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RESEARCH**

APPLICATION NUMBER:

205677Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review - Addendum

Date	October 1, 2014
From	Ronald Farkas, MD, PhD
Subject	Indication statement
NDA/BLA # Supplement#	NDA 205677
Applicant	Vanda
Proprietary Name / Established (USAN) names	Hetlioz (tasimelteon)
Dosage forms / Strength	20 mg
Proposed Indication(s)	Non-24 hour sleep wake disorder in blind patients

Tasimelteon was approved on January 31, 2014, for the treatment of “Non-24-hour sleep-wake disorder (Non-24)” a circadian rhythm sleep disorder that occurs primarily, but not exclusively, in patients with severe visual impairment. The efficacy studies were conducted in patients that were totally blind, a population that is at highest risk for the condition. The indication proposed by the sponsor in the NDA included the following wording “Non-24 hour disorder (Non-24) *in the totally blind*” [emphasis added]. There are estimated to be about 100,000 visually impaired patients in the U.S. with Non-24. Non-24 in normally-sighted patients is considered very rare, and is largely known through individual case reports and case series. This addendum describes the basis for indicating tasimelteon for Non-24 without a qualification based on visual impairment.

Non-24 is defined is defined by a sleep-wake pattern that is progressively delayed with the patient unable to maintain stable entrainment to a 24-hour sleep-wake pattern (International Classification of Sleep Disorders definition). This sleep-wake pattern should be documented by polysomnography or continuous 24-hour temperature monitoring that shows a progressive delay of the circadian body temperature nadir. Visual impairment is not a component of the diagnosis. Inability to entrain to a 24-hour sleep-wake pattern occurs due to dysfunction of the hypothalamic circadian pacemaker itself or due to interruption of the entrainment signal provided by environmental light as detected by specialized retinal ganglion cells. Thus, patients can be diagnosed with Non-24 if the entrainment signal is interrupted by factors ranging from bilateral enucleation to social or environmental deprivation of sunlight.

While tasimelteon was studied only in patients that were totally blind to support the indication in Non-24, the sponsor conducted studies of tasimelteon in other circadian rhythm sleep disorders in sighted patients, including jet-lag disorder, which is related to Non-24 in terms of circadian neurological mechanisms and symptoms affecting sleep and wakefulness. Based in part on evidence of similar clinical and biomarker effects of tasimelteon in sighted individuals in other models of circadian rhythm disruption, DNP concluded that the drug would be effective in the closely related group of Non-24 patients with severe visual impairment who are not *totally* blind. In such patients there is degradation, but not complete absence, of the environmental light signal from the eyes. The amount of damage to the eyes or visual pathways that can result in Non-24 is not well understood. Anatomically different pathways

sense and transmit light for conscious vision and for circadian rhythms, such that typical vision testing may not be a reliable indicator of function of the circadian system.

There are a few case reports of patients with severe brain damage in whom Non-24 seemingly resulted from interruption of circadian pathways while conscious visual pathways remained relatively intact. Treatment with melatonin was reported to be effective in at least some of these patients. An indication that excluded these patients based on vision would thus be problematic even considering that the group is heterogeneous, poorly characterized, and likely includes patients with damage to the circadian system that would not be treatable with melatonin agonists.

While still rare, Non-24 occurs through a well-understood mechanism in patients with psychiatric illness who do not expose themselves to sunlight. While sunlight can be curative in such patients, the mechanism of the condition – interruption of the circadian light signal - closely mimics the mechanism in patients with physical damage. A large body of basic scientific investigation supports that melatonin agonists like tasimelteon can entrain circadian rhythms in sighted patients deprived of circadian light. There are also case reports of such sighted patients with Non-24 who were successfully treated with melatonin. Drug therapy has been reported to be effective in such patients when modification of behavior and environment has failed.

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/s/

RONALD H FARKAS
10/01/2014

Cross-Discipline Team Leader Review

Date	October 31, 2013
From	Ronald Farkas, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 205677
Applicant	Vanda
Date of Submission	May 31, 2013
PDUFA Goal Date	January 30, 2014
Proprietary Name / Established (USAN) names	Hetlioz (tasimelteon)
Dosage forms / Strength	20 mg
Proposed Indication(s)	Non-24 hour sleep wake disorder in blind patients
Recommended:	Approval

1. Introduction

Tasimelteon is a melatonin MT1 and MT2 agonist developed for the treatment of Non-24 hour sleep-wake disorder (Non-24) in totally blind patients. No drugs are currently approved for Non-24. Tasimelteon is a new molecular entity that has not been marketed in any country.

Non-24 is classified as a circadian rhythm sleep disorder (CRSD). CRSDs involve a mismatch in the timing of the sleep-wake cycle, such that sleep and wakefulness either are not aligned with the 24-hour day, or, in some types of CRSD, not organized into consolidated periods of sleep and wakefulness.

Sleep is a complex biological process that arises from multiple brain regions and neurotransmitters, and that is regulated by numerous physiological and environmental factors. Endogenous, genetically programmed oscillations of gene activity occur throughout many different types of tissues in the body at a frequency that is close to that of the 24 hour day. However, the suprachiasmatic nucleus (SCN) of the hypothalamus serves as the body's lead biological clock. The SCN receives input about environmental light levels from specialized intrinsically light-sensitive retinal ganglion cells that, through small adjusting influences, keep the SCN oscillations aligned with the actual 24 hour day. The SCN then controls other clocks in the brain and throughout the body, both through direct neurotransmission (including neurotransmission to sleep/wakefulness controlling regions like the locus coeruleus and dorsal medial hypothalamus) and control of release of a number of hormones, including melatonin (which is released from the pineal after indirect adrenergic stimulation from the SCN). Sleep/wakefulness centers in the brain other than the SCN also receive direct input from the intrinsically light-sensitive retinal ganglion cells, allowing light to increase wakefulness by an apparently circadian rhythm-independent mechanism.

Melatonin promotes sleep both through feedback effects on the SCN, and direct effects on other parts of the brain and peripheral organs. Melatonin levels peak in roughly the middle of each night, with the peak called 'acrophase'. Stimulation of melatonin receptors in the SCN is thought to favor sleep initiation through a 'hypothalamic sleep switch' that activates either wake-related or sleep-related downstream neuronal pathways.¹ Melatonin also is a feedback-regulator of the circadian clock in the SCN, presumably helping to adjust the timing of the SCN clock and the amplitude of SCN oscillations in concert with input from the light-sensitive retinal ganglion cells.

In completely blind individuals, environmental light input to the SCN from the retina is often absent, and the SCN clock runs at its intrinsic, genetically determined rate, which in most individuals is a little longer than 24 hours, ranging from a few minutes to about an hour longer. This creates a cyclical misalignment of the individual's circadian rhythm with the 24-hour day. The interval between two successive synchronization of the patient's endogenous circadian rhythm and the 24-hour day is referred to as the circadian cycle. The length of the patient's individual circadian rhythm is referred to as " τ " (tau). Thus, a patient with Non-24 who has an endogenous circadian rhythm of 25 hours would, if not for outside social cues, tend to have a sleep/wake cycle that took 25 hours, such that each day their biological bedtime would be one hour later, and similarly their wake time would be one hour later. Attempts by the patient to keep a 24-hour schedule would result in cyclically worsening then improving symptoms of sleep disruption as their internal cycle went from in-phase with the actual day, to out-of-phase, to in-phase again.

FDA reviews

The primary clinical review was conducted by Dr. Devanand Jilapalli, and the primary statistical review was conducted by Dr. Jingyu (Julia) Luan. The primary Clinical Pharmacology review was conducted by Dr. Jagan Parepally, and the primary Nonclinical review was conducted by Dr. Melissa Banks-Muckenfuss.

Dr. Melinda McLawhorn conducted the Office of Prescription Drug Promotion (OPDP) review of labeling. Dr. Julie Neshiewat from the Office of Medication Error Prevention and Risk Management (DMEPA) reviewed the labels for areas of vulnerability that could lead to medication errors. Dr. Katherine Bonson from the Controlled Substance Staff reviewed the abuse potential of tasimelteon.

Primary Chemistry review was conducted by Dr. Rao Kambhampati, while Dr. Ramesh Sood wrote a Summary Basis for Recommended Action from Chemistry, Manufacturing, and Controls (CMC). Dr. Antoine El-Hage from the Division of Good Clinical Practice Compliance, OSI, conducted clinical inspections.

2. Regulatory History

To support approval of tasimelteon for Non-24, as opposed to a less-specific indication for treatment of insomnia, the division expected the sponsor to show that tasimelteon had an effect on the circadian disruption of sleep/wakefulness in Non-24, and not just that it

¹ Reviewed in Hardeland et al (2011) Melatonin – a pleiotropic, orchestrating regulator molecule. Progress in Neurobiology 93:350-384.

increased sleep time in a way that was indistinguishable from a non-specific soporific effect that might be expected from any drug effective for the more general indication of insomnia. The division also expected the sponsor to show that tasimelteon improved sleep in a way that was clinically meaningful to the patient, not only that it changed a biochemical marker of circadian rhythm like melatonin. The sponsor argued that it would not be possible to power a study based on clinical endpoints due to the inability to adequately power studies due to the rarity of Non-24, and that the division should accept improvement in the melatonin rhythm (“entrainment”), as determined by mathematical analysis of levels of the urinary metabolite of melatonin (6-hydroxymelatonin sulfate [aMT6s]) as sufficient evidence of both clinical benefit (or the likelihood of clinical benefit) and of a specific effect on the circadian mechanism of the disease. The division noted that feasibility of showing clinical benefit for tasimelteon was seemingly supported by multiple published reports that melatonin treatment resulted in both circadian entrainment and large, statistically significant clinical benefit for sleep in Non-24 patients. The sponsor, understanding that agreement had not been reached on primary endpoints, decided to conduct two clinical studies with entrainment, as determined by the melatonin biomarker, as the primary endpoint, while including clinically meaningful endpoints of nighttime and daytime sleep as secondary endpoints. The division explained to the sponsor that evaluation of an NDA filing would be based on clinically meaningful endpoints.

2. CMC

The overall conclusion of CMC was that the application was recommended for “approval” from a CMC perspective, provided all the manufacturing and testing facilities are acceptable to the Office of Compliance.

CDTL: Final recommendation from the Office of Compliance was pending at the time of this review.

3. Nonclinical Pharmacology/Toxicology

Dr. Banks-Muchenfuss notes that the sponsor conducted a full battery of nonclinical studies in support of clinical development (under IND 54776) and marketing approval. The nonclinical team’s overall conclusion was that these studies were adequate to support approval of the NDA, with appropriate labeling.

Hetlioz acts as a melatonin receptor agonist with full agonist activity at the MT1 and MT2 receptors. Dr. Banks-Muckenfuss notes that tasimelteon’s activity at MT1 and MT2 receptors is believed to contribute to its sleep-promoting properties, as these receptors, acted upon by endogenous melatonin, are thought to be involved in the maintenance of the circadian rhythm underlying a number of physiological processes including the sleep-wake cycle.

The primary target organs of tasimelteon toxicity include the CNS, liver, kidney, and reproductive organs. Effect doses were approximately 20 times the recommended human dose (RHD). Reproductive studies showed altered cyclicity in female rats (and possibly in

female monkeys), and persistent effects on growth of offspring exposed during gestation and lactation.

In rat, the following neoplasms were identified as drug-related: uterus (endometrial adenocarcinoma at the HD), uterus and cervix (squamous cell carcinoma at the HD), and liver (adenoma in MDF and HDF; adenoma and carcinoma combined in MDM and HDM). The positive findings in uterus were statistically significant.

CDTL: I agree that safety issues identified in nonclinical studies can be adequately addressed in labeling.

4. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology's overall conclusion was that the NDA was acceptable from a clinical pharmacology perspective provided that agreement is reached between the Sponsor and the Agency on labeling.

Dr. Parepally notes that C_{max} ranges from about 0.5- to 3 hours, and mean elimination half-life ranges from 1.3- to 2.6 hours. Fed conditions decreased C_{max} by nearly half, and delayed T_{max} from 0.75 to 2.5 hours.

CYP1A2 and CYP3A4 are the major isozymes involved in the metabolism of tasimelteon. Inhibition of CYP1A2 resulted in 6.5-fold increase in tasimelteon AUC, such that coadministration should be avoided. Induction of CYP3A4 decreased exposure by about 90%, and co-administration of drugs that induce CYP3A4 should be avoided. Induction of CYP1A2 increased decreased tasimelteon AUC by about 40%. Metabolite M13 had a parent to metabolite ratio of about 1, but was about 13-times lower in potency at MT1 and MT2 receptors.

The AUC of tasimelteon increased 43% and 110% in patients with mild and moderate hepatic impairment, respectively.

The 20 mg dose was the only dose studied in Non-24 patients, such that no dose-response relationship could be established.

CDTL: I agree that the issues identified by Clinical Pharmacology can be adequately addressed in labeling.

5. Clinical/Statistical – Efficacy

The sponsor conducted two placebo-controlled trials of tasimelteon in Non-24, study 3201, a parallel arm study, and study 3203, a randomized-withdrawal study that enrolled patients who had been entrained by tasimelteon both from study 3201 and from a parallel open-label study conducted with patients who had a wider range of circadian periodicities (for study

3203, enrollment was open to any patient with a tau > 24.1, while 3201 was limited to patients with a tau between 24.25 and 24.75, a population that the sponsor considered likely to be more easily entrained by tasimelteon).

CDTL note: A wider range of tau values in 3203 increases ability to generalize findings to patients with a tau values outside the enrolment criteria for study 3201.

Study 3201

Study 3201 was a parallel-group placebo-controlled study in 84 totally blind subjects with Non-24 randomized 1:1 to 20 mg tasimelteon or placebo. Each patient's circadian cycle length was estimated through measure of the urinary melatonin metabolite during a ≈5-to 6 week pre-randomization phase, and the sponsor attempted to begin drug/placebo treatment when patient's circadian rhythms were coming into alignment with the 24-hour day, while acknowledging that the estimate of circadian phase was not very precise.

CDTL note: In contrast to how the clinical studies were conducted, the sponsor does not propose requiring that treatment be initiated based on a test of melatonin. Instead, patients would estimate the period in their circadian cycle based on symptoms. This seems acceptable, as patient symptoms appear to be a reasonably accurate reflection of circadian phase, and even if tasimelteon treatment is initiated at a less than ideal part of the cycle, continued use for a full cycle would result in drug presence when the patient's circadian rhythms were coming into alignment with the 24-hour day.

The following were the clinical endpoints:

- *Nighttime total sleep time (nTST)*
This endpoint was expected by the division to be less sensitive to benefit from tasimelteon because it includes both days when patients are out-of-alignment with the 24 hour day, and are expected to suffer the most severe disordered sleep, and days when patients are in-alignment, and expected to suffer much less severe of no symptoms.
- *Lower Quartile of nTST (LQ-nTST)*
This endpoint compared the worst quarter of nights (nights with lowest TST) of placebo and drug-treated arms. During development, the division suggested to the sponsor that when Non-24 patients were about 12-hours out of alignment, nighttime sleep should be most disturbed, and should coincide with the 'worst quarter of nights' in the patient's full circadian cycle. If tasimelteon was effective in aligning patient's circadian rhythms, the beneficial effect should be very large (much more than 20 or 30 minutes, the expected size of benefit from a soporific effect of a melatonergic) during this period of maximum misalignment.

Note, however, that this endpoint did not select the specific 25% of days predicted to be the most out-of-alignment and compare these, within-patient, to the days in which the patient's circadian cycle was in-phase with the 24 hour day; this type of comparison was proposed by the division, but the sponsor indicated that the lack of precision in estimation of the circadian cycle would

introduce too much random noise for such a within-patient endpoint to be reliably positive. As discussed below (under *Additional Efficacy Analyses*), the division did ask the sponsor to conduct such an analysis post-hoc, which was positive.

- *Daytime total sleep duration (dTSD)*

There was considerable uncertainty when planning the study about the pattern and duration of daytime napping in Non-24 patients, and concern that patient's efforts to fit their activities into the normal 24-hour day would mask beneficial effects of tasimelteon on daytime naps. However, a large beneficial effect on daytime naps, if shown, would suggest that the effect of tasimelteon was more than what might be expected if the effect was only a non-specific soporific effect, not an effect on circadian rhythms.

- *Upper quartile of dTSD (UQ-dTSD)*

Similar to the explanation above for LQ-nTST was designed to focus on the period in the circadian cycle in which benefit from tasimelteon was likely to be largest.

- *Clinical Global Impression of Change (CGI-C)*

This was an investigator-rated endpoint of the patient's sleep/wake symptoms and impact on relationships, and ability to do daily tasks including employment. The scale ranged from 1, very much improved, to 7, very much worse.

A CGI endpoint can provide important evidence that the size and nature of a more objectively measured endpoint (like sleep time) is of clinically meaningful benefit to the patient.

- *Midpoint of Sleep Timing (MoST)*

The MoST endpoint was designed by the sponsor to measure the degree to which sleep was consolidated at night. When aligned with the 24-hour day, a patient with Non-24 might have sleep that is well-consolidated at night, but when out of alignment, sleep would be disrupted at night, more sleep would take place during the day. The MoST was calculated in such a way that, for example, a nap at noon represented more fragmented sleep than a nap at closer to night, say at 9 AM or 6 PM. However, it was not clear to the division that there was necessarily any clinically meaningful difference in when a patient felt it necessary to take a nap during the day – a nap at any time of day when conflicting with scheduled activities could seemingly be indistinguishably disruptive. Also, the MoST seems susceptible to 'improvement' from a long-lasting soporific effect that would keep patients sleeping through their usual wake-time; this would consolidate sleep, but would not necessarily be beneficial.

- *Non-24 Clinical Response Scale*

This endpoint combined a responder analysis of 4 of the above endpoints: LQ-nTST \geq 45 minutes increase, UQ-dTSD \geq 45 minutes decrease, MoST \geq 30 minutes increase and a standard deviation \leq 2 hours during the double-masked phase, and \leq 2.0 score on CGI-C from the average of Day 112 and Day 183 compared to baseline. However, as discussed above, the MoST was not of clear clinical meaning, decreasing the value of this composite endpoint for demonstrating clinically meaningful efficacy.

CDTL: Discussions between the sponsor and division about efficacy endpoints appropriate to show the specific effect of tasimelteon in Non-24 were hindered by a paucity of natural history data on the sleep/wake cycle in this disease. A sleep record for a patient with a free-running sleep/wake pattern should, absent outside social constraints, have a very distinctive pattern (Figure 1, see legend for additional explanation). However, the sponsor was concerned that this pattern would not be observed because patients would be trying to adjust their sleep/wake patterns to the 24-hour day.

Figure 1: Example of Non-24 Patient With Free-Running Sleep/Wake Pattern

IVRS Summary Report for 606-1002 : No Acrophase

(3201 Screening Tau=24.29; cycle=84)

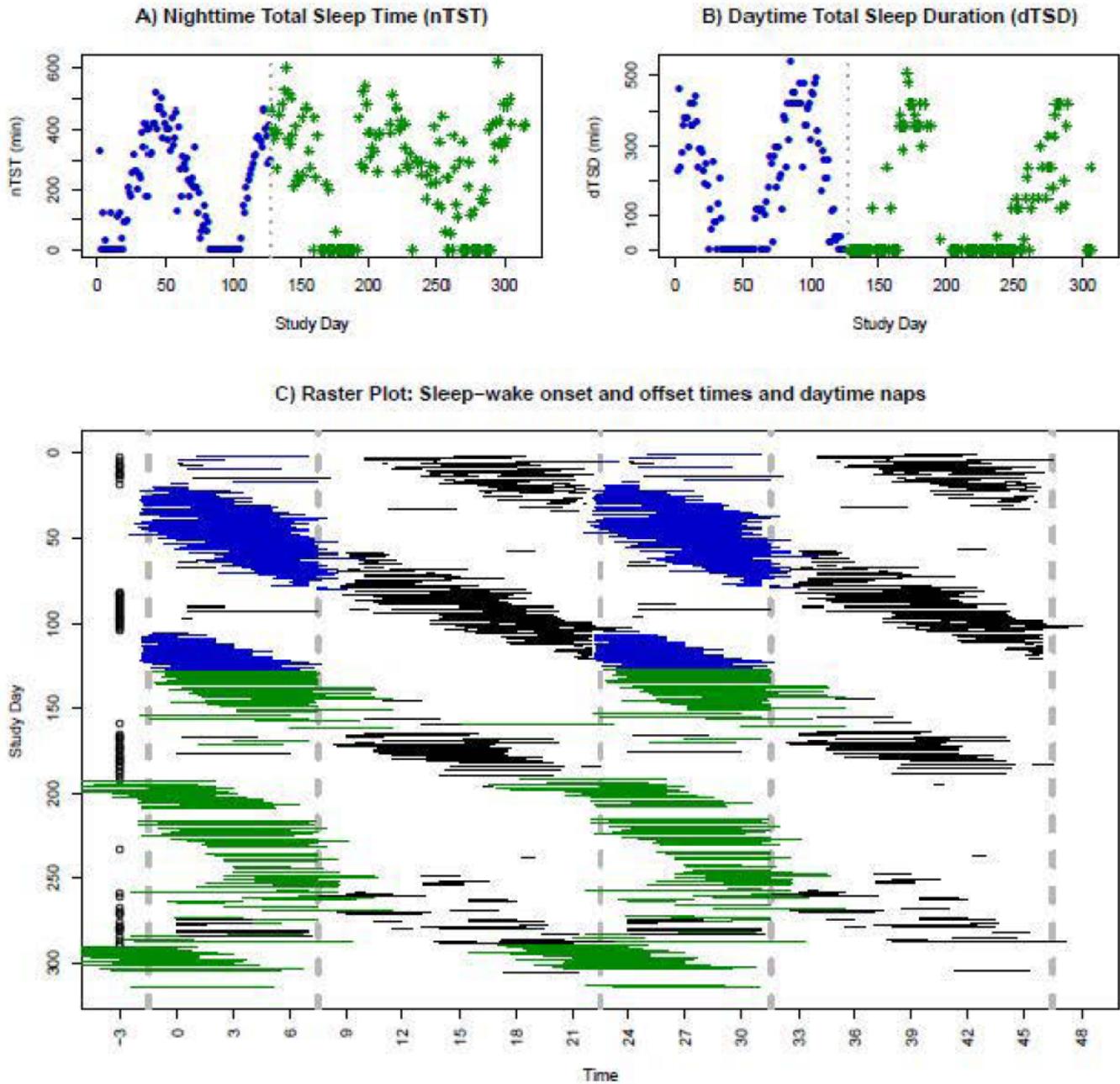


Figure 1, A and B: nTST and dTSD show a cyclical pattern of “less nighttime sleep / more daytime sleep” vs. “more nighttime sleep / less daytime sleep” as the patient’s endogenous circadian rhythm is first misaligned with the 24-hour day (day 0), then aligned (about day 50), then misaligned (about day 100). C: Raster plot shows nighttime sleep in the run-in period in blue, and nighttime sleep in the treatment period

in green. Daytime naps are shown in black for both periods. This patient was randomized to placebo in study 3201. On each successive day, the patient went to sleep about 20 minutes later, and woke about 20 minutes later, than the day before. Each complete cycle was about 3 months.

Efficacy Results, Study 3201

Dr. Luan describes the sponsor's primary efficacy analysis that was based on melatonin biomarker 'entrainment'. The primary efficacy endpoint was defined as the proportion of the number of Non-24 patients who were entrained after placebo or tasimelteon treatment during the Randomization Phase. If the primary null hypothesis was rejected then 'Non-24 Clinical Response Scale' was to be tested in a step-down approach.

Entrainment was defined as having a post-baseline τ value less than 24.1 and a 95% CI that included 24.0. The sponsor concluded that the proportion of Non-24 patients who were entrained after tasimelteon treatment during the randomization phase was statistically significantly greater than the proportion of Non-24 patients who were entrained after placebo treatment (% difference = 17.4; $p = 0.0171$). The Clinical Response Rate was defined as the coincident demonstration of entrainment of the aMT6s rhythm and a score of ≥ 3 on the N24CRS. The proportion of patients who were entrained (aMT6s) and had a clinical response rate (N24CRS) ≥ 3 after tasimelteon treatment during the Randomization Phase was statistically significantly greater than the proportion of patients who were entrained and had a clinical response rate ≥ 3 after placebo treatment (% difference = 23.7; $p = 0.0028$).

Dr. Luan's efficacy analysis was based on the following clinical endpoints: LQnTST, UQ-dTSD, MoST, CGIC, nTST and dTSD. She notes that the p-values for these endpoints should be considered nominal because of the lack of agreement about the study primary endpoint. She found that the nominal p-values were nominally statistically significant or marginally significant for LQ-nTST, UQ-dTSD, MoST, CGIC and dTSD, but not for nTST.

Study 3203

Study 3203 was a randomized withdrawal placebo-controlled study designed to evaluate the long-term maintenance effect and safety of 20 mg of tasimelteon versus placebo in patients with Non-24. Patients who met the entrance criteria and who had previously participated in, or were screened for, Study 3201 were eligible to participate. Twenty patients were randomized 1:1 to receive tasimelteon (20 mg/day) or placebo during the randomized withdrawal phase.

Efficacy Results, Study 3203

Dr. Luan describes the sponsor's primary efficacy analysis that was based on melatonin biomarker 'entrainment'. The primary efficacy endpoint was the proportion of non-entrainment of the circadian melatonin rhythm after randomized withdrawal as measured by urinary aMT6s. The proportion of Non-24 patients who became nonentrained to a 24-hour day after randomization to tasimelteon was statistically significantly less than the proportion of Non-24 patients who became non-entrained after randomization to placebo treatment (% difference = -70.0; $p = 0.0026$).

Dr. Luan's efficacy analysis was based on the same endpoints as used in study 3201, with similar findings: the nominal p-values were statistically significant or marginally significant for LQ-nTST, UQ-dTSD, MoST, CGIC and dTSD, but not for nTST.

Additional Efficacy Analyses

Dr. Jillapalli generally agreed with the efficacy findings of Dr. Luan. Dr. Jillapalli additionally reviewed the graphic representation of the sleep diary data for each individual subject in Studies 3201 and 3203. He notes that the visual assessment of benefit on the cyclical nature of the nighttime and daytime sleep using the graphical representation in an individual subject is very subjective. However, despite the subjective nature of such an assessment, he concluded that the proportion of subjects (14/42; 33.3%) who appear to have had a positive effect on stabilizing the cyclical nighttime and daytime symptoms in the tasimelteon subjects was numerically higher than that in placebo subjects (4/42; 9.5%). In most of the subjects who appeared to have had a benefit on the cyclicity of symptoms, the benefit seemed to begin within about the first 30 - 50 days of treatment with tasimelteon.

Dr. Jillapalli additionally asked the sponsor to conduct an analysis for study 3201 based on within-patient difference in nTST between maximum alignment (in-phase period of cycle) as predicted by the urinary melatonin biomarker, and maximum misalignment (out-of-phase period in cycle), for drug vs. placebo. The difference between these two means is a reflection of the most symptomatic phase. The tasimelteon arm had statistically significantly lower mean absolute value than the placebo group, indicating a significant benefit in stabilizing the cyclical pattern of nighttime and daytime symptoms in Non-24.

CDTL: Both Drs. Luan and Jillapalli found evidence supportive of the clinical efficacy of tasimelteon in both studies 3201 and 3203, on both nighttime sleep and daytime napping, and physician global impression of change. MoST was also positive, but of less clear clinical meaning. Benefit on sleep and napping was most evident for the 'worst quarter' of days, consistent with the cyclical nature of Non-24. Similarly, additional analyses conducted by Dr. Jillapalli suggest a positive effect on the cyclical nature of Non-24. Dr. Jillapalli notes that by inspection about a third of tasimelteon patients experienced a positive effect on stabilizing the cyclical symptoms of Non-24, vs. about 10% in placebo patients. This is reflected in study 3201 numerically by a secondary endpoint in study 3201 of the proportion of patients that improved by both 45 minutes on LQ-nTST and UQ-dTSD: 32% for tasimelteon and 9% for placebo (p = 0.06).

6. Safety

Dr. Jillapalli notes that 1,346 subjects received at least one dose of tasimelteon during the course of 22 clinical studies, and 621 subjects received at least one dose of tasimelteon 20 mg. all chronic exposures > 12 weeks occurred only in subjects with the Non-24 Hour Disorder (n=149). Overall, 183 subjects with Non-24 Hour Disorder received tasimelteon 20 mg dose with a mean duration of exposure of 252 days (median = 243 days). As of the cut-

off date of 11/30/12, 111 out these 183 subjects were treated for at least 6 months, and 44 treated for at least one year.

Dr. Jillapalli did not find an association of tasimelteon with serious adverse effects. Increased alanine aminotransferase was identified as common treatment-emergent adverse event, but Dr. Jillapalli did not find evidence of potential for tasimelteon to cause more serious drug-induced liver injury, such as marked elevations of transaminases (e.g. there was essentially no evidence of increases of 5x ULN that could be attributed to tasimelteon) or increased bilirubin.

Dr Jillapalli concluded that somnolence was not a safety signal in non-elderly adult subjects with Non-24 Hour Disorder or insomnia, but that elderly female subjects with insomnia taking tasimelteon had a higher incidence of somnolence compared to placebo control. Dr. Jillapalli identified an excess of dizziness events in the tasimelteon group compared to placebo group due to events in healthy volunteers participating in pharmacokinetic studies in the context of day-time dosing in many of these early studies. However, there was no safety signal with regard to dizziness, syncope and falls in subjects with Non-24 Hour Disorder or insomnia when tasimelteon was dosed around bedtime.

CDTL: Dr. Jillapalli concludes, and I agree, that the size of the safety database was adequate for this orphan condition, and that serious adverse effects of tasimelteon were not identified.

7. Advisory Committee Meeting

As noted in Dr. Jillapalli's review, The Peripheral and Central Nervous System Drugs Advisory Committee met on November 14, 2013 to consider the efficacy and safety of tasimelteon. The majority of the Committee voted in the affirmative to the following questions:

- Is Non-24 appropriate as an indication for an FDA-approved drug therapy?
- Are the clinical endpoints used in the tasimelteon development program appropriate to support an indication in Non-24?
- Has substantial evidence of efficacy has been presented for tasimelteon in Non-24?
- Has the safety of tasimelteon in Non-24 been adequately addressed?

8. Other Relevant Regulatory Issues

- CSS concluded that tasimelteon should not be recommended for scheduling under the Controlled Substance Act because there were no signs that the drug produces abuse potential or physical dependence in animal or human studies submitted in the NDA.

- DMEPA asked the sponsor to perform a Braille Label Comprehension study of Braille labeling on the Hetlioz bottle. DMEPA found the study acceptable, and found the sponsor's proposals to improve clarity of the Braille text reasonable.
- OPDP labeling recommendations were incorporated into the Hetlioz label.
- Four clinical investigator sites were inspected by OSI and, overall, the data submitted from these sites was considered acceptable to support the pending application.
- No significant QTc prolongation effects for tasimelteon were found after review of the TQT study by the Interdisciplinary Review Team for QT Studies.

9. Recommendations, Risk-Benefit Assessment

Recommended Regulatory Action

As discussed in more detail below under '*Risk-Benefit Framework*,' I conclude that the risk-benefit profile of tasimelteon in Non-24 is acceptable, and recommend approval. Since tasimelteon improves symptoms readily perceived by patients, the risk-benefit profile is positively shifted by the ability of patients experiencing insufficient efficacy or unacceptable adverse effects to discontinue treatment. Tasimelteon was not found to cause serious or irreversible adverse effects, such that a therapeutic trial does not pose an unacceptable risk to patients that might not respond. A reasonable proportion of patients can be expected to experience a clearly clinically meaningful improvement of nighttime sleep and daytime napping, on the order of hours, unaccompanied by serious adverse effects.

Risk-Benefit Framework

Analysis of the condition and current treatment options

Non-24 is a type of circadian rhythm sleep disorder that occurs in totally blind individuals due to loss of the normal input from the eyes to the hypothalamus and other brain regions about environmental light levels –in simple terms, when it is day versus night. While all humans possess a genetically-based internal clock that controls circadian functions such as sleep and wakefulness, in most individuals this clock 'runs slow' versus the 24-hour day, and is mainly kept on-time by a daily 'nudge' provided mainly by environmental light levels, as sensed by specialized cells in the retina, and transduced through complex neural systems. In the absence of such information about light levels, most individuals will tend to fall asleep a few minutes later each night (some tens of minutes, but longer or shorter depending on the individual) and wake a corresponding number of minutes later, in a continuous cycle that is never truly aligned with the 24-hour day, except for brief periods when, as for any two clocks running at slightly different speeds, alignment approaches, occurs, then passes. Therefore, patients with Non-24 must either force themselves to adhere to the activity schedule of the external 24 hour day, even though most of the time this goes against their own, strong, biological schedule, or live according to their own endogenous time, which is constantly shifting relative to the daily activities of those around them. Adhering to the 24-hour day

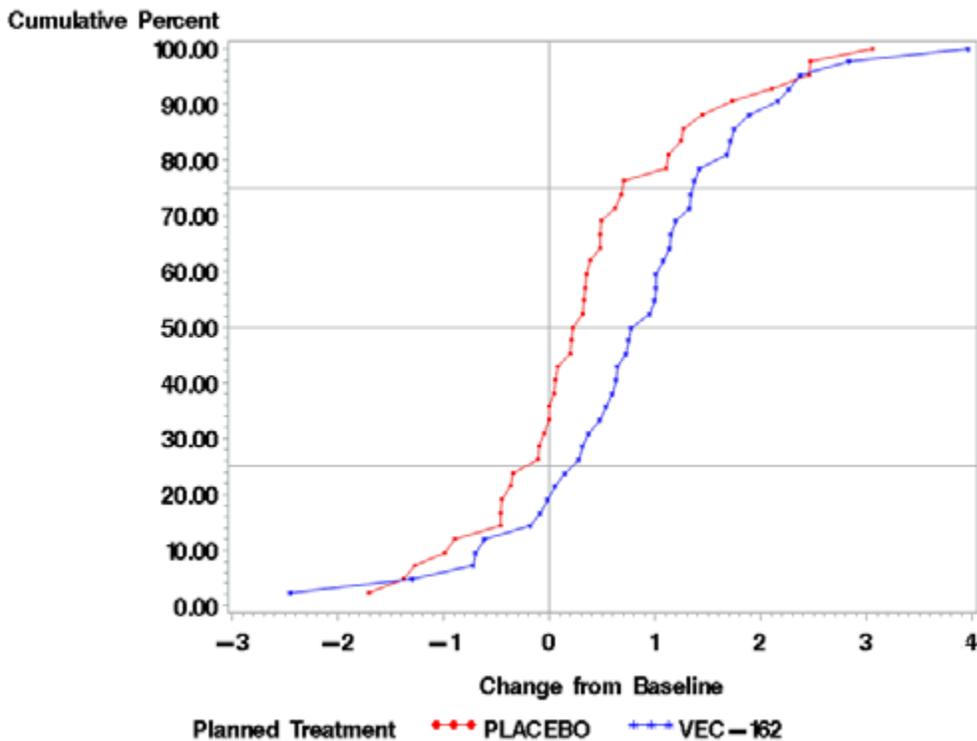
results in severe cyclical daytime sleepiness and nighttime insomnia, while adhering to their internal schedule results in profound social separation from others.

Currently no drugs are FDA approved for Non-24. Melatonin, widely available as a dietary supplement, is an agonist at MT1 and MT2 receptors, similar to tasimelteon, and has been described in published studies as effective in Non-24. Comparative safety and efficacy data for melatonin and tasimelteon in Non-24 are not available. However, there is little reason to believe that the risk-benefit profile of tasimelteon in Non-24 is substantially altered by the availability of melatonin as an unapproved therapy.

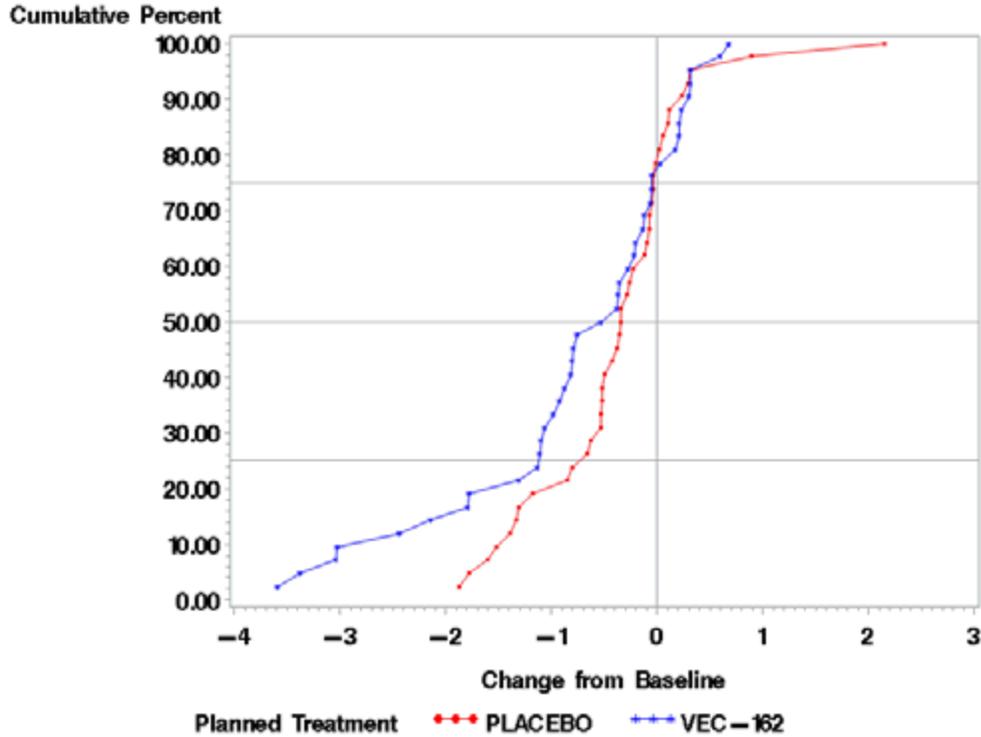
Benefit

The Cumulative Distribution Functions (CDFs) generated by Dr. Luan for sleep endpoints illustrate the range of benefit gained by different patients from tasimelteon.

The figure below shows the CDF of change in LQ-nTST for tasimelteon and placebo arms in study 3201 (in hours). Chosen for illustrative purposes only, about half the tasimelteon patients gained about an hour of sleep with treatment, compared to about 20% of patients treated with placebo.



Similarly, the figure below shows the CDF of change in UQ-nTSD. Chosen for illustrative purposes only, about 15% of tasimelteon patients had a decrease in daytime nap time of 2 hours or more, compared to none for placebo.



risk

Serious adverse effects or irreversible harm from tasimelteon were not revealed in the clinical studies, in a safety database that included 183 Non-24 subjects treated for at least 6 months, and 44 treated for at least one year.

The potential remains that serious adverse effects of tasimelteon remain undiscovered, but the available data doesn't indicate that special postmarketing vigilance or risk evaluation strategies are warranted.

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/s/

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