The JET8 study: a double-blind, placebo-controlled study to investigate tasimelteon in healthy subjects with jet lag type insomnia induced by an 8-hour phase advance

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Sponsor: Vanda Pharmaceuticals Inc.
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Study Product: Tasimelteon

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Study Phase III

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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: The JET8 study: a double-blind, placebo-controlled study to investigate tasimelteon in healthy subjects with jet-lag type insomnia induced by an 8-hour phase advance.	
Study center(s): Multicenter (USA)	
Studied period: Estimated date first subject enrolled: October 2017 Estimated last subject enrolled: December 2017	**Phase of development:** Phase III
Number of subjects (planned): Up to 300 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: Healthy males or females 18-75 years of age, inclusive, who meet inclusion criteria.	
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: 1 day/1 night	
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:

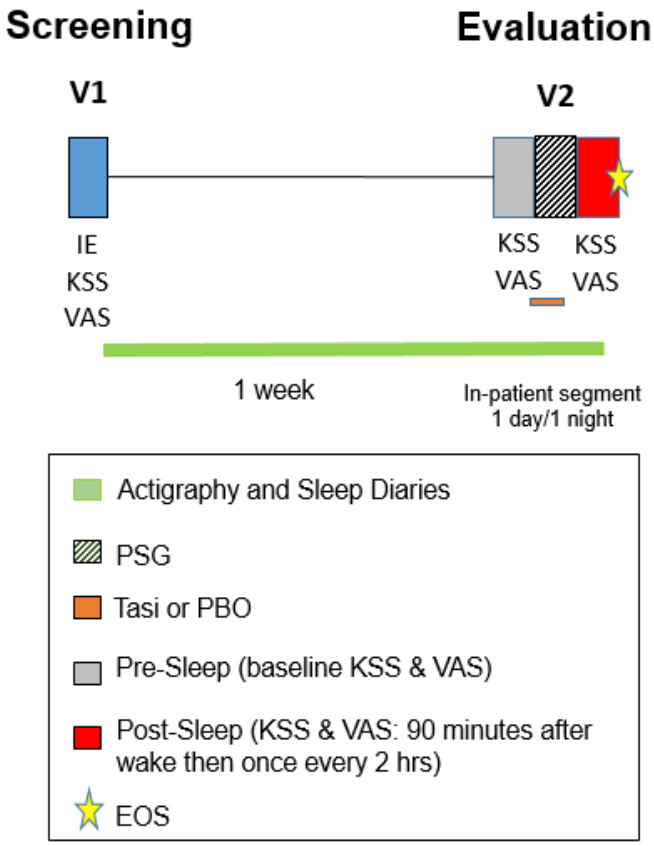
1. To assess the effects of tasimelteon 20 mg on nighttime sleep parameters as measured by Polysomnography (PSG) after an 8-hour phase advanced bedtime representative of transmeridian travel across 8 time zones.

Secondary Objectives:

1. To assess the effects of tasimelteon 20 mg on nighttime objective sleep parameters.
2. To assess the effects of tasimelteon 20 mg on nighttime and daytime subjective parameters.
3. To assess the safety and tolerability of single oral doses of tasimelteon 20 mg.

Overall Design:

This is a multicenter, randomized, double-blind, placebo-controlled, parallel pivotal trial to investigate the efficacy and safety of a single 20 mg oral dose of tasimelteon and matching placebo in healthy male and female subjects with jet lag type insomnia from an 8-hour phase advance.

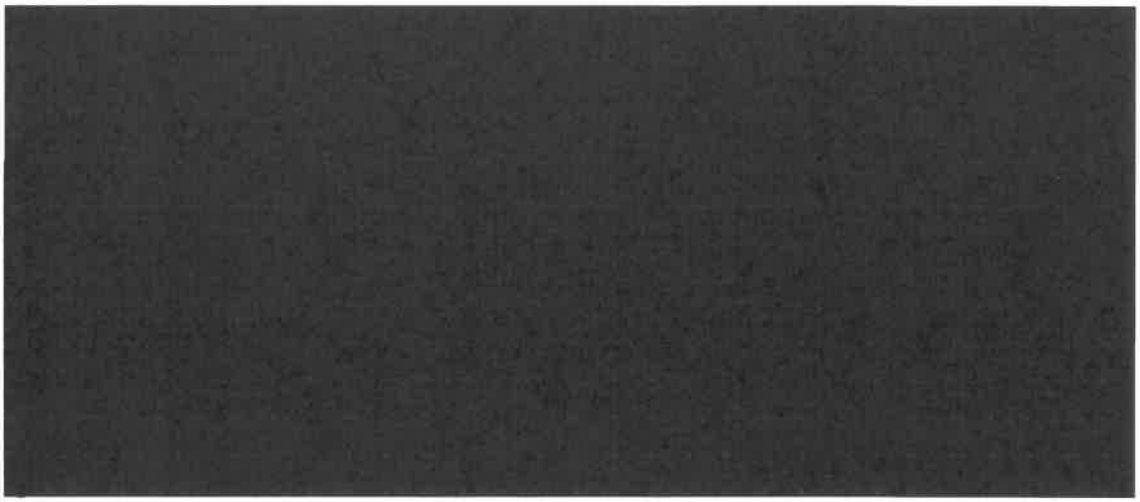


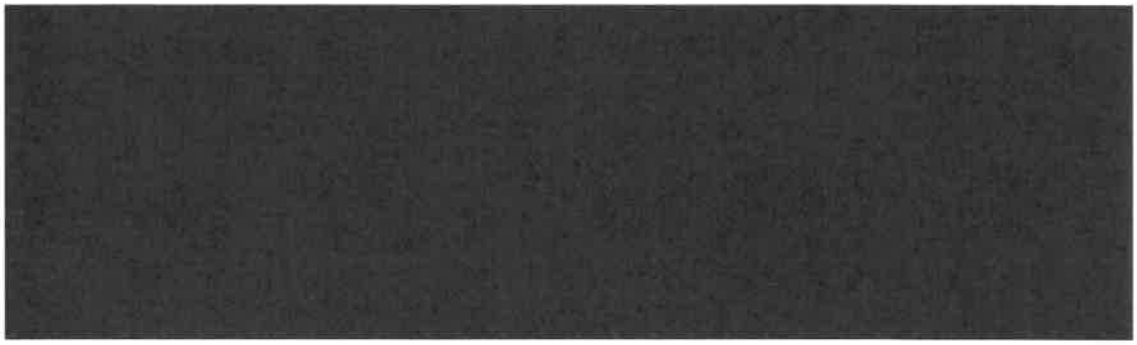
This study will be divided into 2 phases: the screening phase and the randomization/evaluation phase. The screening phase consists of the screening visit, during which inclusion/exclusion criteria will be assessed and the baseline evaluations will be conducted. The randomization phase consists of a 1-day/1-night double-blind evaluation period in which the subject's bedtime is advanced 8 hours. The screening visit and day/night in sleep clinic will be separated by at least 1 week. Subjects meeting all entry criteria for the study will enter the randomization phase. Eligible subjects will be admitted to a sleep clinic for one day and night of evaluation. Bedtime will be determined by their habitual bedtime (as determined from screening) in the originating time zone. For example, if a subject has a habitual bedtime of 22:00 they will be put to bed at 14:00, or 22:00 in the new "time zone." A PSG will be performed throughout the night beginning prior to bedtime in the "new time zone." Following the 8-hour phase advanced sleep, subjects will complete post-sleep questionnaire, KSS and VAS assessments. During this time subjects will also be provided with breakfast and lunch. After completing all required study procedures, the subjects be discharged from the study clinic. Throughout the study the subject's sleep pattern will be monitored with an actiwatch and through subject reported sleep diaries.

Statistical Methods:

Nighttime sleep will be assessed by analysis of variance, with treatment group, clinical site, as 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.





7. STATISTICAL PLAN

This section describes the planned statistical analyses in general terms. A complete description of the methodology will be specified in a statistical analysis plan (SAP), which will be finalized prior to unblinding. Any changes in the statistical methods described in this protocol that occur prior to unblinding will be documented in the statistical analysis plan and will not require a protocol amendment.

7.1. General Statistical Design

The study is a multi-center, two-arm, placebo-controlled parallel group pivotal study of the effect of tasimelteon in healthy subjects with jet lag type insomnia. Subjects will be randomized to receive either an active dose of tasimelteon 20 mg or placebo. The primary aim of the study is to ascertain whether tasimelteon is superior to placebo for the reduction of jet lag type insomnia. This study will investigate the effect of treatment on "first-night" jet lag type insomnia by measuring sleep objectively through PSG and the next-day residual effects of treatment. The primary outcome measure is total sleep time (TST) during the first 2/3 of the night (denoted by $TST_{2/3}$) following 8-hour phase advance bedtime, other

objective measures (TST in other time intervals, SE, LPS, WASO, Total REM sleep time, total Non-REM sleep time, Latency to REM, and time to accumulate 30 minutes of REM sleep) and subjective next-day effects (KSS and VAS) being secondary outcomes that will provide supportive evidence. The safety and tolerability of tasimelteon will also be explored.

The randomization will be in a 1:1 ratio between the 20mg and placebo groups, and will be stratified by investigative site. The length of follow-up (a screening stage plus day into overnight assessment stage) was chosen in order to assess the "first-night effect" of tasimelteon in healthy volunteers.

7.2. Sample Size and Accrual

The standard deviation is based on data from the tasimelteon Study VP-VEC-162-3101 comparing doses of VEC-162 and placebo in healthy volunteers in a 5 hour phase advance model. To detect a 30 minute difference in $TST_{2/3}$ between tasimelteon-treated subjects versus placebo with a standard deviation (SD) of 75, a sample size of 150 subjects per arm provides approximately 93% power with a two-sided alpha=0.05. This sample size also provides at least 85% power to detect the difference of 28 mins (SD 80) in TST between tasimelteon treated vs. placebo group.

7.3. Subject Population(s) for Analysis

Three subject populations will be defined for this study:

Intent-To-Treat population: Any subject randomized into the study that received a dose of study drug and had polysomnography data.

All-treated population: Any subject randomized into the study that received a dose of study drug.

Protocol-compliant population: Any subject who was randomized and received the protocol required study drug exposure and required protocol processing.

The primary analyses will be performed on the intent-to-treat population. Secondary analyses of efficacy endpoints will be performed on the protocol-compliant population. Safety summaries will be based on the all-treated population, in which all subjects who receive any study drug are included.

7.4. Subject Disposition

Study completion and reasons for discontinuation for all randomized subjects in the double-blind phase will be summarized for each treatment group by simple tabulation. Discontinuations by reason will be tabulated by visit for each treatment group.

7.5. Demography and Other Baseline Data

The data documented in this trial and the parameters measured at screening/baseline will be summarized using classic descriptive statistics: mean, median, SD, CV%, minimum and maximum values (for quantitative variables) and by frequencies (qualitative variables). Data not available will be assessed as "missing values". Past and current medical history will be summarized by treatment group using the system organ class (SOC) as coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

7.6. Prior/Concomitant Therapy

Any medications or therapy present before the first dose of study medication (Visit 2) will be considered as prior medications. Concomitant medications (medications present while on study medication) will be recorded throughout the study and at early discontinuation. These medications will be coded using the WHO-drug dictionary. The number of subjects from the Safety Set using prior or concomitant medications will be categorized by the WHO-drug category and preferred term, and presented for each treatment group. In any given category (e.g., drug category) a subject will be counted only once.

7.7. Outcomes

7.7.1. Primary outcome (including definition)

One primary outcome will be considered in this study:

- $TST_{2/3}$ which is defined as the total sleep time during the first 2/3 of night following an 8-hour phase advance bedtime, as measured by polysomnography.

The primary null hypothesis is that there is no difference in $TST_{2/3}$ between subjects receiving tasimelteon and subjects receiving placebo. $TST_{2/3}$ will be assessed by analysis of variance with treatment group, and clinical site as a main effect. The primary efficacy analysis will be based on the ITT population.

Details on the complete analysis can be found in the Statistical Analysis Plan.

7.7.2. Secondary outcomes

The secondary outcomes of the study are as follows:

- WASO, as measured by polysomnography. WASO is defined as the time spent awake in the period between onset of persistent sleep and lights on.
- LPS by PSG which is defined as the length of time elapsed between light-out and onset of persistent sleep. Persistent sleep is defined as the point at which 10 minutes of non-wake sleep has begun.
- The full night (as well as parts of the night) SE, defined as the total sleep time (measured by polysomnography) as a percentage of the total time spent in bed between lights off and lights on and full night TST.
- TST in other time intervals of the night, e.g. $TST_{3/4}$ as the total sleep time during the first ¾ of the night (i.e. first 6 hours).
- Total REM sleep time, total Non-REM sleep time, Latency to REM, time to accumulate 30 minutes of REM sleep.
- The subjective post sleep assessments of sleep quality, sleep latency, and total sleep time as collected via post-sleep questionnaire.
- The next day residual effects of tasimelteon:
  KSS, VAS and post-sleep questionnaire (PSQ)
- The safety and tolerability of 20 mg tasimelteon.

For the continuous secondary efficacy variables, descriptive statistics will be presented by treatment group, and the scores will be summarized and analyzed in a manner similar to that for the primary endpoint. When baseline is available for endpoint, analysis of covariance will be used by including baseline as a covariance. Categorical variables will also be summarized and evaluated. Details of the analysis will be described in the SAP.

7.8. Safety Evaluation

7.8.1. Adverse Events

Adverse events will be recorded throughout the study and at early discontinuation. Adverse events and medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Treatment-emergent adverse events will be defined as those events, which are newly occurring or worsening from baseline. In all cases, only treatment emergent adverse events will be summarized.

Treatment-emergent adverse events will be summarized by presenting for each group the number and percentage of subjects having any treatment-emergent AE, having an AE in each body system, and having each individual AE. (Note: In any given category [e.g. body system] a subject will only be counted once.) Similar displays will be provided for prior (conditions ending prior to the first dose of study medication) and current (conditions present while on study medication) medical conditions.

Adverse events will further be categorized by severity, relationship to study medication, and action taken. Other information collected will be listed, as appropriate. Any event starting more than 3 days after the final dose of study medication will be excluded from the above tables and only listed, unless the event caused discontinuation.

The proportions of subjects experiencing SAEs and AEs resulting in discontinuation from the study will also be summarized.

7.8.2. Laboratory Data

The summary statistics of raw data (hematology and chemistry) and change from baseline values (means, medians, standard deviations, ranges) will be presented, as well as shift tables from baseline to post-baseline values using normal ranges. For urinalysis parameters, the number and percentage of subjects falling under each category of the test will be presented.

Clinical laboratory data will be summarized for each treatment group by presenting the proportions of subjects with clinically notable abnormalities (Table 9).

Clinically notable values will be identified according to the criteria identified in the FDA's "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates" (Revised 2-APR-87) provided by the FDA Division of Neuropharmacological Drug Products (DNDP).

7.8.3. Vital Signs and Body Measurements

Data from vital signs will be listed, clinically notable values as previously defined (Section 13.3) will be flagged, and any other information collected will be listed. Data will be summarized by group using mean change from baseline and proportions of subjects with values outside the normal range, and values that were clinically notable.

7.8.4. Electrocardiogram (ECG)

Results from the ECG will be listed for each subject. These data will also be summarized for each treatment group by presenting subjects with ECG abnormalities; shift tables; summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges).

7.9. Subgroup Analysis

The subgroup analysis (such as, gender, age, race etc.) for efficacy variables and safety variables may be conducted as described in the SAP.

7.9.1. Interim Analysis

No interim analysis planned.

7.9.2. Deviations in Analysis from Statistical Plan and Other Issues

During the analysis and reporting process, any deviations from the statistical plan designed for this protocol will be described and justified in the final report.