CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214517Orig1s000

PRODUCT QUALITY REVIEW(S)

Center for Devices and Radiological Health (CDRH)
Inter Center Consult Request (ICCR) Memorandum

THT5A3: Neurodiagnostic Devices Team
DHT5A: Division of Neurosurgical, Neurointerventional and Neurodiagnostic Devices
OHT5: Office of Neurological and Physical Medicine Devices

From:	Patrick Antkowiak, PhD Team Lead, Neurodiagnostics team
CC:	Jay Gupta, M.S.E *Assistant Director, Neurodiagnostic Devices Team*
To:	Latrice Wilson, PharmD, RAC Senior Regulatory Project Manager Psychiatry Group / Division of Regulatory Operations for Neuroscience Office of Regulatory Operations Center for Drug Evaluation and Research
Product Information:	Tasimelteon
Sponsor:	Vanda Pharmaceuticals
Subject:	ICC00022724 - NDA 214517 engineering consult
Study Title:	A double blind, randomized, two-period crossover study evaluating the effects of tasimelteon vs. placebo on sleep disturbances of individuals with Smith-Magenis syndrome (SMS)
Date:	November 9, 2020
Recommendation:	**The review team concluded that the actigraphy data could not be used to support regulatory decision making on the effectiveness of tasimelteon in the treatment of sleep disturbances in SMS.**

Reviewer's signature	Patrick Antkowiak -S 2020.11.09 18:13:28 -05'00'

Consult instructions: Lead center requestor Latrice Wilson sent the following consult instructions:

Vanda Pharmaceutical submitted accelerometer-measured data as a secondary efficacy endpoint related to sleep disturbances in Smith-Magenis Syndrome (SMS). The specific tool they used in the study is a Philips-Respironics Actiwatch. The Applicant and FDA did not have any discussion during the IND phase about what the Applicant needed to do to validate use of this tool to measure sleep in the SMS population or what information should be submitted with the NDA. The Applicant responded to an information request we sent recently with a number of questions regarding the accelerometry data, which we have attached for this consult. We request assistance from CDRH to help with verification of the Actiwatch. Specifically,

1) *Has the Applicant submitted the appropriate information for verification of the Actiwatch?*

2) *From a device perspective, do you believe that the accelerometry data collected by this tool is reliable for use in a secondary efficacy endpoint?*

We are also consulting the Division of Clinical Outcome Assessments within CDER for assistance in the clinical validation of data collected by this tool.

Reviewer's comment: I am providing feedback on the appropriateness of the data to support the Actiwatch and whether the data collected by the watch could be considered reliable for use as a secondary efficacy endpoint in support of a new drug application.

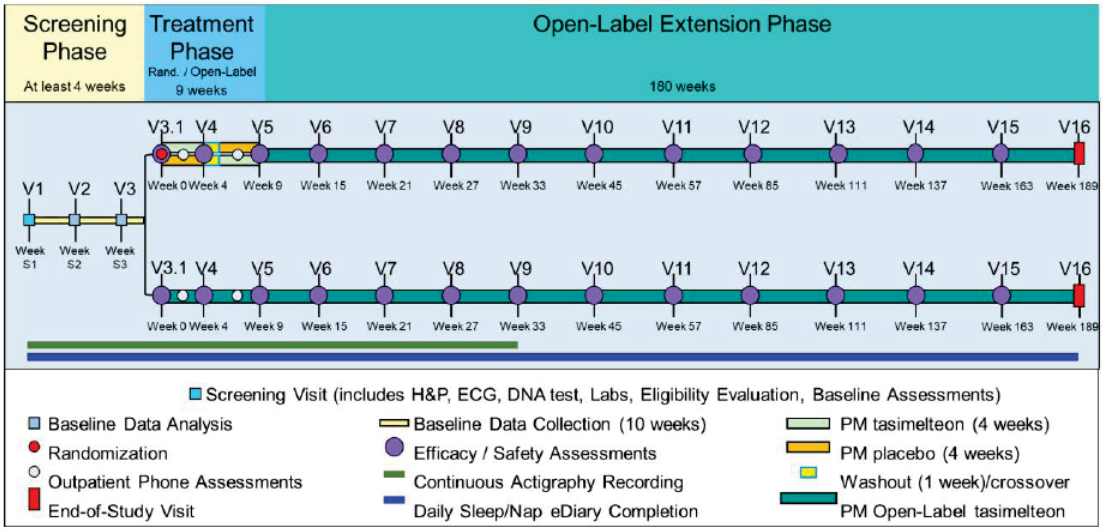
In general, I recommend that data collected from an actigraph may be suitable to support a secondary efficacy endpoint. **However, this is only appropriate when the actigraph has been demonstrated to accurately and reliably measure the endpoint (or concepts associated with the endpoint) precisely, within a well-described level of meaningfulness to the patient.** This prior information has not been provided by sponsor Vanda Pharmaceuticals in this application. While the accuracy and reliability of actigraph-derived measurements of sleep has been described in the literature, it has not been established in this patient population, and nor has it been established what would represent a meaningful change in these measurements.

Because of this, and for reasons described in the actigraphy review issue template that include an analysis of the data in this submission, I do not recommend that actigraphy may be used to support a secondary efficacy endpoint for this study in an SMS patient population.

Study design: For the actigraphy-related study design aspects, the sponsor used a Phillips Actiwatch Spectrum Classic device to measure the following parameters, according to the schedule in the study schematic below:

- Total amount of nighttime sleep (TST),
- Latency to persistent sleep (LPS),
- Number and length of nighttime awakenings.
- The percentage of wake periods within the nighttime sleep interval was calculated using the total wake time during the sleep duration (WASO).

Figure 1: Study Schematic



ECG = electrocardiogram; eDiary = electronic diary; H&P = medical history and physical examination; Rand. = Randomization; S = Screening; V = Visit.
Source: Study Protocol (Appendix 16.1.1)

Reviewer's comment: The sponsor is using an actigraph that is a Class II medical device, cleared via the 510(k) review process in K983533 with the following indications for use:

Indications for Use:

The Actiwatch® is an ultra-compact, lightweight, wrist-worn activity and ambient light monitor that can be used to analyze circadian rhythms, automatically collect and score data for sleep parameters, and assess activity in any instance where quantifiable analysis of physical motion is desirable.

This indications for use language is consistent with a "tool" claim, rather than a claim of specific clinical utility for assessment of sleep in a particular patient population.

Actigraphy devices incorporate accelerometers and various other sensors, and they generally measure the number of "counts" (units of activity in which the integrated accelerometry data reaches some threshold over a certain period of time) over time. They then perform a separate software analysis that

interprets the raw count data to represent steps or energy expenditure. Clearance as a medical device signifies that CDRH has determined that these products are substantially equivalent to another legally-marketed medical device (a "predicate") in terms of safety and effectiveness for their intended use; clearance as a device does not itself suggest that the device may have utility as an outcome assessment in a particular patient population.

From my own review of the documentation provided in the marketing application for the Actiwatch marketing submission, it is not clear what data were cited to support the sleep analysis claims; however, this does not represent a concern for this NDA review. There may also have been changes to the device since the original clearance more than 20 years ago. For this reason, I am relying primarily on the data and information provided in the NDA submission as the basis of my recommendations. The particular SMS patient population was not discussed in the original marketing application for the actigraph.

I do not have any comments on the study design or timing of the assessments with the device.

Sponsor rationale for including wearable in study: The sponsor suggested that they were interested in including actigraphy assessments to support their claims because actigraphy provides an "objective assessment" of sleep.

Effectiveness data provided: The sponsor provides Table 4 below

2.2.4.2.1. Secondary Efficacy: Randomization Phase (2401B)

Table 4: Randomization Phase Secondary Efficacy Results (2401B)

N=25[1]	Variable	Placebo[2]	Tasimelteon[2]	Difference	p-value
Actigraphy (Objective)	Average of 50% Worst Daily Length of Nighttime Awakenings (minutes)	1.7	-3.4	-5.1	(b) (4)
	Average of 50% Worst Daily Number of Nighttime Awakenings	-0.3	0.6	0.9	
	Average of 50% Worst Daily Total Amount of Nighttime Sleep – hours (minutes)	0.0 (2.6)	0.4 (22.4)	0.3 (19.8)	
	Average of 50% Worst Latency to Sleep (minutes)	-0.7	0.1	0.8	
	Average of Daily Length of Nighttime Awakenings (minutes)	2.4	-2.3	-4.7	
	Average of Daily Number of Nighttime Awakenings	0.1	0.5	0.4	
	Average of Daily Total Amount of Nighttime Sleep - hours (minutes)	0.0 (1.9)	0.3 (20.2)	0.3 (18.2)	
	Average of Latency to Sleep (minutes)	0.1	0.0	-0.1	

Consultant comment: The actigraphy-derived results are provided by the sponsor above. I have the following comments related to these data:

1. It is not clear what a meaningful change in activity is in this patient population, and it is further unclear whether the Actiwatch is sufficiently accurate and precise to measure this change.

2. It is not clear what the variability of actigraphy measurements of activity and sleep is in the proposed patient population due to variations in patient activity. A clear understanding of the variability of actigraphy measurements of motion and sleep is needed to understand whether it is appropriate or even feasible to use an actigraphy-based assessment as an endpoint in this patient population.

3. It is not clear whether differences in patients wear the device (including wear on the dominant vs. non-dominant hand, looseness, patient forgetfulness/compliance) would potentially affect the validity of the device's measurements to represents the efficacy endpoints.

I note that there was a recent publication that provided case-control actigraphy data for children with SMS, but this only compared actigraphy-derived sleep parameters between children with SMS and typically-developing counterparts; it did not establish the validity of the actigraphy measurements themselves or define what a meaningful difference would represent**. For these reasons, I do not recommend that the specific data provided in this NDA should be considered to support the proposed secondary efficacy endpoints.** I cannot comment on the meaningfulness of the results provided for this reason.

I note that I do believe that actigraphy-derived measurements of activity and sleep could be used in support of secondary endpoints for NDAs *in general*, **if** data from preliminary investigations can be provided addressing the 3 points above. If these data are not provided, then the interpretation of the meaningfulness of any efficacy endpoints derived from actigraphy measurements will prove difficult.

APPENDIX A: REVIEW ISSUE TEMPLATE FOR ACTIGRAPHY DATA

Usability of actigraphy data for supporting the primary endpoint in the evaluation of efficacy.

Reviewer's comment: This review issue template was primarily compiled by Drs. Valentina Mantua, Andrew Potter and Ji Li from CDER. I have provided some input on the document and agree with the conclusion and factual information presented within the document.

Issue

The Applicant specified "*To determine the efficacy of tasimelteon compared to placebo, as measured by improvements in actigraphy parameters*" as a secondary objective of pivotal study VP-VEC-162-2401. Actigraphy devices rely on an accelerometer to measure patterns of activity (motion) and estimate sleep/wake states based on the assumption that motion implies wake, and no-motion implies sleep. Due to their small size and comfort, actigraphy watches are designed to be worn at all times and thus are suitable for prolonged recordings in non-laboratory settings. Actigraphy is used for sleep monitoring as an objective measure of continuous patient data outside a laboratory setting.

Use of a home-based actigraphy device to estimate sleep parameters has particular relevance to patients with SMS or other intellectual disabilities, considering that use of the gold standard method, polysomnography, may not be feasible.

Actigraphy is considered to be a Digital Health Technology (DHT)[1] and this is the first time that data collected by means of a DHT[i] are submitted as supportive evidence of efficacy in the context of an NDA. As the field is evolving, the requirements for the use of DHTs for remote assessment of clinical or behavioral or physiologic parameters in late stage drug development are being determined. The review team assessed the suitability of actigraphy data to support the efficacy evaluation of tasimelteon in the treatment of sleep disturbances in SMS.

Assessment

Subjects enrolled in study VP-VEC-162-2401 (hereafter referred to as Study 2401) wore an actigraphy watch for the entire duration of the study from the screening phase to the open label extension phase. The actigraphy watch used in Study 2401 was the Philips Spectrum Classic. The review team assessed the characteristics of the actigraphy watch as well as the information provided by the Applicant regarding the processing pipeline and the algorithm used to generate the secondary endpoints. Subjects (b) (6) and (b) (6) was chosen as a case-study to compare sleep and wake periods between

[1] Digital health technologies use computing platforms, connectivity, software, and sensors for health care and related uses. These technologies span a wide range of uses, from applications in general wellness to applications as a medical device. They include technologies intended for use as a medical product, in a medical product, as companion diagnostics, or as an adjunct to other medical products (devices, drugs, and biologics). They may also be used to develop or study medical products. https://www.fda.gov/medical-devices/digital-health-center-excellence/what-digital-health

actigraphy-generated data and eDiary reports. The review team also assessed the compliance of subjects enrolled in Study 2401 to actigraphy watch use and the amount of missing data.

Characteristics of the actigraphy watch

The motion sensor is a solid-state accelerometer, range 0.5 – 2 G, resolution 100 counts or 0.02 G, sampling at 32 Hz. The off-wrist sensor is a capacitor formed by 2 metal plates as part of a bi-stable multivibrator, with on-wrist activation distance of < 2 mm. The light sensor is a radiometer recording RGB irradiance or weighted white light illuminance. The single axis acceleration data is transformed into activity counts per minute using a proprietary algorithm. These counts reflect a feature of the total magnitude of acceleration observed during each minute; however, the details of the algorithm were not submitted with this NDA.

Usability and feasibility of the actigraphy watch for subjects with SMS

The Applicant evaluated suitability of the actigraphy watch for use in patients with SMS in a naturalistic study (VP-1401), in which activity data was collected prior to the initiation of pivotal study VP-VEC-162-2401 using the same actigraphy watch. Despite there are no established standards for the conduction of feasibility or usability studies, these are a necessary part of the analytical validation of DHTs to ascertain whether the tool is suitable to the target population. In addition, the Applicant provided scientific literature in support of the use of actigraphy watches in patients with SMS. The Applicant claimed that the watch was well tolerated, however data on the compliance or tolerability were not submitted and perhaps the prolonged use of the watch Study 2401 consists of 4 weeks screening phase and 9 weeks treatment phase) as compared to the short duration of study 1401 (36 hours) proved challenging for some patients.

- *Bakker, J.P. et al. A systematic review of feasibility studies promoting the use of mobile technologies in clinical research. npj Digit. Med. 2, 47 (2019).*
- *G. Agar, C. Oliver, J. Trickett, L. Licence, and C. Richards, "Sleep disorders in children with Angelman and Smith-Magenis syndromes: The assessment of potential causes of disrupted settling and night time waking," Res. Dev. Disabil., vol. 97, 2020.*
- *J. Trickett et al., "Sleep in children with smith-magenis syndrome: A case-control actigraphy study," Sleep, vol. 43, no. 4, 2020.*
- *J. Trickett et al., "Multi-Method Assessment of Sleep in Children With Angelman Syndrome: A Case–Controlled Study," Front. Psychiatry, vol. 10, 2019.*
- *C. M. Smith, R. S. Morse, W. Introne, and W. C. Duncan, "Twenty-four-hour motor activity and body temperature patterns suggest altered central circadian timekeeping in Smith–Magenis syndrome, a neurodevelopmental disorder," Am. J. Med. Genet. Part A, vol. 179, no. 2, pp. 224–236, 2019.*

Actigraphy compliance data in pivotal study VP-VEC-162-2401

The actigraphy watch Spectrum Classic includes an off-wrist sensor that indicates when the subject is not wearing the device.

According to the Applicant, 5 out of 25 patients in the ITT population did not have any actigraphy data.

Caregivers were instructed to inform the study coordinator if the patient refused to wear the watch. Participation in all study phases, including the Screening, Randomized, and Open Label Treatment phases, was not affected by whether or not the patient wore the actigraphy watch. There was no compliance requirement for inclusion in the analysis for the Screening or Treatment phases. Compliance was determined by the same diary compliance requirements (data from ≥14 days for each period to allow for the 50% worst calculation). However, except for the 5 patients with no actigraphy data, there were no other patients deemed noncompliant with actigraphy by these requirements as there was sufficient data in patients who wore the watch and whose data was scorable.

The processing pipeline

For Study VP-VEC-162-2401, the actigraphy watch Spectrum Classic device captures motion and light data during wear by the patient. Once removed from the patient, the Spectrum Classic device is then connected to a Spectrum Dock, which is then connected via USB connection to a site computer with the study-specific Actiware CT software installed. The Dock enables the data collected on the Spectrum Classic device to be downloaded by the Actiware software onto the site computer. For this study, the datasets were then sent by site personnel via e-mail to the Motion Biosensors scoring team. A Motion Biosensors scoring team member stored the received datasets on a secure Philips-owned server. The Motion Biosensors team used the Actiware software to score the received data for sleep and activity endpoints via validated algorithms within the software. The endpoint data were then sent back to Vanda via password-protected e-mail.

Performance metrics of the algorithm used

The Applicant provided metrics based on a published study by Kushida et al. which determined that the actigraphy algorithm was capable of detecting sleep at each minute epoch with sensitivity of 0.96 (medium-threshold algorithm), specificity of 0.38, and accuracy of 0.77 when compared with polysomnography (PSG), where sensitivity is the probability that the actigraphy algorithm scores an epoch as sleep when PSG scores it as sleep, specificity is the probability that the algorithm scores an epoch as awake when PSG scores as awake, and accuracy is the probability of correctly scoring any epoch over the total number of epochs scored. These performance metrics were estimated from a population of adults with sleep disorders.

- *Kushida et al. (2001). Comparison of Actigraphic, Polysomnographic, and Subjective Assessment of Sleep Parameters in Sleep-Disordered Patients. Sleep Medicine. 2(5). 389-96.*

As explained in de Zambotti et al., paper, for Philips Respironics algorithms, the “low” threshold requires smaller activity counts to deem an epoch as wake, therefore increasing specificity but at the cost of sensitivity. Conversely, the “medium” threshold increases sensitivity at the cost of specificity, due to the greater activity count threshold required for wake.

In addition, in the context of drug development, and particularly in a pivotal study to support an NDA application, the algorithm needs to be validated in the relevant patient population, assuming that conditions like SMS may influence the amount of activity both during wake and during sleep.

In the case of study VP-VEC-162-2401, where the aim of the investigation was to determine improvement in nighttime sleep duration (total sleep time) following administration of tasimelteon, high accuracy in wake detection should be prioritized.

- *de Zambotti M, Cellini N, Goldstone A, Colrain IM, Baker FC. Wearable Sleep Technology in Clinical and Research Settings. Med Sci Sports Exerc. 2019;51(7):1538-1557*

Case study

The case study compared the activity data with the caregiver eDiary reports of time of sleep and to awake with the goal of exploring the relationship between these to data sources. In Figure 1 and Figure 2, the log activity counts (dark colored lines) are plotted against time of day (midnight = 0h). The wear status and sleep status (asleep vs. awake) are plotted with yellow, green, and blue points respectively. The eDiary reported sleep and wake times are indicated by black dashed lines. For both patients, the days can be divided into two types of activity count patterns: a period of time where the log activity counts are relativity constant with intermittent drops – count derived day – and a period characterized by zero to low activity with periodic spikes of activity counts of least 2-3 logs – count derived night. The clinical meaning of both the nighttime spikes and relatively constant daytime activity is unclear without evidence from either video logs or caregiver reports.

Comparing both the scored sleep and count derived night periods to the caregiver reported sleep times, notice that the quality of the caregiver reporting differs between patients (b) (6) and (b) (6). For patient (b) (6), the actigraphy watch implied that the patient may have stayed awake after the caregiver reported initiation of sleep. For patient (b) (6), the eDiary time to sleep is close to the switch between count derived day and count derived night. However, patient (b) (6) may wake up before the caregiver reports awakening. Without further validation, these impressions are limited to the data reported in Figure 1 and Figure 2.

Figure 1: Activity Counts, Wear Status, and Sleep Status a Sample Patient ((b) (6)) on a Sample Day (Day 196)

Figure 2: Activity Counts, Wear Status, and Sleep Status for Two Patients on Multiple Days

Anchoring DHT-generated data to a known clinical scale or, as in this case, to a patient reported outcome is a necessary step development process to be able to measure the face-validity of DHT data (analytical validation). However, if high accuracy in wake detection is the purpose of the actigraphy measurement, to increase the specificity of the algorithm to an acceptable level, part of this step in the development process should have been conducted in a laboratory setting with either the gold standard for sleep assessment (i.e., polysomnography), or video recording, to be able to "train" and verify the algorithm to detect wake as true wake.

An additional complexity is represented by the clinical characteristics of the population of subjects with SMS, whose sleep architecture and level of activity during both sleep and wake may differ from healthy individuals.

The claimed algorithm performance metrics were estimated in a healthy population. In an adult population with sleep disorders, the sleep scoring algorithm uses a weighted average of ±2 minutes on either side of each minute epoch. This average is then compared to a threshold. If the average is greater than the threshold, the minute epoch is scored as awake. Although this algorithm may be effective in detecting sleep in adults with sleep disorders patients, the Applicant provided no evidence about how the spikes of activity counts could affect this algorithm in patients with SMS. In addition, the Applicant did not submit any information about the patient behavior that created the activity count spikes or how the activity counts are derived from the measured accelerations to help understand the spikes. In addition, transparent definitions of an activity count that can be compared across different activity monitors could also aid regulatory decision making.

Conclusion

The review team concluded that the actigraphy data could not be used to support regulatory decision making on the effectiveness of tasimelteon in the treatment of sleep disturbances in SMS.

APPENDIX B: INTERACTIVE REVIEW QUESTIONS RELATED TO ACTIWATCH

Question 1. Make and model of the actigraphy watch used in the study
Vanda Response*: The actigraphy watch used in Study VP-VEC-162-2401 was the Philips Actiwatch Spectrum Classic.*

Question 2. Type of sensor(s) and sensor measurement properties (accuracy, precision, error) of the watch
Vanda Response*: The motion sensor is a solid-state accelerometer, range 0.5 – 2 G, resolution 100 counts or 0.02 G, sampling at 32 Hz. The off-wrist sensor is a capacitor formed by 2 metal plates as part of a bi-stable multivibrator, with on-wrist activation distance of < 2 mm. The light sensor is a radiometer recording RGB irradiance or weighted white light illuminance.*

Question 3. Watch software and software settings used during the study
Vanda Response*: The study used Actiware CT software. Please refer to the Actiware CT Software Requirements for the VP-VEC-162-2401 Study located in Appendix A.*

Question 4. Training materials provided to patients and caregivers for use of the actigraphy watch
Vanda Response*: Training materials provided to parents and caregivers for use of the actigraphy watch are provided in Appendices B and C.*

Question 5. How watch tolerability and compliance were defined during the Screening, Treatment, and Open-Label phases
Vanda Response: *Tolerability was judged by the patient caregiver. Caregivers were instructed to inform the study coordinator if the patient refused to wear the watch. Participation in all study phases including the Screening, Treatment, and Open-Label phases was not affected by whether or not the patient wore the actigraphy watch. There was no significant compliance restriction for inclusion in the analysis for the Screening, Treatment, and Open-Label phases. Compliance was determined by the same diary compliance requirements (as at least 14 day data for each period to allow the 50% worst calculation); however, this rule was not applied as there was sufficient data in patients who wore the watch and whose data was scorable.*

Question 6. How it was determined whether the actigraphy watch was being worn during a given time period
Vanda response*: The Spectrum Classic includes an off-wrist sensor that indicates when the subject is not wearing the device; as described above, it is a capacitor with on-wrist activation distance of < 2 mm.*

Question 7. The data processing pipeline for the actigraphy watch data, starting with when the actigraphy watch measured an acceleration and ending with the analysis datasets. This should include information about how the data was transmitted from the watch to a server, any signal processing procedures, and all algorithms used to process the data to determine sleep and activity status.
Vanda response*: For Study VP-VEC-162-2401, the Spectrum Classic device captures motion and light data during wear by the patient. Once removed from the patient, the Spectrum Classic*

device is then connected to a Spectrum Dock, which is then connected via USB connection to a site computer with the study-specific Actiware CT software installed. The Dock enables the data collected on the Spectrum Classic device to be downloaded by the Actiware software onto the site computer. For this study, the datasets are then sent by site personnel via e-mail to the Motion Biosensors scoring team. A Motion Biosensors scoring team member stores the received datasets on a secure Philipsowned server. The Motion Biosensors team uses the Actiware software to score the received data for sleep and activity endpoints via validated algorithms within the software. The endpoints are then sent back to Vanda via password-protected e-mail.

Question 8. Performance metrics for all algorithms used to process the data into sleep parameters and differentiate sleep from wake (sensitivity, specificity, etc.)
Vanda response: *These metrics vary based on the patient population being studied. Kushida et al. determined the Actigraphy algorithm capable of detecting sleep with sensitivity of 0.96 (medium-threshold algorithm), specificity of 0.38, and accuracy of 0.77 when compared with polysomnography. Kushida et al. (2001). Comparison of Actigraphic, Polysomnographic, and Subjective Assessment of Sleep Parameters in Sleep-Disordered Patients. Sleep Medicine. 2(5). 389-96.*

Reviewer's comment: The sponsor is correct that there are many variables that affect the device's performance at differentiating sleep from wake, and this includes the specific patient population being studied.

Question 9. Any feasibility studies with the actigraphy watch that have been conducted in the SMS or similar patient population that may have been conducted by the actigraphy watch vendor and/or have been described in the scientific literature
Vanda response*: The Sponsor conducted an observational study (VP-1401) in patients with Smith-Magenis Syndrome in which actigraphy was collected prior to the efficacy study (VP-VEC-162-2401). The same actigraphy vendor was used in Studies VP-1401 and VP-VEC-162-2401. A listing of relevant scientific literature with the actigraphy watch that have been conducted in the SMS or similar patient population is shown below.*

[1] G. Agar, C. Oliver, J. Trickett, L. Licence, and C. Richards, "Sleep disorders in children with Angelman and Smith-Magenis syndromes: The assessment of potential causes of disrupted settling and night time waking," *Res. Dev. Disabil.*, vol. 97, 2020.

[2] J. Trickett *et al.*, "Sleep in children with smith-magenis syndrome: A case-control actigraphy study," *Sleep*, vol. 43, no. 4, 2020.

[3] J. Trickett *et al.*, "Multi-Method Assessment of Sleep in Children With Angelman Syndrome: A Case–Controlled Study," *Front. Psychiatry*, vol. 10, 2019.

[4] A. C. M. Smith, R. S. Morse, W. Introne, and W. C. Duncan, "Twenty-four-hour motor activity and body temperature patterns suggest altered central circadian timekeeping in Smith–Magenis syndrome, a neurodevelopmental disorder," *Am. J. Med. Genet. Part A*, vol. 179, no. 2, pp. 224–236, 2019.

Please note that the vendor Mini-Mitter Co was acquired by Respironics in 2005 and Respironics was acquired by Philips in 2008. Therefore, some publications may refer to the devices as being produced by Mini-Mitter, Respironics, or Philips Respironics.

Question 10. Any additional supportive evidence that the actigraphy watch used in your study provides valid sleep measurements in patients with SMS (or other neurodevelopmental disorders). The evidence should be from patients of similar ages and with the same wear location and data processing algorithms as in your study.
***Vanda response**: In the scientific literature described above in Vanda's response to Question 9, the supportive evidence was collected in patients of similar ages, wear location, and data processing algorithms as in the VP-VEC-162-2401 study (Table 1).*

Table 1. Study demographics and actigraphy collection procedures

Study	**Diagnosis, N**	**Age range** Mean (SD), Range	**Wear location**	**Data processing algorithm**
Study VP-VEC-162-2401 (ITT)	SMS, 25	17.4 (9.46), 3-39	non-dominant wrist	Actiware
Agar et al 2020	AS, 12 SMS, 11	8.0 (2.81), 4-13 8.8 (2.18), 6-15	wrist or ankle	Actiware
Smith et al 2019	SMS, 47	10.2 (7.0), 2-32	non-dominant wrist	Actiware
Trickett et al 2019	SMS, 20	8.7 (2.7), 4-15	wrist or ankle	Actiware
Trickett et al 2019	AS, 22	9.4 (3.7), 4-13	wrist or ankle	Actiware

AS = Angelman syndrome; SMS = Smith-Magenis Syndrome; ITT = Intent-to-Treat Population

Question 11. All information collected from the patient caregivers in the sleep diary
***Vanda Response**: The sleep diary contained a nighttime post sleep questionnaire and a daytime sleep questionnaire. Please refer to the annotated CRFs located in Appendix D (version dated 28 Oct 2015) and Appendix E (version dated 29 Apr 2016). The modification was an addition of the study drug questionnaire module. There were no changes to the sleep diary questions between versions.*

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LATRICE WILSON
12/01/2020 03:26:12 PM

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 214517
Assessment 1

Drug Product Name	Tasimelteon 4 mg/mL suspension
Dosage Form	suspension
Strength	4 mg/mL
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Vanda Pharmaceuticals Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 7; eCTD 0007	1 Jun 20	All, resubmission
Supporting document 11; eCTD 0011	24 Jul 20	Biopharmaceutics
Supporting document 15; eCTD 0015	21 Aug 20	Process and manufacturing
Supporting document 17; eCTD 0016	28 Aug 20	Process and manufacturing
Supporting document 21; eCTD 0021	21 Sep 20	Drug product
Supporting document 26; eCTD 0026	9 Oct 20	Drug product
Supporting document 28; eCTD 0028	15 Oct 20	Process and manufacturing
Supporting document 30; eCTD 0030	20 Oct 20	Drug product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Larry Perez	Donna Christner
Drug Product	Mariappan Chelliah	Julia Pinto
Manufacturing	Joanne Wang	N/A

Microbiology	Shannon Heine	Daniel Schu
Biopharmaceutics	Yang Zhao	T-Chen Wu
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	Mariappan Chelliah	Julia Pinto

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommends approval for this application based on drug substance, drug product, process and facilities, biopharmaceutics and microbiology reviews.

The proposed shelf-life of 36 months, when stored refrigerated between 2° and 8°C (36° and 46° F) is acceptable.

The applicant has agreed to the following postmarketing commitments (PMC):
Biopharmaceutics - 3932-1 Study to optimize the in vitro dissolution method
Process and facilities - 3932-2 Studies to finalize Critical Process Parameter for the proposed (b) (4) commercial batch size.
Drug product - 3932-3 Conduct a formal palatability study of the formulation in a clinical trial
See CMC PMC template dated 27 Oct 20 in DARRTS for additional details.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Tasimelteon 4 mg/mL suspension is white to yellow opaque oral suspension packaged in (b) (4) (b) (4) bottles with white (b) (4) caps.

The proposed shelf-life of 36 months, when stored refrigerated between 2° and 8°C (36° and 46° F) is acceptable.

Originally this NDA was filed 21 Jan 20 and was refuse-to-file with a letter sent 12 Mar 20. This review is looking at the resubmission submitted 1 Jun 20.

Proposed Indication(s) including Intended Patient Population	Patients with sleep disorder in Smith-Magenis Syndrome (SMS)
Duration of Treatment	chronic
Maximum Daily Dose	20 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance tasimelteon is a synthetic small molecule that was approved under NDA205677 in January 2014 for the treatment of non-24-hour sleep–wake disorder.
It is commercially manufactured by (b) (4) with (b) (4) as an alternate manufacturer. The drug substance is stored (b) (4) immediately prior to its use in the drug product manufacturing (both for capsule as detailed in NDA205677 and for suspension as detailed in NDA214517).
Based upon the available stability data, the proposed retest period of (b) (4) (b) (4) Similarly, the proposed (b) (4) month retest period (b) (4) used in the suspension drug product has been adequately justified.

Drug Product: Adequate

The proposed commercial formulation is same as that was used in the BE clinical study.
Tasimelteon drug substance has an inherent bitter taste. Therefore, the palatability of this pediatric formulation is critical. Although the formulation was optimized to have the best possible taste, it's palatability was not formally assessed in a clinical study. However, the Applicant has agreed to a postmarketing commitment to conduct a formal palatability assessment in a clinical study.

Although particle size distribution (PSD) is a critical quality attribute of the suspension product, the particle size data in this product is essentially dominated by the two excipients (b) (4) and (b) (4) Therefore, while the PSD can be used as a quality control test, it should not be used as a true measure of the drug substance's physical nature in the drug product.

The Applicant provided stability data with durations of ≥12 months for only two batches per the proposed commercial packaging configurations. These batches were manufactured by (b) (4). To determine the shelf-life, the Applicant relies on the stability data from the supportive batches that were manufactured by (b) (4). The only trending noted is decrease in assay of ascorbic acid. Because ascorbic acid is used as (b) (4) this is not unexpected. The proposed storage condition is refrigerated, 2°C to 8°C (36°F to 46°F).

The suspension is packaged in two different fill configurations: 2 oz. (b) (4) bottles (48 mL) and 6 oz. (b) (4) bottles (158 mL). The bottles will be co-packaged with a press-in bottle adapter and a dosing syringe. The Applicant performed adequate extractable studies using the 2 oz. bottles. The low levels of extractables in the 2 oz. bottles support that a leachable study is not required. The comparative contact surface area of the container per mL of suspension demonstrates that the 2 oz. bottle is the worst case for extractable and the data for this container can be extrapolated to the 6 oz. bottles.

The proposed shelf-life of 36 months, when stored under refrigeration is acceptable.

Labeling: Adequate

Manufacturing: Adequate

This DP is the oral suspension dosage form of the CDER approved NDA 205677 (capsule dosage form). The manufacturing process comprises (b) (4) (b) (4) Since the manufacturing process is fairly standard, and the manufacturing site has demonstrated sufficient understanding of the process and their past experience suggested capability, we accepted their proposal of finalizing the range of the Critical Process Parameter for the (b) (4) scale upon completion of the manufacturing process validation batches. The PMC number is 3932-2.

Both DS manufacturing sites are used in the manufacture of the capsule dosage form, and they are recommended for approval based on their inspectional history. The DP manufacturing site is also recommended for approval, but a post-approval inspection is recommended, to ensure that they are able to carry out (b) (4) filling consistently for more than just a limited number of batches.

Biopharmaceutics: Adequate

Review Objective: The Biopharmaceutics Review evaluated the adequacy of (1) the proposed dissolution method and acceptance criterion for QC testing of the proposed drug product at batch release and during stability, and (2) bridging between batches/drug product manufactured at (b) (4) site.

ASSESSMENT:
1. Dissolution Method and Acceptance Criterion: The following table summarizes the proposed dissolution method for batch release and stability testing. The current dissolution rotation speed appears too high for an oral suspension drug product because of very rapid dissolution ((b) (4)% dissolution at (b) (4)minutes) under this study condition; therefore, dissolution rotation speed needs to be optimized, i.e., investigating lower speeds. A post marketing commitment (PMC) will be issued for the Applicant to collect additional data optimizing dissolution rotation speed. Based on the dissolution data for clinical batches, the following dissolution acceptance criterion is deemed acceptable for the proposed Tasimelteon suspension.

Current dissolution method and acceptance criterion for Tasimelteon suspension

USP Apparatus	Speed	Medium/Temp	Volume (mL)	Acceptance Criterion
USP 2 (paddle)	50 rpm	0.1N HCl/37 °C	500	Q = (b) (4)% at 15 minutes

2. Bridging between different drug product manufacturing sites: The Applicant established the bridge for drug product batches manufacturing at (b) (4) site with comparable dissolution profile data, using the proposed dissolution method. The bridging approach is acceptable.

3. Post-Marketing Commitment: The selection of paddle speed for the proposed dissolution method (USP 2 at 50 rpm, in 500 mL of 0.1N HCl) is not adequately investigated and justified. The selected 50 rpm is considered too fast for an oral suspension drug product, resulting in

nearly complete dissolution at the first time-point (b) (4) minutes, while paddle speed of (b) (4) rpm resulting incomplete dissolution (b) (4). The Division of Biopharmaceutics accepted the currently proposed dissolution method and acceptance criterion on an interim basis. The Applicant was recommended to investigate slower paddle speeds between (b) (4), collect dissolution profile data using the optimal dissolution method, and propose new dissolution acceptance criterion based on newly generated dissolution profile data using the optimal method as a Post-Marketing Commitment (PMC) (see Appendix 2). On October 23, 2020, the Applicant agreed to the terms of the PMC.

RECOMMENDATION:
The following dissolution method and acceptance criterion are acceptable on an interim basis for the quality control testing of Tasimelteon suspension, 4 mg/mL, at release and on stability:

Current dissolution method and acceptance criterion for Tasimelteon suspension

USP Apparatus	Speed	Medium/Temp	Volume (mL)	Acceptance Criterion
USP 2 (paddle)	50 rpm	0.1N HCl/37 °C	500	Q = (b) (4)% at 15 minutes

From the Biopharmaceutics perspective, NDA 214517 for Tasimelteon suspension, 4 mg/mL is recommended for approval with a PMC pertaining to the optimization of dissolution method.

Microbiology (if applicable): Adequate

The applicant provided an acceptable microbial limits specification for the drug product. The applicant has provided acceptable method suitability testing data for microbial limits. The applicant has submitted stability data to date supports the microbiological quality of the subject drug product. (b) (4) effectiveness has been demonstrated at the minimum label claim for (b) (4) content.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations / Comments**

(b) (4)

Assay, Stability		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/ equipment • Site	L		Acceptable	
Physical stability (phase separation)	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	L		Acceptable	
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	L		Acceptable	
Dosing accuracy	• Dosing device • Formulation • Process parameters • Scale/ equipment • Site	L		Acceptable	
Palatability	• Formulation • Excipient change • Process parameters • Scale/ equipment • Site	M		Acceptable	
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	L		Acceptable	
Leachables	• Formulation • Container closure • Process parameters • Scale/ equipment • Site	M		Acceptable	

Dissolution for Suspension only	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	L	(b) (4)	Acceptable	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments

(b) (4)	III	(b) (4)	4		
	III		4		
	III		4		
	III		4		
	III		4		
	III		4		
	III		4		
	III		4		
	III		4		

Action codes for DMF Table:
1 – DMF Reviewed.
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
NDA	205677	Tasimelteon capsules
IND	054776	

IND	123408	
IND	(b) (4)	

0. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

Screenshot of Inspection View in Panorama take 29 Oct 20

(b) (4)

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: adequate

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	HETLIOZ	adequate
Established name(s)	Tasimelteon	adequate
Route(s) of administration	Oral	adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Capsules: 20 mg Oral suspension: 4 mg/mL	adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	n/a
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	n/a	n/a

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Shake HETLIOZ Oral Suspension well for at least (b) (4) seconds before every administration. Remove seal and insert press-in bottle adapter (included in the package) into the neck of the bottle until a tight seal is made. (b) (4) Turn the bottle upside down and withdraw the prescribed amount of HETLIOZ® from the bottle. Leave the press-in bottle adapter in place on bottle neck and replace cap on bottle.	Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Capsules and oral suspension	adequate
Strength(s) in metric system	Capsules: 20 mg Suspension: 4 mg per mL	adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	n/a	n/a
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	white to slightly yellow opaque suspension in (b) (4) mL or (b) (4) mL bottles.	adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	n/a
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	n/a	n/a

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	HETLIOZ, tasimelteon	adequate
Dosage form(s) and route(s) of administration	Capsule, oral Oral suspension	adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	n/a	n/a
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	n/a	n/a
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	n/a
Statement of being sterile (if applicable)	n/a	n/a
Pharmacological/ therapeutic class	Yes	adequate
Chemical name, structural formula, molecular weight	Yes	adequate
If radioactive, statement of important nuclear characteristics.	n/a	n/a
Other important chemical or physical properties (such as pKa or pH)	n/a	n/a

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	n/a	n/a
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	n/a	n/a

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Capsules and oral suspension	adequate
Strength(s) in metric system	Capsules: 20 mg suspension: 4 mg/mL	adequate
Available units (e.g., bottles of 100 tablets)	Capsules: bottles of 30 Suspension: bottles of 48 mL and 154 mL	adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	white to slightly yellow opaque suspension	adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	n/a
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	n/a	n/a

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Protect from exposure to light.	Per the ICH photostability studies, the drug product is not light sensitive. We will ask the Applicant to justify this statement.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	n/a	n/a
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	5°C (41°F); excursions permitted to 2°C to 8°C (36°F t o 46°F)	adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	n/a	n/a
Include information about child-resistant packaging	Each bottle has a child resistant cap.	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Vanda Pharmaceuticals Inc. Washington, D.C. 20037 USA www.hetlioz.com	adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): n/a

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Hetlioz LQ (tasimelteon)	The initially submitted carton labels had "Hetlioz" as the trade name. However, in SN0019, the Applicant revised the trade name to "Hetlioz LQ". If this trade name is approved, the trade name will be harmonized across all the labeling.
Dosage strength	4 mg/mL	adequate
Route of administration	ROA is missing	We will be asking the Applicant to replace "(b) (4)" with "Oral Suspension"
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	n/a	n/a
Net contents (e.g. tablet count)	(b) (4)	Since the Applicant has proposed to revise the labeled volume based on the deliverable volume, we will ask the Applicant to edit the net contents accordingly.
"Rx only" displayed on the principal display	Yes	adequate
NDC number	NDC numbers are included, though all the digits are not defined yet.	This is acceptable at this time. Once the labeling is finalized, they will contain the all the digits.
Lot number and expiration date	Yes	

Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store in refrigerator at 5°C (41 °F); excursions permitted to 2°C to 8°C (36°F to 46 °F)	adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	n/a	n/a
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	n/a	n/a
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	n/a
Bar code	Yes	adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes	adequate
Medication Guide (if applicable)	n/a	n/a
No text on Ferrule and Cap overseal	n/a	n/a
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	n/a	n/a
And others, if space is available	n/a	n/a

Assessment of Carton and Container Labeling: *Adequate*
The carton and container labels as proposed do not meet some of the labeling requirement as commented above. However, these are minor edits. We will ask the Applicant to edit them to ensure that they meet the appropriate labeling regulations.

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation:
Adequate

Primary Labeling Assessor: Mariappan V. Chelliah

Secondary Assessor: Julia Pinto

Mariappan Chelliah

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Date: 10/26/2020 11:28:12AM
GUID: 5399cb2c00032b7c21877aa0d4d5f794

Julia Pinto

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BIOPHARMACEUTICS

NDA: 214517-ORIG-1-RESUB-7

Drug Product Name/Strengths: Tasimelteon Suspension/4 mg/mL in [redacted] (b) (4) container closure system

Route of Administration: Oral

Applicant Name: Vanda Pharmaceuticals Inc.

Indication: Treatment of the Sleep Disorder Associated with Smith-Magenis Syndrome

List of Reviewed Submissions:
01/13/2020 (Original submission)
06/01/2020 (Resubmission)
07/24/2020 (Response to the Biopharmaceutics Information Request)

Primary Reviewer: Yang Zhao, Ph.D.
Secondary Reviewer: Ta-Chen Wu, Ph.D.

REVIEW SUMMARY:

The Applicant submitted NDA 214517 seeking approval for Tasimelteon Suspension, 4 mg/mL, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for the treatment of the Sleep Disorder in Smith-Magenis Syndrome (SMS).

Review Objective: The Biopharmaceutics Review evaluated the adequacy of **(1)** the proposed dissolution method and acceptance criterion for QC testing of the proposed drug product at batch release and during stability, and **(2)** bridging between batches/drug product manufactured at [redacted] (b) (4) site.

ASSESSMENT:

1. **Dissolution Method and Acceptance Criterion:** The following table summarizes the proposed dissolution method for batch release and stability testing. The current dissolution rotation speed appears too high for an oral suspension drug product because of very rapid dissolution [redacted] (b) (4) under this study condition; therefore, dissolution rotation speed needs to be optimized, i.e., investigating lower speeds. A post marketing commitment (PMC) will be issued for the Applicant to collect additional data optimizing dissolution rotation speed. Based on the dissolution data for clinical batches, the following dissolution acceptance criterion is deemed acceptable for the proposed Tasimelteon suspension.

Current dissolution method and acceptance criterion for Tasimelteon suspension				
USP Apparatus	**Speed**	**Medium/Temp**	**Volume (mL)**	**Acceptance Criterion**
USP 2 (paddle)	50 rpm	0.1N HCl/37 °C	500	Q = (b) (4)% at 15 minutes

2. **Bridging between different drug product manufacturing sites:** The Applicant established the bridge for drug product batches manufacturing at (b) (4) site with comparable dissolution profile data, using the proposed dissolution method. The bridging approach is acceptable.

3. **Post-Marketing Commitment:** The selection of paddle speed for the proposed dissolution method (USP 2 at 50 rpm, in 500 mL of 0.1N HCl) is not adequately investigated and justified. The selected 50 rpm is considered too fast for an oral suspension drug product, resulting in nearly complete dissolution at the first time-point (b) (4) minutes, while paddle speed of (b) (4) rpm resulting incomplete dissolution (b) (4). The Division of Biopharmaceutics accepted the currently proposed dissolution method and acceptance criterion on an interim basis. The Applicant was recommended to investigate slower paddle speeds (b) (4), collect dissolution profile data using the optimal dissolution method, and propose new dissolution acceptance criterion based on newly generated dissolution profile data using the optimal method as a Post-Marketing Commitment (PMC) (see Appendix 2). On October 23, 2020, the Applicant agreed to the terms of the PMC.

RECOMMENDATION:

The following dissolution method and acceptance criterion are acceptable **on an interim basis** for the quality control testing of Tasimelteon suspension, 4 mg/mL, at release and on stability:

Current dissolution method and acceptance criterion for Tasimelteon suspension				
USP Apparatus	**Speed**	**Medium/Temp**	**Volume (mL)**	**Acceptance Criterion**
USP 2 (paddle)	50 rpm	0.1N HCl/37 °C	500	Q = (b) (4)% at 15 minutes

From the Biopharmaceutics perspective, NDA 214517 for Tasimelteon suspension, 4 mg/mL is recommended for approval with a PMC pertaining to the optimization of dissolution method.

BIOPHARMACEUTICS ASSESSMENT

1. BACKGROUND OF THE PROPOSED DRUG PRODUCT:

1.1 Regulatory history:

On 01/31/2014, FDA approved HETLIOZ (Tasimelteon Capsules, 20 mg, NDA-205677, manufactured by Vanda Pharmaceuticals, Inc.), a melatonin agonist, for the treatment of Non-24 Hour Sleep Wake Disorder. The same Applicant is proposing a formulation in the pediatric population (ages 3 to (b) (4) years) for treatment of sleep disorders in Smith Magenis Syndrome (SMS) patients. The Applicant conducted a combined open label, double-blind, randomized, two-period crossover study (VP-VEC-162-2401) evaluating the effects of tasimelteon on sleep disturbances of pediatrics and adults with SMS.

Per Applicant's proposed labeling, Tasimelteon suspension 4 mg/mL is recommended to be taken without food and the dose should be given based on weight, with 0.7 mg/kg one hour before bedtime for ≤28 kg body weight and 20 mg one hour before bedtime for >28 kg body weight.

1.2 Composition:

Tasimelteon suspension 4 mg/mL is white to yellow opaque suspension, with formulation composition shown in Table 1. (b) (4)

Table 1. Qualitative and quantitative composition of Tasimelteon Suspension, 4 mg/mL

Ingredient	%w/v	Amount (mg/mL)
Tasimelteon	(b) (4)	4.0
Polysorbate 80		(b) (4)
Microcrystalline cellulose and carboxymethylcellulose sodium (b) (4)		
Mannitol		
Sucrose		
Sucralose		
Sodium chloride		
(b) (4) cherry (b) (4)		
Ascorbic acid		
Sodium benzoate		
(b) (4) water		

2. PROPOSED DISSOLUTION METHOD AND ACCEPTANCE CRITERION:

The proposed dissolution method and dissolution acceptance criterion for Tasimelteon suspension are as follows:

Proposed dissolution method and acceptance criterion for Tasimelteon suspension				
USP Apparatus	**Speed**	**Medium/Temp**	**Volume (mL)**	**Acceptance Criterion**
USP 2 (paddle)	50 rpm	0.1N HCl/37 °C	500	Q = (b) (4)% at 15 minutes

As outlined in ***Appendix 1***, in the original submission dated 01/13/2020 and re-submission dated 06/01/2020, the Applicant did not provide a dissolution method development report or data/information to support the selection of dissolution conditions. In the Information Request dated 07/02/2020, the Applicant was requested to provide a dissolution method development report for the proposed suspension product. In the Response dated 07/24/2020, the Applicant provided a dissolution method development report[1] in support of the NDA. Per method development report (page 27)[2], 5 mL of the sample (i.e., 20 mg tasimelteon) was used for dissolution testing.

(b) (4)

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(b) (4)

Reviewer's Assessment on Proposed Dissolution Method:

The Applicant proposed a dissolution method (USP 2 at 50 rpm, in 500 mL of 0.1N HCl). This Reviewer considers that the selection of USP 2 apparatus, dissolution medium of 0.1N HCl and 500 mL volume is reasonable. However, the selection of paddle speed needs to be further evaluated and optimized due to very rapid dissolution (b) (4) at 50 rpm and incomplete dissolution up to (b) (4). This issue could not be addressed during the review cycle because of issues related to short review time and insufficient time to generate new data. The Applicant was recommended to test paddle speed range (b) (4), typically for oral suspension drug products. Under a PMC, the Applicant will need to test different paddle speed, (b) (4) to optimize the dissolution method, collect additional dissolution profile data based on the selected dissolution test condition, and proposed a new acceptance criterion based on the newly generated data.

The Division considered that the currently proposed dissolution method [USP 2 (paddle) at 50 rpm, in 500 mL of 0.1N HCl] is acceptable as an interim basis.

2.6 Dissolution profile data:

The Applicant provided dissolution profile data for clinical and registration batches manufactured at (b) (4) site. Note that Batches 3161998 and 3161956 were manufactured at (b) (4) site, and Batches GMP18020, GMP18021, GMP19004, GMP19005, GMP19041 were manufactured at (b) (4) site. More than (b) (4)% dissolution at 15 minutes was observed for all clinical and registration batches (Table 6).

Table 6. Dissolution profile data for Tasimelteon suspension clinical and registration batches using the proposed method [USP 2 (paddle) at 50 rpm, in 500 mL of 0.1N HCl]

Batch	% Dissolved (n = 12)							
GMP18020 (clinical/stability)	**Time (min)**	**5**	**10**	**15**	**20**	**30**	**45**	**60**
	Range (%)	(b) (4)						
	Mean (%)	92	92	92	92	91	92	92
	%RSD	2.6	2.6	2.5	2.5	2.4	2.3	2.6
GMP18021 (clinical/stability)	**Time (min)**	**5**	**10**	**15**	**20**	**30**	**45**	**60**
	Range (%)	(b) (4)						
	Mean (%)	98	98	97	96	96	96	96
	%RSD	0.8	0.8	0.7	0.7	0.7	0.7	0.8
GMP19004 (stability)	**Time (min)**	**5**	**10**	**15**	**20**	**30**	**45**	**60**
	Range (%)	(b) (4)						
	Mean (%)	96	96	96	96	95	95	95
	%RSD	1.7	2.0	1.8	1.7	2.1	2.0	1.9
GMP19005 (stability)	**Time (min)**	**5**	**10**	**15**	**20**	**30**	**45**	**60**
	Range (%)	(b) (4)						
	Mean (%)	97	97	97	97	97	97	97
	%RSD	1.0	1.3	0.9	1.1	1.0	1.0	1.2
GMP19041 (stability)	**Time (min)**	**5**	**10**	**15**	**20**	**30**	**45**	**60**
	Range (%)	(b) (4)						
	Mean (%)	97	101	101	101	100	100	100
	%RSD	2.1	1.4	1.5	1.4	1.4	1.6	1.7
3161998 (clinical/stability)	**Time (min)**	**5**	**10**	**15**	**20**	**30**	**45**	**60**
	Range (%)	(b) (4)						
	Mean (%)	95	99	100	101	102	103	103
	%RSD	3.6	2.0	1.4	0.9	0.6	0.6	0.7
3161956 (clinical/stability)	**Time (min)**	**5**	**10**	**15**	**20**	**30**	**45**	**60**
	Range (%)	(b) (4)						
	Mean (%)	89	97	100	101	102	102	103
	%RSD	5.0	3.4	2.6	2.2	1.8	1.5	1.5

2.7 Dissolution stability data:

In the original submission dated 01/13/2020, the Applicant submitted dissolution data at 15 minutes for stability samples. All dissolution data at 15 minutes for stability samples meet S1 testing. No dissolution profile data were provided for stability samples.

2.8 Dissolution acceptance criterion:

Based on the provided dissolution data of clinical batches and registration batches, this Reviewer considered that the Applicant's proposed dissolution acceptance criterion of "Q = (b) (4)% at 15 minutes" is acceptable as an interim basis. Once an optimal dissolution method is available under the PMC, newly generated dissolution profile data will be assessed and dissolution acceptance criterion will be determined.

3. BRIDGING OF PRODUCTS MANUFACTURED AT DIFFERENT SITES:

The Applicant manufactured Tasimelteon uspension 4 mg/mL clinical batches (including Batches 3132113, 3156523, 3161998, 3151804, 3161956) at (b) (4). The Applicant reported that (b) (4) site was unable to support scaleup and commercial manufacturing of the proposed Tasimelteon suspension and, therefore, manufacturing activities were transferred to (b) (4). The Applicant reported that (b) (4) site used the same formulation composition and manufacturing process as (b) (4), in addition, (b) (4) site used equipment of similar design and principle of operation to the equipment at (b) (4). Batch GMP19041 manufactured at (b) (4) site used drug substance of (b) (4) source, instead of (b) (4) source used for manufacturing other batches.

Dissolution profile data for the proposed Tasimelteon suspension manufactured at both (b) (4) site and (b) (4) site were similar with more than (b) (4)% dissolution at 15 minutes (Table 6). Dissolution similarity factors were not calculated due to the very rapid dissolution.

Reviewer's Assessment on Bridging of Products Manufactured at Different Sites:

Batches manufactured at (b) (4) site and (b) (4) site have similar and very rapid dissolution profiles using the proposed dissolution method [USP 2 (paddle) at 50 rpm, in 500 mL of 0.1N HCl]. This Reviewer considers the bridging among batches manufactured at different sites and batches manufactured with different drug substance sources are adequately established.

4. POST-MARKETING COMMITMENT:

The selection of paddle speed for the proposed dissolution method (USP 2 at 50 rpm, in 500 mL of 0.1N HCl) is not adequately investigated and justified. The selected 50 rpm is considered too fast for an oral suspension drug product, resulting in nearly complete dissolution at the first time-point (b) (4) minutes. Paddle speed of (b) (4) rpm generated (b) (4)% dissolution at (b) (4) minutes. The Biopharmaceutics Reviewer has recommended that a range of slower paddle speeds (b) (4)

(b) (4) typically for oral suspension products, be investigated for the proposed oral suspension. The studies to be performed under this PMC agreement are aimed toward developing an optimal dissolution method to ensure adequate quality control at the time of batch release and during stability testing of the Tasimelteon Suspension. This issue could not be adequately addressed during the review cycle because of short review time and the need of dissolution stability data generated using an optimized dissolution method. Therefore, the current dissolution method and acceptance criterion are accepted only on an interim basis. As the development of a more optimized dissolution method may take several months, the Applicant will be allowed to investigate various test conditions, collect dissolution profile data using the new method, and propose new dissolution acceptance criterion as a PMC (see ***Appendix 2***).

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	214517
Assessment Cycle Number	1
Drug Product Name/ Strength	Tasimelteon, 4 mg/mL
Route of Administration	oral suspension
Applicant Name	Vanda Pharmaceuticals, Inc.
Therapeutic Classification/ OND Division	Melatonin Receptor Agonist/OND/ODEI/DNP
Manufacturing Site	(b) (4)
Method of Sterilization	N/A (non-sterile product)

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
Seq 0001 (1)	13 January 2020
Seq 0003 (3)	6 February 2020
Seq 0004 (4)	14 February 2020
Seq 0007 (7)	1 June 2020
Seq 0011 (11)	24 July 2020
Seq 0015 (15)	21 August 2020

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The subject drug product is a white to yellow opaque oral suspension presented in either 2 oz. ((b) (4) fill volume) or 6 oz. ((b) (4) fill volume) bottles indicated for the treatment of Non-24-Hour Sleep-Wake Disorder in Smith-Magenis Syndrome in adults and children 3 years old and older. A deficiency was conveyed to the applicant in a Process and Facilities Information Request dated 19 August 2020.

The submission is recommended for approval from the standpoint of product quality microbiology.

Concise Description of Outstanding Issues: N/A

Supporting Documents: N/A

S DRUG SUBSTANCE

The manufacturing process for the drug substance is not reviewed because the drug product is non-sterile.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product**

  The subject drug product is a white to yellow opaque oral suspension presented in either 2 oz. ((b) (4) fill volume) or 6 oz. ((b) (4) fill volume) bottles.

- **Drug product composition**

Ingredient	mg per mL	Function
Tasimelteon	4.0	Active ingredient
Microcrystalline cellulose/carboxy methyl cellulose (b) (4)	(b) (4)	
Mannitol		
Ascorbic acid		
Sodium benzoate		
Sucrose		
Sodium chloride		
Polysorbate 80		
Sucralose		
(b) (4) cherry (b) (4)		
(b) (4) water		

- **Description of container closure system**

Configuration	Component	Description	Manufacturer
2 oz. (b) (4) fill volume	Bottle	Round, amber, (b) (4) bottle	(b) (4)
	Closure	Closure, white, (b) (4) child-resistant, (b) (4)	
	Induction seal liner	(b) (4)	
6 oz. (b) (4) fill volume	Bottle	oval, amber, (b) (4)	
	Closure	Closure, white, (b) (4) child-resistant, (b) (4)	
	Induction seal liner	(b) (4)	

Assessment: Adequate
The applicant provided an adequate description of the drug product composition and the container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

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Valerie Amspacher

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/s/

VALERIE R AMSPACHER
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