2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Axsome Therapeutics</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
Not Applicable</td></tr>
<tr><td>Name of Active Ingredient:
Solriamfetol</td></tr>
<tr><td colspan="3">Title of Study: 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</td></tr>
<tr><td colspan="3">Principal Investigator: 22 Principal Investigators are involved in this study</td></tr>
<tr><td colspan="3">Study sites:
This study was conducted at 22 study sites in 5 countries (Italy, Netherlands, Spain, United Kingdom, and United States).</td></tr>
<tr><td colspan="3">Publications (reference):
None</td></tr>
<tr><td colspan="2">Studied period (years):
Date first patient enrolled: 05 June 2021
Date last patient completed: 16 June 2022</td><td>Phase of development:
Phase 4</td></tr>
<tr><td colspan="3">Objectives:
Primary:
To evaluate the effectiveness of solriamfetol on cognitive function in adult participants with excessive daytime sleepiness (EDS) associated with Obstructive sleep apnea (OSA) plus impaired cognitive functioning.
Secondary:
To further evaluate the effectiveness of solriamfetol on cognitive function in adult participants with EDS associated with OSA plus impaired cognitive functioning.
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.
To evaluate the effectiveness 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.
To evaluate the effectiveness of solriamfetol on improving EDS in adult participants with EDS associated with OSA plus impaired cognitive functioning.
To evaluate the safety and tolerability of solriamfetol administered once daily in adult participants with EDS associated with OSA plus impaired cognitive functioning.</td></tr>
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Methodology:

This was a Phase 4, double-blind, placebo-controlled, randomized, crossover, multicenter study comparing solriamfetol 150 mg to placebo on tests of cognitive function in participants with EDS due to OSA.

Participants were in the study for approximately 8 weeks, that included a 2-week solriamfetol treatment period (Treatment Period 1; Visits 4 and 5), 1-week washout period (Visit 6), and a 2-week placebo treatment period (Treatment Period 2; Visits 7 and 8). Each participant received both double-blind treatments in a balanced 2 × 2 Latin square design.

Cognitive functions in this study were assessed by an objective test, Digit Symbol Substitution Test (DSST) Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and a subjective test, British Columbia Cognitive Complaints Inventory (BC-CCI).

Participants were randomly assigned to 1 of 2 treatment sequences in a 1:1 ratio at the end of baseline and randomization visit. In this 2-way crossover study, participants in Sequence 1 received solriamfetol in Treatment Period 1 and placebo in Treatment Period 2, while participants in Sequence 2 received placebo in Treatment Period 1 and solriamfetol in Treatment Period 2. During the active treatment, participants received 75 mg solriamfetol for the first 3 days and 150 mg solriamfetol for the remaining days.

In Treatment Period 1, participants administered the first dose of study treatment at home upon waking the first day of the period. Participants had the study treatment at home until the next visit, but were instructed not to take the final dose until after arrival at the study site, and to bring pill bottle/blister pack of study treatment to the site. Participants had to visit the site on the last day of the treatment period to take the final dose in the presence of site staff. At the end of the site visit, participants were provided with a supply of double-blind crossover study intervention for Treatment Period 2.

The last day of Treatment Period 1 is followed by a 1-week (7-days) washout period. Participants were instructed to not to take any doses of Treatment Period 2 until after the washout. At the end of the washout period, site staff reminded the participant to start Treatment Period 2.

During Treatment Period 2, participants administered the study treatment once daily at home in the morning upon wakening. Participants had to visit the site on the last day of the treatment period to take the final dose in the presence of site staff and to undergo the assessments outlined.

Participants also completed either the Safety Follow-up (SFU) or the Early Discontinuation (ED) visit.

The same procedures were administered during the SFU or ED visits. The SFU/ED visit could be virtual or onsite based on local regulations and/or site preference. The SFU visit occurred 4 to 10 days after the final dose of study treatment. The ED visit occurred ≥ 4 days after the last dose taken for participants who did not take all planned doses of either Treatment Period 1 or Treatment Period 2.

Number of patients (planned and analyzed):

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 participants (58 participants per treatment sequence) were planned to be randomized into the study.

A total of 58 participants, 59 participants, 59 participants, and 49 participants were randomized into modified intent-to-treat (mITT), safety, Intent-to-treat (ITT), and per-protocol population, respectively.

Diagnosis and main criteria for inclusion:

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, with body mass index from 18.5 to < 40 kg/m^2.
2. Diagnosis of OSA according to International Classification of Sleep Disorders, Third Edition criteria.
3. Participants reported (with clinician concurrence) of at least 1 of the following primary OSA therapy criteria:
   - Consistent number of hours of primary positive airway pressure (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. Participant had an age-corrected scaled score ≤ 8 on the DSST Wechsler Adult Intelligence Scale, Fourth Edition at the Screening visit.
5. BC-CCI ≥ 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.

Test product, dose and mode of administration, lot number:

The active treatment in this study was solriamfetol and the matching control was placebo. During the active treatment, participants received solriamfetol 75 mg tablet orally for the first 3 days and solriamfetol 150 mg tablet orally for the remaining days.

Lot Number: 9165192-A and 9165192-C for blister active or placebo and 9165192-B and 9165192-D for bottle active or placebo.

Duration of treatment:

The total duration of study was 10 weeks, that included 4-week screening period, followed by 2-week double-blind treatment period (Treatment Period 1) and 2-week double-blind cross-treatment period (Treatment Period 2), and 1 week follow-up period. Both treatment periods are separated by 1-week washout period.

Criteria for evaluation:

Efficacy:

Primary Efficacy Analysis

- Change from baseline in DSST RBANS score to end of treatment periods (Visit 5 and Visit 8).

Secondary Efficacy Analysis

- Difference in mean overall BC-CCI scores from baseline to the end of double-blind treatment periods (Visit 5 and Visit 8).
- Percentage of participants with an at least 1 category improvement in the BC-CCI score from baseline to Visit 5 and Visit 8 in each treatment group.
- Change in mean DSST RBANS scores baseline to 2-, 4-, 6-, and 8-hours postdose.
- Difference in mean Patients Global Impression of Severity (PGI-S) score from baseline to Visit 5 and Visit 8 between solriamfetol and placebo.
- Percentage of participants with at least 1 category improvement in the PGI-S score from baseline to Visit 5 and Visit 8 in each treatment group.
- Difference in mean ESS score from baseline to Visit 5 and Visit 8 between solriamfetol and placebo.

Safety:

Safety evaluations were based on the incidence and severity of adverse events, as well as on electrocardiogram (ECG) measurements, vital signs, and Columbia Suicide Severity Rating Scale (C-SSRS).

Statistical methods:

Statistical analyses were conducted using statistical analysis system (SAS) version 9.4 and all hypothesis tests were conducted at a 2-sided significance level of 0.05.

Continuous data were summarized using descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Frequencies and percentages were used to summarize categorical (discrete) data. Presentations of categorical data were generally suppressed the percentages for items where the count was zero in order to draw attention to the non-zero counts.

Both primary and secondary analyzes were performed on the mITT population.

The primary effectiveness variable was analyzed using a Mixed Model with Repeated Measures. The model included 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 were assumed. The treatment effects, the 2-sided 95% confidence interval (CI) of treatment difference (solriamfetol-placebo) were presented.

The secondary effectiveness variables related to percentages were analyzed via exact methods. Percentages of responders for the 2 treatments were presented. The percentages, percentage differences, and the 2-sided 95% CI of the differences as well as the p-values of the differences were presented.

Safety analyzes were performed on the Safety population. Safety evaluations were based on the incidence and severity of adverse events (AEs), as well as on ECG measurements, vital signs, and C-SSRS. Safety variables were tabulated and presented by study treatment actually received.

SUMMARY – CONCLUSIONS

A total of 173 participants were enrolled in the study, of which 59 participants (30 participants in the Solriamfetol treatment group and 29 participants in the Placebo treatment group) were randomized.

All randomized participants were part of the Safety and ITT population. A total of 58 (98.3%) participants and 49 (83.1%) participants were enrolled into the mITT and PP population, respectively. Fifty-seven (96.6%) participants in the Safety population and 57 (98.3%) participants in the mITT population completed the study.

The majority of participants were White (43 [72.9%] participants) and not Hispanic or Latino (49 [83.1%] participants) in the Safety population. The mean (SD) age of participants was 52.2 (10.70) years. The majority of participants were males (38 [64.4%]). Mean (SD) body mass index of participants was 32.2 (4.38) kg/m^2. The mean (SD) values at baseline for DSST age-corrected scaled score and total number correct were 6.8 (1.07) and 42.8 (10.76), respectively. The most frequently reported medical history by preferred term was sleep apnoea syndrome (58 [98.3%] participants).

EFFICACY RESULTS:

Primary Endpoint

- The least squared (LS) mean (SD) change from baseline in DSST RBANS scores was 6.49 (0.650) in the Solriamfetol treatment group and 4.75 (0.646) in the Placebo treatment group. The difference (solriamfetol – placebo) in LS mean (SD) change from baseline in DSST RBANS scores was 1.75 (0.643) with 95% CI of (0.46, 3.04) and p-value = 0.009, indicating a statistically significant better improvement in DSST RBANS score in Solriamfetol treatment group compared with Placebo treatment group.

Secondary Endpoints

- The LS mean (SD) change from baseline in BC-CCI score was −4.70 (0.483) in the Solriamfetol treatment group and -3.11 (0.480) in the Placebo treatment group. The difference (solriamfetol – placebo) in LS mean (SD) change from baseline in BC-CCI score was −1.58 (0.474) with 95% CI of (−2.53, −0.63) and p-value = 0.002, indicating a statistically significant better improvement in BC-CCI score in Solriamfetol treatment group compared with Placebo treatment group.
- The LS mean (SD) change from baseline in PGI-S score was −0.90 (0.104) in the Solriamfetol treatment group and -0.61 (0.103) in the Placebo treatment group. The difference (solriamfetol – placebo) in LS mean (SD) change from baseline in PGI-S score was −0.29 (0.136) with 95% CI of (−0.57, -0.02) and p-value = 0.034, indicating a statistically significant better improvement in PGI-S score in Solriamfetol treatment group compared with Placebo treatment group.
- The LS mean (SD) change from baseline in ESS score was −4.41 (0.570) in the Solriamfetol treatment group and −2.31 (0.564) in the Placebo treatment group. The difference (solriamfetol – placebo) in LS mean (SD) change from baseline in ESS score was −2.10 (0.706) with 95% CI of (−3.51, −0.68) and p-value = 0.004, indicating a statistically significant better improvement in ESS score in Solriamfetol treatment group compared with Placebo treatment group.
- A total of 54 (94.7%) subjects in the Solriamfetol treatment group and 50 (86.2%) subjects in the Placebo treatment group had an at least 1 category improvement in the BC-CCI from baseline to the end of treatment period. The difference in percentage was 8.53% with 95% CI of (−2.62, 20.83) and p-value = 0.079. There was an increased, albeit not statistically significant, percentage difference (8.53%) in participants with an at least 1 category improvement in BC-CCI for the Solriamfetol treatment group, which was in correlation with statistically significant improvement in change in BC-CCI score from baseline to the end of treatment periods.
- A total of 37 (64.9%) participants in the Solriamfetol treatment group and 30 (51.7%) participants in the Placebo treatment group had at least 1 category improvement in the PGI-S

score from baseline with a percentage difference of 13.19% (95% CI: −5.13, 30.99, p-value = 0.054).

SAFETY RESULTS:

- Overall, 16 (27.1%) participants reported treatment-emergent adverse events (TEAEs) during the study; 11 (19.0%) participants in solriamfetol treatment group and 6 (10.3%) participants in Placebo treatment group.
- A total of 7 (11.9%) participants reported TEAEs related to the study treatments; 5 (8.6%) participants in solriamfetol treatment group and 2 (3.4%) participants in Placebo treatment group.
- No severe TEAEs were reported during the study.
- Three (5.2%) mild TEAEs and 2 (3.4%) moderate TEAEs were related to solriamfetol. One (1.7%) mild TEAE and 1 (1.7%) moderate TEAE were related to the Placebo treatment group.
- No serious AEs, deaths, or discontinuations due to TEAEs were reported during the study.
- A total of 11 (19.0%) participants reported 23 AEs in Solriamfetol treatment group and 6 (10.3%) participants reported 6 AEs in the Placebo treatment group. No participants reported more than 1 TEAE during the study. Most common TEAEs reported were nausea (4 events in 4 [6.9%] participants) and anxiety (2 events in 2 [3.4%] participants).
- Five (8.6%) TEAEs were related to solriamfetol and 2 (3.4%) TEAEs were related to placebo. Nausea was the most common related TEAE; 3 [5.2%] events in Solriamfetol treatment group and 1 [1.7%] event in Placebo treatment group, followed by anxiety; 2 (3.4%) events in Solriamfetol treatment group.
- There were no clinically meaningful changes in mean values from baseline to Visit 5 and Visit 6 for vital sign parameters. No important treatment group differences in the mean change from baseline were noted.
- No clinically significant ECG results or C-SSRS scores were reported.

CONCLUSION:

Solriamfetol was safe and well-tolerated in participants with EDS due to OSA, with no report of SAEs. The 150 mg dose of Solriamfetol improved cognitive function in participants with cognitive impairment associated with OSA and EDS.