CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214517Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	Resubmission: NDA and Efficacy Supplement
Application number(s)	214517 and 205677-007
Priority or standard	Priority
Submit date(s)	6/1/2020
Received date(s)	6/1/2020
PDUFA goal date	12/1/2020
Division/office	Division of Psychiatry (DP)
Review completion date	11/30/2020
Established/proper name	Tasimelteon
(Proposed) proprietary name	Hetlioz
Pharmacologic class	Melatonin receptor agonist
Code name	VEC-162
Applicant	Vanda Pharmaceuticals Inc.
Dosage form(s)/formulation(s)	Capsules: 20 mg Suspension (4 mg/mL)
Dosing regimen	Pediatric patients 3 to 15 years of age: ≤28 kg: 0.7 mg/kg suspension by mouth one hour before bedtime >28 kg: 20 mg suspension by mouth one hour before bedtime Patients ≥16 years of age: 20 mg capsule by mouth one hour prior to bedtime
Applicant proposed indication(s)/ population(s)	Sleep Disorder in Smith Magenis Syndrome
Proposed SNOMED indication	401315004 | Smith-Magenis syndrome (disorder)|
Regulatory action	Approval
Approved dosage (if applicable)	Pediatric patients 3 to 15 years of age: ≤28 kg: 0.7 mg/kg suspension by mouth one hour before bedtime >28 kg: 20 mg suspension by mouth one hour before bedtime Patients ≥16 years of age: 20 mg capsule by mouth one hour prior to bedtime
Approved indication(s)/ population(s) (if applicable)	Nighttime sleep disturbances in Smith-Magenis Syndrome
Approved SNOMED term for indication (if applicable)	401315004 | Smith-Magenis syndrome (disorder)|

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Glossary

ABC	Aberrant Behavior Checklist
ADHD	attention deficit hyperactivity disorder
AE	adverse event
AET	antimicrobial effectiveness test
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASD	autism spectrum disorder
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BLQ	below the limit of quantitation
BMC	bone mineral content
CBD	cannabidiol
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
CGI-C	Clinical Global Impression of Change Scale
CGI-S	Clinical Global Impression of Severity Scale
CI	confidence interval
CL/F	apparent total clearance of the drug from plasma after oral administration
C_{max}	maximum plasma concentration
CNS	central nervous system
CSR	clinical study report
CYP1A2	cytochrome P450, family 1, subfamily A, polypeptide 2
CYP3A4	cytochrome P450, family 3, subfamily A, polypeptide 4
DDSQ	daily diary sleep quality
DDSQ50	average 50% worst daily diary sleep quality
DDTST	daily diary total sleep time
DDTST50	average 50% worst daily diary total sleep time
DHT	Digital Health Technology
ECG	electrocardiogram
eCTD	electronic common technical document
eDiary	electronic diary
EOS	end-of-study
EU	European Union
FAERS	FDA Adverse Events Reporting System
FDA	Food and Drug Administration
FOB	functional observational battery
GLP	good laboratory practice
GMR	geometric mean ratio
HD	high dose
i.e.	id est, that is
ICH	International Conference on Harmonisation
ID	identification
IND	investigational new drug application

ITT	intent-to-treat
kg	kilogram
L	liter
LD	low-dose
MD	mid-dose
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mm	millimeter
MT1	melatonin receptor 1
MT2	melatonin receptor 2
NDA	new drug application
NISS	newly identified safety signal
Non-24	Non-24-Hour Sleep-Wake Disorder
NORD	National Organization for Rare Disorders
OLE	Open-Label Extension
PDSSS	Postmarket Drug Safety Surveillance Summary
PK	pharmacokinetic
PMC	postmarketing commitment
PND	postnatal day
PreSQ	Pre-Sleep Questionnaire
PSG	polysomnography
PSQ	Post-Sleep Questionnaire
PT	preferred term
RAI1	retinoic acid induced 1
RTF	Refuse to File
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SMS	Smith-Magenis syndrome
SOC	system organ class
SSI	Supplemental Sleep Interview
SSQ	Smith-Magenis Syndrome Sleep Questionnaire
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TST	total amount of nighttime sleep measured by actigraphy
V1/F	central volume of distribution
V2/F	peripheral volume of distribution
VEC-162	tasimelteon

I. Executive Summary

1. Summary of Regulatory Action

Tasimelteon is a melatonin receptor agonist that was approved on January 31, 2014, as Hetlioz, for the treatment of non-24-hour sleep-wake disorder under New Drug Application (NDA) 205677. On January 13, 2020 and January 21, 2020, Vanda submitted NDA 214517 and NDA 205677-007, respectively. On March 12, 2020, the Division of Psychiatry issued a Refuse to File (RTF) letter to Vanda in response to the original submissions of NDA 214517 and NDA 205677-007. A Type A meeting was held on May 8, 2020 to discuss the RTF decision.

Vanda Pharmaceuticals Inc. submitted a resubmission for NDA 214517 and NDA 205677-007 on June 1, 2020. NDA 214517 provides for a suspension formulation of Hetlioz (tasimelteon) for the treatment of sleep disorder in Smith-Magenis syndrome (SMS) in pediatric patients (age 3 to 15 years). The NDA 205677-007 resubmission provides for addition of the indication of treatment of sleep disorder in SMS in patients age ≥16 years. In support of this NDA, an efficacy study was conducted in patients with SMS. This study enrolled both adult and pediatric patients (3 years of age and older) with SMS. Patients age ≥16 years received the capsule formulation (approved under NDA 205677) and pediatric patients age 3 to 15 years received the suspension formulation.

These applications were granted Priority Review on the basis of clinical judgment that sleep disorders in SMS represent a serious aspect of the condition with a genetically determined cause and are associated with morbidity that has a substantial impact on day-to-day functioning. Because no drug is approved for sleep disorders in SMS, tasimelteon would represent a significant improvement in the treatment of this serious condition.

The Applicant conducted one study to support the SMS indication, "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)." The Randomized Treatment Arm of Study 2401 (2401B) provided the primary basis for evaluating the efficacy and safety of tasimelteon for the treatment of sleep disturbances in SMS. Study 2401B used a crossover design, which is not typically accepted by the Division for pivotal studies of psychiatric conditions because of their potential for differential carryover effects that may bias treatment comparisons. The crossover design was considered acceptable in this case, given the limits of feasibility with this rare disease; refer to Section 6.3.3 for assessment of possible biases introduced by the crossover design. Data from the Open-Label Treatment Arm of Study 2401 (2401A), as well as data from the Open-Label Extension (OLE), provided supportive evidence of safety.

Evidence of efficacy could be evaluated in only Study 2401B. Nevertheless, the characteristics of the trial permitted a valid comparison with a control (placebo) and comparability between groups (randomization); the trial also involved methods to minimize bias in trial conduct (blinding). Together, these features define an adequate and well-controlled trial. The overall efficacy and safety evaluation is also informed by the clinical review of NDA 205677 for the marketing of the capsule formulation for the treatment of non-24 disorder. Non-24 disorder and

SMS exhibit altered sleep patterns as a consequence of a disrupted melatonin cycle and could be considered related conditions for the purpose of clinical evaluation of efficacy and safety. Because tasimelteon is an approved and marketed product, the safety assessment also included information obtained in the postmarketing setting.

The phase 1 pharmacokinetic study VP-VEC-162-4201 supported weight-based dose selection for the pediatric population in Study 2401.

The PK difference between the suspension and capsule formulations of tasimelteon was evaluated using PK data from healthy adults treated with the capsule formulation (Study VP-VEC-162-4101) and pediatric subjects (3 to less than 18 years old) treated with the suspension formulation (Study VP-VEC-4201).

Although the Applicant initially proposed an indication for the treatment of the sleep disorder of SMS, SMS can entail both daytime and nighttime sleep disturbances. The review team concluded that the application provided substantial evidence of safety and effectiveness for tasimeltion in the treatment of nighttime sleep disturbances in SMS, and the Applicant agreed to this modified indication. The application will be approved for this indication, with dosage and administration instructions reflecting the two formulations and two age groups studied (capsules for patients ≥16 years of age; oral suspension for pediatric patients ages 3 to 15 years).

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Smith-Magenis syndrome (SMS) is a genetic disorder usually caused by deletions in chromosome 17p11.2 and, less frequently, by a heterozygous pathogenic variant of the retinoic acid-induced 1 (*RAI1)* gene. • SMS is a rare disease with an estimated prevalence of ~1 in 15,000 globally (Smith et al. 2019) • Insufficient longitudinal data are available to accurately determine life expectancy in patients with SMS. However, in the absence of major organ involvement, life expectancy is not expected to differ from that of individuals with other intellectual disabilities (Smith et al. 2019). • Common clinical features of SMS include distinct physical abnormalities, developmental delay, cognitive impairment, behavioral abnormalities, sleep disturbances, and childhood-onset abdominal obesity. • Sleep disturbances, including decreased overnight sleep time, frequent nocturnal awakenings, and excessive daytime sleepiness, occur in ~95% of individuals with SMS. These sleep disturbances are thought to depend on haploinsufficiency of the *RAI1* gene, which regulates transcription of the CLOCK gene that in turn regulates genes involved in circadian rhythms (Williams et al. 2012). Inversion of the typical melatonin secretion pattern is a hallmark of SMS, and patients have increased levels of melatonin during the day and decreased levels overnight as compared to typically developing children. • Sleep disturbances in SMS begin as early as 6 months of age and continues throughout life, often placing a considerable burden on patients and caregivers	Sleep disturbances are a biologically determined core feature of SMS. Inversion of the melatonin secretion cycle is a hallmark of the disease. Sleep disturbances in SMS are considered to be a serious medical condition, imposing a substantial burden on patients and caregivers, increasing safety risks overnight, and impairing functioning during the day.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(Shayota and Elsea 2019). Unsupervised nocturnal awakenings can pose safety risks to patients, and excessive daytime sleepiness impairs functioning. • The association between sleep disturbances and daytime behavioral dysregulation is not well-understood. Therefore, it is unknown whether improving sleep disturbances would lead to improvements in other behavioral symptoms associated with SMS.	
Current Treatment Options	• There are no Food and Drug Administration (FDA)-approved treatments for sleep disturbances in SMS. • Management of sleep disturbances in patients with SMS includes behavioral modifications, off-label pharmacotherapy, and dietary supplements. • Prolonged-release melatonin is approved in the European Union (EU) for the treatment of insomnia in children and adolescents with autism spectrum disorder (ASD) and SMS. The randomized controlled trial supporting the EU approval included 4 subjects with SMS and 121 subjects with ASD. • There is limited evidence from two open-label studies (N=9, N=10) in support of morning administration of the β1 antagonist acebutolol, given alone or in combination with nighttime administration of melatonin. Beta receptor antagonists inhibit the secretion of melatonin (De Leersnyder et al. 2001b). • A retrospective case series of 62 subjects with SMS examined the effects of psychostimulants, antidepressants, antipsychotics, mood stabilizers, α2-agonists, and hypnotics on the symptoms of SMS, including sleep disturbances. None of these treatments showed clear evidence of benefit (Laje et al. 2010). • The use of sedating medications (e.g., benzodiazepines, antipsychotics) to promote sleep is discouraged due to adverse behavioral and metabolic effects, which could interact adversely with the underlying disease (Smith et al. 2019).	There is a significant unmet need for an evidence-based treatment for sleep disturbances in SMS. Given the high likelihood of lifetime treatment for sleep disturbances in this population, it is important to adequately characterize the safety profile of any potential pharmacotherapy and how it might interact with the underlying genetic condition.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The efficacy of tasimelteon for the treatment of sleep disturbances in SMS is supported by a single randomized, placebo-controlled, two-period crossover study (Study 2401). In this study, 26 patients (age 3 to 39 years) were randomized to receive tasimelteon 20 mg (or a weight-based equivalent suspension dose in pediatric patients) or placebo by mouth nightly for 4 weeks (period 1). After a 1-week washout phase, subjects received the other treatment for 4 weeks (period 2). • Study 2401 had two prespecified primary efficacy endpoints: average of 50% worst daily nighttime sleep quality from a caregiver-reported daily diary (DDSQ50), and average of 50% worst daily total amount of nighttime sleep from the caregiver-reported daily diary (DDTST50). There were no secondary endpoints for which type 1 error was controlled. • The standard for objective measurement of sleep parameters, polysomnography, is considered infeasible for use in pediatric patients and adults with intellectual and neurobehavioral disabilities. There are no objective measures for sleep parameters that have been validated in this population. Although the accuracy of caregiver-estimated total sleep time may not be optimal, it provides daily assessments of a relevant sleep parameter and is considered acceptable in this context. • Sleep quality, as reported by caregivers, is a multidimensional construct that tends to reflect changes in important sleep parameters (e.g., total sleep time, number of nocturnal awakenings) in the study population. This subjective assessment of sleep is considered acceptable in this case, although uncertainties remain about how the concept of sleep quality was defined and understood by caregiver raters. • The average of sleep quality ratings (1= poor, 2=fair, 3=average, 4=good, 5=excellent) from the 50% worst nights was 0.4 points better (diffference in least	• Tasimelteon is a melatonin receptor agonist, and nighttime administration was hypothesized to restore nighttime melatonin activity. • Study 2401 is considered to be an adequate and well-controlled investigation, as it includes randomized, double-blind treatment assignment, a placebo comparator, acceptable primary efficacy endpoints, and an appropriate statistical analysis plan. The small number of subjects in the study is acceptable considering the limited number of individuals with the rare disease of SMS. • Tasimelteon was found to be statistically superior to placebo on the primary efficacy endpoint of DDSQ50. This finding was evident despite the small sample size and the variability that the sleep quality measure may introduce due to its subjectivity. Accordingly, the nature of this finding provides reassurance that the treatment benefit will be appreciable by patients with SMS and their caregivers. • Tasimelteon also numerically increased mean total sleep time as reported by caregiver daily diary. Although the DDTST50 did not reach statistical significance, the secondary efficacy endpoint, which evaluated all nights as opposed to the 50% worst nights, was nominally significant. • Tasimelteon was previously demonstrated to be efficacious for treating non-24-hour sleep-wake disorder, a condition that shares with SMS the pathophysiological mechanism of inadequate nighttime melatonin secretion. The efficacy results from Study 2401, in conjunction with the prior efficacy results for non-24-hour sleep-wake disorder, provide substantial evidence of effectiveness for tasimelteon for the treatment of nighttime sleep disturbances in SMS. Tasimelteon would represent the first FDA-approved medication for the treatment of any clinical features of SMS.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	squares [LS] means) when patients received tasimelteon versus placebo (p=0.0139 <0.025). Exploratory descriptive analyses found that approximately 50% of patients had an average sleep quality improvement of 0 to 1 category when receiving tasimelteon versus placebo, and approximately 20% had an improvement of 1 to 2 categories. Similar results where obtained when considering all nights rather than only the 50% worst; approximately 70% of patients had a positive improvement in sleep quality (difference >0) with tasimelteon versus placebo. • The mean total sleep time from the 50% worst nights was 18.5 minutes longer when patients received tasimelteon versus placebo (not statistically significant; p=0.0556 >0.025). Exploratory descriptive analyses found that for roughly 60% of patients, the mean total sleep time improved by up to 1 hour, and approximately 15% of patients had an improvement between 1 and 1.5 hours with tasimelteon versus placebo. When all nights were included in the analysis rather than only the 50% worst nights, the mean difference was 21.1 minutes in favor of tasimelteon (nominal p=0.0134). • The LS mean number of nightly awakenings was 1.54 when patients received tasimelteon and 1.79 when patients received placebo (nominal p=0.08). Ten patients (40%) had a mean reduction of nightly awakenings ≥0.5, and four patients (16%) had a reduction ≥1 when receiving tasimelteon versus placebo. • Activity data were collected from subjects using a watch device with an accelometer and light sensor. These data were submitted to support secondary efficacy endpoints. The Applicant used the device manufacturer's medium threshold algorithm, which is reported to have 97% sensitivity for correctly classifying true sleep as sleep and 38% specificity for correctly classifying true wake as wake. Although there was	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	some alignment between activity data and caregiver diaries, we cannot accept the actigraphy data to support the primary endpoint because the algorithm has poor specificity for classifying true wake as wake. • The Aberrant Behavior Checklist (ABC) total score from Baseline to Week 4 showed numeric improvements irrespective of whether patients received placebo or tasimelteon. The LS mean difference of 4 in favor of placebo did not reach nominal significance (nominal p=0.09). • There were no apparent differences in efficacy between patients age 3 to 15 years who received the suspension formulation of tasimelteon (n=11) and patients age 16 to 38 years (n=15) who received the capsule formulation. Although the subgroup sample sizes were small, this suggests that the treatment benefits may be generalizable to the target real-world population.	
Risk and Risk Management	• In addition to the new safety data from the SMS population, the overall understanding of the safety profile for tasimelteon is informed by the toxicology, safety pharmacology, and clinical safety review of NDA 205677 for the treatment of non-24-hour sleep-wake disorder. In addition, the postmarketing safety database for Hetlioz was reviewed for newly identified safety signals (NISS), which are not presented in the current labeling. • The safety assessment for tasimelteon within the intended population of subjects with SMS is based on data from Study 2401, which included a randomized, placebo-controlled treatment arm (N=26), a 9-week Open-Label Treatment Arm (N=22), and an ongoing long-term Open-Label Extension Arm (N=47). • The safety database is adequate for a comprehensive safety assessment of tasimelteon for the proposed indication, dosage, and expected treatment duration. The small number of patients with SMS exposed to	• The safety profile of tasimelteon is well-characterized when considering the entire safety database across all development programs. Tasimelteon exposure in patients with SMS is limited by the rarity of the disease and is acceptable to support this application. • There were no serious safety concerns evident in the SMS development program, and the overall safety and tolerability of tasimelteon in this population appears benign. • Two NISS (suicidal ideation and behavior, somnambulism) have been identified in the Hetlioz postmarketing safety database for continued monitoring. Neither of these safety findings were observed in patients with SMS, but pharmacovigilance in the postmarketing setting should monitor for these events in the SMS population. • Although there were no differences in the incidence of infections between tasimelteon and placebo in the randomized treatment arm, ~20% of patients receiving tasimelteon experienced infections when considering

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	tasimelteon in the development program is acceptable considering the rarity of SMS. • Study 2401 included a wide age range of subjects (3 to 39 years) with different clinical manifestations of SMS. Pediatric subjects (n=18) represented 38% of the safety population. • There were no clear imbalances in adverse event incidences between tasimelteon and placebo in the randomized treatment arm. • When pooling both the randomized and the open-label data, a substantial number of patients receiving tasimelteon (n=10; 21.3%) experienced adverse events in the infections and infestations system organ class (SOC). The types of infections were diverse, including both bacterial and viral infections of many body systems. Given the complex medical histories and the increased predisposition to infections in the SMS population, it is not clear whether there is a causal relationship with tasimelteon use. • Tasimelteon did not appear to cause meaningful changes in vital signs or laboratory parameters in patients with SMS. • Upon review, serious adverse events (n=6) and adverse events leading to discontinuation (n=2) in subjects with SMS were deemed not related to tasimelteon exposure. • There have been no deaths in subjects receiving tasimelteon across all clinical studies conducted by the Applicant.	both open-label and randomized treatment data. Current Hetlioz labeling presents upper respiratory tract and urinary tract infections as common adverse reactions in patients with non-24-hour sleep-wake disorder. We cannot rule out the possibility that tasimelteon may similarly increase the risk for infections in the SMS population. Therefore, the product label will not make distinctions in safety profiles between the two conditions. • Safety concerns can be managed by product labeling and routine pharmacovigilance.

2.2. Conclusions Regarding Benefit-Risk

Tasimelteon is a melatonin receptor agonist currently approved for the treatment of non-24-hour sleep-wake disorder. In these current applications (supplementary NDA for tasimelteon capsule and NDA for tasimelteon oral suspension), the Applicant proposes that tasimelteon be indicated for the treatment of sleep disorder in SMS. We recommend that both applications be approved for the treatment of nighttime sleep disturbances in SMS.

In the pivotal study supporting these applications (Study 2401), patients receiving tasimelteon demonstrated statistically significant improvement compared to those receiving placebo (intrapatient comparison) on a caregiver-reported item on nighttime sleep quality, rated on a scale from 1 (poor) to 5 (excellent). This efficacy measure is expected to capture a clinically meaningful concept to patients and caregivers, because 'sleep quality' represents a comprehensive caregiver judgment about nighttime sleep. Exploratory descriptive analyses of the demonstrated treatment effect (LS mean difference=0.4 points, p=0.0139 <0.025) found that approximately 20% of patients had an improvement in sleep quality of greater than 1 category, and approximately 70% of patients had a positive improvement (difference >0) in sleep quality. Although the second prespecified primary endpoint (caregiver-reported total nighttime sleep in the 50% worst nights) did not reach statistical significance, the corresponding secondary endpoint, which included all nights rather than only the 50% worst, found that patients receiving tasimelteon had a numerically increased total sleep duration versus those receiving placebo (mean difference=21.1 minutes, nominal p=0.0134). Exploratory descriptive analyses of total sleep time found that approximately 15% of patients had an improvement of greater than 1 hour when receiving tasimelteon versus placebo. The results from the adequate and well-controlled Study 2401, in conjunction with confirmatory evidence of benefit for the treatment of another condition similarly characterized by inadequate nighttime melatonin secretion (non-24-hour sleep wake disorder), provides substantial evidence of effectiveness. Because there are no approved treatments for sleep disturbances in SMS, tasimelteon would represent the first treatment to demonstrate benefit in an adequate and well-controlled clinical trial.

The safety profile of tasimelteon is well-characterized from studies investigating its use for other conditions, including the approved indication of non-24-hour sleep-wake disorder (non-24). In this current development program, there were no newly identified safety concerns, and the overall safety and tolerability of tasimelteon in this population appear benign. In Study 2401, there were no deaths, no serious adverse events or treatment discontinuations deemed related to the study drug, and no clear differences in adverse event incidences, laboratory parameters, or vital signs between tasimelteon and placebo. The safety concerns can be managed by product labeling and routine pharmacovigilance.

Tasimelteon, as a melatonin receptor agonist, is thought to target the underlying pathophysiology of sleep disturbances in SMS, namely inadequate melatonin secretion at night. Sleep disturbances in SMS are considered to be a serious medical condition and an area of unmet medical need because there are no treatments currently approved for this indication. Tasimelteon demonstrated statistically significant improvement on caregiver-reported sleep quality and nominally significant improvement on caregiver-reported total sleep time. As such, both of these improvements indicate that tasimelteon addresses an unmet need. These improvements, in conjunction with a benign and well-characterized safety profile, result in a favorable benefit/risk balance supportive of approval.

II. Interdisciplinary Assessment

3. Introduction

Tasimelteon is a melatonin receptor agonist that was approved, as Hetlioz, on January 31, 2014, for the treatment of non-24 under New Drug Application (NDA) 205677. The Applicant, Vanda Pharmaceuticals Inc. submitted a supplemental NDA (sNDA) for Hetlioz capsule and an NDA for Hetlioz suspension for the following indications:

- Hetlioz capsules for the treatment of:
  - Non-24 in adults (1)
  - Sleep disorder in Smith-Magenis syndrome (SMS) in patients 16 years and older
- Hetlioz oral suspension for the treatment of:
  - Sleep disorder in SMS in pediatric patients 3 to 15 years of age

Tasimelteon was granted orphan-drug designation for the treatment of sleep disorder in SMS by FDA on April 30, 2010.

SMS is a rare disease with a prevalence of 1 in 25,000 individuals globally, but is likely underdiagnosed and may have a true prevalence closer to 1 in 15,000 individuals (Smith et al. 2019). SMS is typically the result of haploinsufficiency of the retinoic acid induced 1 gene (*RAI1*), due to a ~3.7 Mb interstitial deletion of chromosome 17p11.2, including *RAI1*; however, ~10% of cases may be secondary to pathogenic variants of the gene itself. Common clinical features in SMS include distinct physical abnormalities, developmental delay, cognitive impairment, behavioral abnormalities, sleep disturbances, and childhood-onset abdominal obesity. Less commonly, patients may present with seizures, hearing loss, renal anomalies, ocular anomalies, and cleft lip and/or palate.

Sleep disturbances are evident in about 95% of children and adults with SMS and consist of reduced total amount of nighttime sleep, frequent nocturnal awakenings, early morning arousal, and excessive daytime sleepiness. Management of the sleep disturbances in patients with SMS typically requires a combination of behavioral modifications and medication interventions. There is no drug approved for sleep disorders in SMS (or other clinical aspects of SMS) in the United States. In Europe, Slenyto (controlled-release melatonin) is approved for "treating insomnia (difficulty sleeping) in children and adolescents (2 to 18 years old) who have autism spectrum disorder (ASD) and SMS."

These applications were granted Priority Review on the basis of clinical judgment that sleep disorders in SMS represent a serious aspect of the condition with a genetically determined cause and are associated with morbidity that has a substantial impact on day-to-day functioning. Because no drug is approved for sleep disorders in SMS, tasimelteon would represent a significant improvement in the treatment of this serious condition.

The Applicant's goal in the SMS development program was to demonstrate superiority of tasimelteon compared to placebo on improvement in nighttime sleep quality, as measured by

changes in the daily diary sleep quality (DDSQ), and in daily diary total sleep time (DDTST), both evaluated by means of a caregiver-rated Post-Sleep Questionnaire (PSQ).

The Applicant conducted a single pivotal study, VP-VEC-162-2401 (hereafter referred to as Study 2401), which consisted of two treatment arms. In the Open-Label Treatment Arm (referred to as 2401A), 19 patients were treated with open-label tasimelteon 20 mg nightly for 9 weeks. The randomized treatment arm (referred to as 2401B) had a double-blind, two-period, crossover design, in which 26 patients were randomized to receive tasimelteon 20 mg nightly then placebo (n=13), or placebo then tasimelteon 20 mg nightly (n=13) for 4 weeks each, separated by a 1-week washout period. The patients in 2401A and 2401B could enter an Open-Label Extension phase consisting of 232 weeks of treatment.

The clinical trial population in Study 2401 consisted of pediatric subjects (3 to 15 years of age) who were administered tasimelteon suspension and adults (16 years of age and above) who were administered tasimelteon capsules. The Applicant did not conduct a bioavailability study to establish a pharmacokinetics (PK) bridge between the two formulations. Per Food and Drug Administration (FDA) advice following a Type A Meeting held on May 8, 2020, the proposed labeling specifies that tasimelteon suspension would be indicated only in pediatric patients (age 3 to 15 years) and tasimelteon capsules would be indicated only in patients 16 years of age and above. The intent-to-treat (ITT) population in Study 2401, in which the efficacy endpoints were analyzed, includes both groups. See Section 12 for a complete regulatory history.

The key review issues related to evaluation of benefit and risk were addressed by an interdisciplinary review team approach, and each applicable discipline contributed to the overall conclusions.

3.1. Review Issue List

The review team identified six key review issues that had a significant impact on the overall determination of approvability. Some of these issues were identified prior to submission of the sNDA and NDA, whereas others emerged during the review. In-depth analyses of the benefit and risk review issues can be found in Sections 6.3 and 7.7.

- Benefit Issue 1: Assessment of the similarity in exposures and responses to tasimelteon in adult subjects who received the capsules and pediatric subjects who received the suspension.
- Benefit Issue 2: Acceptability and clinical relevance of the DDSQ50 and DDTST50 as primary outcome measures.
- Benefit Issue 3: Assessment of possible biases introduced by the crossover design or the re-enrollment of five subjects from the open-label cohort into the Randomized Treatment Arm of study VP-VEC-162-2401.
- Benefit Issue 4: Assessment of the impact of patients on concomitant beta-adrenergic receptor antagonists in the efficacy evaluation.
- Benefit Issue 5: Usability of actigraphy data to support the primary endpoint in the evaluation of efficacy.
- Risk Issue 1: Infections and infestations as adverse events derived from a potential drug-disease interaction.

3.2. Approach to the Review

Table 3 provides an overview of the clinical trials conducted to support the benefit-risk assessment of tasimelteon for the treatment of sleep disturbances in SMS.

The Randomized Treatment Arm of Study 2401 (2401B) provided the primary basis of evaluating the efficacy and safety of tasimelteon for the treatment of sleep disturbances in SMS. Study 2401B used a crossover design, which is not typically accepted by the Division for pivotal studies of psychiatric conditions because of their potential for differential carryover effects that may bias treatment comparisons. The crossover design was considered acceptable in this case, given the limits of feasibility with this rare disease; refer to Section 6.3.3 for assessment of possible biases introduced by the crossover design. Data from the Open-Label Treatment Arm of Study 2401 (2401A), as well as data from the Open-Label Extension (OLE), provided supportive evidence of safety.

Evidence of efficacy could be evaluated in only one trial (Study 2401B). Nevertheless, the characteristics of the trial permitted a valid comparison with a control (placebo) and comparability between groups (randomization); the trial also involved methods to minimize bias in trial conduct (blinding). Together, these features define an adequate and well-controlled trial. The overall efficacy and safety evaluation is also informed by the clinical review of NDA 205677 for the marketing of the capsule formulation for the treatment of non-24 disorder. Non-24 disorder and SMS exhibit altered sleep patterns as a consequence of a disrupted melatonin cycle and could be considered related conditions for the purpose of clinical evaluation of efficacy and safety. Because tasimelteon is an approved and marketed product, the safety assessment also included information obtained in the postmarketing setting.

The phase 1 pharmacokinetic study VP-VEC-162-4201 supported weight-based dose selection for the pediatric population in Study 2401.

The PK difference between the suspension and capsule formulations of tasimelteon was evaluated using PK data from healthy adults treated with the capsule formulation (Study VP-VEC-162-4101) and pediatric subjects (3 to less than 18 years old) treated with the suspension formulation (Study VP-VEC-4201).

Table 3. Clinical Trials Submitted in Support of Efficacy and Safety Determinations

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Patients Planned; Actual Randomized	No of Centers and Countries
NCT02231008 VP-VEC-162-2401 (2401B): Randomized Treatment Arm	Patients with a confirmed clinical diagnosis of Smith-Magenis syndrome (SMS) and with observed sleep disturbances	DB, R, PC, TPC, MC	Tasimelteon 20 mg (adults) or weight-based (0.7 mg/kg for weight ≤28 kg or 20 mg for >28 kg) (pediatrics) QHS (N=26) for 4 weeks Placebo (N=26) QHS for 4 weeks Duration: 9 weeks (two 4-week treatment periods separated by a 1-week washout period)	Primary: 1) the average of 50% worst daily nighttime sleep quality and 2) the average of 50% worst daily subjective total nighttime sleep.	Up to 48; 26	4 centers in 1 country (US)
NCT02231008 VP-VEC-162-2401 (2401A) Open-Label Treatment Arm	Patients with a confirmed clinical diagnosis of SMS	OL, MC	Tasimelteon 20 mg (adults) or weight-based (0.7 mg/kg for weight ≤28 kg or 20 mg for >28 kg) (pediatrics) QHS (N=22) Duration: 9 weeks	Primary: 1) the average of 50% worst daily nighttime sleep quality and 2) the average of 50% worst daily subjective total nighttime sleep.	Up to 100; 22	4 centers in 1 country (US)

Source: Created by the Reviewer.
Abbreviations: DB, double-blind; MC, multicenter; OL, open-label; PC, placebo-controlled; QHS, at bedtime; R, randomized; TPC, two-period crossover

4. Patient Experience Data

The Applicant developed a caregiver electronic diary as an Android application installed on a tablet. Caregivers were instructed to complete the patient's information section and the nighttime and daytime sleep questionnaires. Two items of the nighttime sleep questionnaire were selected as primary endpoints for the pivotal study. For a complete description of the diary, refer to Section 15.

The review team requested a patient listening session, which was organized by the Patient Affairs Staff (Office of the Commissioner), together with the National Organization for Rare Disorders (NORD) and the Reagan-Udall Foundation for the FDA. The patient listening session reached out to the community of patients with SMS and their caregivers to discuss their experience with sleep disturbances in SMS. A summary of the session can be found in Section 19.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☐	Patient-reported outcome	
☒	Observer-reported outcome	Caregiver-rated eDiary Appendices, Section 15.1
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other:	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☒	Perspectives shared at patient stakeholder meeting	Patients Listening Session Appendices, Section 19
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

The PK and clinical pharmacology of the capsule formulation of tasimelteon were reviewed extensively when NDA 205677 was submitted for the treatment of non-24. Please refer to the clinical pharmacology review by Jagan Mohan Parepally submitted in the Document Archiving, Reporting and Regulatory Tracking System on November 7, 2013. The PK of tasimelteon is summarized in Table 5.

Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
Pharmacologic activity	
Established pharmacologic class	Melatonin receptor (MT_1 and MT_2) agonist
Mechanism of action	The mechanism by which tasimelteon exerts its therapeutic effect in patients with non-24 sleep-wake disorder is unclear. However, tasimelteon is an agonist at melatonin MT_1 and MT_2 receptors which are thought to be involved in the control of circadian rhythms.
Active moieties	Tasimelteon
General information	
Bioanalysis	Plasma concentrations of tasimelteon and its metabolites, M9, M11, M12, M13, and M14 were measured by a validated liquid chromatography-tandem mass spectrometry assay. The bioanalytical method meets the FDA criteria for 'method validation' and 'application to routine analysis' and is acceptable.
Dosage proportionality	3 mg to 300 mg
Accumulation	No accumulation of tasimelteon and its metabolites with repeated daily administration.
Absorption	
Bioavailability	Absolute oral bioavailability: 38%
T_{max}	Tasimelteon capsules: 0.5 to 3 hours; tasimelteon suspension: 15 to 30 minutes
Food effect	When administered with a high-fat meal, the C_{max} of tasimelteon was 44% lower than when given in a fasted state, and the median T_{max} was delayed by approximately 1.75 hours. Therefore, tasimelteon should be taken without food.
Distribution	
Volume of distribution	59 to 126 L
Plasma protein binding	90%

Characteristic	Drug Information
Elimination	
Mass balance results	Following oral administration of radiolabeled tasimelteon, 80% of total radioactivity was excreted in urine and approximately 4% in feces, resulting in a mean recovery of 84%. Less than 1% of the dose was excreted in urine as the parent compound.
Half-life	1.3±0.4 hours
Metabolic pathway(s)	CYP1A2 and CYP3A4 mediated oxidation at multiple sites and oxidative dealkylation resulting in opening of the dihydrofuran ring followed by further oxidation to give a carboxylic acid. Phenolic glucuronidation is the major phase II metabolic route.

Source:
Abbreviations: C_{max}, maximum plasma concentration; CYP, cytochrome P450; T_{max}, time to maximum plasma concentration

5.1. Nonclinical Assessment of Potential Effectiveness

There were no nonclinical studies submitted with NDA 214517 or NDA 205677-007 that are relevant to assessing the effectiveness of tasimelteon for the treatment of nighttime sleep disturbances in SMS. Please refer to the pharmacology/toxicology review of NDA 205677 (tasimelteon for the treatment of non-24) for detailed review of the primary pharmacology studies submitted with NDA 205677.

As described in Section 12.2 (Pharmacodynamics) of the current Hetlioz labeling, tasimelteon is an agonist at melatonin receptor 1 (MT_1) and melatonin receptor 2 (MT_2) receptors with greater affinity for the MT_2 as compared to the MT_1 receptor (K_i, 0.304 and 0.07nM, respectively). The major metabolites of tasimelteon have less than one-tenth of the binding affinity of the parent molecule for both the MT_1 and MT_2 receptors. The MT_1 and MT_2 receptors are thought to be involved in controlling the circadian rhythm.

Although the mechanism by which tasimelteon exerts a therapeutic effects in patients with nighttime sleep disturbances in SMS is unclear, it is plausible that it involves agonism of melatonin receptors, because SMS is characterized by decreased nighttime melatonin secretion.

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

The Applicant's proposed dose of tasimelteon capsules is 20 mg by mouth, administered 1 hour prior to bedtime. The capsule formulation is indicated for patients age 16 years and older. The 20-mg dose was selected for use in Study 2401 because this dose has previously been demonstrated to be effective for the non-24 indication.

Non-24 is a chronic disorder that occurs when individuals are unable to synchronize their endogenous body clock to the 24-hour light-dark cycle. The majority of reported cases occur in blind patients with no perception of light. In these blind individuals, the circadian pacemaker may revert to its endogenous non-24-hour rhythm, leading to periodic desynchronization of the timing of melatonin and cortisol production and the sleep-wake cycle with respect to the external 24-hour day. Individuals with SMS also show a disrupted pattern of melatonin secretion and, as

such, the two conditions appear to be related from a clinical and biological perspective. For this reason, the choice of the same 20-mg dose appears to be reasonable.

For pediatric patients age 3 to 15 years, a body weight-based dose equivalent to the 20-mg tasimelteon capsule was administered orally as a 4 mg/mL liquid suspension. The suspension dose selection was based on the findings from Study VP-VEC-162-4201 (hereafter referred to as Study 4201).

Study 4201 was an open-label, single-dose, noncontrolled study to evaluate the PK and safety of tasimelteon suspension in children and adolescents (age 3 to 17 years) who were legally blind and met the diagnostic criteria for non-24 or circadian rhythm sleep-wake disorder, and/or were diagnosed with a neurodevelopmental disorder (e.g., autism spectrum disorder, SMS) and had a nighttime sleep complaint.

A single body weight-based dose of tasimelteon suspension was administered as below:

10 to <20 kg, 6 mg; 20 to <40 kg, 12 mg; 40 to <60 kg, 16 mg; and ≥60 kg, 20 mg

PK analysis suggests that the clearance of tasimelteon suspension was influenced by body weight up to 28 kg. Based on these findings, systemic exposure in children was found to be comparable to that in adults receiving a 20 mg capsule with the following doses:

- • Children ≤28 kg: weight (kg) ÷ 28 • 20 mg
- • Children >28 kg: 20 mg

The peak maximum plasma concentration (C_{max}) of tasimelteon occurs approximately 0.5 to 3 hours after fasted oral administration. Consequently, tasimelteon was administered 1 hour before bedtime in the phase 3 pivotal study VP-VEC-162-2401.

Of note, the Applicant did not conduct a bioavailability study to establish a PK bridge between the capsule and suspension formulations. Please refer to Key Review Issue 1 (Section 6.3.1) for discussion of this issue.

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. Results of Analyses, Study VP-VEC-162-2401

6.2.1.1. Study VP-VEC-162-2401, Trial Design

Study 2401 is considered to be an adequate and well-controlled investigation, as it includes randomization as a comparability method between groups, double-blinded treatment assignment, a placebo comparator, acceptable primary efficacy endpoints (Section 6.3.2), and an appropriate statistical analysis plan. Because SMS is a rare condition, one study that enrolls a sufficient number of patients to detect a treatment difference was considered acceptable to support marketing approval, in conjunction with confirmatory evidence from the non-24 development program.

Study 2401 consisted of a Screening Phase, a Treatment Phase, and an OLE. The Treatment Phase included an open-label study (referred to as the Open-Label Treatment Arm in the protocol (amendment 10, dated August 13, 2019) and a randomized, double-blind, two-period cross-over

study (referred to as the Randomized Treatment Arm in the protocol (amendment 10, dated August 13, 2019).

For the purpose of the efficacy assessment, the review team considered only the Randomized Arm of the Treatment Phase, because the Open-Label Treatment Arm lacked blinded treatment assignment and a treatment comparator.

The Randomized Treatment Arm had a crossover design and consisted of two periods of 4 weeks each, separated by a 1-week wash-out period. The assessment of possible biases introduced by the crossover design, including of a potential carryover effect, is discussed in Section 6.3.3.

The Open-Label Extension Phase (currently ongoing) consisted of up to 232 weeks of open-label treatment during which all patients received open-label tasimelteon.

For a full description of the clinical trial design, please refer to Section 15.

6.2.1.2. Eligibility Criteria, Study VP-VEC-162-2401

Key eligibility criteria are summarized below; the full criteria are presented in Section 15.

Key Inclusion Criteria

- A confirmed clinical diagnosis of SMS, with a prior positive genetic test result as indicated by the parent/guardian
- Informed consent from the patient or their legal guardian. When possible, assent provided by the individual with SMS
- Male or female and 3 to 65 years of age
- Recent history of sleep disturbances
- Demonstrate fragmented nighttime sleep during the Screening Phase, as measured by actigraphy and scored by a central scorer (for the Randomization Arm of the Treatment Phase only)
- Have an appointed caregiver who can complete the required outpatient assessments
- Willing and able to comply with study requirements and restrictions
- Demonstrate impaired sleep quality during the Screening Phase (for the Randomization Arm of the Treatment Phase only)

Of note, "Demonstrate fragmented night-time sleep during the screening phase, as measured by actigraphy and scored by a central scorer" and "Demonstrate impaired sleep quality during the screening phase" are key criteria for inclusion in the Randomized Treatment Arm of Study 2401. Subjects not meeting these criteria were enrolled in the Open-Label Treatment Arm.

The criterion "Demonstrate fragmented night-time sleep during the screening phase, as measured by actigraphy and scored by a central scorer" was met if subjects demonstrated significant awakening within the sleep interval based on the actigraphy data.

The criterion "Demonstrate impaired sleep quality during the screening phase" was met if the average of sleep quality across all nights was <3.0 (average) Sleep quality was rated on a 5-point scale: 1 (poor), 2 (fair), 3 (average), 4 (good), and 5 (excellent). However, in June 2018, before protocol amendment 8, the Applicant re-evaluated the sleep quality criterion, and modified it to be the average of the 50% worst of sleep quality ratings <3 during the screening period.

Key Exclusion Criteria

- Failure to confirm diagnosis of SMS by molecular cytogenetic methods and/or DNA-based mutation analysis of the *RAI1* gene
- Indication of impaired liver function (values for aspartate aminotransferase [AST], alanine aminotransferase [ALT], or bilirubin greater than two-fold the normal limit)
- Pregnant or lactating females
- A positive test for drugs of abuse at the screening visit (only performed for subjects >14 years of age)
- Worked night, rotating, or split (period of work, followed by break, and then return to work) shift work within 1 month of the screening visit, or plan to work these types of shifts during the study
- Exposure to any investigational drug, including placebo, within 30 days or five half-lives (whichever was longer) of screening
- Unwilling or unable to follow the medication restrictions, including the washout from use of a prohibited medication
- Any other sound medical reason as determined by the clinical investigator or the Applicant

The inclusion and exclusion criteria are acceptable. Refer to Section 15 for considerations on the adequacy of the inclusion criteria.

6.2.1.3. Statistical Analysis Plan

The statistical analysis plan (SAP, version 1.0) for Study VP-VEC-162-2401 is dated December 4, 2018. It was initially submitted via email on March 28, 2019, and then officially under SN 29 on June 7, 2019. The SAP is based on protocol amendment 9, also dated December 4, 2018.

Primary Efficacy Endpoints

The primary efficacy endpoints are listed as: "The average of 50% worst daily nighttime sleep quality" (DDSQ50) and "The average of 50% worst daily subjective total nighttime sleep"(DDTST50). The acceptability and clinical relevance of the primary endpoints are discussed in Section 6.3.2.

Analysis Population

The ITT population is defined as all patients randomized into the Treatment Phase who had an evaluable efficacy assessment in both periods of the double-blind phase while on study drug.

Efficacy Analysis

The primary efficacy outcomes will be analyzed using a mixed-effects model that includes the fixed, categorical effects of treatment, period, and sequence.

The SAP for Study 2401 is brief but adequately specifies the primary efficacy analyses.

6.2.1.4. Results of Analyses of Clinical Trials Intended to Demonstrate Benefit to Patients

This section summarizes the subject disposition, baseline demographics, clinical characteristics, and primary efficacy results to support the efficacy of tasimelteon for the treatment of sleep

disturbances in SMS. The Randomized Treatment Arm of Study 2401 is the only source of data from the study considered acceptable to evaluate the benefit of tasimelteon.

6.2.1.4.1. Disposition, Baseline Demographics, and Baseline Clinical Characteristics

Disposition

Subject disposition information for Study 2401 is summarized in Table 6. Six (11.1%) subjects screened for participation were not enrolled in the trial. Twenty-six subjects were randomized, and only one subject discontinued during the crossover study. Twenty-two subjects were enrolled in the Open-Label Treatment Arm. In response to a clinical information request dated October 26, 2020, the Applicant clarified that 19 patients were enrolled in the Open-Label Arm until database lock (December 4, 2018). Following database lock, three new subjects requested to enroll in the study, and sites were instructed to enroll the patients into the Open-Label Treatment Arm.

Table 6. Patient Disposition, Trial VP-VEC-162-2401

Patients screened[1]				54
Not randomized/assigned, n (%)				6 (11.1)
Screen failures, n (%)				6 (11.1)
	Randomized N=26		**Open-Label Tasimelteon N=22**	**Total N=48**
	Placebo N=26	Tasimelteon N=26		
Patients randomized/assigned[2]	26	26	22	48
ITT population, n (%)	25 (96.2)	25 (96.2)		
Safety population, n (%)	26 (100.0)	25 (96.2)	22 (100.0)	48 (100.0)
Per protocol population, n (%)	25 (96.2)	25 (96.2)		
Discontinued study, n (%)[2]				
Non-compliance with study procedures	0 (0.0)	0 (0.0)	3 (13.6)	3 (6.3)
Withdrawal by subject	0 (0.0)	1 (3.8)	3 (13.6)	4 (8.3)

Source: Applicant
Abbreviations: N, number of patients in the treatment arm; n, number of patients in a specific population or group; %, 100×n÷N
[1] Percentages are based on screened patients. Patients may have more than one reason for screen failure.
[2] Percentages are based on randomized/assigned patients.

Baseline Demographics and Clinical Characteristics

Table 7 summarizes the baseline demographics and clinical characteristics of the randomized population. Forty-six percent of subjects were male, and the mean age was 19.5 years (SD=9.22). Overall, the sample has a wide age range distribution, which is considered representative of the population of subjects with SMS. The vast majority of subjects (96.2%) were identified as white of non-Hispanic ethnicity. Although SMS has been identified worldwide in all ethnic groups, it is likely underdiagnosed in some minority groups. For the purpose of the clinical review, there is no reason to believe that tasimelteon would have a different effect in different ethnic groups and, for this reason, the lack of racial and ethnic diversity in the clinical trial population is acceptable. The four trial sites were all located in the United States. Four subjects had a concomitant diagnosis of seizure disorder, and one subject was diagnosed with Lennox-Gastaut syndrome. The scientific literature confirms that about one third of subjects with SMS has seizures or a diagnosis of a seizure disorder (Smith et al. 2019). Nine subjects (18.8%) were diagnosed with attention deficit/hyperactivity disorder (ADHD) and 6 subjects (12.5%) with autism. Attention

deficits, stereotypic behavior, tantrums, and impaired cognition are common features of SMS, which overlap with the phenomenological expression of other neurodevelopmental disorders such as ADHD and ASD.

Table 7. Baseline Demographic and Clinical Characteristics, Trial VP-VEC-162-2401

	Randomized		Open-Label Tasimelteon N=22	Total N=48
Characteristic	**Placebo N=26**	**Tasimelteon N=26**		
Sex, n (%)	26 (100.0)	26 (100.0)	22 (100.0)	48 (100.0)
Male	11 (42.3)	11 (42.3)	11 (50.0)	22 (45.8)
Female	15 (57.7)	15 (57.7)	11 (50.0)	26 (54.2)
Age, years				
Mean (SD)	17.4 (9.46)	17.4 (9.46)	21.9 (8.49)	19.5 (9.22)
Median (min, max)	18.5 (3, 38)	18.5 (3, 38)	20.5 (5, 39)	19.0 (3, 39)
Age groups (years),n (%)	26 (100.0)	26 (100.0)	22 (100.0)	48 (100.0)
≥3 to <16	11 (42.3)	11 (42.3)	3 (13.6)	14 (29.2)
≥16 to ≤65	15 (57.7)	15 (57.7)	19 (86.4)	34 (70.8)
Race, n (%)	26 (100.0)	26 (100.0)	22 (100.0)	48 (100.0)
White	25 (96.2)	25 (96.2)	21 (95.5)	46 (95.8)
Asian	1 (3.8)	1 (3.8)	0 (0.0)	1 (2.1)
Black/African American	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	1 (4.5)	1 (2.1)
Ethnicity, n (%)	26 (100.0)	26 (100.0)	22 (100.0)	48 (100.0)
Hispanic	1 (3.8)	1 (3.8)	1 (4.5)	2 (4.2)
Non-Hispanic	25 (96.2)	25 (96.2)	21 (95.5)	46 (95.8)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Country of participation, n (%)	26 (100.0)	26 (100.0)	22 (100.0)	48 (100.0)
United States	26 (100.0)	26 (100.0)	22 (100.0)	48 (100.0)
Clinical baseline characteristics, n (%)				
Concomitant illness, n (%)				
Anxiety disorder	1 (3.8)	1 (3.8)	0 (0.0)	1 (2.1)
Attention deficit/hyperactivity disorder	6 (23.1)	6 (23.1)	3 (13.6)	9 (18.8)
Autism	4 (15.4)	4 (15.4)	2 (9.1)	6 (12.5)
Depression	0 (0.0)	0 (0.0)	1 (4.5)	1 (2.1)
Lennox-Gastaut syndrome	1 (3.8)	1 (3.8)	0 (0.0)	1 (2.1)
Obsessive-compulsive disorder	1 (3.8)	1 (3.8)	1 (4.5)	2 (4.2)
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS)	1 (3.8)	1 (3.8)	0 (0.0)	1 (2.1)
Post-traumatic stress disorder	0 (0.0)	0 (0.0)	2 (9.1)	2 (4.2)
Seizure	4 (15.4)	4 (15.4)	0 (0.0)	4 (8.3)
Speech disorder developmental	1 (3.8)	1 (3.8)	0 (0.0)	1 (2.1)
Duration of disease (years)[1]				
Mean (SD)	17.4 (9.46)	17.4 (9.46)	21.9 (8.49)	19.5 (9.22)
Median (min, max)	18.5 (3, 38)	18.5 (3, 38)	20.5 (5, 39)	19.0 (3, 39)

Source: Applicant
Abbreviations: N, number of patients in the treatment arm; n, number of patients with a given characteristic; SD, standard deviation; %, 100 × n÷N
[1] Duration of disease was assumed to be identical to age because SMS is a genetic disease.

6.2.1.4.2. Primary and Key Secondary Efficacy Results

The Applicant's primary efficacy results were confirmed by the statistical review team.

Primary Efficacy Endpoints

Two primary efficacy endpoints were prespecified: 1) Average of 50% worst daily nighttime sleep quality and 2) average of 50% worst daily total amount of nighttime sleep. The comparison in this crossover study is within-patient (i.e., each patient was exposed to tasimelteon and placebo in subsequent periods of this two-period crossover trial). There were no further efficacy endpoints prespecified (i.e., alpha is spent only on the two primary efficacy endpoints). Refer to Table 8 for the primary efficacy analyses.

On average, patients' 50% worst daily nighttime sleep quality improved by 0.4 on the 1=poor to 5=excellent scale of the post-sleep questionnaire when treated with tasimelteon versus placebo. This difference is statistically significant (p=0.0139 <0.05/2). On average, the 50% worst daily total amount of nighttime sleep increased by 18.5 minutes when a patient was treated with tasimelteon versus placebo. This improvement is not statistically significant (p=0.0556 >0.05/2).

Table 8. Primary Efficacy Endpoints Results

Primary Efficacy Endpoint	Baseline* Mean	Placebo LS Means (n=25)	Tasimelteon LS Means (n=25)	Difference (TAS − PLA) [95% CI]	p-value	Significance Threshold
Average of 50% worst daily nighttime sleep quality	2.1	2.4	2.8	0.4 [0.1, 0.7]	0.0139	0.025
Average of 50% worst daily total amount of nighttime sleep – hours (minutes)	6.4	6.7	7.0	0.3 (18.5) [0.0, 0.6]	0.0556	0.025

Source: Applicant-provided; results confirmed by the Statistical Reviewer
Abbreviations: CI, confidence interval; LS, least squares; n, number (of sample); PLA, placebo; TAS, tasimelteon
*Baseline value established during the Screening Phase

Of note, when the patient averages are based on 100% of the collected daily data points versus being limited to the 50% worst nights (secondary endpoints in Study 2401), the point estimates for DDSQ and DDTST are similar to those of the primary analyses, and the total amount of nighttime sleep duration endpoint achieves nominal statistical significance at alpha=0.05/2 (Table 9).

Table 9. Results on Two Secondary Efficacy Endpoints Closely Related to the Primary Efficacy Endpoints

Secondary Efficacy Endpoint	Baseline* Mean	Placebo LS Means (n=25)	Tasimelteon LS Means (n=25)	Difference (TAS − PLA) [95% CI]	Nominal p-value
Average of daily nighttime sleep quality	2.7	2.9	3.3	0.3 [0.1, 0.6]	0.0155
Average of daily total amount of nighttime sleep – hours (minutes)	7.0	7.3	7.7	0.4 (21.1) [0.1, 0.6]	0.0134

Source: Applicant-provided; results confirmed by the Statistical Reviewer
Abbreviations: CI, confidence interval; LS, least squares; n, number (of sample); PLA, placebo; TAS, tasimelteon
*Baseline value established during the Screening Phase

***FDA Clinical Reviewer's Comment**: Tasimelteon was found to be superior to placebo in improving daily nighttime sleep quality as rated by the caregiver. The fact that the primary endpoint DDSQ50 is a subjective caregiver-rated measure may have potentially introduced variability in the ratings. However, and notwithstanding, the analysis detected a statistically significant difference, providing reassurance regarding the treatment benefit.*

Please refer to Section 6.3.2 for discussion of the acceptability and clinical relevance of the DDSQ and DDTST.

6.2.1.4.3. Subgroup Analyses of the Primary Endpoint

Study 2401 was entirely conducted in the United States and enrolled almost exclusively patients classified as White. A subgroup analysis by sex did not suggest differences in effect between male and female patients. A subgroup analysis by age (pediatrics versus adults) is provided in Section 6.3.1. Sensitivity analyses excluding subjects re-enrolled from the open-label cohort or excluding subjects on concomitant beta-adrenergic receptor antagonists are included in Sections 6.3.3 and 6.3.4, respectively.

6.3. Key Review Issues Relevant to Evaluation of Benefit

- Issue 1: Assessment of similarity in exposures and responses to tasimelteon in adult subjects who received the capsules and pediatric subjects who received the suspension.
- Issue 2: Acceptability and clinical relevance of the DDSQ50 and DDTST50 as primary outcome measures.
- Issue 3: Assessment of possible biases introduced by the crossover design or the re-enrollment of five subjects from the open-label cohort into the Randomized Treatment Arm of Study VP-VEC-162-2401.
- Issue 4: Assessment of the impact of patients on concomitant beta-adrenergic receptor antagonists in the efficacy evaluation.
- Issue 5: Usability of actigraphy data for supporting the primary endpoint in the evaluation of efficacy.

6.3.1. Assessment of Similarity in Exposures and Responses to Tasimelteon in Adults Who Received Capsules and Pediatrics Who Received Suspension

Issue

In the clinical trial of safety and efficacy (Study 2401), adult subjects and pediatric subjects older than 15 years were treated with 20 mg tasimelteon capsules, and pediatric subjects 3 to 15 years were treated with tasimelteon suspension (4 mg/mL; weight [kg]÷28 kg×20 mg). However, the bioequivalence between capsule (adults) and suspension (pediatrics) formulations of tasimelteon was not established. Furthermore, it is not known whether the clinical response to tasimelteon is similar between pediatrics and adults with SMS. Therefore, the review team intended to ascertain whether PK or age-related differences could have been responsible for differences in efficacy.

The acceptability of the ITT population is dependent on the similarity in exposures and responses to tasimelteon in adults and pediatrics.

Assessment

a) Assessment of exposure similarity between capsule and suspension formulations of tasimelteon

The Applicant performed population PK analyses, rather than a dedicated relative bioavailability study, to compare the PK of the capsule (healthy adults; VP-VEC-162-4101) and suspension (pediatrics 3 to less than 18 years of age; VP-VEC-162-4201) formulations. The population PK analyses were used primarily to identify covariates that influence the PK of tasimelteon, prior to comparing the PK of tasimelteon in children and adults. The population PK analyses suggest that body weight is the only covariate that significantly influences the PK of tasimelteon, and an increase in body weight up to 28 kg was associated with an increase in tasimelteon clearance. Based on this finding, the Applicant proposed a 0.7 mg/kg dose of tasimelteon suspension in pediatric patients who weigh less than 28 kg and a 20 mg dose for those weighing greater than or equal to 28 kg and adults. The PK of the suspension and capsule formulations of tasimelteon were compared, following normalization of systemic exposures in pediatrics with the proposed dosing recommendation. The results suggest that systemic exposures are relatively similar between the suspension and capsule formulations (Table 10). However, the precision (90% confidence intervals [CI]) around PK parameters did not meet the bioequivalence criterion of 80% to 125%. This could be a result of the smaller number of subjects treated with the capsule formulation (n=13) compared to those treated with the suspension formulation (n=24).

Table 10. Comparison of PK Parameters Between Capsules (Adults; Study VP-VEC-162-4101) and Suspension (Pediatric Patients 3 Years to Less Than 18 Years Old; Study VP-VEC-162-4201) Formulations

PK Parameter	Suspension (T) Geo Mean (CV%) N=24	Capsules (R) Geo Mean (CV%) N=13	GMR (T/R) [90% CI]
Cmax (ng/mL)	260.76 (58)	231.10 (65)	1.13 [0.81-1.57]
AUC_{4h} (ng/mL*h)	312.95 (45)	285.82 (65)	1.09 [0.80-1.50]
AUC_{inf} (ng/mL*h)	328.44 (48)	310.03 (68)	1.06 [0.76-1.47]
Tmax (min)#	15 (15-30)	30 (30-60)	-
T1/2 (min) #	41 (24-110)	62 (49-95)	-

Source: Reviewer's analysis, based on data from Studies VP-VEC-162-4101 and VP-VEC-162-4201.
Abbreviations: #, median (range); AUC_{inf}, area under the curve to the time of the last concentration; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; GMR, geometric mean ratio; PK, pharmacokinetics; $T_{1/2}$, apparent terminal half-life; T_{max}, time to maximum plasma concentration

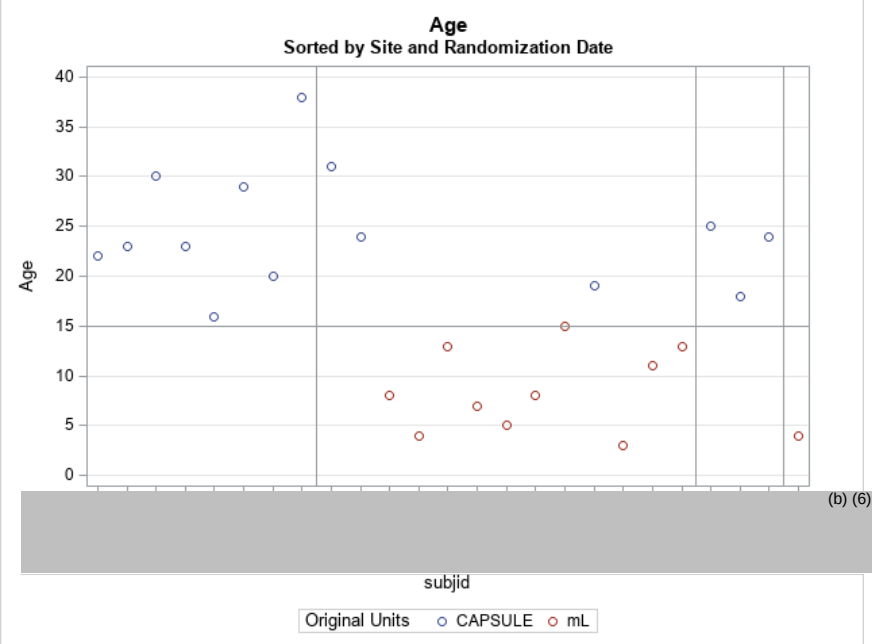
In general, a cross study comparison-based analysis is the less-preferred approach to evaluate relative bioavailability between two different formulations, as compared to a dedicated relative bioavailability study. However, with respect to tasimelteon, the risk associated with the use of a cross-study comparison-based approach appears to be minimal, based on the population PK analyses presented above and the favorable PK characteristics of tasimelteon. Both suspension

and capsules are immediate-release dosage forms, and tasimelteon has high solubility and high permeability. Therefore, the PK differences between these formulations are expected to be minimal. In addition, the PK variability of tasimelteon is approximately 50%, and a high degree of overlap in systemic exposures between the suspension and capsule formulations was observed. In a drug-drug interaction study with a cytochrome P450 (CYP)3A inhibitor, ketoconazole caused a 50% increase in exposure to tasimelteon. Smokers had approximately 40% lower systemic exposure compared to nonsmokers (refer to the package insert for Hetlioz®). However, no dose adjustment was warranted for the above scenarios for the non-24 indication. This suggests that slightly higher exposures in pediatric patients with the suspension, compared to that in adults with the capsule, are not expected to affect the safety and effectiveness of tasimelteon.

b) Assessment of response similarity to tasimelteon in adults and pediatrics

To determine whether the efficacy of tasimelteon is similar between adult and pediatric patients with SMS, the review team performed subgroup analyses of the primary efficacy endpoints in Study 2401. Subjects aged 3 to 15 years received the suspension, and those 16 years and older received the capsule formulation.

Figure 1. Age and Formulation by Site, Study 2401

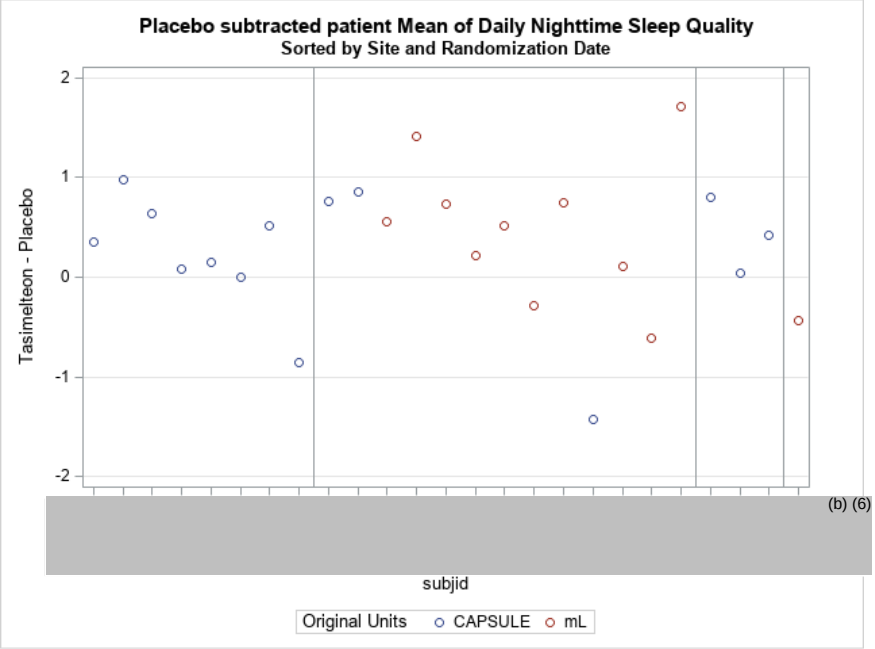


Source: Statistical Reviewer

Patient ages ranged from 3 to 38 years. The age brackets, 3 to 15 years and 16 to 38 years, align with receiving the suspension and capsule formulation, respectively, as planned in Study 2401. The suspension was administered only at clinical site (b) (6) and to one patient at site (b) (6) making this in essence a single-site study for the suspension formulation.

Figure 2 shows the difference between the two treatments in the average sleep quality rating for each patient by age group/formulation. Note that values greater than zero indicate a better average sleep quality rating on tasimelteon compared to placebo. A preliminary visual assessment of the data in this figure does not suggest differential efficacy by age group/formulation.

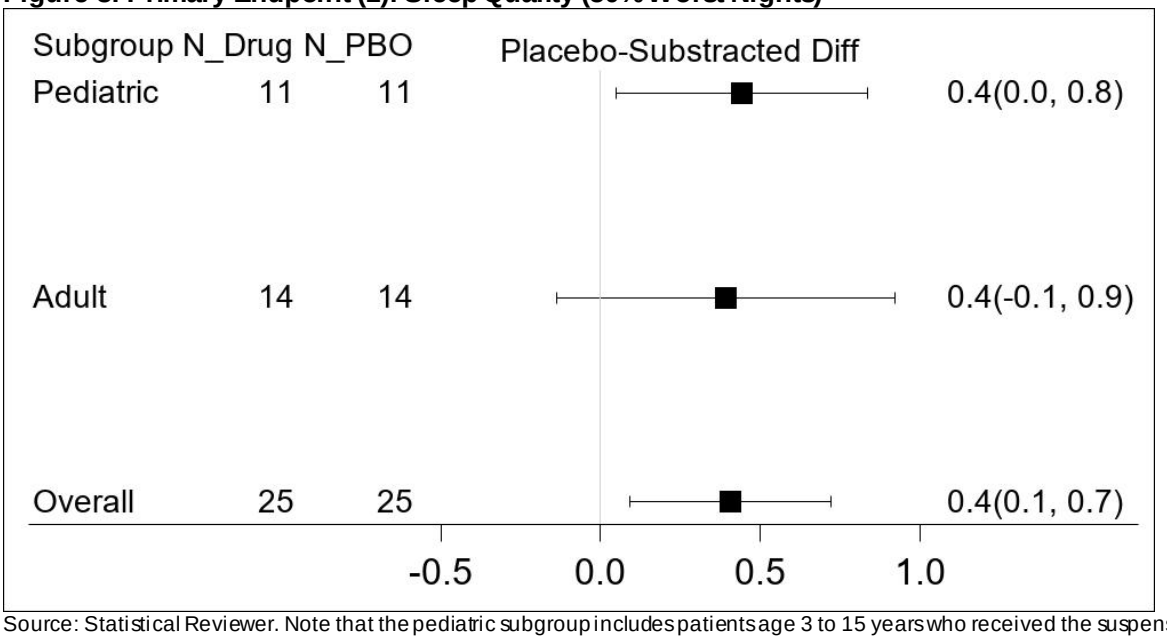
Figure 2. Sleep Quality Efficacy Endpoint (Based on 100% of Data)



Source: Statistical Reviewer

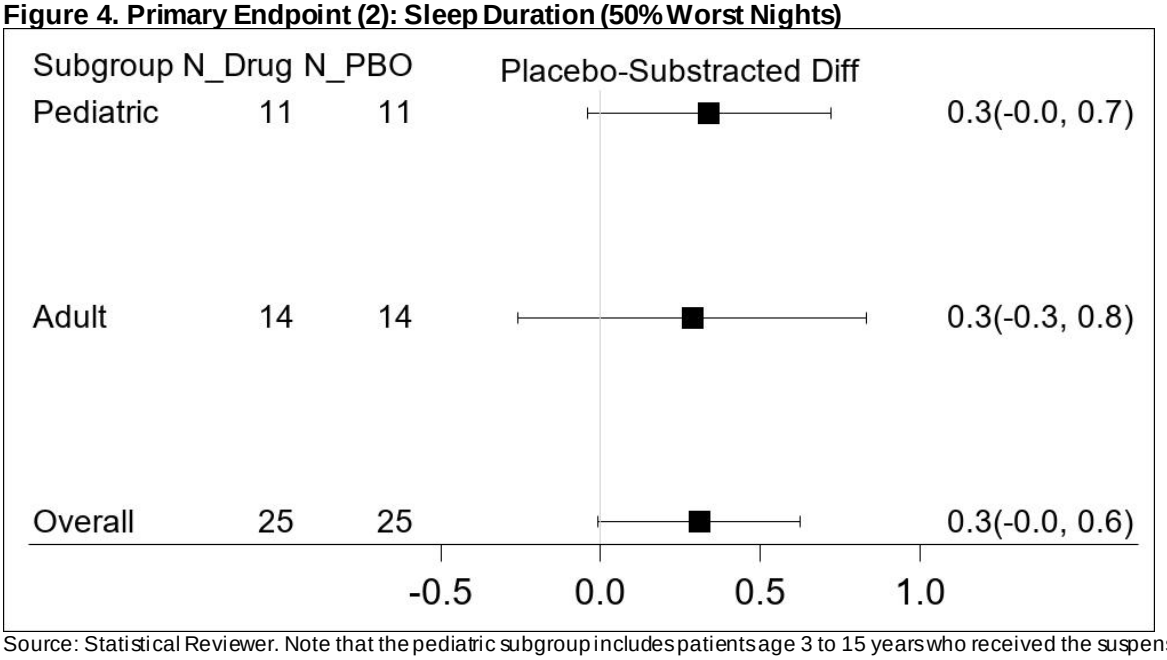
The following two forest plots explore the consistency of the treatment effects across the pediatric and adult subgroups in a more formal manner. Because there are no prespecified subgroup analyses, those conducted aim only to identify serious heterogeneity.

Figure 3. Primary Endpoint (1): Sleep Quality (50% Worst Nights)



Source: Statistical Reviewer. Note that the pediatric subgroup includes patients age 3 to 15 years who received the suspension formulation, and the adult subgroup includes patients 16 years and older who received the capsule formulation.

Figure 4. Primary Endpoint (2): Sleep Duration (50% Worst Nights)



Source: Statistical Reviewer. Note that the pediatric subgroup includes patients age 3 to 15 years who received the suspension formulation, and the adult subgroup includes patients 16 years and older who received the capsule formulation. Sleep duration endpoint is not statistically significant at alpha=0.025 for overall population; any subgroup analyses for the sleep duration data are purely exploratory.
Blacksquares, respective LS means; 95% confidence intervals are in parentheses.

There appears to be no difference between the pediatric and adult subgroups in the results of the two primary efficacy endpoints. In summary, exploratory statistical subgroup analyses of the two primary efficacy endpoints do not yield evidence supporting heterogenous treatment effects between adult and pediatric patients.

Conclusion

The PK assessment found that the two formulations yield sufficiently similar systemic exposures. The statistical assessment found no evidence of heterogeneity in the distribution of efficacy data between the two subpopulations. Based on this information, data from adults and pediatric patients in Study 2401 can be considered together for the primary efficacy evaluation and, therefore, the ITT population is acceptable for the purpose of efficacy evaluation.

6.3.2. Acceptability and Clinical Relevance of the DDSQ50 and DDTST50 as Primary Outcome Measures

Issue

The primary efficacy endpoints of Study 2401 were not agreed with the FDA during the IND development program.

On December 18, 2018, the Applicant submitted protocol Amendment 9 to Study 2401. Prior to Amendment 9, the primary efficacy endpoint was: “improvement in nighttime sleep”, defined as the reduction of the percentage of wake periods within the sleep interval measured by means of an actigraphy watch. With Amendment 9, the primary efficacy endpoint was changed to include two independent endpoints:

- 50% worst daily diary sleep quality (DDSQ50). Sleep quality was recorded daily on the parental Post-Sleep Questionnaire (PSQ). The actual question asked was: "How would you describe the overall quality of their sleep last night?" The average of the 50% worst rating of sleep quality was determined and compared between the placebo and treatment periods for each participant. Sleep quality was rated as follows: 5=excellent; 4=good; 3=average; 2=fair; 1=poor.
- 50% worst daily diary total sleep time (DDTST50). Sleep duration was recorded daily by the parental PSQ. The question was: "How many hours do you think they slept last night?" The average of the 50% worst ratings of sleep duration was determined and compared between the placebo and treatment periods for each participant.

The change in primary efficacy endpoint occurred close to database lock. For this reason, and because of the limited interactions with the Applicant, the FDA could not evaluate, during the IND stage, the clinical meaningfulness and content relevance of the concepts measured by key study endpoints or the content validity and measurement properties (reliability, construct validity, and ability to detect within-patient change) of the instrument used to assess the concepts of interest.

This section summarizes the key factors that the review team considered prior to deciding to accept the prespecified DDSQ50 and DDTST50 as primary measures of outcome.

Assessment

The review team appraised the scientific literature on sleep disorder in SMS and organized a patient listening session to gather information on the disease experience directly from caregivers of individuals with SMS. The review team then carried out additional statistical analyses, including of the secondary endpoints that were identified as clinically relevant, such as "number of nighttime awakenings."

Literature Review on the Ascertainment and Characteristics of Sleep Disturbances in SMS

The typical sleep disturbances associated with SMS are decreased nocturnal sleep time, frequent nocturnal awakenings, early morning awakenings, excessive daytime sleepiness, and daytime napping.

Three methods have been used to quantify the sleep of patients with SMS: clinical polysomnography, actigraphy, and subjective questionnaires or diaries.

A single-night polysomnography study of 28 children and adults with SMS demonstrated that the total sleep time for 43% of the sample was less than 7 hours and that 89% of individuals had more than 10 spontaneous awakenings throughout the night (Potocki et al. 2000).

Polysomnography is the gold standard for evaluating sleep and sleep disorders. However, in individuals with SMS who frequently have sensory and behavioral problems, polysomnography may be unfeasible or uncomfortable to the patient and may disturb sleep (Gropman et al. 2006), especially if observation is prolonged for several days.

Total sleep duration in children with SMS has been assessed using actigraphy in two studies, including 8 and 12 children with SMS. Both studies found a reduced total sleep time compared to age-matched controls (De Leersnyder et al. 2001a; Gropman et al. 2006).

Trichet et al. investigated sleep quality in 20 children with SMS (mean age 8.70 years; SD 2.70 years) and 20 typically developed children using both actigraphy and a paper-based sleep diary (Trickett et al. 2020). Sleep quality was defined by the following parameters: onset latency, sleep onset and offset time, sleep duration, duration of night waking, and sleep efficiency. Sleep in children with SMS was characterized by the total amount of nighttime sleep measured by actigraphy (TST), extended night waking, shorter sleep onset, more daytime naps, and earlier morning waking compared to typically developed children. Considerable interday and interindividual variability in sleep quality was found in the SMS group, so caution is required when generalizing the results.

Actigraphy is less invasive than polysomnography and is therefore more tolerable to patients of all ages. However, as per the literature provided by the Applicant, the ability of actigraphy to detect wakefulness (awakenings during sleep) was low (specificity=0.38) (Kushida et al. 2001), which may limit the usefulness of actigraphy data for obtaining an objective measurement of sleep parameters. For discussion of the limitations of actigraphy data, see Section 6.3.5).

Questionnaires and sleep diaries can be a practical method for clinicians and parents to quantify and evaluate sleep changes during pharmacological and behavioral interventions, provided that caregivers are instructed to use them correctly and check for awakenings during the night (Greenberg et al. 1996; Smith et al. 1998; Gropman et al. 2006).

Patient-Listening Session

Six parents of six patients with SMS participated in the listening session. The age of the subjects with SMS ranged from 5 to 30 years and all were experiencing sleep disorders. Patients who participated in Study 2401 were excluded.

Caregivers were asked 13 questions on three topics, grouped as follows:

- Experience in caring for someone with SMS: evolution of the disease with development and comorbidities;
- Sleep disturbances in SMS: relevance of nighttime compared to daytime experience, clinical meaningfulness of quality of sleep;
- Treatments for sleep disturbances in SMS: medications, supplements, behavioral therapy, and which sleep symptoms were the most or least responsive to treatment.

All caregivers confirmed that sleep disturbances have an early onset and persist throughout life. Caregivers identified difficulty in staying asleep during the night as the most problematic aspect of sleep disturbances, particularly because of the risk of self-harm associated with the subject being awake unsupervised. Initial difficulty falling asleep was not considered a problematic aspect of sleep disturbances. Meltdowns and irritability were considered the most problematic aspects of behavior during daytime; however, the correlation with nighttime sleep was not consistent, and behavioral disorders as a distinct feature of the underlying disease may be a confounder. All six caregivers attributed approximately 80% of the burden associated with sleep disturbances in SMS to the nighttime experience, and 20% to the daytime experience. Daytime naps were beneficial and restorative for some patients, but could be burdensome for others, because they interfered with daytime functioning. Caregivers defined quality of sleep as increased length of continuous (non-interrupted) nighttime sleep, often defined as restorative or deep sleep. Caregivers also reiterated that if they had access to a new treatment for sleep

disturbances, they would desire a drug that allowed the patient to sleep for a duration sufficient to provide deep, restorative sleep.

Statistical Assessment of Using the Average of the 50% Worst Nighttime Ratings of the DDSQ and DDTST

The Applicant reported that the calculation of the average of 50% worst DDSQ was performed by taking the average of the sleep quality in the 50% of nights when the sleep quality was worst. The DDSQ data were first sorted from worst to best, then the average of the 50% worst days was calculated. The average of 50% worst DDTST was calculated in the same way. From a clinical standpoint, in consideration of the high interday variability of sleep disturbances in each SMS subject, the Applicant's approach might be interpreted as aiming to reduce variability and affirm the treatment effect on the most burdensome nights. From a statistical standpoint, cutting the database in half (i.e., by including only the 50% worst days in the mean calculation) tends to introduce greater variability around the means calculated. This might be offset by narrowing the range of the daily values to the 50% worst. Of note, as reported in Section 6.2.1.4, the estimates for the two primary efficacy endpoints based on 50% worst days or on all days are similar. That observation alleviates the statistical concerns about the choice of the 50% worst days as the basis for the primary efficacy endpoints.

Assessment of Clinical Meaningfulness of Daily Diary Sleep Quality

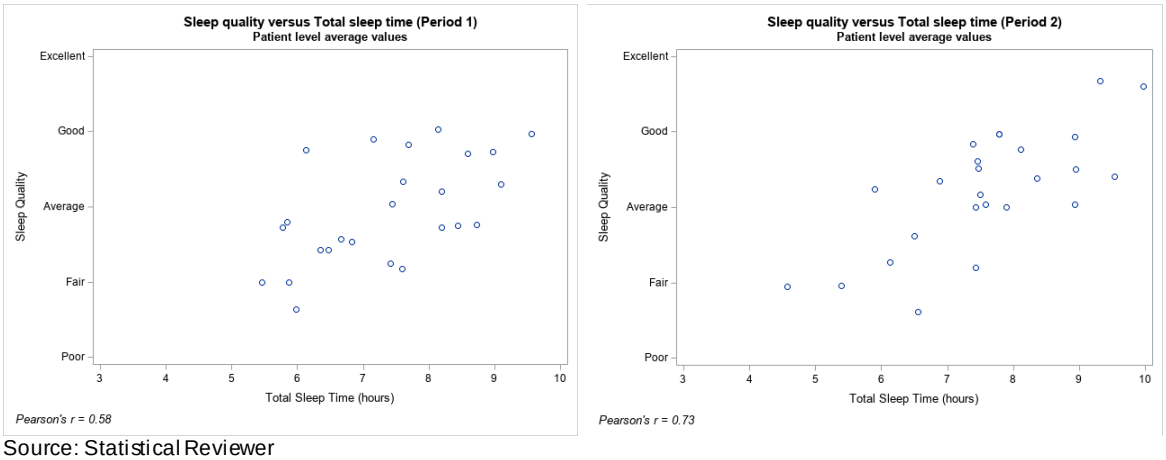
Sleep quality is a multidimensional concept; however, the Applicant did not provide sufficient training or clear training material to establish which aspects of sleep the caregivers considered when rating the sleep quality of the patients.

The concept of sleep quality may include various aspects and/or components related to sleep (e.g., duration of sleep, number and duration of awakenings, latency to persistent sleep). To determine the clinical meaning of the sleep quality item as rated by the caregiver using the electronic diary (eDiary), we explored the relationship between daily diary sleep quality and at least two important sleep parameters: total sleep time and number of nighttime awakenings.

Correlation Between DDSQ and TST

As described above in the literature review on sleep disturbances in SMS, total sleep time is consistently reduced in patients with SMS. In Study 2401, TST is reported in the eDiary as a time unit in response to the question: "How many hours do you think they slept last night?" We found a moderate positive correlation between daily diary sleep quality and daily diary total sleep time (Pearson's r=0.58) in period 1 of Study 2401 and a stronger positive correlation in period 2 (Pearson's r=0.73) (Figure 5).

Figure 5. Correlation Between Quality of Sleep and Total Sleep Time



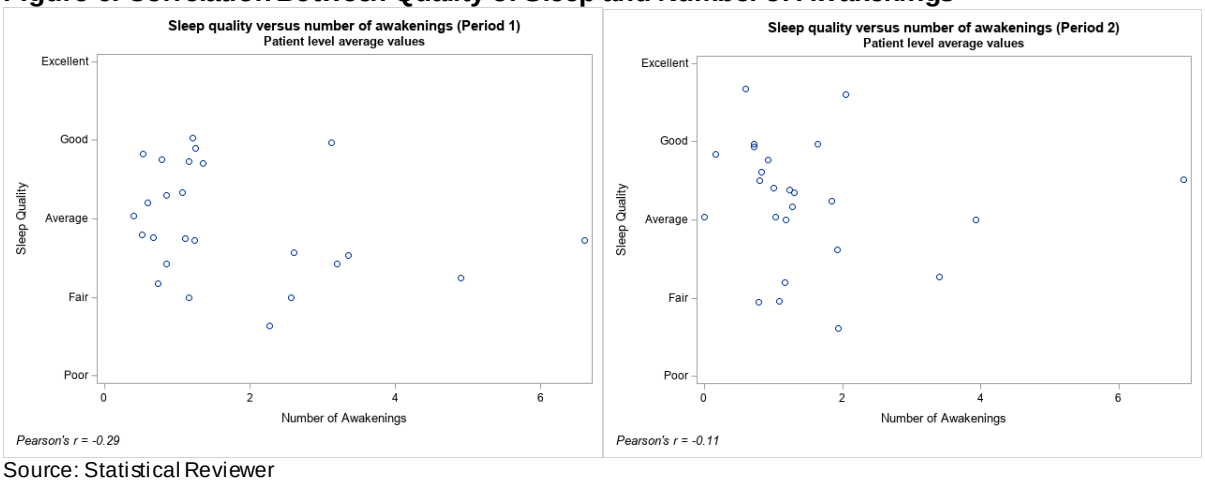
Source: Statistical Reviewer

Correlation Between DDSQ and Number of Awakenings

Nighttime awakenings expose patients to risk of harm and are considered by the caregivers to be one of the most problematic aspects of sleep disorders. The number of awakenings was reported in the eDiary in response to the question: "How many times did they wake up during the night as you are aware?"

We found a weak negative correlation between DDSQ and the number of awakenings (Pearson's r=−0.29) in period 1 of Study 2401 and a weak negative correlation in period 2 (Pearson's r=−0.11) (Figure 6).

Figure 6. Correlation Between Quality of Sleep and Number of Awakenings



Source: Statistical Reviewer

Assessment of the Clinical Relevance of the Five Category Definitions in the DDSQ

The response options for the item DDSQ include five categories—*poor, fair, average, good,* and *excellent*. Due to the lack of qualitative research with caregivers (e.g., concept elicitation and cognitive debriefing), it was unclear whether caregivers would be able to distinguish the response options of *fair* and *average*. It was also unclear whether the change from *fair* to *average* was clinically meaningful in terms of treatment benefit to patients. The review team carried out a sensitivity analysis combining the *fair* and *average* categories to assess the impact of the *fair* and *average* ratings on the primary efficacy analysis. Originally the DDSQ coding had a range from 1=*poor* to 5=*excellent*, in increments of one unit. The coding for this sensitivity analysis has a reduced range, with the *excellent* category being assigned a value of 4, because the *fair* and *average* categories are combined under the numerical value of 2.

This analysis did not impact the overall conclusion (nominal p=0.022, which implies that the statistically significant difference between tasimelteon and placebo in average sleep quality would be unchanged). However, the point estimate of the difference would be reduced from 0.4 to 0.2 (95% CI=0.03, 0.40). This is consistent irrespective of whether we consider the 50% worst days or all days for the sleep quality ratings.

Conclusion

Sleep disturbances in SMS are characterized by increased sleep latency, reduced total sleep time, increased number of nighttime awakenings, early arousal, daytime sleepiness, and daytime naps. The patient listening session confirmed that nighttime continuous restorative sleep is the most important parameter when defining the quality of sleep of patients with SMS. The literature review confirms that caregiver diaries are an acceptable method to assess sleep disturbances in SMS, considering that other methods, such as polysomnography, would not be feasible in this population. That being said, it would have been preferable if caregivers had additional training in rating the items in the daily diary (i.e., sleep quality). The additional analyses conducted by the review team led to the conclusion that the use of the caregiver daily diary was acceptable to inform both primary efficacy measures.

The statistical analysis confirmed that the caregiver's rating of sleep quality improves when patients sleep for a longer period of time and tends to worsen when patients wake up more frequently at night. Limiting the analysis to the 50% worst nights, as compared with all nights, does not change the overall conclusions on efficacy. Although there was initial concern that the DDSQ category definitions (specifically, the response options of 2=*fair* and 3=*average*) might affect the interpretation of results, a sensitivity analysis that collapsed *fair* and *average* into one category found that the statistically significant difference between tasimelteon and placebo would remain.

The review team concluded that the item Daily Diary Quality of Sleep is an acceptable outcome measure because its rating reflects changes in two important parameters of nighttime sleep known to be impaired in SMS and that are relevant for caregivers and patients with SMS.

The item daily diary total sleep time is also an acceptable primary endpoint because, based on the review of the scientific literature, the total duration of nighttime sleep is consistently reduced in patients with SMS and also because the caregivers who participated in the patient listening session confirmed that sleep duration is a relevant sleep parameter.

6.3.3. Assessment of Possible Biases Introduced by the Crossover Design or the Re-enrollment of Five Subjects From the Open-Label Cohort Into the Randomized Treatment Arm of Study VP-VEC-162-2401

Issue

Study 2401 is designed as a two-period crossover trial. According to the Applicant, the choice of the clinical trial design was meant to incentivize enrolment and minimize exposure to placebo. However, the design comes with the assumption of no carryover (or confounded) effect. If the untestable assumption is violated, a differential carryover effect may bias the efficacy results.

In addition, a cohort of 11 patients was initially treated with tasimelteon in an open-label manner to generate data to optimize the study design and schedule of assessments for the Randomized Treatment Arm. Patients enrolled in this cohort were eligible to re-enroll in the randomized portion of Study 2401 after open-label study completion. This practice may have generated a bias in the efficacy results, because patients or caregivers who perceived some benefit from treatment with tasimelteon might have been more likely to opt for re-enrollment.

This section summarizes the evaluation of possible biases in the efficacy results introduced by the study design or the re-enrollment of five subjects from the open-label cohort into the randomized pivotal study.

Assessment

Assessment of Differences Between Treatment Sequences A and B of Study 2401

Numerical differences are noted in the primary efficacy results between the two treatment sequences (i.e., Sequence A, TAS then PLA; Sequence B, PLA then TAS), with Sequence B exhibiting an almost one-DDSQ-category difference (0.8) between tasimelteon and placebo treatment, but Sequence A showing almost no difference (0.1). The main difference between the two sequences appears to arise from differences in the mean sleep quality ratings on tasimelteon (2.5 in Sequence A and 3.1 in Sequence B), whereas the mean sleep quality scores were almost identical for the placebo treatment (Table 11).

Table 11. Primary Efficacy Results for Sleep Quality (DDSQ50) by Treatment Sequence

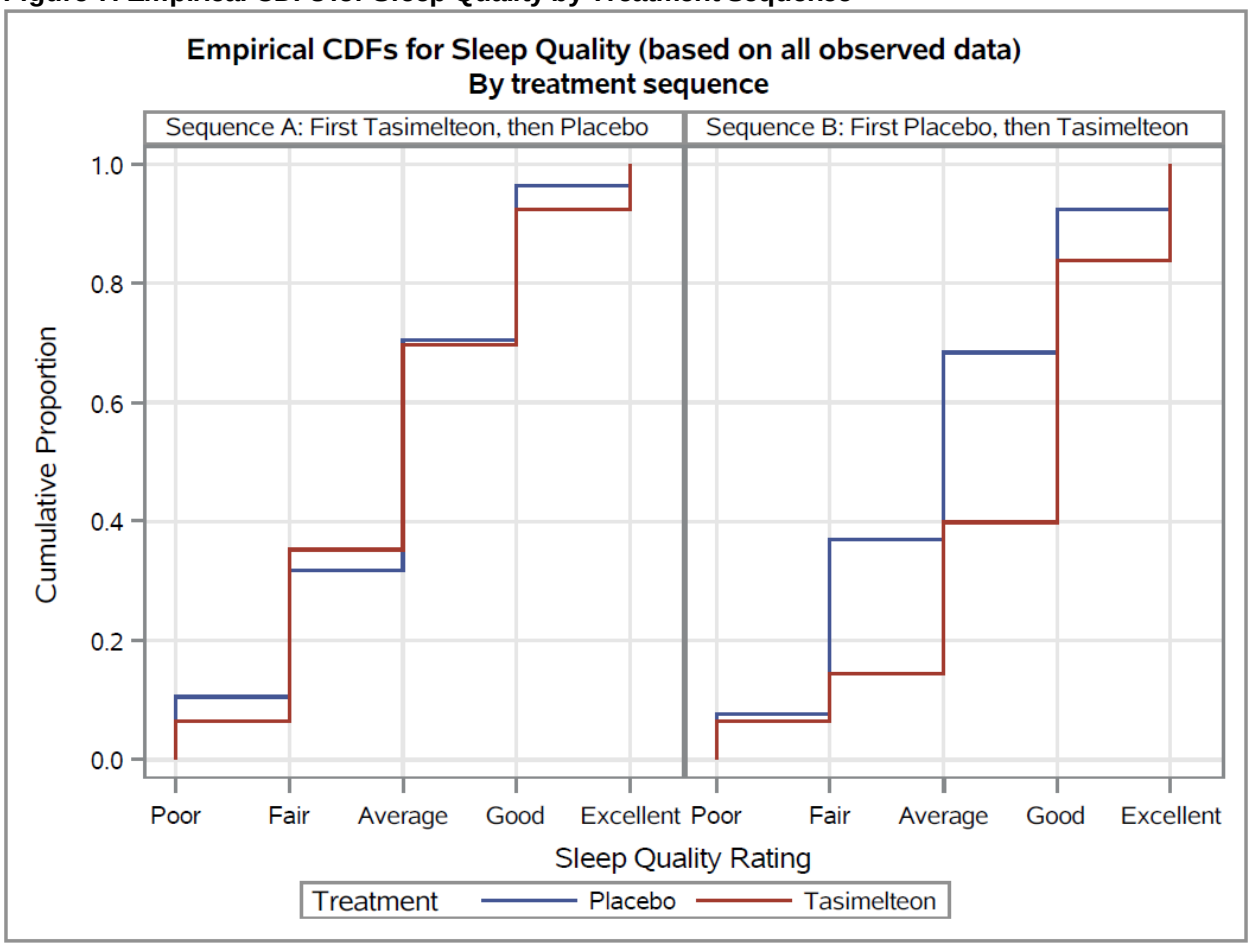
Sequence	Period 1	Washout	Period 2	Difference
	TAS		PLA	
Sequence A	2.5		2.4	0.1
	PLA		TAS	
Sequence B	2.3		3.1	0.8

Source: Statistical Reviewer.
Abbreviations: PLA, placebo; TAS, tasimelteon

The apparent difference between the two treatment sequences can also be observed from the empirical cumulative distribution function (eCDF) curves (based on 100% of the data, not only the 50% worst as in the primary analysis) in Figure 7. There is almost no difference between the proportions of patients on tasimelteon or placebo rated at a certain sleep quality level for

Sequence A (left panel). However, there are notable differences, especially for the *fair* and *average* ratings, for Sequence B (right panel).

Figure 7. Empirical CDFs for Sleep Quality by Treatment Sequence



Source: Statistical Reviewer
Abbreviation: CDF, cumulative distribution function

With period, sequence, and carryover effect being aliased in the two-period crossover design, a closer examination is warranted. Any potential treatment by period interaction is not of a qualitative type in Study 2401. We observed the same trend (i.e., the sleep quality average rating is better for tasimelteon compared to placebo) in both sequences.

The observed difference between the sequences; i.e., treatment difference of 0.1 (95% CI=−0.4, 0.5) for Sequence A and 0.8 (95% CI=0.2, 1.3) for Sequence B, could be a result of random fluctuations.

A pharmacological carryover, if any, can occur only in sequence A, with tasimelteon administered in the first period and placebo in the second. However, the average sleep quality rating during the placebo treatment in sequence A (2.4) is not notably larger than the average placebo sleep quality rating in sequence B (2.3). That negates the possibility of a pharmacological carryover.

The remaining potential issue for period 2, namely that patients would somehow know they were taking drug in period 2 because of their experience with placebo in period 1, seems unlikely given the benign safety and tolerability profile of tasimelteon.

The considerations above led to the overall conclusion that the extent of potential bias in estimating treatment effect from a crossover design (with the inherent assumption of no carryover effect) is negligible in this trial.

Sensitivity Analysis of the ITT Population Excluding the Five Patients Re-enrolled From the Open-Label Cohort

To assess the impact of the five re-enrolled patients on the efficacy results, the review team carried out a sensitivity analysis of the ITT population excluding the five re-enrolled patients. The results of the sensitivity analysis are consistent with those of the primary efficacy analysis (Table 12 and Section 6.2.1.4.2).

An additional sensitivity analysis was conducted for two secondary endpoints—average DDSQ and average DDTST (Table 12). The results of the sensitivity analysis show the same differences between tasimelteon and placebo in the ITT population and in the ITT population without the five re-enrolled patients.

Table 12. Sensitivity Analyses Without Five Re-enrolled Subjects

Primary Efficacy Endpoints and Variant	Placebo	Tasimelteon	Difference (TAS – PLA)	Nominal p-value
[1a] Average of 50% worst daily nighttime sleep quality (n=25)	2.4	2.8	0.4	0.0139
[1a*] (n=20)	2.2	2.7	0.5	0.0056
[1b] Average of daily nighttime sleep quality (n=25)	2.9	3.3	0.3	0.0155
[1b*] (n=20)	2.7	3.2	0.4	0.0053
[2a] Average of 50% worst daily total amount of nighttime sleep – hours (minutes) (n=25)	6.7	7.0	0.3 (18)	0.0556
[2a*] (n=20)	6.6	7.0	0.4 (24)	0.0083
[2b] Average of daily total amount of nighttime sleep – hours (minutes) (n=25)	7.3	7.7	0.4 (21)	0.0134
[2b*] (n=20)	7.2	7.6	0.5 (27)	0.0028

Source: CSR and Statistical Reviewer
Abbreviations: PLA, placebo; TAS, tasimelteon

The re-enrollment of five patients appears to have had a conservative effect on the efficacy results.

Conclusion

From a clinical standpoint, the two-period crossover design is acceptable because it minimizes exposure to placebo. From a biostatistical perspective, the extent of potential bias in estimating treatment effect from a crossover design (with the inherent assumption of no carryover effect) is negligible. A sensitivity analysis showed no difference in the efficacy results between the ITT population with or without the five subjects re-enrolled from the open-label cohort.

The review team concluded that the clinical trial design and the re-enrollment of five patients from an open-label cohort into the Randomized Treatment Arm of the pivotal study do not introduce bias for the purpose of the efficacy evaluation.

6.3.4. Assessment of Impact of Subjects on Concomitant Beta-Adrenergic Receptor Antagonists in the Efficacy Evaluation

Issue

The current label for Hetlioz includes the following statement in section 14: *The efficacy of HETLIOZ in treating non-24 may be reduced in subjects with concomitant administration of beta-adrenergic receptor antagonists*. The synthesis and release of melatonin are stimulated by norepinephrine via beta1-adrenoceptors, which is potentiated by stimulation of alpha1-adrenoceptors (Brismar et al. 1988; Stoschitzky et al. 1999). Beta blockers have been shown to reduce the production of melatonin by specifically inhibiting beta-1 adrenergic receptors, and their use is associated with sleep disturbances, including awakenings at night and nightmares.

Unlike patients with non-24, those with SMS show an inverted melatonin cycle, and beta-adrenergic receptor antagonists may be beneficial for daytime sleepiness if taken between 10 am and 12 pm, the period of peak melatonin secretion.

Study 2401 includes five patients on concomitant beta-adrenergic receptor antagonists. Specifically, subjects (b) (6) and (b) (6) were on acebutolol; subject (b) (6) was on atenolol, and subjects (b) (6) and (b) (6) were on propranolol. To ascertain the impact of patients on concomitant beta-adrenergic receptor antagonists on the efficacy results and to inform labeling, the review team performed additional sensitivity analyses.

Assessment

To assess the impact of the five subjects on concomitant beta-adrenergic receptor antagonists on the efficacy results, the review team carried out primary efficacy analyses of the ITT population excluding these five subjects.

Tasimelteon was statistically superior to placebo in improving average DDSQ50 (difference=0.47, p=0.01). Tasimelteon was superior to placebo in improving DDTST50; however, the difference did not reach statistical significance (difference=0.34, p=0.06). The results are consistent with those of the primary efficacy analysis.

Table 13. Sensitivity Efficacy Analyses Without Five Patients on Beta-Adrenergic Receptor Antagonists

Primary Efficacy Endpoints	Placebo	Tasimelteon	Difference (TAS − PLA) [95% CI]	p-Value
[1a] Average of 50% worst daily nighttime sleep quality (n=25)	2.4	2.8	0.41 [0.1, 0.7]	0.01
[1a^] Without 5 patients on “eta-blockers (n=20)	2.35	2.81	0.47 [0.1, 0.8]	0.01
[2a] Average of 50% worst daily total amount of nighttime sleep − hours (minutes) (n=25)	6.7	7.0	0.31 (18) [−0.01, 0.62]	0.06
[2a^] Without 5 patients on beta-blockers (n=20)	6.7	7.0	0.34 (20) [−0.02, 0.71]	0.06

Source: CSR and Statistical Reviewer
Abbreviations: CI, confidence interval; PLA, placebo; TAS, tasimelteon

The exclusion of patients on concomitant beta-adrenergic receptor antagonists led to a minimal and not clinically significant increase in the point estimates. A further exploratory analysis on the set of five patients on concomitant beta-adrenergic receptor antagonists alone suggests no effect on DDSQ50 (difference=0) and a potentially small benefit on DDTST50 (difference=0.2).

Conclusion

The sensitivity analysis shows that the inclusion of five subjects on concomitant therapy with beta-adrenergic receptor antagonists in Study 2401 does not affect the efficacy evaluation. However, the wording of the label should take into account the pharmacological interaction between the two drugs, particularly if they are coadministered during the night.

6.3.5. Usability of Actigraphy Data for Supporting the Primary Endpoint in the Evaluation of Efficacy

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 Study 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 nonlaboratory 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, because 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 have been 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, behavioral, or physiological 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 2401wore 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) were chosen as a case-study to compare sleep and wake periods between actigraphy-generated data and eDiary reports. The review team also discussed the compliance of subjects enrolled in Study 2401 with use of the actigraphy watch and the amount of missing data.

Characteristics of the Actigraphy Watch

The motion sensor is a solid-state accelerometer, range 0.5 to 2 G, resolution 100 counts or 0.02 G, and sampling at 32 Hz. The off-wrist sensor is a capacitor formed by two metal plates as part of a bistable multivibrator, with an on-wrist activation distance of <2 mm. The light sensor is a radiometer recording red, green, blue irradiance or weighted white-light illuminance. The single-axis acceleration data are transformed into activity counts per minute using a proprietary algorithm. These counts reflect a feature of the total magnitude of acceleration 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 were collected prior to the initiation of pivotal study VP-VEC-162-2401 using the same actigraphy watch. Despite the lack of established standards for the conduct of feasibility or usability studies, these are a necessary part of the analytical validation of DHTs to ascertain their suitability for the target population (Bakker et al. 2019). In addition, the Applicant provided scientific literature in support of the use of actigraphy watches in patients with SMS (Agar et al. 2020; Trickett et al. 2020). The Applicant claimed that the watch was well tolerated; however, data on compliance or tolerability were not submitted and perhaps prolonged use of the watch (Study 2401 consisted of a 4-week

[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 general wellness to medical devices. 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

Screening Phase and 9-week Treatment Phase) as compared to the short duration of Study 1401 (36 hours) proved challenging for some patients.

Actigraphy Compliance Data in Study 2401

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

According to the Applicant, 5 of 25 patients in the ITT population did not have 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 Phase. 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 five patients with no actigraphy data, no other patients were deemed noncompliant with actigraphy based on these requirements, because there was sufficient data in patients who wore the watch and had scorable data.

The Processing Pipeline

For Study 2401, the *Spectrum Classic* actigraphy watch captures motion and light data during wear by the patient. Once removed from the patient, the *Spectrum Classic* device is connected to a *Spectrum Dock*, which is connected via Universal Serial Bus to a site computer with the study-specific Actiware CT software installed. The *Spectrum 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 sent by site personnel via e-mail to the vendor scoring team. A scoring-team member stored the received datasets on a secure Philips-owned server. The vendor used Actiware software to score the received data for sleep and activity endpoints via validated algorithms within the software. The endpoint data were then returned to the Applicant via a password-protected e-mail.

Performance Metrics of the Algorithm

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 a 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 it as awake, and accuracy is the probability of correctly scoring any epoch over the total number of epochs scored (Kushida et al. 2001). These performance metrics were estimated from a population of adults with sleep disorders.

As explained by de Zambotti et al., for Philips Respironics algorithms, the *low* threshold requires smaller activity counts to deem an epoch as wake, increasing specificity but at the cost of

sensitivity. Conversely, the *medium* threshold increases sensitivity at the cost of specificity, as a result of the greater activity count threshold required for wake (de Zambotti et al. 2019).

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 influence the amount of activity during both wake and 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.

Case Study

The case study compared the activity data with the caregiver eDiary reports of time of sleep and to awake to explore the relationship between these two data sources. In Figure 8 and Figure 9, the log activity counts (dark-colored lines) are plotted against time of day (midnight=0 hours). The wear status and sleep status (asleep versus awake) are plotted as 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 activity count patterns: a period of time when 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 to 3 logs (count-derived night). The clinical meaning of the nighttime spikes and relatively constant daytime activity is unclear without evidence from video logs or caregiver reports.

Comparing the scored sleep and count-derived night periods to the caregiver-reported sleep times, notice that the quality of the caregiver reporting differs between subjects (b) (6) and (b) (6). For subject (b) (6), the actigraphy watch indicated that the patient may have stayed awake after the caregiver reported initiation of sleep. For subject (b) (6), the eDiary time to sleep was close to the switch between count-derived day and count-derived night. However, subject (b) (6) may have awakened before the caregiver reported awakening. Without further validation, these impressions are limited to the data in Figure 8 and Figure 9.

Figure 8. Activity Counts, Wear Status, and Sleep Status a Sample Patient ((b) (6)) on a Sample Day (Day 196)

Source: Statistical Reviewer

Figure 9. Activity Counts, Wear Status, and Sleep Status for Two Patients on Multiple Days

(b) (6)

Source: Statistical Reviewer

Anchoring DHT-generated data to a known clinical scale or, as in this case, to a patient-reported outcome is necessary 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., PSG) or video recording to train and verify the algorithm as able to detect wake as true wake.

The complexity is increased by the clinical characteristics of the population of subjects with SMS, whose sleep architecture and level of activity during sleep and wake may differ from those of 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, the Applicant

provided no evidence on the effects of spikes of activity counts on this algorithm in patients with SMS. In addition, the Applicant did not submit information on 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 activity monitors would 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.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

No nonclinical studies were submitted in support of NDA 205677-007 for the treatment of sleep disorder in SMS in adult patients. One nonclinical study, a juvenile rat toxicity study (study no. TAJ0026; see Section 13.2), was submitted to NDA 214517 in support of the indication for the treatment of sleep disorder in SMS in pediatric patients. No significant safety concerns were identified when tasimelteon was administered to juvenile rats for 10 weeks followed by a 4-week recovery period (refer to Sections 8.3 and 13.2). The toxicities observed in juvenile animals—including premature deaths, tremors, decreases in body weight and bone growth, increases in motor activity, decreases in prepulse inhibition, and delays in sexual maturation—were observed at high multiples (>178 times) of the proposed maximum recommended human dose in pediatric patients. Due to the large safety margin, the potential risk to humans is low and can be adequately addressed through a description of the animal data in Section 8.4 of the label. A complete nonclinical safety evaluation of tasimelteon was conducted in support of the non-24 indication under NDA 205677 and all identified safety concerns and potential risks were addressed in the approved label for tasimelteon. Refer to the pharmacology/toxicology review under the original NDA 205677 for the complete safety review.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

No specific class adverse reactions have been described for melatonin receptor agonists. There is only one other FDA-approved drug with a mechanism of action similar to that of tasimelteon. Ramelteon is a melatonin receptor agonist with high affinity for both melatonin MT_1 and MT_2 receptors and relative selectivity for the MT_3 receptor. Ramelteon is indicated for the treatment of insomnia characterized by difficulty with sleep onset. The following warnings and precautions are listed in the product label for ramelteon: severe anaphylactic reactions, abnormal thinking, and behavioral changes in association with hypnotics (including suicidal ideation and completed suicides), complex sleep behavior, effects on the central nervous system (CNS), and effects on reproductive hormones. Of note, differences in melatonin receptor-binding affinities (selectivity

of MT_3 receptors) and the differences in the target population could result in differences in the safety profile of ramelteon as compared to tasimelteon.

The safety of tasimelteon capsules was evaluated for the indication of non-24 in NDA 205677. In this section, we report the main conclusions of the clinical safety review of NDA 205677.

Across the entire safety database submitted for NDA 205677, there were no deaths and few nonfatal serious adverse events. The incidence of serious adverse events was comparable between patients receiving tasimelteon and placebo, and there were no clear patterns in the nature of events to suggest a causal signal.

The proportion of subjects who experienced any treatment-emergent adverse event that led to early termination was even between the treatment groups in the entire safety database. Treatment-emergent adverse events that led to early discontinuations in two or more subjects in the tasimelteon group were: nightmare (n=3), rash (n=3), insomnia/middle insomnia (n=3), and blood CK increased (n=2).

Tasimelteon was not associated with adverse effects due to abrupt withdrawal, as assessed by the Tyrer Benzodiazepine Withdrawal Symptoms Questionnaire and other appropriate safety data which were considered adequate for such an assessment. Similarly, tasimelteon was not associated with next-day residual effects, as assessed by Digit Symbol Substitution Test, Visual Analog Scale (mood scale assessing sleepy/alert), and the Karolinska Sleepiness Scale.

Somnolence, as a next-day residual effect, was not a safety signal in nonelderly adult subjects with non-24 when tasimelteon was administered around bedtime. However, elderly female subjects with insomnia taking tasimelteon had a higher incidence of somnolence compared to placebo control.

Tasimelteon was not associated with an adverse effect on suicidal ideation and behavior, as assessed by the Columbia-Suicide Severity Rating Scale and other safety data considered adequate for such an assessment.

The following common treatment-emergent adverse events, defined as events experienced by at least three subjects in the tasimelteon group and at a more than two-fold greater frequency than in the placebo group, were identified in subjects with non-24: headache, alanine aminotransferase increased, abnormal dreams/nightmare, cardiac conduction disorder, sleep disorder, upper respiratory tract infection, somnolence, and urinary tract infection.

Tasimelteon did not adversely affect other laboratory measures of liver injury, and the available data are sufficient to conclude that the potential for tasimelteon-induced liver injury is low. Tasimelteon does not adversely affect other metabolic or endocrine laboratory parameters.

Tasimelteon was not associated with adverse changes in electrocardiogram or cardiac-related adverse events. Overall, the potential for an adverse effect of tasimelteon on cardiac repolarization is low based on the available data, which are sufficient for such a determination.

Tasimelteon does not have adverse effects on vital signs.

FDA clinical reviewer's comment*: The review of NDA 205677 indicates that tasimelteon has a fairly benign safety profile in patients with non-24, with few nonfatal serious adverse events and no effect on suicidal ideation and behavior or metabolic and endocrinologic laboratory parameters. Most treatment-emergent adverse events (TEAEs) are related to abnormal sleep, consistent with knowledge of formulations containing melatonin, and infections.*

7.3. Potential Safety Concerns Identified Through Postmarket Experience

The Division of Pharmacovigilance (DPV) completed a Postmarket Drug Safety Surveillance Summary (PDSSS) for tasimelteon in April 2019 (summarized in Section 7.3.3). To assist with this NDA review, DPV performed an updated search of the FDA Adverse Events Reporting System (FAERS) database. DPV also performed a disproportionality assessment for selected adverse events in Empirica Signal (Section 7.7.1). DPV's objectives included identifying any safety concerns that might be present in postmarket data and potentially impact the safety review of this application. DPV focused on adverse events of interest, including respiratory tract infection, upper respiratory tract infection, and urinary tract infections, as well as all pediatric adverse event reports.

7.3.1. FAERS Search Strategy

DPV searched the FAERS database using the strategy described in **Table 14**.

Table 14. FAERS Search Strategy*

Date of search	August 19, 2020
Time period of search	January 15, 2019† to August 18, 2020
Search type	Product-Manufacturer Reporting Summary
Product terms	Tasimelteon
MedDRA search terms (version 22.1)	All adverse events

Source: DPV Pharmacovigilance Memorandum; November 3, 2020.
Abbreviation: MedDRA, Medical Dictionary for Regulatory Activities.
† Update from Postmarket Drug Safety Surveillance Summary completed on April 1, 2019 (data lock date January 14, 2019).

7.3.2. FAERS Results

The updated FAERS search retrieved 1,141 reports, bringing the total number of reports for tasimelteon in FAERS to 3,300 from approval to August 18, 2020. Table 15 lists the characteristics of the adverse event reports for tasimelteon received by the FDA from January 15, 2019 to August 18, 2020. Report counts may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse), miscoded reports, or unrelated reports. Reported outcomes for this section are the coded outcomes submitted to FDA; the causality and role of the product in the coded outcome have not been determined for all reports.

Table 15. Descriptive Characteristics of FAERS Reports With Tasimelteon, All Reports Received by FDA From January 15, 2019 to August 18, 2020*

Characteristic	N=1,141†
Sex, (n=1,133)	
Male	432
Female	701
Age group, years (n=181)	
≥7 to <18	1
≥18 to <65	110
≥65	70
Country of participation, n (%)	
United States	1,135
Other	6

Characteristic	N=1,141[†]
Report type	
Expedited	187
Periodic	954
Serious outcomes[‡] (n=189)	
Death	53
Hospitalization	79
Disability	1
Other serious	72

Source: DPV Pharmacovigilance Memorandum; November 3, 2020.
* Update from Postmarket Drug Safety Surveillance Summary (PDSSS) completed on April 1, 2019 (data lock date January 14, 2020).
[†] May include duplicates.
[‡] For the purposes of this document, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. A report may have one or more outcome.

7.3.3. DPV Assessment

Safety Signals From April 2019 PDSSS

Upon completion of the PDSSS for tasimelteon in April 2019, DPV identified three newly identified safety signals (NISS) that required further workup:

- Seizures (no signal upon further review, as described in the Melatonin Receptor Agonists and Seizures Pharmacovigilance Memorandum[2])
- Somnambulism (monitoring)
- Suicidal ideation and behavior (monitoring)

DPV identified three cases of completed suicide in FAERS through January 14, 2019 as described in the April 2019 PDSSS. DPV did not identify additional cases of completed suicide in the updated search. Two of the three cases lacked sufficient information for assessment regarding underlying psychiatric comorbidities and temporal associations. One case occurred in a patient with underlying schizoaffective disorder and post-traumatic stress disorder prior to the use of tasimelteon. The remaining case (FAERS #14226934) occurred in a 54-year-old female who was hit by a train in a suspected suicide per the patient's spouse. This event occurred approximately 3 weeks after initiating therapy with tasimelteon. The report stated that the patient's spouse inquired about "whether tasimelteon was associated with suicidal ideations or tendencies." The report did not provide the patient's medical history or concomitant medications.

The clinical safety review of tasimelteon for the treatment of non-24 (NDA205677) concluded that tasimelteon was not associated with suicidality as assessed by the Columbia Suicide Severity Rating Scale. Of note, the Warnings and Precautions section of the labeling for ramelteon, another melatonin receptor agonist, includes worsening of depression (including suicidal ideation and completed suicides).[3]

[2] Harbourt, K. Melatonin Receptor Agonists and Seizures Pharmacovigilance Memorandum, June 3, 2019. RCM 2019-874, DARRTS Ref ID: 4442574.

[3] Rozerem [Package Insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; December 2018 (Accessed September 16, 2020).

See Section 7.7.1 for postmarketing analyses specific to respiratory tract infections, upper respiratory tract infections, and urinary tract infections.

Pediatric Reports

DPV retrieved a total of 10 reports in patients less than 18 years of age from FAERS for tasimelteon, only one of which was received by FDA after January 15, 2019. These 10 pediatric adverse event reports occurred in patients of ages 12 to 17 years, the majority of whom were female (n=7). Of these 10 reports, one patient died for a reason unrelated to tasimelteon (progression of malignant astrocytoma). The remaining nine reports were nonserious and reported preferred terms (PTs) including, but not limited to: *Abdominal discomfort, Constipation, Diarrhea, Dyssomnia, Fatigue, Headache, Product prescribing error,* and *Urticaria*.

DPV did not identify any postmarketing safety issues that would affect the review of NDA 205677/S-7 or NDA 214517 and will continue routine pharmacovigilance for tasimelteon.

7.4. FDA Approach to the Safety Review

7.4.1. Sources of Data for Clinical Safety Assessment

Data from Study 2401 formed the basis of the clinical safety evaluation of tasimelteon in the SMS population.

A summary of the design of Study 2401 can be found in Section 6.2.1.1, and a full description of the trial design in Section 15.

Study 2401 recruited only from U.S. sites. Although SMS has been identified worldwide in all ethnic groups, the clinical trial population consists only of subjects defined as white and, as such, may not represent the diversity of the U.S. general population. Based on the known safety profile of tasimelteon and the other approved melatonin receptor agonist, ramelteon, we do not expect the safety profile to differ according to ethnicity.

In the judgement of the review team, the size of the safety database and the duration of exposure permit a safety evaluation in a reasonable number of patients over a duration of time consistent with the intended use of the drug.

7.4.2. Safety Analysis Plan and Definitions

No major data quality or integrity issues were identified that would preclude performing a safety review for this NDA. The Applicant translated verbatim terms to Medical Dictionary for Regulatory Activities (MedDRA) PTs for the events reported in Study 2401; the translations were reviewed and found to be acceptable.

Use of descriptive statistics for summarizing the safety outcomes was predefined in the protocol.

Adverse events (AEs) were protocol-defined as any untoward medical occurrence in a clinical investigation patient who does not necessarily have a causal relationship with treatment.

Because SMS subjects may have several pre-existing conditions, these conditions were recorded as an AE if the frequency, intensity, or characteristics of the condition worsened during the study period.

Serious adverse events (SAEs) were protocol-defined as any untoward medical occurrence that occurs during the clinical study and that:

- Results in death.
- Is life-threatening (defined as an event that, in the opinion of the investigator, would have resulted in immediate fatality in the absence of medical intervention. This does not include an event that would have been fatal if it had been more severe).
- Requires inpatient hospitalization (defined as an event that results in admission to hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility).
- Causes prolongation of existing hospitalization (defined as an event that occurs while the patient is hospitalized and prolongs the hospital stay).
- Is a congenital anomaly/birth defect (defined as an anomaly detected at or after birth, or any anomaly that results in fetal loss).
- Results in persistent or significant disability/incapacity (defined as an event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include transient interruptions of daily activities or experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma).
- Is an important medical event (defined as an important medical event that, based on medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of a patient, life-threatening, inpatient hospitalization, prolongation of existing hospitalization, congenital anomaly, or persistent or significant disability/incapacity).

Treatment-emergent adverse events were defined in the protocol as AEs newly occurring or worsened from baseline (i.e., adverse events that started after the first dose of study drug) and started no more than 3 days after the date of the final dose of study drug.

However, the review team noted that tasimelteon is almost completely eliminated from the body by ~6 hours. Tasimelteon does not accumulate in the circulation upon repeat once-daily administration; therefore, it is highly unlikely that adverse events occurring >24 hours after the last dose are caused by tasimelteon.

For the purposes of the NDA review, TEAEs are considered to be AEs that began after the first dose of a treatment and no later than 24 hours after the last dose.

Adverse drug reactions are defined as any TEAE considered related to the study drug with reasonable likelihood.

7.4.3. Reviewer's Approach to the Safety Evaluation

Clinical trial data were independently analyzed using JMP Clinical. The Applicant provided safety tables; the data therein were verified by the Associate Director of Biomedical Informatics to accurately reflect the data from the submitted datasets and case report forms.

Study 2401 included both adult subjects who took the capsule formulation and pediatric subjects (3 years to 15 years) who took the suspension formulation.

Given that adult and pediatric subjects were evaluated together in Study 2401 and the PK of the capsule and suspension formulations are relatively similar (Section 6.3.1), the TEAEs observed in adult and pediatric subjects are reported together in the safety tables.

Safety in the pediatric population is reviewed separately in Section 17.

The safety population includes subjects in both the Randomized Treatment Arm and the Open-Label Arm of Study 2401.

When pooling the two arms, subjects in the Randomized Treatment Arm are counted twice because they were exposed to both tasimelteon and placebo during the two periods of the crossover study.

Because of the crossover design of the Randomized Treatment Arm, AEs could occur during period 1, period 2, or the washout period. For example, AEs occurring in period 1 could last several days and persist during the washout period or during period 2. To facilitate interpretation of the safety data, the review team established that AEs were counted as occurring during a period (e.g., period 1 placebo or tasimelteon) if they began after the first treatment dose of that period but not >24 hours after the last dose. For example, adverse events that began 3 days into the washout period were not included in the AE tabulations for either treatment period. If AEs began in period 1 and continued into period 2 without resolution, they were not counted again for period 2.

7.5. Adequacy of the Clinical Safety Database

The safety database is adequate for a comprehensive safety assessment of tasimelteon for the indication of sleep disturbances in SMS for the proposed dose regimen and duration. The International Council on Harmonisation (ICH) guidance for industry E1A *The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* (March 1995) describes expected exposure for chronically used drugs for non-life-threatening conditions, but these expectations do not apply to rare diseases and the guidance states that a smaller number of patients may be acceptable when the intended treatment population is small.

SMS is a rare genetic disorder that affects at least 1 in 25,000 individuals globally (Greenberg et al. 1991) but is likely underdiagnosed and may have a true prevalence closer to 1 in 15,000 individuals (Smith and Duncan 2005).

Importantly, Study 2401 includes a wide age range (3 to 39 years) of subjects and therefore multiple phenotypic subtypes and pediatric subjects are represented in the safety population. In addition, and despite the small sample size, a placebo arm is included in the study, facilitating interpretation of adverse event causality.

Table 16 summarizes the exposure periods for Study 2401; of note, the Open-Label Extension is ongoing. The mean (SD) duration of exposure is 97.6 (60.97) weeks for the group exposed to tasimelteon and 3.7 (0.81) weeks for the group exposed to placebo. The duration of exposure in the SMS development program, in conjunction with the long-term exposure data from the overall tasimelteon development program, is adequate to allow a safety assessment to support prolonged daily use in subjects with SMS. Table 17 shows exposure data in the overall tasimelteon

development program: more than 380 subjects were exposed to tasimelteon for at least 6 months and more than 170 subjects for at least 1 year.

Table 16. Duration of Exposure, Safety Population, Patients With SMS

Parameter[1]	Tasimelteon 20 mg N=47	Placebo N=26
Duration of treatment, weeks		
Mean (SD)	97.6 (60.97)	3.7 (0.81)
Median (min, max)	104.4 (5.3, 206.1)	3.9 (0.4, 4.4)
Range	37.4-120.4	3.6-4.1
Total exposure (person, years)	4587.3 (87.9)	95.1 (1.8)
Patients treated, by duration, n (%)		
Any duration (at least 1 dose)	47 (100.0)	26 (100.0)
<1 month	0 (0.00)	14 (53.8)
≥1 month	47 (100.0)	12 (46.2)
≥3 months	44 (93.6)	0 (0.00)
≥6 months	43 (91.5)	0 (0.00)
≥12 months	31 (66.0)	0 (0.00)

Source: Applicant
Abbreviations: N, number of patients in the treatment arm; n, number of patients with a given treatment duration; range, interquartile range; SD, standard deviation
[1] Includes data up to October 2, 2020.

Table 17. Duration of Exposure, Safety Population, Pooled Analysis[1]

Parameter	Tasimelteon <20 mg N=191	Tasimelteon 20 mg N=1337	Tasimelteon >20 mg N=555	Tasimelteon N=2083	Active Control[2] N=156	Placebo N=955
Duration of treatment, weeks						
Mean (SD)	2.6 (1.83)	25.2 (56.00)	1.6 (2.03)	16.8 (46.25)	0.2 (0.13)	4.0 (5.32)
Median (min, max)	3.9 (0.1, 5.3)	5.0 (0.1, 472.3)	0.3 (0.1, 8.1)	2.0 (0.1, 472.3)	0.1 (0.1, 0.4)	1.9 (0.1, 31.4)
Range	0.1-4.0	0.3-28.0	0.1-4.0	0.1-8.9	0.1-0.4	0.4-7.7
Total exposure (person, years)	487.4 (9.3)	33682 (645.5)	892.4 (17.1)	35062 (672.0)	38.6 (0.7)	3774.4 (72.3)
Patient treated by duration, n (%)						
Any duration (at least one dose)	191 (100.0)	1337 (100.0)	555 (100.0)	2083 (100.0)	156 (100.0)	955 (100.0)
<1 month	101 (52.9)	628 (47.0)	401 (72.3)	1130 (54.2)	156 (100.0)	529 (55.4)
≥1 month	90 (47.1)	709 (53.0)	154 (27.7)	953 (45.8)	0 (0.00)	426 (44.6)
≥3 months	0 (0.00)	499 (37.3)	0 (0.00)	499 (24.0)	0 (0.00)	36 (3.8)
≥6 months	0 (0.00)	383 (28.6)	0 (0.00)	383 (18.4)	0 (0.00)	31 (3.2)
≥12 months	0 (0.00)	173 (12.9)	0 (0.00)	173 (8.3)	0 (0.00)	0 (0.00)

Source: Applicant

Abbreviations: N, number of patients in the treatment arm; n, number of patients with a given treatment duration; range, interquartile range; SD, standard deviation

[1] Includes patients and healthy volunteer from studies in ISS, 4101, 4102, 3202 (ongoing), 2102, 3107, 1201, and 2401 (ongoing). The Open-Label Extension Phases of ongoing studies 3202 and 2401 include data up to October 2, 2020.

[2] Active control includes midazolam, moxifloxacin, fluvoxamine, ketoconazole, rifampin and rosiglitazone.

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

The safety evaluation of tasimelteon was adequate and the demonstrated safety profile of tasimelteon in subjects with SMS is acceptable at the indicated dose. Overall, there is no clear pattern of safety issues; however, the causality assessment is complicated by the confounding effect of the complex medical history of the subjects, their comorbidities, and the small size of the safety population due to the rarity of the disorder.

No deaths were reported in Study 2401. The SAEs, as well as the AEs leading to discontinuation, were deemed not related to tasimelteon.

Because of the small size of the safety population it is not possible to determine the frequency of the most common AEs; however, infections and infestations are the most frequent AEs and TEAEs. The frequency of infections increases with increasing exposure. Therefore, considering the predisposition of subjects with SMS to develop spontaneous infections, the review team concluded that it is not necessary to monitor occurrence of infections in the postmarketing setting beyond routine pharmacovigilance.

No clinically relevant changes in chemistry, hematology, or urinalysis parameters were observed over time and between treatment groups, consistent with the known safety profile of tasimelteon. Tasimelteon did not affect electrocardiograms (ECGs) or vital signs.

7.6.1. Safety Findings and Concerns, Study VP-VEC-162-2401

7.6.1.1. Overall Adverse Event Summary

Table 18 provides a summary of TEAEs reported as occurring in subjects enrolled in the Randomized Treatment Arm of Study 2401. Because of the crossover design, TEAEs are reported only if newly occurring in each study period. Although the number of reported AEs in period 1 is higher in the tasimelteon group, the number of reported AEs in period 2 was higher in the placebo group. The review team concluded that the frequency of AEs is overall very low, with no clinically significant difference between placebo and tasimelteon.

Table 19 also includes subjects treated with tasimelteon in the Open-Label Arm and OLE of Study 2401. When pooling the two arms, the overall frequency of any AE is higher in subjects exposed to tasimelteon. However, because of the crossover design, randomized subjects are counted twice because they were exposed to both tasimelteon and placebo. Moreover, the duration of exposure to placebo is 4 weeks in the Randomized Treatment Arm, and the duration of exposure to tasimelteon is 9 weeks in the Open-Label Arm and up to 197 weeks in the OLE. Therefore, a possible alternative explanation is that longer exposure increases the likelihood that subjects will experience AEs caused by the underlying condition or that might otherwise occur spontaneously.

Table 18. Overview of Treatment-Emergent Adverse Events,[1] Randomized Population

Event	Period_1 Tasimelteon N=13 n (%)	Period_1 Placebo N=13 n (%)	Period_2 Tasimelteon N=12 n (%)	Period_2 Placebo N=13 n (%)
SAEs[2]	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
SAEs with fatal outcome	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Life-threatening SAEs	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
SAEs requiring hospitalization	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
SAEs resulting in substantial disruption of normal life functions	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Congenital anomaly or birth defect	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Other	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
AE leading to permanent discontinuation of study drug	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
AE leading to dose modification of study drug	1 (7.69)	0 (0.00)	0 (0.00)	0 (0.00)
AE leading to interruption of study drug	1 (7.69)	0 (0.00)	0 (0.00)	0 (0.00)
AE leading to reduction of study drug	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
AE leading to dose delay of study drug	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Other	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Any AE	5 (38.46)	3 (23.08)	1 (8.33)	4 (30.77)
Severe	1 (7.69)	0 (0.00)	0 (0.00)	0 (0.00)
Moderate	2 (15.38)	3 (23.08)	1 (8.33)	0 (0.00)
Mild	2 (15.38)	0 (0.00)	0 (0.00)	4 (30.77)

Source: Applicant
Abbreviations: AE, adverse event; N, number of patients in the treatment arm; n, number of patients with at least one event; SAE, serious adverse event
[1] Treatment-emergent AEs (TEAEs) are defined as AEs that newly occurred or worsened from baseline (i.e., AEs that started after the first dose of study drug) and started no more than 24 hours after the date of the last dose of study drug. AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA version 18.0) coding dictionary.
[2] Patients are counted only once under the highest severity level.

Table 19. Overview of Treatment-Emergent Adverse Events,[1] Safety Population[2, 3, 4]

Event	Tasimelteon (N=47) n (%)	Placebo (N=26) n (%)
SAEs	0 (0.00)	0 (0.00)
SAEs with fatal outcome	0 (0.00)	0 (0.00)
Life-threatening SAEs	0 (0.00)	0 (0.00)
SAEs requiring hospitalization	0 (0.00)	0 (0.00)
SAEs resulting in substantial disruption of normal life functions	0 (0.00)	0 (0.00)
Congenital anomaly or birth defect	0 (0.00)	0 (0.00)
Other	0 (0.00)	0 (0.00)
AE leading to permanent discontinuation of study drug	0 (0.00)	0 (0.00)
AE leading to dose modification of study drug	2 (4.26)	0 (0.00)
AE leading to interruption of study drug	2 (4.26)	0 (0.00)
AE leading to reduction of study drug	0 (0.00)	0 (0.00)
AE leading to dose delay of study drug	0 (0.00)	0 (0.00)
Other	0 (0.00)	0 (0.00)

Event	Tasimelteon (N=47) n (%)	Placebo (N=26) n (%)
Any AE	19 (40.43)	6 (23.08)
Severe	1 (2.13)	0 (0.00)
Moderate	9 (19.15)	3 (11.54)
Mild	9 (19.15)	3 (11.54)

Source: Applicant
Abbreviations: AE, adverse event; N, number of patients in the treatment arm; n, number of patients with at least one event; SAE, serious adverse event
[1] Treatment-emergent AEs (TEAEs) are defined as AEs that are newly occurred or worsened from baseline (i.e., AEs that started after the first dose of study drug) and started no more than 24 hours after the date of the last dose of study drug.
[2] Patients are counted only once under the highest severity level.
[3] Patients who received both placebo and tasimelteon in this crossover study are counted under both tasimelteon and placebo.
[4] AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA version 18.0) coding dictionary.

7.6.1.2. Deaths

None of the subjects died during participation in clinical studies of tasimelteon.

7.6.1.3. Serious Adverse Events

Across the Randomized Treatment Arm and the Open-Label Treatment Arm of Study 2401, no subject experienced a nonfatal SAE.

However, six events corresponding to the protocol definition of SAEs occurred during the study. Four SAEs in subjects (b) (6), and (b) (6) were reported during the Open-Label Extension Phase after the patients' last visit during the treatment period (V5, Week 9), and two SAEs, both in subject (b) (6), were reported during the Screening Phase before the first dose of medication. These six SAEs were regarded as non-treatment-emergent by the Applicant.

Given the small number of SAEs as well as their medical complexity, the clinical narratives submitted by the Applicant with the reviewer's comments on causality are provided below.

Subject (b) (6), a (b) (6) year-old (b) (6) with a previous nonserious AE of UTI, experienced an SAE of *sepsis post cystoscopy*. The subject signed informed consent on (b) (6), and was randomized to tasimelteon on (b) (6). The subject entered the open-label phase on Study Day 64 ((b) (6)). During the course of the study, the subject showed three urine cultures positive for coagulase-negative *Staphylococcus* and the subject was reported to be asymptomatic. On Study Day 221, computed tomography revealed a nonobstructing renal stone. The treating physician noted that the nephrolithiasis was an unlikely cause of the subject's recurrent UTIs and prescribed a cystoscopy. On Study Day 244, the subject presented to the hospital with complaints of abdominal pain, fatigue, and a fever of 101.8°F, unrelieved by acetaminophen or ibuprofen. The treating physician suspected the fever to be related to postcystoscopy bacteremia. Treatment of the event involved acetaminophen, alprazolam, ciprofloxacin-dexamethasone, famotidine, heparin, ibuprofen, ketorolac, senna-docusate, sulfamethoxazole-trimethoprim, intravenous normal saline, vancomycin, ceftriaxone, and cefazolin. Additional diagnoses during the subject's hospitalization were neutropenia, hypocalcemia, ECG abnormalities, leukocytosis, elevated bilirubin, and thrombocytopenia. The study medication was interrupted due to the event on Study Day 244. On Study Day 246 the event was considered resolved and the subject was discharged from the hospital. The study medication was restarted on Day 251, the subject was continued in the study.

The subject's medical history included right eye myopia (progressive), congenital strabismus, left prosthetic eye, bilateral mixed hearing loss, hearing aid (bilateral), acid reflux, elevated alkaline phosphatase (bone), mild hypoglycemia, anxiety, heart murmur, blepharitis, scleral shell, ear canal erythema, and allergy to Ceclor (hives) (able to take other cephalosporins).

The investigator considered the event of sepsis postcystoscopy as severe in intensity, unrelated to study drug, and reported the cystoscopy procedure as its suspected cause.

FDA Clinical reviewer's comment: *The subject reported UTIs several times during the course of the clinical study. Infections and urinary tract abnormalities are common in patients with SMS. The subject underwent cystoscopy, and such a procedure in presence of a UTI could result in sepsis. I concur with the investigator and the Applicant that the event is not likely related to tasimelteon.*

Subject (b) (6), a (b) (6)-year-old (b) (6) with a history of seizure disorder (since (b) (6)) who had been seizure-free since (b) (6), experienced an SAE of *tonic-clonic seizure*. The subject signed informed consent on (b) (6) and was randomized to tasimelteon on (b) (6). The last dose of study medication prior to the onset of the event was administered on Study Day 91 (b) (6)).

On Study Day 98, at approximately 09:00 the subject experienced a tonic-clonic seizure consisting of stiffening, decorticate posturing, generalized convulsions, and urinary incontinence for 2 minutes. The subject was subsequently transported to hospital but was not hospitalized. In the emergency department, an electrocardiogram revealed possible right ventricular conduction delay but an otherwise normal presentation. X-ray of the chest revealed no infiltrate or effusion. The event was considered resolved on Study Day 98. Treatment of the event included oxcarbazepine, levetiracetam, and vitamin B. The subject was referred to neurology for follow-up and was prescribed oxcarbazepine. No action related to study medication was taken as a result of the event, because the study medication had been interrupted 7 days prior due to antibiotics being administered as treatment for bronchitis.

The subject's medical history included chronic constipation, menstrual cramps, hypotonia, ventricular septal defect, intermittent swollen left groin lymph node, salmonella, and keratosis pilaris.

Concomitant medications (taken at the time of the event) included sertraline, fish oil, probiotic, polyethylene glycol 3350, iron supplement, and ibuprofen.

The investigator considered the event of tonic-clonic seizure as severe in intensity, an important medical event, and unrelated to study medication. The investigator reported reoccurrence of the subject's seizure disorder as an alternate etiology of the event. The Applicant considered the event of tonic-clonic seizure as unrelated to study medication.

FDA Clinical reviewer's comment: *Seizures are clinical features in 11% to 30% of individuals with SMS. The subject had a history of seizures (since (b) (6)) and, therefore, the SAE is likely related to the underlying condition rather than to the study drug.*

Subject (b) (6), a (b) (6)-year-old (b) (6) reported a history of small bowel obstruction and postileostomy status, experienced an SAE of *enteritis*. The subject signed informed consent on (b) (6), and was in screening at the time of the event. Study medication had not been initiated at the time of the event.

On (b) (6), the subject began to experience symptoms of enteritis. On (b) (6), the subject presented to the emergency department with complaints of nausea, diarrhea, vomiting, and worsening abdominal pain. The subject was subsequently admitted to the hospital for further evaluation and treatment of enteritis. Treatment of the event included naloxone, flumazenil, ionhexol ondansetron, potassium chloride, metronidazole, levofloxacin, hydromorphone, pantoprazole, and sodium chloride. On (b) (6), a physical examination revealed a soft abdomen, normal bowel sounds, no distention, and no tenderness. On the same date, the event was considered resolved and the subject was discharged from the hospital. No action related to the study medication was taken as a result of the event. The subject continued in the study. Their medical history included anxiety disorder, neurogenic bladder, scoliosis, eight-segment spinal fusion, seborrhea, dental implant failure, chronic pain syndrome, and neuropathy (nonspecific).

Concomitant medications (taken at the time of the event) included oxybutynin ER, promethazine, lorazepam, hydrocodone/acetaminophen, aripiprazole, and xulane patch.

FDA Clinical reviewer's comment*: The nature and duration of the event suggest it to be infectious. The subject had not yet taken the study medication at the time of the event; therefore, a relationship to tasimelteon can be excluded.*

On (b) (6) (Day −131) the same subject experienced *drug-induced liver injury.*

Central laboratory testing at Visit 3 revealed an ALT of 226 U/L, AST of 160 U/L, and ALP of 141 U/L. Upon receipt of the laboratory results, the investigator instructed the subject to defer initiation of study medication until further notice and referred the subject to her primary care physician for additional follow-up. The subject was referred to the emergency department and subsequently admitted to the hospital on (b) (6), for further evaluation and treatment of levofloxacin-induced hepatitis. During the hospitalization, the subject's liver enzymes reportedly improved with intravenous sodium chloride. Treatment of the event included docusate sodium, ondansetron, morphine, hydromorphone, pantoprazole, and lorazepam. On (b) (6), the event of levofloxacin-induced hepatitis was considered resolved with sequelae of "elevated liver enzymes (nonserious adverse event)," and the subject was discharged from the hospital with instructions to continue to withhold initiation of study medication until further notice. On (b) (6), the subject underwent an outpatient evaluation by a gastroenterologist and the investigator reported, "Since all tests are coming back negative, [the gastroenterologist] thinks the likely cause of the liver issue was a reaction to the Levaquin (levofloxacin) (b) (6) was on after her May hospitalization."

On (b) (6), the subject underwent liver biopsy, which revealed that "findings were minimal and nonspecific but could be compatible with drug/medication effect."

The subject was continued in the study and treatment with study medication was initiated on (b) (6).

The subject's medical history included enteritis (previously reported SAE) nausea, anxiety disorder, scoliosis, neurogenic bladder, seborrhea, dental implant failure, chronic pain syndrome, and neuropathy.

Concomitant medications (taken at the time of the event) included oxybutynin ER, promethazine, lorazepam, Xulane, hydrocodone/acetaminophen, and aripiprazole.

The investigator and the Applicant considered the event of levofloxacin-induced hepatitis as severe in intensity and unrelated to study medication (subject had not initiated study medication at the time of the event).

FDA Clinical reviewer's comment*: The event has a temporal relationship with the administration of levofloxacin, for which hepatitis is among the serious and sometimes fatal adverse reactions reported in the label. The event cannot be related to tasimelteon administration, because the full narrative reported that treatment initiation was deferred until after the event was resolved.*

Subject (b) (6), a (b) (6)-year-old (b) (6) with a sleep disturbance related to their diagnosis of SMS, and a history of chronic lung disease of prematurity, experienced an SAE of *parainfluenza pneumonia*. Informed consent was signed on (b) (6) (b) (6) and the subject was randomized to tasimelteon on (b) (6). The subject entered the open-label phase on Study Day 62 ((b) (6)).

The first dose of study medication was administered on (b) (6). The last dose prior to the onset of the event was administered on Study Day 202 ((b) (6)).

On Study Day 203 ((b) (6)), the subject experienced wet cough, runny nose and chest congestion. Home dose of albuterol, unspecified steroids, and azithromycin were given but did not improve the symptoms. On Study Day 210 ((b) (6)), the subject's symptoms worsened with low-grade fever, coughing spells with emesis, and increased lethargy. On Study Day 211 ((b) (6)), the subject presented to the pediatric clinic and was directed to the hospital for further evaluation. Laboratory testing revealed a white blood cell count of 8.9, c-reactive protein level of 76.8, and elevated glucose of 145 (normal range [NR] and units not provided). Blood cultures were obtained and yielded negative results. Respiratory virus profiling by polymerase chain reaction-based test was positive for parainfluenza. A chest x-ray revealed prominent interstitial markings throughout both lungs, and some degree of interstitial pulmonary edema could not be excluded. An ECG revealed a normal sinus rhythm, left axis deviation, and a right bundle branch block. The ECG also revealed mild tricuspid valve regurgitation, normal right ventricular systolic function, qualitatively normal left ventricular size and systolic function, no significant pulmonary stenosis, post-Melody valve placement status, post-Tetralogy of Fallot surgery status, mild dilation of the right ventricle, trivial pulmonary valve regurgitation, no intracardiac shunt, and no pericardial effusion. Treatment of the event included albuterol sulfate, budesonide, cetirizine, montelukast, fluticasone, and oxygen. On Study Day 213 ((b) (6)), symptoms improved, and the subject was discharged from the hospital. The event was considered resolved on the same day. No action related to the study drug was taken as a result of this event. The subject continued in the study.

The subject's medical history included immune deficiency, laryngomalacia, scoliosis, methicillin-resistant *Staphylococcus aureus* infection, recurrent thrush, hypogammaglobulinemia, and allergies to Augmentin, Bactrim, and ketamine.

Concomitant medications (taken at the time of the event) included budesonide, montelukast, risperidone, epinephrine, Gamunex, and acetylsalicylic acid.

The investigator and the Applicant considered the event of parainfluenza pneumonia as severe in intensity and unrelated to study medication.

***FDA Clinical reviewer's comment**: I concur that the event was caused by a viral infection and therefore is not related to the study drug.*

Subject [redacted] is a [redacted]-year-old [redacted] with a sleep disturbance related to the diagnosis of SMS experienced an SAE of *pneumonia (aspiration)*. The subject signed informed consent on [redacted] and was randomized to tasimelteon or placebo on [redacted]. The subject entered the open-label phase on Study Day 64 ([redacted]).

The first dose of study medication was administered on [redacted]. The last dose prior to the onset of the event was administered on Study Day 958 ([redacted]).

On Study Day 965 ([redacted]), the subject was admitted to the hospital with aspiration pneumonia related to being bed-ridden and immobile. Further details and treatment of the event had not been provided at the time of this report. On Study Day 986 ([redacted]), the event was considered resolved. The subject remained hospitalized at the time of this report (to be confirmed). The study medication was interrupted because of the event. The subject continued in the study.

The subject's medical history included lung congestion, seizures, and Lennox-Gastaut syndrome.

Concomitant medications (taken at the time of the event) included phenobarbital, Diastat rectal gel, rufinamide, scopolamine, Depo-Provera, levetiracetam, clobazam, Valproic acid, and lacosamide.

The investigator and the Applicant considered the event of pneumonia (aspiration) as severe in intensity and unrelated to study medication.

***FDA clinical reviewer's conclusion**: The event of aspiration pneumonia was caused by prolonged immobility and lethargy, the latter suggesting that a relationship to the study drug cannot be excluded. However, a more plausible explanation is the combination of multiple antiepileptics and their effect on CNS-related motricity.*

7.6.1.4. Dropouts and/or Discontinuations Due to Adverse Events

Two subjects had AEs leading to study drug interruption (Table 20); both were receiving tasimelteon, one in the Randomized Treatment Arm and the other in the Open-Label Treatment Arm of Study 2401.

Table 20. Adverse Events Leading to Drug Interruption

Subject ID	AE Term	AE Start Date	AE End Date	AE Action	AE Causality	Date of First Exposure in Period 01	Date of Last Exposure in Period 01	Date of First Exposure in Period 02	Date of Last Exposure in Period 02
[redacted]	STOMACH FLU	[redacted]	[redacted]	Drug Interrupted	Not Related	[redacted]	[redacted]		
	INFECTED BUG BITE			Drug Interrupted	Not Related				[redacted]

Source: Applicant's response to a clinical information request.
Abbreviations: AE, adverse events; flu, influenza; ID, identification

Below are the narratives, as provided by the Applicant, for subjects who reported AEs leading to drug discontinuation.

Subject [redacted] was a [redacted]-year-old [redacted]. His medical history included seasonal allergy [redacted], back pain [redacted] bladder spasm [redacted], sleep apnea syndrome [redacted], attention deficit/hyperactivity disorder [redacted], cytogenetic abnormality [redacted], ASD [redacted], and apraxia [redacted]. [redacted] began dosing with 20 mg of tasimelteon on [redacted] (Day 1), and ended dosing with 20 mg of tasimelteon on [redacted] (Day 286).

On [redacted] (Day 53) the subject experienced a *viral gastroenteritis (stomach flu)* (moderate) which was considered a significant AE. On the day of the event, the subject was taking 20 mg of tasimelteon, as [redacted] had been for 53 days. The AE occurred 52 days after the first dose of any study medication. The therapeutic measure administered for the event was ibuprofen. Concomitant medications taken at the onset of the AE were aripiprazole, ibuprofen, loratadine, methylphenidate hydrochloride, naltrexone, and solifenacin succinate. The Applicant considered the AE to be not related to study medication. The event ended on [redacted] (Day 54) with a final outcome of recovered/resolved.

Subject [redacted] was a [redacted]-year-old [redacted]. [redacted] medical history and concomitant medications are described in Section 7.6.1.3.

On [redacted] (Day 34) the subject experienced an *infected bite (infected bug bite)* (mild) which was considered a significant AE. On the day of the event, the subject was taking 20 mg of tasimelteon, as [redacted] had been for 2 days. The AE occurred 33 days after the first dose of any study medication. Therapeutic measures were administered for the event. AEs occurring within a ±30-day window of AE onset were respiratory tract infection (mild). Concomitant medications being taken at AE onset were clindamycin, fish oil, ibuprofen, iron, macrogol, probiotics, and sertraline hydrochloride. The Applicant considered the AE to be not related to study medication. The event ended on [redacted] (Day 46) with a final outcome of recovered/resolved.

***FDA reviewer's conclusion**: Based on their nature, I concur that these events leading to discontinuation of study drug (viral infection and infected bite) were likely not treatment-related.*

7.6.1.5. Treatment-Emergent Adverse Events

A combination of data from the Randomized and Open-Label Treatment Arms were used to assess the general AE profile of tasimelteon in the SMS population. However, only data from the Randomized Treatment Arm will be considered for inclusion in a common AE table, because the Open-Label Arm lacks a treatment comparator.

The review team felt that the causality assessment was very challenging in this population because of the small sample size, but most importantly because of the complexity of the clinical manifestations of the underlying condition. For this reason, the possibility to compare the AE incidences to placebo was indispensable to present data in an interpretable tabular view.

The crossover design added complexity to the assessment and, for this reason, the clinical review team established that TEAEs were counted as occurring during a period only (e.g., period 1) if they began after the first treatment dose of that period but not >24 hours after the last dose of treatment. For example, adverse events that began 3 days into the washout period were not included in the AE tabulations for the treatment periods. If AEs began in period 1 and continued into period 2 without resolution, they were not counted again for period 2. Table 21 summarizes all TEAEs by PT; Table 22 summarizes all TEAEs by system organ class (SOC).

Table 21. Patients With Common TEAEs,[1] Randomized Population[2, 3, 4]

Preferred Terms	Period 1 Tasimelteon N=13 n (%)	Period 1 Placebo N=13 n (%)	Period 2 Tasimelteon N=12 n (%)	Period 2 Placebo N=13 n (%)
Patients with any TEAE	5 (38.5)	3 (23.1)	1 (8.3)	4 (30.8)
Acne	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)
Anaphylactic reaction	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Anxiety	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)
Dermatillomania	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)
Diarrhoea	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)
Emotional disorder	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Gastroenteritis viral	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)
Infected bites	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Insomnia	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)
Lethargy	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)
Nasopharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)
Otitis externa	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)
Paronychia	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Proteinuria	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory tract infection	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)

Source: Applicant; ADAE1.sas7bdat; software, SAS 9.4.
Abbreviations: AE, adverse event; N, number of patients in the treatment arm; n, number of patients with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event
[1] TEAEs are defined as AEs that newly occurred or worsened from baseline (i.e., AEs that started after the first dose of study drug) and started no more than 24 hours after the date of the last dose of study drug.
[2] Patients are counted only once under the highest severity level.
[3] Adverse events occurring after 24 hours of the last dose of Treatment Phase will be summarized for the Open-Label Extension Phase.
[4] AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA version 18.0) coding dictionary.

Table 22. Patients With Common TEAEs[1] by System Organ Class, Randomized Population

System Organ Class[2]	Period_1 Tasimelteon N=13 n (%)	Period_1 Placebo N=13 n (%)	Period_2 Tasimelteon N=12 n (%)	Period_2 Placebo N=13 n (%)
Patients with any TEAE	5 (38.5)	3 (23.1)	1 (8.3)	4 (30.8)
Infections and infestations	2 (15.4)	1 (7.7)	1 (8.3)	2 (15.4)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)
Nervous system disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)
Psychiatric disorders	1 (7.7)	2 (15.4)	0 (0.0)	1 (7.7)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)
Immune system disorders	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Applicant
Abbreviations: %, 100×n÷N; AE, adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event
[1] TEAEs are defined as AEs that newly occurred or worsened from baseline (i.e., AEs that started after the first dose of study drug) and started no more than 24 hours after the date of the last dose of study drug. AEs are summarized according to the treatment at event onset. AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA version 18.0) coding dictionary. AEs occurring after 24 hours of the last dose of the Treatment Phase will be summarized for the Open-Label Extension Phase.
[2] Patients are counted only once at each level of summation.

In period 1, more TEAEs were reported in subjects on tasimelteon compared to placebo, but in period 2 only one event occurred in subjects on tasimelteon as compared to four newly occurring TEAEs in subjects on placebo. The review team observed that the number of reported AEs was small overall, and there was no clear imbalance between the treatment and placebo groups. The numerical differences may be an expression of the casual distribution of events in

the population. In addition, the list by preferred term shows a heterogeneous group of clinical events targeting multiple body systems, which does not seem to represent a clear pattern of adverse reactions specific to either the mechanism of action or safety profile of tasimelteon. Some events, such as *paronychia*, occur frequently in subjects with SMS, whereas others, such as *infected bites*, are not plausibly related to tasimelteon.

The safety of tasimelteon has been evaluated in the population of subjects with non-24. Patients with non-24 have several clinical features similar to those of patients with SMS, including psychiatric and medical comorbidities. Therefore, the safety results obtained during the review of NDA 205677 are considered informative also of safety in subjects with SMS. Overall, TEAEs in the SMS population did not show any clear association with tasimelteon as compared with placebo. In addition, there was no clear difference compared to TEAEs in the non-24 population, as described in the Hetlioz labeling. Therefore, rather than (b) (4) for Study 2401 in the product labeling, we will instead note that there were no new safety findings as compared to the non-24 program.

7.6.1.6. Laboratory Findings, Study 2401

This section describes the assessment of laboratory imbalances between the tasimelteon and placebo groups and recommendations for Section 6 of the product labeling.

According to the Schedule of Evaluation in protocol VP-VEC-162-2401, laboratory assessments were carried out at baseline (visit 3.1), at week 4 (end of period 1), and at week 9 (end of period 2 and end of study) during the Randomized Treatment Phase.

The review team evaluated changes in laboratory values over time—those from baseline to week 4 and from baseline to week 9 were deemed most informative. The subjects were divided into two sequences: sequence A (subjects assigned to tasimelteon in period 1 and switched to placebo in period 2) and sequence B (subjects assigned to placebo in period 1 and switched to tasimelteon in period 2). Because there was no laboratory assessment at the beginning of period 2 that could serve as a baseline for the second treatment, the reference baseline value was that at study baseline; i.e., prior to the beginning of period 1.

The same Schedule of Evaluation was carried out in the open-label portion of Study 2401; however, because subjects were treated with tasimelteon continuously for 9 weeks, the review team evaluated changes from baseline to week 4 and from baseline to week 9.

Table 23 shows the laboratory parameters of special interest to this review.

The current Hetlioz product label reports increases in ALT. However, the tabulation shows no increase in ALT values from baseline to week 4, a minimal increase from week 4 to week 9 in subjects switched to placebo in sequence A, and a minimal increase from week 4 to week 9 in subjects switched to tasimelteon in sequence B. The review team concluded that these changes were not clinically relevant.

Subjects with SMS may present elevated values of ALP, possibly relates to vitamin D deficiency or altered metabolism, both frequent findings in SMS. Table 23 shows no increase in ALP values from baseline to week 4; a decrease from week 4 to week 9 in subjects switched to placebo in sequence A, and a minimal increase from baseline to week 4 and a minimal decrease from week 4 to week 9 in subjects switched to tasimelteon in sequence B. The review team concluded that these changes were not clinically relevant.

Subjects in sequence B have an elevated baseline level of bilirubin (>5.1 µmol/L), and tasimelteon increased the level of bilirubin from week 4 to week 9. However, based on data from sequence A, in which there was no change in bilirubin level, this finding is not deemed informative of the safety of tasimelteon.

No other clinically relevant change in chemistry, hematology, or urinalysis parameters were observed over time or between the treatment groups.

The outlier analysis presented in Table 24 below was consistent with the laboratory findings described above.

Finally, tasimelteon did not affect ECG or vital signs, consistent with its known safety profile (data not shown).

Table 23. Summary of Quantitative Laboratory Parameters, Safety Population

Category	Parameter	Study Visit[1]	Sequence A Tasimelteon/Period 2 Placebo N=13 Value/Change[2]	Sequence B Placebo/Period 2 Tasimelteon N=13 Value/Change	Open-Label Tasimelteon[3] N=22 Value/Change
Chemistry	Alanine Aminotransferase (U/L)	**Baseline**			
		N	13	13	22
		Mean	25.31	33.85	25.05
		SD	11.722	23.547	17.322
		Median	25.00	28.00	19.00
		Minimum	12.0	11.0	8.0
		Maximum	45.0	87.0	87.0
		Change from Baseline to Week 4			
		N	13/13	12/12	21/21
		Mean	23.69/−1.62	26.58/−3.92	24.10/−0.90
		SD	10.443/5.781	15.012/16.076	14.543/10.807
		Median	22.00/0.00	22.50/−1.00	21.00/1.00
		Minimum	11.0/−15.0	10.0/−50.0	9.0/−35.0
		Maximum	49.0/5.0	61.0/16.0	68.0/23.0
		Change from Week 4 to Week 9			
		N	10/10	11/11	21/21
		Mean	27.70/2.60	29.18/4.45	22.95/−2.62
		SD	15.777/7.442	13.091/12.152	11.608/15.490
		Median	23.50/2.00	28.00/2.00	20.00/0.00
		Minimum	10.0/−7.0	12.0/−23.0	9.0/−61.0
		Maximum	55.0/21.0	50.0/27.0	49.0/21.0

Category	Parameter	Study Visit[1]	Sequence A Tasimelteon/Period 2 Placebo N=13 Value/Change[2]	Sequence B Placebo/Period 2 Tasimelteon N=13 Value/Change	Open-Label Tasimelteon[3] N=22 Value/Change
	Alkaline Phosphatase (U/L)	**Baseline**			
		N	13	13	22
		Mean	169.69	157.46	115.55
		SD	91.065	94.579	65.079
		Median	123.00	130.00	97.00
		Minimum	76.0	56.0	44.0
		Maximum	366.0	375.0	332.0
		Change from Baseline to Week 4			
		N	13/13	12/12	20/20
		Mean	167.08/−2.62	165.75/1.08	118.75/0.05
		SD	90.074/18.671	95.521/12.838	64.719/6.493
		Median	123.00/−4.00	142.50/6.50	100.00/−0.50
		Minimum	71.0/−33.0	63.0/−26.0	43.0/−8.0
		Maximum	356.0/38.0	388.0/13.0	326.0/16.0
		Change from Week 4 to Week 9			
		N	9/9	10/10	21/21
		Mean	123.67/−4.22	160.30/8.30	118.52/1.95
		SD	58.254/15.555	103.36/15.535	69.456/15.606
		Median	104.00/−1.00	125.00/8.50	95.00/−2.00
		Minimum	73.0/−41.0	71.0/−23.0	39.0/−20.0
		Maximum	242.0/12.0	404.0/32.0	312.0/46.0
	Aspartate Aminotransferase (U/L)	**Baseline**			
		N	13	13	22
		Mean	22.31	26.15	20.14
		SD	7.005	12.388	8.796
		Median	22.00	24.00	19.50
		Minimum	10.0	12.0	10.0
		Maximum	36.0	53.0	53.0
		Change from Baseline to Week 4			
		N	13/13	12/12	20/20
		Mean	21.69/−0.62	23.08/−2.00	19.95/−0.35
		SD	6.061/3.595	10.049/9.991	6.878/7.154
		Median	20.00/−1.00	22.50/−1.00	19.50/0.00
		Minimum	14.0/−9.0	12.0/−31.0	12.0/−25.0
		Maximum	35.0/4.0	46.0/9.0	34.0/14.0
		Change from Week 4 to Week 9			
		N	10/10	10/10	21/21
		Mean	22.00/0.80	23.60/2.80	19.62/−1.00
		SD	6.799/4.185	9.513/4.417	6.360/7.969
		Median	20.50/1.00	22.00/3.00	19.00/0.00
		Minimum	12.0/−7.0	13.0/−7.0	11.0/−32.0
		Maximum	35.0/8.0	43.0/11.0	37.0/7.0

Category	Parameter	Study Visit[1]	Sequence A Tasimelteon/Period 2 Placebo N=13 Value/Change[2]	Sequence B Placebo/Period 2 Tasimelteon N=13 Value/Change	Open-Label Tasimelteon[3] N=22 Value/Change
	Bilirubin (umol/L)	**Baseline**			
		N	13	13	22
		Mean	5.02	7.98	6.98
		SD	1.369	3.215	2.552
		Median	4.60	6.80	6.75
		Minimum	3.6	4.6	3.4
		Maximum	8.2	15.6	15.6
		Change from Baseline to Week 4			
		N	13/13	12/12	21/21
		Mean	5.17/0.15	7.51/−0.72	8.35/1.38
		SD	2.012/1.337	4.221/2.437	4.282/2.643
		Median	4.60/0.00	5.90/-0.85	7.20/0.60
		Minimum	3.8/−2.2	4.1/−4.8	3.9/−2.2
		Maximum	11.3/3.1	17.3/5.2	20.9/7.0
		Change from Week 4 to Week 9			
		N	10/10	11/11	21/21
		Mean	5.13/−0.25	8.69/1.03	7.15/0.32
		SD	1.651/2.055	3.200/2.214	3.238/1.542
		Median	4.70/−0.20	7.40/1.20	6.20/−0.10
		Minimum	3.4/−5.0	5.3/−4.8	2.1/−2.1
		Maximum	8.2/2.2	14.7/4.0	18.0/3.9

Source: Applicant-submitted ADLB.sas7bdat in D120; software, SAS 9.4.
Abbreviations: N, number of patients with at least one available laboratory parameter; n, number of patients with a value at baseline and the specified visit; SD, standard deviation
[1] Baseline is defined as the latest nonmissing observation across all visits in the Screening Phase.
[2] In the randomized population, the change at week 4 is from baseline to week 4 and that at week 9 is from week 4 to week 9. In the Open-Label Arm, the change at week 4 is from baseline to week 4 and that at week 9 is from baseline to week 9.
[3] Analyses were based on the data as of October 2, 2020.

Table 24. Patients With One or More Liver Biochemistry Parameters Exceeding the Specified Levels, Safety Population

Parameter	Tasimelteon N=46	Placebo N=22
Alkaline phosphatase, high (U/L)	1 (2.17)	1 (4.55)
Level 1 (>1.5× ULN)	1 (2.17)	1 (4.55)
Level 2 (>2.0× ULN)	1 (2.17)	1 (4.55)
Level 3 (>3.0× ULN)	0 (0.00)	0 (0.00)
Alanine aminotransferase, high (U/L)	0 (0.00)	0 (0.00)
Level 1 (>3.0× ULN)	0 (0.00)	0 (0.00)
Level 2 (>5.0× ULN)	0 (0.00)	0 (0.00)
Level 3 (>10.0× ULN)	0 (0.00)	0 (0.00)
Aspartate aminotransferase, high (U/L)	0 (0.00)	0 (0.00)
Level 1 (>3.0× ULN)	0 (0.00)	0 (0.00)
Level 2 (>5.0× ULN)	0 (0.00)	0 (0.00)
Level 3 (>10.0× ULN)	0 (0.00)	0 (0.00)
Bilirubin, total, high (mg/dL)	0 (0.00)	0 (0.00)
Level 1 (>1.5× ULN)	0 (0.00)	0 (0.00)
Level 2 (>2.0× ULN)	0 (0.00)	0 (0.00)
Level 3 (>3.0× ULN)	0 (0.00)	0 (0.00)

Source: Applicant-submitted ADLB.sas7bdat in D120; software, SAS 9.4.
Abbreviations: LLN, lower limit of normal; N, number of patients with at least one post-baseline collected laboratory parameter in the treatment arm; ULN, upper limit of normal

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Infections and Infestations as Adverse Events Derived by a Potential Drug-Disease Interaction

Issue

The current Hetlioz label reports URIs and UTIs among the AEs, with an incidence >5% and at least two-fold higher in subjects receiving Hetlioz than in those receiving placebo. More than 50% of individuals with SMS have low serum immunoglobulin levels, which may increase susceptibility to sinopulmonary infection. Recurrent otitis media (88%), URIs (61%), pneumonia (47%), and/or sinusitis (42%) requiring antibiotic treatment are frequently reported (Perkins et al. 2017).

The review team assessed whether infections and infestations could be a potential drug-disease interaction.

Assessment

The review team assessed past and current concomitant medical conditions reported for subjects enrolled in Study 2401. The review team also assessed the incidence of TEAEs classified in the SOC infections and infestations for all subjects enrolled in Study 2401. In addition, nonclinical data were evaluated for potential factors that could predispose individuals treated with tasimelteon to infection. Finally, the Division of Pharmacovigilance provided drug safety surveillance results and conducted data mining queries.

Infections as Concomitant Medical Conditions in Subjects Randomized in Study 2401

Table 25 and Table 26 summarize the past and current medical conditions in subjects randomized in Study 2401, as submitted by the Applicant.

Consistent with information in the scientific literature, these data confirm that infections are commonly occurring conditions in subjects with SMS.

Table 25. Past Medical Conditions

SOC Infections and Infestations	Period 1 N=13	Period 2 N=13	Total N=26
Salmonellosis	1	0	1
Tonsillitis	1	0	1
Tooth infection	1	0	1

Source: Clinical reviewer-created

Table 26. Current Medical Conditions

SOC Infections and Infestations	Period 1 N=13	Period 2 N=13	Total N=26
Candida infection	0	1	1
Ear infection	1	0	1
Otitis media	2	2	4
Staphylococcal infection	1	1	2

Source: Clinical reviewer.
Abbreviation: SOC, system organ class

TEAEs Classified as Infections and Infestations in Study 2401

Table 27 shows infections in subjects exposed to placebo or tasimelteon during the two periods of Study 2401. Table 28 and Table 29 include also subjects enrolled in the Open-Label Treatment Arm (n=22) and the OLE. Subjects enrolled in the Randomized Treatment Arm were counted twice because they were exposed to both tasimelteon and placebo, but AEs will not be counted twice because the definition of TEAEs includes only newly occurring events in each period of the crossover. For example, events that began in one period and persisted across another period of the study were not counted twice.

Overall, the frequency of infections in the randomized population is very small. The data in Table 27 do not show an imbalance between the tasimelteon and placebo groups.

The entire safety population data show that the proportion of subjects exposed to tasimelteon who had any event in the SOC infection or infestation was almost three-fold higher than that of subjects exposed to placebo (21.3% compared to 7.7%).

However, there is a difference in exposure to tasimelteon between the placebo group (4 weeks) and the tasimelteon group (up to 197 weeks). The difference in exposure might have increased the likelihood of development of infections spontaneously or due to the underlying condition.

Indeed, the SOC infections and infestations includes heterogeneous clinical events, some of which are highly unlikely to have a causal relationship with tasimelteon. Otitis, viral infections of various body systems (gastroenteritis, nasopharyngitis), and infected bites are clinical events unlikely related to the study drug and common in SMS. Among the infections in subjects enrolled in the open-label phase, there are two reports of tooth infection in the tasimelteon group. However, dental decay occurs in >75% of subjects with SMS (Smith et al. 2019).

Table 27. Patients With Infection and Infestation Adverse Events,[1] Randomized Population[2, 3, 4]

Preferred Term	Period 1 Tasimelteon N=13 n (%)	Period 1 Placebo N=13 n (%)	Period 2 Tasimelteon N=12 n (%)	Period 2 Placebo N=13 n (%)
Patients with any TEAE	5 (38.5)	3 (23.1)	1 (8.3)	4 (30.8)
Gastroenteritis viral	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)
Infected bites	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Nasopharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)
Otitis externa	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)
Respiratory tract infection	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)

Source: Applicant-provided ADAE1.sas7bdat; software, SAS 9.4.
Abbreviations: AE, adverse event; N, number of patients in the treatment arm; n, number of patients with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[1] TEAEs are defined as AEs that newly occurred or worsened from baseline (i.e., AEs that started after the first dose of study drug) and started no more than 24 hours after the date of the last dose of study drug.
[2] Patients are counted only once under the highest severity level.
[3] Adverse events occurring after 24 hours of the last dose of the Treatment Phase will be summarized for the Open-Label Extension Phase.
[4] AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA version 18.0) coding dictionary.

Table 28. Patients With TEAEs[1] by SOC, Safety Population

System Organ Class[2]	Tasimelteon N=47 n (%)	Placebo N=26 n (%)
Patients with any TEAE	19 (40.4)	6 (23.1)
Infections and infestations	10 (21.3)	2 (7.7)

Source: Applicant.
Abbreviations: %, 100×n÷N; AE, adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event.
[1] TEAEs are defined as AEs that newly occurred or worsened from baseline (i.e., AEs that started after the first dose of study drug) and started no more than 24 hours after the date of the last dose of study drug. AEs are summarized according to treatment at the onset of the event. AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA version 18.0) coding dictionary. AEs occurring after 24 hours of the last dose of the Treatment Phase will be summarized for the Open-Label Extension Phase.
[2] Patients are counted only once at each level of summation.

Table 29. Patients With Infection and Infestation Adverse Events,[1] Safety Population[2, 3, 4]

Preferred Term	Tasimelteon (N=47) n (%)	Placebo (N=26) n (%)
Gastroenteritis viral	2 (4.3)	0 (0.0)
Upper respiratory tract infection	2 (4.3)	0 (0.0)
Urinary tract infection	1 (2.1)	1 (3.8)
Gastroenteritis norovirus	1 (2.1)	0 (0.0)
Infected bites	1 (2.1)	0 (0.0)
Nasopharyngitis	1 (2.1)	0 (0.0)
Otitis externa	0 (0.0)	1 (3.8)
Otitis media	1 (2.1)	0 (0.0)
Paronychia	1 (2.1)	0 (0.0)
Respiratory tract infection	1 (2.1)	0 (0.0)
Tooth infection	1 (2.1)	0 (0.0)
Viral infection	1 (2.1)	0 (0.0)

Source: Applicant-provided.
Abbreviations: N, number of patients in the treatment arm; n, number of patients with at least one event
[1] Treatment-emergent AEs are defined as AEs that newly occurred or worsened from baseline (i.e., AEs that started after the first dose of study drug) and started no more than 24 hours after the date of the last dose of study drug.
[2] Patients are counted only once under the highest severity level.
[3] Patients received both placebo and tasimelteon in this crossover study are counted under both tasimelteon and placebo.
[4] AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA version 18.0) coding dictionary.

Nonclinical Evaluation of Drug-Induced Predisposition to Infection

Nonclinical studies in rats and monkeys did not yield findings suggesting that tasimelteon may increase susceptibility to infection.

A finding of chronic progressive nephropathy was observed in rats, but this is not uncommon in rats and occurred at doses much higher (500 mg/kg/day; 25-fold the human exposure) those given to humans (≤ 150 mg), so these findings are likely not clinically relevant.

In monkeys dosed up to 150 mg/kg/day (19-fold the human exposure), there were no urinalysis or immunological findings of note.

Postmarketing Reports of Infections and Infestations

In addition to the FAERS search and results (Section 7.3), DPV also used Empirica Signal software with the strategy described in Table 30 to perform disproportionality analyses on the FAERS data and to identify patterns of associations or unexpected occurrences (i.e., "potential signals) for the PTs *Respiratory tract infection*, *Upper respiratory tract infection*, and *Urinary tract infection*, as requested by DP. A drug-event combination with a score (EB05) of ≥2 indicates 95% confidence that the drug-event combination appears at more than two-fold the expected rate when considering all other drugs and events in the database. Data mining scores do not themselves indicate causal associations; rather, they serve as signals for further investigation.

Table 30. Data Mining Search Strategy[1]

Data refresh date	As of August 22, 2020
Product terms	Tasimelteon
Empirica signal run name	PAI (S)
MedDRA search strategy (version 22.1)	Preferred terms: respiratory tract infection, upper respiratory tract infection, and urinary tract infection

Source: DPV Pharmacovigilance Memorandum; November 3, 2020.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PAI (S), product active ingredient (suspect)
[1] See Appendix A for description of data mining of FAERS using Empirica Signal.

The data-mining scores obtained from the updated screen of Empirica Signal are shown in Table 31. Although none of the EB05 scores was >2, DPV performed a manual review of cases reporting *Respiratory tract infection*, *Upper respiratory tract infection*, and *Urinary tract infection* to determine causality.

Table 31. Disproportionality Assessment for Tasimelteon and Adverse Events of Interest

Preferred Term[1]	N	EB05	EBGM	EB95
Respiratory tract infection	12	1.31	2.15	3.35
Upper respiratory tract infection	19	1.37	2.02	2.89
Urinary tract infection	46	1.23	1.58	2.00

Source: DPV Pharmacovigilance Memorandum; November 3, 2020.
[1] DP specifically requested that DPV evaluate these three PTs using data mining.

DPV Assessment of Respiratory Tract Infection, Upper Respiratory Tract Infection, and Urinary Tract Infection

Upon review of the cases reporting *Respiratory tract infection*, *Upper respiratory tract infection*, and *Urinary tract infection*, DPV found that most reports lacked sufficient information to assess causality, such as time to onset of the AE, dates of administration of tasimelteon, and presence or absence of underlying risk factors for RTIs, URIs, or UTIs. These

AEs occur frequently in the general population and in those with SMS; therefore, determining their relatedness to study drug based on spontaneous AE reports is problematic.

DPV identified one nonserious case of recurrent UTIs with positive dechallenge and rechallenge, as described below. However, DPV did not identify a convincing causal relationship between tasimelteon and the development of UTIs.

FAERS #16578642: A (b) (6)-year-old (b) (6) patient with a history of blindness in both eyes was treated with tasimelteon 20 mg once daily on unknown dates (first shipment date 1 month prior to the report) for Circadian rhythm disorder, free-run type. The patient reportedly discontinued use of tasimelteon because (b) (6) "had too many urinary tract infections." It was noted in the report that the patient's healthcare provider discontinued tasimelteon, the symptoms of recurrent UTIs resolved, and when the patient resumed tasimelteon, the UTIs recurred. This was noted in the case as a positive dechallenge and positive rechallenge. Concomitant medications included an unknown blood pressure medication that had caused *kidney issues* in the past; no other medications were specified.

***Reviewer's comment**: This medically confirmed case suggests a temporal relationship between tasimelteon and the occurrence (and reoccurrence) of UTIs. Although this case also describes positive dechallenge and rechallenge, this reviewer assessed this case as* possible *because of the lack of information regarding the time to onset of UTI as well as the temporal relationship of UTIs with the discontinuation and resumption of tasimelteon.*

DPV did not identify any cases of RTIs or URIs related to tasimelteon. All reports were confounded by concomitant medications for respiratory symptoms/seasonal allergies or lacked sufficient information to assess causality, such as dates of therapy and times to onset of AEs.

Conclusion

Because of the small number of subjects in the safety population and the difference in exposure between randomized subjects and those assigned to the open-label phase, it is difficult to draw conclusions on a causal relationship between tasimelteon and the occurrence of clinical events coded as infections or infestations. Analysis of postmarketing data found no clear signal for an increased infection risk in the larger tasimelteon database. In addition, the nonclinical review of toxicological studies does not support the possibility that treatment with tasimelteon increases predisposition to infections.

The review team concluded that despite the predisposition of individuals with SMS to infections, as confirmed by the scientific literature, treatment with tasimelteon does not appear to cause an increased frequency of infections and infestations. The review team does not recommend any postmarketing action beyond routine pharmacovigilance.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Not applicable for this submission. Current product labeling notes that tasimelteon has not been studied in patients with severe hepatic impairment and is not recommended in these patients.

8.2. Drug Interactions

The current product labeling specifies that use of tasimelteon in combination with strong CYP1A2 inhibitors should be avoided because of increased exposure, and in combination with rifampin or other CYP3A4 inducers because of decreased exposure.

Refer to Section 6.3.4 for discussion of the potential interaction between tasimelteon and nighttime administration of beta-adrenergic receptor antagonists. This potential interaction, which is noted in Section 14 of the current label for the non-24 indication, will be described in Section 7 of the labeling revision associated with review of these NDAs.

8.3. Plans for Pediatric Drug Development

The capsule formulation of Hetlioz is currently marketed under NDA 205677 and a marketing application for the suspension formulation was submitted under NDA 214517.

For the sleep disturbances in SMS indication, the capsule formulation was studied in patients 16 years and older, and the suspension formulation in patients 3 to 15 years of age. The PKs of the capsule and suspension formulations are sufficiently similar (Section 6.3.1). Statistical assessment suggests no apparent difference in safety or efficacy between the two formulations.

Therefore, upon approval the DPMH recommends that the dosing recommendations in the labeling mirror the formulations studied in the respective age groups (i.e., suspension for patients 3 to 15 years of age, and capsules for patients 16 years and older).

DPMH recommends that Section 8.4 of the product labeling specify the basis of pediatric approval; that Hetlioz will be approved for this indication based on one adequate and well-controlled study involving pediatric patients ages 3 years and older.

A study was conducted in which juvenile rats received tasimelteon at 50, 150, or 450 mg/kg by oral gavage from weaning (Day 21) through adulthood (Day 90). At 450 mg/kg/day, mortality (females only), tremors, and unsteady gait were observed. A decrease in growth and development was also observed at 450 mg/kg/day in both sexes compared to controls, as indicated by a decrease in body weight gain, which correlated with a decrease in food consumption; decreases in bone growth, bone mineral content, and bone ossification; and a delay in attainment of sexual maturation (delay in vaginal opening for females and in completion of the preputial opening for males). Liver weights were increased at ≥150 mg/kg/day with corresponding histopathological findings of slight centrilobular hepatocyte hypertrophy at 450 mg/kg/day. Motor activity was increased compared to control animals at doses of ≥150 mg/kg/day, and enhancement of prepulse inhibition (a neurobehavioral assay of sensory motor gaiting) was observed at 450 mg/kg/day. Most of these findings were reversible after a 4-week recovery period. Tasimelteon had no effect on fertility, reproduction, or learning and memory. The no observed adverse effect level is 150 mg/kg/day, which is approximately 178-fold the maximum recommended human dose based on the area under the concentration-time curve (AUC). Please refer to the full study report in Section 13.2.

8.4. Pregnancy and Lactation

No new reproductive data were submitted with these applications. Refer to Sections 8.1, 8.2, 8.3, and 13.1 of the current product labeling for considerations regarding fertility, pregnancy, and lactation with use of tasimelteon.

9. Product Quality

Chemistry, Manufacturing, and Controls 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°C and 8°C (36°F and 46°F), is acceptable.

The Applicant has agreed to the following postmarketing commitments (PMCs):

- 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

Refer to the Office of Product Quality reviews for additional information.

10. Human Subjects Protections / Clinical Site and Other Good Clinical Practice Inspections / Financial Disclosure

The Applicant stated that "to the best of our knowledge, the studies submitted in this application were designed to ensure adherence to Good Clinical Practices and to ensure the protection of the patients."

After considering preliminary efficacy data and enrollment numbers by site and whether or not a site had been previously inspected, two sites that enrolled patients for the single pivotal study supporting the proposed indication were selected for inspection. The Office of Scientific Investigations performed inspections and data audits, concluding that the data in support of clinical efficacy and safety at the two sites inspected are considered reliable. The Applicant has submitted Form 3454, in which Christos Polymeropoulos, Medical Director, certifies that he has not entered into any financial arrangement with the clinical investigators where the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a), and that each investigator did not have financial interests as defined in 21 CFR 54.2(b). The Applicant provided a list of investigators (principal investigators and subinvestigators) who participated in clinical studies VP-VEC-162-2401, VP-VEC-162-4201, and VP-1401, certifying that none has a proprietary interest in tasimelteon or a significant equity interest in Vanda as defined in 21 CFR 54.2(b) and was not the recipient of significant payment of other type as defined in 21 CFR 54.2(f).

11. Advisory Committee Summary

This application was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

III. Appendices

12. Summary of Regulatory History

Tasimelteon was granted orphan-product designation by the Food and Drug Administration (FDA) on April 30, 2010, for the treatment of sleep-wake disorder in Smith-Magenis syndrome (SMS) associated with diurnal melatonin secretion. Therefore, the Applicant is exempt from the requirements in the Pediatric Research Equity Act. Tasimelteon was first approved by the FDA on January 31, 2014, as Hetlioz for the treatment of non-24-hour sleep-wake disorder (non-24) (IND 054776, NDA 205677).

On September 5, 2014, the Applicant submitted investigational new drug (IND) 123408, proposing to investigate tasimelteon for the treatment of sleep disorder in SMS associated with diurnal melatonin secretion. IND 123408 included the initial protocol for the pivotal study VP-VEC-162-2401 (Study 2401) as well as protocol amendment 3 for study VP-1401, an observational study investigating the melatonin and circadian rhythms of individuals with SMS. Of note, the initial protocol for Study 2401 was a nonrandomized study in which subjects underwent successive 2-day periods of treatment with tasimelteon 20 mg, metoprolol 100 mg, and tasimelteon 20 mg + metoprolol 100 mg. The Applicant did not request a Pre-IND meeting to discuss the development program prior to IND submission. On October 9, 2014, the Division of Psychiatry issued a May Proceed letter.

Amendment 1 for Study 2401, submitted on September 21, 2015, significantly changed the protocol to a randomized, placebo-controlled crossover study comparing treatment with tasimelteon versus placebo and removing metoprolol treatment. Protocol amendments 4 and 5 were not submitted to the FDA at the times of implementation (April 21, 2016, and May 31, 2016, respectively) but were reviewed with the submission of protocol amendment 6 on August 26, 2016. On November 1, 2016, the Division communicated to the Applicant that clinical protocol amendments were required under 21 CFR 312.30 to be submitted to FDA prior to their implementation. In addition, the Division communicated that re-enrollment of subjects who completed open-label tasimelteon treatment into the Randomized Treatment Arm was not acceptable, because only patients or caregivers who perceived some benefit from open-label treatment would likely re-enroll, possibly biasing the study sample.

Amendment 9 to IND 123408 was submitted on December 18, 2018; this amendment specified that the primary efficacy endpoint would be changed from "improvement in nighttime sleep defined as the reduction of the percentage of wake periods within the sleep interval" to two independent primary endpoints: 50% worst daily diary sleep quality (DDSQ50) and 50% worst daily diary total sleep Time (DDTST50). On December 28, 2018, the Division communicated that the rationale for the change in the primary efficacy endpoint was not specified and requested that the Applicant clarify this change and describe how the new endpoints would be assessed. Additional biostatistical comments regarding amendment 9 were communicated on March 28, 2019, which included a request to submit the statistical analysis plan (SAP) for review as soon as possible and to clarify and provide the rationale for the changes to the primary efficacy analysis. The SAP, dated December 4, 2018, was submitted to FDA by email on March 28, 2019, and officially to the IND on June 7, 2019. On June 18, 2019, with reference to the SAP, the Division communicated that changes in study endpoints at or near study

completion, even if blinded, raise issues regarding the adequacy of statistical control. The Division recommended that the Applicant request a formal meeting to obtain agreement on the development plan.

The first formal meeting with the Division for IND 123408 was a Pre-sNDA meeting held on November 13, 2019. At that meeting, in response to a question seeking agreement that data from Study 2401 would be adequate to inform labeling for an indication of treatment of sleep disorder in SMS, the Division indicated that its adequacy to assess efficacy and inform labeling would be reviewed under the NDA. The Division and the Applicant agreed that the randomized, double-blind arm of Study 2401 would be considered the registration study. The Division noted a lack of agreement on the primary efficacy evaluation and recommended that the Applicant provide support for the clinical meaningfulness of the change in the application. The Division indicated that the safety database from Study 2401, in conjunction with data from pediatric PK Study VP-VEC-162-4201, would be sufficient for filing of the NDA from a safety perspective. Regarding the use of both capsule and suspension formulations of tasimelteon in Study 2401, the Division indicated that the Applicant would need to demonstrate a PK bridge between the formulations and submit a new original NDA to support marketing of the suspension formulation.

The Applicant initially submitted NDA 214517 (suspension formulation of tasimelteon for the treatment of sleep disorder in SMS) on January 13, 2020, and NDA 205677 S-007 (capsule formulation for the same indication) on January 21, 2020. After a preliminary review, the FDA found that the applications were not sufficiently complete to permit a substantive review under 21 CFR 314.101(d), due to the lack of an established PK bridge between the capsule and suspension formulations of tasimelteon, as well as missing information regarding the USP <51> antimicrobial effectiveness test (AET). The FDA issued a Refuse-to-File Letter on March 12, 2020, requesting that the Applicant provide a relative bioavailability study in healthy subjects under fasted conditions. The FDA also requested summary data for the AET of the drug product, (b) (4) proposed in the drug product release and stability specifications. A Type A meeting was held on May 8, 2020, to discuss the contents of the Refuse-to-File Letter. During this meeting, the Agency identified a path forward for resubmission and filing; the Applicant was instructed to specify in the submissions and draft labeling that the capsule is only intended to be indicated for adult patients and the suspension only for pediatric patients. This approach was intended to obviate the need for a PK bridge for filing. The Applicant agreed to submit the AET results in the sNDA and NDA resubmissions. The Division also requested that the Applicant provide adequate support for the shelf-life of batch-packaging configurations and submit a dissolution method development report in the resubmissions. The Agency noted that the review clock would start on the date on which the application resubmissions were received.

The FDA received resubmissions of NDA 214517 and NDA 205677 S-007 on June 1, 2020.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

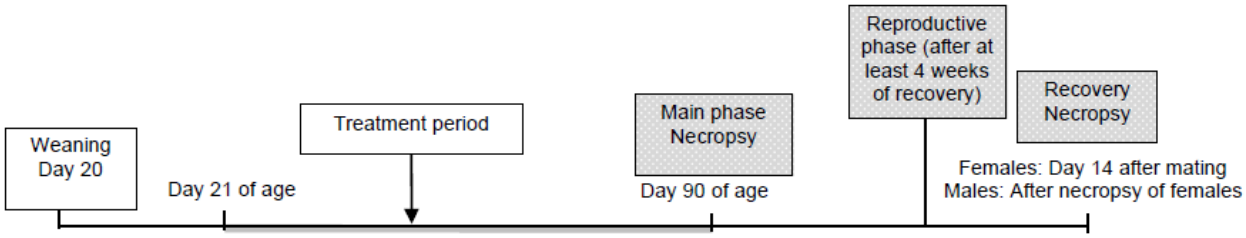
N/A

13.2. Individual Reviews of Studies Submitted to the NDA

Study Title: Tasimelteon: 10-Week Juvenile Toxicity Study in the CD Rat by Oral Gavage Administration Followed by a 4-Week Recovery Period

Study no.:	TAJ0026
Study report location:	eCTD 0018, SDN 18/ eCTD 0137, SDN 273
Conducting laboratory and location:	(b) (4)
Duration:	10 weeks for the main study followed by a 4-week recovery period before a 2-week reproductive assessment
Duration units:	Weeks
GLP compliance:	Yes
Drug, lot no., and percentage purity:	Tasimelteon, F19913001, 99.5%

Figure 10. Design of the Juvenile Animal Study



Source: Study no. TAJ0026

Scientific Justification for the Study

To evaluate the safety (including general toxicity, neurobehavioral testing, growth, and reproductive development) and toxicokinetics of tasimelteon administered daily via oral gavage to juvenile rats at postnatal day (PND) 21 to 90 and assess recovery of findings. PND 21 rats are equivalent to humans approximately 2 years of age. Therefore, this study was adequately designed to conduct a safety assessment of tasimelteon for the proposed indication of the treatment of sleep disorder in SMS in adults and children 3 years of age and older.

JAS-Specific Toxicity

- Premature sacrifice of two high-dose females due to CNS-related clinical signs
- Dose-dependent decreases in body weight and body-weight gain in both sexes, which was >10% compared to the controls at the high dose
- Tremors observed in several mid- and high-dose males, and in one high-dose female
- Decreases in bone growth, bone mineral content and density, and ossification in high-dose males and females
- Delay in sexual maturation in high-dose animals
- Increased motor activity in mid- and high-dose males and decreased prepulse inhibition in high-dose males
- Dose-dependent increases in liver weight with histopathological findings of slight centrilobular hepatocyte hypertrophy in high-dose males and females
- No observed adverse effect level=150 mg/kg/day due to possibly drug-related mortality, decreased body weight, and CNS-related clinical signs at 450 mg/kg/day
- Safety margins 44-fold the maximum recommended human dose[4]

[4] Safety margins calculated from clinical study no. VP-VEC-162-4101, in which 24 pediatric subjects (3 to 18 years of age) received 20 mg tasimelteon suspension with a Day-1 AUC_{inf} of 328 ng/mL*hr. A PND 21 dose of 50 mg/kg was averaged for male and female animals (AUC_{inf} of 14,300 ng/mL*hr).

Table 32. Tasimelteon: 10-Week Juvenile Toxicity Study Design

Methods	Details
Doses:	0, 50, 150, 450 mg/kg/day
Frequency of dosing:	Once daily
Number/Sex/Group:	Main group: 10/sex/group Recovery/reproductive: 20/sex/group (see table below)
Dose volume:	2.5 mL/kg
Formulation/Vehicle:	100% polyethylene glycol-400 (PEG400)
Route of administration:	ORAL GAVAGE
Species:	Rat
Strain:	CD Sprague-Dawley rat
Age at start of experiment:	PND 21
Period of development studied:	Juvenile to sexual maturation
Comment on Study Design and Conduct:	This juvenile animal study comprised a toxicity, recovery/reproductive, and a toxicokinetic portion
Parameters and Key Endpoints Evaluated:	Rats were treated with vehicle or tasimelteon from PND 21 to 90. Clinical observations, body weight, food consumption, limb measurements, sexual maturation, neurobehavioral assessments, blood, urine, TK, estrus cycles, organ weight, sperm parameters, reproductive assessment and litter parameters, bone density, gross and histopathology
Dosing Solution Analysis:	Analyzed formulations were within 8% of nominal concentrations

Table 33. Tasimelteon: 10-Week Juvenile Toxicity Study Treatment Arms

	Dose	Number of Animals	
Treatment	(mg/kg/day)	Males	Females
Main Phase			
Control	0	10	10
Tasimelteon	50	10	10
Tasimelteon	150	10	10
Tasimelteon	450	10	10
Recovery/ Reproductive Phase			
Control	0	20	20
Tasimelteon	50	20	20
Tasimelteon	150	20	20
Tasimelteon	450	20	20

Source: Data in study no. TAJ0026

Observations and Results

Mortality

Three animals died during treatment. One low-dose male (LDM) (#101) was found dead on PND 80 after 60 days of treatment, but no clinical signs were observed prior to death. The histopathological findings consisted of cortical vacuolation in the adrenal glands and mandibular lymph nodes, but it was not apparent that these findings were drug-related because there were no gross pathological findings in this animal. The cause of death of this LDM is most likely not drug-related. Two high-dose females (HDFs; #205 and 206) were euthanized during the dosing phase of the study. The first HDF was euthanized on Day 30 of treatment due to clinical signs of piloerection, partially closed eyelids, abnormal gait, and hunched posture.

Gross pathological findings showed dilation of the kidneys and decreased spleen size with a histopathological finding of centrilobular hypertrophy in the liver. On Day 31, an HDF was euthanized due to piloerection, partially closed eyelids, and abnormal gait. Necropsy findings showed kidney dilation, thin optic nerves, hemorrhaged tongue, and distended stomach. Histopathological findings in this animal were minimal and consisted of uterine/cervix and stomach dilation; a drug-related reason for death cannot be ruled out. The animals were observed daily for morbidity and mortality.

Clinical Signs

Tremors were observed in seven high dose males (HDMs), two MDMs, and one HDF during the functional observational battery (FOB) in the treatment portion of the study; tremor was observed in one HDM during the recovery phase. These tremors were single instances and of short duration; the animals experiencing tremors had no other findings of note, including abnormally high drug exposure levels. Clinical signs observed sporadically included eye closure, piloerection, hypoactivity, and abnormal gait. Several instances of chin rubbing and salivation were noted in all treated groups, but were likely due to gavage procedures. Animals were inspected visually at least twice daily for evidence of ill-health or reaction to treatment with detailed examinations on the day of arrival and weekly thereafter.

Table 34. Arena Observations—Summary of Findings on Day 72/73 of Age (During Treatment)

Group	:	1	2	3	4
Compound	:	Control	Tasimelteon	Tasimelteon	Tasimelteon
Dose (mg/kg/day)	:	0	50	150	450

Group/sex:		1M	2M	3M	4M	1F	2F	3F	4F
Number of animals:		15	15	15	15	15	15	15	15
Parameter	Grade								
Palpebral closure (0-3,U)	0	15	14	14	12	15	15	15	15
	1	0	1	1	1	0	0	0	0
	2	0	0	0	2	0	0	0	0
Posture	S	15	15	15	14	15	15	15	15
	H	0	0	0	1	0	0	0	0
Gait (0-3,U)	0	15	15	15	12	14	13	12	13
	1	0	0	0	3	1	1	3	2
	2	0	0	0	0	0	1	0	0
Arousal (1-5)	3	15	14	15	15	15	15	14	15
	4	0	1	0	0	0	0	1	0
Tremor (0-3)	0	15	15	13	8	15	15	15	14
	1	0	0	2	5	0	0	0	1
	2	0	0	0	2	0	0	0	0

Source: Study no TAJ0026
Abbreviations: H, hunched posture; S, sitting or standing normally; U, unable to assess

Body Weight

The mean body weight at the end of the dosing phase on PND 91 and body weight gain (PND 21 to PND 91) were statistically significantly decreased in HDMs compared to the controls, 11% and 13%, respectively, with the largest decreases occurring in the first 30 days of dosing. The mean body weight and body weight gain were statistically significantly decreased in MDFs by 5% and 6%, respectively, and in HDFs by 9% and 12%, respectively, compared to controls.

The effects on body weight in males and females correlated with decreases in food consumption.

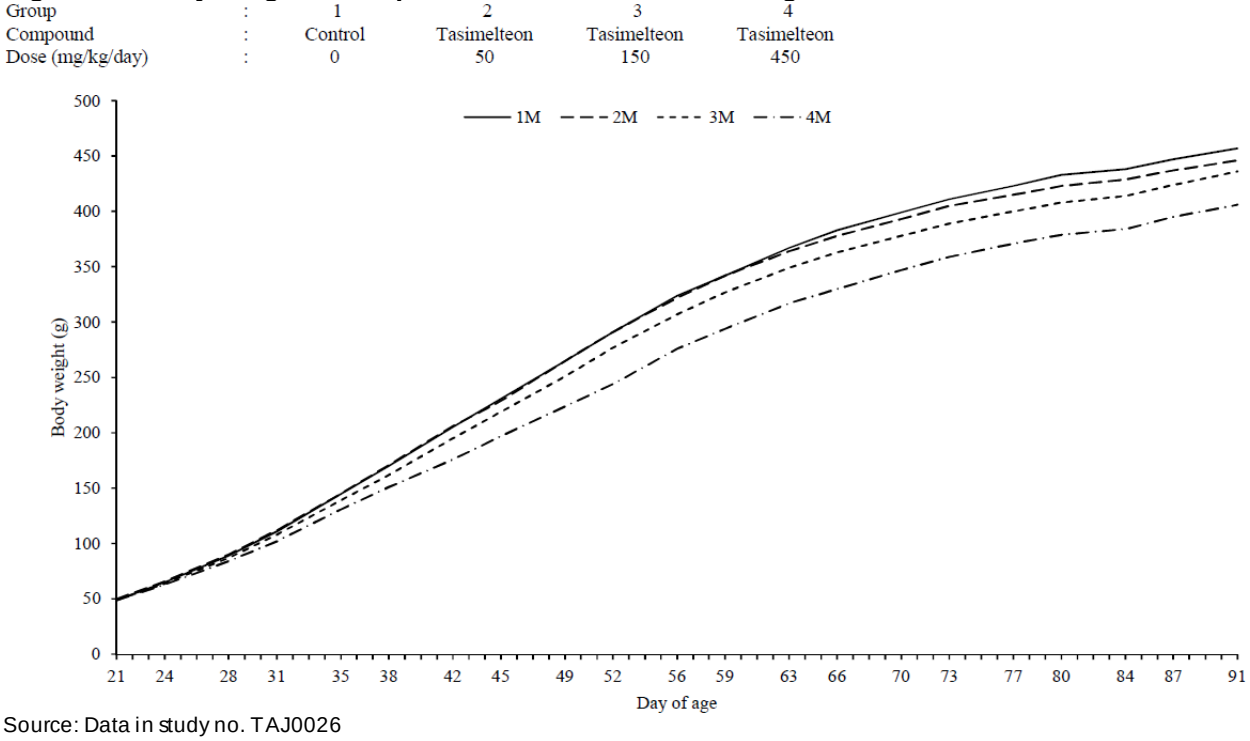
Body weight gains were decreased in the first part of the study, days 1 to 31 (PND 21 to 52), in MDM/Fs (6% and 8%) and HDM/Fs (24% and 12%) compared to the controls. The body weight gains in MDM/Fs and HDMs became more similar to the controls at days 32 to 70 (PND 52 to 91) but in HDFs remained lower than the controls.

Table 35. Body Weight of Males

Dose (mg/kg/day)	PND 21 (g)	PND 91 (g)	% Control Body Weight	BWG (PND 21-91)	% Control BWG
0	49	457		408	
50	50	446	−2.4%	396	−2.9%
150	49	436	−4.6%	387	−5.1%
450	49	406**	−11%	357**	−13%

Source: Data in study no. TAJ0026
Abbreviations: BWG, body weight gain; PND, postnatal day
* p<0.05, ** p<0.01 compared to the controls

Figure 11. Body Weight—Group Mean Values for Males During Treatment



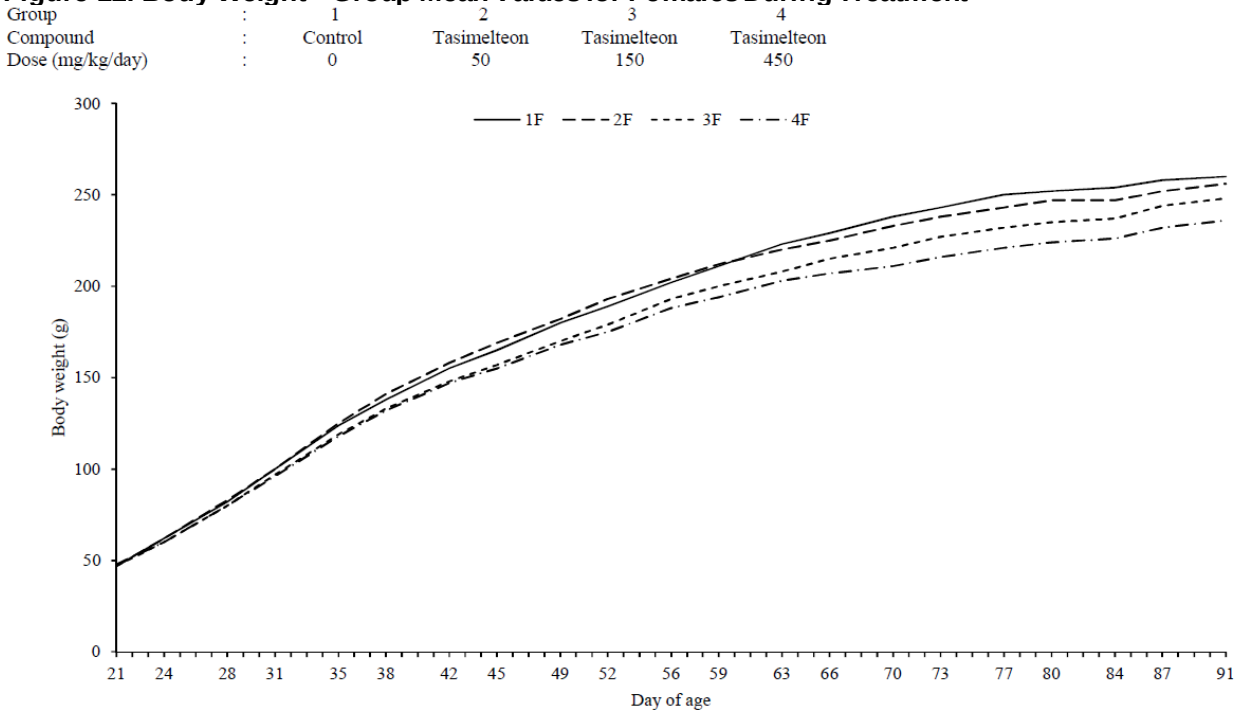
Source: Data in study no. TAJ0026

Table 36. Body Weight of Females

Dose (mg/kg/day)	PND 21 (g)	PND 91 (g)	% Control Body Weight	BWG (PND 21-91)	% Control BWG
0	47	260		213	
50	47	256	−1.5%	209	−1.7%
150	47	248*	−4.6%	201*	−5.6%
450	48	236**	−9.2%	188**	−12%

Source: Data in study no. TAJ0026
BWG, body weight gain; PND, postnatal day
* p<0.05, ** p<0.01 compared to controls

Figure 12. Body Weight—Group Mean Values for Females During Treatment



Source: Data in study no. TAJ0026

During the recovery period and prior to mating, the body-weight gains were increased males and females in all drug-treated groups (≤21% for males and 16% for females compared to the controls), indicating partial recovery.

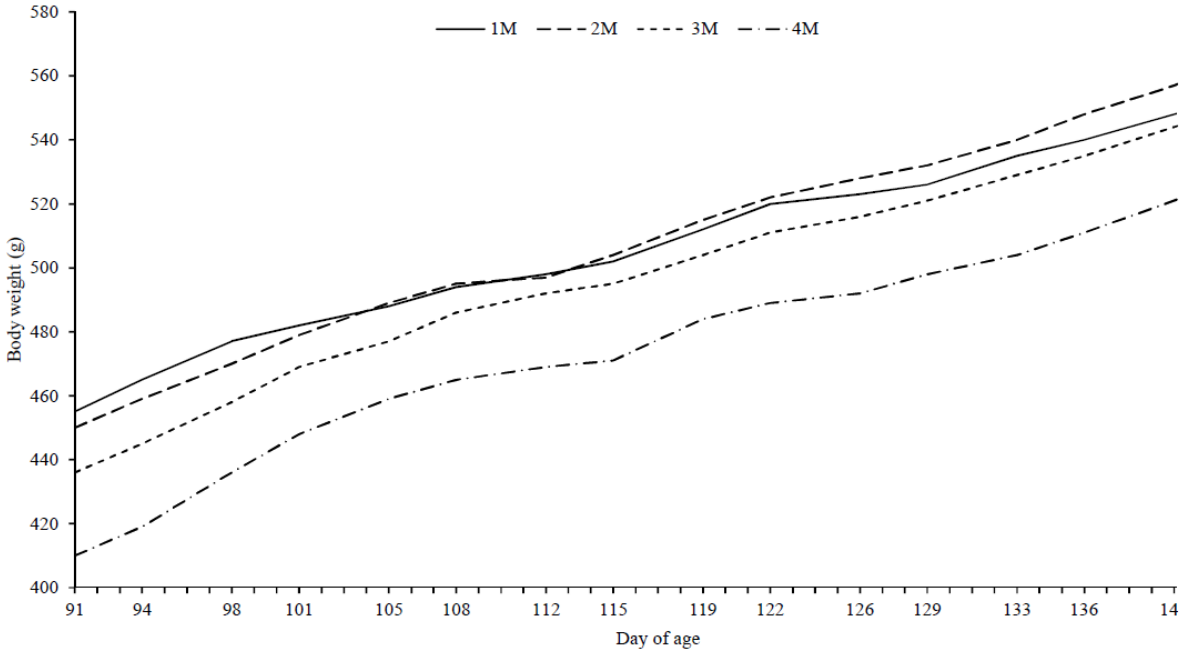
Table 37. Recovery of Body Weight in Males

	Average Wt (g)		BWG (g)	% Control
Dose (mg/kg/day)	PND 91	PND 143	(PND 91 – 143)	BWG
0	455	554	99	
50	450	566	116*	17%
150	436	551	115*	16%
450	410**	530	120**	21%

Source: Data in study no. TAJ0026.
BWG, body weight gain, PND, postnatal day; Wt, weight
* p<0.05, ** p<0.01 compared to controls

Figure 13. Body Weight—Group Mean Values for Males During Recovery

Group	:	1	2	3	4
Compound	:	Control	Tasimelteon	Tasimelteon	Tasimelteon
Dose (mg/kg/day)	:	0	50	150	450



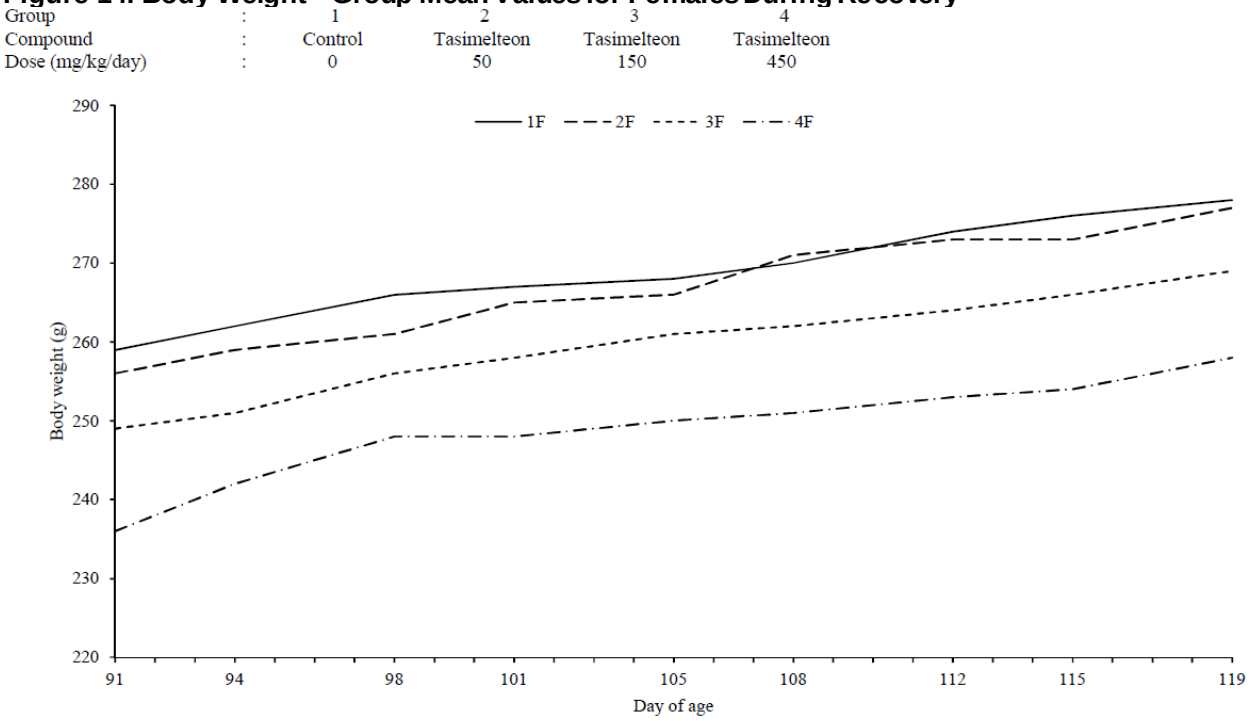
Source: Data in study no. TAJ0026

Table 38. Female Body Weight: Recovery

Dose (mg/kg/day)	Average Wt (g) PND 91	Average Wt (g) PND 119	BWG (g) (PND 91 – 119)	% Control BWG
0	259	278	19	
50	256	277	21	11%
150	249	269	20	5.30%
450	236*	258*	22	16%

Source: Data in study no. TAJ0026
Abbreviations: BWG, body weight gain; PND, postnatal day; Wt, weight

Figure 14. Body Weight—Group Mean Values for Females During Recovery



Source: Data in study no. TAJ0026

For Recovery/Reproductive phase females during early gestation (gestation days [GD] 0 to 14), the overall body-weight change for HDF was statistically significantly increased by 17% compared to the controls. The overall body-weight change was nonsignificantly higher for LD and MD females. The overall body-weight change of untreated females paired with males previously treated with tasimelteon at 50, 150, and 450 mg/kg/day was similar in all groups.

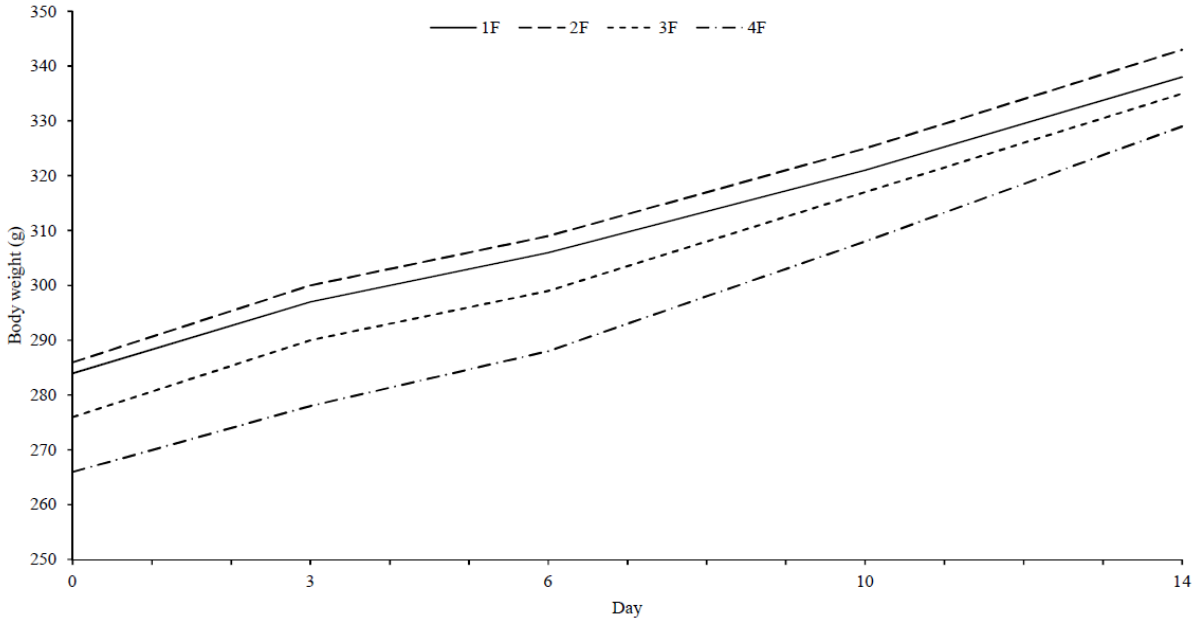
Table 39. Female Body: Gestational Period

	Average Wt (g)			% Control
Dose (mg/kg/day)	GD 0	GD 14	BWG (g)	BWG
0	284	338	54	
50	286	343	57	5.6%
150	276	335	59	9.3%
450	266*	329	63*	17%

Source: Data in study no. TAJ0026
Abbreviations: BWG, body-weight gain; GD, gestation days; Wt, weight
* p<0.05, compared to the controls

Figure 15. Body Weight—Group Mean Values for Recovery/Reproductive-Phase Females During Gestation

Group	:	1	2	3	4
Compound	:	Control	Tasimelteon	Tasimelteon	Tasimelteon
Dose (mg/kg/day)	:	0	50	150	450



Source: Data in study no. TAJ0026

Body weights were measured on Day 20 and weekly starting Day 21 to the end of the study. Reproductive/recovery females were weighed at days 0, 3, 6, 10, and 14 after mating.

Food Consumption

Food consumption by HDM and HDF was statistically significantly decreased compared to the controls at all weeks of the treatment period. MDMs had sporadic observations of decreased food consumption, which were statistically significant at weeks 1, 3, and 5. MDFs had statistically significant decreased food consumption compared to the controls at week 8 of the study. During week 1 of recovery, HDFs had slightly higher food consumption than the controls, and slightly lower food consumption at weeks 2 to 4. There were no differences in food consumption compared to control males during the recovery period, and no differences in food consumption were observed at the LD in either males or females. The effects on food consumption correlated with those on body weight. Food consumption per animal was measured weekly.

Table 40. Food Consumption—Group Mean Values (g/Animal/Week) for Males During Treatment

Group	:	1	2	3	4
Compound	:	Control	Tasimelteon	Tasimelteon	Tasimelteon
Dose (mg/kg/day)	:	0	50	150	450

Group /Sex		Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13
Statistical test:		Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1M	Mean	78	118	161	185	212	208	207	205	197	202
	SD	5.3	7.1	11.6	12.8	25.5	17.8	15.1	17.5	19.8	13.8
	N	12	12	12	12	12	12	12	12	12	12
2M	Mean	76	117	158	180	198	201	198	198	186	195
	SD	5.2	8.5	11.6	14.6	20.4	22.4	20.7	20.6	25.0	24.2
	N	12	12	12	12	12	12	12	12	12	12
3M	Mean	73**	113	152*	174	193*	198	196	197	188	197
	SD	3.8	6.4	9.4	11.3	12.2	12.7	14.9	15.8	17.8	13.2
	N	12	12	12	12	12	12	12	12	12	12
4M	Mean	67**	105**	137**	155**	171**	183**	184**	185**	173**	187*
	SD	5.5	8.7	10.2	13.3	15.0	15.8	15.7	13.2	19.2	15.7
	N	12	12	12	12	12	12	12	12	12	12

Week refers to week of age
Source: Data in study no. TAJ0026
Abbreviations: N, number in the population; SD, standard deviation; Week, week of age
*p<0.05, **0<0.01 compared to the controls

Table 41. Food Consumption—Group Mean Values (g/Animal/Week) for Females During Treatment

Group	:	1	2	3	4
Compound	:	Control	Tasimelteon	Tasimelteon	Tasimelteon
Dose (mg/kg/day)	:	0	50	150	450

Group /Sex		Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13
Statistical test:		Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1F	Mean	71	101	120	126	127	132	137	139	131	135
	SD	4.5	6.3	9.3	7.1	6.1	7.6	6.3	5.2	6.0	6.0
	N	12	12	12	12	12	12	12	12	12	12
2F	Mean	72	102	122	126	131	133	135	135	127	135
	SD	4.5	5.4	6.3	10.3	14.0	15.0	13.7	9.8	10.2	11.4
	N	12	12	12	12	12	12	12	12	12	12
3F	Mean	70	99	116	122	126	129	130	128**	123	129
	SD	6.5	6.4	7.4	8.8	8.5	8.9	9.6	8.4	11.1	9.1
	N	12	12	12	12	12	12	12	12	12	12
4F	Mean	66*	95*	112*	117*	117*	119*	116**	114**	110**	119**
	SD	4.7	6.0	8.3	8.8	7.0	12.6	10.9	8.1	10.4	9.7
	N	12	12	12	12	11	11	11	11	11	11

Source: Data in study no. TAJ0026
Abbreviations: N, number in the population; SD, standard deviation
*p<0.05, **p<0.01 compared to the controls

Ophthalmoscopy

Eye examinations were not conducted.

Hematology

Neutrophil counts were statistically higher than in the controls at week 10, but this finding is unlikely to be biologically relevant because no other corresponding hematological or immunological finding was observed. Blood (sublingual vein) and urine samples were collected at week 10 and an adequate battery of hematology, clinical chemistry, and urinalysis parameters was evaluated.

Clinical Chemistry

Clinical chemistry findings of higher cholesterol levels in MDFs and HDM/Fs, higher triglyceride levels in MDFs and HDFs, and higher alanine aminotransferase levels in HDFs after 10 weeks of treatment were observed. These levels were within the historical control range for this species and therefore are considered not biologically relevant.

Urinalysis

A statistically significantly lower urine pH was observed in HDMs compared to historical control data (6.4 versus 6.5 to 8.7) and a greater urine volume was measured in HDFs, although within the historical control range. Several other statistically significant findings were noted, but the changes were small and likely not biologically relevant or related to treatment. Urine was collected overnight in metabolism cages at week 10 and assessed for appearance, volume, pH, specific gravity, glucose, ketones, bile, and blood pigments. A microscopic examination of urine sediment was also performed.

Limb Measurement

Ulna growth for HDMs and HDFs from PND 21 to 91, was statistically significantly decreased compared to the controls (HDMs, 15.6 versus 16.8 mm; HDFs, 12.3 versus 13.2 mm, respectively), as was ulna growth for MDMs (16.0 versus 16.8 mm for the controls). Measurement of the left ulna was performed every 2 weeks starting on Day 21.

Sexual Maturation

There was a delay in attainment of sexual maturation by HDMs and HDFs compared to the controls. HDFs had a statistically significant delay in vaginal opening of 1.5 days compared to control animals, possibly in part a result of decreased body-weight gain in this group. Similarly, the age of completion of preputial opening in HDMs was delayed compared to the controls (46 versus 53 days). Males in the recovery/reproductive phase were assessed daily starting on Day 38 until balano-preputial separation, and females were assessed daily until vaginal opening.

Table 42. Sexual Maturation—Group Mean Age and Body Weight at Attainment

Group	:	1	2	3	4
Compound	:	Control	Tasimelteon	Tasimelteon	Tasimelteon
Dose (mg/kg/day)	:	0	50	150	450

Group		Balano preputial separation		Vaginal opening	
		Age of completion	Body weight (g) at completion	Age at completion	Body weight (g) at completion
Statistical test:		Sh	Wi	Sh	Wi
1	Mean	45.6	236	33.7	116
	SD	2.62	20.7	1.55	10.6
	N	30	30	30	30
2	Mean	45.5	236	34.5	122
	SD	2.78	30.7	1.68	12.4
	N	30	30	30	30
3	Mean	48.1	244	34.5	116
	SD	5.01	31.8	2.15	10.1
	N	30	30	30	30
4	Mean	52.7**	252	35.2*	117
	SD	5.75	36.4	2.97	9.8
	N	30	30	30	30

Source: Data in study no. TAJ0026
Abbreviations: N, number of population; SD, standard deviation
*p<0.05, **p<0.01 compared to the controls

Reproductive Capacity

The majority of mating pairs in all groups mated at the first estrus cycle after pairing; there was no effect of previous treatment on mating and there were no differences in estrus cycle activity between the groups. Additionally, the conception rate and fertility index was 95% to 100% in all treatment groups. The majority of females in all groups were pregnant with viable offspring. Tasimelteon had no effect on estrous cycle activity, precoital interval, mating performance, sperm parameters, or fertility. After the recovery period, the reproductive capacity of the animals was assessed using recovery/reproductive-phase males and females previously treated with tasimelteon. Animals were paired at 17 weeks of age for up to 2 weeks and were checked daily for copulation plugs were conducted. The precoital interval was calculated as the time elapsing between initial pairing and detection of mating. The pairs comprised control males and control females, previously treated males and untreated females, and previously treated females and stock males.

CNS/Neurobehavioral Assessment

Several neurobehavioral tests were administered during the in-life portion of the study to main phase animals and during the recovery phase to five recovery/reproductive phase animals per group. The assessments comprised motor activity, FOB (in-hand and arena observations), prepulse inhibition of auditory startle, and learning and memory via the Morris water maze.

Motor activity: Motor activity was tested using an automated infrared sensor system on treatment days 70/71 and recovery days 105/106. The number of high- and low-beam breaks binned into 6-minute intervals was assessed. HDMs had statistically significantly more high- and low-beam breaks at the 6-, 12-, 18-, and 24-minute intervals, respectively, compared to the

controls. MDMs had statistically significantly more high- and low-beam breaks at the 6- and 12- and the 18- and 24-minute intervals, respectively, compared to the controls. Statistically significantly more high-beam breaks were observed for MDFs at the 6- and 18-minute intervals compared to the controls. All groups performed at the level of the controls during the recovery period.

FOB: Parameters (in-hand and arena observations) were measured on treatment days 72 to 73 and recovery days 107 to 108. HDM/Fs and MDFs had increased observations of piloerection compared to the controls. Additionally, eight M/HDFs had coat staining and several MDs and HDs had reduced body tone. These findings resolved during the recovery period apart from a single HDM with piloerection. During the arena observations, single instances of tremor were noted during treatment in two MDMs, seven HDMs, and one HDF. One tremor was noted in a HDM during recovery. There were no corresponding findings in the FOB or body-weight changes in the animals that had tremors.

Prepulse inhibition: Sensory motor gaiting was measured by prepulse inhibition during treatment (Day 76) and recovery (Day 110). HDMs trended towards a shorter latency to peak with and without the prepulse compared to control animals, but this did not reach statistical significance. Strength (as measured by the amplitude of the response) was statistically decreased in HDMs compared to the controls. No treatment-related effects were observed in females in any group. During recovery, there was no clear effect of previous treatment on auditory startle prepulse inhibition in males or females.

Table 43. Auditory Startle Response Pre-Pulse Inhibition—Group Mean Values on Day 75/76 of Age (During Treatment)

Group	:	1	2	3	4
Compound	:	Control	Tasimelteon	Tasimelteon	Tasimelteon
Dose (mg/kg/day)	:	0	50	150	450

			Latency to peak (ms)		Peak amplitude (g)		
Group /Sex	Number of animals		Stimulus without pre-pulse	Stimulus with pre-pulse	Stimulus without pre-pulse	Stimulus with pre-pulse	Percentage inhibition
Statistical test:			Wi	Wi	lWi	Sh	Wi
1M	15	Mean	16.9	21.9	763.8	560.8	23.8
		SD	3.5	8.0	263.0	132.4	11.9
2M	15	Mean	16.5	20.3	683.3	501.7	25.2
		SD	2.8	4.4	119.2	55.5	10.9
3M	15	Mean	17.3	20.5	633.5	497.9	20.0
		SD	3.2	6.5	115.6	47.8	9.5
4M	15	Mean	15.2	18.1	645.1	467.7*	26.0
		SD	3.8	6.9	204.5	119.2	10.0

Source: Data in study no. TAJ0026
Abbreviations: SD, standard deviation
* p<0.05 compared to the controls

Morris water maze: Learning and memory were tested in the Morris water maze during treatment on Day 78 and during recovery on Day 112; rats were tested in three trials per day for 4 days. There were no treatment-related effects or changes in any of the groups tested.

Bone Evaluation

At the end of dosing, HD males had statistically significant decreases in femur length (4%) and width (10%) as well as decreases in femur metaphysis total area (13%) and bone mineral content (BMC) (11%) compared to the controls. In the diaphysis portion of the femur, HDMs had decreases in the total area, cortical area, BMC, thickness, and periosteal and endosteal circumferences compared to the controls. HD females also had statistically significant decreases in BMC and density, the magnitude of which was greater in trabecular bone (37% and 35% compared to the controls, respectively) compared to cortical/subcortical bone (10% and 5% compared to the controls, respectively). These findings are likely a result of melatonin receptor agonism and its downstream effects on physical development and bone formation. Reversibility was not evaluated. Bone density was evaluated on Day 91 and consisted of measurement, densitometry, and quantitative computed tomography of the cortical/subcortical and trabecular regions of the left femur.

Gross Pathology

There were no gross pathological findings in animals that survived to the end of the study. Findings in animals found dead or euthanized during study are described in Mortality. A full macroscopic evaluation of all animals was performed after euthanasia. For females in the reproductive/recovery phase, the reproductive tract and the ovaries were dissected and the numbers of corpora lutea, implantation sites, resorption sites and embryos were recorded. The vas deferens, epididymis, and testes were examined for males.

Organ Weights

After 10 weeks of treatment, femur weights in MDMs and HDMs were statistically significantly decreased compared to the controls. Additional organ-weight changes were observed in males: liver, thymus, and spleen weights were significantly increased in treated males compared to the controls. Heart weights trended higher than that of controls and pituitary weights were decreased at all dose levels. In females, organ-weight changes included higher kidney and liver weights at all doses, and lower pituitary weights at HD compared to the controls. All organ-weight changes resolved during the recovery/reproductive period, with the exceptions of the increases in liver weight in MDFs and HDFs and the decreases in pituitary weight in MDMs and HDM/Fs. There were no changes in the weights of reproductive organs.

Table 44. Organ-weight Differences Between Treatment Groups

	Control M	LDM	MDM	HDM	Control F	LDF	MDF	HDF
Organ-weight percentage differences from the controls after 10 weeks of treatment								
Terminal bodyweight (adjusted mean)	461g	95%	94%	87%*	260g	99%	95%	92%*
Femur	1.397g	99%	93%*	92%**	-	-	-	-
Heart	1.34g	108%	104%	109%*	-	-	-	-
Kidneys	-	-	-	-	1.852g	109%*	111%*	104%*
Liver	16.81g	104%	119%*	141%**	10.151g	107%*	119%**	139%**
Pituitary	0.014g	86%**	86%**	86%**	0.016g	88%	94%	81%*
Spleen	0.735g	107%	112%	116%*	-	-	-	-
Thymus	0.351g	113%	134%*	134%*	-	-	-	-
Organ-weight percentage differences from the control after recovery								
Liver	-	-	-	-	13.6g	99%	105%*	108%**
Pituitary	0.015g	93%	87%*	87%*	0.018g	88%	94%	81%*

Source: Data in study no. TAJ0026
Abbreviations: HDF, high-dose female; HDM, high-dose male; LDF, low-dose female; LDM, low-dose male; MDF, mid-dose female; MDM, mid-dose male
* p<0.05, ** p<0.01

Histopathology

By microscopic examination after 10 weeks of treatment, minimal to slight centrilobular hepatocyte hypertrophy was observed in the livers of HDMs and HDFs, a common finding in drug-treated rodents. This finding corresponded with increased liver weights in HD animals. These changes were not apparent after a period of recovery. There were no other findings.

Table 45. Treatment-Related Findings in the Liver of Animals Euthanized After 10 Weeks of Treatment

Group/sex	1M	2M	3M	4M	1F	2F	3F	4F
Dose (mg/kg/day)	**0**	**50**	**150**	**450**	**0**	**50**	**150**	**450**
Hepatocyte Hypertrophy, Centrilobular								
Minimal	0	0	1	1	0	0	0	1
Slight	0	0	0	9	0	0	0	9
Total	0	0	1	10	0	0	0	10
Number of tissues examined	10	10	10	10	10	10	10	10

Source: Data in study no. TAJ0026
Abbreviations: F, female; M, male

Complete tissues and organs were removed from 10 main-phase animals, sectioned, and stained with hematoxylin and eosin for histopathology. Findings were either reported as *present* or assigned a severity grade. Seven brain slices were taken per (Bolon et al. 2013).

Toxicokinetics

Blood samples (approximately 0.3 mL) from recovery/reproductive group animals were collected on days 21 and 90 and the plasma concentrations of tasimelteon and metabolites M9, M12, M13, and M14 were measured. For tasimelteon, time to maximum concentration (T_{max}) generally occurred at 1-hour postdose and later at higher doses (range, 1 to 8 hours). Exposure to tasimelteon increased with increasing dose, albeit in a less-than-dose-proportional manner. There was little to no accumulation of tasimelteon after repeated dosing from days 21 to 90, except in LDFs. There were no apparent sex differences in exposure to tasimelteon.

Table 46. TK Parameters of Tasimelteon in Rat Plasma Following Once-Daily Oral Gavage Administration for 10 Weeks

	Males					
	C_{max} (ng/mL)			AUC_{0-24} (h*ng/mL)		
Dose (mg/kg/day)	Day 21	Day 90	Accum. Ratio	Day 21	Day 90	Accum. Ratio
50	4770	4600	0.96	15,600	11,800	0.76
150	6960	5740	0.82	73,600	39,900	0.54
450	14,900	7120	0.48	161,000	102,000	0.63
	Females					
	C_{max} (ng/mL)			AUC_{0-24} (h*ng/mL)		
Dose (mg/kg/day)	Day 21	Day 90	Accum. Ratio	Day 21	Day 90	Accum. Ratio
50	4230	6650	1.57	13,000	27,800	2.14
150	6530	10,400	1.59	59,200	76,900	1.30
450	22,400	10,900	0.49	178,000	144,000	0.81

Source: Data from study no. TAJ0026.
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; TK, toxicokinetics
Accum. Ratio, accumulation ratio (C_{max} or AUC on Day 90 ÷ C_{max} or AUC on Day 21).

For M9, the T_{max} was similar to tasimelteon and generally occurred at 1-hour postdose and later at higher doses (range, 1 to 24 hours). Exposure to tasimelteon increased as dose increased, and accumulation of M9 was slightly greater after repeated dosing of tasimelteon from days 21 to 90 (1.6- to 4.4-fold), as indicated by the AUC and C_{max}.

Table 47. TK Parameters for M9 in Rat Plasma Following Once-Daily Oral Gavage Administration for 10 Weeks

Dose mg/kg/day	Males					
	C_{max} (ng/mL)			AUC_{0-24} (h*ng/mL)		
	Day 21	Day 90	Accum. Ratio	Day 21	Day 90	Accum. Ratio
50	303	918	3.03	1600	3340	2.09
150	477	1170	2.45	4540	9740	2.15
450	566	3180	5.62	9700	42900	4.42
Dose mg/kg/day	**Females**					
	C_{max} (ng/mL)			AUC_{0-24} (h*ng/mL)		
	Day 21	Day 90	Accum. Ratio	Day 21	Day 90	Accum. Ratio
50	399	677	1.70	1480	4930	3.33
150	446	1130	2.53	3780	10900	2.88
450	1180	1950	1.65	16000	25900	1.62

Source: Data from study no. TAJ0026.
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; TK, toxicokinetics

For M12, the T_{max} was similar to that of tasimelteon and occurred at 2 hours postdose (range, 1 to 8 hours). Exposure to tasimelteon increased with increasing dose, albeit in a less-than-dose-proportional manner, and there was no evidence of drug accumulation after repeated dosing of tasimelteon, although exposure (AUC) decreased in males and females from days 21 to 90.

Table 48. TK Parameters for M12 in Rat Plasma Following Once-Daily Oral Gavage Administration for 10 Weeks

	Males					
	C_{max} (ng/mL)			AUC_{0-24} (h*ng/mL)		
Dose mg/kg/day	Day 21	Day 90	Accum. Ratio	Day 21	Day 90	Accum. Ratio
50	9350	5640	0.60	55,800	21,900	0.39
150	15,500	7850	0.51	214,000	67,400	0.31
450	19,500	11,200	0.57	393,000	157,000	0.40
	Females					
	C_{max} (ng/mL)			AUC_{0-24} (h*ng/mL)		
Dose mg/kg/day	Day 21	Day 90	Accum. Ratio	Day 21	Day 90	Accum. Ratio
50	7150	10,800	1.51	43,300	73,000	1.69
150	13,500	12,300	0.91	176,000	126,000	0.72
450	24,200	13,400	0.55	357,000	160,000	0.45

Source: Data in study no. TAJ0026
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; TK, toxicokinetics

For M13, the T_{max} ranged from 1 to 8 hours, similar to the parent. Exposure to M13 increased with increasing dose, albeit in a less-than-dose-proportional manner, and there was no evidence of accumulation after repeated dosing.

Table 49. TK Parameters for M13 in Rat Plasma Following Once Daily Oral Gavage Administration for 10 Weeks

	Males					
	C_{max} (ng/mL)			AUC_{0-24} (h*ng/mL)		
Dose mg/kg/day	Day 21	Day 90	Accum. ratio	Day 21	Day 90	Accum. ratio
50	187	158	0.84	564	412	0.73
150	328	240	0.73	2390	1630	0.68
450	646	356	0.55	7670	4890	0.64
	Females					
	C_{max} (ng/mL)			AUC_{0-24} (h*ng/mL)		
Dose mg/kg/day	Day 21	Day 90	Accum. ratio	Day 21	Day 90	Accum. ratio
50	154	94	0.61	484	477	0.99
150	207	186	0.90	2440	2030	0.83
450	619	209	0.34	8370	3150	0.38

Source: Data in study no. TAJ0026
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; TK, toxicokinetics

For M14, the T_{max} ranged from 1 to 8 hours, similar to the parent compound. Exposure to M14 increased with increasing dose, albeit in a less-than-dose-proportional manner. There was no evidence of drug accumulation after repeated dosing.

Table 50. TK Parameters for M14 in Rat Plasma Following Once-Daily Oral Gavage Administration for 10 Weeks

	Males					
	C_{max} (ng/mL)			AUC_{0-24} (h*ng/mL)		
Dose mg/kg/day	Day 21	Day 90	Accum. ratio	Day 21	Day 90	Accum. ratio
50	1550	805	0.52	10500	3050	0.29
150	2650	1440	0.54	38200	8360	0.22
450	3180	1790	0.56	54500	23900	0.44
	Females					
	C_{max} (ng/mL)			AUC_{0-24} (h*ng/mL)		
Dose mg/kg/day	Day 21	Day 90	Accum. ratio	Day 21	Day 90	Accum. ratio
50	1680	1320	0.79	10300	10400	1.01
150	2240	1890	0.84	28900	14800	0.51
450	4780	2500	0.52	65800	26000	0.40

Source: Data in study no. TAJ0026
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; TK, toxicokinetics

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

No new in vitro studies were submitted in this NDA.

14.2. In Vivo Studies

Open-Label Study to Investigate the Pharmacokinetics and Safety of Tasimelteon in Children and Adolescents (VP-VEC-162-4201)

This study evaluated the PK, safety, and tolerability of tasimelteon suspension (4 mg/mL) after a single oral administration to children and adolescents with non-24 who were legally blind. Based on PK characteristics, the dose of tasimelteon suspension in pediatrics that achieves exposures (AUC) equivalent to those of adults administered a 20-mg dose was determined.

Study Design

Population: Children and adolescents from 3 to less than 18 years of age who were legally blind and who met the DSM-V criteria for non-24 and/or who were diagnosed with a neurodevelopmental disorder, including ASD and SMS.

Sample size: 24 subjects (9 children from 3 to less than 6 years old; 9 children from 6 to less than 12 years old; and 6 adolescents from 12 to less than 18 years old).

Cohorts: Subjects were dosed based on an allometric approach [20×(weight (kg)÷70)^0.75] to the following weight bands:

- 10 to less than 20 kg: 6 mg
- 20 to less than 40 kg: 12 mg
- 40 to less than 60 kg: 16 mg
- Greater than or equal to 60 kg: 20 mg

PK sampling: 0, 0.25, 0.5, 1, 2 and 4 h time points

Plasma concentrations of tasimelteon and its metabolites (M9, M11, M12, M13, and M14) were quantitated using a validated liquid chromatography-tandem mass spectrometry assay.

Results: The PK of tasimelteon suspension in pediatrics was analyzed using a population PK model. A two-compartment linear model with first-order absorption adequately describes the PK of tasimelteon suspension in pediatrics (refer to Section 14.3 for additional information). Covariate-parameter analysis suggests that body weight was the only influential covariate for the apparent total clearance of the drug from plasma after oral administration (CL/F) of tasimelteon suspension. A linear relationship between body weight and CL/F of tasimelteon suspension was observed in pediatrics weighing ≤ 28 kg. In children weighing >28 kg, the clearance was similar to that observed in adults.

Based on these findings, systemic exposures in children comparable to that in adults can be achieved using the following doses: Children ≤28 kg, 0.7 mg/kg; children >28 kg, 20 mg.

The PK of tasimelteon was compared between adults administered tasimelteon capsules (20 mg; Study VP-VEC-162-4101) and pediatrics administered tasimelteon suspension (10 to <20 kg, 6 mg; 20 to <40 kg, 12 mg; 40 to <60 kg, 16 mg and ≥60 kg, 20 mg; Study VP-VEC-162-4201). The exposures in pediatrics were scaled based on the proposed doses (≤ 28 kg, 0.7 mg/kg and >28 kg, 20 mg) prior to comparing the exposures in adults.

The results from this cross-study comparison suggest that systemic exposures (C_{max} and $AUC_{0-\infty}$) to tasimelteon are similar in adults and pediatrics (Section 6.3.1). The geometric mean ratios (GMRs), but not the 90% CIs, of PK parameters (C_{max}, AUC_{last} and $AUC_{0-\infty}$) are within the bioequivalence criterion (80% to 125%). The 90% CIs around the GMR of PK parameters being outside of the bioequivalence limit could be a result of the cross-study comparison between adults and pediatrics and the smaller sample size in adults receiving the capsule formulation (N=13) compared to pediatrics receiving the suspension (N=24). Following oral administration, the median T_{max} of tasimelteon suspension and tasimelteon capsules occurs at around 15 and 30 minutes, respectively. Considerable overlap in exposures to all metabolites (M9, M11, M12, M13, and M14) was observed between adults and pediatrics.

Conclusion: PK analysis in pediatrics suggest that tasimelteon suspension (4 mg/mL) can be administered at a dose of 0.7 mg/kg to children weighing less than 28 kg and at a dose of 20 mg to those weighing more than 28 kg.

14.3. Pharmacometrics Review

Summary of Applicant's Population PK Analysis

A population PK analysis of tasimelteon suspension was conducted using PK data from a study in pediatric subjects (3 to less than 18 years old) with non-24 (VP-VEC-162-4201, N=24). The PK samples were collected at: predose and 0.25, 0.5, 1, 2 and 4 h postdose. All predose samples were below the limit of quantitation (BLQ) and were excluded from the analysis. No postdose samples were BLQ. Summaries of the key demographics and covariates for the pediatric population are presented in Table 51, Table 52 and Table 53. The final population PK model was a two-compartment linear model with first-order absorption with body weight as a covariate on CL/F, central and peripheral volume of distribution (V1/F and V2/F). Final model parameters and bootstrap analysis of the final population PK model are shown in Table 54 and

Table 55, respectively. The eta shrinkages are 0.1%, 0.1%, and 10% for CL/F, V1/F and absorption rate constant (K_a), respectively. The goodness-of-fit plots are shown in Figure 16.

Table 51. Summary of Demographic Characteristics by Dose

	By Dose (mg)			
Category[a]	**6 N=5**	**12 N=13**	**16 N=3**	**20 N=3**
Age (years)				
Mean (SD)	3.6 (0.89)	8.5 (2.93)	11.0 (2.00)	15.7 (1.53)
Median (range)	3.0 (3-5)	8.0 (5-14)	11.0 (9-13)	16.0 (14-17)
Gender n (%)				
Female	4 (80.0)	5 (38.5)	0	1 (33.3)
Male	1 (20.0)	8 (61.5)	3 (100.0)	2 (66.7)
Race n (%)				
White	4 (80.0)	10 (76.9)	3 (100.0)	3 (100.0)
Black or African American	1 (20.0)	3 (23.1)	0	0
Height (cm)				
Mean (SD)	95.4 (6.47)	128.2 (12.56)	152.0 (11.14)	174.3 (9.50)
Median (range)	96.0 (86-104)	125.0 (110-147)	154.0 (140-162)	174.0 (165-184)
Weight (kg)				
Mean (SD)	14.20 (1.984)	28.42 (6.985)	43.97 (4.007)	78.23 (14.365)
Median (range)	13.60 (11.7-16.6)	24.50 (21.9-37.8)	42.50 (40.9-48.5)	84.50 (61.8-88.4)
BMI (kg/m²)				
Mean (SD)	15.56 (0.979)	16.98 (2.178)	19.13 (2.316)	26.23 (7.245)
Median (range)	15.30 (14.5-17.1)	17.00 (14.0-21.1)	18.50 (17.2-21.7)	27.90 (18.3-32.5)

BMI=body mass index; SD=standard deviation.
Source: Table 6, pediatric PK study report (VP-VEC-162-4201)

Table 52. Summary of Categorical Covariates

Covariate	Value	Descriptor	Count	Percentage
Sex	1	Male	14	58.33
	2	Female	10	41.67
Race	1	White	20	83.33
	2	Black	4	16.67

Table 53. Summary of Continuous Covariates

Descriptor	Mean	Standard Deviation	Median	Minimum	Maximum
Age (years)	8.66667	4.22895	8.5	3	17
Weight (kg)	33.4958	20.3961	25.2	11.7	88.4
Height (cm)	130.125	26.2617	125	86	184
BSA (m^2)	1.0811	0.41764	0.916	0.529	2.021
BMI (kg/m^2)	18.108	4.30752	17.15	14	32.5
Albumin (gm/dL)	4.15417	0.31205	4.2	3.4	4.7
Alkaline Phosphatase (IU)	271.125	100.891	233.5	130	467
ALT (IU)	26.375	9.40311	25	10	49
AST (IU)	23.625	6.92075	25.5	12	36
Total Bilirubin (µmol/L)	0.33917	0.16165	0.3	0.2	0.8
Serum Creatinine (mg/dL)	0.48292	0.15535	0.46	0.2	0.82
GFR* (Schwartz, ml/min/1.73m^2)	159.96	44.612	148.85	121.1	341

* Also known as creatinine clearance.
Source: Tasimelteon population PK analysis report
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; GFR, glomerular filtration rate

Table 54. Final Population PK Parameter Estimates of Tasimelteon (VP-VEC-4201)

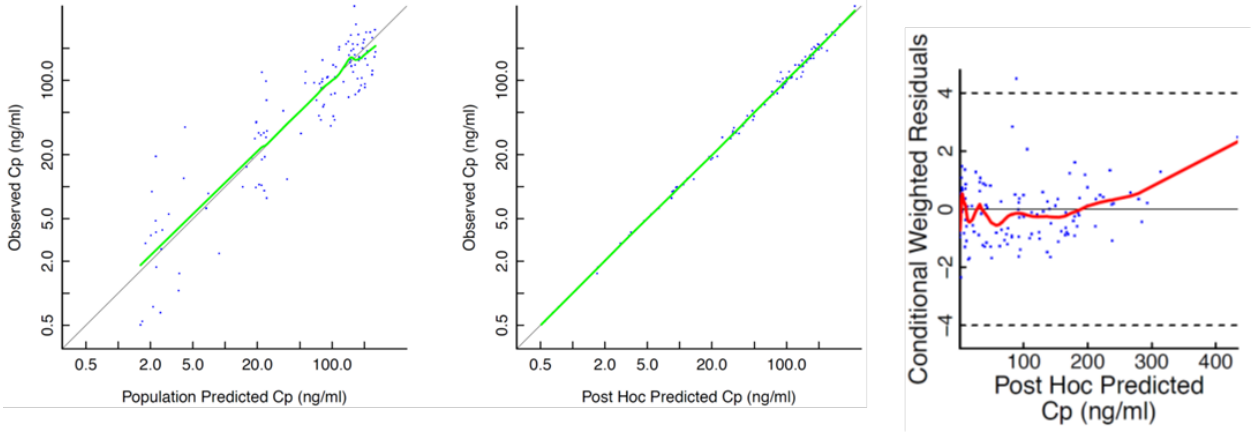
Parameter	Estimate	Inter-Individual Variability*
CUTPOINT (kg)	28.1275	—
SCALE		
Weight ≤ CUTPOINT	WT / CUTPOINT	
Weight > CUTPOINT	1	
Clearance/F (L/day)	1472.81 • SCALE	0.4926
V_1/F (L)	28.2699 • SCALE	0.544
Distributional Clearance/F (L/day)	477.387 • SCALE	0.7252
V_2/F (L)	10.9211 • SCALE	0.7027
Absorption Rate (/day)	110.463	0.5869

OMEGA #	Applies to THETA	Variance	Correlation
1	Clearance/F	0.151274	—
2	V_1/F	0.0765796	—
1 / 2	—	—	0.4605
3	Distributional Clearance/F	0.0875074	—
1 / 3	—	—	0.394
2 / 3	—	—	-0.576
4	V_2/F	0.107659	—
1 / 4	—	—	-0.2113
2 / 4	—	—	0.1765
3 / 4	—	—	-0.02965
5	Absorption Rate	0.308576	—

SIGMA	Variance	Square Root Variance
Proportional component	0.0786063	0.2804
Additive component	0.0333189	0.1825

Source: Tasimelteon population PK analysis report
*Square root of the variance of interindividual variability (OMEGA); SIGMA indicates residual variability.

Figure 16. Goodness-of-Fit Plots of the Final Pharmacokinetics Model for Tasimelteon



Source: Tasimelteon population PK analysis report

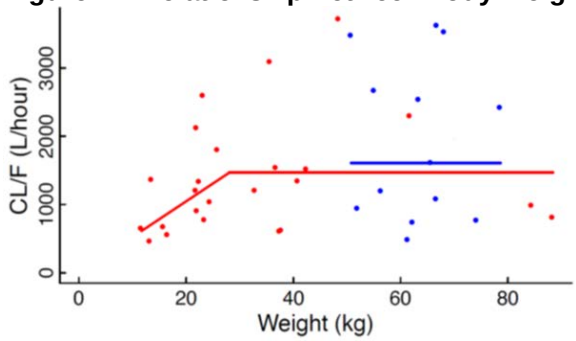
Table 55. Summary of the Bootstrap Analysis of the Final Population Pharmacokinetics Model for Tasimelteon

				Percentile		
THETA	**Estimate**	**Mean**	**SD**	**5**	**50**	**95**
All (N = 500)						
Clearance/F	1474.29	1499.96	229.15	1145.97	1484.69	1922.94
V_1/F	28.28	27.43	7.38	12.64	28.49	37.23
Distributional Clearance/F	479.22	526.22	267.93	176.12	493.01	999.10
V_2/F (L)	10.96	12.37	4.75	6.08	11.31	21.44
Absorption Rate	110.33	112.48	41.27	54.90	108.51	174.14
Cutpoint	28.15	29.18	5.30	22.00	28.26	36.80

Source: Tasimelteon population PK analysis report

To determine whether the systemic exposures observed in children are comparable to those in adults, the Applicant developed a population PK model using PK data from healthy adults (Study VP-VEC-162-4101). A two-compartment model with first-order absorption describes the PK of tasimelteon in adults. No covariates other than body weight influence the PK of tasimelteon. Body weight influences the clearance in children up to 28 kg; clearance in children of body weight >28 kg is similar to that in adults (Figure 17).

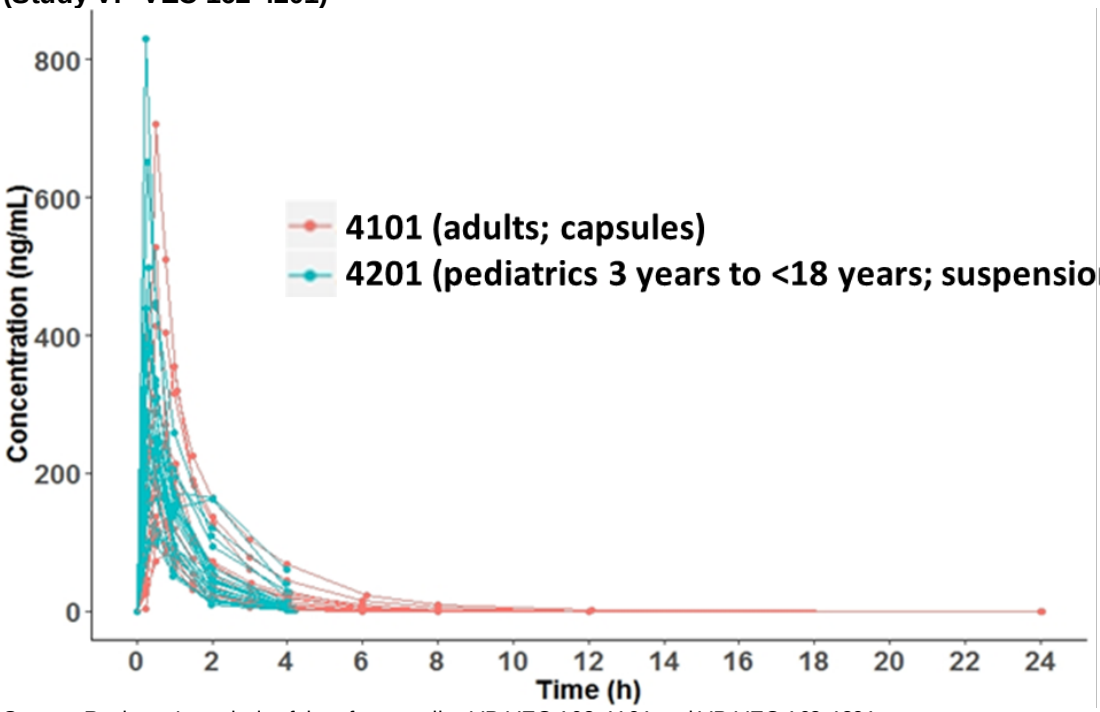
Figure 17. Relationship Between Body Weight and CL/F for Tasimelteon in Children and Adults



Red circles, children (VP-VEC-162-4201, n=24); blue circles, adults (VP-VEC-162-4101, N=13). Lines display modeled values for children and adults

A high degree of overlap in systemic exposures (Figure 18) was observed between the capsule and suspension formulations after normalization of systemic exposures in pediatric subjects on the proposed dosing regimen (0.7 mg/kg for subjects weighing <28 kg and 20 mg for subjects ≥28 kg). A comparison of PK parameters of the capsule and suspension formulations is provided in Table 10 in Section 6.3.1.

Figure 18. Mean Plasma Concentration-Time Profiles of Adults Who Received the Capsule Formulation (Study VP-VEC-162-4101) and Pediatrics Who Received the Suspension Formulation (Study VP-VEC-162-4201)



Source: Reviewer's analysis of data from studies VP-VEC-162-4101 and VP-VEC-162-4201

Reviewer's comments: *The reviewer was able to verify the Applicant's analyses and replicate the results. The results suggest that the two-compartment PK model with first-order absorption adequately describes the PK of tasimelteon. Body weight was the only influential covariate on CL/F and volume of distribution (V1/F and V2/F). The relationship between body weight and clearance suggests that an increase in body weight is associated with an increase in clearance up to 28 kg; thereafter, an increase in body weight did not affect clearance. The clearance in subjects weighing >28 kg is similar to that in adults. The proposed doses, 0.7 mg/kg once daily for subjects weighing <28 kg and 20 mg for those ≥28 kg, are acceptable.*

14.4. Summary of Bioanalytical Method Validation and Performance

The plasma concentrations of tasimelteon and its metabolites, M9, M11, M12, M13, and M14 were measured using a validated liquid chromatography-tandem mass spectrometry assay. Because this assay has been fully validated ([(b) (4)] 208-1202), a partial validation was performed

prior to quantitating the analytes in plasma samples from a PK study, VP=VEC-162-4201. It was found that:

- The precision and accuracy values (Table 56) of at least two-thirds of the overall QC samples from the supporting bioanalytical reports were within ±15% (±20% at the lower limit of quantitation).
- Tasimelteon and its metabolites were found to be stable in plasma after at least five freeze-thaw cycles at −70°C, 98 days at −20°C, 475 days at −70°C, and at room temperature in human plasma over at least 19 h. In processed samples, analytes are stable over 344 h at 4°C.
- The QC sample accounting for dilution (50-fold) showed acceptable precision (<8.2%) and bias (<12%). No carryover effect was found for tasimelteon or its metabolites.
- More than two-thirds of the incurred sample reanalysis fell within 20% deviation.

The bioanalytical methods satisfy the criteria for 'method validation' and 'application to routine analysis' set by the *Guidance for Industry: Bioanalytical Method Development* and are acceptable.

Table 56. Summary of Bioanalytical Method Validation

Applicant's study no. VP-VEC-162-4201 Bioanalytical study nos. (b) (4) 208-1202 and (b) (4) 208-1701	Analyte	Sample Volume	Analytical Range (ng/mL)	Precision (CV %)	Accuracy (%)
	Tasimelteon	200 µL	0.3-300	0.4-4.9	95.3-100.7
	M9	200 µL	1.0-1000	1.1-4.4	93.8-101.3
	M11	200 µL	0.3-300	0.9-4.9	100.0-104.3
	M12	200 µL	0.3-300	1.4-14.4	97.3-100.8
	M13	200 µL	1.0-1000	1.2-4.7	95.2-101.5
	M14	200 µL	0.326-326.279	1.8-14.1	88.0-102.3

Source: Bioanalytical Reports (b) (4) 208-1202 and (b) (4) 208-1701
Abbreviation: CV, coefficient of variation

15. Trial Design: Additional Information and Assessment

15.1. Applicant's Protocol Synopsis

Clinical Protocol Synopsis for Study VP-VEC-162-2401, Incorporating Amendment 10, Dated August 13, 2019.

Protocol Title

A double-blind, randomized, two-period crossover study evaluating the effects of tasimelteon versus placebo on sleep disturbances of individuals with SMS.

Studied Period

- Estimated date first patient enrolled: September 2015
- Estimated date last patient completed: December 2020

Study Phase

Phase 2b/3

Number of Patients (Planned)

Up to 48 randomized; up to 100 open label

Nonrandomized Cohorts

- Cohort 1: The first cohort of adults 16 to 65 years of age will enter directly into the Open- Label Phase (n ≤20); this cohort is no longer enrolling.
- Cohort 2: The first cohort of children and adolescents 3 to <16 years of age will enter directly the Open-Label Phase (n ≤ 20); this cohort is no longer enrolling.

Randomized Cohorts

- Cohort 3: Adults 16 to 65 years of age who may be eligible to be randomized.
- Cohort 4: Children and adolescents 3 to <16 years of age who may be eligible to be randomized.

Duration of Treatment

Up to 241 weeks.

Rationale for Tasimelteon in SMS

SMS patients examined to date in the VP-1401 study (Please refer to Section 16.2) have shown plasma melatonin secreted abnormally during the daytime instead of at night. These results are consistent with several studies, which have reported that in most SMS patients melatonin secretion is high during the day and low at night, which is opposite the normal pattern (Potocki et al. 2000; De Leersnyder et al. 2001a).

Tasimelteon is a dual melatonin receptor agonist. In non-24 patients, daily treatment with 20 mg tasimelteon resulted in a significant improvement in several sleep parameters, including the duration and timing of nighttime sleep and daytime nap duration [HETLIOZ® label]. The same 20 mg was selected for the VP-VEC-162-2401 study as it has been shown to be safe and effective in non-24 patients, and is approved by the FDA for this indication. For maximum efficacy, it is hypothesized that the time of maximum plasma concentration of tasimelteon should coincide with the time that patients go to bed. The peak maximum plasma concentration (C_{max}) of tasimelteon is reached at approximately 0.5 to 3 hours after fasted oral administration. Consequently 1 hour before bedtime was chosen for the time of tasimelteon administration in the current study.

Primary Objectives

To determine the efficacy of tasimelteon administered daily compared to placebo, as measured by improvement in nighttime sleep.

Secondary Objectives

- To determine the efficacy of tasimelteon administered daily compared to placebo, as measured by the Post-Sleep Questionnaire (PSQ) and Pre-Sleep Questionnaire (PreSQ).
- To determine the efficacy of tasimelteon administered daily compared to placebo as measured by improvements in actigraphy parameters.
- To determine the efficacy of tasimelteon compared to placebo, as measured by changes in the Clinical Global Impression of Change scale (CGI-C).

- To determine the efficacy of tasimelteon compared to placebo, as measured by changes in the Clinical Global Impression of Severity scale (CGI-S).
- To evaluate the impact of sleep improvement on behavior, as measured by the Aberrant Behavior Checklist (ABC).
- To determine the efficacy of tasimelteon administered daily compared to placebo, as measured by the SMS Sleep Questionnaire (SSQ).
- To determine the efficacy of tasimelteon compared to placebo, as measured by the supplemental Sleep Interview (SSI).
- To explore the safety and tolerability of repeated doses of tasimelteon.

Overall Design

The study will consist of three phases: a Screening Phase followed by a Treatment Phase and an Open-Label Extension Phase. The Treatment Phase will consist of either a Randomization Arm or an Open-Label Arm, depending on eligibility after analysis of the screening data. The Randomization Arm will comprise treatment with both tasimelteon and placebo (separated by a 1-week washout) administered in a double-blinded, randomized, two-period, crossover manner.

Screening Phase

The Screening Phase will be at least 4 weeks in duration. During the screening visit (V1; Week S1), participants will provide consent/assent and initial eligibility will be evaluated based on sleep and medical history and physical examination, prior/current medication use, vital signs, electrocardiogram (ECG), and clinical laboratory results. Female patients of child-bearing potential will be tested for pregnancy and information regarding their menstrual cycle will be collected. Patients will be asked to provide information regarding their prior SMS diagnosis, to complete all baseline behavioral assessments and quality of life questionnaires, and a blood sample will be obtained for genetic testing. All blood samples will be sent to a core genetic laboratory for a detailed analysis of the *RAI1* gene (results of the analysis do not need to be returned before patient can begin the trial if diagnosis meets eligibility criteria), to perform an exploratory pharmacogenomics and metabolomics analyses. If it is determined that the patient meets all initial eligibility criteria, they will begin washing out of prohibited medications, if needed, and will be fitted with an Actiwatch, which will be worn daily until Visit 9. Actiwatch data will be monitored and the patient's caregiver will complete daily charting at home, for approximately 10 weeks during screening. Patients may return to the clinic at least 2 weeks after screening for Visit 2 (V2; Week S2) and at least 4 weeks after Visit 1 for Visit 3 (V3; Week S3), if needed. Returning to the clinic for V2 and V3 will be up to the discretion of the Investigator. These visits may be conducted remotely as the patient's Actiwatch can be exchanged via courier service for a newly charged one and the data downloaded by the site. For remote visits, the site will be responsible for conducting a phone call to query and record adverse events and changes to concomitant medications. The data collected during the Screening Phase must be reviewed in order to determine eligibility for enrollment into the Randomization Arm of the Treatment Phase. Data review will be performed following at least 4 weeks of data collection. Patients who continue to meet all eligibility criteria will be enrolled into Randomization Arm of the Treatment Phase at Visit 3.1 (V3.1). Patients who do not meet the sleep deficit criteria for randomization but still meet all other eligibility criteria, will be offered enrollment into the Open-Label Arm of the Treatment Phase at V3.1. If the

Randomization Arm of the Treatment Phase is no longer enrolling, patients will be offered enrollment into the Open-Label Arm of the Treatment Phase at V3.1

Treatment Phase (Randomization Arm)

The Randomization Arm of the Treatment Phase will last approximately 9 weeks and will consist of treatment with tasimelteon and placebo administered in a double-blinded, randomized, two-period, crossover design. The 2 periods will be separated by a 1-week washout. At Visit 3.1 (V3.1; Week 0), eligible patients will be randomized to either tasimelteon or placebo which will be taken every night, 1 hour before bedtime for 4 weeks. At Visit 4 (V4), patients will complete safety assessments, actigraphy data collection, and the completion of behavioral and Clinical Global Impression (CGI) scales. They will also be dispensed additional investigational product, which they will begin taking after a 1-week (7 days) washout, and will contain the alternate study treatment to be taken every night, one hour before bedtime for another 4 weeks. Two reminder calls 6 and 8 days after V4 will be placed by the site to confirm the patient washed out of investigational product and began dosing with the alternate treatment. Outpatient phone assessments will occur at weeks 2 and 7. At Visit 5 (V5), patients will complete safety assessments, actigraphy data collection, and will complete the behavioral and CGI scales. Any remaining investigational product will be collected. A blood sample for exploratory analyses may be obtained at each visit during the Randomization Arm of Treatment Phase (V4 and V5; Week 4 and Week 9, respectively). All visit windows are ± 3 days. At V5, all patients will continue into the Open-Label Extension.

Treatment Phase (Open-Label Arm)

Patients who enter into the Open-Label Arm of the Treatment Phase at Visit 3.1 (V3.1; Week 0) will be treated with open-label tasimelteon for 9 weeks and will follow the same visit and evaluation schedule as patients in the Randomization Arm of the Treatment Phase. All visit windows are ± 3 days.

Open-Label Extension Phase

The Open-Label Extension Phase consists of 232-weeks of open-label treatment where all patients will receive open-label tasimelteon. At Visits 6 to 17, routine safety and exploratory efficacy assessments will be completed. A blood sample for exploratory analyses may be obtained at each visit during the Open-Label Extension Phase. Actigraphy data will be downloaded at Visits 6, 7, 8, and 9. Daily eDiary completion will continue until EOS. Open-label medication will be dispensed at each of these visits and compliance will also be assessed. All visit windows are ± 7 days. At the end of the Open-Label Extension Phase (or at the time of early termination/discontinuation), End-of-study (EOS; V18) assessments will be performed. EOS assessments include safety evaluations, exploratory efficacy evaluations, and the collection of remaining investigational product, the e-diary tablet and if necessary, the collection of the patient's actigraphy watch (if not already collected, such as in the case of termination/discontinuation prior to V9).

Study Drug

Tasimelteon will be administered orally as 20 mg capsules for adult patients or as an age-appropriate liquid suspension formulation based on weight for pediatric patients:

- ≤28 kg—0.7 mg/kg 1 hour before bedtime
- >28 kg—20 mg 1 hour before bedtime

Efficacy Assessment

Sleep diaries will be used to complete the Post-Sleep Questionnaire (PSQ) and the Pre-Sleep Questionnaire (Pre-SQ). Sleep diaries are uploaded as an android application on a tablet which is provided to caregivers and investigators together with an instructions manual and user guide. When the questionnaires are completed, data are automatically synchronized to central database.

The PSQ comprises the following questions/entries:

- Did the individual with SMS sleep last night?
- What time did they go to bed?
- What time did they fall asleep?
- How many times did they wake up during the night as you are aware?
- What time did they wake up for the day?
- How many hours do you think they slept last night?
- How would you describe the overall quality of their sleep last night?

The Pre-SQ comprises the following questions/entries:

- Number of daytime naps
- What time did the nap start?
- How long did it last?

An **actigraphy watch** will be worn by each patient to measure gross motor activity and will be used to assess the sleep/wake patterns of patients in the study. The actigraphy watch used in Study VP-VEC-162-2401 was the Philips Actiwatch Spectrum Classic. 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 Philips-owned 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 the Applicant via password-protected e-mail

The CGI-S is a 7-point scale in which the clinician rates the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of illness at the time of rating 1: normal, not at all ill; 2: borderline ill; 3: mildly ill; 4: moderately ill; 5: markedly ill; 6: severely ill; or 7: extremely ill.

The CGI-C is a 7-point rating scale where Investigators rate the patients' improvement in symptoms relative to the start of the study. It is rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse. To establish a baseline for the CGI-C, the clinician should utilize the Sleep Complaint Questionnaire, the Sleep History Interview, and the Supplemental Sleep Interview as a basis for making assessments of improvement.

The ABC is a validated symptom checklist for parents and caregivers to assess problem behaviors of children and adults with mental retardation. The 58 items resolve into five subscales: (1) Irritability, Agitation, (2) Lethargy, Social Withdrawal, (3) Stereotypic Behavior, (4) Hyperactivity, Noncompliance, and (5) Inappropriate Speech.

The SSI is a supplement to the baseline sleep interview, to be administered by the clinician and is a questionnaire that assess the presence, absence, and details of general sleep complaints over a period of the previous 2 weeks, compared to baseline.

The SSQ is a 7-point rating scale where caregivers rate the patients' improvement in symptoms relative to the start of the study. It is rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.

DCOA reviewer's comment: *Analyses of data from Open-Label cohort 1 appeared to be an inadequate method to select the primary efficacy endpoint for pivotal study VP-VEC-162-2401 as caregivers' and/or patients' knowledge of treatment assignment may lead to systematic overestimation or underestimation of the treatment effect, the magnitude of which is currently unknown.*

In addition, it is noted that the Applicant did not provide any documentation to demonstrate the developmental history of parental PSQ, or any evidence to support validity and reliability of parental PSQ.

- *Despite different versions of PSQ found in the public domain, the Applicant did not provide any specific literature on parental PSQ used in this pivotal study.*
- *The Applicant mentioned several of their own clinical trials with the use of PSQ, however these PSQs were not caregiver questionnaires and self-reported by patients.*

Statistical Considerations: Sample Size

The sample size chosen for this study is not based on the statistical consideration. As this is a very rare orphan disease, up to 48 randomized patients are planned in the cross-over study, with up to 100 patients in open-label.

Statistical Reviewer's comment*: *The Applicant randomized 26 patients, with 25 being included in the ITT population. It is true that a cross-over design provides additional power compared to a parallel group design with the same number of subjects, because each subject acts as its own control which decreases variability in the measurements. It is somewhat remarkable that the study achieved a statistically significant result given the lower than planned for number of participants, on the other hand the sample size planning for this initially titled exploratory study did not involve statistical considerations.

Stats IR 07/17/2020 Regarding Randomization

In the study report (CSR) of study 2401 you describe randomization to treatment sequence as being stratified by site and formulation. Furthermore "Within each site, patients were

randomized according to a randomization list with a block of four crossover sequences for each formulation" (CSR p. 31). This reviewer could not find a description of the randomization procedure in the statistical analysis plan nor the protocol.

(1) Please provide the full randomization list. The listing of the actual treatment assignments in the appendix of the CSR is not sufficient.
(2) Please review the attached summary of the randomization dates and assignments (*randomization.pdf*). It appears that there is a deviation from the above described algorithm ("block of 4 crossover sequences for each formulation") for site (b) (6) There were three patients randomized to "Treatment B: Placebo, Tasimelteon 20mg" within the first block. This apparent mistake was "corrected" in the next block where three patients were randomized to "Treatment A: Tasimelteon 20mg, Placebo." Please explain.

Subjid	**Kit (actual)**	**Seq/TRT group (actual)**	**Kit (planned)**	**Seq/TRT group (planned)**
(b) (6)	1001	1 (Active/Placebo)	1000	1
	1002	**2** (Placebo/Active)	1001	**1**
	1003	2	1002	2
	1004	2	1003	2
	1005	**1**	1004	**2**
	3151	1	1005	1
	3184	1	1006	1
	3397	2	1007	2

Applicant's Responses

Re a)"Initially, this study only enrolled adult patients. Due to the small sample size, the randomization was directly done by the IP vendor through labeling and packaging. […] When the study started enrolling pediatric patients, a central IWRS was created for randomization because the number of bottles of liquid formulation distributed at each visit had to be calculated based on patients' weight." The Applicant provides the randomization codes for adult and pediatric patients in appendices A and B to their response.
Re b) "The reason for the observed randomization order is explained by an error in the shipment of the first sequence of bottles.

Statistical reviewer's comment: *The randomization error appears to be a honest mistake. The randomization procedure appears to be valid overall.*

Primary Endpoints

The primary efficacy endpoints are derived from two items of the PSQ:

50% Worst Daily Diary Sleep Quality (DDSQ50)

Sleep quality was recorded daily by the parental Post-Sleep Questionnaire (PSQ). The actual question asked was: "How would you describe the overall quality of their sleep last night?." The average of the 50% worst ratings of sleep quality was determined and compared across placebo and treatment periods for each participant. Sleep quality was rated as follows: 5=excellent; 4=good; 3=average; 2=fair; 1=poor.

50% Worst Daily Diary Total Sleep Time (DDTST50)

Sleep duration was recorded daily by the parental PSQ. The actual question asked was: "How many hours do you think they slept last night?" The average of the 50% worst ratings of sleep duration was determined and compared across placebo and treatment periods for each participant.

Secondary Endpoints

PSQ

- Average of 50% Worst Daily Number of Nighttime Awakenings
- Average of 50% Worst Latency to Sleep (minutes)
- Average of Daily Nighttime Sleep Quality
- Average of Daily Number of Nighttime Awakenings
- Average of Daily Total Amount of Nighttime Sleep – hours (minutes)
- Average of Latency to Sleep (minutes)

Actigraphy

- Average of 50% Worst Daily Length of Nighttime Awakenings (minutes)
- Average of 50% Worst Daily Number of Nighttime Awakenings
- Average of 50% Worst Daily Total Amount of Nighttime Sleep – hours (minutes)
- Average of 50% Worst Latency to Sleep (minutes)
- Average of Daily Length of Nighttime Awakenings (minutes)
- Average of Daily Number of Nighttime Awakenings
- Average of Daily Total Amount of Nighttime Sleep - hours (minutes)
- Average of Latency to Sleep (minutes)

Clinical Global Impression – Severity (CGIS) change from baseline

Clinical Global Impression – Change (CGIC) change from baseline

Analysis of the ABC Using Mixed Effects Model Change From Baseline Treatment Comparison

Analysis of the SMS Sleep Questionnaire Using Mixed Effects Model Change From Baseline to Time Point Treatment Comparison

Analyses

A mixed-effects model approach was used to analyze the primary efficacy outcome. The Mixed model includes the fixed, categorical effects of treatment group assignment, period and sequence. The period is included in the repeated statement and an unstructured covariance matrix is used to adjust for the within-patient covariance. The following sample SAS code was included with the SAP:

(b) (4)

Least squares (LS) means, standard errors, 95% confidence intervals (CI), and p-values will be presented by treatment and for the treatment difference (tasimelteon - placebo). A paired (tasimelteon - placebo) t-test will also be used to analyze the primary endpoint.

Statistical reviewer's comment: *Note the following statement is included in the protocol (page 71): "If the crossover effect is significant, only the data from the first period will be used to compare between treatment arms using ANCOVA." This statement led to several communications to the Applicant prior NDA submission inquiring about the inherent assumption of no "carry-over" effect in cross-over designs and what is meant by the Applicant's term "cross-over" effect.*

Continuous secondary endpoints were to be summarized and analyzed in a manner similar to the primary endpoint (protocol page 71, SAP page 16).

15.1 Study VP-VEC-162-2401 Full Eligibility- Criteria

Inclusion Criteria

1. A confirmed clinical diagnosis of SMS;

a. Prior positive genetic test result as indicated by parent/guardian;

2. Informed consent from the patient or the legal guardian. When possible, assent provided by the patient with SMS;

3. Male or female between 3 and 65 years of age;

4. Recent history of sleep disturbances;

5. Had an appointed caregiver who could complete the required outpatient assessments;

6. Was willing and able to comply with study requirements and restrictions; and

7. Demonstrated impaired sleep quality during the Screening Phase (for Randomization Arm of Treatment Phase only).

FDA Clinical reviewer's comment: *Following an Information Request, the Applicant clarified that the average of sleep quality <3.0 (Average) was used for the inclusion criteria at the beginning of the randomization. However, the enrollment rate was dramatically slow with only four patients randomized for two years. Therefore, in June of 2018, before protocol amendment*

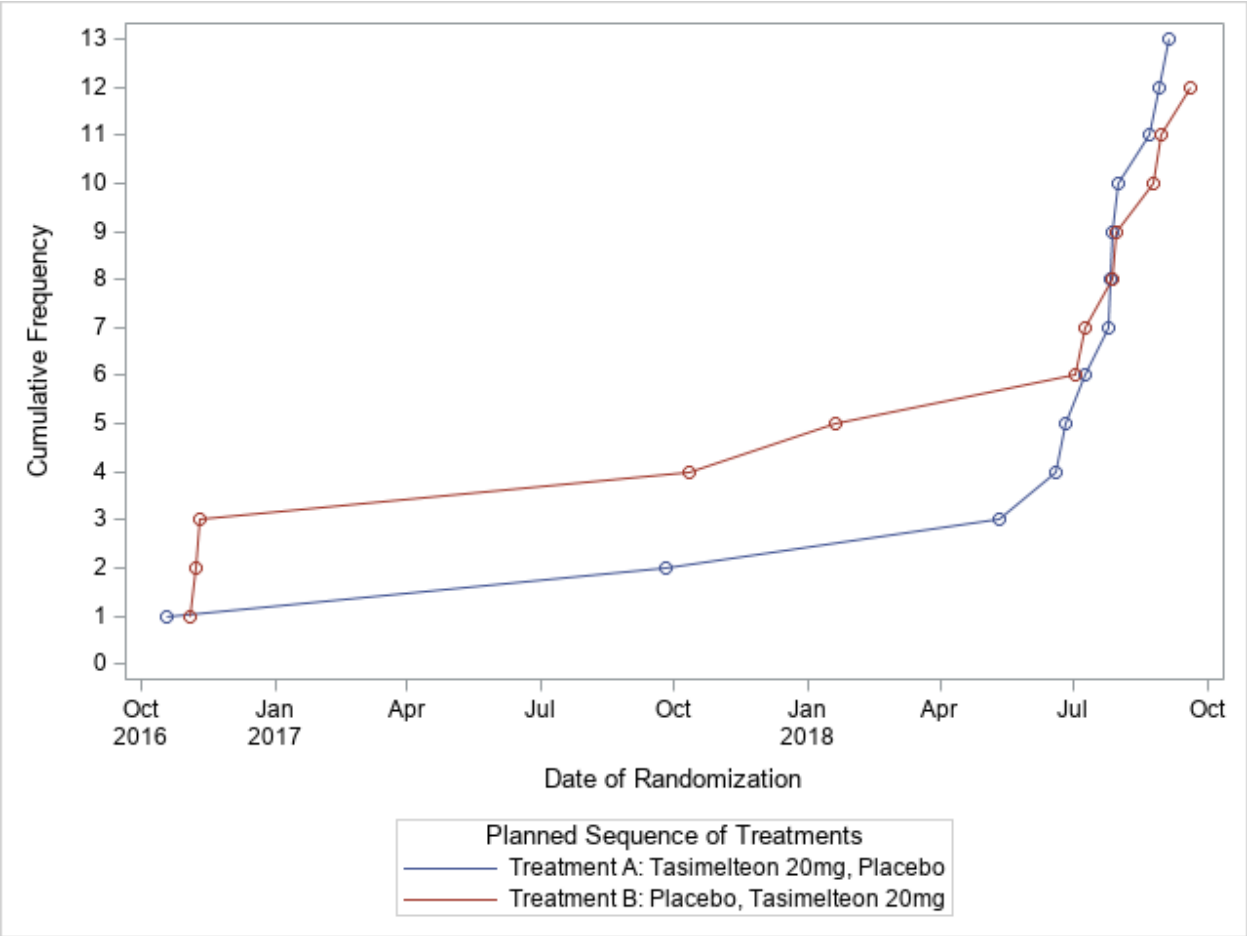
8, the Applicant re-evaluated the sleep quality criteria, and modified it to the average of 50% worst of sleep qualities <3 during the screening period.

Including subjects with impaired quality of sleep at baseline could be interpreted as an enrichment strategy to reduce intersubject variability and select a patient population with moderate or severe sleep impairment with the purpose of increasing the likelihood of detecting a treatment effect. Changing the threshold for inclusion during recruitment, on the other hand could increase variability and reduce the likelihood of an efficacy signal detection. In consideration of the clinical trial results and particularly the statistically significant difference between tasimelteon and placebo in DDSQ50, the strategies described above and the change in the threshold for inclusion do not appear to have reduced the efficacy signal.

Following an Information Request, the Applicant clarified that the inclusion criterion for the fragmented nighttime sleep was determined as having demonstrated significant (more than 10%) wake time (awakenings) within the sleep interval as measured by the actigraphy watch. The clinical relevance of the 10% threshold was determined by the Applicant using data from the open label cohort 1.

The Actiware software used for the analysis of the actigraphy data, however, has limited (38%) specificity for detecting wake, and therefore we believed that this criterion has not appropriately selected an homogeneous population of patients (refer to Section 6.3.5 for a discussion on the use of actigraphy data). Similarly to the considerations made for sleep quality inclusion criterion, we believe that failure to recruit an homogeneous population with similar baseline degree of impairment in sleep parameters may have increased the variability within the sample and it would have been useful to discuss with the Applicant and agree on inclusion criteria at time of protocol development (IND stage). However, for the purpose of the clinical review and in consideration of the demonstrated treatment benefit these criteria are considered acceptable.

Figure 19. Randomization in Study 2401 Over Time



Source: Statistical Reviewer

The Applicant also used actigraphy data to detect periods of awakenings during sleep to demonstrate that subjects to be enrolled in the study had fragmented nighttime sleep. Similar to the inclusion criterion evaluating sleep quality, actigraphy data were used to select a homogeneous population with impaired night-time sleep at baseline. As described in Section 6.3.5, actigraphy devices have low specificity to detect "wake"; therefore this strategy may not have achieved its goal.

This notwithstanding, both inclusion criteria are acceptable from a clinical standpoint.

Exclusion Criteria

1. Failure to confirm diagnosis of SMS by molecular cytogenetic methods and/or DNA-based mutation analysis of the RAI1 gene;

2. Unable to dose daily with medication;

3. Indication of impaired liver function (values for aspartate transaminase [AST], alanine transaminase [ALT], or bilirubin >2× the normal limit);

4. Pregnant or lactating females;

5. A positive test for drugs of abuse at the Screening Visit (only patients >14 years of age);

6. Worked night, rotating, or split (period of work, followed by break, and then return to work) shift work within 1 month of the Screening Visit or planned to work these shifts during the study;

7. Exposure to any investigational drug, including placebo, within 30 days or 5 half-lives (whichever was longer) of Screening;

8. Unwilling or unable to follow the medication restrictions including the washout from use of a prohibited medication; or

9. Any other sound medical reason as determined by the clinical Investigator or the Applicant.

Prohibited Medications

- Any medication known to cause sedation or stimulation;
  Note: These medications were considered on a case-by-case basis and must have been
- approved by the Applicant.
- Dietary supplements and other preparations containing melatonin;
- Strong Cytochrome P450 1A2 inhibitors (e.g., fluvoxamine);
- Strong Cytochrome P450 3A4 inducers (egg, rifampin);
- Melatonin agonists; and
- Any other investigational medicine or placebo.

16. Efficacy: Additional Information and Assessment

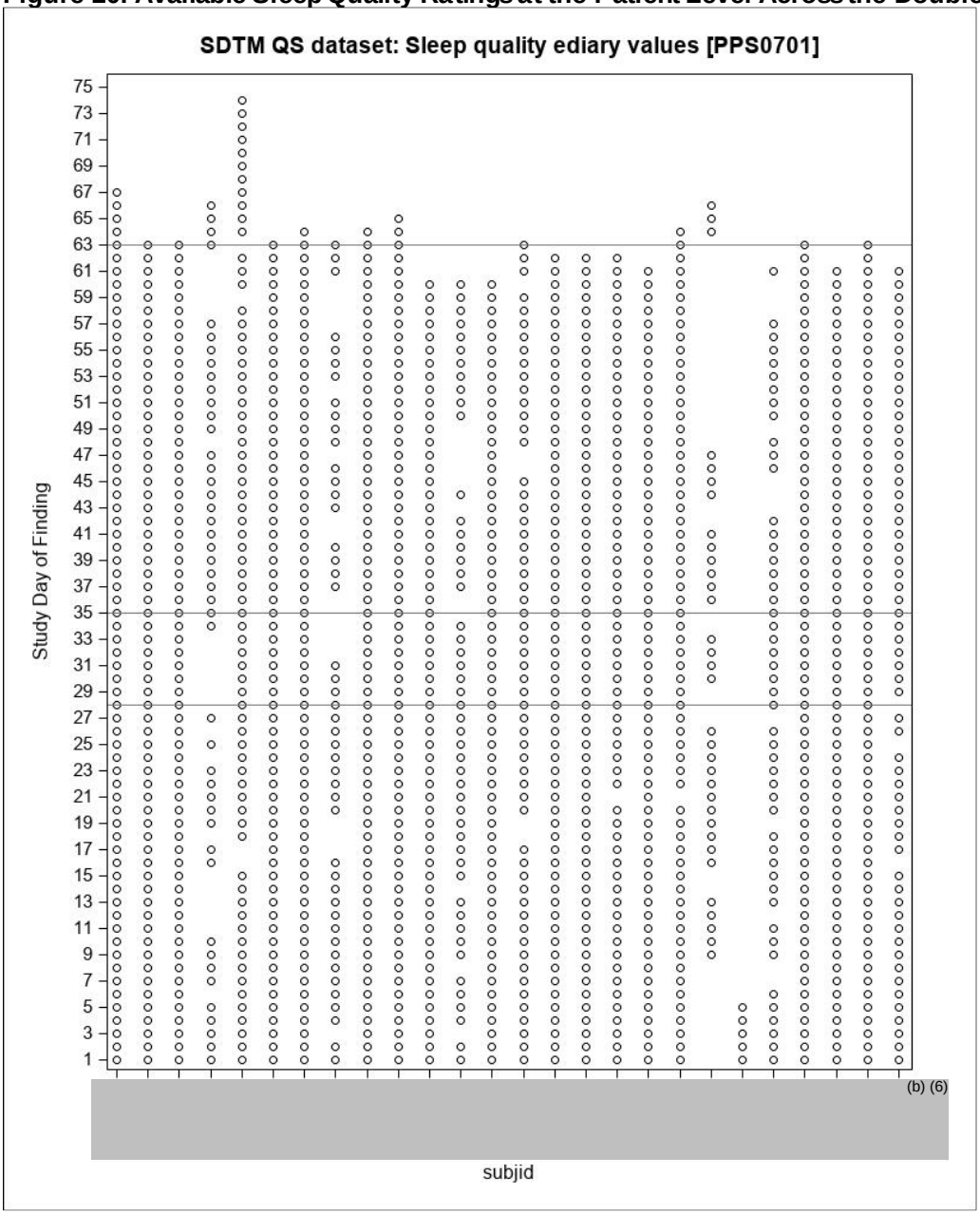
This section supplements the analyses presented in Section 6.2.1.4.2.

16.1. Study 2401

Additional Information on the Primary Efficacy Endpoints: Available Patient-Level Data

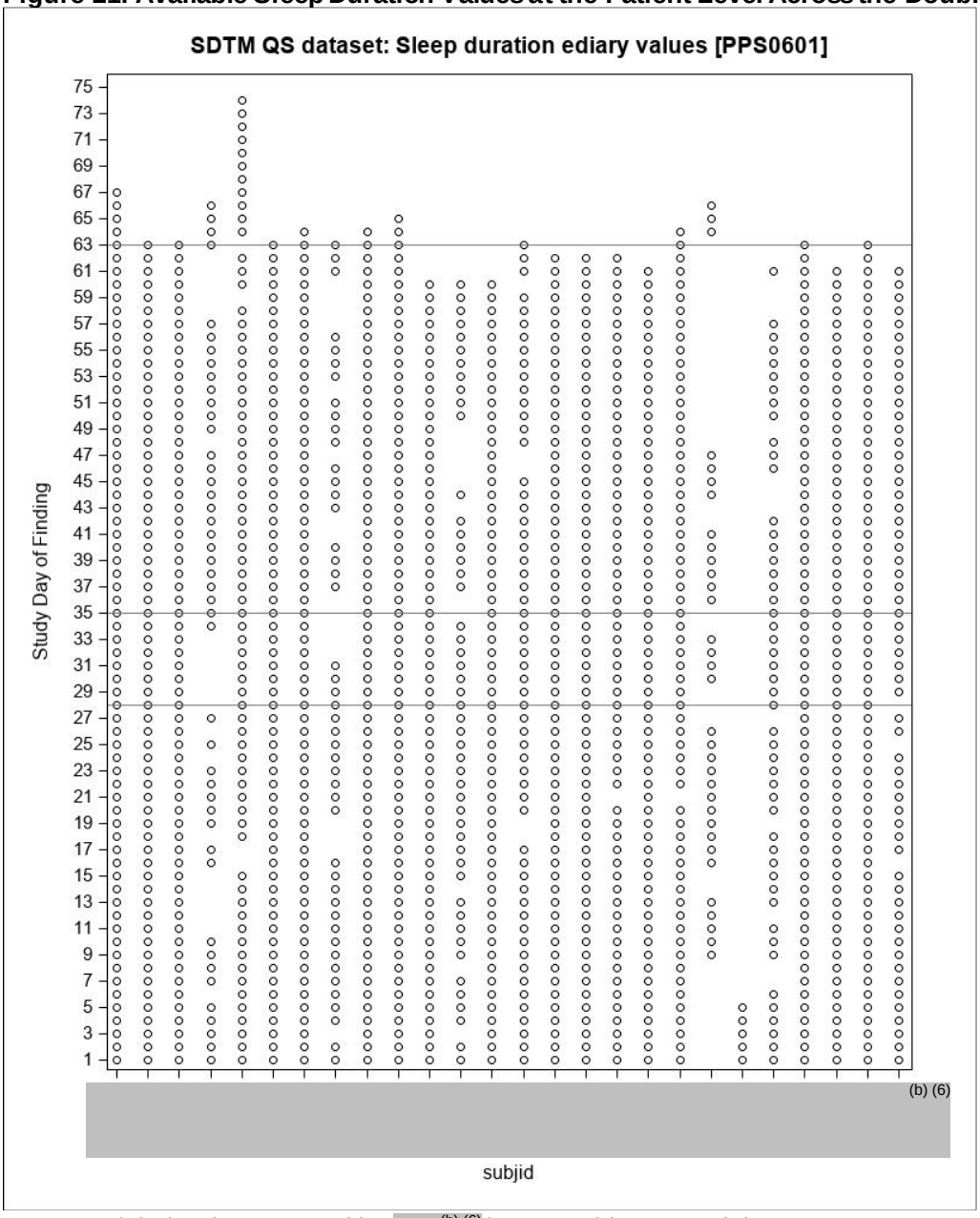
Figure 20 and Figure 21 show the available patient-level data for both primary efficacy endpoints across the double-blind phase of Study 2401. Note that the 1-week washout period is included. Period 1, washout, and Period 2 are delineated by horizontal lines. The figures illustrate that the missing data rate is low and that there is consistency in the days with data between the two primary efficacy endpoints (i.e., when sleep quality was reported by the caregiver, sleep duration was also reported). Note that subject (b) (6) is not part of ITT population, because this patient withdrew early in the study. The efficacy results for the other patients with some missing data (e.g., (b) (6), and (b) (6)) favor tasimelteon or placebo in about equal proportions. The Applicant required at least 50% of the data to be nonmissing to calculate a value for the period average at the patient level. At the extreme that implies, that the average could have been calculated based on seven available days (14 days available out of 28 and the 50% worst days are used). Fortunately, this extreme scenario only applied to subject (b) (6), a patient the Applicant suggested excluding from the primary analysis set due to compliance issues. Retaining this patient in the ITT set (as for the primary analyses) has a conservative effect on the results.

Figure 20. Available Sleep Quality Ratings at the Patient Level Across the Double-Blind Phase



Source: Statistical Reviewer; Note, subject (b) (6) is not part of the ITT population.

Figure 21. Available Sleep Duration Values at the Patient Level Across the Double-Blind Phase



Source: Statistical Reviewer; Note, subject (b) (6) is not part of the ITT population.

Additional Analyses Related to the Primary Efficacy Outcome Measures

Table 57, Table 58, Table 59, and Table 60 list the frequencies of the DDSQ ratings (all, not limited to the 50% worst ratings) by treatment sequence and period of the crossover design. As noted in review issue 3, numerical results differ to some degree between the two treatment sequences to which the patients were randomized. Sleep quality results on average are indistinguishable between the treatments for patients first treated with tasimelteon and then crossed over to placebo (sequence A). However, differences are observed on average for sequence B (placebo first, followed by tasimelteon). The difference in the averages can be illustrated by considering the frequencies at which the response options were chosen between

the two treatments. For sequence B, about 32% of responses describing sleep quality fall into the *good* and *excellent* categories when patients are treated with placebo. This compares to about 60% when patients are treated with tasimelteon. By contrast, 37% of responses fall into the *poor* and *fair* categories when the patients are on placebo. This compares to 15% when the patients received tasimelteon.

Table 57. DDSQ Ratings for Pla-TAS Treatment Sequence During Placebo Treatment

QSSTRESC_N	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Poor	24	7.67	24	7.67
Fair	92	29.39	116	37.06
Average	98	31.31	214	68.37
Good	75	23.96	289	92.33
Excellent	24	7.67	313	100.00

Source: Statistical Reviewer

Table 58. DDSQ Ratings for Pla-TAS Treatment Sequence During Tasimelteon Treatment

QSSTRESC_N	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Poor	19	6.42	19	6.42
Fair	24	8.11	43	14.53
Average	75	25.34	118	39.86
Good	130	43.92	248	83.78
Excellent	48	16.22	296	100.00

Source: Statistical Reviewer

Table 59. DDSQ Ratings for TAS-Pla Treatment Sequence During Tasimelteon Treatment

QSSTRESC_N	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Poor	22	6.41	22	6.41
Fair	99	28.86	121	35.28
Average	118	34.40	239	69.68
Good	78	22.74	317	92.42
Excellent	26	7.58	343	100.00
Frequency Missing = 1				

Source: Statistical Reviewer

Table 60. DDSQ Ratings for TAS-Pla Treatment Sequence During Placebo Treatment

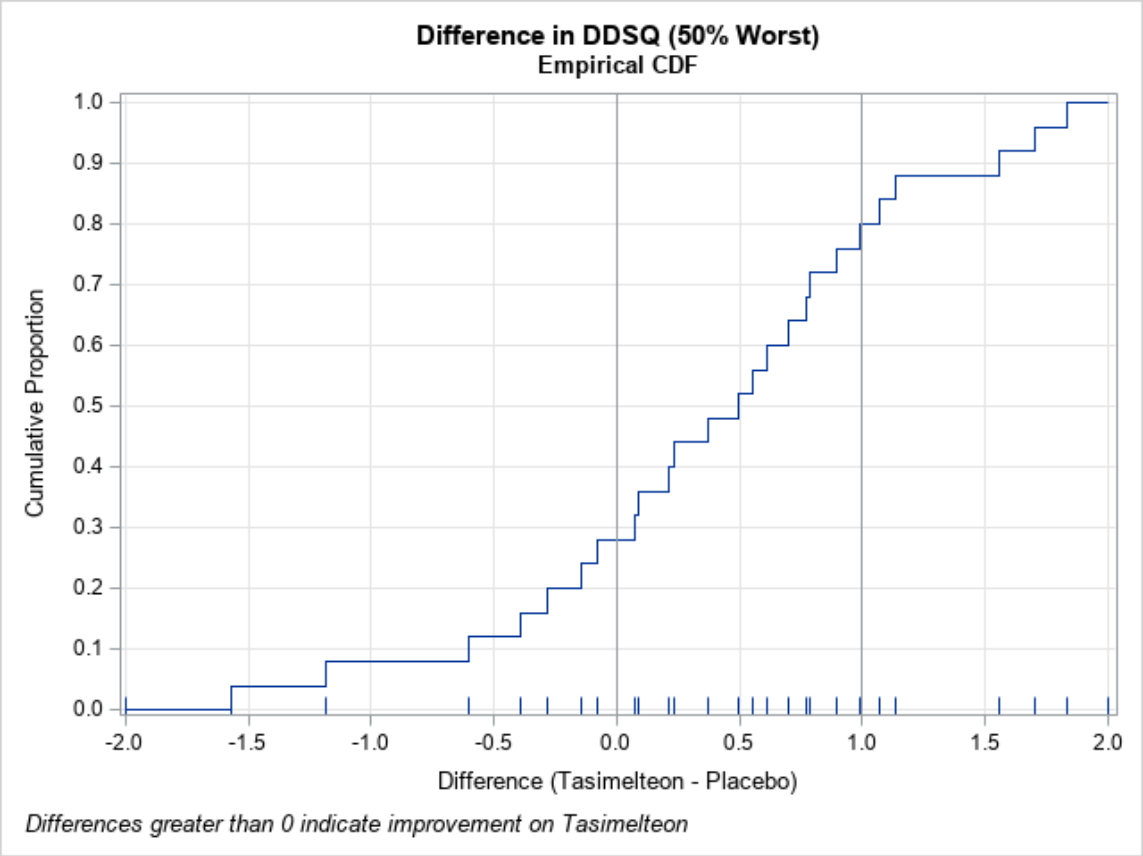
QSSTRESC_N	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Poor	35	10.57	35	10.57
Fair	70	21.15	105	31.72
Average	128	38.67	233	70.39
Good	86	25.98	319	96.37
Excellent	12	3.63	331	100.00
Frequency Missing = 1				

Source: Statistical Reviewer

Focusing on the sleep quality primary endpoint based on the 50% worst ratings, the following observations (Figure 22) can help to contextualize the mean difference of −0.4 in favor of tasimelteon. Recall that the average sleep quality baseline score is 2.1 (*fair*) and the post-sleep questionnaire ratings range from 1=*poor* to 5=*excellent*.

- Average sleep quality rating worsened when on tasimelteon in <30% of patients.
- About 50% of patients are rated having an average improvement of greater than 0 but less than 1 category on the sleep quality scale when treated with tasimelteon versus placebo. Roughly 20% see an average improvement of greater than 1 but less than 2 categories.
- The average differences range from −1.6 to 1.8.

Figure 22. Primary Endpoint (1): Distribution of Differences in Patient Level Period Averages in DDSQ50

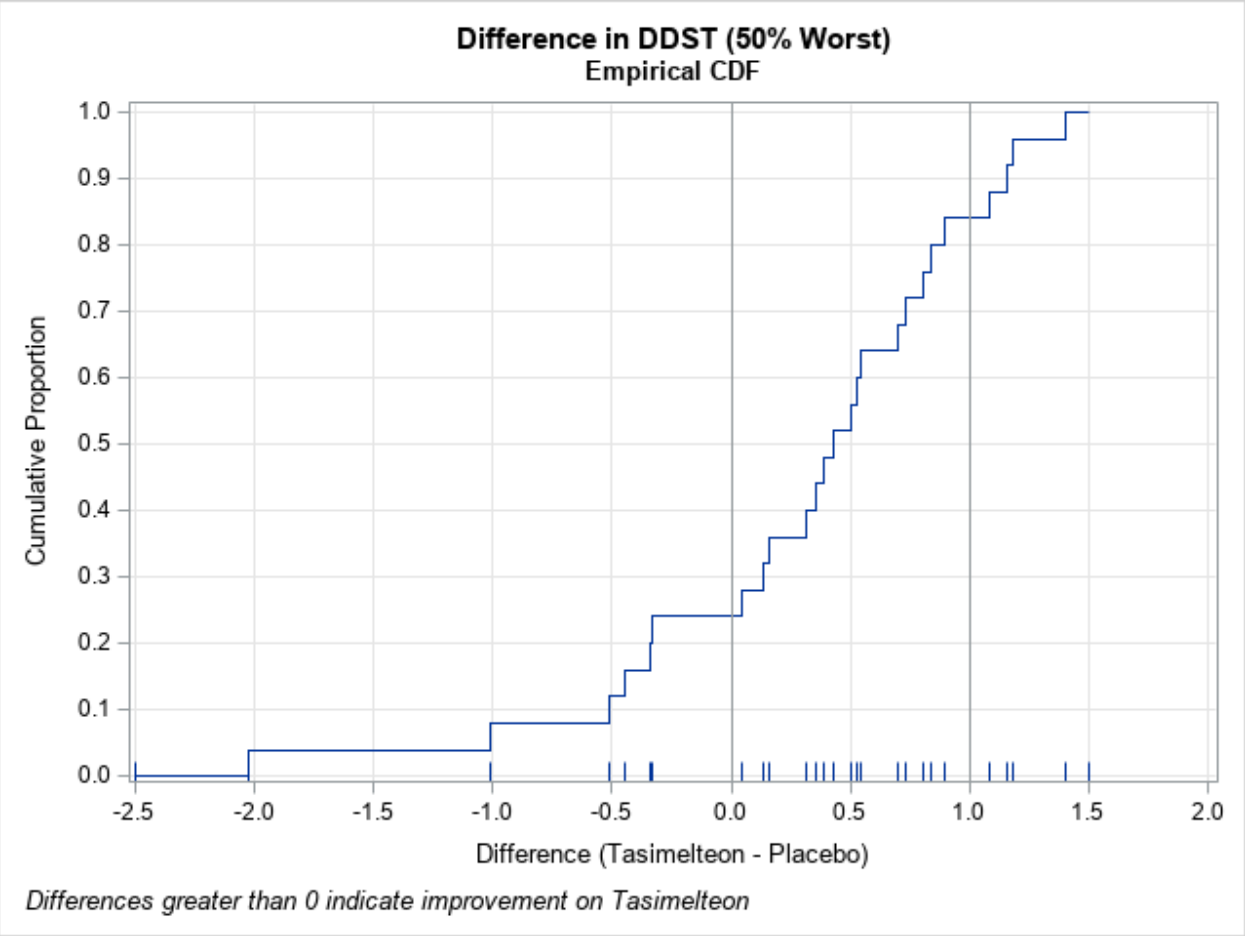


Source: Statistical Reviewer; based on the 50% worst ratings per period.

To contextualize the mean difference of 0.3 hours or 18.5 minutes favoring tasimelteon on the sleep duration primary endpoint it is helpful to consider the distribution of the differences (Figure 23):

- Less than 25% of patients had a reduced average sleep time when treated with tasimelteon compared to placebo.
- For roughly 60% of patients, the reported average sleep time improved by up to 1 hour when on tasimelteon. About 15% of patients had an improvement of greater than 1 hour but less than 1.5 hours.
- Differences in average sleep time between the treatments range from −2.0 to 1.4 hours.

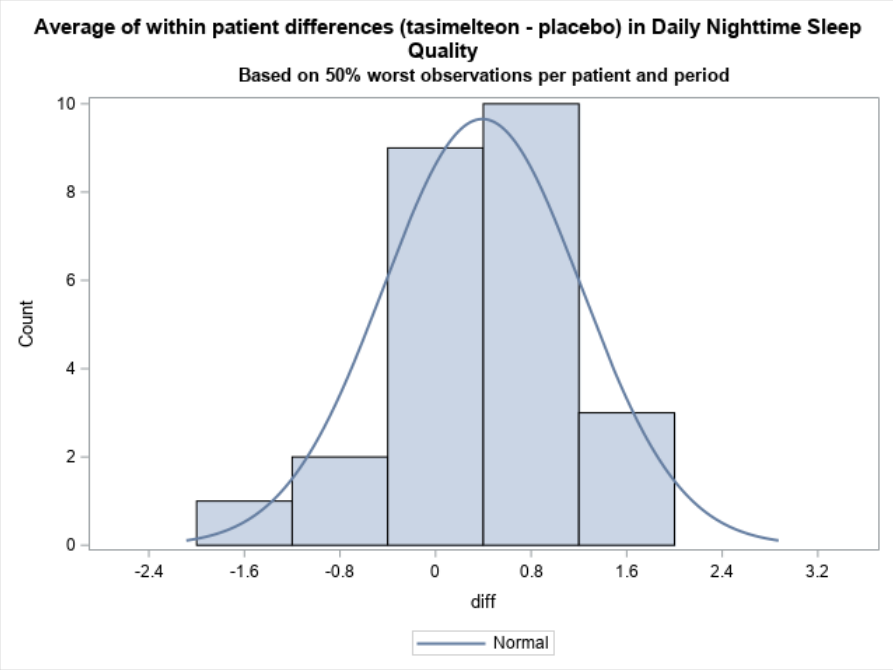
Figure 23. Primary Endpoint (2): Distribution of Differences in Patient Level Period Averages in DDST in Hours



Source: Statistical Reviewer; based on the 50% worst ratings per period

To investigate adherence of the data to the normality assumption, which is needed as a basis for statistical testing of the primary efficacy endpoints, the reviewer plotted the differences in sleep quality (Figure 24). Despite the five-point scale, there is no noticeable violation in the normality assumption when considering the difference in the period averages.

Figure 24. Average of Within Patient Differences in Daily Nighttime Sleep Quality



Source: Statistical Reviewer

The statistical reviewer also explored alignment between the reported sleep time (second primary efficacy endpoint) and calculated sleep time (difference between when the patient went to bed and when the patient got up in the morning as reported by the caregiver). For most patients, both ways of reporting sleep duration are well aligned, with the calculated value consistently somewhat larger than the reported value. This can be explained by the duration of awake periods after initially falling asleep. An information request was sent to the Applicant to explain several large differences between reported and calculated sleep times. Besides the duration of awakenings, for which we do not have reliable data because of the actigraphy issues, the Applicant states "the calculated total sleep time should also subtract terminal awakening time, which is the time after awakening but before leaving the bed." This assumes that the caregiver has deducted the terminal awakening time from the reported sleep time.

Secondary Endpoints

ABC Total Score

The ABC total score is the sum of five subscale scores (*irritability, agitation, crying*; *lethargy, social withdrawal*; *stereotypic behavior*; *hyperactivity, noncompliance*; and *inappropriate speech*). The higher the score, the greater the overall severity of the issues.

The baseline mean ABC total score was 55.9. At Day 29 the scores were decreased (improved) for both treatments (LS means, placebo 42.8, tasimelteon 46.8). The difference of 4.0 (95% CI, −0.7, 8.7) favoring placebo treatment has a nominal p-value of 0.09, indicating it not to be statistically significant.

Clinical Global Impression Severity (CGI-S) Score

At baseline the average rating was 4.6, indicating a global severity rating between 4=*moderately ill* and 5=*markedly ill*. At Day 29 a numerical improvement in the means was manifest (LS

means, placebo 4.4 and tasimelteon 4.0). The difference between the treatments of −0.4 (95% CI: −0.9, 0.1) favoring tasimelteon did not reach nominal statistical significance (p=0.08).

Clinical Global Impression–Change (CGI-C) From Baseline

The global rating of change compared to baseline was 3.6 for placebo treatment and 3.0 for tasimelteon treatment, for a difference of −0.6 (95% CI, −1.3, 0.1) favoring tasimelteon. The difference does not reach nominal statistical significance (p=0.09). For context, a global rating of 3 stands for *minimally improved* and 4 indicates *no change*.

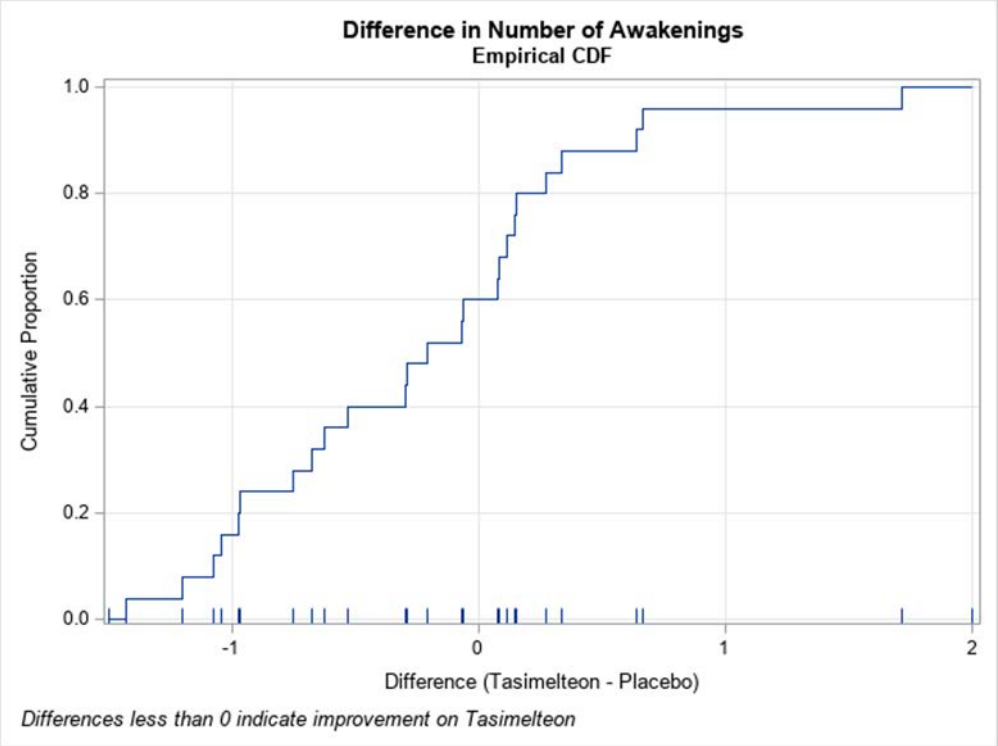
SMS Sleep Questionnaire

The Applicant also included an instrument named the SMS sleep questionnaire. Per the clinical reviewer's assessment this instrument should be regarded as exploratory, because we have little knowledge of its validity and reliability. Numerical results are omitted here. The Applicant concluded that there were no differences between treatments based on this instrument.

Number of Nightly Awakenings

The LS means for the number of nightly awakenings are 1.79 for placebo and 1.54 for tasimelteon, for a difference of −0.25. That difference is not nominally statistically significant (p=0.08). Based on all eDiary records over the double-blind phase (including washout) in Study 2401, the following distribution of the number of nightly awakenings emerges: 0 (18%), 1 (42%), 2 (18%), 3 (10%), 4 (5%), and 5 (3%). Considering the distribution of the difference between treatments (Figure 25), on the one hand 16% (n=4) of patients experienced a reduction in nighttime awakenings by 1 or more and 40% (n=10) by 0.5 or more when treated with tasimelteon versus placebo. On the other hand, for 40% of patients the number of nighttime awakenings increased to some degree when on tasimelteon treatment. The vast majority of patient-level average differences in the number of nightly awakenings fall between minus 1 and plus 1. For this statistical reviewer, it is not clear whether an average reduction of 0 to 1 nightly awakenings corresponds to a clinically meaningful effect.

Figure 25. Secondary Efficacy Endpoint—Number of Nightly Awakenings



Source: Statistical Reviewer

Observed Variability in the Distribution of Caregivers' Ratings of the Primary Endpoints

[Stats IR 07/17/2020]

Division request for Applicant: Please comment on the attached (*sleep_qual_sdtm_panel.pdf* and *sleep_dur_sdtm_panel.pdf*) data patterns for DDSQ and DDTST (plots are based on qs dataset). We are wondering about the low variability in the reporting of sleep quality/sleep duration for some of the patients. Consider especially the data of the following patients:

- Describe the quality of sleep last night? [PPS0701]
  - (b) (6) (almost no variability, most 4 [Good])
  - (not much variability, most 3 [Average])
  - (clusters)
  - (little variability, most 3 [Average])
  - (missing data [beginning and towards the end])
  - (little variability, most 2 [Fair])
- How long do you think they slept last night? [PPS0601]
  - (b) (6) (little variability, especially at the beginning)
  - (little variability)
  - (little variability)
  - (missing data [beginning and towards the end])
  - (little variability)

For the purposes of this review, only two examples (Figure 26 and Figure 27) are included.

(b) (6)

Question

(b) (6)

Figure 27. Subject (b) (6): Resposnes to How Long Do You Think They Slept Last Night Question

Applicant's response: "*We have reviewed the individuals that have been specified. There is no specific explanation for the amount of variability in the data of these individuals.*"

Statistical reviewer's comment: *Although it remains unclear why so little variability is observed in the responses by some of the caregivers, the impact on the overall efficacy results is limited (constancy is neither favoring tasimelteon nor placebo).*

16.2. Study VP-1401

Study Design

This is a naturalistic study in which participants with a genetically confirmed diagnosis of SMS underwent collection of plasma melatonin and cortisol at 1-hour intervals for 36 hours on three separate occasions (separated by 1 to 2 weeks).

Population

Eight participants (7 to 35 years old; one female, seven males) were enrolled.

Primary Objective

To characterize the circadian rhythms of individuals with SMS as determined by the plasma levels of melatonin, cortisol, and other circadian analytes.

Results: Cortisol and Melatonin Secretion Patterns

Participants in Study 1401 demonstrated normal cortisol secretion timing; however, all patients had a markedly abnormal melatonin secretion pattern. In Figure 28, the plasma cortisol and melatonin concentrations are plotted for the eight individuals. The peak cortisol concentration is normal for all individuals studied. Additionally, the cortisol secretion pattern is normal with acrophase in the morning at approximately 6:00 to 9:00 AM. In contrast, on average, these individuals have lower absolute melatonin levels. Unlike the typical melatonin pattern, the peak melatonin concentrations are markedly lower than normal, and the peak of the circadian rhythm of melatonin concentration occurs during the daytime hours for many of the participants.

Conclusion

Study VP-1401 showed that participants with SMS exhibit an abnormal pattern of melatonin secretion, with lower absolute amounts and acrophases during the day.

Figure 28. Plasma Melatonin and Cortisol Concentrations, Study 1401

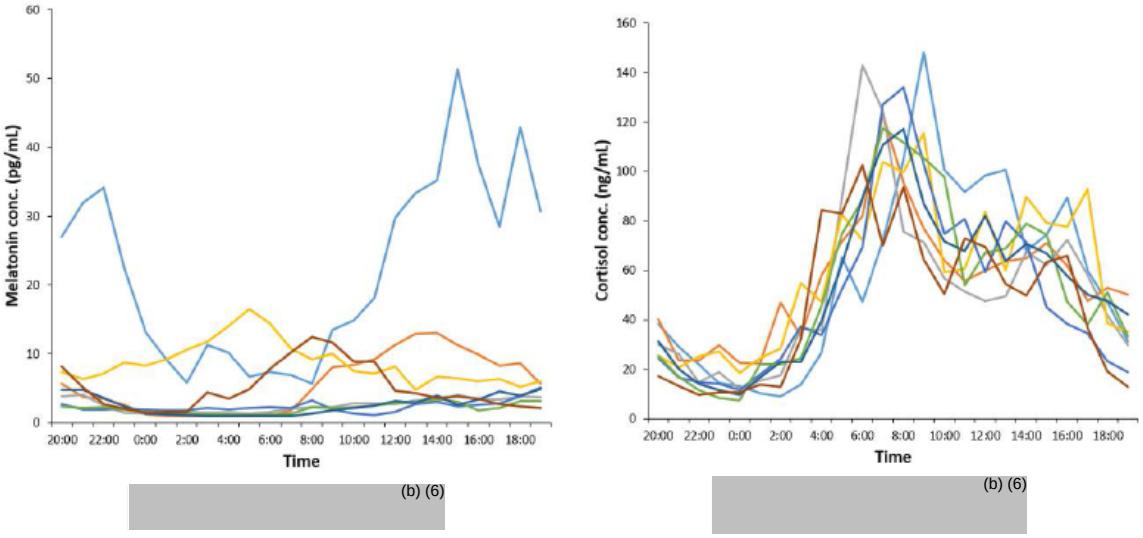


Figure 1 shows the average 24-hour plasma melatonin (left) and cortisol (right) concentration time plots for each patient in Study 1401. Patients were admitted for an overnight observation to determine plasma melatonin and cortisol secretion patterns over a 36-hour period. Samples were collected hourly beginning at 8:00PM on the day of admission. These collections were repeated on three separate occasions (Week 1, 2, and 4). Each line denotes the average of all three data collections for each patient.

Source:

17. Clinical Safety: Additional Information and Assessment

17.1. Clinical Safety Assessment in the Pediatric Population

Data from subjects enrolled in Study 2401 aged 3 to 17 years form the basis of the safety assessment of tasimelteon in pediatric subjects with SMS. In addition, safety is informed by the nonclinical review of the juvenile animal study (refer to Section 13.2) and the review of postmarketing data (refer to Section 7.3).

On August 1, 2016, the Applicant submitted Amendment 6 to Protocol VP-VEC-162-2401, which included a pediatric population and the pediatric formulation of tasimelteon in the phase 3 pivotal study. The amendment was reviewed, and it was felt that there was no specific safety concern in expanding the study population to children as young as 3 years and no special monitoring was required at that time.

The extent of the pediatric population, the distribution of age, and the assignment to the Randomized or Open Label Treatment Arm of Study 2401 are reported in Table 61.

Given that the PK of the capsule and suspension formulations is relatively similar (refer to Section 6.3.1) and the formulation is unlikely to affect safety, the treatment-emergent adverse events (TEAEs) observed in pediatric subjects are reported irrespective of the formulation received.

Table 61. Pediatric Patients in Study 2401

Subject ID	Age	Arm	Formulation
(b) (6)	(b) (6)	Open Label	Capsules
		Open Label	Capsules
		Randomized	Capsules
		Open Label then re-enrolled (b) (6)	Capsules
		Screen Failed	Capsules
		Open Label	Capsules
		Randomized	Suspension
		Randomized	Suspension
		Randomized	Suspension
		Randomized	Suspension
		Open Label	Suspension
		Randomized	Suspension
		Randomized	Suspension
		Randomized	Suspension
		Randomized	Suspension
		Open Label	Suspension
		Randomized	Suspension
		Randomized	Suspension
		Randomized	Suspension

Overall Adverse Event Summary – Pediatric Population

- No deaths occurred during the clinical studies with tasimelteon.
- Subject # (b) (6) experienced a generalized tonic-clonic seizure, which was considered a serious adverse event (SAE). This SAE, as described in detail in Section 7.6.1.3, occurred during the Open-Label Extension Phase, and it was deemed not related to tasimelteon because the subject had a documented medical history of seizures.
- Subject # (b) (6) experienced an event (infected bite) that led to discontinuation of tasimelteon, and this was deemed not related to the study drug. The event is described in detail in Section 7.6.1.4.
- Only three TEAEs were reported in subjects exposed to tasimelteon during the randomized phase of Study 2401, and three events occurred in subjects exposed to placebo (Table 62).
- The overall count of adverse events was very small and, from a clinical standpoint, it is difficult to establish causality, because the events affect multiple body systems and a clear pattern cannot be identified.
- SMS is a complex genetic condition, and the multiple clinical manifestations need to be taken into account when evaluating the safety events. Paronychia, otitis, tooth fracture, and infected bites are common occurrences in subjects with SMS and are unlikely related to the study drug. Subjects with SMS suffer from frequent allergies, and the anaphylactic reaction may be due to underlying condition.
- Respiratory tract infection, somnolence, and lethargy are common adverse reactions reported in the current label for Hetlioz.
- Table 63 shows a higher frequency of AEs in the tasimelteon group. However, the safety population combines subjects exposed to tasimelteon for 4 weeks (Randomized Treatment Arm) as well as for 9 weeks (Open-Label Arm), while the maximum duration of exposure for the placebo group is 4 weeks. A longer exposure may be one of the reasons why more events are reported in the tasimelteon group.
- Overall, the safety profile in the pediatric population appears similar to that in the entire safety population including adult subjects.

Table 62. Patients With Common Treatment-Emergent Adverse Events,[2] Randomized Population Ages 3 to 17 Years[1, 3, 4, 5]

Preferred Term	Period 1 Tasimelteon (N=7) n (%)	Period 1 Placebo (N=5) n (%)	Period 2 Tasimelteon (N=5) n (%)	Period 2 Placebo (N=7) n (%)
Patients with any TEAE	3 (42.9)	1 (20.0)	0 (0.0)	1 (4.3)
Anaphylactic reaction	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)
Infected bites	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
Lethargy	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)
Otitis externa	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)
Paronychia	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory tract infection	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Applicant; ADAE1.sas7bdat; software, SAS 9.4.
Abbreviations: N, number of patients in the treatment arm; n, number of patients with at least one event; TEAE, treatment-emergent adverse events
[1] Subjects aged 3 to 17 years are included.
[2] Treatment-emergent AEs are defined as AEs that newly occurred or worsened from baseline (i.e., AEs that started after the first dose of study drug) and started no more than 24 hours after the date of the last dose of study drug.
[3] Patients are counted only once under the highest severity level.
[4] Adverse events occurring after 24 hours of the last dose of the Treatment Phase will be summarized for the Open-Label Extension Phase.
[5] AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA version 18.0) coding dictionary.

Table 63. Patients With Common Treatment-Emergent Adverse Events[2], Safety Population Ages 3 to 17 Years[1, 3, 5, 6]

Preferred Term	Tasimelteon (N=18)[4] n (%)	Placebo (N=12)[4] n (%)
Patients with any TEAE	6 (33.3)	2 (16.7)
Anaphylactic reaction	1 (5.6)	0 (0.0)
Blood phosphorus increased	1 (5.6)	0 (0.0)
Diarrhea	0 (0.0)	1 (8.3)
Dry mouth	1 (5.6)	0 (0.0)
Gastroenteritis norovirus	1 (5.6)	0 (0.0)
Infected bites	1 (5.6)	0 (0.0)
Lethargy	0 (0.0)	1 (8.3)
Nasopharyngitis	1 (5.6)	0 (0.0)
Otitis externa	0 (0.0)	1 (8.3)
Paronychia	1 (5.6)	0 (0.0)
Respiratory tract infection	1 (5.6)	0 (0.0)
Somnolence	1 (5.6)	0 (0.0)
Tooth fracture	1 (5.6)	0 (0.0)

Source: Applicant; ADAE1.sas7bdat; software, SAS 9.4.
Abbreviations: N, number of patients in the treatment arm; n, number of patients with at least one event; TEAE, treatment-emergent adverse events
[1] Subjects aged 3 to 17 years are included.
[2] Treatment-emergent AEs are defined as AEs that newly occurred or worsened from baseline (i.e., AEs that started after the first dose of study drug) and started no more than 24 hours after the date of the last dose of study drug.
[3] Patients are counted only once under the highest severity level.
[4] Patients received both placebo and tasimelteon in this crossover study are counted under both tasimelteon and placebo.
[5] Adverse events occurring after 24 hours of the last dose of the Treatment Phase will be summarized for the Open-Label Extension Phase.
[6] AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA version 18.0) coding dictionary.

17.2. Trial VP-VEC-162-2401: Supplementary Information

This section reports data from subjects pooled from the Randomized and Open-Label Treatment Arms of Study 2401, as well as safety data from the Open-Label Extension (OLE) which is currently ongoing. The Applicant submitted with the 120-Day Safety Update all reports of new safety information for patients in the OLE up to October 2, 2020. The maximum duration of exposure in the OLE phase is 197 weeks.

The OLE phase of Study 2401 consists of open-label treatment with 20 mg tasimelteon capsules or an age-appropriate suspension taken every night 1 hour before bedtime. Patients are queried during study visits and requested to report any and all AEs to the sites at any time.

None of the patients experienced any AE or TEAE resulting in death in the OLE phase.

Four patients experienced SAEs in the OLE phase. The clinical evaluation of all SAEs reported in the SMS program can be found in Section 7.6.1.3.

Five patients interrupted tasimelteon during the OLE phase. AEs leading to drug discontinuation were: upper respiratory tract infections (n=2), bronchitis (n=1), pneumonia (n=1), postprocedural sepsis (n=1; this event was considered serious and is described in Section 7.6.1.3), generalized tonico-clonic seizures (n=1; this event was considered serious and is described in Section 7.6.1.3), seizure (n=1), and abnormal behavior (n=1).

Full narratives for the above-listed AEs leading to drug discontinuation are not available because AEs not reported as serious do not meet the criteria outlined in the Safety Monitoring Plan (consistent with ICH E3 guidance) to have corresponding narratives.

The most commonly reported AEs during the OLE phase of Study 2401 were infections.

The imbalance in the frequency of AEs related to the SOC infections and infestations is discussed in Section 7.7.

Treatment-Emergent Adverse Events

This section reports all TEAEs that occurred during the SMS program, including the Randomized and Open-Label Arm of Study 2401 and the OLE.

Of note, the tasimelteon group includes subjects exposed to tasimelteon for 4 weeks (one period of Study 2401) and 9 weeks (Open-Label Arm of Study 2401) and then rolled over to the OLE; these subjects have been exposed to tasimelteon for up to 197 weeks.

The placebo arm includes subjects exposed to placebo during Study 2401. Because of the crossover design, all 26 patients randomized were exposed to placebo either in Period 1 or 2, but the maximum duration of exposure to placebo was 4 weeks.

Table 64 summarizes TEAEs by preferred term and Table 65 summarizes TEAEs by SOC.

The overall frequency of TEAEs is higher in patients exposed to tasimelteon (40.4%) compared to placebo (23.1%). However, the frequency of AEs increases with increasing exposure duration, and the spontaneous occurrence of events caused by the underlying condition could be considered a plausible explanation of this difference.

Indeed, the list of AEs does not indicate a consistent pattern, and events refer to multiple body systems. In addition, some isolated events—such as *acne*, *tooth infection*, *tooth fracture*, *infected bite*, *laceration*, and *aggression*—cannot be attributed to the study drug, being instead spontaneous occurrences.

Although there were no differences in the incidence of infections between tasimelteon and placebo in the Randomized Treatment Arm, 21.3% of patients receiving tasimelteon (n=10) experienced infections when pooling both the Randomized and the Open-Label Arms. Subjects with SMS are predisposed to infections; the review team assessed a possible drug-treatment interaction in Section III.7.7 and concluded that it is not clear whether there is a causal relationship with tasimelteon use.

The current Hetlioz product label reports upper respiratory tract and urinary tract infections as common adverse reactions; tasimelteon may similarly increase the risk for infections in the SMS population. Therefore, a statement that the safety profile of tasimelteon is similar to that for the non-24 indication will be included in Section 6 of the product label with no need for additional postmarketing monitoring other than routine pharmacovigilance.

Table 64. Patients With Common Treatment-Emergent Adverse Events,[1] Safety Population[2, 3, 4]

Preferred Term	Tasimelteon (N=47) n (%)	Placebo (N=26) n (%)
Patients with any TEAE	19 (40.4)	6 (23.1)
Gastroenteritis viral	2 (4.3)	0 (0.0)
Upper respiratory tract infection	2 (4.3)	0 (0.0)
Urinary tract infection	1 (2.1)	1 (3.8)
Abdominal pain upper	1 (2.1)	0 (0.0)
Acne	0 (0.0)	1 (3.8)
Aggression	1 (2.1)	0 (0.0)
Anaphylactic reaction	1 (2.1)	0 (0.0)
Anxiety	0 (0.0)	1 (3.8)
Asthma	1 (2.1)	0 (0.0)
Blood phosphorus increased	1 (2.1)	0 (0.0)
Cough	1 (2.1)	0 (0.0)
Dermatillomania	0 (0.0)	1 (3.8)
Diarrhea	0 (0.0)	1 (3.8)
Disorientation	1 (2.1)	0 (0.0)
Dry mouth	1 (2.1)	0 (0.0)
Ear canal erythema	1 (2.1)	0 (0.0)
Emotional disorder	1 (2.1)	0 (0.0)
Gastroenteritis norovirus	1 (2.1)	0 (0.0)
Headache	1 (2.1)	0 (0.0)
Infected bites	1 (2.1)	0 (0.0)
Insomnia	0 (0.0)	1 (3.8)
Laceration	1 (2.1)	0 (0.0)
Lethargy	0 (0.0)	1 (3.8)
Nasopharyngitis	1 (2.1)	0 (0.0)
Otitis externa	0 (0.0)	1 (3.8)
Otitis media	1 (2.1)	0 (0.0)
Paronychia	1 (2.1)	0 (0.0)
Proteinuria	1 (2.1)	0 (0.0)
Respiratory tract infection	1 (2.1)	0 (0.0)
Somnolence	1 (2.1)	0 (0.0)
Tooth fracture	1 (2.1)	0 (0.0)
Tooth infection	1 (2.1)	0 (0.0)
Vertebral lesion	1 (2.1)	0 (0.0)
Viral infection	1 (2.1)	0 (0.0)
Weight increased	1 (2.1)	0 (0.0)

Source: Applicant
Abbreviations: N, number of patients in the treatment arm; n, number of patients with at least one event; TEAE, treatment-emergent adverse event
[1] Treatment-emergent AEs are defined as AEs that newly occurred or worsened from baseline (i.e., AEs that started after the first dose of study drug) and started no more than 24 hours after the date of the last dose of study drug.
[2] Patients are counted only once under the highest severity level.
[3] Patients who received both placebo and tasimelteon in this crossover study are counted under both tasimelteon and placebo.
[4] AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA version 18.0) coding dictionary.

Table 65. Patients With Treatment-Emergent Adverse Events[1] by System Organ Class, Safety Population[2, 3, 4]

System Organ Class	Tasimelteon (N=47) n (%)	Placebo (N=26) n (%)
Patients with any TEAE	19 (40.4)	6 (23.1)
Infections and infestations	10 (21.3)	2 (7.7)
Psychiatric disorders	3 (6.4)	3 (11.5)
Gastrointestinal disorders	2 (4.3)	1 (3.8)
Nervous system disorders	2 (4.3)	1 (3.8)
Injury, poisoning, and procedural complications	2 (4.3)	0 (0.0)
Investigations	2 (4.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	2 (4.3)	0 (0.0)
Ear and labyrinth disorders	1 (2.1)	0 (0.0)
Immune system disorders	1 (2.1)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (2.1)	0 (0.0)
Renal and urinary disorders	1 (2.1)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (3.8)

Source: Applicant
Abbreviations: N, number of patients in the treatment arm; n, number of patients with at least one event; TEAE, treatment-emergent adverse event
[1] Treatment-emergent AEs are defined as AEs that newly occurred or worsened from baseline (i.e., AEs that started after the first dose of study drug) and started no more than 24 hours after the date of the last dose of study drug. AEs are summarized by treatment at the onset of the event.
[2] Patients are counted only once under the highest severity level.
[3] Patients who received both placebo and tasimelteon in this crossover study are counted under both tasimelteon and placebo.
[4] AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA version 18.0) coding dictionary.

Laboratory Findings

This section provides additional information regarding assessment of the changes in laboratory parameters in the safety population, including subjects enrolled in the Open-Label Arm of Study 2401 and the safety evaluations carried out during the OLE. The review team carried out an analysis of the severity of abnormalities and identified outliers.

The results of the analysis are summarized in Table 66 (chemistry), Table 67 (kidney function), Table 68 (liver function), Table 69 (cholesterol), and Table 70 (hematology). Overall, the safety profile of tasimelteon appears benign with only a few sporadic changes in laboratory parameters, which are not deemed clinically significant. Of note, subjects with SMS often report hypercholesterolemia primary or secondary to hypothyroidism (Table 69). However, tasimelteon is not known to affect lipids or metabolic parameters, and Table 69 shows similar cholesterol values in subjects exposed to tasimelteon and placebo.

Table 66. Patients With One or More Chemistry Analyte Values Exceeding Specified Levels for General Chemistry, Safety Population

Parameter	Tasimelteon N=46	Placebo N=22
Sodium, low (mEq/L)	**0 (0.00)**	**0 (0.00)**
Level 1 (<134)	0 (0.00)	0 (0.00)
Level 2 (<132)	0 (0.00)	0 (0.00)
Level 3 (<125)	0 (0.00)	0 (0.00)
Sodium, high (mEq/L)	**0 (0.00)**	**0 (0.00)**
Level 1 (>144)	0 (0.00)	0 (0.00)
Level 2 (>150)	0 (0.00)	0 (0.00)
Level 3 (>155)	0 (0.00)	0 (0.00)
Potassium, low (mEq/L)	**0 (0.00)**	**0 (0.00)**
Level 1 (<3.6)	0 (0.00)	0 (0.00)
Level 2 (<3.4)	0 (0.00)	0 (0.00)
Level 3 (<3.0)	0 (0.00)	0 (0.00)
Potassium, high (mEq/L)	**1 (2.17)**	**1 (4.55)**
Level 1 (>5.5)	1 (2.17)	1 (4.55)
Level 2 (>6.0)	0 (0.00)	0 (0.00)
Level 3 (>6.5)	0 (0.00)	0 (0.00)
Chloride, low (mEq/L)	**0 (0.00)**	**0 (0.00)**
Level 1 (<95)	0 (0.00)	0 (0.00)
Level 2 (<88)	0 (0.00)	0 (0.00)
Level 3 (<80)	0 (0.00)	0 (0.00)
Chloride, high (mEq/L)	**2 (4.35)**	**1 (4.55)**
Level 1 (>108)	2 (4.35)	1 (4.55)
Level 2 (>112)	0 (0.00)	0 (0.00)
Level 3 (>115)	0 (0.00)	0 (0.00)
Glucose, low (mg/dL)	**0 (0.00)**	**0 (0.00)**
Level 1 (<70)	0 (0.00)	0 (0.00)
Level 2 (<54)	0 (0.00)	0 (0.00)
Level 3 (<40)	0 (0.00)	0 (0.00)
Glucose, random, high (mg/dL)	**0 (0.00)**	**0 (0.00)**
Level 1 (>200)	0 (0.00)	0 (0.00)
Level 2 (>250)	0 (0.00)	0 (0.00)
Level 3 (>500)	0 (0.00)	0 (0.00)
Calcium, low (mg/dL)	**0 (0.00)**	**0 (0.00)**
Level 1 (<8.4)	0 (0.00)	0 (0.00)
Level 2 (<8.0)	0 (0.00)	0 (0.00)
Level 3 (<7.5)	0 (0.00)	0 (0.00)
Calcium, high (mg/dL)	**0 (0.00)**	**0 (0.00)**
Level 1 (>10.5)	0 (0.00)	0 (0.00)
Level 2 (>11.0)	0 (0.00)	0 (0.00)
Level 3 (>12.0)	0 (0.00)	0 (0.00)
Magnesium, low (mg/dL)	**0 (0.00)**	**0 (0.00)**
Level 1 (<1.5)	0 (0.00)	0 (0.00)
Level 2 (<1.2)	0 (0.00)	0 (0.00)
Level 3 (<0.9)	0 (0.00)	0 (0.00)
Magnesium, high (mg/dL)	**9 (19.57)**	**3 (13.64)**
Level 1 (>2.3)	9 (19.57)	3 (13.64)
Level 2 (>4.0)	0 (0.00)	0 (0.00)
Level 3 (>7.0)	0 (0.00)	0 (0.00)

Parameter	Tasimelteon N=46	Placebo N=22
Phosphate, low (mg/dL)	**0 (0.00)**	**0 (0.00)**
Level 1 (<2.5)	0 (0.00)	0 (0.00)
Level 2 (<2.0)	0 (0.00)	0 (0.00)
Level 3 (<1.4)	0 (0.00)	0 (0.00)
Protein, total, low (g/dL)	**0 (0.00)**	**0 (0.00)**
Level 1 (<6.0)	0 (0.00)	0 (0.00)
Level 2 (<5.4)	0 (0.00)	0 (0.00)
Level 3 (<5.0)	0 (0.00)	0 (0.00)
Albumin, low (g/dL)	**0 (0.00)**	**0 (0.00)**
Level 1 (<3.1)	0 (0.00)	0 (0.00)
Level 2 (<2.5)	0 (0.00)	0 (0.00)
Level 3 (<2.0)	0 (0.00)	0 (0.00)
CK, high (U/L)	**0 (0.00)**	**0 (0.00)**
Level 1 (>3× ULN)	0 (0.00)	0 (0.00)
Level 2 (>5× ULN)	0 (0.00)	0 (0.00)
Level 3 (>10× ULN)	0 (0.00)	0 (0.00)
Amylase, high (U/L)	**3 (6.52)**	**2 (9.09)**
Level 1 (>1.1× ULN)	3 (6.52)	2 (9.09)
Level 2 (>1.5× ULN)	2 (4.35)	1 (4.55)
Level 3 (>3.0× ULN)	0 (0.00)	0 (0.00)

Source: Applicant; ADLB.sas7bdat in D120; Software: SAS 9.4.
Abbreviations: CK, creatine kinase; N, number of patients with at least one postbaseline collected laboratory test value in the treatment arm; n, number of patients with the indicated laboratory test value; ULN, upper limit of normal

Table 67. Patients With One or More Kidney Function Analyte Values Exceeding Specified Levels for Kidney Function, Safety Population

Parameter	Tasimelteon N=46	Placebo N=22
Blood urea nitrogen, high (mg/dL)	1 (2.17)	1 (4.55)
Level 1 (>23)	1 (2.17)	1 (4.55)
Level 2 (>27)	0 (0.00)	1 (4.55)
Level 3 (>31)	0 (0.00)	1 (4.55)
Creatinine, high (mg/dL)	0 (0.00)	0 (0.00)
Level 1 (≥1.5× baseline)	0 (0.00)	0 (0.00)
Level 2 (≥2.0× baseline)	0 (0.00)	0 (0.00)
Level 3 (≥3.0× baseline)	0 (0.00)	0 (0.00)

Source: Applicant; ADLB.sas7bdat in D120; software, SAS 9.4.
Abbreviations: N, number of patients with at least one postbaseline nonmissing laboratory test value in the treatment arm; n, number of patients with the indicated laboratory test value

Table 68. Patients With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels for Liver Biochemistry, Safety Population

Parameter	Tasimelteon N=46	Placebo N=22
Alkaline phosphatase, high (U/L)	**1 (2.17)**	**1 (4.55)**
Level 1 (>1.5× ULN)	1 (2.17)	1 (4.55)
Level 2 (>2.0× ULN)	1 (2.17)	1 (4.55)
Level 3 (>3.0× ULN)	0 (0.00)	0 (0.00)
Alanine aminotransferase, high (U/L)	**0 (0.00)**	**0 (0.00)**
Level 1 (>3.0× ULN)	0 (0.00)	0 (0.00)
Level 2 (>5.0× ULN)	0 (0.00)	0 (0.00)
Level 3 (>10.0× ULN)	0 (0.00)	0 (0.00)
Aspartate aminotransferase, high (U/L)	**0 (0.00)**	**0 (0.00)**
Level 1 (>3.0× ULN)	0 (0.00)	0 (0.00)
Level 2 (>5.0× ULN)	0 (0.00)	0 (0.00)
Level 3 (>10.0× ULN)	0 (0.00)	0 (0.00)
Bilirubin, total, high (mg/dL)	**0 (0.00)**	**0 (0.00)**
Level 1 (>1.5× ULN)	0 (0.00)	0 (0.00)
Level 2 (>2.0× ULN)	0 (0.00)	0 (0.00)
Level 3 (>3.0× ULN)	0 (0.00)	0 (0.00)

Source: Applicant; ADLB.sas7bdat in D120; software, SAS 9.4.
Abbreviations: N, number of patients with at least one postbaseline nonmissing laboratory test value in the treatment arm; n, number of patients with the indicated laboratory test value; ULN, upper limit of normal

Table 69. Patients With One or More Lipids Analyte Values Exceeding Specified Levels for Lipids, Safety Population

Parameter	Tasimelteon N=46	Placebo N=22
Cholesterol, total, high (mg/dL)	11 (23.91)	7 (31.82)
Level 1 (>200)	11 (23.91)	7 (31.82)
Level 2 (>240)	4 (8.70)	2 (9.09)
Level 3 (>300)	0 (0.00)	0 (0.00)

Source: Applicant; ADLB.sas7bdat in D120; software, SAS 9.4.
Abbreviations: N, number of patients with at least one postbaseline nonmissing laboratory test value in the treatment arm; n, number of patients with the indicated laboratory test value

Table 70. Patients With One or More Hematology Analyte Values Exceeding Specified Levels, Randomized Treatment Period, Safety Population

Parameter	Tasimelteon N=46	Placebo N=22
WBC, low (cells/µL)	**0 (0.00)**	**0 (0.00)**
Level 1 (<3500)	0 (0.00)	0 (0.00)
Level 2 (<3000)	0 (0.00)	0 (0.00)
Level 3 (<1000)	0 (0.00)	0 (0.00)
WBC, high (cells/µL)	**4 (8.70)**	**0 (0.00)**
Level 1 (>10,800)	4 (8.70)	0 (0.00)
Level 2 (>13,000)	2 (4.35)	0 (0.00)
Level 3 (>15,000)	1 (2.17)	0 (0.00)
Hemoglobin, low (g/dL)	**0 (0.00)**	**0 (0.00)**
Level 2 (>1.5 dec. from baseline)	0 (0.00)	0 (0.00)
Level 3 (>2 dec. from baseline)	0 (0.00)	0 (0.00)
Hemoglobin, high (g/dL)	**1 (2.17)**	**0 (0.00)**
Level 2 (>2 inc. from baseline)	1 (2.17)	0 (0.00)
Level 3 (>3 inc. from baseline)	0 (0.00)	0 (0.00)

Parameter	Tasimelteon N=46	Placebo N=22
Platelets, low (cells/µL)	**3 (6.52)**	**0 (0.00)**
Level 1 (<140,000)	3 (6.52)	0 (0.00)
Level 2 (<125,000)	1 (2.17)	0 (0.00)
Level 3 (<100,000)	0 (0.00)	0 (0.00)
Lymphocytes, low (cells/µL)	**1 (2.17)**	**0 (0.00)**
Level 1 (<1000)	1 (2.17)	0 (0.00)
Level 2 (<750)	0 (0.00)	0 (0.00)
Level 3 (<500)	0 (0.00)	0 (0.00)
Lymphocytes, high (cells/µL)	**2 (4.35)**	**1 (4.55)**
Level 1 (>4000)	2 (4.35)	1 (4.55)
Level 2 (>10,000)	0 (0.00)	0 (0.00)
Level 3 (>20,000)	0 (0.00)	0 (0.00)
Neutrophils, low (cells/µL)	**2 (4.35)**	**1 (4.55)**
Level 1 (<2000)	2 (4.35)	1 (4.55)
Level 2 (<1000)	0 (0.00)	0 (0.00)
Level 3 (<500)	0 (0.00)	0 (0.00)
Eosinophils, high (cells/µL)	**0 (0.00)**	**1 (4.55)**
Level 1 (>650)	0 (0.00)	1 (4.55)
Level 2 (>1500)	0 (0.00)	0 (0.00)
Level 3 (>5000)	0 (0.00)	0 (0.00)

Source: Applicant; ADLB.sas7bdat in D120; software, SAS 9.4.
Abbreviations: N, number of patients with at least one postbaseline nonmissing laboratory test value in the treatment arm; n, number of patients with the indicated laboratory test value; WBC, white blood cell; inc., increase; dec., decrease

Vital Signs

The clinical safety review for NDA 205677 (tasimelteon for the treatment of non-24) found that tasimelteon was not associated with adverse changes in electrocardiogram or cardiac-related adverse events and that tasimelteon did not have adverse effects on vital signs.

Because subjects with SMS may suffer from hypertension and often are treated with beta receptor antagonists, we report here an analysis of the effect of tasimelteon on blood pressure in the safety population.

Table 71 shows the percentage of subjects by category of blood pressure in the randomized population and Table 72 in the overall safety population. The analysis shows that two subjects in the tasimelteon group have a systolic blood pressure >140 mmHg compared to none in the placebo group (Table 71 and Table 72); however, the small number does not represent a clear safety signal. Table 73 shows no difference in the percentage of subjects with maximum diastolic blood pressure (>90 mmHg) by category between the tasimelteon and placebo groups. Table 74 shows that a higher percentage of subjects on placebo meet hypotension levels postbaseline; however, the overall count is small and deemed not suggestive of a direct effect of tasimelteon on blood pressure. Overall, these findings do not indicate a clinically relevant effect of tasimelteon on blood pressure.

Table 71. Percentage of Patients With Maximum Systolic Blood Pressure by Category of Blood Pressure, Postbaseline, Randomization Population

Systolic Blood Pressure (mmHg)	Period 1 Tasimelteon (N=12) n (%)	Period 1 Placebo (N=12) n (%)	Period 2 Tasimelteon (N=12) n (%)	Period 2 Placebo (N=11) n (%)
<90	0 (0.0)	2 (16.7)	2 (16.7)	1 (9.1)
>90	11 (91.7)	10 (83.3)	10 (83.3)	10 (90.9)
>120	4 (33.3)	4 (33.3)	4 (33.3)	4 (36.4)
>140	1 (8.3)	0 (0.0)	1 (8.3)	0 (0.0)
>160	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)
>180	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Applicant; ADLB.sas7bdat; software, SAS 9.4
Abbreviations: %, 100×n÷N, where n is the number of patients with the indicated blood pressure and N is the number of patients with nonmissing blood pressure postbaseline

Table 72. Percentage of Patients With Maximum Systolic Blood Pressure by Category of Blood Pressure, Postbaseline, Safety Population

Systolic Blood Pressure (mmHg)	Tasimelteon (N=46) n (%)	Placebo (N=23) n (%)
<90	2 (4.3)	3 (13.0)
>90	43 (93.5)	20 (87.0)
>120	16 (34.8)	8 (34.8)
>140	2 (4.3)	0 (0.0)
>160	1 (2.2)	0 (0.0)
>180	0 (0.0)	0 (0.0)

Source: Applicant; ADLB.sas7bdat in D120; software, SAS 9.4
Abbreviations: %=100×n÷N, where n is the number of patients with the indicated blood pressure; N is the number of patients with nonmissing blood pressure postbaseline.
Patients received both placebo and tasimelteon in this crossover study.

Table 73. Percentage of Patients With Maximum Diastolic Blood Pressure by Category of Blood Pressure Postbaseline, Safety Population, Trial VP-VEC-162-2401

Diastolic Blood Pressure (mmHg)	Tasimelteon (N=46) n (%)	Placebo (N=23) n (%)
<60	5 (10.9)	4 (17.4)
>60	39 (84.8)	18 (78.3)
>90	2 (4.3)	1 (4.3)
>110	0 (0.0)	0 (0.0)
≥120	0 (0.0)	0 (0.0)

Source: Applicant; ADLB.sas7bdat in D120; software, SAS 9.4
Abbreviations: %, 100×n÷N, where n is the number of patients with the indicated blood pressure and N is the number of patients with nonmissing blood pressure postbaseline.
Patients received both placebo and tasimelteon in this crossover study.

Table 74. Percentage of Patients Meeting Specific Hypotension Levels Postbaseline, Safety Population, Trial VP-VEC-162-2401

Blood Pressure (mmHg)	Tasimelteon (N=46) n (%)	Placebo (N=23) n (%)
Systolic <90	2 (4.3)	3 (13.0)
Diastolic <60	6 (13.0)	4 (17.4)

Source: Applicant; ADLB.sas7bdat in D120; software, SAS 9.4
Abbreviation: %, 100×n÷N, where n is the number of patients with the indicated blood pressure and N is the number of patients with nonmissing blood pressure postbaseline
Patients received both placebo and tasimelteon in this crossover study.

18. Mechanism of Action / Drug Resistance: Additional Information and Assessment

This section is not applicable to this review.

19. Other Drug Development Considerations: Additional Information and Assessment

19.1. SMS—FDA-Requested Listening Session

The session took place on August 12, 2020. The information below is from the public summary of the listening session, as prepared by the Patient Affairs Staff (Office of the Commissioner).

Objectives of the Session

(1) Understand the experiences of patients with SMS and their caregivers.
(2) Understand the burden of sleep disorders for patients diagnosed with SMS.
(3) Understand the impact of the following on patients' and families' daily life:

a) Daytime sleepiness
b) Daytime naps
c) Duration of nighttime sleep
d) Frequency of nighttime awakenings

(4) Understand the pharmacological and nonpharmacological strategies that caregivers use (or were prescribed to the patient) to manage sleep disorders in SMS (in the context of no approved therapy available).

Discussions in FDA Listening Sessions are informal and meant not to replace, but rather complement, existing patient engagement opportunities in the Agency. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report summarizes the input provided by patients and those representing patients with SMS at the meeting. To the extent possible, the terms used in this summary to describe specific manifestations of SMS, and the health effects and impacts, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire population of patients with SMS or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.

Summary of the Discussion by Question

- What has it been like, overall, to care for a patient with SMS? How has your experience caring for a patient with SMS changed with the patient's age/development?
  - All of the caregivers indicated that patients with SMS experience sleep disturbances and behavioral issues throughout their lives. A majority of the caregivers added that although patients' needs may change with development, the level of care remains challenging and complex, requiring constant surveillance.

  - Caregivers described patients' sleep disturbances as lack of sleep, long periods of overnight awakening, falling asleep standing up during the day, having difficulty staying awake during the day, waking up at odd hours overnight, and the inability to remain asleep overnight.

- Has the patient been diagnosed with other medical, psychological, or neurological conditions besides SMS?

  - All caregivers reported that patients have been diagnosed with other medical, psychological, or neurological conditions. All but one caregiver indicated that patients have received multiple diagnoses.
  - A majority of the caregivers indicated that patients had developmental delays, intellectual disabilities, and/or cognitive impairments. In addition to SMS, some patients also received diagnoses of autism, attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), pervasive developmental disorders (PDD), and hearing impairment as well as speech and language disabilities.
  - One caregiver shared a patient's diagnosis of epilepsy.

- When thinking about the patient's experiences *during the night* related to sleep disturbances, which are most problematic? For example, taking too long to fall asleep, waking up frequently, having trouble falling back to sleep, and problematic activities when awake during the night.

  - All of the caregivers identified frequent awakenings during the night as most problematic. Caregivers said that patients awaken and are unable to go back to sleep, interrupting the sleep of other household members. Caregivers stated that patients had problematic or disruptive behavior during long periods of being awake overnight.
  - Caregivers described problematic and disruptive behaviors while patients were awake during the night as wandering around the house, inappropriate self-stimulating behavior, escape attempts, noise making such as hand clapping and speaking loudly. Disruptive behaviors while awake overnight also included threats to family members and self-injurious behavior such as head-banging and ripping at skin.
  - Most caregivers indicated that in order to maintain patient's and/or household members' safety, they lock doors and windows, secure refrigerators and cabinets, and hide dangerous or sharp items such as knives.

- When thinking about how sleep disturbances affect the patient's experiences *during the day*, which experiences are most problematic? For example, feeling sleepy during the day, difficulties completing desired activities due to a need for naps, and irritable behavior due to poor nighttime sleep.

  - Four caregivers specifically cited patients' meltdowns as most problematic during the day. Caregivers added that patients' meltdowns in some cases are exacerbated by lack of sleep or naps and typically occur multiple times per day or even per hour.
  - One caregiver identified the patient's most troublesome behaviors due to lack of sleep as irritability, exhaustion, poor decision-making, and inability to focus and

concentrate. The caregiver shared that lack of sleep increases the number and severity of the patient's seizures.
  - A majority of the caregivers stated that meltdowns can be triggered by insignificant actions such as hanging up a telephone, turning off bath water or a vacuum, and yawning.

- When you think about all the sleep disturbances that your child experiences, how much of those disturbances are related to *overnight versus daytime experiences*? Please estimate a percentage as best as possible. For example, 75% nighttime disturbances & 25% daytime disturbances.
  - The consensus among the caregivers was that patients' experiences are 80% overnight disturbances and 20% daytime disturbances.

- Can you tell us what *quality of sleep* means to you and your family? For example, this might mean the length of time your child sleeps, how frequently your child wakes up at night, and daytime nap frequency/duration.
  - Two caregivers defined *quality of sleep* for the patient as the length of time or duration of sleep without or with fewer awakenings. Caregivers shared their desire for patients to sleep without getting out of bed or roaming the house for hours. Caregivers said they would be able to sleep undisturbed if the patients were able to sleep for longer.
  - Two caregivers defined *quality of sleep* for their families as the quality and depth of sleep rather than its duration. The caregivers indicated that a few hours of deep sleep are more impactful than multiple hours of poor-quality sleep. Caregivers added that prolonged poor-quality sleep does not produce a good day for patients, as compared to even 30 minutes of solid, deep sleep, which can improve their behavior.
  - One caregiver stated that both length and depth constitute *quality of sleep*. The caregiver mentioned the desire for the patient to experience fewer awakenings and restorative sleep, which helps with the patient's behaviors and health.

- What has been your experience with medications to treat sleep disturbances in SMS? Which aspects of sleep have been *most improved* by medication therapy, and which aspects have been *least improved*?
  - All but one caregiver indicated that patients are currently using medications to treat sleep disturbances associated with SMS.
  - All caregivers who are currently using medications to treat sleep disturbances in SMS currently use melatonin. A majority of these caregivers use cannabidiol (CBD) with melatonin to assist patients in falling asleep. Caregivers indicated that although these medications assist patients with going to sleep, they do not help patients stay asleep.
  - A majority of caregivers said they have tried several medications, many of which were disruptive to patients' sleep or had adverse side effects. Antidepressants, antipsychotics, benzodiazepines, clonidine, and blood pressure medications were among the drug classes named.

- If you are not currently using any medications to treat sleep disturbances in SMS, have you used medications or supplements in past? How has that worked for you?
  - A caregiver not currently using any medication for the patient's sleep disturbances had used melatonin and CBD in the past but were both discontinued because of a failure to provide consistent effects. The caregiver added that prescription medications have never been used nor is there a plan to do so unless absolutely necessary.
- What has been your experience using behavioral therapy or behavioral strategies to treat sleep disturbances in SMS? Which aspects of sleep have been *most improved* by behavioral therapy, and which aspects have been *least improved*? Two examples of behavioral strategies are using a special bed and sealing the windows to light and sound.
  - Most caregivers said that patients maintain a strict bedtime routine and good sleep hygiene.
  - A majority of caregivers stated that they use blackout curtains to keep the room as dark as possible, and white noise machines to promote sleep. Some caregivers shared that music, books, and shows are played on a tablet or device to help patients sleep.
  - Caregivers stated strategies including creating a safe, calm, and secure environment for patients while they sleep. Caregivers discussed their use of monitors, cameras, and alarms to surveil patients. In addition, caregivers shared the use of weighted blankets, safety sleepers, window locks, and alarms on doors. Caregivers expressed removing furniture, televisions, and toys from patients' bedrooms to decrease distractions.
  - Caregivers emphasized that behavioral strategies and interventions do not actually *treat* SMS patients' sleep disturbances, but rather are attempts to train their sleep and support a conducive sleep environment.
- If you could create a treatment (i.e., drug or medication) for sleep disturbances associated with SMS, which experience/behavior would be the *first and most important* symptom you would want to improve or treat?
  - All caregivers expressed a desire for an SMS treatment to allow patients to sleep for a duration that provides deep, restorative sleep. Caregivers believe restorative sleep at night would improve behaviors. Caregivers expressed concern regarding the impact a lifetime of a lack of sleep will have on patients.
  - A caregiver also identified patient's self-injurious behaviors as an important symptom to treat, describing these behaviors as difficult to manage and scary.
- If you were not able to treat all the sleep disturbances the patient experiences, which aspect(s) would be least problematic to manage if untreated?
  - One caregiver indicated that all aspects of sleep disturbances are problematic and important, adding that the issues are linked and complex.
  - Two caregivers said that the inability to fall asleep is the least problematic. Caregivers highlighted difficulty coping with behaviors like patient's threatening siblings or hitting strangers. Caregivers reiterated the desire for restorative sleep.

- Additional comments
  - Some caregivers emphasized that patients' lack of sleep affect all members of the family. Caregivers believed restorative sleep would impact not only the patient, but all individuals around the patient. Caregivers added that consistent sleep every night would allow patients to meet the other challenges in their lives.
  - Caregivers expressed a desire for a treatment or medication to reduce patient's aggressive behaviors.
  - Caregivers said they could be better patients if patients were able to get restorative sleep, adding that the least bit of help would be useful.

Partner Organizations

The National Organization for Rare Disorders (NORD) helped identify and prepare patient community participants. The Reagan-Udall Foundation for the FDA assisted with producing the summary of this meeting. NORD and the Reagan-Udall Foundation were present during the listening session.

FDA Divisions Represented

- **Office of the Commissioner**, Patient Affairs Staff (*organizer*); Office of Orphan Products Development; Office of Combination Products
- **Center for Biologics Evaluation and Research (CBER)**, Office of the Director
- **Center for Drug Evaluation and Research (CDER),** Office of Neurology, Division of Psychiatry (*requestor*); Office of New Drugs/Office of Neurology; Office of New Drugs/Office of Neurology/Division of Neurology I; Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine, Division of Rare Diseases and Medical Genetics (DRDMG); Office of Regulatory Operations (ORO), Division of Regulatory Operations for Neuroscience (DRO-ON); Office of Translational Sciences (OTS), Office of Biostatistics, Division of Biometrics I; Office of Drug Evaluation and Science (ODES), Division of Clinical Outcome Assessment (DCOA)
- **Center for Devices and Radiological Health (CDRH),** Office of Strategic Partnerships and Technology Innovation/ Division of All Hazards Response, Science and Strategic Partnerships; Office of Product Evaluation and Quality (OPEQ), Office of Health Technology (OHT1), Division of Health Technology - Anesthesia, Respiratory, & ENT Devices; Division of Sleep Disordered Breathing Devices; Office of Science and Engineering Laboratories (OSEL), Division of Biomedical Physics

Patients and Caregivers Represented

Six caregivers participated in the listening session, representing six patients with SMS.

- The patient are 5 to 30 years of age.
- The age of onset varied. For example, one patient was diagnosed with SMS at the age of 17 years and another at 10 days.

Prior to the Listening Session, Caregivers Shared

- Problematic aspects of sleep disturbances: Lack of sleep, roaming around home unmonitored, inability to focus, early rising, behavioral issues, and outbursts.

- Management of SMS: Melatonin, CBD, and Clonidine (on occasion).

Financial Interest

Caregivers/patients did not identify any conflict of interest relevant to this listening session and are not receiving compensation.

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

The clinical investigators Drs. Helene Emsellem and Daniel Norman were inspected by the Office of Scientific Investigations in support of this NDA. Based on the results of these inspections, Protocol VP-VEC-162-2401 appears to have been conducted adequately, and the data generated by these clinical investigators in support of the indication appear reliable.

21. Labeling Summary of Considerations and Key Additional Information

Prescribing Information

General:

Information highlighted below are significant changes made to the Full Prescribing Information (FPI) from the Applicant-proposed label submitted on June 1, 2020.

- Given that the new formulation, HETLIOZ LQ (tasimelteon) oral suspension, has a similar safety profile, shares similar (but not all) indications, and has a similar health care practitioner audience, it was decided to have a single FPI covering both the oral suspension and the capsules.
- A table was added to HL to clearly convey the dosage recommendations for the oral suspension which is weight-based (versus fixed-dose for capsules).

1 INDICATION AND USAGE

- The Applicant proposed the indication of "Sleep Disorder in Smith Magenis Syndrome," and the review team changed the wording of the indication to: "Nighttime Sleep Disturbances in Smith Magenis Syndrome" for the following reasons:
  - Sleep Disturbances do not represent a distinct disorder but are part of a complex clinical phenotype;
  - Sleep disturbances do not simply co-occur with SMS but are actually a biologically-determined core feature SMS; therefore the wording "in" SMS was preferred over "(b) (4)";
  - Sleep disturbances in SMS typically consist of decreased nocturnal sleep time, frequent nocturnal awakenings, early morning arousals, and excessive daytime sleepiness, however the Applicant demonstrated substantial effectiveness only in the treatment of nighttime sleep disturbances.

- The formulations have different indications and patient populations, so the indication statements were separated:

1.1 Non-24-Hour Sleep-Wake Disorder (Non-24)

- HETLIOZ capsules are indicated for the treatment Non-24-Hour Sleep-Wake Disorder in adults.

1.2 Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS)

- HETLIOZ capsules are indicated for the treatment of nighttime sleep disturbances in SMS in patients 16 years and older.
- HETLIOZ LQ oral suspension is indicated for the treatment of nighttime sleep disturbances in SMS in pediatric patients 3 to 15 years of age.

2 DOSAGE AND ADMINISTRATION

- The development program did not include a bioequivalence study, so we added the following statement to section 2.1 to convey that the two formulations are not substitutable.

2.1 Non-Interchangeability between HETLIOZ Capsules and HETLIOZ LQ Oral Suspension

HETLIOZ capsules and HETLIOZ LQ oral suspension are not substitutable *[see Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

The clinical safety review found that there are no new safety signals and an update of the safety information is not necessary (refer to Section 7.6 of the review).

- Exposure was updated with data from the SMS program, including the open label extension (ongoing)
- A sentence was added to Section 6.1 to indicate that the safety information for the SMS indication is similar to the Non-24-Hour Sleep-Wake Disorder.

7 DRUG INTERACTIONS

- The currently approved labeling includes a sentence under Section 14.1 stating that the efficacy of HETLIOZ in treating Non-24 may be reduced in subjects with concomitant administration of beta-adrenergic receptor antagonists. The Applicant proposed a similar statement under Section 14.2 (the SMS indication). The statement was moved from Section 14.2 to Section 7 as new Subsection 7.3. Refer to Section 6.3.4 of the review for discussion of this issue.

7.3 Beta-adrenergic Receptor Antagonists (e.g.,

- Nighttime administration of beta-adrenergic receptor antagonists may reduce the efficacy of HETLIOZ.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

- Added regulatory statements noting the study in SMS:
  - Safety and effectiveness of HETLIOZ LQ oral suspension for the treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) have been established in pediatric patients 3 years and older. Refer to Section 6.3.1 of the review for discussion of this issue.
  - Safety and effectiveness of HETLIOZ for the treatment of nighttime sleep disturbances in SMS have not been established in patients younger than 3 years old.

(1) Juvenile Animal Toxicity Data section was added. Refer to Section 13.1 of the review for additional information.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Pharmacokinetic information was added to the subsection titled *Specific Populations* to describe relevant PK exposure measures and findings in the indicated pediatric population.

- *Pediatric Patients*

Pharmacokinetic information in pediatric patients are available only for the suspension. Body weight was found to have significant effect on the pharmacokinetics. The increase in body weight was associated with increase in tasimelteon clearance up to 28 kg. The average dose normalized C_{max} and AUC_{inf} at the recommended dose was 231 ng/mL and 310 ng.h/mL. No data are available in patients less than 3 years old.

14 CLINICAL STUDIES

Description and results from the study in support of the Nighttime Sleep Disturbances in Smith Magenis Syndrome indication (referred to as study 3) was added to Section 14 under a new subsection:

14.2 Nighttime Sleep Disturbances in SMS

- Efficacy results from the Open label Treatment Arm of Study 2401 were not considered in the clinical review for the assessment of benefit.
- Only results of the primary analysis of the Randomized Arm of Study 2401 were described in the Clinical Studies section.
- Only primary endpoints were included in the efficacy table, because the Applicant did not prespecify any testing for secondary endpoints with adequate control for type I error.
  - Secondary endpoints: 1) *50% worst total nighttime sleep duration* and 2) O*verall sleep quality and overall nighttime sleep,* were numerically significant (versus statistically significant) and were described as such via text in the study results description.
- The following statement was revised and relocated to Section 7.3: The use of beta-adrenergic receptor antagonist may reduce effectiveness of Hetlioz only if administered at nighttime.

PATIENT LABELING

- HETLIOZ approved labeling does not include any type of patient labeling, e.g., Medication Guide (MG) or Instructions for Use (IFU), and the Applicant did not propose any such document. Given that the oral suspension is intended for administration by the patient/caregiver, we requested that the applicant submit an IFU.

22. Postmarketing Requirements and Commitments

The following postmarketing commitments (PMCs) will be issued at the time of approval.

- PMC 3932-1: Study to optimize the in vitro dissolution method
  - Milestone: Final report submission December 1, 2021
- PMC 3932-2: Studies to finalize critical process parameters for the proposed (b) (4) commercial batch size.
  - Milestone: Final report submission December 1, 2022
- PMC 3932-3: Conduct a formal palatability study of the formulation in a clinical trial
  - Milestone: Final report submission December 1, 2022

23. Financial Disclosure

Table 75. Covered Clinical Studies: VP-VEC

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 6		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): N/A		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): N/A		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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25. Review Team

Table 76. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Latrice Wilson
Nonclinical Reviewer	Julie Frank; Amy Avila
Nonclinical Supervisor	Aisar Atrakchi
Office of Clinical Pharmacology Reviewer(s)	Venki ChithambaramPillai
Office of Clinical Pharmacology Team Leader(s)	Luning (Ada) Zhuang
Clinical Reviewer	Valentina Mantua
Clinical Team Leader	Michael Davis
Statistical Reviewers	Thomas Birkner; Andrew N Potter
Statistical Team Leader	Peiling Yang
Cross-Disciplinary Team Leader	Michael Davis
Division Director (pharm/tox)	Lois Freed
Division Director (OCP)	Mehul Mehta
Division Director (OB)	Hsien Ming James Hung
Division Director (clinical)	Tiffany R. Farchione

OCP, Office of Clinical Pharmacology
OB, Office of Biostatistics

Table 77. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ Team Lead	Valerie Amspacher
Microbiology	Shannon Heine
OPDP	Christine Bradshaw
DMPP/PLT	Ruth Mayrosh
OSI	Christian Shenouda
CDRH	Patrick Antkowiak
DPMH	Ethan Hausman
DPMH Team Leader	Shetarra Walker
CSS	Chad Reisseg
OSE/DEPI	Dinci Pennap
OSE/DEPI Team Leader	Kira Leishear
OSE/DMEPA	Loretta Holmes
OSE/DMEPA Team Leader	Sevan Kolejian
OSE/DPV	Kelly Harbourt
OSE/Drug Use	Silvia PerezVilar

OPQ, Office of Pharmaceutical Quality
OPDP, Office of Prescription Drug Promotion
OSI, Office of Scientific Investigations
OSE, Office of Surveillance and Epidemiology
DEPI, Division of Epidemiology
DMEPA, Division of Medication Error Prevention and Analysis
DRISK, Division of Risk Management

Table 78 Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Bernard Fischer	OND/ON - DP	Entire Review ☐ Authored ☐ Contributed ☒ Approved
Deputy Director	**Signature:** Bernard A. Fischer IV -S Digitally signed by Bernard A. Fischer IV -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0014393264, cn=Bernard A. Fischer IV -S Date: 2020.11.30 23:56:26 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Michael Davis	OND/ ON - DP	Entire Review ☒ Authored – Section 2 ☒ Contributed ☒ Approved
Cross-Disciplinary Team Lead	**Signature:** Michael C. Davis -S Digitally signed by Michael C. Davis -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001865966, cn=Michael C. Davis -S Date: 2020.11.30 18:07:42 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Valentina Mantua	OND/ON - DP	Section 2, 3, 4, 6, 7, 10, 15, 16, 17, 19, 20, 23, 24. ☒ Authored ☒ Contributed – Section 21 ☒ Approved
Reviewer	**Signature:** Valentina Mantua -S2 Digita ly signed by Valentina Mantua S2 DN: c US o U S Government ou HHS ou FDA ou People 0 9 2342 19200300 100 1 1 2002940414 cn Valentina Mantua S2 Date: 2020 11 30 17:15:05 05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Kimberly Updegraff	OND/ ON - DP	Section 21 ☒ Authored ☐ Contributed ☐ Approved
Associate Director for Labeling	**Signature:** Kimberly S. Updegraff -S Digital y signed by Kimber y S Updegraff S DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0 9 2342 19200300 100 1 1=1300395112 cn=Kimberly S Updegraff S Date: 2020 11 30 18:47:52 05 00		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Statistical	Hsien Ming J Hung	OB/DBI	Sections 6, 15, 16 ☐ Authored ☐ Contributed ☒ Approved
Division Director	**Signature:** Hsienming J. Hung -S Digitally signed by Hsienming J. Hung -S Date: 2020.12.01 11:17:34 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Statistical	Peiling Yang	OB/DBI	Sections 6, 15, 16 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Peiling Yang -S Digitally signed by Peiling Yang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Peiling Yang -S, 0.9.2342.19200300.100.1.1=1300147876 Date: 2020.12.01 09:42:48 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Statistical	Thomas Birkner	OB/DBI	Sections 6, 15, 16 ☒ Authored ☒ Contributed ☒ Approved
Reviewer	**Signature:** Thomas Birkner -S Digitally signed by Thomas Birkner -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Thomas Birkner -S, 0.9.2342.19200300.100.1.1=2000961704 Date: 2020.12.01 09:25:36 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Statistical	Andrew Potter	OB/DBI	Section 6.3.5 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:** Andrew N. Potter -S Digitally signed by Andrew N. Potter -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002175238, cn=Andrew N. Potter -S Date: 2020.12.01 09:37:22 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Pharmacology/Toxicology	Aisar Atrakchi	OND/DPT-N	Section 5.1, 7.1 and 8.4; Appendix 13 ☐ Authored ☐ Contributed ☒ Approved
Supervisor	**Signature:** Aisar H. Atrakchi -S Digitally signed by Aisar H. Atrakchi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300078962, cn=Aisar H. Atrakchi -S Date: 2020.12.01 10:55:32 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Pharmacology/Toxicology	Julie Frank	OND/DPT-N	Section 5.1, 7.1 and 8.4; Appendix 13 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:** Julie G. Frank -S Digitally signed by Julie G. Frank -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Julie G. Frank -S, 0.9.2342.19200300.100.1.1=2002370131 Date: 2020.12.01 11:10:50 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Pharmacology/Toxicology	Amy Avila	OND/DPT-N	Section 5.1, 7.1 and 8.4; Appendix 13 ☐ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:** Amy M. Avila -S Digitally signed by Amy M. Avila -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Amy M. Avila -S, 0.9.2342.19200300.100.1.1=1300384227 Date: 2020.12.01 11:03:54 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical Pharmacology	Mehul Mehta	OTS/OCP	Section 5, 6.3.1, 14.1 and 14.2 ☐ Authored ☐ Contributed ☒ Approved
Division Director	**Signature:** Mehul U. Mehta -S Digitally signed by Mehul U. Mehta -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mehul U. Mehta -S, 0.9.2342.19200300.100.1.1=1300039057 Date: 2020.12.01 14:42:39 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical Pharmacology	Luning Zhuang	OTS/OCP	Section 5, 6.3.1, 14.1 and 14.2 ☒ Authored ☒ Contributed ☒ Approved
Team Leader	**Signature:** Luning Zhuang -S Digitally signed by Luning Zhuang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Luning Zhuang -S, 0.9.2342.19200300.100.1.1=2001341990 Date: 2020.12.01 11:36:02 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical Pharmacology	Venkateswaran ChithambaramPillai	OTS/OCP	Section 5, 6.3.1, 14.1 and 14.2 ☒ Authored ☒ Contributed ☒ Approved
Reviewer	**Signature:** Venkateswaran Chithambaram Pillai -S Digitally signed by Venkateswaran Chithambaram Pillai -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001855894, cn=Venkateswaran Chithambaram Pillai -S Date: 2020.12.01 11:57:07 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Regulatory Operations	Latrice Wilson	OND/ORO-DRON	Appendix 13 ☐ Authored ☒ Contributed ☒ Approved
Project Manager	**Signature:** Latrice Wilson -S Digitally signed by Latrice Wilson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Latrice Wilson -S, 0.9.2342.19200300.100.1.1=2001287414 Date: 2020.12.01 12 52:52 -05'00'		

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/s/

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