TASIMELTEON

AMENDMENT #4 VP-VEC-162-2102

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL PROOF OF CONCEPT STUDY TO EVALUATE THE EFFECTS OF MULTIPLE ORAL DOSES OF TASIMELTEON AND MATCHING PLACEBO IN TRAVELERS WITH JET LAG DISORDER

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Sponsor:	Vanda Pharmaceuticals Inc. 2200 Pennsylvania Avenue NW Suite 300 East Washington, DC 20037
Study Product:	Tasimelteon
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Study Phase:	Phase 2
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Name of Sponsor/Company: Vanda Pharmaceuticals Inc.	
Name of Investigational Product: Tasimelteon/VEC-162	
Name of Active Ingredient: Tasimelteon/VEC-162	
Title of Study: A multicenter, randomized, double-blind, placebo-controlled, parallel proof-of-concept study to evaluate the effects of multiple oral doses of tasimelteon and matching placebo in travelers with Jet Lag Disorder	
Study center(s): Multicenter (USA and EU)	
Studied period: Estimated date first subject enrolled: Aug 2016 Estimated study duration: approximately 4-6 weeks Screening: ≥ 3 weeks, Randomization: 4 days/3 nights	**Phase of development:** Phase 2
Number of subjects (planned): Up to 90 eligible subjects will be randomized and assigned to 20 mg tasimelteon or placebo in a 1:1 ratio. Treatment assignments will be made according to a randomization schedule.	
Diagnosis and main criteria for inclusion/exclusion: Males or females 18-75 years of age, inclusive, who demonstrate sleep disturbances associated transmeridian travel in study VP-VEC-162-0101.	
Investigational product, dosage and mode of administration: Tasimelteon will be administered orally as a dose of 20 mg. Tasimelteon dosage form will be size 1, dark blue, opaque, hard gelatin capsules with two white bars on the capsule body and cap, and filled with white to off-white powder.	
Duration of treatment: 3 nights	
Reference therapy, dosage and mode of administration: Placebo capsules will be provided in size and appearance identical to those containing tasimelteon and will be administered orally	

Objectives:

Primary Objectives:

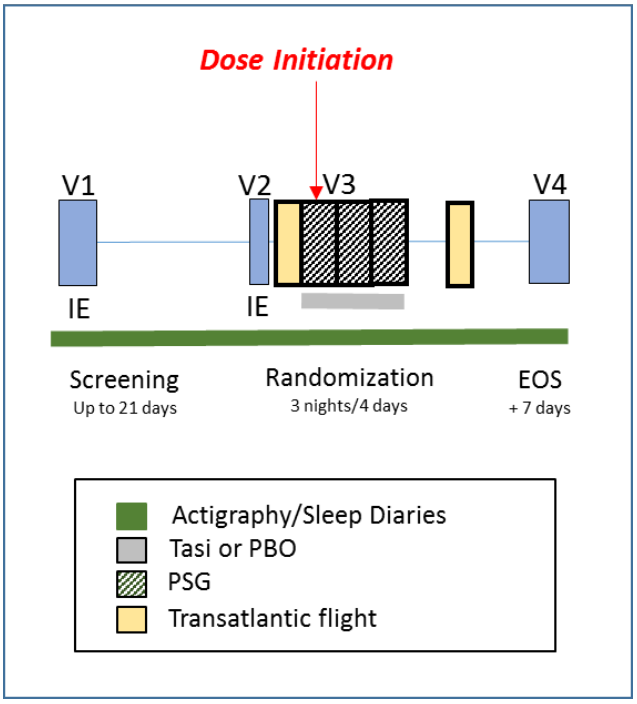
1. To assess the effects of tasimelteon 20 mg on nighttime sleep parameters as measured by Polysomnography (PSG) after transmeridian travel.

Secondary Objectives:

1. To assess the effects of tasimelteon 20mg on nighttime objective parameters.
2. To assess the effects of tasimelteon 20mg on nighttime subjective parameters.
3. To assess the effect of tasimelteon 20mg on a daytime objective parameter.
4. To assess the effects of tasimelteon 20mg on daytime subjective parameters.
5. To assess the effects of tasimelteon 20mg as measured by a combined scale of nighttime and daytime symptoms.

Overall Design:

This is a multicenter, international, randomized, double-blind, placebo-controlled, parallel proof-of-concept trial to investigate the efficacy and safety of multiple 20 mg oral doses of tasimelteon and matching placebo in male and female travelers with Jet Lag Disorder (JLD). Subjects will be recruited at sites throughout the United States of America (USA) and those that meet inclusion/exclusion criteria will be flown from the USA to Europe experiencing a 5-8 hour time zone change.



This study will be divided into 2 phases: the screening phase and the randomization phase. The screening phase consists of the screening visit a visit to re-confirm inclusion/exclusion criteria and to conduct the baseline evaluations, and the initial travel period to Europe. The randomization phase consists of a 3-night/4 day double-blind evaluation period in the new time zone, and the return travel period to the USA. The screening visit and the travel period will be separated by approximately 3 weeks. Baseline evaluations will occur approximately three days (± 1 day) prior to the transmeridian flight. Subjects meeting all entry criteria for the study will enter the randomization phase. Eligible subjects will be flown to Europe on a commercial non-stop, transatlantic, over-night flight. Subjects will reside in a clinical site in Europe for 4 days and 3 nights. During the evaluation period, subjects will be instructed to take the study medication 30 minutes (± 15 min) prior to bedtime and attempt to sleep for 8 hours. Bedtime will be determined by their habitual bedtime in the originating time zone. For example, if a subject has a habitual bedtime of 22:00 pm they will be put to bed at 22:00 pm in the new time zone. A PSG will be performed each night beginning the first night in the new time zone. On Day 4, subjects will be discharged from the study clinic after completing all required study procedures and will participate in supervised guided tours. On Day 5, subjects will take a return flight to the USA. Post-travel, subjects will also be instructed to maintain a sleep schedule allowing for an 8-hour sleep opportunity including a bed time consistent with that used while in domicile in Europe (± 1 hour). Throughout the study the subject's sleep pattern will be monitored with an actiwatch and through patient reported sleep diaries.

Criteria for evaluation:

Efficacy:

The primary efficacy variable is TST in the first 2/3 of the night after flying across 5-8 time zones. A comparison will be made between subjects treated with tasimelteon 20 mg and placebo.

Other variables include, PGI-S, $TST_{2/3}$, TST_{fn}, LPS, WASO, SE, TST_s, SL, SQ_s, KSS, and JLQ.

Safety:

The safety and tolerability measures will include the recording of adverse events (AEs) including suicidal ideation and behavior, clinical laboratory evaluations, vital signs, and electrocardiograms (ECGs).

Statistical Methods:

The primary efficacy variable is TST in the first 2/3 of the night after flying across 5-8 time zones. Nighttime sleep will be assessed by analysis of covariance, with treatment group, clinical site, baseline and time zone as a main effect. A comparison will be made between the subjects treated with tasimelteon 20 mg and placebo. The primary efficacy analysis will be based on the ITT population.

The statistical analyses will be detailed in the Statistical Analysis Plan.