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APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	31 January 2014
From	Ellis F. Unger, MD Director, Office of Drug Evaluation 1
Subject	Office Director Decisional Memo
NDA	205677
Applicant Name	Vanda Pharmaceuticals
Date of Submission	31 May 2013
PDUFA Goal Date (post-extension)	31 January 2014
Proprietary Name / Established (USAN) Name	Hetlioz tasimelteon
Dosage Forms / Strength	20 mg oral
Proposed Indication(s)	Non-24 Hour Sleep-Wake Disorder in Blind Patients
Action:	Approval

Material Reviewed/Consulted	Names of discipline reviewers
Clinical Review	Devanand Jillapalli, MD
Biostatistics Review	Jingyu (Julia) Luan, PhD, Steven Thompson, PhD, Kun Jin, PhD
Pharmacology/Toxicology Review	Melissa Banks-Muckenfuss, PhD, Lois Freed, PhD
ONDQA Biopharmaceutics Review	Kareen Riviere, PhD, Angelica Dorantes, PhD
Chemistry Manufacturing Controls (CMC) Review	Rao Kambhampati, PhD, Wendy Wilson-Lee, PhD, Martha Heimann, PhD, Ramesh Sood, PhD, Teshara Bouie, PhD, Don Henry, PhD, Michael Trehy, PhD
Statistical Review – Carcinogenicity Study	Karl Lin, PhD
Office of Prescription Drug Promotion	Melinda McLawhorn, PharmD, BCPS
Office of Manufacturing and Product Quality	Mahesh Ramanadham, PhD, Christina Capacci-Daniel, PhD, Bryan Riley, PhD, (Microbiologist)
Division of Medical Policy Programs	Twanda Scales, BSN, MSN, Melissa Hulett, MSBA, BSN, LaShawn Griffiths, MSHS-PH, BSN, Carol McAlman
Division of Scientific Investigations	Antoine El Hage, PhD, Susan Thompson, PhD, Susan Leibenhaut, PhD
Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology	Julie Neshiewat, PharmD, BCPS, Melissa Hulett, MSBA, BSN, Irene Chan, PharmD, Ermias Zerisslassie, PharmD
QT/IRT	Norman Stockbridge, MD, Moh Jee Ng, MD
Cross-Discipline Team Leader	Ronald Farkas, MD, PhD
Director, Division of Neurology Products	Billy Dunn, MD, Eric Bastings, MD
CDER OND IO Rare Diseases	Anne Pariser, MD, Kathryn O'Connell, MD
Regulatory Project Manager	Cathleen Michaloski, BSN, MPH, RAC

1. Introduction

Tasimelteon is a first-in-class new molecular entity under review for the treatment of Non-24 hour sleep-wake disorder (Non-24) in totally blind patients. Non-24 is a disorder of completely blind individuals, characterized by phase shifts between the sleep-wake cycle and the 24-hour day caused by a lack of environmental light input. Because the period of the “biological clock” is >24 hours in most people, the absence of light input creates a cyclic misalignment of sleep and wakefulness with the 24-hour day.

Tasimelteon is an agonist of melatonin MT1 and MT2 receptors. These receptors are thought to mediate the effects of melatonin on the circadian rhythms underlying a number of physiological processes, including the sleep-wake cycle.

No drugs are currently approved for Non-24, and tasimelteon is not marketed in any country.

2. Regulatory History

As discussed by Drs. Jillapalli, Farkas, and Bastings, there is no precedent for regulatory approval of a drug for this indication. Despite extensive interactions with the applicant during the drug development program, no agreement could be reached regarding the acceptability of the 1° endpoints to be used in the pivotal efficacy studies. The applicant insisted on using an unvalidated surrogate biomarker, the urinary metabolite of melatonin (6-hydroxymelatonin sulfate [aMT6s]) to assess “entrainment.” The division noted that there were published reports showing that melatonin treatment resulted in significant increases in sleep in Non-24 patients. Given the feasibility of showing benefit on clinical endpoints, the division was clear that the applicant’s proposal for the surrogate endpoint was not acceptable. Understanding that agreement had not been reached on primary endpoints, the applicant nevertheless conducted the two pivotal efficacy studies using “entrainment” as the 1° endpoint. The studies also included endpoints that the division had identified as important measures of clinical benefit in Non-24: assessments of the duration of nighttime sleep and daytime naps. Whereas the applicant had defined these clinical endpoints as secondary, the division considered them to be primary. As discussed by Dr. Farkas, the division expected the applicant to show that tasimelteon had an effect on the circadian disruption of sleep/wakefulness, and not just that it increased sleep time in a non-specific manner that would be expected from any drug for insomnia. The division clearly communicated to the applicant that evaluation of an NDA filing would be based on clinically meaningful endpoints.

3. Chemistry Manufacturing Controls

I concur with the conclusions reached by Dr. Kambhampati and Dr. Riviere regarding the acceptability of manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. There are no outstanding CMC issues precluding approval.

4. Nonclinical Pharmacology/Toxicology

The nonclinical team’s overall conclusion was that these studies were adequate to support approval of the NDA, with appropriate labeling.

There was considerable discussion regarding appropriate language for section 12.1 of the package insert, mechanism of action. The final agreed upon text is: “The precise mechanism by which tasimelteon exerts its therapeutic effect in patients with Non-24 is not known. Tasimelteon is an agonist at melatonin MT1 and MT2 receptors. These receptors are thought to be involved in the control of circadian rhythms.”

5. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology's overall conclusion was that the NDA was acceptable for approval. The mean elimination half-life is 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, leading to the recommendation that Tasimelteon should be taken without food.

CYP1A2 and CYP3A4 are the major isoenzymes involved in the metabolism of tasimelteon. Inhibition of these isoenzymes causes marked increases in exposure, and induction decreases exposure. Thus, the package insert directs that co-administration of strong inducers and inhibitors of these isoenzymes should be avoided.

Tasimelteon exposure increased 43% and 110% in patients with mild and moderate hepatic impairment, respectively, and no dose adjustment is needed in such patients. Tasimelteon was not been studied in patients with severe hepatic impairment (Child-Pugh Class C); therefore, use is not recommended in these patients.

The pharmacokinetics of tasimelteon was compared in subjects with severe renal impairment, end-stage renal disease requiring hemodialysis, and healthy controls. There was no apparent relationship between renal function tasimelteon CL/F, such that no dose adjustment is necessary for patients with renal impairment.

The 20 mg dose was the only dose studied in Non-24 patients, and the dose-response is unknown.

6. Clinical/Statistical – Efficacy

The applicant conducted two placebo-controlled trials to support efficacy in Non-24: studies 3201 and 3203. As discussed above, the applicant's proposed surrogate primary endpoint was not accepted by the division, and only clinical endpoints were considered by the division in their assessment of efficacy.

Study 3201

Study 3201 was a randomized, double-masked, placebo-controlled study wherein 84 totally blind subjects with Non-24 were randomized in a 1:1 ratio to 20 mg tasimelteon or placebo, at a time when the patient's circadian rhythm was thought to be coming into alignment with the 24-hour day (as measured by a urinary melatonin biomarker). The applicant's 1^o endpoint was the proportion of patients who were entrained (determined on the basis of urinary melatonin measurements). A second biomarker measure, the "Non-24 Clinical Response Scale1," was to be tested in a step-down approach. Nominal p -values for both biomarkers were < 0.05 , but, as noted above, these were not considered demonstrative of tasimelteon's efficacy. The review team focused on clinical endpoints, as follows:

- Nighttime total sleep time (nTST)
- Lower Quartile of nTST (LQ-nTST)
The worst quartile of nights (nights with lowest nTST) of placebo and drug-treated arms.
- Daytime total sleep duration (dTSD)
- Upper quartile of dTSD (UQ-dTSD)
The worst quartile of days (with highest dTSD) of placebo and drug-treated arms.

- Clinical Global Impression of Change (CGI-C)

CGI-C 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.

As discussed by Dr. Farkas, the division found the LQ-nTST and the UQ-dTSD to be the most relevant measures for Non-24, because they were best adapted to the cyclical nature of the disorder.

In Study 3201, the comparisons for tasimelteon vs. placebo were nominally significant for UQ-dTSD, MoST, CGIC, and dTSD, and marginally significant for LQ-nTST (table). The difference in nTST was not statistically significant. Dr. Luan noted that the *p*-values for these endpoints should be considered nominal because of the lack of agreement about the study primary endpoint.

Summary of the FDA statistical analyses for the intent-to-treat population:

Endpoint	Placebo	Tasimelteon	P-value
LQ-nTST	0.37	0.83	0.051
UQ-dTSD	-0.36	-0.81	0.012
MoST	0.25	0.54	0.037
CGIC ¹	3.34	2.63	0.008
nTST	0.35	0.6	0.115
dTSD	-0.18	-0.36	0.017

¹For CGIC, n=71; CGIC was missing for 13 patients.

For LQ-nTST, MoST and nTST, larger values indicate better outcomes.

For UQ-dTSD, CGIC and dTSD, smaller values indicate better outcomes.

Study 3203

Study 3203 was a double-masked, placebo-controlled, randomized withdrawal study designed to evaluate the long-term maintenance effect and safety of 20 mg of tasimelteon. Twenty (20) subjects were randomized 1:1 to receive tasimelteon (20 mg/day) or placebo during the randomized withdrawal phase, which took place after ~11 weeks of treatment. The applicant's proposed 1^o endpoint was the proportion of non-entrainment of the circadian melatonin rhythm as measured by urinary melatonin metabolite aMT6s. As in Study 3201, the division did not agree with the biomarker-based endpoint, and the assessment of efficacy by the review team was based instead on clinical endpoints.

The biomarker-based primary endpoint showed a statistically significant benefit favoring tasimelteon. As in Study 3201, the comparisons for tasimelteon vs. placebo were nominally significant for LQ-nTST, UQ-dTSD, MoST, and dTSD. The results for nTST were not statistically significant. Results from the FDA statistical reviewer (Dr. Julia Luan) are tabulated below:

Endpoint	Placebo	Tasimelteon	P-value
LQ-nTST	-1.23	-0.11	0.023
UQ-dTSD	0.83	-0.16	0.027
MoST	0.83	-0.16	0.027
nTST	-0.74	-0.2	0.132
dTSD	0.3	-0.05	0.055

7. Clinical/Safety

Dr. Jillapalli notes that 1,346 subjects received at least one dose of tasimelteon, including 621 subjects who received 20 mg, the to-be-marketed dose. In total, 183 subjects with Non-24 received tasimelteon 20 mg with a mean exposure of 252 days. As of 11/30/12, 111 of these subjects were treated for ≥ 6 months, and 44 were treated for ≥ 1 year.

Dr. Jillapalli did not find an association of tasimelteon with serious adverse events. Increased alanine aminotransferase was identified as common treatment-emergent adverse event, but marked elevations of transaminases and increased bilirubin were not observed.

Dr. Jillapalli concluded that somnolence was not a safety signal in non-elderly adult subjects with Non-24 or insomnia, but that elderly female subjects with insomnia taking tasimelteon had a higher incidence of somnolence compared to placebo subjects.

At a dose 15 times the maximum recommended dose, tasimelteon does not prolong QTc to any clinically relevant extent.

The review team concludes, and I agree, that the size of the safety database was adequate for this orphan condition, and that serious toxicity was not identified.

8. 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 affirmatively on 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 been presented for tasimelteon in Non-24?
- Has the safety of tasimelteon in Non-24 been adequately addressed?

9. 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 applicant to perform a Braille label comprehension study of Braille labeling on the Hetlioz bottle. DMEPA found the study acceptable, and found the applicant's proposals to improve clarity of the Braille text reasonable.
- Four clinical investigator sites were inspected by OSI and, overall, the data submitted from these sites were considered acceptable to support the pending application.

10. Recommendations

Recommended Regulatory Action

The applicant submitted two adequate and well-controlled studies to support the efficacy of tasimelteon in Non-24. The review team unanimously supports approval of this drug for Non-24, and I agree with their conclusions.

The unusual aspect of this NDA is that the Division and applicant never agreed on the 1^o endpoint to be used in the pivotal studies. The applicant espoused the position that the studies would be underpowered to succeed on a clinical (sleep) endpoint, and opted to use biochemical endpoints that would demonstrate 'entrainment' of circadian rhythm. Although such evidence of entrainment could provide mechanistic support for efficacy, the Division's position was simply that it should not be necessary to resort to a surrogate endpoint for this condition. Their view was that studies of reasonable and practicable size, reasonable even for an orphan indication, were likely to be capable of succeeding on a clinical endpoint. There was no need, therefore, to resort to a surrogate endpoint for this development program.

Results in both studies were positive for the endpoints that the division had prospectively identified as clinically important and relevant for the indication, as well as for the 1^o endpoints prospectively specified in the statistical analytical plans.

I agree with Dr. Bastings' conclusion, that under these circumstances it seems reasonable to consider the main clinical endpoints of interest, and not use the primary endpoints selected by the applicant. All of the endpoints were statistically significantly in favor of tasimelteon in both studies.

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. Because tasimelteon improves symptoms readily perceived by patients, the risk-benefit profile is positively affected: patients experiencing insufficient efficacy or unacceptable adverse effects can simply discontinue treatment without fear of harm. A reasonable proportion of patients can be expected to experience clinically meaningful increases in nighttime sleep and decreases in daytime napping, on the order of hours, unaccompanied by serious adverse effects.

11. Benefit-Risk Framework

Analysis of condition

Non-24 is a sleep disorder that occurs in totally blind individuals caused by loss of light input. In the absence of information about ambient light, most individuals will tend to fall asleep a few minutes later each night and wake correspondingly later each morning. Thus, patients with Non-24 must either make efforts to adhere to the activity schedule of the external 24-hour day, or live according to their own endogenous time, which is constantly shifting relative to the daily activities of those around them. Adherence to the 24-hour day can result in cyclical daytime sleepiness and nighttime insomnia, whereas adhering to their internal schedule can cause social separation. Non-24 is not a life-threatening condition, but it can have a major negative impact on quality of life.

Current treatment options

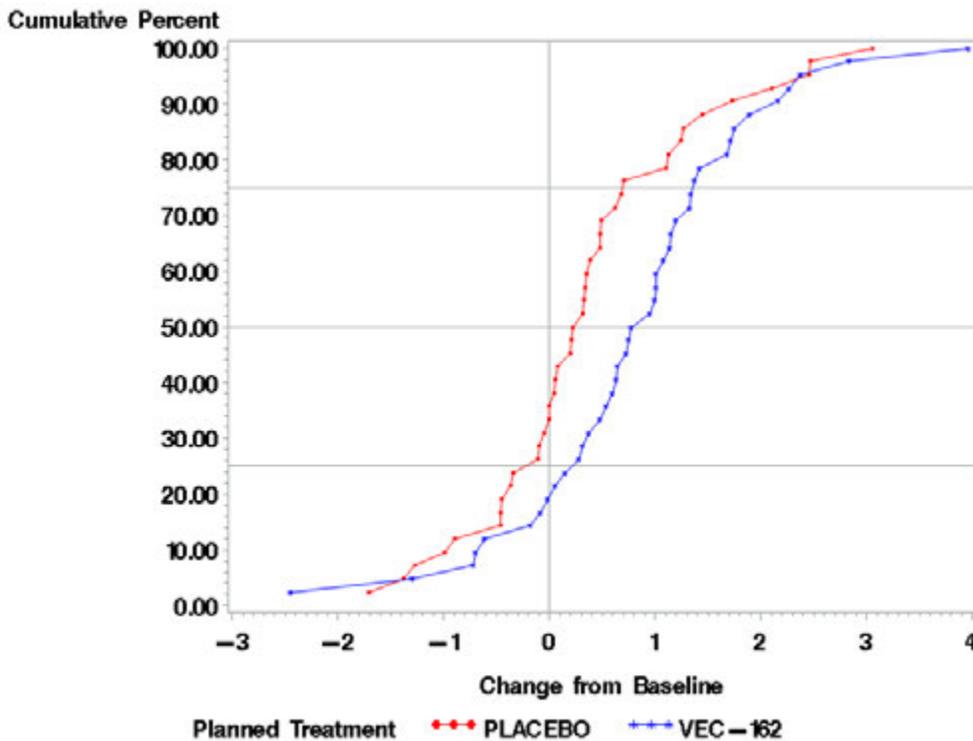
No drugs are FDA approved for Non-24. Melatonin, widely available as a dietary supplement, is an agonist at MT1 and MT2 receptors, similar to tasimelteon, and has been described in published studies as effective in the treatment of Non-24. Because melatonin is not regulated

as a drug, its benefit and risk have not been well characterized and cannot be contrasted with those of tasimelteon. Though not proven, many on the review team and some members of the Advisory Committee expressed the view that tasimelteon was not likely to be more effective than melatonin.

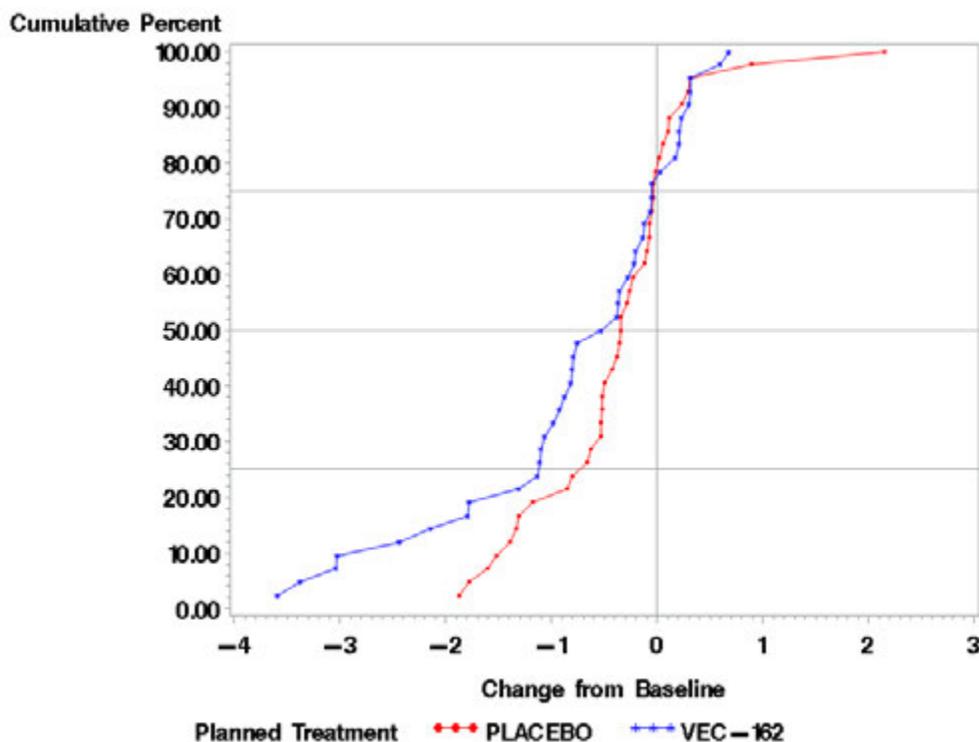
Benefit

The data submitted from two adequate and well controlled trials are persuasive in their support of tasimelteon for the Non-24 indication. As noted above, the division chose the endpoints it deemed to be most clinically relevant. One of the studies (3203) showed durability of tasimelteon effects through ~11 weeks.

Cumulative Distribution Functions (CDFs) generated by Dr. Luan for sleep endpoints illustrate the range of benefit provided by tasimelteon. The figure below shows the CDF of change in LQ-nTST for tasimelteon and placebo arms in study 3201 (in hours). Approximately 50% of the tasimelteon patients gained ~1 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. Approximately 15% of tasimelteon patients had a decrease in daytime nap time of 2 hours or more, compared to none for placebo.



Increasing nighttime sleep and decreasing daytime naps might have benefits on quality of life, although such benefits were not well characterized.

Risk

No important risks were identified in the clinical development program. The safety database included 183 Non-24 subjects treated with tasimelteon for at least 6 months, and 44 treated for at least one year. Several hundred (438) additional subjects received the to-be-marketed dose for other indications.

Although the size of the database and the exposure are deemed adequate for this orphan indication, it is clear that significant adverse events – even adverse events that are moderate in frequency, and certainly those that are uncommon – could have gone undetected in this development program. Nevertheless, the available data do not suggest that particular risk evaluation strategies are warranted beyond usual labeling.

12. Important Missing Information

We recognize that there are no dose-response data for patients with Non-24. But given the size of the available patient population for study, and given the lack of significant toxicity in the face of the efficacy, further studies to characterize dose-response seem unnecessary at present.

There are no data on use of tasimelteon with melatonin, though coadministration will be highly likely in real-world use, especially for patients who do not respond to tasimelteon or melatonin used singly. Despite the lack of data, the review team has opined that co-administration is unlikely to be harmful; therefore, an additional safety trial will not be required. The package insert will be silent on coadministration of tasimelteon and melatonin.

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/s/

ELLIS F UNGER
01/31/2014