Introduction: Tasimelteon

Mihael H. Polymeropoulos MD
Vanda Pharmaceuticals

Peripheral and Central Nervous System Drugs Advisory Committee
November 14, 2013
Silver Spring, MD
Tasimelteon in Non-24

- Tasimelteon: proposed trade name Hetlioz™
- Proposed Indication: for the treatment of Non-24-Hour Disorder in the totally blind
- Proposed Class: Circadian Regulator
Non 24 Hour Disorder (Non-24): A Circadian Disorder

- Circadian Rhythm Disorder
- Inability to entrain the master clock at the suprachiasmatic nucleus (SCN) to a 24-hour rhythm
- Inability to entrain hormone secretion under circadian control; i.e. melatonin (pineal), cortisol (adrenal)
Master Clock is Entrained by Light

- Internal master clock has a period (tau) greater than 24 hours

- Light sensed by the intrinsically photosensitive retinal ganglion cells (ipRGCs) of the retina travels through the retinohypothalamic tract to the SCN resetting the Master Clock to a period (tau) equal to 24 hours

- The SCN in turn entrains hormone secretion under circadian control; i.e. melatonin (pineal), cortisol (adrenal)
Non-24 in the Totally Blind

- In the totally blind, the inability to sense light results in inability to entrain the master clock resulting in Non-24.

- Totally blind with Non-24 have circadian period lengths of approximately 24.5 hours.

- Circadian hormone secretion and physiological functions are perpetually delaying by a half hour each day leading to dyssynchrony with the 24 hour world.
Circadian Timing System

- **Suprachiasmatic nucleus**
- **Clock genes**
- **Sleep/wakefulness**
- **Cortisol**
- **Melatonin**
- **Temperature**
- **Heart rate**
- **Circadian clocks in peripheral organs**

Main Environmental Entrainer:
- **Light/Dark**

Cardiovascular, Metabolic, Immune System, Cell Cycle

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Non-24 is Prevalent in the Totally Blind

- Rare, orphan disorder; approximately 80,000 people in the US are expected to be totally blind with Non-24
- Serious, debilitating, chronic disorder with no available treatment
- Severe cyclical sleep-wake symptoms; inappropriate timing and consolidation of sleep episodes
- Significant impairment in social and occupational functioning
- Effects on cardiovascular and metabolic homeostasis are beginning to be understood
Regulatory Status of Tasimelteon

- 2010: US FDA Orphan Designation for the treatment of Non-24-Hour Disorder in the totally blind
- 2011: EMA Orphan Designation for the treatment of Non-24-Hour Disorder in the totally blind
- July 2013: US FDA Priority Review designation
Development Considerations for Tasimelteon

- Rare, orphan disorder with low awareness in the blind community
- No approved treatment
- Endpoint concepts
  - "Entrainment" in the causal pathway
  - "Sleep amount and timing" a key consideration in developing a clinical composite
  - "Cyclicity" a key consideration in calculating endpoints
Clinical Development Program of Tasimelteon

- SET study (26 week duration)
  - Entrainment
  - Clinical response

- RESET study (19 week duration)
  - Maintenance of entrainment
  - Maintenance of clinical response
Clinical Trials: Evidence Supports Approval

- Entrainment and Clinical Response measures demonstrate a specific and clinically meaningful effect
- Safety database establishes tasimelteon to be safe and well-tolerated
- A positive benefit-risk ratio for the treatment of Non-24
## Agenda

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<td>Charles A. Czeisler, PhD, MD, FRCP</td>
<td>Chair, Scientific Advisory Board, Vanda Harvard Medical School</td>
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<td>Paolo Baroldi, MD, PhD</td>
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<td>Joseph Sliman, MD, MPH</td>
<td>Vanda Pharmaceuticals</td>
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<td><strong>Phase Analysis</strong></td>
<td>Mihael H. Polymeropoulos, MD</td>
<td>Vanda Pharmaceuticals</td>
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# Vanda Experts*

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<tr>
<th>Name</th>
<th>Institution / Position</th>
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<tbody>
<tr>
<td>Gary Koch, PhD</td>
<td>UNC Gillings School of Global Public Health</td>
</tr>
<tr>
<td></td>
<td>Professor of Biostatistics</td>
</tr>
<tr>
<td>Eugene Laska, PhD</td>
<td>Nathan Kline Institute for Psychiatric Research</td>
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<td></td>
<td>Director of Statistical Sciences and Epidemiology</td>
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<tr>
<td></td>
<td>NYU Medical Center</td>
</tr>
<tr>
<td></td>
<td>Professor of Psychiatry</td>
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<tr>
<td>D. Alan Lankford, PhD, ABSM</td>
<td>Sleep Disorders Center of Georgia</td>
</tr>
<tr>
<td></td>
<td>Co-founder &amp; Administrative Director</td>
</tr>
<tr>
<td>Todd Swick, MD</td>
<td>Houston Sleep Center</td>
</tr>
<tr>
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<td>Medical Director</td>
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</table>

*These participants are paid consultants of Vanda Pharmaceuticals. They have received reimbursement for their travel & expenses as well as compensation for their time at this advisory committee meeting.*
Non-24-Hour Disorder
History and Pathophysiology

Charles A. Czeisler, Ph.D., M.D.*
Chair, Scientific Advisory Board, Vanda Pharmaceuticals, Inc.

Baldino Professor of Sleep Medicine, Harvard Medical School

Chief, Division of Sleep Medicine, Department of Medicine,
Brigham and Women’s Hospital

* DR. CZEISLER WAS NOT AN INVESTIGATOR ON THE CLINICAL TRIALS EVALUATING THE EFFICACY AND SAFETY OF TASIMELTEON, AS HE IS A PAID CONSULTANT TO AND HAS AN EQUITY INTEREST IN VANDA PHARMACEUTICALS, INC. Dr. Czeisler also is/was a consultant to Bombardier, Boston Celtics, Boston Red Sox, Cephalon, Citgo, Michael Jackson’s mother and children, Koninklijke Philips Electronics, Novartis, Purdue Pharma, Teva, United Parcel Service, Valero; receives royalties from McGraw Hill, Houghton Mifflin Harcourt and Philips Respironics; has an equity interest in Somnus and Vanda Pharmaceuticals; is an expert witness in legal cases; and is the incumbent of a Harvard professorship endowed by Cephalon, Inc.
History of Non-24-Hour Disorder in the Blind

- Remler (1948) first reported circadian rhythm and sleep disturbance in totally blind \([N=75;\) inverse or flat core body temperature (43%), BP, HR, urine rhythms; the predominant clinical symptom by far is sleep disturbance (45%), with some “only having sleep disturbance at times ... followed by periods of regular sleep”\]

- Case study by Miles et al., 1977 \((\tau \approx 24.9 \text{ h})\) \([N=1;\) non-24-H period of sleep-wake cycle together with non-24-h period of circadian rhythms of body temperature, alertness, performance, cortisol secretion and urinary electrolyte excretion\]

- Studies by Orth et al., 1979; Sack et al., 1992; Nakagawa et al., 1992; and Klein et al., 1993 [non-24-h period of circadian rhythms of cortisol and body temperature despite 24-h period of sleep-wake cycle\]

- Discovery of ocular circadian photoreception and of dedicated retinal photoreceptor: Czeisler et al., 1995; Gooley et al., 2001; Berson et al., 2002; Hattar et al., 2002.
The Circadian Master Clock in the SCN

- Suprachiasmatic nucleus (SCN) is a cluster of ~50,000 neurons in the human hypothalamus
- SCN generates a self-sustained oscillation with an intrinsic period ($\tau_i$) that, on average, is longer than 24.0 h
- Retinal sensors (intrinsically photosensitive retinal ganglion cells, ipRGCs) transmit light information to the SCN via a monosynaptic retinohypothalamic tract
- Periodic light-dark cycle ($T = 24$ h) entrains the SCN to an observed period ($\tau_o$) of 24.0 h in normally sighted people and in a minority of blind people with intact ipRGCs
The SCN Master Clock Controls Peripheral Rhythms

- Endocrine rhythms (e.g., pineal melatonin, adrenal cortisol, thyroid hormone)
- Sleep-wake patterns (via circadian rhythms in sleepiness, in alertness, in ability to sleep and in wakefulness)
- Performance rhythms (e.g., cognitive throughput, reaction time, memory, coordination)
- Cardiovascular rhythms (e.g., blood pressure, heart rate)
- Metabolic rhythms (e.g., insulin secretion, glucose tolerance, lipids)
- Immune system rhythms (e.g., lymphocytes)
- Renal rhythms (e.g., urinary electrolytes, urine production)
Melatonin and Cortisol

- Coordinately regulated by the SCN
- Melatonin peaks at night
- Cortisol peaks in the morning
- In blind people with Non-24-H Disorder, both melatonin and cortisol rhythms:
  - continue to oscillate with near-24-h period
  - are NOT entrained to 24-h day

24-hour light-dark cycle resets the circadian clock on a daily basis

Neuroanatomy of the circadian system

Neuroanatomy of the circadian system

Neuroanatomy of the circadian system

Adapted from Wehr TA et al. Arch Gen Psych 2001; 58: 1110;
Urinary aMT6s Rhythms (48 h/week) in the Visually Impaired

Entrained
Normal phase (1:00 - 7:00 h)
(e.g., $T = 24.0$ h; $\tau_0 \approx 24.00$ h)

Non-entrained
Non-24-hour rhythm
(e.g., $T = 24.0$ h; $\tau_0 \approx 24.7$ h;

*circadian beat cycle* $\approx 34 \text{ days}$)

Circadian Beat Cycle: ~133 days ($\tau_0 \approx 24.18$ h)

Circadian Beat Cycle: ~72.7 days ($\tau_0 \approx 24.33$ h)

Circadian Beat Cycle: ~25.5 days ($\tau_0 \approx 24.94$ h)

$\tau_0 \approx 24.4 \pm 0.3$ h
Timing of Sleep of Propensity: Circadian and Homeostatic Regulation

- Timing of sleep-wake patterns in patients with Non-24 influenced by:
  - Circadian rhythms of alertness, sleepiness, sleep drive and wake drive ($\tau_o \neq 24$ h)
  - Homeostatic regulation of alertness, sleepiness, sleep propensity and wake propensity
  - Work schedule (usually $T = 24$ h)
  - Social schedule (usually $T = 24$ h)
  - Cultural expectations ($T = 24$ h)
Chronic Circadian Non-entrainment has Profound Health Consequences

- Disturbed sleep wake cycle
- Severe impact in social/occupational functioning
- Adverse impact on cognitive function and learning
- Adverse impact of circadian disruption on cardiovascular and metabolic homeostasis (Kawachi et al., 1995, Toshihiro et al., 2008, Buxton et al., 2012)

Non-24-H Disorder and the Martian Day

- 1997 Mars Pathfinder Mission: Living on Mars day taxed NASA JPL personnel at Cal Tech “beyond reasonable limits,” prompting a “rebellion,” as investigated in 2001
- 2006: Lab simulation of Mars 24.65-h day revealed:
  - Circadian misalignment
  - Chronic sleep disruption
  - Cognitive impairment
  - Impaired ability to learn

Earth Solar Day \((T = 24.00 \text{ h}; \tau_o \approx 24.00 \text{ h})\)
Mars Solar Day \((T = 24.65 \text{ h}; \tau_o \approx 24.15 \text{ h})\)
Non-24-H Disorder \((T = 24.00 \text{ h}; \tau_o \approx 24.5 \text{ h})\)

Need for an Effective Therapeutic for Non-24 Disorder in Blind People

- Non-24-H Disorder patients suffer from recurrent delaying of their internal circadian clock with respect to 24-h day.

- To be effective, a therapeutic must be able to reset the master circadian clock in totally blind patients without conscious light perception.

- Gold standard measure of effectiveness of a treatment for Non-24-H Disorder must be entrainment or synchronization of the circadian clock to the 24-h day.

- Improvement in sleep-wake timing should occur as a consequence of entraining the master clock and synchronizing the sleep-wake cycle to a 24-h Earth day.
Literature Cited

Clinical Trial Endpoints

Louis Licamele, PhD
Vanda Pharmaceuticals Inc.
Clinical Trial Endpoints

- Entrainment: Resetting the Master clock to 24.0 hrs
- N24CRS (Non-24 Clinical Response Scale): Improvement in sleep-wake measures and overall functioning
Nighttime Total Sleep Time (nTST) & Daytime Total Sleep Duration (dTSD)

- Not specific endpoints for Non-24
  - Not focused on periodic misalignment between circadian period and the external 24-hour clock
  - Minimal disruption expected in nTST/dTSD when in-phase

- Reduced detection power for this rare and orphan disorder
Clinical Trial Endpoints

- Entrainment
- N24CRS (Non-24 Clinical Response Scale)
Entrainment

- Entrainment is a measure of synchronization of the Master Clock to the 24-hour day
- Analyte: aMT6s (melatonin metabolite) or cortisol
- Acrophase: Peak time of endogenous analyte secretion is calculated over a 48 hour period; repeated weekly
- $\tau$ (tau): measured by the linear regression across these acrophases
# Acrophase Measurements Over 4 Weeks

<table>
<thead>
<tr>
<th>Week</th>
<th>Acrophase (Time)</th>
<th>SE (Hours)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>1:49 PM</td>
<td>0.44</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>2</td>
<td>5:23 PM</td>
<td>0.43</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>3</td>
<td>9:34 PM</td>
<td>0.27</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>4</td>
<td>3:01 AM</td>
<td>0.57</td>
<td>0.001</td>
</tr>
</tbody>
</table>
τ: Linear Regression of Acrophase Measurements Over Time

τ = 24.58
CI: 24.48-24.67
Cycle Length = 42 days
Composite of 4 Different $\tau$ Values

**Entrained: $\tau = 24.0$**

**Not Entrained: $\tau = 24.3$**
Cycle = 80 days

**Not Entrained: $\tau = 24.5$**
Cycle = 48 days

**Not Entrained: $\tau = 24.8$**
Cycle = 30 days
Composite of Raster Plots for $\tau$ Values

Entrained: $\tau = 24.0$

Not Entrained: $\tau = 24.3$

Not Entrained: $\tau = 24.5$

Not Entrained: $\tau = 24.8$
## N24CRS Components

<table>
<thead>
<tr>
<th>Component</th>
<th>What is Measured</th>
</tr>
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<tbody>
<tr>
<td>LQ-nTST</td>
<td>Worst 25% of nights (total nighttime sleep)</td>
</tr>
<tr>
<td>UQ-dTSD</td>
<td>Worst 25% of days (total daytime sleep duration)</td>
</tr>
<tr>
<td>MoST</td>
<td>Timing and consolidation of sleep</td>
</tr>
<tr>
<td>CGI-C</td>
<td>Global functioning</td>
</tr>
</tbody>
</table>
LQ-nTST Measured Over Study Period
Enrichment for “Worst” Nights

Nighttime Total Sleep Time Across Circadian Cycle

Nighttime Total Sleep Time (minutes)

Percentage LQ-nTST within Bin (%)

In-Phase

Out-of-Phase

In-Phase
LQ-nTST Endpoint Properties

- Enriches for "worst night" analysis reflective of the cyclical nature of Non-24
- Highly correlated with circadian phase
- Clinically meaningful as a direct reflection of amount of sleep when patients are suffering the most
UQ-dTSD Measured Over Study Period

![Graph showing UQ-dTSD measurements over a study period. The x-axis represents study days, ranging from 0 to 120, and the y-axis represents dTSD, ranging from 0 to 350. The data points indicate variability in dTSD measurements across different study days.](image-url)
Enrichment for “Worst” Days

Daytime Total Sleep Duration Across Circadian Cycle

Daytime Total Sleep Duration (min)

In-Phase  Out-of-Phase  In-Phase

CT-44
Enrichment for “Worst” Days

Daytime Total Sleep Duration Across Circadian Cycle

Daytime Total Sleep Duration (min) vs. Percent UQ-dTSD within Bin (%)

In-Phase: Blue Line
Out-of-Phase: Red Line
UQ-dTSD Endpoint Properties

- Enriches for "worst day" analysis reflective of the cyclical nature of Non-24
- Highly correlated with circadian phase
- Clinically meaningful as a direct reflection of a patient's ability to reduce daytime sleep
Sleep Amount and Sleep Timing

- **Sleep Amount**
  - LQ-nTST
  - UQ-dTSD

- **Sleep Timing**
  - MoST
Midpoint of Sleep Timing (MoST)

- Mean weighted average of all sleep in a 24 hour period relative to a patient’s desired bedtime
- Measure of timing and consolidation of sleep
- Potential scores range from -12 to +12 hours
- 7-8 hours of nighttime sleep at desired bed time with no daytime sleep will have a MoST value of ~3.5-4.0
Introducing MoST: Raster Plot of a Non-24 Patient

![Raster Plot](image1)

- **Nighttime sleep (screening)**
- **Daytime sleep**
- **aMT6s acrophase times**

MoST

Represents average value for a person sleeping 8-hours at their desired bedtime
Introducing MoST: Raster Plot of a Non-24 Patient

Raster Plot

MoST

In-Phase

- Blue: Nighttime sleep (screening)
- Black: Daytime sleep
- Red: aMT6s acrophase times

Represents average value for a person sleeping 8-hours at their desired bedtime
Introducing MoST: Raster Plot of a Non-24 Patient

Raster Plot

- **Nighttime sleep (screening)**
- **Daytime sleep**
- **aMT6s acrophase times**

MoST

Represents average value for a person sleeping 8-hours at their desired bedtime
MoST Across Circadian Cycle

MoST (hours)

In-Phase    Out-of-Phase    In-Phase

MoST (hours)

2.0  2.5  3.0  3.5
MoST Endpoint Properties

- Measures timing of sleep episodes over the full 24 hour period
- Highly correlated with "out of phase" portion of the circadian cycle
- Clinically meaningful as a direct reflection of a patient's desire to consolidate most of their sleep at night
Clinical Global Impression of Change (CGI-C)

- Physician reported outcome of overall improvement relative to the start of the study
- 7-point scale
CGI-C Scale

1 Very much improved
2 Much improved
3 Minimally improved
4 No change
5 Minimally worse
6 Much worse
7 Very much worse

Improved

Worsened
# N24CRS Components: Responder Thresholds

<table>
<thead>
<tr>
<th>Component</th>
<th>Criteria</th>
<th>Score if Criteria Not Met</th>
<th>Score if Criteria Met</th>
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</thead>
<tbody>
<tr>
<td>LQ-nTST</td>
<td>( \geq 45\text{min} ) night sleep improvement</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>UQ-dTSD</td>
<td>( \geq 45\text{min} ) daytime sleep reduction</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>MoST</td>
<td>( \geq 30\text{min} ) improvement (SD &lt;120min)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>CGI-C</td>
<td>( \leq 2 ) score</td>
<td>0</td>
<td>1</td>
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</table>

N24CRS Score = Sum of all component scores with a possible range of 0 to 4
Clinical Response

- Clinical response:
  1. Entrainment (aMT6s) and
  2. N24CRS ≥3
Example Responder Calculation for Primary Clinical Endpoint

Raster Plot

MoST

Represents average value for a person sleeping 8-hours at their desired bedtime.
### Example Responder Calculation for Primary Clinical Endpoint

<table>
<thead>
<tr>
<th>Component</th>
<th>Observed Value</th>
<th>Criteria Met</th>
<th>Score (if Applicable)</th>
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</thead>
<tbody>
<tr>
<td>Entrainment</td>
<td>Yes</td>
<td>✓</td>
<td></td>
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<tr>
<td>LQ-nTST</td>
<td>136 min</td>
<td>✓</td>
<td>1</td>
</tr>
<tr>
<td>UQ-dTSD</td>
<td>-128 min</td>
<td>✓</td>
<td>1</td>
</tr>
<tr>
<td>MoST</td>
<td>72 min (SD=1.9 hrs)</td>
<td>✓</td>
<td>1</td>
</tr>
<tr>
<td>CGI-C</td>
<td>1</td>
<td>✓</td>
<td>1</td>
</tr>
<tr>
<td>N24CRS</td>
<td>Sum of component scores</td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

- Patient is **entrained with a N24CRS ≥3**
- Considered a **responder** for the primary clinical endpoint
Example Non-Responder Calculation for Primary Clinical Endpoint

Raster Plot

MoST

[Graph showing sleep patterns with lines and markers indicating nighttime and daytime sleep during screening and placebo treatment]

Screening
Placebo Treatment Study Day

Daytime sleep

Nighttime sleep (screening)

Nighttime sleep (placebo treatment)

aMT6s acrophase times

Represents average value for a person sleeping 8-hours at their desired bedtime
Example Non-Responder Calculation for Primary Clinical Endpoint

<table>
<thead>
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<th>Component</th>
<th>Observed Value</th>
<th>Criteria Met</th>
<th>Score (if Applicable)</th>
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<tbody>
<tr>
<td>Entrainment</td>
<td>No</td>
<td>X</td>
<td></td>
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<tr>
<td>LQ-nTST</td>
<td>12 min</td>
<td>X</td>
<td>0</td>
</tr>
<tr>
<td>UQ-dTSD</td>
<td>-37 min</td>
<td>X</td>
<td>0</td>
</tr>
<tr>
<td>MoST</td>
<td>12 min (SD=1.9 hrs)</td>
<td>X</td>
<td>0</td>
</tr>
<tr>
<td>CGI-C</td>
<td>4</td>
<td>X</td>
<td>0</td>
</tr>
<tr>
<td>N24CRS</td>
<td>Sum of component scores</td>
<td></td>
<td>0</td>
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- Patient is not entrained
- Considered a non-responder for the primary clinical endpoint
**Clinical Measurements of LQ-nTST, UQ-dTSD and MoST are Predictive of Entrainment Status**

<table>
<thead>
<tr>
<th>Clinical Endpoint</th>
<th>Entrained* (n=57)</th>
<th>Non-Entrained* (n=121)</th>
<th>Delta</th>
<th>p-value</th>
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<tbody>
<tr>
<td>LQ-nTST</td>
<td>4.38 hrs</td>
<td>3.25 hrs</td>
<td>-1.13 hrs</td>
<td>&lt;0.0001</td>
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<tr>
<td>UQ-dTSD</td>
<td>1.34 hrs</td>
<td>2.41 hrs</td>
<td>1.07 hrs</td>
<td>&lt;0.0001</td>
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<tr>
<td>MoST</td>
<td>3.51 hrs</td>
<td>2.79 hrs</td>
<td>-0.72 hrs</td>
<td>&lt;0.0001</td>
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* These data are from the screening phase of the SET study for 178 patients who had both entrainment status and clinical data.
# Endpoint Summary

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<thead>
<tr>
<th>Endpoint</th>
<th>Possible Score</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>Entrainment</td>
<td>YES/NO</td>
<td>Resetting the Master Clock</td>
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<tr>
<td>Clinical Responder: Entrainment + N24CRS</td>
<td>YES/NO</td>
<td>a) Resetting the Master Clock and b) Clinical improvement in sleep wake measures and global functioning</td>
</tr>
<tr>
<td>N24CRS</td>
<td>0 - 4</td>
<td>Clinical improvement in sleep wake measures and global functioning</td>
</tr>
<tr>
<td>LQ-nTST</td>
<td>Minutes</td>
<td>Change in nighttime sleep</td>
</tr>
<tr>
<td>UQ-dTSD</td>
<td>Minutes</td>
<td>Change in daytime sleep</td>
</tr>
<tr>
<td>MoST</td>
<td>Minutes</td>
<td>Shift of midpoint of sleep</td>
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<tr>
<td>CGI-C</td>
<td>1-7</td>
<td>Global functioning</td>
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Key Methods References


Clinical Program
Efficacy

Marlene Dressman, PhD
Vanda Pharmaceuticals Inc.
# Tasimelteon Clinical Development Program

## 1652 Patients and Healthy Volunteers
1346 Tasimelteon Treated

### Phase I

<table>
<thead>
<tr>
<th>Healthy Volunteers</th>
<th>PK/PD (n=5)</th>
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<tbody>
<tr>
<td></td>
<td>CYP3A4 (n=2)</td>
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<td>CYP1A2 (n=1)</td>
</tr>
<tr>
<td></td>
<td>CYP2C8 (n=1)</td>
</tr>
<tr>
<td></td>
<td>Alcohol DDI (n=1)</td>
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</tbody>
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| Elderly | PK/PD (n=1) |

<table>
<thead>
<tr>
<th>Special Populations</th>
<th>Hepatic (n=1)</th>
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<tbody>
<tr>
<td></td>
<td>Renal (n=1)</td>
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<tr>
<td></td>
<td>Smokers (n=1)</td>
</tr>
</tbody>
</table>

### Phase II

<table>
<thead>
<tr>
<th>Elderly Insomnia</th>
<th>Safety and Efficacy (n=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Volunteers</td>
<td>2101 (PoC)</td>
</tr>
</tbody>
</table>

### Phase III

<table>
<thead>
<tr>
<th>Healthy Volunteers</th>
<th>3101 Circadian Induced Transient Insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Insomnia</td>
<td>3104</td>
</tr>
<tr>
<td></td>
<td>3201 (SET)</td>
</tr>
<tr>
<td></td>
<td>3203 (RESET)</td>
</tr>
<tr>
<td></td>
<td>Safety 3202 and 3204</td>
</tr>
</tbody>
</table>
### Tasimelteon Dose Selection

- **20 mg** is the minimum dose demonstrating effectiveness in circadian and clinical parameters.

<table>
<thead>
<tr>
<th></th>
<th>Circadian Rhythm Regulation</th>
<th>Clinical Measures of Sleep</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Vivo and Ex Vivo SCN Studies</td>
<td>☑</td>
<td>Not measured</td>
<td>Equivalent to 10-50 mg in 70 kg person</td>
</tr>
<tr>
<td>2101</td>
<td>☑</td>
<td>☑</td>
<td>20, 50, and 100 mg</td>
</tr>
<tr>
<td>3101</td>
<td>Not measured</td>
<td>☑</td>
<td>20 and 50 mg</td>
</tr>
</tbody>
</table>
Phase 3 Pivotal Efficacy Studies

- SET study (26 week duration)
  - Entrainment
  - Clinical response

- RESET study (19 week duration)
  - Maintenance of entrainment
  - Maintenance of clinical response
SET Study

- **Safety and Efficacy of Tasimelteon**
  - Randomized double-masked, placebo-controlled, multicenter, parallel-group trial

- 84 totally blind patients between the ages of 23-74 years with Non-24 who had both
  - Non-entrained circadian rhythm (aMT6s)
    - \( \tau \geq 24.25 \) (95% CI 24.1–24.9)
  - Sleep-wake symptoms (SWQ)

- 33 Sites (United States: 27, Germany: 6)

- First Patient First Visit: August 25, 2010

- Database Lock: December 12, 2012
SET Study Design

Screening Phase

Double-Masked Phase

- Tasimelteon 20 mg
  - N=42
- Placebo
  - N=42

Month 1

In-Phase Transition

- ~3 months
- 6 months

- τ estimation
- Sleep diary collection
- Safety evaluations
- CGI-C evaluations

Month 1

Month 7

N=17
SET Study

Primary Objectives

- Primary 1: Entrainment
  - $\tau < 24.1$ (95% CI includes 24.0)

- Primary 2: Clinical Response
  - Entrainment plus N24CRS $\geq 3$
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Target of Assessment</th>
<th>Time of Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entrainment (cortisol)</td>
<td>Circadian rhythm</td>
<td>Month 1</td>
</tr>
<tr>
<td>LQ-nTST</td>
<td>Nighttime sleep, 25% worst</td>
<td>Daily for 6 months</td>
</tr>
<tr>
<td>UQ-dTSD</td>
<td>Daytime sleep, 25% worst</td>
<td>Daily for 6 months</td>
</tr>
<tr>
<td>MoST</td>
<td>Timing of sleep</td>
<td>Daily for 6 months</td>
</tr>
<tr>
<td>CGI-C</td>
<td>Global function</td>
<td>Months 4 and 6</td>
</tr>
</tbody>
</table>
SET Study
Causes of Blindness

- Congenital Glaucoma: 8.9%
- Glaucoma: 10.1%
- Ocular Trauma: 14.9%
- Other: 20.2%
- Retinoblastoma: 13.1%
- Retinopathy of Prematurity: 32.7%
- Retinopathy of Prematurity: 32.7%
- Other: 20.2%
- Ocular Trauma: 14.9%
- Glaucoma: 10.1%
- Congenital Glaucoma: 8.9%

Other causes include:
- Cataracts
- Cornea Death
- Detached Retina
- Diabetes
- Optic Artery Blood Clot
- Optic Atrophy
- Optic Neuritis
- Retinal Detachment
- Retinitis Pigmentosa
- Rheumatoid Arthritis
- Sarcoidosis
- Surgical Damage
- Unknown
## SET Study
### Demographics

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=42</th>
<th>Tasimelteon N=42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at screening (years) (SD)</td>
<td>50.7 (13.15)</td>
<td>50.8 (12.63)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male %</td>
<td>59.5</td>
<td>57.1</td>
</tr>
<tr>
<td>Female %</td>
<td>40.5</td>
<td>42.9</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White %</td>
<td>81.0</td>
<td>85.7</td>
</tr>
<tr>
<td>Black, African, or African American %</td>
<td>14.3</td>
<td>9.5</td>
</tr>
<tr>
<td>Other %</td>
<td>4.8</td>
<td>4.8</td>
</tr>
<tr>
<td>BMI kg/m² (SD)</td>
<td>27.73 (3.93)</td>
<td>28.16 (4.06)</td>
</tr>
</tbody>
</table>
## SET Study
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Placebo (N=42)</th>
<th>Tasimelteon (N=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circadian period (τ): aMT6s</td>
<td>24.45 (0.17)</td>
<td>24.49 (0.16)</td>
</tr>
<tr>
<td>Circadian period (τ): Cortisol</td>
<td>24.43 (0.32)</td>
<td>24.48 (0.25)</td>
</tr>
<tr>
<td>LQ-nTST (hours)</td>
<td>3.25 (1.61)</td>
<td>3.25 (1.19)</td>
</tr>
<tr>
<td>UQ-dTSD (hours)</td>
<td>2.53 (1.71)</td>
<td>2.29 (1.66)</td>
</tr>
<tr>
<td>MoST</td>
<td>2.61 (1.18)</td>
<td>2.82 (0.89)</td>
</tr>
</tbody>
</table>
SET Study

Statistical Analysis Populations

- **ITT (n=78):** All patients randomized who had circadian period ($\tau$) calculated post-randomization
  - Entrainment primary endpoint
  - Entrainment secondary endpoint

- **Analysis (n=72):** All patients in the ITT population who had at least 70% of one circadian cycle of nighttime total sleep time (nTST) data during each of screening and treatment
  - Clinical response primary endpoint
  - Clinical secondary endpoints

- **ITT* (n=84):** All patients who received at least one dose of treatment and had one efficacy assessment
  - FDA requested post-hoc analysis
## SET Study
### Primary Endpoint Results

<table>
<thead>
<tr>
<th>Results</th>
<th>Placebo n/N (%)</th>
<th>Tasimelteon n/N (%)</th>
<th>p-value(^a)</th>
<th>p-value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entrainment(^c)</td>
<td>1/38 (2.6)</td>
<td>8/40 (20.0)</td>
<td>0.0171</td>
<td>0.0291</td>
</tr>
<tr>
<td>Clinical Response (Entrainment(^d) + N24CRS ≥3)</td>
<td>0/34 (0.0)</td>
<td>9/38 (23.7)</td>
<td>0.0028</td>
<td>0.0025</td>
</tr>
</tbody>
</table>

\(^a\) p-value was based on Barnard’s Exact Test, two-sided (pre-specified for primary test).

\(^b\) p-value was based on Fisher’s Exact Test, two-sided.

\(^c\) Entrainment measured at month 1.

\(^d\) Entrainment defined as a post-baseline \(\tau\) value < 24.1 and 95% CI that included 24.0. Results based on month 1 or month 7.

*Clinical Response was tested as a step-down primary.
## SET Study
### Clinical Response: Sensitivity Analyses

<table>
<thead>
<tr>
<th>Sensitivity Analysis</th>
<th>Placebo n/N (%)</th>
<th>Tasimelteon n/N (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N24CRS $\geq$ 3 + Entrainment (Month 1)</td>
<td>0/34 (0.0)</td>
<td>5/38 (13.2)</td>
<td>0.0286</td>
</tr>
<tr>
<td>N24CRS $\geq$ 2 + Entrainment (Months 1 &amp; 7)</td>
<td>0/34 (0.0)</td>
<td>11/38 (28.9)</td>
<td>0.0006</td>
</tr>
<tr>
<td>N24CRS $\geq$ 3</td>
<td>1/34 (2.9)</td>
<td>11/38 (28.9)</td>
<td>0.0031</td>
</tr>
<tr>
<td>N24CRS $\geq$ 2</td>
<td>7/34 (20.6)</td>
<td>22/38 (57.9)</td>
<td>0.0014</td>
</tr>
</tbody>
</table>
SET Study
Primary Endpoints and Sensitivity Analyses

- Entrainment month 1
- Entrainment + N24CRS ≥ 3
- Entrainment + N24CRS ≥ 3
- Entrainment + N24CRS ≥ 2
- N24CRS ≥ 3
- N24CRS ≥ 2

\[ \text{Entrainment measured at month 1 (SET) and month 7 (RESET).} \]

p-value

0.0171
0.0028
0.0286
0.0006
0.0031
0.0014

\( \text{Favors Placebo} \quad \leftarrow \quad \text{Favors Tasimelteon} \)
SET Study
Patient Flow Chart Entrainment Rate Tasimelteon

Tau at Month 1

42

8 E

40

32 NE

13 E

4 NE

0 NE

6 E

7 NE

42 Entrainment Rate = 20%

4 Entrainment Rate = 59%

E = Entrained
NE = Not Entrained
# Tasimelteon Entrains Cortisol Circadian Rhythms

<table>
<thead>
<tr>
<th>Category Statistic</th>
<th>Placebo</th>
<th>Tasimelteon 20 mg</th>
<th>Treatment Difference (Tasimelteon minus Placebo)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entrainment (cortisol), n (%)</td>
<td>1/38 (2.6)</td>
<td>7/40 (17.5)</td>
<td>14.9</td>
<td>0.031</td>
</tr>
</tbody>
</table>
## SET Study
### Secondary Endpoints: Analysis Population

<table>
<thead>
<tr>
<th>Category Statistic</th>
<th>Placebo (n=34)</th>
<th>Tasimelteon 20 mg (n=38)</th>
<th>Treatment Difference (Tasimelteon minus Placebo)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQ-nTST (mean minutes)</td>
<td>17.08</td>
<td>56.80</td>
<td>39.71</td>
<td>0.0055</td>
</tr>
<tr>
<td>UQ-dTSD (mean minutes)</td>
<td>-17.87</td>
<td>-46.48</td>
<td>-28.61</td>
<td>0.0050</td>
</tr>
<tr>
<td>MoST (mean minutes)</td>
<td>14.48</td>
<td>35.00</td>
<td>20.52</td>
<td>0.0123</td>
</tr>
<tr>
<td>CGI-C</td>
<td>3.4</td>
<td>2.6</td>
<td>-0.8</td>
<td>0.0093</td>
</tr>
</tbody>
</table>

*a* p-value based on the analysis of co-variance model.

*b* p-value based on analysis of variance model.

*c* The placebo arm had N=33 and tasimelteon arm had N=36.
## SET Study

### Exploratory Analyses of Clinical Measures (p-values): ITT Population

<table>
<thead>
<tr>
<th>Population</th>
<th>LQ-nTST</th>
<th>UQ-dTSD</th>
<th>MoST</th>
<th>CGI-C&lt;sup&gt;a&lt;/sup&gt;</th>
<th>nTST</th>
<th>dTSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT (78)</td>
<td>0.0034</td>
<td>0.0029</td>
<td>0.0470</td>
<td>0.0086</td>
<td>0.0289</td>
<td>0.0067</td>
</tr>
<tr>
<td>ITT* (84)</td>
<td>0.0232</td>
<td>0.0031</td>
<td>0.0229</td>
<td>0.0104</td>
<td>0.0658</td>
<td>0.0026</td>
</tr>
</tbody>
</table>

<sup>a</sup> For CGI-C n=71

ITT = Intent-to-treat population as defined in SET.

ITT* = Post-hoc analysis population at the request of the agency.
SET Study
Forest Plot of ITT and ITT* Population Analyses

ITT (n=78)

ITT* (n=84)

LQ-nTST

UQ-dTSD

MoST

nTST

dTSD

Favors Placebo  Favors Tasimelteon

Favors Placebo  Favors Tasimelteon
### SET Study
### Secondary Endpoints II: Analysis Population

<table>
<thead>
<tr>
<th>Category Statistic</th>
<th>Placebo</th>
<th>Tasimelteon 20 mg</th>
<th>Treatment Difference (Tasimelteon minus Placebo)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQ-nTST and UQ-dTSD ≥45 min, n (%)</td>
<td>3 (8.8)</td>
<td>12 (31.6)</td>
<td>22.8</td>
<td>0.0177</td>
</tr>
<tr>
<td>LQ-nTST and UQ-dTSD ≥90 min, n (%)</td>
<td>1 (2.9)</td>
<td>5 (13.2)</td>
<td>10.2</td>
<td>0.1312</td>
</tr>
<tr>
<td>Entrained and ≥45 minute improvement in LQ-nTST, n (%)</td>
<td>0 (0.0)</td>
<td>10 (26.3)</td>
<td>26.3</td>
<td>0.0013</td>
</tr>
<tr>
<td>Entrained and ≥45 minute improvement in UQ-dTSD, n (%)</td>
<td>0 (0.0)</td>
<td>11 (28.9)</td>
<td>28.9</td>
<td>0.0006</td>
</tr>
<tr>
<td>Entrained and ≥30 min improvement in MoST and SD ≤2.0 hours, n (%)</td>
<td>0 (0.0)</td>
<td>8 (21.1)</td>
<td>21.1</td>
<td>0.0046</td>
</tr>
<tr>
<td>Entrained and ≤2.0 in average CGI-C, n (%)</td>
<td>0 (0.0)</td>
<td>7 (19.4)</td>
<td>19.4</td>
<td>0.0078</td>
</tr>
</tbody>
</table>

1 Sensitivity analysis
SET Study
Secondary Endpoints II

- 45 min Improvement in LQ-nTST and UQ-dTSD
  Favors Placebo: -60 to 0, Favors Tasimelteon: 0 to 60
  Difference: -40, p-value: 0.0177

- 90 min Improvement in LQ-nTST and UQ-dTSD
  Favors Placebo: -60 to 0, Favors Tasimelteon: 0 to 60
  Difference: -20, p-value: 0.1312

- Entrainment + 45 min improvement in LQ-nTST
  Favors Placebo: -60 to 0, Favors Tasimelteon: 0 to 60
  Difference: -30, p-value: 0.0013

- Entrainment + 45 min improvement in UQ-dTSD
  Favors Placebo: -60 to 0, Favors Tasimelteon: 0 to 60
  Difference: -10, p-value: 0.0006

- Entrainment + 30 min improvement in MoST
  Favors Placebo: -60 to 0, Favors Tasimelteon: 0 to 60
  Difference: -10, p-value: 0.0046

- Entrainment + improvement in Global Functioning
  Favors Placebo: -60 to 0, Favors Tasimelteon: 0 to 60
  Difference: -10, p-value: 0.0078
SET Study
Clinical Response to Tasimelteon Treatment Among Entrained Population

Entrainment status from month 1 (n=8) and/or month 7 (n=6). One person excluded because they did not have 70% of one cycle in both baseline and screening.

* A decrease in UQ-dTSD is represented here as a positive value.
SET Study
Tasimelteon Treated Patients

Patient 1

Patient 2

Nighttime sleep (screening)
Nighttime sleep (treatment)
Daytime sleep

aMT6s acrophase times
## SET Study
### Evolution of Primary Endpoint

<table>
<thead>
<tr>
<th>Amendment (Date)</th>
<th>Endpoint</th>
<th>Etiology</th>
<th>Clinical</th>
<th>Specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (24May2010)</td>
<td>Average nTST for weeks 3,4,5, and 6</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3 (10Nov2010)</td>
<td>Average nTST for 15 days while out-of-phase (1&lt;sup&gt;st&lt;/sup&gt; circadian cycle)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4 (25Jan2011)</td>
<td>nTST</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>9 (21May2012)</td>
<td>Entrainment of circadian rhythms</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>10 (02Oct2012)</td>
<td>Entrainment of circadian rhythms</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Entrainment + Improvement in key clinical measure(s)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>11 (11Dec2012)</td>
<td>Entrainment of circadian rhythms</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Entrainment + N24CRS ≥ 3</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
SET Study

Efficacy Conclusions

Tasimelteon is a specific and effective treatment for Non-24-Hour disorder in the totally blind:

- Entrains the master clock
  - Melatonin
  - Cortisol

- Provides clinically meaningful effects on the sleep-wake cycle
  - Timing and amount of sleep

- Improves measures of global functioning
RESET Study

- Randomized-withdrawal Study of the Safety and Efficacy of Tasimelteon
  - Randomized withdrawal, double-masked, placebo-controlled, multicenter, parallel-group trial

- 20 totally blind patients between the ages of 27-68 years with Non-24 who entrained during open-label 20mg tasimelteon treatment were randomized to placebo or to continue on 20mg tasimelteon

- 18 Sites: United States

- First Patient First Visit: September 15, 2011

- Database Lock: January 16, 2013
RESET Study
Design

**Tasimelteon Run-in**
- 20 mg Tasimelteon
- Weeks 6-9
- 24/48 Entrained

**Randomized Withdrawal**
- Tasimelteon 20 mg (N=10)
- Weeks 3-6
- Placebo (N=10)

**Weeks**
- 11 Weeks
- 8 Weeks

- \( \tau \) estimation
- Sleep diary collection
- Safety assessments
RESET Study
Objectives: Maintenance of Effect

- Primary
  - Maintenance of entrainment

- Secondary
  - Maintenance of entrainment (cortisol)
  - LQ-nTST
  - UQ-dTSD
  - MoST
  - nTST
  - dTSD
  - Maintenance of effect (entrainment + nTST)
  - Time to relapse (nTST)
# RESET Study

## Demographics

<table>
<thead>
<tr>
<th>Randomized Withdrawal</th>
<th>Placebo N=10</th>
<th>Tasimelteon N=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at screening (years) (SD)</td>
<td>52.1 (12.0)</td>
<td>51.3 (12.9)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male %</td>
<td>60.0</td>
<td>60.0</td>
</tr>
<tr>
<td>Female %</td>
<td>40.0</td>
<td>40.0</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White %</td>
<td>90.0</td>
<td>90.0</td>
</tr>
<tr>
<td>Black, African, or African American %</td>
<td>10.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Other %</td>
<td>0.0</td>
<td>10.0</td>
</tr>
<tr>
<td>BMI kg/m² (SD)</td>
<td>28.04 (3.6)</td>
<td>29.24 (3.3)</td>
</tr>
</tbody>
</table>
## RESET Study
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Average During Run-in Phase</th>
<th>Placebo (N=10)</th>
<th>Tasimelteon (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circadian period (τ): aMT6s</td>
<td>23.99 (0.03)</td>
<td>24.00 (0.04)</td>
</tr>
<tr>
<td>Circadian period (τ): cortisol</td>
<td>23.99 (0.08)</td>
<td>24.01 (0.09)</td>
</tr>
<tr>
<td>nTST (hours)</td>
<td>6.80 (1.03)</td>
<td>6.81 (0.86)</td>
</tr>
<tr>
<td>LQ-nTST (hours)</td>
<td>5.34 (1.36)</td>
<td>5.51 (0.94)</td>
</tr>
<tr>
<td>dTSD (hours)</td>
<td>0.35 (0.28)</td>
<td>0.34 (0.45)</td>
</tr>
<tr>
<td>UQ-dTSD (hours)</td>
<td>0.99 (0.90)</td>
<td>0.96 (1.11)</td>
</tr>
<tr>
<td>MoST (hours)</td>
<td>2.91 (1.01)</td>
<td>3.63 (0.96)</td>
</tr>
</tbody>
</table>
## Primary Endpoints

- Maintenance of entrainment (aMT6s)
  - Categorical: Yes/No (weeks 3-8)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo n/N (%)</th>
<th>Tasimelteon n/N (%)</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance of entrainment&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>2/10 (20.0)</td>
<td>9/10 (90.0)</td>
<td>0.0026</td>
</tr>
</tbody>
</table>

<sup>a</sup>Barnard's Exact Test, two-sided.

<sup>b</sup>Not entrained = post-baseline τ value ≥24.1 or the lower bound of the 95% CI >24.0.

<sup>c</sup>ITT Population.
RESET Study
Primary Endpoint

- Patients that maintained entrainment

- Randomized withdrawal phase \( \tau \)

- Run-in phase \( \tau \)

Tasimelteon

Placebo
# RESET Study

## Cortisol Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo n/N (%)</th>
<th>Tasimelteon n/N (%)</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance of entrainment (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2/10 (20.0)</td>
<td>8/10 (80.0)</td>
<td>0.0118</td>
</tr>
</tbody>
</table>

<sup>a</sup> P-value was based on Barnard's Exact Test, two-sided

<sup>b</sup> Not-entrained is defined as having a post-baseline $\tau$ value $\geq$ 24.1 or the lower bound of the 95% CI $> 24.0$ hours
## RESET Study
### Secondary Endpoints

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Placebo (N=10)</th>
<th>Tasimelteon 20 mg (N=10)</th>
<th>Treatment Difference (Tasimelteon minus Placebo)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQ-nTST (LS mean minutes)</td>
<td>-73.74</td>
<td>-6.74</td>
<td>67.00</td>
<td>0.0233</td>
</tr>
<tr>
<td>UQ-dTSD (LS mean minutes)</td>
<td>49.95</td>
<td>-9.31</td>
<td>-59.25</td>
<td>0.0266</td>
</tr>
<tr>
<td>MoST (LS mean minutes)</td>
<td>-16.05</td>
<td>19.99</td>
<td>36.04</td>
<td>0.0108</td>
</tr>
<tr>
<td>nTST (LS mean minutes)</td>
<td>-44.49</td>
<td>-12.23</td>
<td>32.26</td>
<td>0.1315</td>
</tr>
<tr>
<td>dTSD (LS mean minutes)</td>
<td>17.85</td>
<td>-3.12</td>
<td>-20.97</td>
<td>0.0547</td>
</tr>
<tr>
<td>Non-entrained(^b) and (\geq 30) minute decrement in nTST n (%)(^c)</td>
<td>5/10 (50.0)</td>
<td>1/10 (10.0)</td>
<td>-40.0</td>
<td>0.0623</td>
</tr>
</tbody>
</table>

\(^a\) P-value was based on analysis of covariance model.

\(^b\) Non-entrained is defined as having a post-baseline $\tau$ value of $\geq 24.1$ or the lower bound of the 95% CI $> 24.0$ hours.

\(^c\) P-value was based on Barnard's exact test, two sided.

dTSD = daytime total sleep duration; LQ-nTST = lower quartile of subjective nighttime total sleep time; LS mean = least-squares mean; MoST = midpoint of sleep timing; nTST = nighttime total sleep time; UQ-dTSD = upper quartile of subjective daytime total sleep duration.
RESET Study
Circadian Time to Relapse (nTST) Endpoint

30 min

Survival Probability
0.0 0.2 0.4 0.6 0.8 1.0
0 25 50 75 100 125 150
days

Survival Probability
0.0 0.2 0.4 0.6 0.8 1.0
0 25 50 75 100 125 150 200
days

45 min

Survival Probability
0.0 0.2 0.4 0.6 0.8 1.0
0 25 50 75 100 125 150

Survival Probability
0.0 0.2 0.4 0.6 0.8 1.0
0 25 50 75 100 125 150 200
days

60 min

Survival Probability
0.0 0.2 0.4 0.6 0.8 1.0
0 25 50 75 100 150

Survival Probability
0.0 0.2 0.4 0.6 0.8 1.0
0 25 50 75 100 150 200
days

75 min

Survival Probability
0.0 0.2 0.4 0.6 0.8 1.0
0 25 50 75 100

Survival Probability
0.0 0.2 0.4 0.6 0.8 1.0
0 25 50 75 100 150 200
days

Exploratory analyses.

Tasimelteon  Placebo  Censored

p=0.0457  p=0.0907  p=0.0470  p=0.0181  p=0.0470
RESET Study
Efficacy Conclusions

- Tasimelteon maintains entrainment of the master body clock
  - aMT6s
  - Cortisol

- Tasimelteon maintains clinically meaningful benefit
  - Nighttime sleep
  - Daytime sleep
  - Timing of sleep
Tasimelteon Response and Placebo Withdrawal

Patient 3

Patient 4

Nighttime sleep (screening or placebo)
Nighttime sleep (treatment)
Daytime sleep
aMT6s acrophase times

Time

Day
SET and RESET Data Demonstrate Efficacy of Tasimelteon

---

**SET Study**
- Entrainment
- Entrain^a^+N24CRS ≥3
- Cortisol
- LQ-nTST
- UQ-dTSD
- MoST

**RESET Study**
- Entrainment
- Cortisol
- LQ-nTST
- UQ-dTSD
- MoST
- nTST
- dTSD
- Entrainment + nTST^b^

---

^a^ Entrainment measured at month 1 (SET) and month 7 (RESET).

^b^ Entrainment + nTST = the categorical endpoint of Non-entrained and ≥30 minute decrement in nTST shown.

Note: Improvement (reduction) in UQ-dTSD, dTSD, and Entrainment + nTST combination is shown as a positive value.
Efficacy Conclusions

- Tasimelteon treatment:
  - Entrain the master body clock
  - Improves nighttime sleep
  - Decreases daytime sleep
  - Improves the timing of sleep
  - Improves global functioning

- Continued tasimelteon treatment is needed to maintain benefit
Clinical Program
Clinical Pharmacology

Paolo Baroldi MD, PhD
Vanda Pharmaceuticals Inc.
Tasimelteon

- Metabolic Pathway
- PK Profile
- Receptor Binding
- Extrinsic Factors
Metabolic Pathways of Tasimelteon

Tasimelteon

- CYP1A2 (major)
- CYP3A4 (major)
- CYP1A1 (minor)

M12

- CYP1A2 (major)
- CYP2C9/C19 (minor)
- CYP2D6 (minor)

M13

- CYP1A2 (major)
- CYP2C9/C19 (minor)
- CYP2C19 (minor)

M14

- CYP3A4 (major)

M9

- CYP1A2 (major)
- CYP2C9/C19 (minor)
- CYP2D6 (minor)

M11
## Tasimelteon Clinical PK Highlights

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>$T_{\text{max}}$</strong> Median</td>
<td>0.5 hours</td>
</tr>
<tr>
<td><strong>Terminal $T_{1/2}$</strong> Mean (±SD)</td>
<td>1.3 ± 0.4 hours</td>
</tr>
<tr>
<td><strong>Metabolites</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Terminal $T_{1/2}$</strong> Range of Means (±SD)</td>
<td>1.3 ± 0.5 to 3.7 ± 2.2 hours</td>
</tr>
<tr>
<td><strong>Protein Binding</strong></td>
<td>89 - 90%</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Mostly urine</td>
</tr>
<tr>
<td><strong>Linearity</strong></td>
<td>PK linear over dose range tested (1-300 mg)</td>
</tr>
<tr>
<td>Compound</td>
<td>MT&lt;sub&gt;1&lt;/sub&gt;</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td></td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
</tr>
<tr>
<td>Tasimelteon</td>
<td>0.586</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>M3</td>
<td>3,370</td>
</tr>
<tr>
<td>M9</td>
<td>2,260</td>
</tr>
<tr>
<td>M11</td>
<td>481</td>
</tr>
<tr>
<td>M12</td>
<td>261</td>
</tr>
<tr>
<td>M13</td>
<td>7.69</td>
</tr>
<tr>
<td>M14</td>
<td>198</td>
</tr>
</tbody>
</table>

IC<sub>50</sub> = Concentration producing 50% inhibition; K<sub>i</sub> = dissociation constant for the inhibitor.
# Impact of Extrinsic Factors (EF) on Tasimelteon Pharmacokinetics

<table>
<thead>
<tr>
<th>DDI: Tasimelteon as a Perpetrator</th>
<th>Low potential for interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvoxamine: 6.5-fold increase in tasimelteon’s exposure</td>
<td></td>
</tr>
<tr>
<td>Ketoconazole: 54% increase in tasimelteon’s exposure</td>
<td></td>
</tr>
<tr>
<td>Tobacco smoking: 40% decrease in tasimelteon’s exposure</td>
<td></td>
</tr>
<tr>
<td>Rifampin: 89% decrease in tasimelteon’s exposure</td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td>No additive effects</td>
</tr>
</tbody>
</table>
Clinical Pharmacology Conclusions

- Short half-life of tasimelteon and major metabolites
- Multiple metabolic pathways decrease risk of DDI
- Tasimelteon has significantly higher affinity for MT\(_2\) and MT\(_1\) than its metabolites
Clinical Program: Safety

Joe Sliman, MD, MPH
Vanda Pharmaceuticals
Safety Summary

- Tasimelteon is generally safe and well-tolerated at the target dose of 20 mg once per day
- Tasimelteon is not associated with symptoms of residual, next day effects or somnolence
- Tasimelteon is not associated with increased risk of suicidality or withdrawal
- Tasimelteon is not associated with any endocrine safety signal
## Pooling of Study Groups

<table>
<thead>
<tr>
<th>Group #</th>
<th>Studies Included</th>
<th>Population Studied</th>
<th>Purpose of Group</th>
<th>Tasimelteon N</th>
<th>Placebo N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>All Studies</td>
<td>All subjects in all studies</td>
<td>Overall safety database</td>
<td>1346</td>
<td>306</td>
</tr>
<tr>
<td>2</td>
<td>3201, 3104 &amp; 004</td>
<td>Subjects with insomnia or Non-24</td>
<td>PC repeat dose efficacy studies</td>
<td>429</td>
<td>203</td>
</tr>
<tr>
<td>3</td>
<td>3201 &amp; 3203 (SET &amp; RESET)</td>
<td>Subjects with Non-24</td>
<td>Target indication, PC studies</td>
<td>52</td>
<td>52</td>
</tr>
</tbody>
</table>
## Cumulative Duration of Non-24 Patient Tasimelteon Exposure

<table>
<thead>
<tr>
<th>Exposure Interval</th>
<th>NDA 30 Nov 2012</th>
<th>Safety Update 10 July 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 Day</td>
<td>183</td>
<td>184</td>
</tr>
<tr>
<td>&gt;12 weeks (84 Days)</td>
<td>149</td>
<td>163</td>
</tr>
<tr>
<td>&gt;26 weeks (182 Days)</td>
<td>111</td>
<td>139</td>
</tr>
<tr>
<td>&gt;52 weeks (364 Days)</td>
<td>44</td>
<td>93</td>
</tr>
</tbody>
</table>
## Expanded Safety Analysis
### Summary of Adverse Events

<table>
<thead>
<tr>
<th>Subjects with ≥1</th>
<th>Placebo (N=203) %</th>
<th>Tasimelteon Overall (N=429) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment emergent adverse event</td>
<td>39.4</td>
<td>49.9</td>
</tr>
<tr>
<td>Related treatment emergent adverse event</td>
<td>17.7</td>
<td>23.8</td>
</tr>
<tr>
<td>Severe treatment emergent adverse event</td>
<td>6.4</td>
<td>5.1</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>1.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Treatment emergent serious adverse event</td>
<td>0.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Treatment emergent related serious adverse event</td>
<td>0</td>
<td>0(^a)</td>
</tr>
<tr>
<td>Treatment emergent adverse event resulting in discontinuation</td>
<td>3.0</td>
<td>3.3</td>
</tr>
<tr>
<td>Treatment emergent adverse event with outcome of death</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) An event documented as related by the PI was subsequently assessed to be unrelated to study drug.
## Expanded Safety Analysis

### Most Common Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo (N=203) %</th>
<th>Tasimelteon Overall (N=429) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>7.4</td>
<td>9.6</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6.4</td>
<td>6.5</td>
</tr>
<tr>
<td>Somnolence(^{\text{b}})</td>
<td>1.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Dreams (vivid or unusual)</td>
<td>0.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>1.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Back pain</td>
<td>2.0</td>
<td>2.1</td>
</tr>
</tbody>
</table>

\(^{\text{a}}\) All events with incidence rate > 2.0% of tasimelteon-treated patients

\(^{\text{b}}\) Events of interest identified based upon criteria of:

- incidence rate ≥ 3.0% of tasimelteon-treated patients,
- ≥ 2X rate in placebo patients
Next-Day Effects

- The Visual Analog Scale and Digit Symbol Substitution Tests were assessed in Studies 2101, 3101, and 3104, and the Karolinska Sleepiness Scale was utilized in Study 2101
  - No relevant differences in change from baseline in any test used in any study
  - No relevant differences between treatment groups was found using the Tyrer Benzodiazepine Withdrawal Symptoms Questionnaire in Studies 3104, 3201, or 3203
- Specific adverse event terms were aggregated: somnolence, dizziness, falls, other similar reported terms
  - No clinically relevant difference in rates between tasimelteon- and placebo-treated subjects among Non-24 patients
## SET Study
### Endocrine Safety: Overview

<table>
<thead>
<tr>
<th></th>
<th>PROL</th>
<th>FSH</th>
<th>LH</th>
<th>PROG</th>
<th>FT</th>
<th>TT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males with Endocrine Laboratory Results Outside of the Reference Range</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tasimelteon (n=24)</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>N/A</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Placebo (n=25)</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td>N/A</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td><strong>Females with Endocrine Laboratory Results Outside of the Reference Range</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tasimelteon (n=18)</td>
<td>4</td>
<td>N/A</td>
<td>N/A</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Placebo (n=17)</td>
<td>4</td>
<td>N/A</td>
<td>N/A</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

PROL= prolactin; FSH = follicle-stimulating hormone; LH = luteinizing hormone; FT = free testosterone; TT = total testosterone; PROG = progesterone

- There is no endocrine safety signal identified
- There is no clinically relevant difference in mean changes over time or normal-to-abnormal shifts between tasimelteon-treated patients and placebo-treated patients
Tasimelteon is well-tolerated

No deaths

No serious adverse events related to tasimelteon

Vivid or unusual dreams occur but do not constitute a safety signal

Event types, rates and severity in patients taking daily tasimelteon treatment >1 year are similar to those observed in pivotal studies
Phase Analysis

Mihael H. Polymeropoulos MD
Vanda Pharmaceuticals
Measuring Change in nTST Between In-Phase and Out-of-Phase

Subject A initiates treatment while in-phase, as expected for majority of patients

\[ \Delta nTST = nTST(0-20) - nTST(50-70) = \text{positive} \]

Treatment goal: reduce variability
Confidence Interval of Phase Predictions Over Time

Figure 24 of Vanda Briefing Document
Patient Whose Treatment Initiation Occurred Out-of-Phase

- Patient randomized 180° out-of-phase
- ~16% of SET patients were randomized out-of-phase ($\Delta nTST < -45$ min)

Figure 25 of Vanda Briefing Document
Measuring Absolute Change in nTST Between In-Phase and Out-of-Phase

Subject A is randomized in-phase, while Subject B is randomized 180° out-of-phase:

A: $\Delta nTST = nTST(0-20) - nTST(50-70) = \text{positive}$

B: $\Delta nTST = nTST(0-20) - nTST(50-70) = \text{negative}$

Magnitude of change between two points is relevant for assessing efficacy

$$\text{Abs } | \Delta nTST_A | = \text{Abs } | \Delta nTST_B |$$
## SET Study
### Analysis of Differences Between the In-Phase and Out-of-Phase Parts of the Circadian Cycle

### Absolute Value of the Difference of nTST for In-phase and Out-of-phase

<table>
<thead>
<tr>
<th>Cycle (N)</th>
<th>Placebo (Hour)</th>
<th>Tasimelteon (Hour)</th>
<th>Diff (Hour)</th>
<th>P-Value(^a)</th>
<th>P-Value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1 (N= Placebo: 39; tasimelteon: 39)</td>
<td>1.43</td>
<td>0.53</td>
<td>0.90</td>
<td>0.0005</td>
<td>0.0002</td>
</tr>
<tr>
<td>Cycle 2 (N= Placebo: 33; tasimelteon: 37)</td>
<td>1.00</td>
<td>0.52</td>
<td>0.49</td>
<td>0.0105</td>
<td>0.0087</td>
</tr>
<tr>
<td>Cycle 1+2 (N= Placebo: 39; tasimelteon: 39)</td>
<td>1.17</td>
<td>0.43</td>
<td>0.73</td>
<td>0.0003</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

\(^a\) P-value was based on analysis of variance model.  
\(^b\) P-value was based on the permutation ANOVA t-test.

### Absolute Value of the Difference of dTSD for In-phase and Out-of-phase

<table>
<thead>
<tr>
<th>Cycle (N)</th>
<th>Placebo (Hour)</th>
<th>Tasimelteon (Hour)</th>
<th>Diff (Hour)</th>
<th>P-Value(^a)</th>
<th>P-Value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1 (N= Placebo: 39; tasimelteon: 39)</td>
<td>1.00</td>
<td>0.39</td>
<td>0.61</td>
<td>0.0111</td>
<td>0.0075</td>
</tr>
<tr>
<td>Cycle 2 (N= Placebo: 33; tasimelteon: 37)</td>
<td>0.64</td>
<td>0.29</td>
<td>0.35</td>
<td>0.0181</td>
<td>0.0151</td>
</tr>
<tr>
<td>Cycle 1+2 (N= Placebo: 39; tasimelteon: 39)</td>
<td>0.76</td>
<td>0.30</td>
<td>0.46</td>
<td>0.0132</td>
<td>0.0112</td>
</tr>
</tbody>
</table>

\(^a\) P-value was based on analysis of variance model.  
\(^b\) P-value was based on the permutation ANOVA t-test.

Patient population based on those with Data in the 0-20% and 50-70% Windows
Back-up Slides Used
## Study 3202, ITT Population
Summary of 3202 Open-Label Efficacy Evaluation

<table>
<thead>
<tr>
<th>Category Statistic</th>
<th>CGI-C (N=41)</th>
<th>PGI-C nighttime sleep (N=41)</th>
<th>PGI-C daytime sleep (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>2.26 (0.843)</td>
<td>2.37 (0.820)</td>
<td>2.76 (1.020)</td>
</tr>
<tr>
<td>Response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved¹</td>
<td>36 (87.8)</td>
<td>35 (85.4)</td>
<td>28 (68.3)</td>
</tr>
<tr>
<td>Not improved</td>
<td>5 (12.2)</td>
<td>6 (14.6)</td>
<td>13 (31.7)</td>
</tr>
</tbody>
</table>

1. Very much improved, much improved or minimally improved

CGI-C = Clinical Global Impression of Change;
PGI-C = Patient Global Impression of Change
## SET Study
### Mediation Analysis Treatment vs Entrainment
(Analysis Population)

<table>
<thead>
<tr>
<th>Analysis Endpoints</th>
<th>Treatment Effect (ANCOVA Model Without Entrainment)</th>
<th>Treatment Effect (ANCOVA Model With Entrainment)</th>
<th>Entrainment Effect (ANCOVA Model With Entrainment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQ-nTST</td>
<td>0.0055</td>
<td>0.1215</td>
<td>0.0063</td>
</tr>
<tr>
<td>UQ-dTSD</td>
<td>0.0050</td>
<td>0.4160</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MoST</td>
<td>0.0123</td>
<td>0.5915</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
307.45 Non-24-hour sleep-wake type: A pattern of sleep-wake cycles that is not synchronized to the 24-hour environment, with a consistent daily drift (usually to later and later times) of sleep onset and wake times

Diagnostic Criteria

- A persistent or recurrent pattern of sleep disruption that is primarily due to an alteration of the circadian system or to a misalignment between the endogenous circadian rhythm and the sleep-wake schedule required by an individual’s physical environment or social or professional schedule
- The sleep disruption leads to excessive sleepiness or insomnia, or both
- The sleep disturbance causes clinically significant distress or impairment in social, occupational, and other important areas of functioning
• Tasimelteon will not be available in the Wholesale or Retail channel for ordering or distribution.
• A retailer will not be able to order tasimelteon from a wholesaler.
• A patient will not be able to fill the prescription at a retail pharmacy.
The recommended dose of HETLIOZ is 20 mg per day taken one hour prior to bedtime, preferably at the same time every night. HETLIOZ can be taken with or without food.

Store at 25°C (77°F), excursions permitted to 15°C to 30°C (59°F to 86°F), Protect from light and moisture. Keep out of reach of children.

Hetlioz (talitolalol) capsules 20 mg

Please read the Medication Guide for HETLIOZ. Discard in original container. Do not cover bottle.

Distributed by: Vanda Pharmaceuticals Inc., Washington, DC 20007

NDC 43088-220-01 30 Capsules Rx Only

Hetlioz

#20 mg
## SET Study

### Anophthalmia

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Frequency of Anophthalmia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Two Eyes</td>
</tr>
<tr>
<td>Tasimelteon</td>
<td>19</td>
</tr>
<tr>
<td>Placebo</td>
<td>24</td>
</tr>
<tr>
<td>Randomized Patients</td>
<td>43</td>
</tr>
</tbody>
</table>
## SET Study
### Analysis of Change from Baseline Sleep Quality (SQ) Data

- SQ: 1=Excellent; 2=Good; 3=Fair; 4=Poor.

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Populations</th>
<th>Tasimelteon</th>
<th>Placebo</th>
<th>Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SQ</td>
<td>Analysis (72)</td>
<td>-0.293</td>
<td>-0.106</td>
<td>-0.186</td>
<td>0.0086</td>
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<tr>
<td></td>
<td>ITT* (84)</td>
<td>-0.303</td>
<td>-0.099</td>
<td>-0.204</td>
<td>0.0022</td>
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<tr>
<td>SQ of Worst 25% Sleep Days</td>
<td>Analysis (72)</td>
<td>-0.346</td>
<td>-0.017</td>
<td>-0.329</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td>ITT* (84)</td>
<td>-0.346</td>
<td>-0.050</td>
<td>-0.296</td>
<td>0.0005</td>
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</tbody>
</table>

EF-281
# Pearson Correlation Coefficients of Clinical Parameters in the Analysis Population

<table>
<thead>
<tr>
<th></th>
<th>LQ-nTST</th>
<th>UQ-dTSD</th>
<th>MoST</th>
<th>nTST</th>
<th>dTSD</th>
<th>CGI-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQ-nTST</td>
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<td></td>
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<tr>
<td>UQ-dTSD</td>
<td>-0.44142</td>
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<tr>
<td></td>
<td>0.0001</td>
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<td></td>
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</tr>
<tr>
<td>MoST</td>
<td>0.55138</td>
<td>-0.73297</td>
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<tr>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>nTST</td>
<td>0.8595</td>
<td>-0.33274</td>
<td>0.45839</td>
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<tr>
<td></td>
<td>&lt;0.0001</td>
<td>0.0043</td>
<td>&lt;0.0001</td>
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<tr>
<td>dTSD</td>
<td>-0.45818</td>
<td>0.85968</td>
<td>-0.7547</td>
<td>-0.3776</td>
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<tr>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0011</td>
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<tr>
<td>CGI-C</td>
<td>-0.45608</td>
<td>0.1626</td>
<td>-0.1971</td>
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<tr>
<td></td>
<td>&lt;0.0001</td>
<td>0.1819</td>
<td>0.1045</td>
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<td>0.8368</td>
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</tr>
</tbody>
</table>

EF-35
Response on N24CRS Components by Patient

- Tasimelteon
- Placebo

Responder
Non-Responder
## SET Study Analysis of N24CRS (Excluding MoST)

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Placebo (%)</th>
<th>Tasimelteon (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entrainment and N24CRS = 3</td>
<td>0/34 (0.0)</td>
<td>6/38 (15.8)</td>
<td>0.0158</td>
</tr>
<tr>
<td>Entrainment and N24CRS ≥ 2</td>
<td>0/34 (0.0)</td>
<td>9/38 (23.7)</td>
<td>0.0028</td>
</tr>
<tr>
<td>Entrainment and N24CRS ≥ 1</td>
<td>0/34 (0.0)</td>
<td>13/38 (34.2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>N24CRS = 3</td>
<td>0/34 (0.0)</td>
<td>8/38 (21.1)</td>
<td>0.0046</td>
</tr>
<tr>
<td>N24CRS ≥ 2</td>
<td>6/34 (17.6)</td>
<td>19/38 (50.0)</td>
<td>0.0037</td>
</tr>
<tr>
<td>N24CRS ≥ 1</td>
<td>13/34 (38.2)</td>
<td>28/38 (73.7)</td>
<td>0.0030</td>
</tr>
</tbody>
</table>

### Continuous Data

<table>
<thead>
<tr>
<th>Continuous</th>
<th>Placebo</th>
<th>Tasimelteon</th>
<th>Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N24CRS</td>
<td>0.59</td>
<td>1.45</td>
<td>0.87</td>
<td>0.0007</td>
</tr>
</tbody>
</table>
## SET Study
### Analysis of N24CRS (excluding MoST) in ITT* Population

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Placebo (%)</th>
<th>Tasimelteon (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N24CRS= 3</td>
<td>0/42 (0.0)</td>
<td>8/42 (19.0)</td>
<td>0.0031</td>
</tr>
<tr>
<td>N24CRS≥ 2</td>
<td>8/42 (19.0)</td>
<td>19/42 (45.2)</td>
<td>0.0116</td>
</tr>
<tr>
<td>N24CRS≥ 1</td>
<td>18/42 (42.9)</td>
<td>32/42 (76.2)</td>
<td>0.0019</td>
</tr>
</tbody>
</table>

### Continuous
<table>
<thead>
<tr>
<th>Continuous</th>
<th>Placebo</th>
<th>Tasimelteon</th>
<th>Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N24CRS</td>
<td>0.56</td>
<td>1.46</td>
<td>.89</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
CA-141

Population

Number of Cycles

ITT* (N=84) ITT (N=78) Analysis (N=72)

0.0 0.5 1.0 1.5 2.0 2.5

SET Study
Statistical Analysis Populations

EF-274
SET Study
Forest Plot of ITT/ITT* Populations

ITT
Pre-specified model
(n=78)

LQ-nTST

UQ-dTSD

MoST

nTST

dTSD

-80 -60 -40 -20 0 20 40 60 80

Favors PBO ↔ Favors Tasi

ITT*
Pre-specified model
(n=84)

Favors PBO ↔ Favors Tasi

ITT*
Pooled Site Removed
(n=84)

Favors PBO ↔ Favors Tasi

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