Protocol Registration Receipt
05/31/2012

# An Evaluation of Potential Next-day Residual Effects of Eszopiclone in Healthy Volunteers.

This study has been completed.

| | |
|---|---|
| Sponsor: | GlaxoSmithKline |
| Collaborators: | |
| Information provided by (Responsible Party): | GlaxoSmithKline |
| ClinicalTrials.gov Identifier: | NCT00699608 |

## Purpose

This study will explore potential next-day residual effects of a single evening dose of 3mg of the hypnotic, eszopiclone, 7.5mg of zopiclone, and placebo, in healthy adult subjects.

| Condition | Intervention | Phase |
|---|---|---|
| Healthy Subjects<br>Sleep Initiation and Maintenance Disorders | Drug: GSK1755165; placebo; zopiclone | Phase 3 |

Study Type: Interventional

Study Design: Treatment, Crossover Assignment, Double Blind (Subject, Investigator), Randomized, Safety Study

Official Title: A Randomised, Double-blind, Double-dummy, Placebo-controlled, 3-way Crossover Study to Evaluate Potential Next-day Residual Effects of a Single Evening Dose of 3mg Eszopiclone and 7.5mg Zopiclone in Healthy Adult Subjects.

## Further study details as provided by GlaxoSmithKline:

Primary Outcome Measure:

- Mean Tracking Error Assessed During the Continuous Tracking Test (CTT) [Time Frame: 7.5, 8, 8.5, 9, and 9.5 hours post-dose (double-blind)] [Designated as safety issue: No]

  Analysis was performed on the mean of the five assessments conducted 7.5, 8, 8.5, 9, and 9.5 hours post-dose (double-blind) The CTT is a task (duration of 8 minutes) of psychomotor function that entails using a slider to keep a cursor in alignment with a moving target on a visual display unit screen. The movement of the target is the function of an irregular sine wave, and cursor accuracy is measured by the mean tracking error - the difference between the centers of target and cursor in pixels, sampled 5 times per second, over the test. Lower scores are indicative of more accurate tracking.

Secondary Outcome Measures:

- Mean Tracking Error (MTE) Assessed During the CTT [Time Frame: 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind)] [Designated as safety issue: No]

  Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) . The CTT is a task (8 minute duration) of psychomotor function that entails using a slider to keep a cursor in alignment with a moving target on a visual display unit screen. The movement of the target is the function of an irregular sine wave, and cursor accuracy is measured by the MTE, the difference between the centers of target and cursor in pixels, sampled 5 times per second, over the test. Lower scores are indicative of more accurate tracking.
- CTT Mean Reaction Time [Time Frame: 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind)] [Designated as safety issue: No]

  Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) A further outcome derived from the CTT is a peripheral awareness task where the participant responds to a stimulus presented in the periphery of vision, while simultaneously attending to the tracking test. The mean reaction time, in milliseconds, to these stimuli over the trial period is taken as the response measure for this component of the divided attention task. A lower mean reaction time is indicative of better peripheral awareness.
- Critical Flicker Fusion Test-Ascending Threshold [Time Frame: 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind)] [Designated as safety issue: No]

  Critical Flicker Fusion (CFF) is a validated cognitive assessment task that provides an index of central nervous system (CNS) activity and attention modulated motion detection. Participants are required to discriminate flicker from fusion, and vice versa, in a set of four light-emitting diodes arranged in a one-centimetre square. These diodes are held in foveal fixation when viewed at a distance of one metre. Individual thresholds are determined on four ascending and four descending scales. The mean of the four ascending presentations give the ascending threshold frequency in hertz.
- Critical Flicker Fusion Test -Descending Threshold [Time Frame: 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind)] [Designated as safety issue: No]

  Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) The mean

of the four descending presentations from the CFF give the descending threshold frequency in hertz.

- Critical Flicker Fusion Test-Overall Threshold [Time Frame: 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind)] [Designated as safety issue: No]

  Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) The mean of the four ascending and four descending presentations of the CFF give the overall threshold frequency in hertz.

- Total Number of Attempted Symbol Substitutions, as Assessed by the Digit Symbol Substitution Test [Time Frame: 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind)] [Designated as safety issue: No]

  Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind). The Digit Symbol Substitution Test (DSST) is a pen and paper test that consists of rows of blank squares paired with randomly assigned digits (between 0 and 9). Participants are required to substitute each digit with a different nonsense symbol, according to a key printed at the top of the sheet that indicates the nonsense symbol that corresponds to each digit. Participants are given 120 seconds in which to complete the test.

- Total Number of Correct Symbol Substitutions, as Assessed by the Digital Symbol Substitution Test [Time Frame: 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind)] [Designated as safety issue: No]

  Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind). The Digit Symbol Substitution Test (DSST) is a pen and paper test that consists of rows of blank squares paired with randomly assigned digits (between 0 and 9). Participants are required to substitute each digit with a different nonsense symbol, according to a key printed at the top of the sheet that indicates the nonsense symbol that corresponds to each digit. Participants are given 120 seconds in which to complete the test.

- 1-Back Percentage of Correct Responses [Time Frame: 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind)] [Designated as safety issue: No]

  The N-Back task requires the participant to indicate, using the mouse, whether the current stimulus presented on the screen and the one immediately before it visually match (i.e., "one-back"). In the versions of the tests used in this study, the stimuli are presented on screen for 500 ms, and the interval between stimuli is 2500 ms, with a ratio of 1:2 of "match" trials to non-match trials. The duration of the test is 2 minutes. The percentage of correct responses is the percentage of correct responses given in 2 minutes.

- 3-Back Percentage of Correct Responses [Time Frame: 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind)] [Designated as safety issue: No]

  Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind). In "3-back" tasks, a comparison is made between the current stimulus and the two before the immediately preceding stimulus. In the versions of the tests used in this study, the stimuli are presented on screen for 500 ms, and the interval between stimuli is 2500 ms, with a ratio of 1:2 of "match" trials to non-match trials. The duration of the test is 2 min. The percentage of correct responses is the percentage of correct responses given in 2 min.

- 1-Back Reaction Time [Time Frame: 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind)] [Designated as safety issue: No]

  Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind). Reaction time is the time taken to respond to a stimulus.

- 3-Back Reaction Time [Time Frame: 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind)] [Designated as safety issue: No]

  Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind). Reaction time is the time taken to respond to a stimulus.

- Sedation Score, as Assessed by the Linear Analogue Rating Scales [Time Frame: 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind)] [Designated as safety issue: No]

  The Linear Analogue Rating Scale (LARS) is used as a measure of the subjective effects of psychoactive drugs. Participants mark a series of 10 cm (100 unit line) analogue scales (1-100, 100 = most impaired) relating to dizzy, clumsy, anxious, relaxed, tired, drowsy, alert, energetic, sad, and depressed, indicating their present feeling with regard to a mid-point, representing their "usual" state of mind before treatment began. The higher the score, the more impaired the participant feels. The Tiredness, Alertness, Energy, and Drowsiness scores are averaged to derive an overall Sedation score.
- Mood Score, as Assessed by the Linear Analogue Rating Scales [Time Frame: 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind)] [Designated as safety issue: No]

  Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind). The Anxiety, Depression, Relaxed, and Sadness scores are averaged to derive an overall "Mood" score (as described in Outcome Measure 14). Each item was assessed on a 1-100 point scale, where 100 indicates most impaired.
- Coordination Score, as Assessed by the Linear Analogue Rating Scales [Time Frame: 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind)] [Designated as safety issue: No]

  Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind). The Dizziness and Clumsiness scores are averaged to derive an overall "Coordination" score (as described in Outcome Measure 14). Each item was assessed on a 1-100 point scale, where 100 indicates most impaired.

Enrollment: 91
Study Start Date: July 2008
Study Completion Date: October 2008
Primary Completion Date: October 2008

| Arms | Assigned Interventions |
|---|---|
| Experimental: Crossover<br>All subjects received all three treatments in a randomised order | Drug: GSK1755165; placebo; zopiclone<br>Subjects receive either 3mg GSK1755165, matching placebo or 7.5mg zopiclone |

## Eligibility

Ages Eligible for Study: 25 Years to 40 Years
Genders Eligible for Study: Both
Accepts healthy volunteers.

INCLUSION CRITERIA:

- Healthy male and female subjects providing written informed consent.

EXCLUSION CRITERIA:

- Significant medical disorders;
- Sleeping difficulties; alcohol and/or substance abuse;
- Recent use of psychotropic medications, or need to use them during study;
- Very high BMI or very low BMI or bodyweight;
- Known hypersensitivity to the study medications or their excipients;
- Unwilling or unable to meet certain lifestyle or dietary restrictions during the study.

## Contacts and Locations

### Locations

#### United Kingdom

GSK Investigational Site

Guildford, Surrey, United Kingdom, GU2 7XP

### Investigators

| | | |
|---|---|---|
| Study Director: | GSK Clinical Trials | GlaxoSmithKline |

## More Information

| | |
|---|---|
| Responsible Party: | GlaxoSmithKline |
| Study ID Numbers: | ESZ111503 |
| Health Authority: | United Kingdom: Medicines and Healthcare Products Regulatory Agency |

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# Study Results

## Participant Flow

### Reporting Groups

| | Description |
|---|---|
| Eszopiclone First, Zopiclone Second, Placebo Third | 3 mg eszopiclone during first intervention period, 7.5 mg zopiclone during second intervention period (after 4-14 day washout period), placebo during third intervention period (after 4-14 day washout period) |
| Eszopiclone First, Placebo Second, Zopiclone Third | 3 mg eszopiclone during first intervention period, placebo during second intervention period (after 4-14 day washout period), 7.5 mg zopiclone during third intervention period (after 4-14 day washout period) |
| Zopiclone First, Eszopiclone Second, Placebo Third | 7.5 mg zopiclone during first intervention period, 3 mg eszopiclone during second intervention period (after 4-14 day washout period), placebo during third intervention period (after 4-14 day washout period) |
| Zopiclone First, Placebo Second, Eszopiclone Third | 7.5 mg zopiclone during first intervention period, placebo during second intervention period (after 4-14 day washout period), 3 mg eszopiclone during third intervention period (after 4-14 day washout period) |
| Placebo First, Eszopiclone Second, Zopiclone Third | Placebo during first intervention period, 3 mg eszopiclone during second intervention period (after 4-14 day washout period), 7.5 mg zopiclone during third intervention period (after 4-14 day washout period) |
| Placebo First, Zopiclone Second, Eszopiclone Third | Placebo during first intervention period, 7.5 mg zopiclone during second intervention period (after 4-14 day washout period), 3 mg eszopiclone during third intervention period (after 4-14 day washout period) |

First Intervention

| | Eszopiclone First, Zopiclone Second, Placebo Third | Eszopiclone First, Placebo Second, Zopiclone Third | Zopiclone First, Eszopiclone Second, Placebo Third | Zopiclone First, Placebo Second, Eszopiclone Third | Placebo First, Eszopiclone Second, Zopiclone Third | Placebo First, Zopiclone Second, Eszopiclone Third |
|---|---|---|---|---|---|---|
| Started | 16 | 15 | 15 | 15 | 15 | 15 |
| Completed | 16 | 15 | 14 | 15 | 14 | 15 |
| Not Completed | 0 | 0 | 1 | 0 | 1 | 0 |
| Withdrawal by Subject | 0 | 0 | 1 | 0 | 0 | 0 |
| Protocol Violation | 0 | 0 | 0 | 0 | 1 | 0 |

First 4-14 Day Washout Period

| | Eszopiclone First, Zopiclone Second, Placebo Third | Eszopiclone First, Placebo Second, Zopiclone Third | Zopiclone First, Eszopiclone Second, Placebo Third | Zopiclone First, Placebo Second, Eszopiclone Third | Placebo First, Eszopiclone Second, Zopiclone Third | Placebo First, Zopiclone Second, Eszopiclone Third |
|---|---|---|---|---|---|---|
| Started | 16 | 15 | 14 | 15 | 14 | 15 |
| Completed | 16 | 15 | 14 | 15 | 14 | 15 |
| Not Completed | 0 | 0 | 0 | 0 | 0 | 0 |

Second Intervention

| | Eszopiclone First, Zopiclone Second, Placebo Third | Eszopiclone First, Placebo Second, Zopiclone Third | Zopiclone First, Eszopiclone Second, Placebo Third | Zopiclone First, Placebo Second, Eszopiclone Third | Placebo First, Eszopiclone Second, Zopiclone Third | Placebo First, Zopiclone Second, Eszopiclone Third |
|---|---|---|---|---|---|---|
| Started | 16 | 15 | 14 | 15 | 14 | 15 |

| | Eszopiclone First, Zopiclone Second, Placebo Third | Eszopiclone First, Placebo Second, Zopiclone Third | Zopiclone First, Eszopiclone Second, Placebo Third | Zopiclone First, Placebo Second, Eszopiclone Third | Placebo First, Eszopiclone Second, Zopiclone Third | Placebo First, Zopiclone Second, Eszopiclone Third |
|---|---|---|---|---|---|---|
| Completed | 16 | 15 | 13 | 14 | 14 | 15 |
| Not Completed | 0 | 0 | 1 | 1 | 0 | 0 |
| Adverse Event | 0 | 0 | 1 | 0 | 0 | 0 |
| Withdrawal by Subject | 0 | 0 | 0 | 1 | 0 | 0 |

Second 4-14 Day Washout Period

| | Eszopiclone First, Zopiclone Second, Placebo Third | Eszopiclone First, Placebo Second, Zopiclone Third | Zopiclone First, Eszopiclone Second, Placebo Third | Zopiclone First, Placebo Second, Eszopiclone Third | Placebo First, Eszopiclone Second, Zopiclone Third | Placebo First, Zopiclone Second, Eszopiclone Third |
|---|---|---|---|---|---|---|
| Started | 16 | 15 | 13 | 14 | 14 | 15 |
| Completed | 16 | 15 | 13 | 14 | 14 | 15 |
| Not Completed | 0 | 0 | 0 | 0 | 0 | 0 |

Third Intervention

| | Eszopiclone First, Zopiclone Second, Placebo Third | Eszopiclone First, Placebo Second, Zopiclone Third | Zopiclone First, Eszopiclone Second, Placebo Third | Zopiclone First, Placebo Second, Eszopiclone Third | Placebo First, Eszopiclone Second, Zopiclone Third | Placebo First, Zopiclone Second, Eszopiclone Third |
|---|---|---|---|---|---|---|
| Started | 16 | 15 | 13 | 14 | 14 | 15 |
| Completed | 16 | 15 | 13 | 14 | 14 | 15 |

| | Eszopiclone First, Zopiclone Second, Placebo Third | Eszopiclone First, Placebo Second, Zopiclone Third | Zopiclone First, Eszopiclone Second, Placebo Third | Zopiclone First, Placebo Second, Eszopiclone Third | Placebo First, Eszopiclone Second, Zopiclone Third | Placebo First, Zopiclone Second, Eszopiclone Third |
|---|---|---|---|---|---|---|
| Not Completed | 0 | 0 | 0 | 0 | 0 | 0 |

## Baseline Characteristics

### Reporting Groups

| | Description |
|---|---|
| Entire Study Population | |

### Baseline Measures

| | Entire Study Population |
|---|---|
| Number of Participants | 91 |
| Age, Continuous<br>[units: years]<br>Mean (Standard Deviation) | 29.8 (3.87) |
| Gender, Male/Female<br>[units: participants] | |
| Female | 46 |
| Male | 45 |
| Race/Ethnicity, Customized<br>[units: participants] | |
| White | 63 |
| African American/African | 14 |

| | Entire Study Population |
|---|---|
| Heritage | |
| Asian-Central/South Asian Heritage | 6 |
| Asian-South East Asian Heritage | 5 |
| Asian-East Asian Heritage | 3 |

## Outcome Measures

1. Primary Outcome Measure:

| Measure Title | Mean Tracking Error Assessed During the Continuous Tracking Test (CTT) |
|---|---|
| Measure Description | Analysis was performed on the mean of the five assessments conducted 7.5, 8, 8.5, 9, and 9.5 hours post-dose (double-blind) The CTT is a task (duration of 8 minutes) of psychomotor function that entails using a slider to keep a cursor in alignment with a moving target on a visual display unit screen. The movement of the target is the function of an irregular sine wave, and cursor accuracy is measured by the mean tracking error - the difference between the centers of target and cursor in pixels, sampled 5 times per second, over the test. Lower scores are indicative of more accurate tracking. |
| Time Frame | 7.5, 8, 8.5, 9, and 9.5 hours post-dose (double-blind) |
| Safety Issue? | No |

Analysis Population Description

Intent-to-Treat (ITT) Population: all subjects who gave informed consent, were randomised, and received at least one dose of double-blind medication. Only participants who had assessment of the measure the day after double-blind treatment were analyzed.

Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Eszopiclone | 3 mg Eszopiclone |
| Zopiclone | 7.5 mg Zopiclone |

Measured Values

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| Number of Participants Analyzed | 89 | 87 | 90 |
| Mean Tracking Error Assessed During the Continuous Tracking Test (CTT)<br>[units: pixels]<br>Least Squares Mean (Standard Error) | 10.29 (0.625) | 12.49 (0.634) | 13.48 (0.621) |

Statistical Analysis 1 for Mean Tracking Error Assessed During the Continuous Tracking Test (CTT)

| | |
|---|---|
| Groups | Eszopiclone, Zopiclone |
| Method | ANCOVA |
| P-Value | 0.267 |
| Mean Difference (Final Values) | -0.99 |
| 95% Confidence Interval | -2.74 to 0.76 |

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for

statistical significance:

[Not specified.]

Other relevant information, such as adjustments or degrees of freedom:

ANCOVA used (fixed effects: adjusted period baseline, participant baseline, age, gender, period and treatment group; random effect: participant).

2. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Mean Tracking Error (MTE) Assessed During the CTT |
| Measure Description | Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) . The CTT is a task (8 minute duration) of psychomotor function that entails using a slider to keep a cursor in alignment with a moving target on a visual display unit screen. The movement of the target is the function of an irregular sine wave, and cursor accuracy is measured by the MTE, the difference between the centers of target and cursor in pixels, sampled 5 times per second, over the test. Lower scores are indicative of more accurate tracking. |
| Time Frame | 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) |
| Safety Issue? | No |

Analysis Population Description

Intent-to-Treat (ITT) Population: all participants who gave informed consent, were randomised, and received at least one dose of double-blind study medication. Only participants who had assessment of the measure the day after double-blind treatment were analyzed.

Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Eszopiclone | 3 mg Eszopiclone |

| | Description |
|---|---|
| Zopiclone | 7.5 mg Zopiclone |

Measured Values

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| Number of Participants Analyzed | 89 | 87 | 90 |
| Mean Tracking Error (MTE) Assessed During the CTT<br>[units: pixels]<br>Least Squares Mean (Standard Error) | | | |
| 7.5 hours post-dose | 10.20 (0.596) | 12.80 (0.602) | 13.07 (0.592) |
| 8 hours post-dose | 9.70 (0.830) | 12.72 (0.840) | 13.15 (0.826) |
| 8.5 hours post-dose | 10.08 (0.917) | 12.54 (0.928) | 12.93 (0.913) |
| 9 hours post-dose | 11.02 (0.214) | 13.00 (1.229) | 14.81 (1.208) |
| 9.5 hours post-dose | 10.44 (1.108) | 13.50 (1.121) | 13.55 (1.101) |
| 10 hours post-dose | 10.12 (1.057) | 12.85 (1.069) | 12.53 (1.051) |
| 10.5 hours post-dose | 9.48 (0.757) | 11.38 (0.767) | 11.84 (0.753) |
| 11 hours post-dose | 10.55 (0.822) | 10.86 (0.833) | 11.65 (0.818) |
| 11.5 hours post-dose | 9.18 (0.523) | 10.06 (0.530) | 10.30 (0.521) |

3. Secondary Outcome Measure:

| Measure Title | CTT Mean Reaction Time |
|---|---|
| Measure Description | Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) A further outcome derived from the CTT is a peripheral |

| | |
|---|---|
| | awareness task where the participant responds to a stimulus presented in the periphery of vision, while simultaneously attending to the tracking test. The mean reaction time, in milliseconds, to these stimuli over the trial period is taken as the response measure for this component of the divided attention task. A lower mean reaction time is indicative of better peripheral awareness. |
| Time Frame | 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) |
| Safety Issue? | No |

## Analysis Population Description

Intent-to-Treat (ITT) Population: all participants who gave informed consent, were randomised, and received at least one dose of double-blind study medication.Only participants who had assessment of the measure the day after double-blind treatment were analyzed.

## Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Eszopiclone | 3 mg Eszopiclone |
| Zopiclone | 7.5 mg Zopiclone |

## Measured Values

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| Number of Participants Analyzed | 89 | 87 | 90 |
| CTT Mean Reaction Time<br>[units: milliseconds]<br>Least Squares Mean (Standard Error) | | | |
| 7.5 hours post-dose, n=89, 87, 90 | 746.88<br>(10.36) | 791.99<br>(10.40) | 806.31<br>(10.33) |

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| 8 hours post-dose, n=88, 87, 90 | 744.90 (10.44) | 787.41 (10.50) | 799.53 (10.40) |
| 8.5 hours post-dose, n=89, 87, 90 | 757.72 (10.44) | 793.18 (10.51) | 797.92 (10.39) |
| 9 hours post-dose, n=89, 87, 90 | 760.11 (10.75) | 802.53 (10.81) | 811.11 (10.69) |
| 9.5 hours post-dose, n=89, 87, 90 | 763.65 (10.17) | 793.69 (10.23) | 789.63 (10.13) |
| 10 hours post-dose, n=89, 87, 90 | 756.67 (10.54) | 778.09 (10.60) | 792.00 (10.48) |
| 10.5 hours post-dose, n=89, 87, 90 | 765.98 (10.55) | 774.06 (10.59) | 779.80 (10.51) |
| 11 hours post-dose, n=89, 87, 90 | 762.43 (9.88) | 760.29 (9.95) | 765.56 (9.85) |
| 11.5 hours post-dose, n=89, 87, 90 | 745.26 (9.48) | 750.79 (9.52) | 766.44 (9.44) |

4. Secondary Outcome Measure:

| Measure Title | Critical Flicker Fusion Test-Ascending Threshold |
|---|---|
| Measure Description | Critical Flicker Fusion (CFF) is a validated cognitive assessment task that provides an index of central nervous system (CNS) activity and attention modulated motion detection. Participants are required to discriminate flicker from fusion, and vice versa, in a set of four light-emitting diodes arranged in a one-centimetre square. These diodes are held in foveal fixation when viewed at a distance of one metre. Individual thresholds are determined on four ascending and four descending scales. The mean of the four ascending presentations give the ascending threshold frequency in hertz. |

| | |
|---|---|
| Time Frame | 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) |
| Safety Issue? | No |

## Analysis Population Description

Intent-to-Treat (ITT) Population: all participants who gave informed consent, were randomised, and received at least one dose of double-blind study medication. Only participants who had assessment of the measure the day after double-blind treatment were analyzed.

## Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Eszopiclone | 3 mg Eszopiclone |
| Zopiclone | 7.5 mg Zopiclone |

## Measured Values

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| Number of Participants Analyzed | 89 | 87 | 90 |
| Critical Flicker Fusion Test-Ascending Threshold<br>[units: hertz]<br>Least Squares Mean (Standard Error) | | | |
| 7.5 hours post-dose, n=88, 87, 90 | 30.65 (0.24) | 30.84 (0.24) | 30.93 (0.24) |
| 8 hours post-dose, n=89, 87, 90 | 30.31 (0.24) | 30.30 (0.24) | 30.41 (0.24) |
| 8.5 hours post-dose, n=89, 87, 90 | 30.27 (0.22) | 29.98 (0.22) | 30.17 (0.22) |
| 9 hours post-dose, n=89, 87, 90 | 30.10 (0.23) | 29.90 (0.23) | 30.00 (0.23) |
| 9.5 hours post-dose, n=89, 87, 90 | 30.18 (0.23) | 29.99 (0.23) | 30.05 (0.23) |

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| 10 hours post-dose, n=89, 87, 90 | 30.20 (0.24) | 29.91 (0.24) | 29.97 (0.23) |
| 10.5 hours post-dose, n=89, 87, 89 | 30.26 (0.21) | 29.99 (0.22) | 30.16 (0.21) |
| 11 hours post-dose, n=89, 87, 90 | 30.20 (0.23) | 30.06 (0.23) | 30.04 (0.23) |
| 11.5 hours post-dose, n=89, 87, 90 | 30.31 (0.22) | 30.28 (0.23) | 30.56 (0.22) |

5. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Critical Flicker Fusion Test -Descending Threshold |
| Measure Description | Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) The mean of the four descending presentations from the CFF give the descending threshold frequency in hertz. |
| Time Frame | 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) |
| Safety Issue? | No |

## Analysis Population Description

Intent-to-Treat (ITT) Population: all participants who gave informed consent, were randomised, and received at least one dose of double-blind study medication.Only participants who had assessment of the measure the day after double-blind treatment were analyzed.

## Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Eszopiclone | 3 mg Eszopiclone |
| Zopiclone | 7.5 mg Zopiclone |

Measured Values

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| Number of Participants Analyzed | 89 | 87 | 90 |
| Critical Flicker Fusion Test -Descending Threshold<br>[units: hertz]<br>Least Squares Mean (Standard Error) | | | |
| 7.5 hours post-dose, n=88, 87, 90 | 29.06 (0.35) | 28.37 (0.35) | 28.05 (0.35) |
| 8 hours post-dose, n=89, 87, 90 | 28.52 (0.33) | 27.95 (0.33) | 27.95 (0.33) |
| 8.5 hours post-dose, n=89, 87, 90 | 28.42 (0.34) | 27.75 (0.35) | 27.59 (0.34) |
| 9 hours post-dose, n=89, 87, 90 | 28.07 (0.34) | 27.64 (0.35) | 27.89 (0.34) |
| 9.5 hours post-dose, n=89, 87, 90 | 28.19 (0.34) | 27.81 (0.35) | 27.75 (0.34) |
| 10 hours post-dose, n=89, 87, 90 | 28.18 (0.34) | 27.96 (0.34) | 28.06 (0.34) |
| 10.5 hours post-dose, n=89, 87, 89 | 28.48 (0.34) | 27.99 (0.34) | 28.10 (0.34) |
| 11 hours post-dose, n=89, 87, 90 | 28.53 (0.34) | 28.03 (0.34) | 28.20 (0.34) |
| 11.5 hours post-dose, n=89, 87, 90 | 28.57 (0.33) | 28.69 (0.34) | 28.48 (0.33) |

6. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Critical Flicker Fusion Test-Overall Threshold |
| Measure Description | Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) The mean of the four ascending and four descending presentations of the CFF give the overall threshold frequency in hertz. |
| Time Frame | 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) |

| | |
|---|---|
| Safety Issue? | No |

## Analysis Population Description

Intent-to-Treat (ITT) Population: all participants who gave informed consent, were randomised, and received at least one dose of double-blind study medication. Only participants who had assessment of the measure the day after double-blind treatment were analyzed.

## Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Eszopiclone | 3 mg Eszopiclone |
| Zopiclone | 7.5 mg Zopiclone |

## Measured Values

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| Number of Participants Analyzed | 89 | 87 | 90 |
| Critical Flicker Fusion Test-Overall Threshold<br>[units: hertz]<br>Least Squares Mean (Standard Error) | | | |
| 7.5 hours post-dose, n=88, 87, 90 | 29.82 (0.26) | 29.57 (0.26) | 29.45 (0.26) |
| 8 hours post-dose, n=89, 87, 90 | 29.41 (0.25) | 29.11 (0.25) | 29.00 (0.24) |
| 8.5 hours post-dose, n=89, 87, 90 | 29.36 (0.25) | 28.86 (0.25) | 28.88 (0.25) |
| 9 hours post-dose, n=89, 87, 90 | 29.10 (0.25) | 28.79 (0.25) | 28.96 (0.25) |
| 9.5 hours post-dose, n=89, 87, 90 | 29.19 (0.25) | 28.90 (0.25) | 28.90 (0.25) |
| 10 hours post-dose, n=89, 87, 90 | 29.20 (0.25) | 28.95 (0.25) | 29.02 (0.25) |
| 10.5 hours post-dose, n=89, 87, 89 | 29.38 (0.24) | 29.00 (0.24) | 29.14 (0.24) |

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| 11 hours post-dose, n=89, 87, 90 | 29.37 (0.25) | 29.07 (0.25) | 29.14 (0.25) |
| 11.5 hours post-dose, n=89, 87, 90 | 29.46 (0.24) | 29.50 (0.25) | 29.53 (0.24) |

7. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Total Number of Attempted Symbol Substitutions, as Assessed by the Digit Symbol Substitution Test |
| Measure Description | Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind). The Digit Symbol Substitution Test (DSST) is a pen and paper test that consists of rows of blank squares paired with randomly assigned digits (between 0 and 9). Participants are required to substitute each digit with a different nonsense symbol, according to a key printed at the top of the sheet that indicates the nonsense symbol that corresponds to each digit. Participants are given 120 seconds in which to complete the test. |
| Time Frame | 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) |
| Safety Issue? | No |

Analysis Population Description

Intent-to-Treat (ITT) Population: all participants who gave informed consent, were randomised, and received at least one dose of double-blind study medication. Only participants who had assessment of the measure the day after double-blind treatment were analyzed.

Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |

| | Description |
|---|---|
| Eszopiclone | 3 mg Eszopiclone |
| Zopiclone | 7.5 mg Zopiclone |

Measured Values

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| Number of Participants Analyzed | 89 | 87 | 90 |
| Total Number of Attempted Symbol Substitutions, as Assessed by the Digit Symbol Substitution Test<br>[units: number of substitutions]<br>Least Squares Mean (Standard Error) | | | |
| 7.5 hours post-dose, n=89, 87, 90 | 68.2 (1.09) | 64.7 (1.10) | 63.4 (1.09) |
| 8 hours post-dose, n=87, 84, 88 | 70.4 (1.16) | 66.5 (1.17) | 65.6 (1.15) |
| 8.5 hours post-dose, n=89, 87, 90 | 70.6 (1.13) | 67.4 (1.13) | 66.3 (1.12) |
| 9 hours post-dose, n=88, 87, 90 | 68.1 (1.20) | 65.2 (1.20) | 64.2 (1.19) |
| 9.5 hours post-dose, n=88, 87, 90 | 70.2 (1.12) | 67.2 (1.13) | 66.5 (1.12) |
| 10 hours post-dose, n=89, 87, 90 | 70.9 (1.14) | 68.2 (1.14) | 67.6 (1.13) |
| 10.5 hours post-dose, n=86, 85, 88 | 71.8 (1.16) | 69.7 (1.17) | 67.8 (1.16) |
| 11 hours post-dose, n=88, 87, 90 | 70.9 (1.11) | 68.1 (1.11) | 67.6 (1.10) |
| 11.5 hours post-dose, n=89, 87, 90 | 69.0 (1.16) | 68.0 (1.17) | 68.3 (1.16) |

8. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Total Number of Correct Symbol Substitutions, as |

| | Assessed by the Digital Symbol Substitution Test |
|---|---|
| Measure Description | Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind). The Digit Symbol Substitution Test (DSST) is a pen and paper test that consists of rows of blank squares paired with randomly assigned digits (between 0 and 9). Participants are required to substitute each digit with a different nonsense symbol, according to a key printed at the top of the sheet that indicates the nonsense symbol that corresponds to each digit. Participants are given 120 seconds in which to complete the test. |
| Time Frame | 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) |
| Safety Issue? | No |

## Analysis Population Description

Intent-to-Treat (ITT) Population: all participants who gave informed consent, were randomised, and received at least one dose of double-blind study medication. Only participants who had assessment of the measure the day after double-blind treatment were analyzed.

## Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Eszopiclone | 3 mg Eszopiclone |
| Zopiclone | 7.5 mg Zopiclone |

## Measured Values

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| Number of Participants Analyzed | 89 | 87 | 90 |

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| Total Number of Correct Symbol Substitutions, as Assessed by the Digital Symbol Substitution Test<br>[units: number of substitutions]<br>Least Squares Mean (Standard Error) | | | |
| 7.5 hours post-dose, n=89, 87, 90 | 67.9 (1.10) | 64.3 (1.10) | 63.0 (1.10) |
| 8 hours post-dose, n=87, 84, 88 | 70.2 (1.16) | 66.2 (1.17) | 65.2 (1.16) |
| 8.5 hours post-dose, n=89, 87, 90 | 70.4 (1.13) | 67.0 (1.14) | 66.0 (1.13) |
| 9 hours post-dose, n=88, 87, 90 | 67.9 (1.20) | 64.8 (1.21) | 63.8 (1.20) |
| 9.5 hours post-dose, n=88, 87, 90 | 69.9 (1.12) | 66.9 (1.13) | 66.2 (1.12) |
| 10 hours post-dose, n=89, 87, 90 | 70.8 (1.14) | 68.0 (1.15) | 67.3 (1.14) |
| 10.5 hours post-dose, n=86, 85, 88 | 71.5 (1.17) | 69.5 (1.17) | 67.4 (1.16) |
| 11 hours post-dose, n=88, 87, 90 | 70.6 (1.11) | 67.8 (1.11) | 67.3 (1.10) |
| 11.5 hours post-dose, n=89, 87, 90 | 68.7 (1.16) | 67.8 (1.17) | 68.0 (1.12) |

9. Secondary Outcome Measure:

| Measure Title | 1-Back Percentage of Correct Responses |
|---|---|
| Measure Description | The N-Back task requires the participant to indicate, using the mouse, whether the current stimulus presented on the screen and the one immediately before it visually match (i.e., “one-back”). In the versions of the tests used in this study, the stimuli are presented on screen for 500 ms, and the interval between stimuli is 2500 ms, with a ratio of 1:2 of “match” trials to non-match trials. The duration of the test is 2 minutes. The percentage of correct responses is the percentage of correct responses given in 2 minutes. |

| | |
|---|---|
| Time Frame | 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) |
| Safety Issue? | No |

## Analysis Population Description

Intent-to-Treat (ITT) Population: all participants who gave informed consent, were randomised, and received at least one dose of double-blind study medication. Only participants who had assessment of the measure the day after double-blind treatment were analyzed.

## Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Eszopiclone | 3 mg Eszopiclone |
| Zopiclone | 7.5 mg Zopiclone |

## Measured Values

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| Number of Participants Analyzed | 89 | 87 | 90 |
| 1-Back Percentage of Correct Responses<br>[units: percentage of responses]<br>Least Squares Mean (Standard Error) | | | |
| 7.5 hours post-dose, n=87, 87, 88 | 93.9 (0.95) | 92.2 (0.96) | 90.4 (0.95) |
| 8 hours post-dose, n=89, 87, 89 | 93.3 (0.97) | 92.0 (0.98) | 89.5 (0.97) |
| 8.5 hours post-dose, n=89, 87, 90 | 93.6 (1.05) | 92.8 (1.06) | 89.6 (1.05) |
| 9 hours post-dose, n=89, 87, 90 | 93.5 (1.07) | 91.6 (1.08) | 89.4 (1.07) |
| 9.5 hours post-dose, n=89, 86, 90 | 92.9 (1.02) | 91.2 (1.02) | 90.7 (1.01) |
| 10 hours post-dose, n=89, 87, 90 | 93.0 (0.90) | 92.2 (0.91) | 92.0 (0.90) |

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| 10.5 hours post-dose, n=89, 86, 89 | 94.4 (0.94) | 92.0 (0.95) | 91.7 (0.94) |
| 11 hours post-dose, n=89, 87, 90 | 93.0 (0.92) | 92.6 (0.93) | 91.9 (0.92) |
| 11.5 hours post-dose, n=89, 87, 90 | 93.4 (0.92) | 94.0 (0.92) | 92.0 (0.91) |

10. Secondary Outcome Measure:

| Measure Title | 3-Back Percentage of Correct Responses |
|---|---|
| Measure Description | Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind). In “3-back” tasks, a comparison is made between the current stimulus and the two before the immediately preceding stimulus. In the versions of the tests used in this study, the stimuli are presented on screen for 500 ms, and the interval between stimuli is 2500 ms, with a ratio of 1:2 of “match” trials to non-match trials. The duration of the test is 2 min. The percentage of correct responses is the percentage of correct responses given in 2 min. |
| Time Frame | 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) |
| Safety Issue? | No |

### Analysis Population Description

Intent-to-Treat (ITT) Population: all participants who gave informed consent, were randomised, and received at least one dose of double-blind study medication. Only participants who had assessment of the measure the day after double-blind treatment were analyzed.

### Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |

| | Description |
|---|---|
| Eszopiclone | 3 mg Eszopiclone |
| Zopiclone | 7.5 mg Zopiclone |

Measured Values

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| Number of Participants Analyzed | 89 | 87 | 90 |
| 3-Back Percentage of Correct Responses<br>[units: percentage of responses]<br>Least Squares Mean (Standard Error) | | | |
| 7.5 hours post-dose, n=87, 87, 88 | 84.6 (1.40) | 80.4 (1.41) | 76.9 (1.40) |
| 8 hours post-dose, n=89, 87, 89 | 83.5 (1.55) | 82.3 (1.56) | 76.8 (1.55) |
| 8.5 hours post-dose, n=89, 87, 90 | 82.4 (1.56) | 81.1 (1.57) | 78.3 (1.55) |
| 9 hours post-dose, n=89, 87, 90 | 83.3 (1.61) | 78.9 (1.62) | 77.3 (1.60) |
| 9.5 hours post-dose, n=89, 86, 90 | 82.1 (1.60) | 80.2 (1.61) | 76.9 (1.59) |
| 10 hours post-dose, n=89, 87, 90 | 83.4 (1.53) | 82.0 (1.54) | 79.2 (1.52) |
| 10.5 hours post-dose, n=89, 86, 89 | 82.6 (1.50) | 81.3 (1.51) | 79.7 (1.50) |
| 11 hours post-dose, n=89, 87, 90 | 81.7 (1.44) | 83.2 (1.45) | 79.8 (1.44) |
| 11.5 hours post-dose, n=89, 87, 90 | 82.9 (1.40) | 83.6 (1.41) | 81.1 (1.39) |

## 11. Secondary Outcome Measure:

| Measure Title | 1-Back Reaction Time |
|---|---|
| Measure Description | Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose |

| | |
|---|---|
| | (double-blind). Reaction time is the time taken to respond to a stimulus. |
| Time Frame | 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) |
| Safety Issue? | No |

## Analysis Population Description

Intent-to-Treat (ITT) Population: all participants who gave informed consent, were randomised, and received at least one dose of double-blind study medication. Only participants who had assessment of the measure the day after double-blind treatment were analyzed.

## Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Eszopiclone | 3 mg Eszopiclone |
| Zopiclone | 7.5 mg Zopiclone |

## Measured Values

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| Number of Participants Analyzed | 89 | 87 | 90 |
| 1-Back Reaction Time<br>[units: milliseconds]<br>Least Squares Mean (Standard Error) | | | |
| 7.5 hours post-dose, n=87, 87, 88 | 755.9 (17.81) | 819.3 (17.85) | 840.3 (17.75) |
| 8 hours post-dose, n=89, 87, 89 | 752.7 (16.89) | 783.7 (16.99) | 805.8 (16.87) |
| 8.5 hours post-dose, n=89, 87, 90 | 741.1 (17.09) | 776.1 (17.18) | 778.7 (17.04) |
| 9 hours post-dose, n=89, 87, 90 | 734.8 (16.58) | 784.5 (16.68) | 791.1 (16.58) |
| 9.5 hours post-dose, n=89, 86, 90 | 729.0 (16.84) | 757.2 (16.98) | 784.0 (16.80) |

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| 10 hours post-dose, n=89, 87, 90 | 724.7 (16.39) | 760.8 (16.48) | 759.5 (16.34) |
| 10.5 hours post-dose, n=89, 86, 89 | 713.2 (15.81) | 735.2 (15.92) | 750.7 (15.80) |
| 11 hours post-dose, n=89, 87, 90 | 718.5 (16.26) | 716.9 (16.33) | 741.7 (16.22) |
| 11.5 hours post-dose, n=89, 87, 90 | 709.3 (16.83) | 716.7 (16.92) | 720.5 (16.78) |

## 12. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | 3-Back Reaction Time |
| Measure Description | Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind). Reaction time is the time taken to respond to a stimulus. |
| Time Frame | 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) |
| Safety Issue? | No |

### Analysis Population Description

Intent-to-Treat (ITT) Population: all participants who gave informed consent, were randomised, and received at least one dose of double-blind study medication. Only participants who had assessment of the measure the day after double-blind treatment were analyzed.

### Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Eszopiclone | 3 mg Eszopiclone |
| Zopiclone | 7.5 mg Zopiclone |

Measured Values

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| Number of Participants Analyzed | 89 | 87 | 90 |
| 3-Back Reaction Time<br>[units: milliseconds]<br>Least Squares Mean (Standard Error) | | | |
| 7.5 hours post-dose, n=87, 87, 88 | 959.5 (20.87) | 1020.9 (20.87) | 1076.4 (20.79) |
| 8 hours post-dose, n=89, 87, 89 | 960.0 (21.56) | 1018.5 (21.62) | 1042.2 (21.53) |
| 8.5 hours post-dose, n=89, 87, 90 | 925.9 (21.37) | 997.7 (21.49) | 1024.2 (21.33) |
| 9 hours post-dose, n=89, 87, 90 | 916.9 (21.50) | 1002.2 (21.61) | 1007.8 (21.46) |
| 9.5 hours post-dose, n=89, 86, 90 | 932.9 (21.86) | 992.1 (22.05) | 978.0 (21.81) |
| 10 hours post-dose, n=89, 87, 90 | 907.4 (21.26) | 948.7 (21.36) | 987.5 (21.19) |
| 10.5 hours post-dose, n=89, 86, 89 | 900.3 (20.92) | 961.5 (21.08) | 945.2 (20.89) |
| 11 hours post-dose, n=89, 87, 90 | 915.3 (19.61) | 935.5 (19.70) | 940.4 (19.54) |
| 11.5 hours post-dose, n=89, 87, 90 | 876.2 (20.49) | 903.2 (20.58) | 934.7 (20.39) |

13. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Sedation Score, as Assessed by the Linear Analogue Rating Scales |
| Measure Description | The Linear Analogue Rating Scale (LARS) is used as a measure of the subjective effects of psychoactive drugs. Participants mark a series of 10 cm (100 unit line) analogue scales (1-100, 100 = most impaired) |

| | |
|---|---|
| | relating to dizzy, clumsy, anxious, relaxed, tired, drowsy, alert, energetic, sad, and depressed, indicating their present feeling with regard to a mid-point, representing their “usual” state of mind before treatment began. The higher the score, the more impaired the participant feels. The Tiredness, Alertness, Energy, and Drowsiness scores are averaged to derive an overall Sedation score. |
| Time Frame | 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) |
| Safety Issue? | No |

## Analysis Population Description

Intent-to-Treat (ITT) Population: all participants who gave informed consent, were randomised, and received at least one dose of double-blind study medication. Only participants who had assessment of the measure the day after double-blind treatment were analyzed.

## Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Eszopiclone | 3 mg Eszopiclone |
| Zopiclone | 7.5 mg Zopiclone |

## Measured Values

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| Number of Participants Analyzed | 89 | 87 | 90 |
| Sedation Score, as Assessed by the Linear Analogue Rating Scales<br>[units: points on a scale]<br>Least Squares Mean (Standard Error) | | | |
| 7.5 hours post-dose, n=89, 87, 90 | 54.21 (1.15) | 54.87 (1.16) | 57.00 (1.14) |

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| 8 hours post-dose, n=89, 87, 90 | 54.54 (1.37) | 56.40 (1.15) | 59.21 (1.13) |
| 8.5 hours post-dose, n=89, 87, 90 | 54.07 (1.18) | 54.39 (1.19) | 56.93 (1.18) |
| 9 hours post-dose, n=89, 87, 90 | 53.63 (1.12) | 54.93 (1.12) | 56.01 (1.10) |
| 9.5 hours post-dose, n=89, 87, 90 | 53.84 (1.14) | 55.39 (1.15) | 55.90 (1.13) |
| 10 hours post-dose, n=89, 87, 90 | 53.98 (1.21) | 54.68 (1.23) | 55.73 (1.21) |
| 10.5 hours post-dose, n=89, 87, 90 | 51.77 (1.21) | 53.77 (1.13) | 55.31 (1.12) |
| 11 hours post-dose, n=89, 87, 90 | 51.47 (1.06) | 51.49 (1.06) | 52.79 (1.05) |
| 11.5 hours post-dose, n=89, 87, 90 | 49.02 (1.21) | 49.41 (1.22) | 51.24 (1.20) |

14. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Mood Score, as Assessed by the Linear Analogue Rating Scales |
| Measure Description | Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind). The Anxiety, Depression, Relaxed, and Sadness scores are averaged to derive an overall “Mood” score (as described in Outcome Measure 14). Each item was assessed on a 1-100 point scale, where 100 indicates most impaired. |
| Time Frame | 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) |
| Safety Issue? | No |

Analysis Population Description

Intent-to-Treat (ITT) Population: all participants who gave informed consent, were randomised, and received at least one dose of double-blind study

medication. Only participants who had assessment of the measure the day after double-blind treatment were analyzed.

## Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Eszopiclone | 3 mg Eszopiclone |
| Zopiclone | 7.5 mg Zopiclone |

## Measured Values

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| Number of Participants Analyzed | 89 | 87 | 90 |
| Mood Score, as Assessed by the Linear Analogue Rating Scales<br>[units: points on a scale]<br>Least Squares Mean (Standard Error) | | | |
| 7.5 hours post-dose, n=89, 87, 90 | 47.75 (0.71) | 48.13 (0.72) | 48.03 (0.71) |
| 8 hours post-dose, n=89, 87, 90 | 49.19 (0.71) | 48.42 (0.71) | 49.11 (0.70) |
| 8.5 hours post-dose, n=89, 87, 90 | 48.88 (0.70) | 48.42 (0.70) | 48.30 (0.69) |
| 9 hours post-dose, n=89, 87, 90 | 48.48 (0.74) | 47.67 (0.75) | 48.61 (0.74) |
| 9.5 hours post-dose, n=89, 87, 90 | 48.30 (0.75) | 47.89 (0.76) | 47.54 (0.75) |
| 10 hours post-dose, n=89, 87, 90 | 47.98 (0.79) | 48.25 (0.79) | 48.28 (0.78) |
| 10.5 hours post-dose, n=89, 87, 90 | 47.57 (0.87) | 48.72 (0.88) | 48.47 (0.87) |
| 11 hours post-dose, n=89, 87, 90 | 47.45 (0.85) | 47.07 (0.86) | 47.90 (0.85) |
| 11.5 hours post-dose, n=89, 87, 90 | 45.63 (1.03) | 47.09 (1.40) | 46.08 (1.03) |

15. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Coordination Score, as Assessed by the Linear Analogue Rating Scales |
| Measure Description | Analysis was performed on the individual assessments conducted at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind). The Dizziness and Clumsiness scores are averaged to derive an overall “Coordination” score (as described in Outcome Measure 14). Each item was assessed on a 1-100 point scale, where 100 indicates most impaired. |
| Time Frame | 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours post-dose (double-blind) |
| Safety Issue? | No |

## Analysis Population Description

Intent-to-Treat (ITT) Population: all participants who gave informed consent, were randomised, and received at least one dose of double-blind study medication. Only participants who had assessment of the measure the day after double-blind treatment were analyzed.

## Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Eszopiclone | 3 mg Eszopiclone |
| Zopiclone | 7.5 mg Zopiclone |

## Measured Values

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| Number of Participants Analyzed | 89 | 87 | 90 |

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| Coordination Score, as Assessed by the Linear Analogue Rating Scales<br>[units: points on a scale]<br>Least Squares Mean (Standard Error) | | | |
| 7.5 hours post-dose, n=89, 87, 90 | 49.09 (1.13) | 50.33 (1.15) | 52.42 (1.13) |
| 8 hours post-dose, n=89, 87, 90 | 50.03 (0.92) | 51.21 (0.93) | 52.10 (0.92) |
| 8.5 hours post-dose, n=89, 87, 90 | 49.23 (0.86) | 49.52 (0.87) | 51.76 (0.86) |
| 9 hours post-dose, n=89, 87, 90 | 49.68 (0.94) | 50.38 (0.95) | 50.41 (0.94) |
| 9.5 hours post-dose, n=89, 87, 90 | 49.08 (0.97) | 49.42 (0.98) | 51.41 (0.96) |
| 10 hours post-dose, n=89, 87, 90 | 49.37 (0.96) | 49.72 (0.97) | 50.27 (0.95) |
| 10.5 hours post-dose, n=89, 87, 90 | 48.60 (0.86) | 50.68 (0.87) | 50.40 (0.86) |
| 11 hours post-dose, n=89, 87, 90 | 48.97 (0.83) | 48.51 (0.84) | 49.96 (0.83) |
| 11.5 hours post-dose, n=89, 87, 90 | 48.20 (0.82) | 47.45 (0.83) | 49.82 (0.81) |

## Reported Adverse Events

### Reporting Groups

| | Description |
|---|---|
| Placebo | Placebo |
| Eszopiclone | 3 mg Eszopiclone |
| Zopiclone | 7.5 mg Zopiclone |

### Serious Adverse Events

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| Total # participants affected/at risk | 0/89 (0%) | 0/88 (0%) | 0/90 (0%) |

## Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 0%

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| Total # participants affected/at risk | 12/89 (13.48%) | 44/88 (50%) | 44/90 (48.89%) |
| Eye disorders | | | |
| Eye pain †[A] | | | |
| # participants affected/at risk | 0/89 (0%) | 1/88 (1.14%) | 1/90 (1.11%) |
| # events | | | |
| Eye pruritis †[A] | | | |
| # participants affected/at risk | 0/89 (0%) | 1/88 (1.14%) | 0/90 (0%) |
| # events | | | |
| Gastrointestinal disorders | | | |
| Abdominal pain †[A] | | | |
| # participants affected/at risk | 1/89 (1.12%) | 0/88 (0%) | 0/90 (0%) |
| # events | | | |
| Diarrhoea †[A] | | | |

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| # participants affected/at risk | 1/89 (1.12%) | 1/88 (1.14%) | 0/90 (0%) |
| # events | | | |
| Frequent bowel movements †[A] | | | |
| # participants affected/at risk | 0/89 (0%) | 1/88 (1.14%) | 0/90 (0%) |
| # events | | | |
| Gastrointestinal sounds abnormal †[A] | | | |
| # participants affected/at risk | 0/89 (0%) | 1/88 (1.14%) | 0/90 (0%) |
| # events | | | |
| Nausea †[A] | | | |
| # participants affected/at risk | 3/89 (3.37%) | 4/88 (4.55%) | 4/90 (4.44%) |
| # events | | | |
| Toothache †[A] | | | |
| # participants affected/at risk | 0/89 (0%) | 0/88 (0%) | 1/90 (1.11%) |
| # events | | | |
| General disorders | | | |
| Asthenia †[A] | | | |
| # participants affected/at | 0/89 (0%) | 1/88 (1.14%) | 1/90 (1.11%) |

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| risk | | | |
| # events | | | |
| Fatigue †[A] | | | |
| # participants affected/at risk | 4/89 (4.49%) | 6/88 (6.82%) | 6/90 (6.67%) |
| # events | | | |
| Infections and infestations | | | |
| Urinary tract infection †[A] | | | |
| # participants affected/at risk | 0/89 (0%) | 1/88 (1.14%) | 0/90 (0%) |
| # events | | | |
| Injury, poisoning and procedural complications | | | |
| Skin laceration †[A] | | | |
| # participants affected/at risk | 0/89 (0%) | 0/88 (0%) | 1/90 (1.11%) |
| # events | | | |
| Metabolism and nutrition disorders | | | |
| Anorexia †[A] | | | |
| # participants affected/at risk | 0/89 (0%) | 1/88 (1.14%) | 1/90 (1.11%) |

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| # events | | | |
| Nervous system disorders | | | |
| Balance disorder † [A] | | | |
| # participants affected/at risk | 0/89 (0%) | 0/88 (0%) | 1/90 (1.11%) |
| # events | | | |
| Coordination abnormal † [A] | | | |
| # participants affected/at risk | 0/89 (0%) | 0/88 (0%) | 1/90 (1.11%) |
| # events | | | |
| Disturbance in attention † [A] | | | |
| # participants affected/at risk | 0/89 (0%) | 2/88 (2.27%) | 3/90 (3.33%) |
| # events | | | |
| Dizziness † [A] | | | |
| # participants affected/at risk | 0/89 (0%) | 4/88 (4.55%) | 5/90 (5.56%) |
| # events | | | |
| Dysgeusia † [A] | | | |
| # participants affected/at risk | 0/89 (0%) | 27/88 (30.68%) | 30/90 (33.33%) |
| # events | | | |

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| Headache †[A] | | | |
| # participants affected/at risk | 2/89 (2.25%) | 2/88 (2.27%) | 2/90 (2.22%) |
| # events | | | |
| Memory impairment †[A] | | | |
| # participants affected/at risk | 0/89 (0%) | 0/88 (0%) | 1/90 (1.11%) |
| # events | | | |
| Paraesthesia †[A] | | | |
| # participants affected/at risk | 1/89 (1.12%) | 0/88 (0%) | 1/90 (1.11%) |
| # events | | | |
| Poor quality sleep †[A] | | | |
| # participants affected/at risk | 0/89 (0%) | 1/88 (1.14%) | 0/90 (0%) |
| # events | | | |
| Somnolence †[A] | | | |
| # participants affected/at risk | 1/89 (1.12%) | 11/88 (12.5%) | 7/90 (7.78%) |
| # events | | | |
| Psychiatric disorders | | | |
| Depressed mood †[A] | | | |
| # participants affected/at | 1/89 (1.12%) | 0/88 (0%) | 0/90 (0%) |

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| risk | | | |
| # events | | | |
| Fear † [A] | | | |
| # participants affected/at risk | 0/89 (0%) | 1/88 (1.14%) | 0/90 (0%) |
| # events | | | |
| Hallucination † [A] | | | |
| # participants affected/at risk | 0/89 (0%) | 2/88 (2.27%) | 0/90 (0%) |
| # events | | | |
| Nightmare † [A] | | | |
| # participants affected/at risk | 0/89 (0%) | 2/88 (2.27%) | 0/90 (0%) |
| # events | | | |
| Somnambulism † [A] | | | |
| # participants affected/at risk | 0/89 (0%) | 1/88 (1.14%) | 0/90 (0%) |
| # events | | | |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea † [A] | | | |
| # participants affected/at risk | 0/89 (0%) | 0/88 (0%) | 1/90 (1.11%) |

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| # events | | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dry throat †[A] | | | |
| # participants affected/at risk | 0/89 (0%) | 0/88 (0%) | 1/90 (1.11%) |
| # events | | | |
| Epistaxis †[A] | | | |
| # participants affected/at risk | 0/89 (0%) | 1/88 (1.14%) | 0/90 (0%) |
| # events | | | |
| Rhinorrhoea †[A] | | | |
| # participants affected/at risk | 0/89 (0%) | 1/88 (1.14%) | 0/90 (0%) |
| # events | | | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritis †[A] | | | |
| # participants affected/at risk | 0/89 (0%) | 1/88 (1.14%) | 0/90 (0%) |
| # events | | | |
| Rash †[A] | | | |
| # participants affected/at | 0/89 (0%) | 2/88 (2.27%) | 0/90 (0%) |

| | Placebo | Eszopiclone | Zopiclone |
|---|---|---|---|
| risk | | | |
| # events | | | |

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA

## More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

GSK agreements may vary with individual investigators, but will not prohibit any investigator from publishing. GSK supports the publication of results from all centers of a multi-center trial but requests that reports based on single-site data not precede the primary publication of the entire clinical trial.

Limitations and Caveats:

Results Point of Contact:

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