.1.1. 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 DSST WAIS IV form, participants will receive a number and must match the symbol, as quickly and accurately as possible, within 120 seconds.

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

The DSST RBANS will serve as the primary efficacy endpoint. To complete the DSST 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.

5.2. 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. 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.

Four categories of cognitive complaints have been defined for the BC-CCI total score:

- Broadly normal: 0 to 4
- Mild: 5 to 8
- Moderate: 9 to 14
- Severe: 15 to 18

Three additional, non-scored, 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.

5.3. 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 options are as follows:

- None (0)
- Mild (1)
- Moderate (2)
- Severe (3)
- Very severe (4)

5.4. 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’.

6. ANALYSIS POPULATIONS

6.1. Enrolled Population

The Enrolled Population will include all subjects who sign the informed consent form. This population will be used for analyses of all enrolled subjects disposition.

6.2. Safety Population

The Safety Population will consist of all randomized participants who received 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.

6.3. Intent-To-Treat (ITT) Population

The Intent-to-Treat (ITT) Population will consist of all randomized participants. [redacted]

6.4. Modified Intent-To-Treat (mITT) Population

The modified Intent-to-Treat (mITT) population will consist of all participants who were randomized, received at least 1 dose of study medication, and have Baseline and at least 1 postdose evaluation of the DSST RBANS. If a participant in the mITT population does not have an assessment for a particular endpoint, the missing assessment will be excluded in the analysis of that endpoint.

The primary efficacy analyses will be based on the mITT population.

6.5. Per Protocol Population

The Per Protocol population will include all mITT participants without important major protocol violations. The criteria for important major protocol violation will be determined and documented prior to database lock and unblinding of treatment codes. Participants with important major protocol violations will be flagged in data listings.

Additional efficacy analyses may be performed on the Per Protocol population.

7. GENERAL CONVENTIONS

Unless otherwise stated, all analyses will be performed using SAS Version 9 and all hypothesis tests will be conducted at a two-sided significance level of 0.05. P-values will be presented with 3 decimals and p-values that are less than 0.001 will be presented as <0.001.

Continuous data will be summarized using descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Frequencies and percentages will be used to summarize categorical (discrete) data. Presentations of categorical data will generally suppress percentages for items where the count is zero in order to draw attention to the nonzero counts. In general, mean, SD, median, minimum, maximum, and percentages will be presented with one decimal.

Unless otherwise stated, confidence intervals, when presented, will be constructed at the two-sided 95% level. For binomial variables, the 95% confidence intervals will be constructed using the normal approximation without continuity correction.

Data listings will present all data collected on case report forms (CRFs) by study drug, center, and participant number.

7.1. Definition of Baseline

Unless otherwise stated, the last observed measurement prior to or on the date of randomization will be considered the baseline measurement. For the primary endpoint, baseline for the DSST RBANS will be the average of the 4 DSST RBANS scores (2-, 4-, 6-, and 8 hour) at Visit 3.

[redacted]

7.3. SAP Version Control Convention

The first approved versions of the SAP will be numbered sequentially as Version 1.00. As mentioned in the introduction, the SAP may evolve over time due to reasons such as protocol amendment or regulatory feedback, the subsequent approved version(s) will be numbered as sequentially as Version 1.0i. The reason for the changes must be documented in the SAP history log. The final version to be used for the analysis must be filed before the database lock and labelled as Final Version 1.xy. The Clinical Study Report will document any changes made after the Final Version.

8. DESCRIPTION OF THE STUDY POPULATIONS

All tables, figures, and listings must include a population descriptor (e.g., mITT, Safety, or Per Protocol) in the titles.

8.1. Disposition

Participant disposition summaries will be presented by Sequence and will include the number of participants screened, randomized, and percentage of participants who complete the study. The summaries will also include the reasons for early discontinuation from the study.

Disposition summaries will be presented for Enrolled, Safety, mITT, ITT and Per Protocol (if applicable) populations separately.

8.2. Demographics and Baseline Characteristics

A summary of demographics and baseline characteristics will be presented by the Sequence and overall, for the Safety, mITT, and Per Protocol (if applicable) populations. The demographic characteristics will, at the minimum, consist of age, sex, ethnicity, and race using descriptive statistics. Baseline characteristics may include the WAIS DSST score at screening (i.e., total number correct and age-scaled score).

8.3. Medical History

A medical history listing will be presented for the Safety Population and may also be summarized.

9. PRIOR AND CONCOMITANT MEDICATIONS

All medications recorded on the CRFs will be coded using the WHO Drug Dictionary Version B3 March 2021. Prior and concomitant medications will be summarized by treatment arm in the safety population by WHO Drug base substance preferred name.

Prior medications are defined as medications with stop dates occurring before the date of first administration of any study treatment. Concomitant medications are defined as medications with start dates occurring on or after the date of first administration of any study treatment and no more than 30 days after the last study visit. Medications with start and stop dates that bracket the date of first administration of a study treatment will be summarized as both prior and concomitant medications.

Medications that were clearly stopped prior to the date of first administration of a study treatment will be included in the prior medications table, and medications that were clearly started on or after the date of first administration of any study treatment component will be included in the concomitant medications table. All other medications will be included in both the prior and concomitant medications tables.

Prior and concomitant medications will be summarized for the Safety Population.

10. EFFICACY ANALYSES

10.1. Primary Efficacy Variable

The primary objective of the study is to evaluate the efficacy of solriamfetol as measured by the change from baseline (Visit 3) in the average of the DSST RBANS scores at the end of each double-blind treatment period, where the average is the average of non-missing scores from Hours 2, 4, 6, and 8. It should be noted that the scores obtained at the pre-dosing (practice) are performed to re-orient the participants for the test and these scores will not be included in the average.

10.1.1. Derivations of the Primary Efficacy Variable

The primary efficacy variable is the change from baseline in the average of the DSST RBANS scores at the end of each double-blind treatment period. The change will be calculated as:

Change = Post Baseline - Baseline

A positive change is indicative of improvement.

The estimand will be based on the following four attributes:

1. Population: defined through study design and inclusion/exclusion criteria outlined in Sections 5.1 and 5.2 of the protocol to reflect the targeted patients with EDS associated with OSA plus impaired cognitive functioning;

2. Variable: change from baseline to end of active treatment in the average of the DSST RBANS scores;

3. Intercurrent event: no intercurrent events to be taken into account;

4. Population-level summary: the difference in the primary variable means between active and placebo conditions.

The estimand is then the difference in means between active and placebo in the change from baseline in the primary measurement in the targeted participant population.

10.1.2. Primary Analyses

The primary efficacy variable, change from baseline in the average of the DSST RBANS scores, 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.

10.2. Secondary Efficacy Outcomes

The key secondary endpoints are:

- Change from Baseline in BC-CCI overall score to the end of each treatment period for solriamfetol versus placebo
- Change from Baseline in PGI-S to the end of each treatment period for solriamfetol versus placebo
- Percent of participants with an at least 1 category improvement in the PGI-S from Baseline to the end of each treatment period for solriamfetol versus placebo
- Percent of participants with an at least 1 category improvement in the BC-CCI from Baseline to the end of each treatment period for solriamfetol versus placebo
- Change from Baseline in ESS score to the end of each treatment period to the end of each treatment period for solriamfetol versus placebo
- Change in DSST RBANS score at 2 hours postdose from Baseline to the end of each treatment period for solriamfetol versus placebo
- Change in DSST RBANS score at 4 hours postdose from Baseline to the end of each treatment period for solriamfetol versus placebo
- Change in DSST RBANS score at 6 hours postdose from Baseline to the end of each treatment period for solriamfetol versus placebo
- Change in DSST RBANS score at 8 hours postdose from Baseline to the end of each treatment period for solriamfetol versus placebo

The variables related to change from baseline will be analyzed using the same methods used to analyze the primary efficacy variable.

Variables related to percentages will be analyzed via exact methods. Percentages of responders for the two treatments will be presented. The percentages, percentage differences, and the two-sided 95% confidence intervals of the differences as well as the p-values of the differences will be presented.

In these analyses, missing values will be considered failure.

10.3. 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.

10.4. Missing Value Handling Procedures

Unless otherwise stated, missing values will not be imputed.

10.5. Interim Analyses

No interim analysis will be performed.

[redacted]

10.7. Power and Sample Size Justification

The new Sponsor has determined to conclude the study. The sample size justification provided by the protocol prior to the Amendment is outlined below:

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.

11. SAFETY ANALYSES

Safety analyses will be performed on the Safety Population. Safety evaluations will be based on the incidence and severity of adverse events, as well as on ECG measurements, vital signs and Columbia Suicide Severity Rating Scale (C-SSRS). Safety variables will be tabulated and presented by study drug actually received.

In this crossover study, AEs will be attributed to the last treatment the participant received prior to the AEs.

Because there is no pre-specified safety outcome defined in terms of AEs or vital signs, any formal comparisons between the treatment arms with respect to specific safety parameters will be post-hoc.

11.1. Extent of Exposure

Summary statistics of exposure to study drug will be tabulated by treatment group. The exposure is defined as last dosing date – first dosing date + 1. The exposure will be summarized by summary statistics as well as by weekly frequency. Compliance is calculated as follows: compliance rate (%) = (number of tablets expected to be taken – number of missed doses /number of tablets should have been taken)*100.

11.2. Adverse Events

Each AE and SAE term will be recorded as a verbatim term on the case report forms (CRFs). All AEs and SAEs will be coded by primary System Organ Class (SOC) and mapped to a preferred term using the MedDRA Version 24.0. The investigator will assess AE severity and relationship to the study treatment.

All AEs will be listed. However, only treatment emergent adverse events (TEAEs) will be included in the AE summaries. A TEAE is defined as any AE with an onset date in the interval between the first study treatment dosing date and 7 days after the last study treatment dosing date. In addition, any AEs that the investigators deem to be treatment related will also be considered TEAEs and will be included in the AE summaries.

For the purpose of calculating treatment emergence and inclusion in summary tables, incomplete onset dates will be imputed using the method described in Appendix A.

AEs will be summarized by the number and percentage of participants in each primary SOC and preferred term. Participants will be counted only once for each primary SOC and each preferred term. Summary tables of AEs by primary SOC, preferred term and severity will be provided. If a participant has more than one AE coded to the same preferred term, the participant will be counted only once for that preferred term by using the event with the highest severity. Similarly, if a participant has more than one AE within a primary SOC category, the participant will be counted only once in that SOC category by using the event with the highest severity. AEs by

primary SOC, preferred term and relationship to study drug will be provided as well. If a participant has more than one AE coded to the same preferred term, the participant will be counted only once for that preferred term by using the most related event. Similarly, if a participant has more than one AE within a primary SOC category, the participant will be counted only once in that primary SOC category by using the most related event. In addition, serious adverse events (SAEs) by primary SOC and preferred term will be provided. Deaths and SAEs will be summarized similarly to AEs. All adverse event tables will also include the total number of events, counting multiple events per participant.

In the AE summary, preferred terms within each SOC will appear in descending frequency order within each active treatment group.

Frequencies for deaths and hospitalizations will also be summarized by treatment group and overall.

Columbia–Suicide Severity Rating Scale (C-SSRS) data will be summarized at scheduled visits and will be listed.

Other safety analyses will be performed as appropriate.

11.3. Clinical Laboratory Tests

Clinical laboratory tests including hematology, serum chemistry, urinalysis. and thyroid panel, will be collected at Screening only. The results will be presented in the listings.

11.4. ECG

Electrocardiograms (ECG) will be collected at screening only. ECG results will be presented in a listing.

11.5. Vital Signs

Vital sign values and change from baseline in the vital signs will be summarized by treatment that the participants last received.

11.6. Physical Exam

Physical exam data for each participant will also be presented in a listing.

12. IDENTIFICATION AND SUMMARY OF PROTOCOL DEVIATIONS

Important major protocol deviations, such as entry criteria violation and significant treatment non-compliance will be summarized as far as they can be extracted from numeric or coded study data.

13. DATA QUALITY ASSURANCE

Accurate and reliable data collection will be ensured by verification and cross check of the CRFs against the investigator's records by the study monitor (source document verification) and by the maintenance of a drug–dispensing log by the investigator. Collected data will be entered into a computer database and subject to electronic and manual quality assurance procedures.

14. REFERENCES

Food and Drug Administration. Methods to Identify What Is Important to Patients & Select, Develop or Modify Fit-for-Purpose Clinical Outcomes Assessments. InPatient-focused drug development guidance public workshop 2018 Oct.

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APPENDIX 1. IMPUTATION ALGORITHM FOR PARTIAL AND MISSING DATES

This section describes missing date imputation methods.

For Adverse Events

If onset date is completely missing, onset date is set to date of first dose.

If (year is present and month and day are missing) or (year and day are present and month is missing):

- If year = year of first dose, then set month and day to month and day of first dose
- If year < year of first dose, then set month and day to December 31.
- If year > year of first dose, then set month and day to January 1.

If month and year are present and day is missing:

- If year = year of first dose and
  - If month = month of first dose then set day to day of first dose
  - If month < month of first dose then set day to last day of month
  - If month > month of first dose then set day to first day of month
- If year < year of first dose then set day to last day of month
- If year > year of first dose then set day to first day of month

For all other cases, set onset date to date of first dose.

For Concomitant Medications

Start Date: If start date is completely missing and end date is not prior to date of first dose, then the medication will be classified as concomitant. If start date is completely missing and end date is prior to date of first dose, then the medication will be classified as prior.

If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to January 1. If year and month are present and day is missing then set day to first day of month.

End Date: If end date is completely missing then the medication will be classified as concomitant.

If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to December 31. If year and month are present and day is missing then set day to last day of the month.

Note: that if both start and end dates are missing then the medication will be classified as concomitant.