The clinical trial information provided in this public disclosure synopsis is supplied for informational purposes only.

Please note that the results reported in any single trial may not reflect the overall potential risks or benefits of a product which are based on an evaluation of an entire research program.

Before prescribing any Takeda products, healthcare professionals should consult prescribing information for the product approved in their country.

FINAL REPORT

A Single-Center, Randomized, Double-Blind, Double-Dummy Placebo-Controlled, Crossover Study to Investigate the Next-Morning Effects of Ramelteon (8 mg), Zopiclone (7.5 mg), and Placebo on Actual Driving Performance, Memory Functioning, and Psychomotor Performance in Adults with Chronic Insomnia

Sponsor:	Takeda Global Research and Development Centre (Europe) Ltd. 61 Aldwych London WC2B 4AE United Kingdom
Protocol Number:	TAK-375_107
IND Number:	Not Applicable **EUDRACT Number:** 2007-002875-15
Study Drug:	TAK-375 – Ramelteon (Brand name ROZEREM™ in the United States)
Indication Studied:	Chronic Insomnia
Study Phase:	Phase 4
Study Design:	Phase 4, single-center, double blind, double-dummy, randomized, active and placebo-controlled, 3-way crossover study
Study Dates:	11 March 2008 to 05 May 2008
Early Termination Date:	13 May 2008
Investigator(s):	[redacted]
Sponsor's Responsible Medical Officer:	[redacted] Clinical Science
Report Date:	Final 13 March 2009

This study was performed in accordance with Good Clinical Practice, including the archiving of essential documents.

1.0 SYNOPSIS

Title of Study: A Single-Center, Randomized, Double-Blind, Double-Dummy Placebo-Controlled, Crossover Study to Investigate the Next-Morning Effects of Ramelteon (8 mg), Zopiclone (7.5 mg), and Placebo on Actual Driving Performance, Memory Functioning, and Psychomotor Performance in Adults with Chronic Insomnia	
Name of Sponsor: Takeda Global Research and Development Centre (Europe) Ltd.	
Name of Active Ingredient: TAK-375	
Name of Finished Product: TAK-375 – Ramelteon (Brand name ROZEREM™ in the United States)	
Investigator(s): [redacted]	**Study Center(s):** [redacted]
Publication (reference): None	
Study Period (years): 11 March 2008 to 05 May 2008	**Phase of Development:** Phase 4

OBJECTIVES

Primary:

The primary objective of the study was to evaluate the impact of ramelteon (8 mg), zopiclone (7.5 mg), and placebo on driving performance 8.5 to 9.0 hours after bedtime administration in adults with chronic insomnia.

Secondary:

The secondary objectives of the study were to evaluate the impact of ramelteon (8 mg), zopiclone (7.5 mg), and placebo on next-morning memory and psychomotor performance.

METHODOLOGY

Subjects who met initial screening criteria were assigned to single-blind placebo medication for 7 consecutive days between Days -14 and -3 to assess placebo response. Each subject who continued to meet eligibility criteria was then scheduled to be randomized to receive blinded treatment (placebo, ramelteon 8 mg, or the reference drug zopiclone 7.5 mg) for 1 day and then perform a driving test on the following morning. Each subject was to receive all 3 treatments, each of which was to be separated by a 7-day Washout Period. The study was terminated after the placebo run-in and before randomizing any subject to the blinded treatment.

Number of Subjects:

Planned: Screening: 90 subjects; Randomizing: 30.

Screened: 5 subjects; Randomized: 0; Analyzed: 3 subjects who received only the placebo-run in (study was terminated early).

Diagnosis and Main Criteria for Inclusion:

To qualify for study participation, subjects must have been subjects with chronic insomnia; aged 21 to 64 years, inclusive; been able to comprehend and willing to sign an informed consent form.

Title of Study:

A Single-Center, Randomized, Double-Blind, Double-Dummy Placebo-Controlled, Crossover Study to Investigate the Next-Morning Effects of Ramelteon (8 mg), Zopiclone (7.5 mg), and Placebo on Actual Driving Performance, Memory Functioning, and Psychomotor Performance in Adults with Chronic Insomnia

Test Product, Dose and Mode of Administration/Lot Number:

	Batch/Lot Number
Ramelteon 8 mg tablets, oral	[redacted]
Ramelteon placebo 8 mg tablets, oral	

Reference Therapy, Dose and Mode of Administration, Batch Number:

	Batch/Lot Number
Zopiclone 7.5 mg tablets, oral	[redacted]
Zopiclone placebo 7.5 mg tablets, oral	

Criteria for Evaluation:

Endpoint Evaluation:

The primary endpoint for this study was the impact on driving at 8.5 to 9.0 hours after bedtime dosing as measured by the standard deviation of lateral position (SDLP) in driving tests conducted on the morning of each treatment visit. The key secondary endpoints included the additional driving test variables (standard deviation of speed [SDS], mean lateral position [MLP], mean speed [MS]), memory recall test (MRT), digit symbol substitution test (DSST), and post sleep questionnaire (PSQ) – interactive voice-activated response system (IVRS) assessment of subjective reported morning ability to concentrate and level of alertness.

Safety:

Safety variables included adverse events, clinical laboratory test results, vital signs, and physical examination.

Statistical Methods:

The primary variable was the SDLP in driving tests conducted on the morning following nighttime dosing of each treatment visit.

Secondary variables included the additional driving test variables: SDS, MLP, and MS. Secondary endpoints assessing residual effects on memory and psychomotor performance included the MRT and DSST, and subjective reported morning ability to concentrate and level of alertness collected via PSQ-IVRS.

SUMMARY OF RESULTS

Subject Disposition:

A total of 5 subjects, including 4 male and 1 female subjects, were screened. Two subjects were screen failures and 3 subjects were enrolled to receive placebo run-in. Of the 3 enrolled subjects, 2 subjects did not meet the entrance criteria for the blinded treatment (ramelteon, zopiclone, or placebo) and 1 subject discontinued as [redacted] made other plans after [redacted] was considered placebo responder. No subjects received blinded treatment (placebo, ramelteon, or zopiclone) or completed the study. Efficacy results are not evaluated in this abbreviated report because no subject received blinded study treatment. The study was terminated due to changes in the global clinical development program.

Endpoint Results: Not relevant as all the treated subjects received only the placebo run-in and no subject received the blinded treatment (ramelteon, zopiclone, or placebo).

Title of Study: A Single-Center, Randomized, Double-Blind, Double-Dummy Placebo-Controlled, Crossover Study to Investigate the Next-Morning Effects of Ramelteon (8 mg), Zopiclone (7.5 mg), and Placebo on Actual Driving Performance, Memory Functioning, and Psychomotor Performance in Adults with Chronic Insomnia
Safety Results: Of the 3 subjects who received placebo run-in, adverse events were reported in 2 subjects: 1 subject reported somnolence, fatigue, and headache and the other subject reported xerostomia and fatigue. All adverse events were classified as mild or moderate and only xerostomia was considered possibly related to treatment (placebo) by the principal investigator. All of the adverse events resolved spontaneously. No serious adverse events or deaths occurred in this study.
CONCLUSIONS: No objective conclusions could be drawn from this study because no subject received blinded treatment (ramelteon, zopiclone, or placebo) and the study was terminated early.
Date of Report: Final 13 March 2009