Synopsis – Study 12495A

Title of Study Randomised, double-blind, 3-way crossover, single-dose, placebo-controlled study investigating the effect on postural instability of melatonin and zolpidem in healthy elderly subjects
Investigator Alla Radicke, MD, PAREXEL International GmbH, Klinikum Westend, Haus 31, Spandauer Damm 130, 14050 Berlin, Germany.
Study Centre PAREXEL International GmbH, Klinikum Westend, Haus 31, Spandauer Damm 130, 14050 Berlin, Germany.
Publications None (as of the date of this report)
Study Period *First subject first visit* – 06 April 2009 *Last subject last visit* – 04 May 2009
Objectives • Primary objective: – to compare the effect of melatonin (Circadin® 2 mg, RAD Neurim Pharmaceuticals EEC Limited; Berkshire, United Kingdom) on postural instability with that of placebo when administered as single doses in the evening • Secondary objective: – to compare the effect of zolpidem (Zolpidem STADA® 5 mg, STADApharma, Bad Vilbel, Germany) on postural instability with that of placebo when administered as single doses in the evening
Methodology • This was a randomised, double-blind, 3-way-crossover, single-dose, placebo-controlled, interventional clinical study investigating the effect of melatonin, zolpidem, and placebo on postural instability when administered as single doses in the evening. The matrix used to sustain the release of melatonin had a characteristic smell. In order to avoid unblinding an additional placebo tablet including the matrix (but without the active substance; melatonin) was used to blind this. • The clinical study consisted of a Screening Visit within 28 to 3 days before the first IMP administration, 3 dosing periods with administration of melatonin and placebo capsule, zolpidem and placebo tablet, or placebo capsule and placebo tablet respectively, and a Follow-up Visit 5 to 8 days after the last IMP administration. The 3 administrations were separated by a washout period of at least 7 days. • The postural instability was assessed using body sway measurements at pre-dose, and at 1.5, 3, 5, and 8 hours post-dose (corresponded to assessments before approximately 22:00; and at approximately 23:30; 01:00; 03:00; and 06:00). Dinner was served at approximately 18:00 (that is approximately 4 hours before dosing). The subjects retired to bed within approximately 30 minutes after taking the medication and were encouraged to sleep between the assessments. • Standard clinical laboratory tests for safety were performed at the Screening Visit, on each day of admission to the clinical study site (Day 1, Day 8, and Day 15) in the 3 dosing periods, and at the Follow-up Visit (Day 20 to Day 23). • No pharmacokinetic assessments were performed.

Number of Subjects Planned and Analysed

- 24 healthy elderly subjects were planned for enrolment: a split of 12 subjects of each sex, 4 subjects in each treatment sequence
- 24 subjects were enrolled
- 24 subjects were randomised – 4 subjects in each of the 6 treatment sequences
- 24 subjects were treated – 4 subjects in each of the 6 treatment sequences
- 24 subjects completed the study – 4 subjects in each of the 6 treatment sequences
- 0 subjects withdrew
- 24 subjects were analysed
  - all-subjects-randomised set (ASRS) -24 subjects
  - all-subjects-treated set (ASTS) – 24 subjects
  - all-subjects-completed-set (ASCS) – 24 subjects

Main Inclusion Criteria

Healthy elderly male and female subjects 65 to 75 years of age with a body mass index between 19 and 30 kg/m^2 (extremes included).

Investigational Medicinal Products, Doses and Modes of Administration, Batch Numbers

- Melatonin - Circadin® 2 mg prolonged-release tablets; Batch No. 457027802
- Placebo tablets – matching tablets with smell matching Circadin®; Batch No. 0093C
- Zolpidem – Zolpidem STADA® 5 mg tablets, encapsulated in capsules (no smell); Batch No. PD1801
- Placebo capsules – matching; capsules matching zolpidem capsules (no smell); Batch No. E05324-009E01

Duration of Treatment

Three single doses separated by washout periods of at least 7 days.

Reference Therapy, Dose and Mode of Administration, Batch Number

- Zolpidem – Zolpidem STADA® 5 mg tablets, encapsulated in capsules (no smell)*;* orally; batch No. PD1801

Criteria for Evaluation – Pharmacodynamics

The body sway was assessed by controlling the centre of gravity (COG) with eyes open firm surface (in mm^2) and eyes closed firm surface (in mm^2). The composite COG sway area was reported with:

- Eyes open firm surface (in mm2/eyes open)
- Eyes closed firm surface (in mm2/eyes open)

Criteria for Evaluation – Safety

Adverse events, clinical safety laboratory tests, vital signs, weight, electrocardiograms, and physical examinations.

Statistical Methodology

- The following analysis sets were used:
  - all-subjects-randomised set (ASRS) – all randomised subjects
  - all-subjects-treated set (ASTS) – all subjects in the ASRS who took at least one dose of double-blind investigational medicinal product
  - all-subjects-completed-set (ASCS) – all randomised and treated subjects who completed the study

Primary analysis:

Postural instability (assessed as opened eyes body sway) of melatonin compared with placebo treatment. Based on the results given in a published study with zolpidem, the differences in means for the target analysis were approximately 90 mm^2 (zolpidem approximately 330 mm^2, placebo approximately 240 mm^2). The non-inferiority margin of 40 mm^2 for the comparison melatonin versus placebo was chosen in order to have a margin below 50% of an assumed effect 90 mm^2 when comparing zolpidem with placebo. It was assumed that melatonin induced a small increase (non-inferiority) in body sway, which was not above 40 mm^2 compared to placebo. The statistical analysis was based on a mixed model for cross-over data including fixed factors for treatment, period, and sequence, and with patient within sequence as a random factor. If the *p*-value for the factor period was greater than 10%, it was assumed that the factor period had no effect. If the effects occurred, each period was analysed separately.

Due to the failure in detecting body sway (although visible during the study), the statistical analyses were not performed.

- Safety data (based on the all-subjects-treated-set) were summarised using descriptive statistics.

Pharmacodynamic Results

Pharmacodynamic assessments (body sway), were performed as indicated in the *Clinical Study Protocol*.

After review of the headline results of the body sway data, it was discovered that the area of sway values were much lower than anticipated and that there were no significant differences between the positive control (zolpidem) and placebo. In addition, in approximately 25% of all measurements, across treatments, no body sway was detected (body sway areas of 0). During the study, however, the subjects showed visible body sway.

Due to the failure in detecting body sway (although visible during the study), the body sway data will not be discussed in the *Clinical Study Report* and no conclusions can be made on the effect of melatonin or zolpidem on postural instability.

Safety Results

- There were no deaths, other serious adverse events, or withdrawals due to adverse events.
- In total, 13 adverse events were reported by 6 (25.0%) subjects. Six adverse events were reported for 2 (8.3%) subjects on placebo, 5 adverse events were reported for 3 (12.5%) subjects on melatonin, and 2 adverse events were reported for 2 (8.3%) subjects on zolpidem.
- The highest reported adverse event incidence was for orthostatic hypotension: two adverse events for 1 (4.2%) subject on melatonin and 1 adverse event for 1 (4.2%) subject on placebo and on zolpidem.
- Of the treatment-emergent adverse events reported, 6 events were considered possibly related to the investigational medicinal product and 7 events were considered probably related to the investigational medicinal product. The majority of the treatment emergent adverse events (9 of 13 events) were considered moderate in severity. No severe adverse events were reported.
- Out-of-range haematology and clinical chemistry results and abnormal liver function test and urinalysis results were reported, however, none were considered clinically significant.
- The majority of subjects had at least one abnormal vital sign finding. A total of 4 vital sign findings in 2 subjects were reported as adverse events (orthostatic hypotension).

Conclusions

- Due to the failure in detecting body sway (although visible during the study), no conclusions can be made on the effect of melatonin or zolpidem on postural instability.
- Melatonin and zolpidem were generally safe and well tolerated.

Date of the Report

31 January 2014

This study was conducted in compliance with the principles of *Good Clinical Practice*.