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MEDICAL REVIEW(S)

CLINICAL REVIEW

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(Proposed) Trade Name	Hetlioz
Therapeutic Class	Melatonin receptor agonist
Applicant	Vanda Pharmaceuticals Inc
Formulation(s)	Capsules
Dosing Regimen	20 mg
Indication(s)	Treatment of Non-24-Hour Disorder in the Totally Blind
Intended Population(s)	Blind individuals with no light perception

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval.

1.2 Risk Benefit Assessment

In the paragraphs below, I present the Applicant's conclusion and my conclusion for efficacy followed by safety. I conclude this subsection of review by summarizing the risk-benefit and state my recommendation on regulatory action.

Efficacy:

Applicant's Efficacy Conclusions:

Tasimelteon is a circadian regulator that entrains the master body clock in totally blind patients with Non-24 Hour Disorder. Treatment with 20 mg of tasimelteon one hour before bedtime at approximately the same time every night for 26 weeks entrained circadian rhythms to the 24-hour day and stabilized the sleep-wake cycle. Treatment with tasimelteon significantly increased the lower quartile of nighttime sleep duration and decreased the upper quartile of daytime sleep duration in patients with Non-24. Tasimelteon numerically improves nighttime sleep and decreases daytime nap duration. Tasimelteon significantly improves the timing of sleep relative to the desired bedtime. Tasimelteon is significantly efficacious in treating Non-24 Hour Disorder as measured by clinically meaningful improvement in the Non-24 Clinical Response Scale. Treatment with 20 mg of tasimelteon for 26 weeks significantly improves global functioning as measured by the Clinical Global Impression-Change (CGI-C). Tasimelteon treatment is necessary for entrainment, maintenance of entrainment, and for maintenance of clinical benefits in sleep and wake measures. Development of tolerance to tasimelteon response was not observed. These results support the use of tasimelteon in the treatment of circadian rhythm disorders in patients with Non-24 Hour Disorder who are totally blind.

Reviewer's Efficacy Conclusions:

There were no *pre-specified* primary *clinical* endpoint(s), which by itself (themselves), capable of directly assessing clinical benefit (i.e., how a patient feels or functions) in either Study 3201 or Study 3203 in subjects with Non-24 Hour Disorder (the target population). The pre-specified step-down primary endpoint in Study 3201 combined entrainment with some clinical endpoints; with the exception of Midpoint of Sleep Timing (MoST) endpoint (unknown clinical meaningfulness), these clinical endpoint, by themselves, could support clinical benefit but their use as stand-alone primary endpoint(s) was not pre-specified.

There was a prior agreement between the Agency and the Applicant that nighttime sleep and daytime naps were the two most important direct measures of clinical benefit in Non-24 Hour Disorder. The Agency expressed openness in considering endpoints that looked at ‘worst few days’ in each cycle to help decrease the effect of random variability. The Applicant chose the Lower Quartile of nighttime Total Sleep Time (LQ-nTST) for the “worst night analysis” after determining that LQ-nTST was highly correlated with the phase of the circadian cycle that is 180° out of alignment with the 24-hour day, and therefore was more specific and appropriate in this remitting and relapsing disorder. The Upper Quartile of daytime Total Sleep Duration (UQ-dTSD) was chosen for similar reasons. LQ-nTST and UQ-dTSD are, therefore, appropriate clinical endpoints for evaluation of an effect in Non-24 Hour Disorder.

Analyses of efficacy data conducted by the Agency reveal statistical significance in favor of tasimelteon 20 mg for the clinical endpoints, LQ-nTST, UQ-dTSD, dTSD and CGI-C, in both Study 3201 and Study 3203 in the target population. There was no statistical significance for nTST in either study, and may reflect the expected increase in variability of this measure in a disorder where extreme values likely occur during periods of maximum alignment and maximum misalignment. Compared to the placebo group, there was a numerical advantage for nTST in the tasimelteon group in both Study 3201 and Study 3203.

Choosing clinical outcome(s) such as the LQ-nTST and UQ-dTSD post-hoc to establish efficacy in Study 3201 or Study 3203 risks inflation of Type I error in either study. However, the risk of false discovery in this application is diminished by independent substantiation with statistical significance for the clinical endpoints, LQ-nTST, UQ-dTSD, dTSD and CGI-C, in both Study 3201 and Study 3203.

The visual assessment of benefit on the cyclical nature of the nighttime and daytime sleep using the graphical representation in individual subjects over time (although such assessment is subjective in nature), the statistically significant effect favoring tasimelteon on MoST, and importantly, the statistically significant effect favoring tasimelteon on the absolute value of the difference of between In-phase and Out-of-Phase for cycle 1 and 2 post-randomization, indicate a specific effect of tasimelteon on the cyclical nature of Non-24 Hour Disorder.

Safety:

Applicant's Safety Conclusions:

Based upon the overall safety data as well as the specific analyses performed by Study Group, tasimelteon is generally safe and well-tolerated in both the target population of totally blind individuals with non-24 Hour Disorder as well as a larger population who includes sighted and blind individuals, 18 years of age and older, including elderly patients up to 92 years of age. It is reasonable to conclude, based upon the overall safety data, that tasimelteon is safe and well tolerated and reasonably likely to pose a minimal safety risk to the indicated population. The large majority of adverse events will be mild to moderate in nature, and will occur within the first 30 days of therapy.

Reviewer's Safety Conclusions:

Across the entire safety database, there were no deaths, and there were few non-fatal serious adverse events. Other than, perhaps gastroenteritis, no treatment-emergent serious adverse event was experienced by more than one subject. The proportion of subjects who experienced any treatment-emergent adverse event that led to early termination was fairly even between treatment groups in the entire safety database. Treatment-emergent adverse events which 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 is not associated with adverse effects due to abrupt withdrawal as assessed by the Tyrer Benzodiazepine Withdrawal Symptoms Questionnaire based on safety data which are adequate for such an assessment. Similarly, tasimelteon is not associated with next-day residual effects as assessed by Digit Symbol Substitution Test, Visual Analog Scale (mood scale assessing sleepy/alert), and Karolinska Sleepiness Scale.

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

Tasimelteon is not associated with an adverse effect on suicidality as assessed by the Columbia Suicide Severity Rating Scale based on safety data which are adequate for such an assessment.

The following common treatment-emergent adverse events, defined as experienced by at least 3 subjects in the tasimelteon group and with a ≥ 2 -fold greater frequency than in placebo group, were identified in subjects with Non-24 Hour Disorder: 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 laboratory measures of liver injury, and available data is 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 is 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 available data which are sufficient for such a determination.

Tasimelteon does not have adverse effects on vital signs.

Reviewer's overall benefit-risk assessment: The efficacy for tasimelteon in the treatment of Non-24 Hour Disorder has been demonstrated on clinical outcomes in two clinical studies. There are no major safety issues associated with the use of tasimelteon in the submitted safety database which includes subjects with Non-24 Hour Disorder. The clinical benefit outweighs the risks in subjects with Non-24 Hour Disorder. Therefore, I recommend approval.

1.3 Recommendations for Postmarket Risk Management Activities

I have no recommendations for postmarket risk management activities.

1.4 Recommendations for Postmarket Studies/Clinical Trials

Only one dose – 20 mg, was evaluated in clinical studies of Non-24 Hour Disorder. The Applicant selected this dose in Non-24 Hour Disorder studies based on the extrapolation of data from an in-vivo preclinical pharmacology model of chronic phase-shifting activity and acute phase-shifting activity in humans (healthy volunteers). The lack of dose-response for both safety and efficacy in Non-24 Hour Disorder limits dosing recommendations such as starting dose, dose adjustment and maximum useful dose. Safety data at higher doses in insomnia subjects (up to 50 mg daily for 35 days) and healthy volunteers (150 mg daily for 28 days) show reasonable safety over these doses without any major safety concerns. Evaluation of other doses (lower and higher than 20 mg) could provide additional information on efficacy and dosing recommendations. However, considering the safety profile, the orphan nature of Non-24 Hour Disorder, and trial duration necessary to show an effect on cyclicity, I do not believe that additional dose-response information is necessary for the safe and effective use of tasimelteon. Therefore, I have no recommendation for postmarket clinical trials.

2 Introduction and Regulatory Background

An endogenous circadian pacemaker in the suprachiasmatic nucleus spontaneously generates circadian rhythms. The length of the endogenous circadian period (τ) that governs circadian rhythms is typically a little over 24 hours and ranges between 23.5 and 24.7 hours in healthy *sighted* individuals. These rhythms are synchronized (entrained) to the 24-hour day by exposure to environmental time cues, the strongest of which is the daily light-dark cycle, detected primarily by the photosensitive ganglion cells of the retina. In the absence of light input, synchronization with the 24-hour day is lost; consequently the circadian rhythms follow the intrinsic non-24-hour clock of the endogenous circadian pacemaker which is typically slightly longer than 24 hours.

Among the physiological processes known to be under the regulatory control of the suprachiasmatic nucleus are the rhythmic releases of melatonin and cortisol, and the sleep-wake cycle. Melatonin is secreted by the pineal gland exclusively at night in both nocturnal and diurnal animals. Melatonin is regarded as an accurate marker of human circadian phase because of its tight regulation by the suprachiasmatic nucleus and minimal masking by factors besides light.

The Applicant states that the rhythm of melatonin is, therefore, the accepted measurement of the circadian rhythm/period (referred to as the τ in this review). Onset of melatonin secretion typically begins as the daylight begins to dim. Peak melatonin concentration in the *plasma* occurs about 6 hours prior to waking from sleep, and peak melatonin metabolite concentration in the *urine* occurs about 3.5 hours prior to waking. The main metabolite of melatonin in the urine is 6-sulfatoxymelatonin (aMT6s).

Non-24 Hour Disorder is a chronic disorder that occurs when individuals are unable to synchronize their endogenous body clock to the 24-hour light-dark cycle. The Applicant states that Non-24 Hour Disorder is also known as: Circadian rhythm sleep disorder – nonentrained type; Free running disorder; Non-24-hour circadian rhythm disorder; Non-24-hour sleep-wake disorder; Circadian rhythm sleep disorder – free-running type; and Hypnerynthemeral disorder. The majority of reported cases occur in blind patients with no perception of light. In these blind individuals the pacemaker may revert to its endogenous non-24-hour rhythm leading to periodic desynchronization of timing of melatonin and cortisol production, and the sleep-wake cycle with respect to the external 24-hour day. For example, consider a blind individual who has an endogenous circadian rhythm of 25 hours. On Day 1, if this individual's circadian clock is synchronized with the external 24-hour day at midnight, the first circadian rhythm would not end until 1 AM on Night 2. On each succeeding 24-hour day, the circadian rhythm would end an hour later than on the previous day until the endogenous circadian rhythm synchronizes again with the external 24-hour day at midnight 24 days later. The interval between two successive synchronization of the endogenous circadian rhythm and the 24-hour day (24 days in the above example) is referred to as the circadian cycle. The circadian cycle is calculated as: $[24 \text{ hours/day} \div (\text{endogenous clock in hours} - 24 \text{ hours})]$.

There are approximately 1,300,000 blind people in the United States. Ten percent of these individuals have no light perception. The Applicant cites an estimated prevalence of Non-24 Hour Disorder in the totally blind as being approximately 100,000 individuals in the United States. Non-24 Hour Disorder can occur at any age, and typically results from blindness and complete loss of circadian photoreceptive function, i.e., no perception of light. The progressive shifting of the circadian rhythm in the affected individuals produces a cyclical misalignment and alignment every circadian period (varies from 1 to 16 months depending on the duration of the endogenous clock). During misalignment of the endogenous clock with the external 24-hour clock, affected individuals tend to sleep at inappropriate times (daytime, for example). Around the times when the endogenous clock is aligned with the 24-hour day, remission is experienced and individuals often obtain their total sleep during normal bed time.

There is no approved treatment for Non-24 Hour Disorder.

2.1 Product Information

Tasimelteon is a dual melatonin receptor agonist with selective agonist activity at the melatonin MT1 and MT2 receptors. Tasimelteon was known as BMS-214778 ((Bristol-Myers Squibb designation) and VEC-162 (Vanda Pharmaceuticals designation) during the development

program. VEC-162 and BMS-214778 were used in the original study reports and other documents; these terms and tasimelteon are used synonymously throughout this review.

2.2 Tables of Currently Available Treatments for Proposed Indications

There is no approved treatment for Non-24 Hour Disorder.

2.3 Availability of Proposed Active Ingredient in the United States

Tasimelteon is a new molecular entity and has not been approved in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

Tasimelteon is a new molecular entity. The issue of safety in related drugs is discussed in Section 7.3.5 ‘Submission Specific Primary Safety Concerns’ of this review.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The development program for tasimelteon was conducted under IND 54,776. This IND was initiated by Bristol Myers Squibb and has been active since 3/16/98. IND 54,776 was transferred to Vanda Pharmaceuticals on 5/17/04. Orphan drug designation for the treatment of Non-24-Hour Disorder in blind individuals with no light perception was granted on 1/9/10.

On 12/10/04, a meeting was held to discuss the clinical development of VEC-162 for the proposed indication of improving the symptoms of shift work sleep disorder.

A Type B End of Phase II meeting was held on 4/30/07 to discuss development of VEC-162 for the treatment of the symptoms of insomnia associated with circadian rhythm sleep disorders subtypes where sleep disturbances result from sleep being scheduled earlier than the time when patients are able to initiate and maintain sleep: Shift Work Disorder due to an early morning work schedule, Jet Lag Disorder due to eastward travel, and Delayed Sleep Phase Disorder.

On 6/29/09, an End of Phase II meeting was held to discuss the clinical development of tasimelteon for the treatment of jet lag insomnia (eastward travel).

On 1/6/11, a Type B End of Phase II meeting was held to discuss the development of VEC-162 for the treatment of non-24-hour sleep-wake disorder in totally blind individuals. There was a

discussion on the criteria for the diagnosis of Non-24 Hour Disorder, use of endpoints capable of distinguishing between an effect on the specific condition of Non-24 Hour Disorder versus a non-specific effect on insomnia, dose and dose-timing, and clinical meaningfulness of a statistically significant but small change in sleep. There was agreement that nighttime sleep and daytime naps were the two most important direct measures of clinical benefit. After a discussion on the use of worst night analysis using Lower Quartile of night Total Sleep Time, the Agency expressed openness to considering a clinical endpoint that evaluated the worst few nights/days to help decrease the effect of random variability. There was a discussion on how an effect on the cyclical nature of the condition would need to be demonstrated to support the specificity of the indication. The Applicant offered to collect nighttime sleep and daytime nap data more continuously throughout the post-randomization part of the trial in order to capture the cyclic nature of the clinical symptoms.

Study 3203 protocol was reviewed under the provisions of Special Protocol Assessment. A No-Agreement letter was issued on 8/18/11 because the design and planned analysis of the study did not adequately address the objectives necessary to support a regulatory submission.

On 5/12/12 (in Version 9 of Study 3201 protocol), the Applicant changed the primary endpoint to entrainment of the circadian melatonin rhythm (from average nTST) which required fewer subject numbers to power the study (from 160 to 84) citing difficulty in subject recruitment; secondary endpoints included clinical outcomes, as measured by sleep, daytime naps and functionality.

A Teleconference was held on 7/9/12 to discuss the Agency's position (communicated on 6/8/12) that Subpart H was not an appropriate approval pathway for tasimelteon in the treatment of Non-24 Hour Disorder. Specifically, the Agency's position was that at least one clinical trial demonstrating efficacy on an appropriate clinical outcome was necessary for approval of tasimelteon in Non-24 Hour Disorder, and that Subpart H was not a viable option for filing their NDA.

After a review of the Statistical Analysis Plan for Study 3201, the Agency reiterated its position to the Applicant (11/28/12) that at least one clinical trial demonstrating efficacy on an appropriate clinical outcome was necessary for approval of tasimelteon in Non-24 Hour Disorder, and that subpart H approval based on entrainment was not a viable option for filing an NDA because clinical benefit can clearly be shown in reasonable clinical trials prior to approval. The Agency extended an offer again to meet with the Applicant before the planned unblinding of Study 3201 to discuss and agree upon an acceptable clinical endpoint. Further, that if the Applicant did not accept this offer, the statistical analysis will need to be revised to pre-specify a directly clinically meaningful endpoint to support NDA filing. The Agency stated that it will otherwise select for use in filing decisions a clinical endpoint that it deemed to fulfill the minimum requirements for capability of demonstrating clinically meaningful benefit.

On 12/10/12, a Telecon was held between the Agency and the Applicant which occurred prior to the finalization of the statistical analysis plan for Study 3201 and prior to the database lock and unblinding of Study 3201 which occurred on 12/12/12. During this Telecon, there was no

agreement on the primary endpoint, and no change in the Agency's position that it should be a clinically meaningful endpoint.

A pre-NDA meeting was held on 2/21/13 to discuss the contents and format of the NDA submission.

Additionally, the Applicant was also developing tasimelteon for major depressive disorder under IND 112,702. One phase IIB/III study has been conducted for this IND. The study report is not completed and is not included in this NDA for Non-24 Hour Disorder.

2.6 Other Relevant Background Information

There was no other relevant background information for this application.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In conducting the review of this application, I assessed the consistency of the relevant data contained in this application by an audit. I audited the safety database, comparing the information in the Case Report Forms and other source documents (such as laboratory test reports) to the corresponding narrative summaries for individual subjects, and datasets. Other than a few minor discrepancies, I did not see any systematic problem between the source data and the transcribed data that has the potential to undermine the integrity and reliability of the integrated data analyses.

3.2 Compliance with Good Clinical Practices

The Applicant states that "to the best of our knowledge, the studies submitted in this application were designed to ensure adherence to Good Clinical Practice 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, four sites in the two efficacy studies supporting the proposed indication were selected for inspection. The Office of Scientific Investigations performed inspections and data audit, and concluded that the data in support of clinical efficacy and safety at all the four sites inspected are considered reliable.

3.3 Financial Disclosures

The Applicant has submitted Form 3454 in which Paolo Baroldi, MD, PhD, Chief Medical Officer, 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 (the Applicant provided a listing of all investigators and all clinical studies they participated in) did not have financial interests as defined in 21 CFR 54.2(b).

The Applicant provided a list of investigators (principal and sub-investigators) that participated in following legacy clinical studies of tasimelteon that were conducted by Bristol-Meyers Squibb: CN116-001, CN116-002, CN116-003, CN116-004, and CN116-005. The Applicant states that all of the studies, except for CN116-005, were conducted prior to February 2, 1999 when the regulation to collect financial disclosure documents was promulgated. None of these studies were conducted to demonstrate the efficacy of tasimelteon in Non-24-Hour Disorder in the totally blind, and Study CN116-005 was terminated early. Reviewer's comments: These studies did not directly contribute to the efficacy evaluation of tasimelteon in patients with Non-24 Hour Disorder.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The to-be-marketed drug product is a Size 1, dark blue opaque, hard gelatin capsule printed with "VANDA 20 mg" in white, containing 20 mg of tasimelteon per capsule. This 20 mg capsule formulation was used in the majority of the clinical pharmacology as well as the Phase II and III studies and is the formulation proposed for marketing.

There are no major Chemistry, Manufacturing and Control issues to preclude approval.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

There are no major Pharmacology/Toxicology issues to preclude approval.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Tasimelteon is a dual melatonin receptor agonist with specific affinity to the MT1 and MT2 receptors. All of tasimelteon's main metabolites (M3, M9, M11, M12, M13, and M14) bind to the melatonin receptors but with less affinity than the parent.

4.4.2 Pharmacodynamics

The study design of pharmacodynamic studies is discussed in Section 5.3, and results of these studies in Section 7.2.2 of this review.

4.4.3 Pharmacokinetics

Clinical pharmacology studies demonstrated that the pharmacokinetics of tasimelteon is linear over single doses ranging from 1 to 300 mg.

Based on pharmacokinetic parameters from 115 subjects in 5 studies, the Applicant concludes that tasimelteon 20 mg has a mean C_{max} of 235 ± 128 ng/mL which occurred at a median T_{max} of 0.50 hours, a mean AUC of 411 ± 328 h×ng/mL, and mean t_{1/2} of 1.32 ± 0.43 hours. The pharmacokinetics of tasimelteon and its metabolites did not change with time during repeated dosing of tasimelteon for 15 days.

CYP1A2 and CYP3A4 are the major isozymes involved in the metabolism of tasimelteon. In Study 1111, inhibition of CYP1A2 by treatment with fluvoxamine resulted in an 85% decrease in tasimelteon clearance leading to a 6.5-fold increase in exposure. Studies 1107 and 1112 show that the exposures to tasimelteon and its main metabolites are affected by the induction of CYP1A2 (e.g. cigarette smoking) and/ or CYP3A4/2C19 (e.g. rifampin). Cigarette smoking decreased exposure (AUC) by approximately 40%. Rifampin, a strong CYP3A4 and moderate CYP2C19/2C9 inducer, reduced the exposure to tasimelteon by approximately 90%. The clinical pharmacology review team recommends contraindicating concomitant administration of moderate and strong CYP1A2 inhibitors, and moderate and strong CYP3A4 inducers.

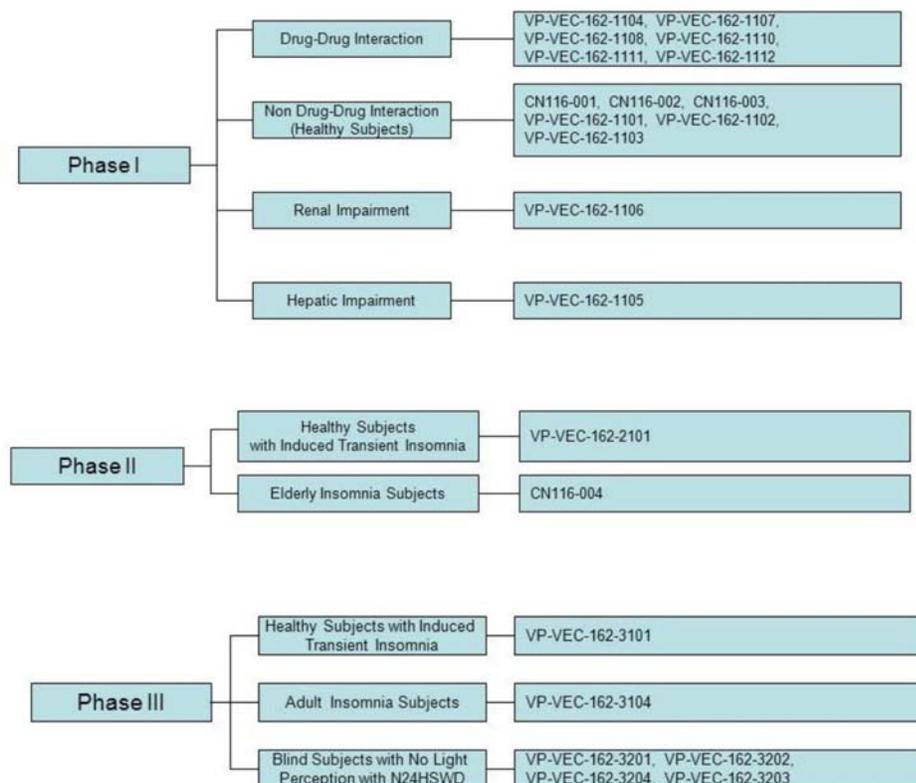
5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The primary source of the clinical data is the database contained in the original NDA submission and subsequent amendments to the NDA including those that were in response to requests for additional information and analyses from reviewers during the review process.

There were a total of 22 clinical studies in the clinical development program. These 22 studies include 14 Phase I studies, 2 Phase II studies and 6 Phase III studies. Four studies (VP-VEC-162-3201, VP-VEC-162-3202, VP-VEC-162-3203 and VP-VEC-162-3204) were conducted in the target population – subjects with Non-24 Hour Disorder. Twenty of the 22 studies have been completed. The remaining two studies are open-label safety studies (VP-VEC-162-3202 and VP-VEC-162-3204) in subjects with Non-24 Hour Disorder which are ongoing. The following Figure provides an overview and listing of these 22 clinical studies.

Figure 1: Listing of clinical studies in the clinical development of tasimelteon.



Source: NDA 205677, 5/31/13: Module 5.35.3 ISS – Integrated Summary of Safety, Appendix 1 – Statistical Analysis Plan, Figure 1, p 9.

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The individual clinical studies, population enrolled, study design, dose used and duration of each study are listed in the following Table.

Table 1: Brief description of individual clinical studies in the development program

Protocol No. Study Start - Stop Date	Population	Study Phase	Study Objective	Study Design	Total Enrollment/ Total Treated	Age Range (years)	Dose	Duration of Treatment*
CN116-001 24Mar1998-08May1998	Healthy Subjects	I	Safety and Tolerability	R, DM, PC, sequential, escalating single dose	48/48	18-44	QD: VEC 1mg, 3mg, 10mg, 30mg, 100mg, 300mg, placebo	1 d
CN116-002 11May1998-27Aug1998	Healthy Subjects	I	Safety and Tolerability	R, DM, PC, sequential, escalating multiple dose	37/32	23-41	QD: VEC 1mg, 10mg, 50mg, 150mg, placebo	28 d
CN116-003 08Feb1999-14May1999	Healthy Subjects	I	Age and Gender effect on PK	R, DM, PC, parallel, 2-period XO, single dose	40/40	25 - 83	QD: VEC 50mg, placebo	1 d
CN116-004 22Sept1998-15Mar1999	Insomnia Patients	II	Safety and Efficacy	R, DM, PC, parallel	347/227	65-92	QD: VEC 1mg, 10mg, 50mg, placebo	4w: DM 1w: SM
VP-VEC-162-1101 10Oct2006-20Oct2012	Healthy Subjects	I	ADME	OL,	6/6	20-26	QD: VEC 100mg	1 d
VP-VEC-162-1102 25Jan2007-10Feb2007	Healthy Subjects	I	Food effect	OL, R, 2-period, 2-sequence XO single dose	26/26	18-49	QD: VEC 100mg	1 d
VP-VEC-162-1103 22Jun2007-16Jul2007	Healthy Subjects	I	Thorough ECG effect	DM, R, 4-period XO multiple dose	44/44	18-44	QD: VEC 20mg, VEC 300mg, moxifloxacin 400 mg, placebo	3 d
VP-VEC-162-1104 26Oct2007-18Nov2007	Healthy Subjects	I	Drug interaction with midazolam	OL, single-sequence, multiple dose	24/23	19-51	QD: VEC 100mg, midazolam 10mg	7 d
VP-VEC-162-1105	Hepatically impaired and Healthy Subjects	I	PK	OL, parallel, single dose	Mild: 8/8 Moderate: 8/8 Healthy: 13/13	46-62	QD: VEC 20mg	1 d
VP-VEC-162-1106	Renally impaired and Healthy Subjects	I	PK	OL, parallel single dose	ESRD: 8/8 Severe: 8/8 Healthy: 16/16	34-74	QD: VEC 20mg	1 d
VP-VEC-162-1107	Healthy Subjects	I	PK, safety, tolerability	OL, Parallel single dose	Young Smokers: 24/24 Young Non-smokers: 24/24 Elderly non-smokers: 12/12	Young: 18-50 Elderly: 65-76	QD: VEC 20mg	1 d
VP-VEC-162-1108	Healthy Subjects	I	PD and PK interactions of drug with ethanol	R, DM, 4-period XO,	28/28	25-54	QD: VEC 20mg + Placebo ethanol, ethanol 0.6 g/kg (females)/0.7 g/kg (males) + placebo VEC, VEC 20mg + ethanol 0.6g/kg (females)/0.7g/kg (males), placebo VEC + placebo ethanol	1 d

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Protocol No. Study Start - Stop Date	Population	Study Phase	Study Objective	Study Design	Total Enrollment/ Total Treated	Age Range (years)	Dose	Duration of Treatment ^a
VP-VEC-162-1110	Healthy Subjects	I	Drug interaction with CYP3A4 and CYP2C8 Enzymes	OL, single-sequence, multiple dose	24/24	22-54	QD: VEC 20mg, midazolam 10mg, rosiglitazon 4mg	14-16 d
VP-VEC-162-1111	Healthy Subjects	I	Drug interaction with CYP1A2 inhibitor	OL, single-sequence, single dose	24/24	19-55	QD: VEC 5mg, fluvoxamine 50mg	1 d
VP-VEC-162-1112	Healthy Subjects	I	Drug interaction with CYP3A4 inhibitor (cohort 1) and CYP3A4 inducer (cohort 2)	OL, single-sequence, single dose	Cohort 1: 24/24 Cohort 2: 24/24	Cohort 1: 18-55 Cohort 2: 20-51	QD: VEC 20mg, ketoconazole 400mg, rifampin 600mg	1 d
VP-VEC-162-2101 14Jul2004-30Mar2005	Healthy Subjects	Ila	the effects of VEC-162 on circadian rhythm	R, DM, PC, parallel	45/39	18-50	QD: VEC 10mg, 20mg, 50mg, 100 mg, placebo	3 d
VP-VEC-162-3101 09Feb2006-21Aug2006	Healthy Subjects with Induced Transient Insomnia	III	Efficacy and safety	R, DM, PC, parallel	412/411	21-50	QD: VEC 20mg, 50mg, 100 mg, placebo	1 d
VP-VEC-162-3104 18Oct2007-13Mar2008	Patients with Primary Insomnia	III	Efficacy and safety	R, DM, PC, parallel	322/321	18-64	QD: VEC 20mg, 50mg, placebo	5 w
VP-VEC-162-3201	Totally Blind Subjects with N24HSWD	III	Efficacy and safety	R, DM, PC, parallel, with OL arm	96/138	21-74	QD: VEC 20mg, placebo	DM: 26 w SM: 2 w OL: 26 w
VP-VEC-162-3202	Totally Blind Subjects with N24HSWD	III	Safety	OL	ongoing	18-75	QD: VEC 20mg	52 w + 52w extension
VP-VEC-162-3203	Totally Blind Subjects with N24HSWD	III	Maintenance effect	RW, DM, PC, parallel	58/58	21-76	QD: VEC 20mg, placebo	Run-in: 12 w RW: 8 w
VP-VEC-162-3204	Totally Blind Subjects with N24HSWD	III	Safety	OL	Ongoing	21-76	QD: VEC 20mg	24 m

Source: NDA 205677, 5/31/13: Module 5.35.3 ISS – Integrated Summary of Safety, Appendix 1 – Statistical Analysis Plan, adapted from Table 1, pp 13-16.

5.2 Review Strategy

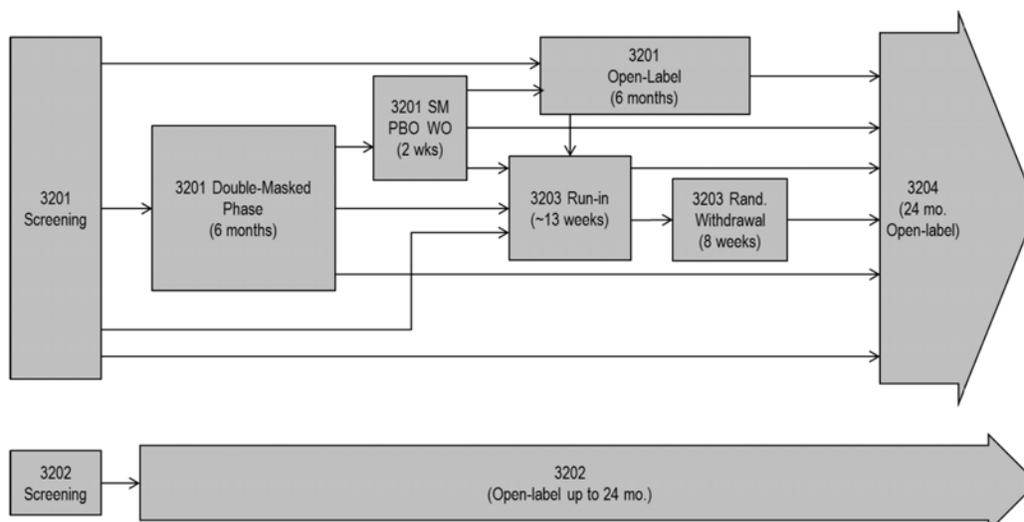
The Applicant submitted the NDA and subsequent amendments using the eCTD format, which was accessed through the GlobalSubmit Review application. Although the primary source of the clinical data was the NDA submission and the subsequent amendments, I also reviewed secondary sources of clinical data (i.e., relevant labels and published medical textbooks and literature) in assessing the safety and efficacy of tasimelteon.

5.3 Discussion of Individual Studies/Clinical Trials

As stated above, 4 studies (VP-VEC-162-3201, VP-VEC-162-3202, VP-VEC-162-3203 and VP-VEC-162-3204) were conducted in the target population, i.e., subjects with Non-24 Hour Disorder. In this review, these 4 studies will be referred to (and used interchangeably) as Study 3201, Study 3202, Study 3203 and Study 3204, respectively. Additionally, Study 3201 is also referred to as the SET study, and Study 3203 as the RESET study. Study 3201 was a multinational (US and Germany), randomized, double-blind, placebo-controlled, parallel group design, and Study 3203 was a randomized, placebo-controlled withdrawal design conducted in the US; together, these two studies provided data to support the efficacy of tasimelteon in subjects with Non-24 Hour Disorder. The remaining 2 studies (Study 3202 and Study 3204) are ongoing open-label studies in subjects with Non-24 Hour Disorder. Study 3202 is being conducted in France, and Study 3204 in both US and Germany.

Subjects with blindness who were screened at the beginning of Study 3201 and were eligible for randomization after completing the Pre-Randomization Phase were randomized to tasimelteon or placebo groups (double-blind period for 6 months), and following completion of the double-blind period were given the option to participate in Study 3203 or Study 3204. Other subjects who were screened in Study 3201 and were ineligible for randomization, could enroll in the open-label extension (6 months) of Study 3201, or in Study 3203 (if all eligibility criteria were met), or in the open-label Study 3204. Subject enrollment in the open-label Study 3202 was mutually exclusive to the other 3 studies. The following Figure illustrates the flow of subject participation in these 4 studies.

Figure 2: Tasimelteon clinical study program in subjects with Non-24 Hour Disorder



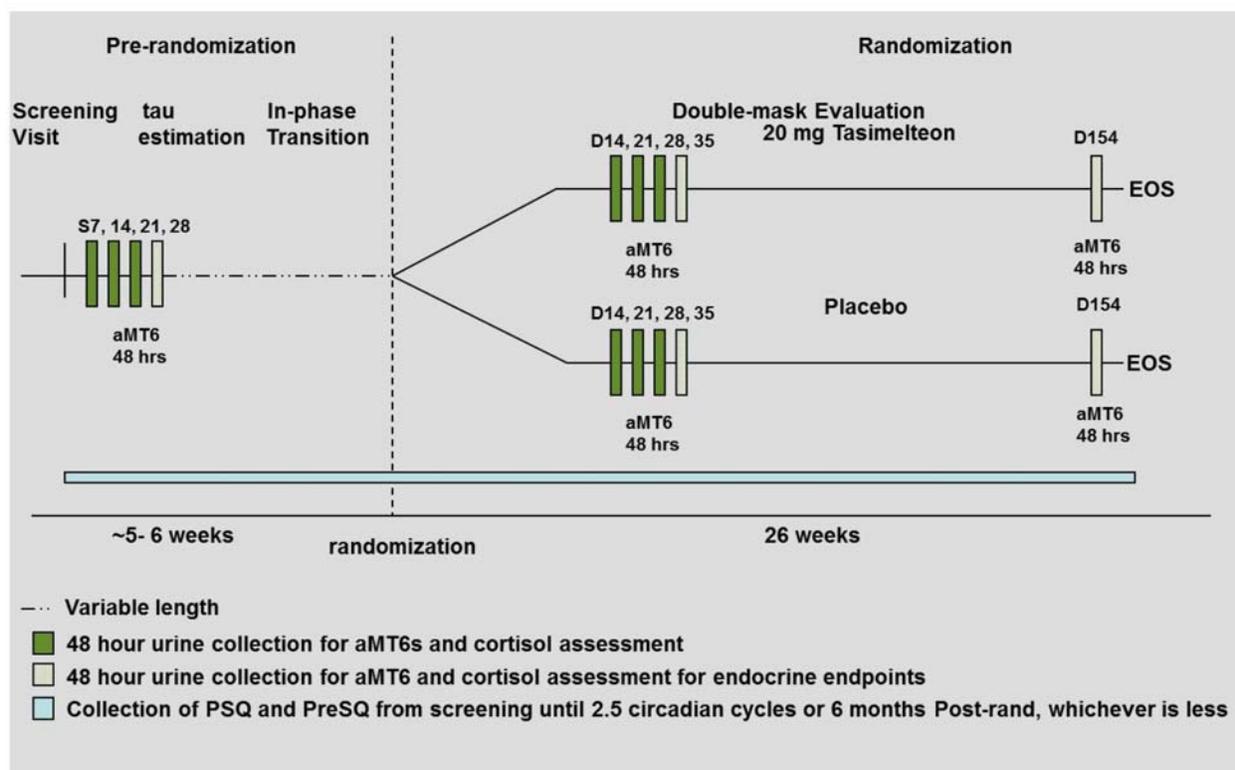
Note: In Germany, subjects who completed the Pre-Randomization Phase entered the Randomization Phase (26 weeks) which was followed by a single blind placebo washout segment (2 weeks); subjects completing this phase of the study were allowed to participate in the optional open-label extension phase, enroll in Study 3203 or Study 3204.
PBO=placebo.

Source: NDA 205677, 5/31/13: Module 5.35.3 ISS – Integrated Summary of Safety, Appendix 1 – Statistical Analysis Plan, Figure 2, p 20.

The individual studies which supported the efficacy of tasimelteon in Non-24 Hour Disorder are discussed further in this section of this review.

Study 3201 (VP-VEC-162-3201; also referred to as the **SET** study) was a randomized, double-blind, placebo-controlled, parallel group study of tasimelteon 20 mg versus placebo in 84 totally blind subjects with non-24 disorder (tasimelteon 42; placebo 42). This study was conducted in 27 centers in the US (n = 76) and 6 centers in Germany (n = 8). The study design is summarized in the following figure. Study 3201 consisted of the Pre-Randomization Phase (approximately 5-6 weeks) which was followed by the Randomization Phase (26 weeks).

Figure 3: Study 3201 design



In Germany, subjects who completed the Pre-Randomization Phase entered the Randomization Phase (26 weeks) which was followed by a single blind washout segment (2 weeks) when the Benzodiazepine Withdrawal Symptom Questionnaire and the Pre-sleep Questionnaire were administered; subjects completing this phase of the study were allowed to participate in the optional open-label extension (OLE; 26 weeks) phase, or enroll in Study 3203 or Study 3204. Earlier versions of the US protocol, i.e., earlier than US Version 6 (8/8/11), also allowed a 2-week washout period.

Source: NDA 205677, 5/31/13: Module 2.7.3 Summary of Clinical Efficacy, Figure 6, p 28.

The Pre-Randomization Phase consisted of the Screening Visit, τ estimation segment and a variable-length in-phase transition segment. During the τ estimation segment, urine samples were collected over a 48 hour period every week for 4 weeks to calculate the τ (see next section of this review for details). The purpose of the Pre-randomization phase was to allow time for the subject's circadian rhythm to be aligned with the subject's target bedtime, as assessed by urinary 6-sulfatoxymelatonin (aMT6s) rhythms (see next section for details). The Applicant states that studies with melatonin have shown that entrainment of blind subjects suffering from Non-24

Hour Disorder may be more likely to occur, and may occur more quickly, if treatment is started in the phase advance portion of the melatonin Phase Response Curve (i.e., the time when a subject's endogenous circadian rhythm is coming into alignment with their bedtime). Based on these data, the duration of an eligible subject's in-phase transition was varied such that randomization and start of study drug dosing was in the phase advance portion of the Phase Response Curve relative to the subject's circadian rhythm. Thus, randomization was done on a day when the subject's acrophase was predicted to occur 3.5 hours before the end of the 9-hour scheduled sleep opportunity. Electronic sleep diary (see next section of this review for details) was reported via Interactive Voice Recording System (IVRS) twice a day during the Pre-randomization and Randomization phases. Urine samples were also collected over a 48 hour period every week for 4 weeks to calculate the τ in the Randomization phase.

Randomization was centrally performed through the IVRS system in blocks of size 4 (each block of 4 contained 2 from each treatment group in random order), and was not stratified by study site.

Key Inclusion Criteria:

- Men or women between 18-75 years of age, inclusive, with no perception of light, and a Body Mass Index (BMI) of ≥ 18 and ≤ 33 kg/m²;
- τ length of ≥ 24.25 hours with lower bound of 95% CI > 24.0 and the upper bound of 95% CI < 24.9 based on urinary aMT6s rhythms. In the original protocol, one of the inclusion criteria was based on a point estimate of the τ . After screening a number of subjects, the Applicant states that it became apparent that utilizing the τ point estimate alone for the inclusion and exclusion criteria was not sufficient to accurately evaluate circadian period and that including the 95% confidence interval provided assurance that individuals with the appropriate τ were randomized. Specifically, a lower bound > 24.1 hours insured that all subjects enrolled could be diagnosed with Non-24 unequivocally.
- Diagnosis of Non-24 Hour Disorder as determined by:
 - History (within the last 3 months) as determined by answering 'yes' to at least one question in the Sleep Complaint Questionnaire (see table below) and urinary aMT6s demonstrating a progressive delay of the aMT6 acrophase.

Table 2: Sleep complaint questionnaire

1.	Within the last 3 months, did you have problems falling asleep?
2.	Within the last 3 months, after falling asleep, did you have problems staying asleep?
3.	Within the last 3 months, did you have problems waking up in the morning?
4.	Within the last 3 months, did you have problems staying awake during the day?
5.	Within the last 3 months, did you nap during the day because of excessive sleepiness?
6.	Do you go through periods of good sleep and periods of bad sleep?

Source: NDA 205677, 5/31/13; Module 5.35.1 – Study Reports of Controlled Clinical Trials; VP-VEC-162-3201; Sample Case Report Form.

- Males, non-fecund females (i.e., surgically sterilized, if procedure was done 6 months before screening or subject is postmenopausal, without menses for 6 months before screening), or females of child-bearing potential using an acceptable method of birth control.

Key Exclusion Criteria:

- Have a probable diagnosis of a current sleep disorder other than Non-24 Hour Disorder that is the primary cause of the sleep disturbance based on clinical investigator medical judgment;
- 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 shifts during the study;
- History (within the 12 months prior to screening) of psychiatric disorders including major depressive disorder, or any other psychiatric disorder, that is not being successfully treated or has not been resolved and that in the opinion of the clinical investigator would affect participation in the study or full compliance with study procedures;
- Subjects who take NSAIDs daily and would not interrupt their use for the 48-hour urine collections and the 24 hours preceding them;
- History of drug or alcohol abuse as defined in DSM-IV within the 12 months prior to screening; or smoke more than 10 cigarettes/day.
- Subjects who have estimated creatinine clearance ≤ 55 mL/min; impaired liver function (values for AST, ALT or bilirubin > 2 times Upper Limit of Normal); clinically significant deviation from normal in clinical laboratory results, vital signs measurements, or physical examination findings at screening as determined by the clinical investigator;
- Subject is at risk of suicide, in the opinion of the Investigator.

Investigational product: Tasimelteon 20 mg or placebo 1 hour prior to their target bedtime during the Randomization Phase. Placebo capsules were identical to those containing tasimelteon in size and appearance.

Table 3: Schedule of evaluations during randomization phase (Study 3201)

Phase	Randomization Phase					EOS/ED
Segment	Double-Masked Evaluation					
Week	0	4	8	12	16	27
Day	D 0	D 28 ⁶	D 56 ⁶	D 84 ⁶	D 112 ⁶	D 183 ⁶
Visit	2	3	4	5	6	7
Informed Consent Form(s)						
Inclusion/ Exclusion Criteria	X ¹					
Labs (Hematology, Chemistry, and Urinalysis)	X	X	X	X	X	X
Endocrine Testing ²	X	X	X	X	X	X
Menstrual Period Information (WOCBP)	X	X	X ³	X	X ³	X
Serum B-HCG (WOCBP)						X
Urine Pregnancy (WOCBP)	X	X	X	X	X	
PG blood draw						
PSQ	Daily for 2.5 circadian cycles or 6 months, whichever is less					
PreSQ	Daily for 2.5 circadian cycles or 6 months, whichever is less					
IVRS ⁴	X					X
Vital Signs	X	X	X	X	X	X
Physical Examination	X					X
ECG	X	X	X	X	X	X
CGI-C			X		X	X
Randomization	X					
Dispense Study Drug	X	X	X	X	X	
Review drug compliance		X	X	X	X	X
Reminder call ¹¹	As needed					
Adverse event query	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X
Prior/Concomitant Medication	X	X	X	X	X	X
48 hr urine collection ⁵	At D14, D21, D28, D35, and D154 (+ 1 week).					

B-HCG= Human Chorionic Gonadotrophin; WOCBP= women of childbearing potential; PSQ= Post Sleep Questionnaire; IVRS= Interactive Voice Response System; ECG= Electrocardiogram; C-SSRS= Columbia Suicide Severity Rating Scale; EOS= End of study; ED= Early discontinuation; PreSQ= Pre-sleep Questionnaire; CGI-C= Clinical Global Impression-Change.

¹Abbreviated- Only required to document changes.

²Blood draw 1-4 hours after scheduled awakening. ACTH Stimulation Test at D0, D112 and D183 only (Fasting).

³The menstrual cycle information is collected for WOCBP that are not currently using a hormonal method of birth control. Information collected at Visits 4 and 6 will be used to schedule a progesterone blood draw about 3-10 days before the first day of the next expected period.

⁴The IVRS will be used to randomize the subject and to assign a double-masked medication kit on Day 0. The IVRS will also be used to report subject completion or discontinuation.

⁵Subjects will collect sequential urine samples approximately every 4-hours (8-10 hours overnight) for 48 hours. The day prior to the urine collections, the study staff will call the subjects to remind them of the correct procedure and timing of the 48-hour urine collection starting on the following day. AE and concomitant medication information will be collected during each call. .

⁶±3 days

¹¹Study staff will call the subjects prior to each 48-urine collection. AE and concomitant medication information will be collected during each call.

Source: NDA 205677, 5/31/13: Module 5.35.1 – Study Reports of Controlled Clinical Trials; VP-VEC-162-3201, Protocol Amendment 11/US; table 3, page 38.

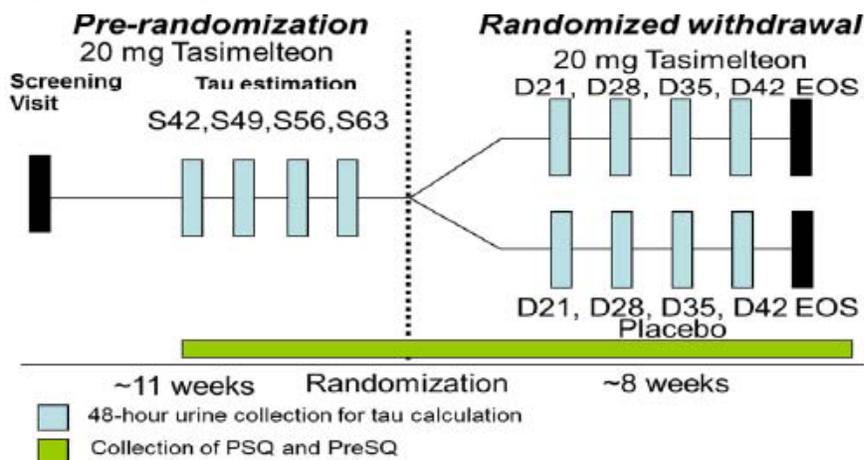
The efficacy endpoints and statistical analyses for Study 3201 are discussed in Section 6 ‘Review of Efficacy’ of this review.

Study 3203 (VP-VEC-162-3203; also known as **RESET** study) was a randomized withdrawal, double-blind, placebo-controlled study in totally blind subjects with non-24 disorder. This study was conducted at 17 investigative sites in the US. Subjects who met the entrance criteria and who had previously participated in, or were screened for, Study 3201 were eligible to participate. The study had 2 phases: a Pre-Randomization Phase (or Run-in Phase) and a Randomized Withdrawal Phase. The Pre-Randomization Phase consisted of an open-label tasimelteon period (all enrolled subjects were treatment with tasimelteon 20 mg) during which the τ was calculated.

After screening, subjects who met all entry criteria for the study entered the tasimelteon Run-in Phase and began tasimelteon 20 mg approximately one hour prior to their target bedtime. τ estimation began after 6 weeks of tasimelteon 20 mg dosing. During the τ estimation period (approximately 5 – 6 weeks), subjects continued to receive tasimelteon 20 mg, completed electronic sleep diaries (see next section of this review for details), and collected urine samples over a 48 hour period every week for 4 weeks (see next section of this review for details).

At the end of the Run-in phase, subjects whose aMT6s τ values indicated entrainment were randomized (1:1) to receive either tasimelteon 20 mg (n = 10) or placebo (n = 10). The Randomized Withdrawal Phase was 8 weeks in duration.

Figure 4: Design of Study 3203



Source: NDA 205677, 5/31/13: Module 2.7.3 Summary of Clinical Efficacy, Figure 8, p 46.

Eligibility criteria: As noted above, subjects who had participated in, or were screened for, Study 3201 and had a $\tau > 24.1$ with a 95% confidence interval that did not include 24.0 were eligible for screening in this study.

Investigational product: Tasimelteon 20 mg (during Pre-randomization and Randomized Withdrawal phases) or placebo (during Randomized Withdrawal phase) approximately 1 hour prior to their target bedtime. Placebo capsules were identical to those containing tasimelteon in size and appearance.

Table 4: Schedule of evaluations during randomization phase (Study 3203)

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Phase	Randomized Withdrawal						EOS/ET
	Week 0	3	4		5	6	
Day	D0	D21	D27	D28	D35	D42	D56 ¹
Visit	V4		V5				V6
Inclusion/exclusion criteria	X ²						
Labs (hematology, chemistry, and urinalysis)	X		X				X
Serum β-HCG (WOCBP)							X
Urine pregnancy test (WOCBP)	X		X				
PSQ and PreSQ	Daily	Daily	Daily	Daily	Daily	Daily	
Interactive Voice Response System	X		X				X
Vital signs	X		X				X
Physical examination	X						X
Electrocardiogram	X		X				X
Randomization	X						
Dispense study drug	X		X				
Review drug compliance	X		X				
Reminder call		X	X	X	X	X	
Adverse event query ³	X	X	X	X	X	X	X
Prior/concomitant medication	X		X				X
48-hour urine collection ⁴		X		X	X	X	
Columbia Suicide Severity Rating Scale	X		X				X
Benzodiazepine Withdrawal Symptom Questionnaire	X ⁵						
Compliance with study drug	X		X				X

β-HCG = beta-human chorionic gonadotropin; EOS = end of study; ET = early termination; PreSQ = Pre-Sleep Questionnaire; PSQ = Post-Sleep Questionnaire; WOCBP = women of childbearing potential.

¹ Patients who discontinued prematurely from the study for any reason were to undergo all procedures and safety assessments detailed for Visit V6 EOS/ET.

² Review of inclusion/exclusion criteria was required only to document any changes.

³ The investigator followed patients with non-serious adverse events that were ongoing at the last study visit until resolution or for 30 days, whichever came first.

⁴ Patients collected sequential urine samples approximately every 4 hours (8 to 10 hours overnight) for 48 hours.

⁵ Questionnaire was administered on Day D0 at the study site, and on Day D1, Day D2, Day D7, and Day D14 by telephone.

Source: NDA 205677, 5/31/13: Module 5.35.1 – Study Reports of Controlled Clinical Trials; VP-VEC-162-3203 Study Report, Table 3, page 23.

The efficacy endpoints and statistical analyses for Study 3203 are discussed in Section 6 ‘Review of Efficacy’ of this review.

The following two studies are ongoing open-label studies in subjects with Non-24 Hour Disorder.

Study 3204 (VP-VEC-162-3204): This study is an ongoing open-label study in subjects with Non-24 Hour Disorder being conducted in the US and Germany. Enrolled subjects are treated with tasimelteon 20 mg, once a day, for up to 2 years. A total of 200 subjects are planned for enrollment; as of the cut-off date (11/30/12) for the integrated safety database, 86 subjects have been enrolled.

Study 3202 (VP-VEC-162-3202): This open-label study is ongoing, and is being conducted in subjects with Non-24 Hour Disorder in France. Enrolled subjects are treated with tasimelteon 20 mg for 52 weeks followed by a 3 year optional sub-study. A total of 140 subjects are planned for enrollment; as of the cut-off date (11/30/12) for the integrated safety database, 49 subjects have been enrolled.

The following two studies were conducted in subjects with primary insomnia.

Study 004 (CN116-004) was a randomized, double-blind, placebo-controlled study of three doses of tasimelteon (1, 10 and 50 mg) versus placebo in 227 *elderly* (≥ 65 years) subjects with primary insomnia. Subjects were randomized (1:1:1:1) to receive either one of the three doses of tasimelteon or placebo. Subjects received four weeks of double-blind treatment (one capsule daily at bedtime) followed by one week of single-blind placebo (to assess withdrawal symptoms or rebound insomnia). Efficacy assessments were based on both subjective patient-diaries and objective polysomnogram which were assessed at Baseline, and Weeks 1, 2, 3, 4 and 5 (Weeks 1 and 4 for polysomnogram).

Study 3104 (VP-VEC-162-3104) was a randomized, double-blind, placebo-controlled, three-arm parallel group study of tasimelteon (20 mg and 50 mg) and placebo for 35 days in 322 subjects, *aged 18-64 years*, with primary insomnia. The study was divided into 2 phases: the pre-randomization phase (screening visit and a 1 week single-blind placebo lead-in that included 2 consecutive nights of polysomnogram assessments) and the randomization phase (5 week double-blind evaluation period and a 1-night single-blind placebo wash-out period). During the double-blind evaluation period, subjects underwent 4 overnight visits (Nights 1, 8, 22, and 29) in which polysomnogram was assessed. Subjects returned to the clinic on Night 36 for an additional night of polysomnogram assessments with single-blind placebo treatment.

The selection of the 20 mg dose for evaluation in clinical studies of Non-24 Hour Disorder was based in part on the results of the following two studies which were conducted in healthy volunteers (see Section 7.2.2 ‘Explorations for Dose Response’ of this review).

Study 2101 (VP-VEC-162-2101) was a randomized, double-blind, placebo-controlled study which assessed 4 doses of tasimelteon (10, 20, 50 or 100 mg) versus placebo in 39 healthy male and female subjects. During Study Days 1 – 3, eligible subjects were given placebo 30 minutes prior to bedtime (11:00 PM) in a single-blind fashion. At 5:00 PM on day 3, subjects started a 19 hour Pre-constant posture segment during which time subjects remained seated in a semi-recumbent position and blood samples were collected approximately every hour to assess each subject’s circadian phase before the start of next phase of study (i.e., sleep advancement). On Study Day 4, subjects were randomized (1:1:1:1) into one the above treatment groups, and on each Study Days 4, 5 and 6, subject sleep-wake routines were advanced 5 hours (subjects were required to sleep from approximately 6:00 PM – 2:00 AM) and treatment administered at 5:30 PM. Blood samples were drawn at specific intervals to assess the circadian phase. The purpose of this study was to investigate the exposure-response to tasimelteon on induction of an advance in the circadian melatonin rhythm as measured by Dim Light Melatonin Onset.

Study 3101 (VP-VEC-162-3101) was a multicenter, randomized, double-blind, placebo-controlled study which assessed the efficacy and safety of a *single* dose of tasimelteon 20, 50 or 100 mg versus placebo in 411 healthy male and female subjects with induced transient insomnia. The study was conducted in a sleep laboratory and transient insomnia was induced via circadian rhythm disruption by a 5-hour bedtime advance. Eligible subjects were randomized (1:1:1:1) into one of the above treatment groups. Polysomnogram was administered, and the polysomnogram-

derived Latency to persistent sleep was the primary endpoint. Secondary endpoints included PSG-derived Wake after sleep onset, defined as the time spent awake between onset of sleep and lights on during Night 1, sleep efficiency, and total sleep time.

6 Review of Efficacy

Efficacy Summary

Applicant's Efficacy Conclusions:

Tasimelteon is a circadian regulator that entrains the master body clock in totally blind patients with Non-24 Hour Disorder. Treatment with 20 mg of tasimelteon one hour before bedtime at approximately the same time every night for 26 weeks entrained circadian rhythms to the 24-hour day and stabilized the sleep-wake cycle. Treatment with tasimelteon significantly increased the lower quartile of nighttime sleep duration and decreased the upper quartile of daytime sleep duration in patients with Non-24. Tasimelteon numerically improves nighttime sleep and decreases daytime nap duration. Tasimelteon significantly improves the timing of sleep relative to the desired bedtime. Tasimelteon is significantly efficacious in treating Non-24 Hour Disorder as measured by clinically meaningful improvement in the Non-24 Clinical Response Scale. Treatment with 20 mg of tasimelteon for 26 weeks significantly improves global functioning as measured by the Clinical Global Impression-Change (CGI-C). Tasimelteon treatment is necessary for entrainment, maintenance of entrainment, and for maintenance of clinical benefits in sleep and wake measures. Development of tolerance to tasimelteon response was not observed. These results support the use of tasimelteon in the treatment of circadian rhythm disorders in patients with Non-24 Hour Disorder who are totally blind.

Reviewer's Efficacy Conclusions:

There were no *pre-specified* primary *clinical* endpoint(s), which by itself (themselves), capable of directly assessing clinical benefit (i.e., how a patient feels or functions) in either Study 3201 or Study 3203 in subjects with Non-24 Hour Disorder (the target population). The pre-specified step-down primary endpoint in Study 3201 combined entrainment with some clinical endpoints; with the exception of Midpoint of Sleep Timing (MoST) endpoint (unknown clinical meaningfulness), these clinical endpoint, by themselves, could support clinical benefit but their use as stand-alone primary endpoint(s) was not pre-specified.

There was a prior agreement between the Agency and the Applicant that nighttime sleep and daytime naps were the two most important direct measures of clinical benefit in Non-24 Hour Disorder. The Agency expressed openness in considering endpoints that looked at 'worst few days' in each cycle to help decrease the effect of random variability. The Applicant chose the Lower Quartile of nighttime Total Sleep Time (LQ-nTST) for the "worst night analysis" after determining that LQ-nTST was highly correlated with the phase of the circadian cycle that is 180° out of alignment with the 24-hour day, and therefore was more specific and appropriate in this remitting and relapsing disorder. The Upper Quartile of daytime Total Sleep Duration (UQ-

dTSD) was chosen for similar reasons. LQ-nTST and UQ-dTSD are, therefore, appropriate clinical endpoints for evaluation of an effect in Non-24 Hour Disorder.

Analyses of efficacy data conducted by the Agency reveal statistical significance in favor of tasimelteon 20 mg for the clinical endpoints, LQ-nTST, UQ-dTSD, dTSD and CGI-C, in both Study 3201 and Study 3203 in the target population. There was no statistical significance for nTST in either study, and may reflect the expected increase in variability of this measure in a disorder where extreme values likely occur during periods of maximum alignment and maximum misalignment. Compared to the placebo group, there was a numerical advantage for nTST in the tasimelteon group in both Study 3201 and Study 3203.

Choosing clinical outcome(s) such as the LQ-nTST and UQ-dTSD post-hoc to establish efficacy in Study 3201 or Study 3203 risks inflation of Type I error in either study. However, the risk of false discovery in this application is diminished by independent substantiation with statistical significance for the clinical endpoints, LQ-nTST, UQ-dTSD, dTSD and CGI-C, in both Study 3201 and Study 3203.

The visual assessment of benefit on the cyclical nature of the nighttime and daytime sleep using the graphical representation in individual subjects over time (although such assessment is subjective in nature), the statistically significant effect favoring tasimelteon on MoST, and importantly, the statistically significant effect favoring tasimelteon on the absolute value of the difference of between In-phase and Out-of-Phase for cycle 1 and 2 post-randomization, indicate a specific effect of tasimelteon on the cyclical nature of Non-24 Hour Disorder.

6.1 Indication

6.1.1 Methods

The design of Study 3201 and Study 3203 were discussed in Section 5.3 of this review. The efficacy measures and results are discussed in this section.

Clinical Endpoints

The following clinical endpoints were assessed in Study 3201.

Nighttime Total Sleep Time (nTST) and Lower Quartile of nTST (LQ-nTST):

Subjects were instructed to report all sleep that occurred during the 10-hour interval between their scheduled nightly dosing until their predefined wake-time as nTST. *Post sleep questionnaire* (PSQ) – the *morning* electronic diary, was used to assess nTST. Subjects were instructed to call the Interactive Voice Recording System (IVRS) and answer the PSQ questions no later than 1 hour after their scheduled awakening. In Study 3201, subjects called the IVRS every day throughout the variable duration of the pre-randomization phase, and daily for two and half circadian cycles or 6 months post-randomization whichever was less during the

randomization phase. The IVRS asked the subjects to answer the following PSQ questions when they called in the morning after awakening:

- Q1. Did you sleep last night? If the answer was ‘yes’, subject was asked Q2.
- Q2. What time did you go to bed? (Subjects were asked to enter values for hours first followed by minutes)
- Q3. How long do you think it took you to fall asleep?
- Q4. How many times did you wake up during the night?
- Q5. How much time did you spend awake after falling asleep?
- Q6. What time did you wake up for the day?
- Q7. How many hours did you sleep last night?
- Q8. How would you describe the overall quality of your sleep last night? (1-excellent; 2-good; 3-fair; and 4-poor)

Patients suffering from Non-24 Hour Disorder may have intervals of trouble sleeping as a result of their circadian sleep cycle being out of synchrony with the 24 hour clock, and intervals of good sleep when their circadian sleep cycle is synchronous with the 24 hour clock. The originally proposed primary endpoint was nTST. However, the Agency did not agree to this endpoint as it is often used in insomnia trials to capture a soporific effect. Therefore, the Applicant chose the LQ-nTST for the “worst night analysis”. The Applicant determined that LQ-nTST was highly correlated with the phase of the circadian cycle that is 180° out of alignment with the 24-hour day, and therefore was more specific and appropriate in this cyclical disorder. During the End-of-Phase 2 meeting (1/6/11), in response to the Applicant’s proposal to use worst night analysis using LQ-nTST, the Agency expressed openness to considering a clinical endpoint that evaluated the worst few nights to help decrease the effect of random variability.

In order to calculate the LQ-nTST in a given subject, all non-missing values (must include > 70% of 1 circadian cycle of nTST data for both baseline and randomized data) of nTST time are ordered from smallest to largest. The first 25% of the records were flagged as belonging to the LQ-nTST, and the average of these values was calculated.

Daytime Total Sleep Duration (dTSD) and Upper Quartile dTSD (UQ-dTSD):

Naps were defined as any sleep event that lasted ≥ 5 minutes occurring during the 14-hours between a subject’s scheduled wake time and daily dosing time. The ***Pre sleep questionnaire*** (Pre-SQ) – the *evening* electronic diary, was used to assess the number of naps and the total amount of dTSD. Subjects were instructed to call the IVRS no later than 15 minutes after daily dosing time to answer the Pre-SQ questions. As in PSQ, subjects called the IVRS every day throughout the variable duration of the pre-randomization phase, and daily for two and half circadian cycles or 6 months post-randomization whichever was less during the randomization phase. The IVRS asked the subjects to answer the following Pre-SQ questions when they called after daily dosing at bedtime:

- Q1. Since your scheduled wake up time, how many naps did you take today? If the answer was ‘> 0’, subject was asked Q2.

- Q2. For Nap number 1, what time did the nap start?
- Q3. For Nap number 1, how long did it last?
- Q3. For Nap number 2, what time did the nap start?
- Q4. For Nap number 2, how long did it last?
- Q5.For each nap, two questions were asked as above.

The Applicant considered the UQ-dTSD as being specific to assess the daytime naps/sleep that tend to occur particularly when a subject's circadian rhythms are out of phase with the 24 hour day and when affected subject may experience a strong urge to nap during the daytime.

Reviewer's comments: Similar to LQ-nTST, a benefit on the UQ-dTSD is also expected to be reflective of an effect on the above noted periodic misalignment between the circadian period and the external 24-hour clock.

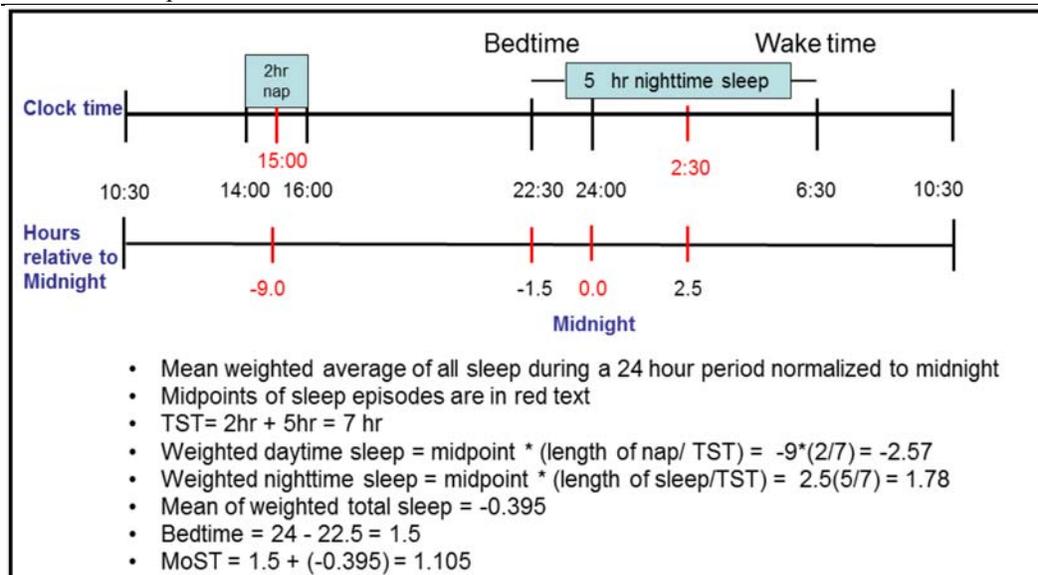
In order to calculate the UQ-dTSD in a given subject, all non-missing values of daytime nap durations were summed for a given day (days for which an individual reported no naps were recorded as 0) and then these daily summations were ranked from largest to smallest. The first 25% of the records were flagged as belonging to the UQ-dTSD, and the average of these values was calculated.

In Study 3203, subjects began calling the IVRS twice a day to complete the morning electronic diary (PSQ) and the evening electronic diary (PreSQ) starting at the beginning of the first day of 48-hour urine collection in the Run-in phase and continuing through the end of the Randomized Withdrawal phase (8 weeks).

Midpoint of Sleep Timing (MoST):

MoST is the mean weighted average of all sleep during a 24 hour period (daytime naps and nighttime sleep), the midpoint of which is normalized to midnight. Patients with Non-24 Hour Disorder typically get the same amount of sleep on average every day although displaced on days when they are out of phase compared to days when they are in-phase. MoST measurement for a calendar day was derived from the Total Sleep Time for the 24-hour day reported in both the Pre-SQ and PSQ. The midpoint of sleep over a calendar day (from -12 hours before designated bedtime until +12 hours after bedtime) was calculated for each day. The total 24-hour sleep time was summed over all sleep episodes in a 24-hour period (i.e., both the nighttime sleep as well as the daytime naps). Each of the individual sleep episodes was then assigned a weight relative to the fraction of 24-hour sleep that it contained. An example of MoST calculation is provided in the Figure below. The average for each daily value for MoST was then compared between screening and post randomization. An individual, who sleeps 8 hours from 10 PM (desired bedtime) to 6 AM and does not have any daytime naps, will have MoST value of 4.0. The average MoST value will trend toward 0 or a negative number as an individual's sleep becomes more fragmented and distributed throughout a 24 hour day.

Figure 5: Calculation of MoST



Source: NDA 205677, 5/31/13: Module 2.7.3 Summary of Clinical Efficacy, Figure 5, p 21.

Clinical Global Impression-Change (CGI-C):

The CGI-C is a 7 point rating scale where Investigators rated the subjects' improvement in symptoms relative to the start of the study. It was 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. This questionnaire was administered to subjects at Baseline and at multiple time points during the treatment phase. To establish a baseline for the CGI-C, the clinician was instructed to:

- Utilize the Sleep Complaint Questionnaire (see Table 2) as a basis for interview and expand on target symptoms for subject and overall sleep/wake history.
- Briefly document in source documents the basic sleep/wake profile and effect of insomnia and/or excessive daytime sleepiness on relationships, ability to do daily tasks, and their job.

Reviewer's comments: CGI-C as an endpoint is not optimal, since a subject's condition is best represented by a report of the subject himself or herself, and not by a proxy such as the clinician.

Biomarker endpoint:

The circadian period (τ) is the time taken to complete one cycle of a circadian rhythm, and is measured from a fixed point within a single cycle, usually peak or trough, to the same fixed point of the next cycle. The peak of a rhythm fitted using a sine function is termed the *acrophase*. As noted earlier, peak melatonin metabolite concentration in the urine occurs about 3.5 hours prior to waking.

τ was calculated by assessing the peak production of aMT6 (major urinary metabolite of melatonin) and cortisol in urine. Subjects collected sequential urine samples approximately every 4 hours during the day and over an 8 to 10-hour period in the night for 48 hours, and recorded the

time of each urine void. At each time point, aMT6 and cortisol were measured in the urine and expressed as rate of secretion (nanograms) per hour. These 48-hour sequential urine samples were collected every week beginning at the Study Days 7, 14, 21 and 28 in the Pre-randomization phase, and at Study Days 14, 21, 28, 35 and 154 of the Randomization phase of Study 3201. From the rate of aMT6 secretions at each time point over a given 48-hour period, a central aMT6s scorer calculated the time of aMT6s peak (acrophase of fitted sine function) at multiple different weeks for each subject, and these data were used to calculate the aMT6's rhythm τ for that subject. The τ was used to determine a given subject's eligibility for the Randomization phase and to predict when a subject's circadian rhythm will be in phase with the subject's preferred timing of sleep. A subject's circadian rhythm was considered to be in phase when the aMT6s acrophase is predicted to occur 3.5 hours before the end of the 9-hour scheduled sleep opportunity.

Reviewer's comments: τ is a biomarker which is used in the diagnostic evaluation of disorders of melatonin rhythms such as Non-24 Hour Disorder; however, it is not a validated surrogate marker that can be used in lieu of primary clinical outcomes. Approval of a drug under Section 505(b)(1) is based on efficacy data on appropriate clinical outcome(s), or on a validated surrogate marker. In the regulatory context, a validated surrogate marker, is one for which there has been a consistent demonstration of a beneficial quantitative relationship between it and the desired clinical outcome(s) across many clinical *trials* and across many *drugs*. For example, such a relationship exists between surrogate markers, blood pressure and serum cholesterol, and clinical outcomes of interest (heart attack, stroke, death, etc).

6.1.2 Demographics

Study 3201: The database lock date for Study 3201 was 12/12/12. Subjects were fairly evenly matched between treatment groups with respect to age, gender, race, weight, body mass index, and τ . Most subjects were between 41 to 65 years old (mean 50.7 years). While the *mean* of LQ-nTST was evenly balanced between the treatment groups, the *median* of LQ-nTST was higher in the tasimelteon group (3.383 hours) by 0.4 hours compared to the placebo group (2.982 hours). There was a 0.24 hour difference between the *mean* UQ-dTSD in the placebo [2.533 (SD 1.7084) hours] and tasimelteon [2.290 (SD 1.6558) hours] groups; the *median* of UQ-dTSD was evenly balance between the treatment groups.

Non-24 patients in Study 3201 had a mean τ of 24.45 hours; majority had a cycle length between 40 and 80 days. During the 3201 study, subject diaries were recorded for an average of 88 days prior to randomization and 133 days during randomization

Study 3203: The database lock date for Study 3203 was 1/16/13. As noted previously, subjects who had previously participated in, or were screened for, Study 3201 were eligible to participate. Baseline data was collected during the tasimelteon open-label run-in phase. Considering the relatively small number of subjects in each treatment group, subjects were fairly evenly matched between treatment groups with respect to age, gender, race, body mass index, *mean* LQ-nTST,

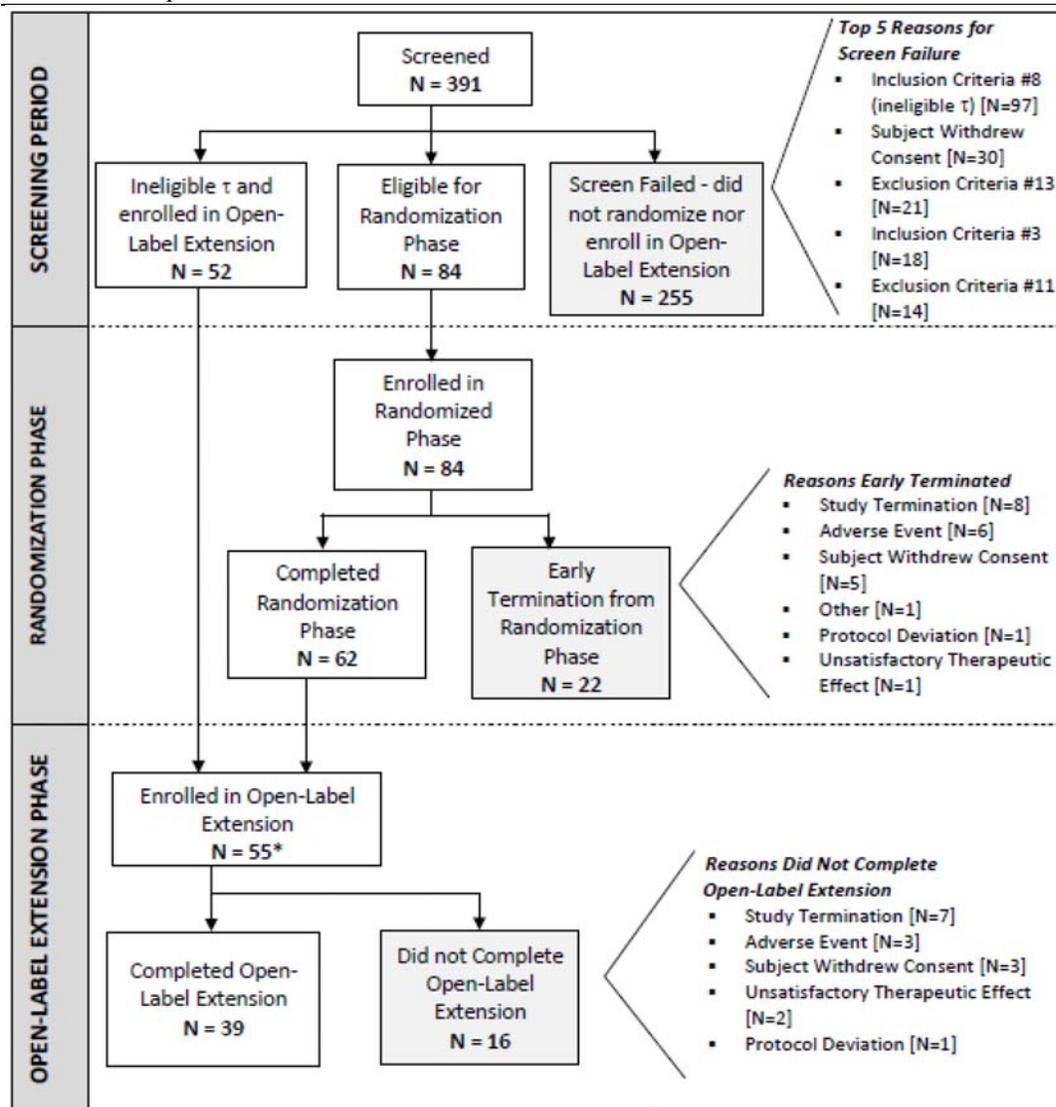
UQ-dTSD, nTST and dTSD, and τ . Subjects in the placebo group had a lower *median* LQ-nTST (2.982 hours) compared to those in the tasimelteon group (3.383 hours).

6.1.3 Subject Disposition

Study 3201: The following Figure outlines the subject disposition in Study 3201. After Screening, a total of 136 subjects enrolled in the Pre-randomization phase. Of these 136 subjects, 84 were eligible for the double-blind randomization phase (United States = 76/84; Germany = 8/84). The remaining 52 subjects were ineligible for randomization, and enrolled directly to the open-label extension (United States = 48/52; Germany = 4/52). As can be seen from this Figure, 22 (22/84; 26.2%) subjects withdrew early from the randomization phase of Study 3201, and 62 subjects completed the randomization phase.

Figure 6: Flow diagram of subject disposition in Study 3201

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*52 patients entered the Open-Label Extension Phase directly from the screening phase and 3 patients rolled over after completing the Randomization Phase.

Inclusion criteria #3: BMI of ≥ 18 and ≤ 33 kg/m² (BMI = weight [kg]/height [m²]); Inclusion criteria #8: Ineligible τ ; Exclusion criteria #11: Indication of impaired liver function (values for AST, ALT or bilirubin >2 times the upper limit of normal); Exclusion Criteria #13: A positive test for drugs of abuse at the screening visit.

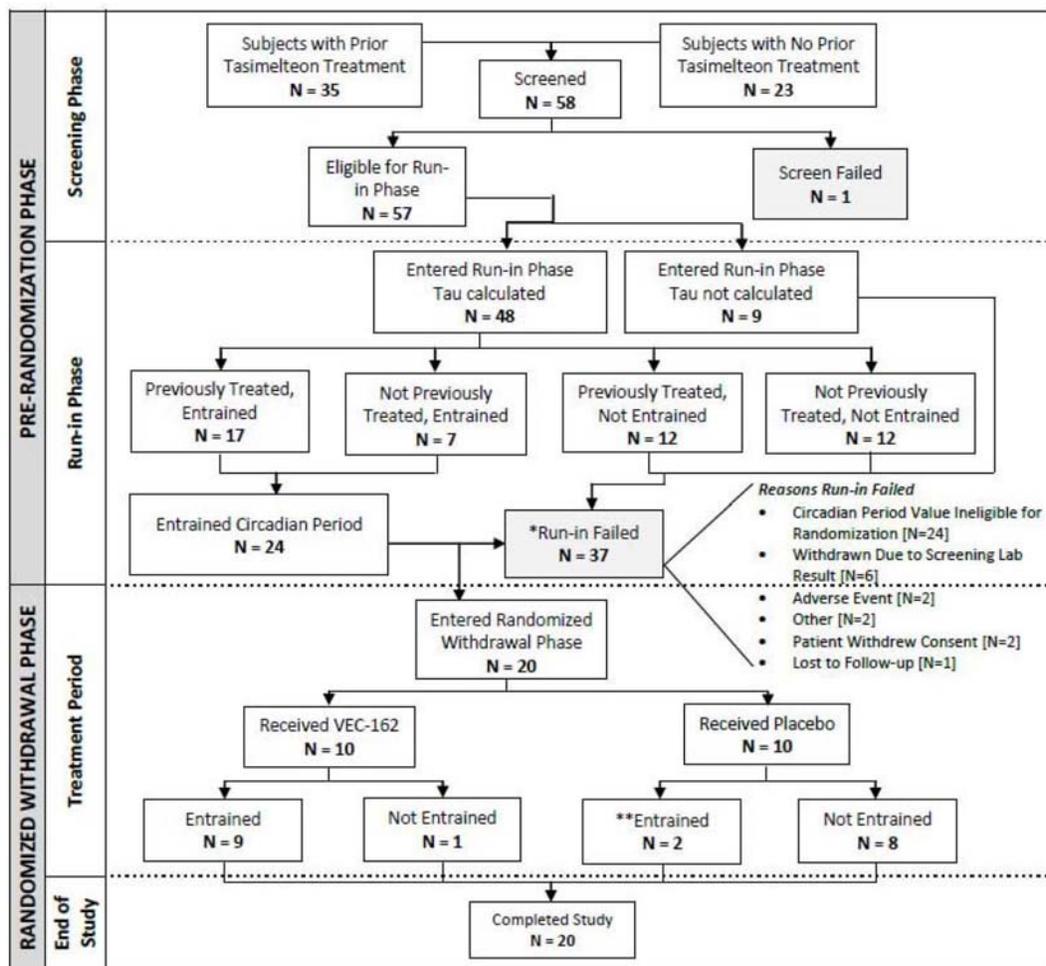
Source: NDA 205677, 5/31/13: Module 2.7.3 Summary of Clinical Efficacy, Figure 7, p 29.

Randomization was done using the IVRS. An equal number of subjects were randomized into each treatment group (tasimelteon = 42; placebo = 42) in the Randomization Phase. Subjects were also evenly balanced between treatment groups in each country (US: tasimelteon = 38, placebo = 38; Germany: tasimelteon = 4, placebo = 4).

Study 3203: Study 3203 was conducted across 17 sites in the United States. A total of 57 subjects were enrolled in the *run-in phase* of Study 3203 (see Figure below). A total of 24 of these 57 subjects (24/57; 42.1%) were considered eligible for randomized withdrawal based on entrainment of the circadian period. Of these 24 subjects, 20 subjects were randomized (1:1); 4

subjects who were entrained during the Run-in Phase but did not enter the Randomized Withdrawal Phase due to the study already reaching a cap of 20 randomized patients. All these 20 subjects completed the study. The average length of diary collection for the 20 randomized patients was 57 days in the Run-in phase and 59 days during the post-randomization phase.

Figure 7: Flow diagram of subject disposition in Study 3203



*Four patients were entrained during the Run-in Phase but did not enter the Randomized Withdrawal Phase due to the study already reaching N=20 for randomized patients (N=2), adverse events during the Run-in Phase (N=1), and the subject met the definition for entrainment but was screen failed by adjudication committee because of data issues (N=1). Therefore, they fell into the Run-in failed group.

**One subject who was entrained with placebo treatment during the Randomized Withdrawal Phase was also previously entrained on placebo during Study 3201.

Source: NDA 205677, 5/31/13: Module 2.7.3 Summary of Clinical Efficacy, Figure 9, p 47.

6.1.4 Analysis of Primary Endpoint(s)

Study 3201 (SET Study)

In the original Study 3201 protocol (5/24/10), the primary efficacy endpoint was the average nTST across weeks 3 to 6, defined as the average nightly amount of actual sleep time between the daily dosing time and the scheduled wake time (a 10 hour interval), as recorded by the PSQ. Secondary efficacy outcomes included average nTST, average daily TST at various time periods, and proportion of subjects considered to have a normal phase (i.e., the aMT6s acrophase occurs within expected range). In Version 9 of Study 3201 protocol (5/21/12), the Applicant changed the primary endpoint to entrainment (of the circadian melatonin rhythm as measured by urinary 6-sulfatoxymelatonin) which required fewer subject numbers to power the study (from 160 to 84) citing difficulty in subject recruitment; secondary endpoints included clinical outcomes, as measured by sleep, daytime naps and functionality.

As described in Section 2.5 ‘Summary of Presubmission Regulatory Activity Related to Submission’ of this review, the Agency did not agree with the use of entrainment biomarker as a primary endpoint since the use of clinical endpoints were feasible, and stated its position that efficacy on an appropriate clinical outcome was necessary for approval of tasimelteon (7/9/12, 11/28/12 and 10/10/12). The Applicant amended Study 3201 protocol (Amendment 11; 12/11/12) prior to unblinding of study data (12/12/12), to include a step-down primary endpoint for entrainment plus the Non-24 Clinical Response Scale (see below for a description), and to add a sleep/wake clinical response endpoint as a key secondary endpoint. However, there was no agreement between the Agency and the Applicant on the primary endpoints; this is discussed further in the subsections below.

Analysis Populations:

Intent-to-Treat (ITT) Population included all subjects randomized into the study that have τ calculated post-randomization. The ITT population was utilized for all circadian rhythm-related outcomes including the primary endpoint of entrainment.

Analysis Population, a subset of the ITT population, included all subjects in the ITT population that had at least 70% of one cycle of data reported during each of Pre-randomization and Randomization phases. The Analysis Population was used for analysis of all other endpoints including the step-down primary and all other clinical efficacy analyses.

ITT* Population (post-hoc, at the request of the Agency), included all patients who received at least one dose of treatment and had one efficacy assessment. The Agency requested additional analyses based on this population during the Pre-NDA meeting on 2/21/13.

Missing Data Imputation Method: The Applicant did not specify imputations for missing data.

Primary endpoints:

Primary efficacy endpoint and analysis (Amendment 11): Proportion of patients with Non-24 Hour Disorder that are entrained (as assessed by urinary 6-sulfatoxymelatonin) after placebo or tasimelteon treatment during the randomization phase of study 3201. Entrainment was defined as having a post-baseline τ value less than 24.1 hours and a 95% CI that included 24.0 hours.

Entrainment classification was done blinded to treatment assignment by an adjudication panel; subjects who did not meet the above definition including those with insufficient or poor quality data or those who entrained later (run-in phase of Study 3203) were classified as not entrained. Barnard’s exact test was used to test the null hypothesis in the ITT population. The Fisher’s exact test was used as the sensitivity analysis method. If the primary null hypothesis was rejected at an alpha level of 0.05, then the step-down primary null hypothesis was also tested at an alpha level of 0.05 (see next paragraph).

Step-down primary endpoint and analysis (Amendment 11): Proportion of patients with Clinical Response, defined as entrainment of the 6-sulfatoxymelatonin rhythm *and* a score of ≥ 3 on the Non-24 Hour Disorder Clinical Response Scale (N24CRS). The following table summarizes the 4 item N24CRS. Each item assessment on the scale is scored as a 1 or 0 depending on whether the pre-specified threshold of response is achieved or not. The N24CRS score is derived by adding the score for each of the four individual assessment, and the total score ranges from 0 – 4 (higher scores reflect improvement). The clinical measurements in the N24CRS for all analyses were derived only from the randomization phase of Study 3201. The Clinical Response rate was analyzed in the same manner of the primary endpoint; however, the analysis population was used in these analyses.

Table 5: Non-24 Clinical Response Scale Components and Criteria for Response

Assessment	Threshold of response
LQ-nTST	≥ 45 minutes increase in average nighttime sleep duration
UQ-dTSD	≥ 45 minutes decrease in average daytime sleep duration
MoST	≥ 30 minutes increase and a standard deviation ≤ 2 hours during double-masked phase
CGI-C	≤ 2.0 from the average of D112 and Day 183 compared to baseline

Source: NDA 205677, 5/31/13: Module 2.7.4 Summary of Clinical Efficacy, Table 3, p 21.

The definition of responders for the step-down primary and subtypes I-IV secondary endpoints (see Section 6.1.5 ‘Analysis of Secondary Endpoints(s)’ of this review) was individuals who were entrained and had a significant improvement from screening in key clinical measure(s). Entrainment status for these endpoints was derived from Study 3201 randomization phase and the tasimelteon open-label run-in phase of Study 3203, i.e., for subjects randomized to tasimelteon 20 mg and who participated in the screening phase of Study 3203, the screening τ from Study 3203 was used if the subject did not become entrained in Study 3201 but did become entrained during the screening phase of Study 3203. The clinical parameters of the step-down primary and the subtypes I-IV secondary endpoints were derived from the 3201 randomized phase.

Applicant's Pre-specified Analysis of the Primary and Step-down Primary Endpoints

There were 78 subjects who met the pre-specified criteria for the ITT Population. Six (6/84; 7.14%) subjects who did not have τ calculated post-randomization were excluded; 4 subjects were in the placebo group and 2 subjects in the tasimelteon group.

The following table summarizes the results of the primary and step down primary endpoint analyses. The proportion of subjects who were entrained, as measured by urinary aMT6s, was statistically significantly higher in the tasimelteon group than that in the placebo group (p-value = 0.0291). Entrainment, assessed by cortisol, did not achieve statistical significance (0.0571; highlighted in table below). Similarly, results of the analysis of the primary step down endpoint (proportion of subjects who entrained and had N24CRS ≥ 3) also showed statistical significance in favor of tasimelteon (p-value = 0.0025).

Several sensitivity analyses were conducted for the step down primary endpoint. As noted earlier, the step down primary Clinical Response was defined as entrainment (based on data from Study 3201 randomization phase, and Study 3203 open-label run-in phase for those that did not entrain in Study 3201) and a score of ≥ 3 on the N24CRS. Sensitivity analyses were conducted defining Clinical Response as entrainment (based on data from only Study 3201) and score of ≥ 3 on the N24CRS, entrainment (based on data from both Studies 3201 and 3203) and score of ≥ 2 on the N24CRS, and based on N24CRS only (without entrainment status) with a score of ≥ 2 or ≥ 3 . As can be seen from the table below, all sensitivity analyses for the step down primary endpoint showed statistical significance in favor of tasimelteon.

Table 6: Results of primary and step down primary endpoints – Study 3201

Category Statistic	Placebo N (%)	Tasimelteon N (%)	P-value (based on Barnard's Exact Test)	P-value (based on Fisher's Exact Test)
Primary endpoint				
Entrainment rate (aMT6s)*	1/38 (2.6)	8/40 (20.0)	0.0171	0.0291
Entrainment rate (cortisol)*	1/38 (2.6)	7/40 (17.5)	0.0313	0.0571
Step down primary endpoint				
Entrainment and N24CRS $\geq 3^{\wedge\#}$	0/34 (0.0)	9/38 (23.7)	0.0028	0.0025
Sensitivity analyses				
Entrainment in Study 3201 and N24CRS $\geq 3^{\wedge\#}$	0/34 (0.0)	5/38 (13.2)	0.0286	0.0558
Entrainment and N24CRS $\geq 2^{\wedge\#}$	0/34 (0.0)	11/38 (28.9)	0.0006	0.0005
N24CRS $\geq 3^{\#}$	1/34 (2.9)	11/38 (28.9)	0.0031	0.0036
N24CRS $\geq 2^{\#}$	7/34 (20.6)	22/38 (57.9)	0.0014	0.0017

aMT6s = 6-sulfatoxymelatonin; N24CRS = Non-24 Clinical Response Scale

*Entrainment based on ITT population using data from Study 3201 only, and defined as having a post-baseline τ value < 24.1 hours and a 95% CI that included 24.0 hours. Using this definition, 1 (1/34; 2.9%) subject in the placebo group and 7 (7/38; 18.4%) subjects in the tasimelteon group were entrained.

\wedge Entrainment based on ITT population using data from Study 3201 randomization phase, and Study 3203 open-label run-in phase for those that did not entrain in Study 3201, and defined as having a post-baseline τ value < 24.1 hours and a 95% CI that

included 24.0 hours. Using this definition, 1 (1/34; 2.9%) subject in the placebo group and 13 (13/38; 34.2%) subjects in the tasimelteon group were entrained.

#Results based on Analysis Population.

Source: NDA 205677, 5/31/13: Module 2.7.3 Summary of Clinical Efficacy, adapted from Tables 5 and 7, pages 33 and 36.

Applicant's Post-hoc Analysis of Entrainment Rates

As noted above, entrainment in the primary endpoint was based on data from Study 3201 randomization phase only. The Applicant conducted post-hoc analysis of entrainment status for all subjects randomized in Study 3201 using τ calculated from all available time-points including data from the run-in phase of Study 3203 for subjects who continued directly from Study 3201 into Study 3203, and who met the following three criteria:

- had at least two aMT6s cosinor fits with $p < 0.05$ for the τ calculation during randomization;
- had a baseline $\tau < 24.75$ hours in Study 3201 (subjects with $\tau \geq 24.75$ hours were excluded based on peer-reviewed publications that suggested that these individuals may not entrain with standard melatonin agonist treatment regimens);
- did *not* have concomitant use of β -adrenoreceptor antagonists (beta-1-blockers are believed to block sympathetic signaling to the pineal gland, resulting in suppression of melatonin levels).

Using all available time points including the run-in phase of Study 3203, 5 subjects treated with tasimelteon in Study 3201 (6 months) who continued on to Study 3203 (6 weeks) entrained during Study 3203. Compared to the entrainment rate of 20% (8/40) in tasimelteon-treated subjects using data from Study 3201 randomization phase only (pre-specified primary analysis), the entrainment rate when these 5 additional subjects were included increased to 34.2% (13/38). The Applicant identified 10 randomized subjects who reported concomitant use of oral beta blockers (2 in the placebo group and 8 in the tasimelteon group); none of these subjects entrained, and were excluded from analysis. Using all three criteria as noted above, a total of 12 subjects were excluded from the tasimelteon group who were in the pre-specified primary analysis. Analysis after excluding these 12 subjects showed an entrainment rate of 54% (15/28).

Applicant's Post-hoc Analyses of FDA-requested Population:

As previously noted, during the Pre-NDA meeting (2/21/13) the Agency requested analyses of pre-specified endpoints based on all subjects who received at least one dose of treatment and had one efficacy assessment. The Applicant designed this population as the ITT* Population. Since entrainment determination requires specific data, for entrainment endpoints (based on aMT6s and cortisol), the per-protocol, ITT, and ITT* all define the same population.

The following table is a summary of the results of the analyses of the primary and step down primary endpoints on the ITT* population. As can be seen, statistical significance in favor of tasimelteon was achieved on all endpoints, and the results are nearly identical to those on the protocol-specified ITT and Analysis populations (see Table 6).

Table 7: Results of primary and step down primary endpoints in ITT* population – Study 3201

Category Statistic	Placebo N (%)	Tasimelteon N (%)	P-value (based on Barnard's Exact Test)
Primary endpoint			
Entrainment rate (aMT6s)*	1/38 (2.6)	8/40 (20.0)	0.0171
Entrainment rate (cortisol)*	1/38 (2.6)	7/40 (17.5)	0.0313
Step down primary endpoint			
Entrainment and N24CRS $\geq 3^{\wedge}$	0/38 (0.0)	9/40 (22.5)	0.002
Sensitivity analyses			
Entrainment and N24CRS $\geq 2^{\wedge}$	0/38 (0.0)	11/40 (27.5)	0.0004
N24CRS ≥ 3	2/42 (4.8)	11/42 (26.2)	0.0065
N24CRS ≥ 2	9/42 (21.4)	22/42 (52.4)	0.0034

aMT6s = 6-sulfatoxymelatonin; N24CRS = Non-24 Clinical Response Scale

*Entrainment based on ITT population using data from Study 3201 only, and defined as having a post-baseline τ value < 24.1 hours and a 95% CI that included 24.0 hours.

\wedge Entrainment based on ITT population using data from Study 3201 randomization phase, and Study 3203 open-label run-in phase for those that did not entrain in Study 3201, and defined as having a post-baseline τ value < 24.1 hours and a 95% CI that included 24.0 hours.

Source: NDA 205677, 5/31/13: Module 2.7.3 Summary of Clinical Efficacy, adapted from Table 9, page 42.

Study 3203 (RESET Study)

All endpoints used in Study 3201 with the exception of CGI-C and N24CRS were included in Study 3203. The Applicant states that CGI-C was not included in Study 3203 because it was a randomized withdrawal study (i.e., CGI-C assessed improvement in symptoms relative start of study) and N24CRS was not included because one of its components is the CGI-C.

Analyses Populations:

Intent-to-Treat (ITT) population: Any subject randomized into the study that had τ calculated post-randomization. Primary and secondary efficacy analyses were performed on the ITT population.

Primary Efficacy Endpoint:

Primary efficacy endpoint: Proportion of subjects who become non-entrained (τ value > 24.1 or the lower bound of 95% CI above 24.0) to a 24 hour day after randomization to tasimelteon or placebo. Barnard's exact test was used to test the null hypothesis in the ITT population. The Fisher's exact test was used as the sensitivity analysis method.

Applicant's Pre-specified Analysis of the Primary Endpoint:

As noted in Section 6.1.3 ‘Subject Disposition’ of this review, 24 of the 57 subjects (24/57; 42.1%) were considered eligible for randomized withdrawal based on entrainment of their circadian period. Of these 24 subjects, 20 subjects were randomized (1:1); 4 subjects were entrained during the Run-in Phase but did not enter the Randomized Withdrawal Phase due to the study already reaching a cap of 20 randomized patients.

Maintenance of entrainment of circadian rhythms as measured by aMT6s in the primary analysis was statistically significant in favor of tasimelteon (see table below). Sensitivity analysis was conducted after excluding one subject who was randomized into Study 3203 (prior to unblinding in 3201) and was subsequently categorized as entrained in the placebo arm of study 3201; this analysis also showed statistical superiority in favor of tasimelteon.

Table 8: Primary endpoint results, Study 3203 (ITT Population)

Category Statistic	Placebo n/N' (%)	Tasimelteon 20 mg n/N' (%)	P-value ¹	P-value ²
Primary analysis				
Non-entrainment rate (aMT6s) ³	8/10 (80.0)	1/10 (10.0)	0.0026	0.0055
Sensitivity analyses				
Non-entrainment rate (aMT6s) ^{3,4}	8/9 (88.9)	1/10 (10.0)	0.0007	0.0011

¹P-value was based on Barnard’s Exact Test, two-sided.

²P-value was based on Fisher’s Exact Test, two-sided.

³Not entrained is defined as having a post-baseline τ value \geq 24.1 or the lower bound of the 95% CI $>$ 24.0 hours.

⁴This analysis excludes one subject who was randomized to the placebo arm of Study 3201 and subsequently categorized as entrained.

aMT6s = 6-sulfatoxymelatonin; ITT = intent-to-treat; N' = number of patients with measurements of τ at specified time point; % = 100*number/N' of post-baseline time point.

Source: NDA 205677, 5/31/13: Module 2.7.3 Summary of Clinical Efficacy, adapted from Table 14, page 53.

FDA-conducted Post-hoc Analyses of Study 3201 and Study 3203 Efficacy Data:

The Agency conducted post-hoc analyses of efficacy data from Study 3201 and Study 3203. These analyses are discussed in Section 6.1.6 ‘FDA-conducted Analyses of Efficacy Data from Study 3201 and Study 3203’ of this review.

6.1.5 Analysis of Secondary Endpoints(s)

Study 3201 (SET Study)

The following are the pre-specified key and additional secondary endpoints in Study 3201.

Key Secondary outcomes:

- Proportion of *responders* with a combined sleep/wake response for nighttime sleep duration and daytime sleep duration defined as:
 - Increase of 90 minutes or greater in the lower quartile of nights of subjective nighttime total sleep time (LQ-nTST), and
 - Decrease of 90 minutes or greater in the upper quartile of days of subjective daytime sleep duration (UQ-dTSD).
- Proportion of subjects with entrainment as assessed by urinary cortisol.

A sensitivity analysis was conducted using Analysis population that was enriched for individuals that had a significant sleep and nap problem at baseline, defined as individuals who had a 90 minute difference between their upper and lower quartiles for both nTST and dTSD.

The responder analysis for the key secondary outcome was conducted in the Analysis Population, and was analyzed in the same manner of the primary endpoint. The cortisol entrainment endpoint was analyzed in the ITT population in the same manner of the primary endpoint.

Additional Secondary outcomes:

- The subtype I response rate (sleep time subtype): proportion of subtype I responders, defined as an individual who was both entrained and had ≥ 45 minute improvement from screening in LQ-nTST.
- The subtype II response rate (daytime sleep subtype): proportion of subtype II responders, defined as an individual who was both entrained and had ≥ 45 minute improvement from screening in UQ-dTSD.
- The subtype III response rate (MoST subtype): proportion of subtype III responders, defined as an individual who was both entrained and had ≥ 30 minute improvement from screening in MoST.
- The subtype IV response rate (CGI-C subtype): proportion of subtype IV responders, defined as an individual who was both entrained and had ≤ 2.0 change from screening in CGI-C.
- Treatment response association with aMT6s excretion rate: association between treatment response, as measured by entrainment of aMT6s circadian rhythms, and the baseline urinary aMT6s excretion rate in tasimelteon-treated patients with Non-24 Hour Disorder.
- Change from baseline in the average of LQ-nTST
- Change from baseline in the average of UQ-dTSD
- Change from baseline in the average of MoST
- Change from baseline in the average of CGI-C
- The entrainment of circadian analytes: proportion of entrainment as assessed by urinary analytes under circadian control.

The responder analysis for the above subtype response variables was analyzed in the Analysis Population, and in the same manner of the primary endpoint. The above continuous efficacy variables were analyzed in the Analysis Population; treatment groups were compared using an

Analysis of Covariance (ANCOVA) model with the terms of treatment group, pooled site and baseline as covariates.

Applicant's Analyses of Pre-specified Secondary Outcomes in Study 3201:

There were 72 subjects who met the pre-specified criteria for the Analysis Population, i.e., had at least 70% of one circadian cycle of electronic diary data reported during each of Pre-randomization and Randomization phases. Twelve (12/84; 14.29%) subjects who did not meet the above criteria were excluded (8 placebo subjects versus 4 tasimelteon subjects).

The following table summarizes the results of the key and additional secondary outcomes in Study 3201. The pre-specified key secondary clinical endpoint and the sensitivity analysis of the key secondary endpoint did not achieve clinical significance (p-value = 0.1312 and 0.767, respectively; p-values are highlighted in the table below). The Applicant conducted a post-hoc analysis, redefining the responder as an increase of 45 minutes or greater in the LQ-nTST and a decrease of 45 minutes or greater in the UQ-dTSD. The proportion of responders, as defined by this post-hoc criteria, in the tasimelteon group was statistically significantly greater (p-value = 0.017) than the proportion in the placebo group.

The results of all additional secondary clinical outcomes showed statistical significance in favor of tasimelteon.

Table 9: Summary of secondary clinical endpoints in Study 3201

Category Statistic	Placebo	Tasimelteon n	Treatment Difference	P-value
Key secondary clinical endpoint				
LQ-nTST and UQ-dTSD ≥ 90 min, n (%) [*]	1 (2.9)	5 (13.2)	10.2	0.1312
LQ-nTST [^] and UQ-dTSD [^] ≥ 90 min, n (%) [*]	1 (4.5)	5 (23.8)	19.3	0.767
LQ-nTST and UQ-dTSD ≥ 45 min, n (%) [*] (<i>post-hoc</i>)	3 (8.8)	12 (31.6)	22.8	0.0177
Additional secondary outcomes				
Entrained and ≥ 45 minute improvement in LQ-nTST, n (%) ^{*#}	0/34 (0.0)	10/38 (26.3)	26.3	0.0013
Entrained and ≥ 45 minute improvement in UQ-dTSD, n (%) ^{*#}	0/34 (0.0)	11/38 (28.9)	28.9	0.0006
Entrained and ≥ 30 min improvement in MoST and SD ≤ 2.0 hours, n (%) ^{*#}	0/34 (0.0)	8/38 (21.1)	21.1	0.0046
Entrained and ≤ 2.0 in average CGI-C, n (%)	0/33 (0.0)	7/36 (19.4)	19.4	0.0078
LQ-nTST (LS mean hours [LS mean minutes]) [@]	0.28 [17.08]	0.95 [56.80]	0.66 [39.71]	0.0055
UQ-dTSD (LS mean hours [LS mean minutes]) [~]	-0.30 [-17.87]	-0.77 [-46.48]	-0.48 [-28.61]	0.0050

MoST (LS mean hours [LS mean minutes]) [~]	0.24 [14.48]	0.58 [35.00]	0.34 [20.52]	0.0123
CGI-C (LS mean) [@]	3.4	2.6	-0.8	0.0093

For UQ-dTSD and CGI-C, smaller numbers indicate improvement; LS = least Squares; Treatment Difference = Tasimelteon minus Placebo

*Results for LQ-nTST, UQ-dTSD, MoST, and CGI-C assessments were based on the Analysis Population (N=34 in the placebo group and N=38 in the tasimelteon group); the LQ-nTST and UQ-dTSD ≥ 45 minute sleep/wake response was a post-hoc analysis.

[^]Subjects included in this analysis had to have a significant sleep and nap problem at baseline, defined as those subjects with at least a 90-minute difference between their upper and lower quartiles for both baseline nTST and dTSD.

[#]Entrainment was defined as having a post-baseline τ value < 24.1 hours and a 95% CI that included 24.0 hours, and was based on data from Study 3201 randomization and Study 3203 run-in phase if subject did not become entrained in Study 3201 but did become entrained during the run-in of Study 3203.

[~]P-value was based on analysis of covariance model.

[@]P-value was based on analysis of variance model.

Source: NDA 205677, 5/31/13: Module 2.7.3 Summary of Clinical Efficacy, adapted from Table 8, page 38.

Applicant's Post-hoc Analyses of FDA-requested Population:

During the Pre-NDA meeting (2/21/13) the Agency requested analyses of pre-specified secondary endpoints based on all subjects who received at least one dose of treatment and had one efficacy assessment (designated as ITT* Population). Results of analyses of the key secondary and additional secondary clinical endpoints on the ITT* population are summarized in the table below (p-values that are not significant are highlighted). As in the protocol-specified Analysis Population (p-value = 0.1312), the key secondary clinical endpoint did not achieve clinical significance (p-value = 0.1733) in the ITT* population. However, for the key endpoint redefining the responder as an increase of 45 minutes or greater in the LQ-nTST and a decrease of 45 minutes or greater in the UQ-dTSD, in contrast to the *post-hoc* results obtained with the Analysis Population (p-value = 0.0177), post-hoc analysis in the ITT* population, did not show statistical significance (p-value = 0.063).

The results of other additional secondary clinical outcomes in the ITT* population showed statistical significance in favor of tasimelteon.

Table 10: Results of post-hoc secondary clinical endpoints in ITT* population – Study 3201

Category Statistic	Placebo	Tasimelteon	P-value
Key secondary clinical endpoint			
LQ-nTST and UQ-dTSD ≥ 90 min, n (%) [^]	2/28 (7.14)	5/24 (20.8)	0.1733
LQ-nTST and UQ-dTSD ≥ 45 min, n (%)	5/42 (11.9)	12/42 (28.6)	0.063
Additional secondary outcomes			
LQ-nTST (LS mean minutes)	17.35	53.16	0.0232
UQ-dTSD (LS mean minutes)	-16.94	-50.45	0.0031
MoST (LS mean minutes)	13.01	33.79	0.0229
CGI-C (LS mean)	3.4	2.6	0.0104

For UQ-dTSD and CGI-C, smaller numbers indicate improvement; LS = least Squares.

^{*}Subjects included in this analysis had to have a significant sleep and nap problem at baseline, defined as those subjects with at least a 90-minute difference between their upper and lower quartiles for both baseline nTST and dTSD; this analysis was not pre-specified, and is post-hoc.

Source: NDA 205677, 5/31/13: Module 2.7.3 Summary of Clinical Efficacy, adapted from Tables 10-11, pages 42-43.

Study 3203 (RESET Study)

The following are the pre-specified secondary endpoints in Study 3203.

Secondary endpoints:

- Time to relapse (circadian cycle time, as a percentage of circadian cycle length, to first relapse): Relapse was defined as a 45 minute or greater decrement in the weekly average nTST (minimum of 3 days of nTST data was required to calculate this average for a given week) in the Randomized Withdrawal phase compared to the Run-in Phase. The last day of the week during which the first relapse occurred was considered the actual time of relapse.

Subjects with Non-24 Hour Disorder were expected to most likely relapse in the middle of their cycle or before. Circadian periods (τ) in enrolled subjects with Non-24 Hour Disorder varied from subject to subject; consequentially, cycle length ranged from approximately 21 days to 184 days. Therefore, it was difficult to compare the actual time of relapse between subjects unless the time was standardized. In order to do this, the Applicant used the percentage of the subject's circadian cycle length, calculated as the (actual time/circadian cycle length) x 100. The actual time was also used as a sensitivity analysis. The τ used to calculate circadian time was estimated during the screen phase of Study 3201.

The null hypothesis stated that there was no difference between the treatment groups on the distribution of cycle time to relapse. Circadian cycle time to first relapse event (expressed as percentage of circadian cycle length) was analyzed via Kaplan-Meier product-limit survival curve estimates and an unstratified log-rank test for treatment group comparison. Subjects who did not meet the criteria for a relapse event during the Randomized Withdrawal phase were censored at the cycle time of the discontinuation or completion of the study. A similar analysis, including the Kaplan-Meier plot, was also done with actual calendar time to first relapse.

- Non-entrainment of the circadian rhythms as measured by cortisol
- Proportion of patients with non-entrainment and an average decrease in nTST of at least 30 minutes compared to the run-in phase
- Change in average nTST from the run-in phase
- Change in average LQ-nTST from the run-in phase
- Change in average dTSD from the run-in phase
- Change in average UQ-dTSD from the run-in phase
- Change in MoST from the run-in phase

- Symptoms of withdrawal as measured by BWSQ

Treatment groups were compared using an analysis of covariance (ANCOVA) model with the terms of treatment group and the corresponding efficacy value in Run-in phase (baseline) as covariates. These analyses were conducted in the ITT Population.

Applicant's Analyses of Pre-specified Secondary Outcomes in Study 3203:

The results of the pre-specified secondary endpoints are summarized in the table below (endpoints for which p-values are *not* significant are highlighted). For the pre-specified secondary endpoint of Time to Relapse, while there was a numerical trend in favor of tasimelteon, there were no significant differences between the treatment groups using either the circadian cycle time to relapse (p-value = 0.0907) or the actual time to relapse (p-value = 0.1481). A sensitivity analysis, defining the time to relapse as 60 minute or greater decrement in the weekly average of nTST compared to the Run-in Phase, was conducted; treatment difference for the circadian time to relapse was statistically significant (p-value = 0.0181) in favor of tasimelteon, suggesting that a greater treatment effect was evident over longer follow-up period.

Table 11: Summary of secondary endpoints, Study 3203

Category Statistic	Placebo (N=10)	Tasimelteon 20 mg (N=10)	Treatment Difference (Tasimelteon minus Placebo)	P-value
Circadian time to first relapse ¹ (median percentage of cycle) ²	24.7	NE ¹	NA	0.0907
Actual time to first relapse ¹ (median weeks) ²	4.0	NE ¹	NA	0.1481
Circadian time to first relapse (alternate definition) ³ (median) ²	32.4	NE ¹	NA	0.0181
Non-entrainment rate (cortisol) ⁴ n (%) ⁵	8 (80.0)	2 (20.0)	-60.0	0.0118
Non-entrained and ≥30 minute decrement in nTST ⁴ n (%) ⁵	5 (50.0)	1 (10.0)	-40.0	0.0623
nTST (LS mean hours [LS mean minutes]) ⁶	-0.74 [-44.49]	-0.20 [-12.23]	0.54 [32.26]	0.1315
LQ-nTST (LS mean hours [LS mean minutes]) ⁶	-1.23 [-73.74]	-0.11 [-6.74]	1.12 [67.00]	0.0233
dTSD (LS mean hours [LS mean minutes]) ⁶	0.30 [17.85]	-0.05 [-3.12]	-0.35 [-20.97]	0.0547
UQ-dTSD (LS mean hours [LS mean minutes]) ⁶	0.83 [49.95]	-0.16 [-9.31]	-0.99 [-59.25]	0.0266
MoST (LS mean hours [LS mean minutes]) ⁶	-0.27 [-16.05]	0.33 [19.99]	0.60 [36.04]	0.0108

LS mean = least-squares mean; NA = not applicable; NE = non-estimable (there were no observed relapses during the 8 week study).

¹Time to relapse with relapse defined as a 45 minute or greater decrement in the weekly average of nTST compared to the Run-in Phase.

²Log-rank p-value based on Kaplan-Meier.

³Time to relapse with relapse defined as a 60 minute or greater decrement in the weekly average of nTST compared to the Run-in Phase.

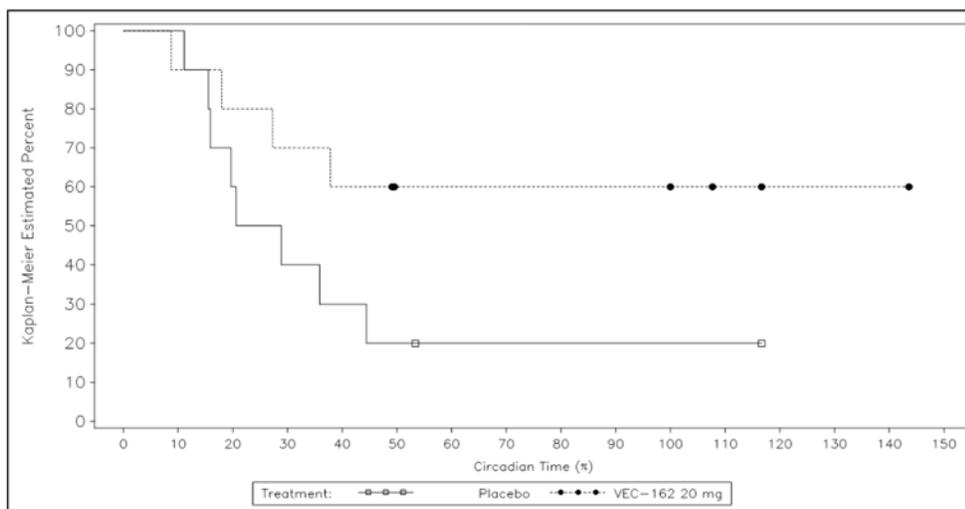
⁴Not entrained is defined as having a post-baseline τ value ≥ 24.1 or the lower bound of the 95% CI > 24.0 hours.

⁵P-value was based on Barnard's Exact Test, two-sided.

⁶P-value was based on analysis of covariance model.

A higher percentage of subjects in the placebo group (8/10; 80%) had a relapse event and at an earlier time point (as measured by circadian % time) compared to subjects in the tasimelteon group (4/10; 40%) (see figure below). As discussed above, the difference in proportion between the two treatment groups was not statistically significant. Those subjects that did relapse did so within 50% of their circadian cycle time when subjects are expected to have maximum misalignment between their endogenous circadian rhythm and the 24-hour clock.

Figure 8: Kaplan-Meier curve of circadian time (%) to first relapse event, Study 3203



A subject was defined as relapsed if the subject experienced a 45 minute or greater decrement in weekly average subjective nTST compared to the Run-in Phase.

Source: NDA 205677, 5/31/13: Module 2.7.3 Summary of Clinical Efficacy, Figure 10, page 56.

There was no statistical significance for the results of the endpoints ‘Proportion of patients with non-entrainment and an average decrease in nTST of at least 30 minutes compared to the run-in phase’ and ‘Change in average nTST from the run-in phase’ (p-values = 0.0623 and 0.1315, respectively); however, there was a numerical trend in favor of tasimelteon group for both these endpoints. In contrast, the least squares mean change from baseline in LQ-nTST after tasimelteon treatment during the Randomized Withdrawal Phase was statistically significantly less than the least squares mean change from baseline in LQ-nTST after placebo treatment (p-value = 0.0233).

The results of ‘Change in average dTSD from the run-in phase’, ‘Change in average UQ-dTSD from the run-in phase’, and ‘Change in MoST from the run-in phase’ secondary clinical outcomes showed statistical significance in favor of tasimelteon (p-value = 0.0547, 0.0266 and 0.0108, respectively).

6.1.6 FDA-conducted Analyses of Efficacy Data from Study 3201 and Study 3203

As previously noted, at the time of unblinding Study 3201 data the Agency did not agree with the Applicant regarding the use of entrainment biomarker as a primary endpoint (communications dated 7/9/12, 11/28/12 and 10/10/12). The Agency reiterated its position on several occasions that biomarker findings are less reliable evidence of efficacy than clinically meaningful endpoints, and are not appropriate for Non-24 Hour Disorder, a condition with clear symptoms that a drug could be expected to improve in a study of reasonable size and duration.

During the End-of-Phase 2 meeting on 1/6/11, there was an agreement between the Agency and the Applicant that nighttime sleep and daytime naps were the two most important direct measures of clinical benefit. The Agency expressed openness in considering endpoints that looked at ‘worst few days’ in each cycle to help decrease the effect of random variability. The Applicant chose the LQ-nTST for the “worst night analysis” after determining that LQ-nTST was highly correlated with the phase of the circadian cycle that is 180° out of alignment with the 24-hour day, and therefore was more specific and appropriate in this remitting and relapsing disorder. Since regulatory approval of a drug product is based on an effect on direct assessment of treatment benefit (i.e., via endpoints that directly evaluate how a patient feels or functions; US v. Rutherford, 1979) demonstrated in adequate and well-controlled trials, and in consideration of the foregoing, the Agency believes that LQ-nTST and UQ-dTSD are appropriate clinical endpoints for evaluation of an effect in Non-24 Hour Disorder. The pre-specified step-down primary endpoint also combines entrainment with some clinical endpoints. With the exception of MoST (unknown clinical meaningfulness), the clinical endpoint(s), by itself (themselves), could support clinical benefit but their use as stand-alone primary endpoint(s) was not pre-specified. These issues are further discussed in the Section 6.1.10 ‘Additional Efficacy Issues/Analyses’ of this review.

The following are the Agency’s analyses of the efficacy data on clinical outcomes in Study 3201 and Study 3203. These analyses were conducted by Dr. Jingyu Luan, the Agency’s statistician. Please refer to Dr. Luan’s review for details. These analyses were conducted on the Intent-to-Treat population (mITT), defined as all randomized subjects who received at least one dose of treatment and had one efficacy assessment (same population which the Applicant referred to as ITT*), using the permutation ANCOVA test that includes baseline, site (for Study 3201 only) and treatment groups as covariates. In Study 3201, the sleep electronic diaries were recorded for an average of 88 days during Pre-randomization and 133 days during Randomization. In Study 3203, average length of electronic diary collection for the 20 randomized subjects was 57 days in the Run-in phase and 59 days during the Post-randomization. Due to the fairly large amount of electronic diary data collected in both studies, all available data was utilized in the analyses (no imputation was assigned missing data).

The following table summarizes the permutation ANCOVA test with baseline, site and treatment groups as covariates. A total of 100000 permutations of observations across the treatment groups were performed. The results in the table below are for the seed (3201/3203, 11, 04, 2013, 100000) which was chosen at random. A different seed may produce very slightly different results. As can be seen, the p-values for LQ-nTST, UQ-dTSD, MoST, CGIC and dTSD are all

significant, while the p-value for nTST did not reach statistical significance (highlighted), in both studies.

Table 12: Summary of the results of Permutation ANCOVA in Studies 3201 and 3203 (mITT population)

Results of Permutation ANCOVA (Study 3201, n=84, mITT)

Endpoint	ANCOVA	Permutation ANCOVA				
		Seed=3201	Seed=11	Seed=14	Seed=2013	Seed=100000
LQ-nTST	0.0515	0.0589	0.0585	0.0598	0.0597	0.0595
UQ-dTSD	0.0097	0.0110	0.0119	0.0109	0.0117	0.0113
MoST	0.0284	0.0320	0.0321	0.0314	0.0321	0.0326
CGIC	0.0086	0.0102	0.0111	0.0109	0.0104	0.0107
nTST	0.1296	0.1414	0.1409	0.1408	0.1421	0.1426
dTSD	0.0192	0.0213	0.0218	0.0211	0.0218	0.0214

Results of Permutation ANCOVA (Study 3203, n=20, mITT)

Endpoint	ANCOVA	Permutation ANCOVA				
		Seed=3203	Seed=11	Seed=14	Seed=2013	Seed=100000
LQ-nTST	0.0233	0.0226	0.0227	0.0234	0.0237	0.0235
UQ-dTSD	0.0266	0.0069	0.0064	0.0074	0.0070	0.0067
MoST	0.0108	0.0063	0.0067	0.0075	0.0068	0.0064
nTST	0.1315	0.1532	0.1530	0.1546	0.1548	0.1523
dTSD	0.0547	0.0224	0.0229	0.0234	0.0224	0.0235

Source: Dr. Jingyu Luan's analyses.

The LS mean change from baseline for clinical efficacy parameters in Study 3201 and Study 3203 are summarized in the tables below. Statistical significance in favor of tasimelteon was achieved for LQ-nTST, UQ-dTSD, MoST, CGIC and dTSD, in both studies. There was no statistical significance for the LS mean change from baseline for nTST (highlighted) in both studies.

Table 13: LS Mean in Hours and P-value from ANCOVA (Study 3201, ITT, n=84)

Endpoints	Placebo	Tasimelteon	P-value
LQ-nTST	0.35	0.86	0.0515
UQ-dTSD	-0.33	-0.82	0.0097
MoST	0.22	0.54	0.0284
CGIC ¹	3.4	2.6	0.0086
nTST	0.33	0.60	0.1296
dTSD	-0.17	-0.36	0.0192

¹For CGIC, n=71 since CGIC was missing for 13 patients
 Source: Dr. Jingyu Luan's analyses.

Table 14: LS Mean in Hours and P-value from ANCOVA (Study 3203, ITT, n=20)

Endpoints	Placebo	Tasimelteon	P-value
LQ-nTST	-1.23	-0.11	0.0233
UQ-dTSD	0.83	-0.16	0.0266
MoST	0.83	-0.16	0.0266
nTST	-0.74	-0.20	0.1315
dTSD	0.30	-0.05	0.0547

Source: Dr. Jingyu Luan's analyses.

6.1.7 Subpopulations

The Applicant defined the following population subgroups for post-hoc analyses of aMT6s entrainment rate in Studies 3201 and 3203:

- Individuals with $\tau < 24.75$ hours
- Individuals without concomitant use of β -adrenoreceptor antagonists
- Individuals treated for at least one circadian cycle length

Individuals with $\tau < 24.75$ hours: This subgroup was identified based on peer-reviewed publications which suggest that individuals with $\tau < 24.75$ (i.e., > 32 day circadian cycle length) are more likely to respond to treatment with a melatonin agonist. The Applicant conducted analyses of entrainment rate based on the above τ categories (i.e., $\tau < 24.75$ versus ≥ 24.75) in Studies 3201 and 3203 (data reviewed but not included in the review), and concluded that there are not enough data in 3201 to support a possible difference in entrainment rate between τ lower or higher than 24.75 hours but that data from Study 3203 suggest that a τ period ≥ 24.75 hours may be less likely to entrain with tasimelteon treatment.

Individuals without concomitant use of β -adrenoreceptor antagonists: The Applicant identified subjects with concomitant β -adrenoreceptor antagonists (beta blockers) usage as a subgroup for analysis based on published reports that they block sympathetic signaling to the pineal gland, possibly resulting in a decrease of nighttime levels of melatonin. A total of 10 unique subjects with concomitant beta blocker usage were identified in Studies 3201 and 3203; none of these subjects entrained in either study. The Applicant concludes that although evidence exists in the literature that beta blockers suppress melatonin secretion, the above noted sample size and design of Studies 3201 and 3203 are inadequate to definitively know whether concomitant beta blocker's usage reduces efficacy of tasimelteon or confound assessment of circadian rhythms with aMT6s measurements.

Individuals treated for at least one circadian cycle length: This issue is discussed in Section 6.1.8 of this review.

The Applicant did not present subgroup analyses for major demographic characteristics. Dr. Jingyu Luan, the Agency's statistician, analyzed the efficacy data, and these analyses showed no significant differences in efficacy with regard to major demographic characteristics. Please see Dr. Luan's review for details.

Efficacy in subjects who smoke: Pharmacokinetic data indicate that cigarette smoking decreases tasimelteon AUC by approximately 40%. In study 3201, smoking information was systematically collected for current use (YES/NO), type (cigarettes, cigars, other), and frequency (days, months or years). Eleven out of the 84 subjects (11/84; 13 %) randomized reported smoking a pipe, cigarettes or cigars (6 subjects in the tasimelteon group versus 5 in the placebo group). The mean treatment effects (tasimelteon group mean – placebo group mean) for LQ-nTST and UQ-dTSD were numerically higher among smokers (44.5 minutes and -86.2 minutes, respectively) compared to non-smokers (27.3 minutes and -23.4 minutes, respectively). This seemingly better point estimate for efficacy among smokers is unexpected given the reduction of AUC by cigarette smokers. However, the proportion of randomized subjects who smoke was small, and therefore, limits meaningful inference.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Only one dose – 20 mg, was evaluated in the efficacy studies of Non-24 Hour Disorder. The recommended dose of tasimelteon is 20 mg per day taken 1 hour prior to bedtime, at the same time every night based on the time of tasimelteon administration in the efficacy studies in Non-24 Hour Disorder.

The Applicant states that published studies with melatonin have shown that entrainment of blind subjects suffering from Non-24 Hour Disorder may be more likely to occur, and may occur more quickly, if treatment is started in the phase advance portion of the melatonin Phase Response Curve (i.e., the time when a subject's endogenous circadian rhythm is coming into alignment with their bedtime). Based on these data, the duration of an eligible subject's in-phase transition in Study 3201 was varied such that randomization and start of study drug dosing would start when a given subject's endogenous circadian rhythm was aligned with his or her bedtime. However, despite these efforts to time the start of the study drug based on the acrophase of urinary melatonin metabolite, the Applicant estimates that about 30 - 40% of subjects randomized in Study 3201 may not have been in-phase at the start of dosing (Teleconference on 9/26/13).

In Study 3201, the range of circadian cycle lengths in enrolled subjects was 30 to 114 days (corresponding to τ range: 24.21 to 24.8 hours); majority of subjects had a cycle length between 40 and 80 days (corresponding to τ range: 24.3 to 24.6 hours). The range of circadian cycle length in enrolled subjects in Study 3203 was 21 to 184 days (corresponding to τ range: 24.13 to 25.14 hours) for Study 3203. In Study 3201, subjects were treated for 2.5 cycles or 6 months, whichever was shorter. In Study 3203, subjects were treated for approximately 11 – 12 weeks in the Run-in phase before randomized withdrawal.

Subjects who entrained in Study 3201 did so by Week 3 after the start of dosing, i.e., entrainment as assessed by urinary aMT6). I performed a subjective assessment of the graphic representation of sleep diary data (see Section 6.1.10 of this review for a description of graphic representation of sleep diary data) which showed that most of those subjects who improved in their nighttime and daytime sleep parameters did so within the first 30 – 50 days of start of treatment. In Study 3203, of the 48 subjects who had their circadian period assessed in the Run-in period, 24 (50%) entrained after tasimelteon treatment over approximately 11 weeks.

However, 5 subjects treated with tasimelteon in Study 3201 who continued on to Study 3203 did not entrain in Study 3201 but did so in the Run-in phase of Study 3203, i.e., after 6 months of treatment in 3201 plus 6 weeks in 3203. In 3 of these 5 subjects who entrained late, the graphic presentation of their sleep diary data showed slower but gradual improvement in stabilization of both nighttime and daytime sleep over time. Reviewer's comments: some subjects may need to take tasimelteon for at least 6 months to experience improvement of symptoms.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In Study 3203, subjects were treatment with tasimelteon for approximately 11 – 12 weeks in the Run-in phase which was followed by the Randomized withdrawal phase for 8 weeks.

The proportion of subjects who became non-entrained after randomization (randomized withdrawal) to tasimelteon was statistically significantly less than the proportion of subjects randomized to placebo treatment ($p = 0.0026$). As previously discussed in Section 6.1.5 of this review, the pre-specified secondary endpoint of Time to Relapse (≥ 45 minute decrement in weekly average of nTST compared to the Run-in Phase) did not reach statistical significance (p -value = 0.0907); there were 4 (4/10; 40%) subjects with relapse in the tasimelteon group versus 8 (8/10; 80%) in placebo group. Those subjects that did relapse did so within 50% of their circadian cycle time when subjects are expected to have maximum misalignment between their endogenous circadian rhythm and the 24-hour clock (see Figure 8 in Section 6.1.5 of this review). A sensitivity analysis, defining the time to relapse \geq as 60 minute decrement), was statistically significant (p -value = 0.0181) in favor of tasimelteon.

The results of 'Change in average dTSD from the run-in phase', 'Change in average UQ-dTSD from the run-in phase', 'Change in average LQ-nTST from the run-in phase' and 'Change in MoST from the run-in phase' secondary clinical outcomes showed statistical significance in favor of tasimelteon (p -value = 0.0547, 0.0266, 0.0233 and 0.0108, respectively).

6.1.10 Additional Efficacy Issues/Analyses

In the previous Section 6.1.6 ‘FDA-conducted Analyses of Efficacy Data from Study 3201 and Study 3203’, I discussed the lack of agreement on the primary endpoint between the Agency and the Applicant at the time of unblinding of Study 3201. In this section, I explore issues arising from the lack of an agreed-upon pre-specified primary endpoint, and lines of evidence supporting the specific effect of tasimelteon on the cyclical nature of Non-24 Hour Disorder.

Lack of Agreed-upon Pre-specified Primary Endpoint in Study 3201 and Study 3203:

The basis for a new drug approval is the demonstration of efficacy and acceptable safety by adequate and well-controlled trials. Among the many characteristics of an adequate and well-controlled trial (21 CFR 314.126) is that the results reflect a clear prior hypothesis documented in the protocol, and is intended to reduce the risk of false discovery or inflation of Type I error. In Study 3201, there were no pre-specified primary clinical endpoint(s), which by itself (themselves), capable of demonstrating benefit in patients. In this setting and as previously noted, choosing clinical outcome(s) such as the LQ-nTST and UQ-dTSD post-hoc to establish efficacy in Study 3201 or Study 3203 risks inflation of Type I error in either study. While such post-hoc selection of clinical endpoints is not ordinarily desirable, the risk of false discovery in this application is diminished by the following:

- Independent substantiation with statistical significance for the clinical endpoints, LQ-nTST, UQ-dTSD, dTSD and CGIC, in both Study 3201 and Study 3203.
- Although several subjects participated in both Study 3201 and Study 3203, the design of Study 3203 (randomized withdrawal) is different than that of Study 3201, and such differences in study design between replicative studies increase the likelihood of independent substantiation as compared to studies with similar design. Both studies were conducted at multiple sites.

Evidence of Effect on the Cyclical Nature of Non-24 Hour Disorder:

The development program of tasimelteon in the treatment of Non-24 Hour Disorder was novel. There were no regulatory precedents with regard to endpoints and study design. During the development program, the Agency stated that to support a claim for the syndrome of Non-24 Hour Disorder, benefit would have to be shown for the fundamental clinical symptoms of the disease (1/6/11). Specifically, the Agency opined that an effect on the cyclical nature of the condition would need to be demonstrated to support the specificity of the indication, and an effect beyond that of an ordinary soporific. In the following paragraphs, I discuss whether the evidence supports a specific effect of tasimelteon on the cyclical nature of the condition.

Graphical Representation of Sleep Parameters (from Electronic Diary) Over Time:

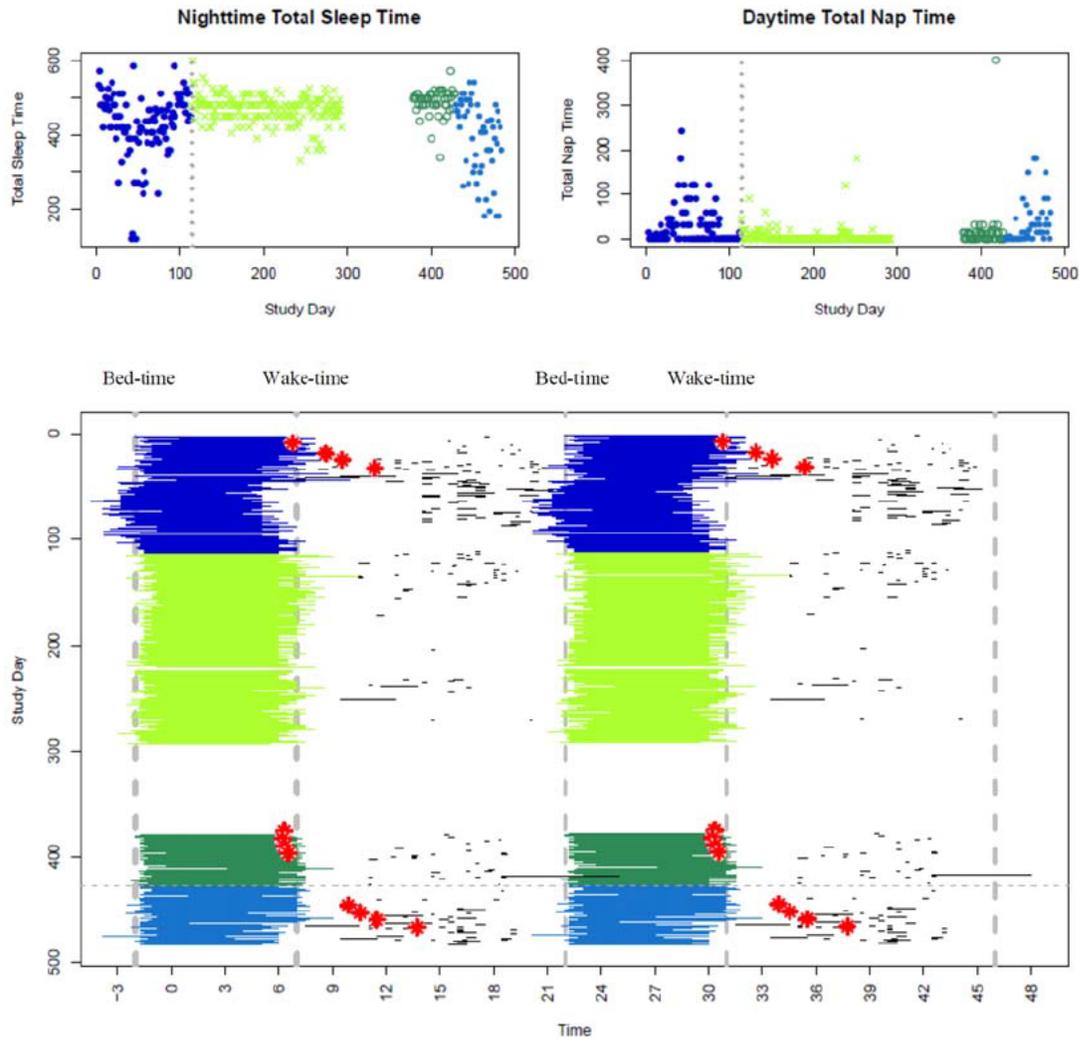
Non-24 Hour Disorder is cyclical in nature with periods of problems with nighttime sleep and daytime naps alternating with periods of good sleep at night. Electronic sleep diary was collected daily (PSQ in the morning and Pre-SQ before bedtime) for considerably long duration in Study 3201, i.e., during the Pre-randomization phase for up to 70% of one circadian cycle time, and in the Randomization phase for at least 2.5 circadian cycles or 6 months (which ever was less). In Study 3203, the electronic diary was collected daily in the Run-in phase (average 57 days) and

the Randomized withdrawal phase (average 59 days). Graphical presentation of these data over time in a given individual subject helps understand the cyclical nature of the symptoms and the treatment effect, if any, on this cyclicity.

The following is a graphical presentation of the sleep diary data over time for a subject highlighted by the Applicant (Subject (b) (6)), who first enrolled in the Screening phase of Study 3201 followed Open-label treatment phase, then in the Run-in phase of Study 3203 and finally in the Randomized withdrawal phase (randomized to placebo). In the upper left box, there is a fair amount of variation in the nTST with several nights of poor sleep during Screening (blue dots), followed by almost regular full night sleep during the Open-label treatment (bright green dots) which continue in the Run-in phase of Study 3203 (dark green dots), and poor sleep again during Randomized withdrawal phase (randomized to placebo). In the upper right box, a similar but inverse pattern emerges for dTSD. In the double plotted raster plot at the bottom, the colored bars represent nTST at various phases of treatment – Screening, Open-label treatment, Run-in, and Randomized withdrawal phase (color code similar to that for the dots in the box above), interval between vertical lines represent desired night time sleep, black bars represent daytime naps, and red stars depict aMT6's secretion acrophase. Each raster plot line starts at the time a subject fell asleep (time in bed + time to fall asleep) and ends when a subject woke up for the day (wake time after sleep onset is not reflected). As can be seen, during Screening the subject appears to progressively sleep earlier at night with many daytime naps which also appear progressively at later time points, and during the Open-label treatment the night time sleep is regular with very few daytime naps – a pattern which continues during the Run-in phase when the red stars (melatonin acrophase) appear before 6 AM. However, after beginning placebo during the Randomized withdrawal phase, poor night time sleep and increase of daytime naps emerge, and the red stars begin drifting at later time points similar to the pattern seen during Screening. The overall pattern in this subject indicates an effect of tasimelteon on the cyclical nature of symptoms, and who also is entrained by melatonin acrophase data.

Figure 9: Graphic depiction of sleep diary data over time for Subject (b) (6) in Studies 3201 and 3203.

OLE - IVRS Summary Report for (b) (6) Tau=24.19; cycle=126



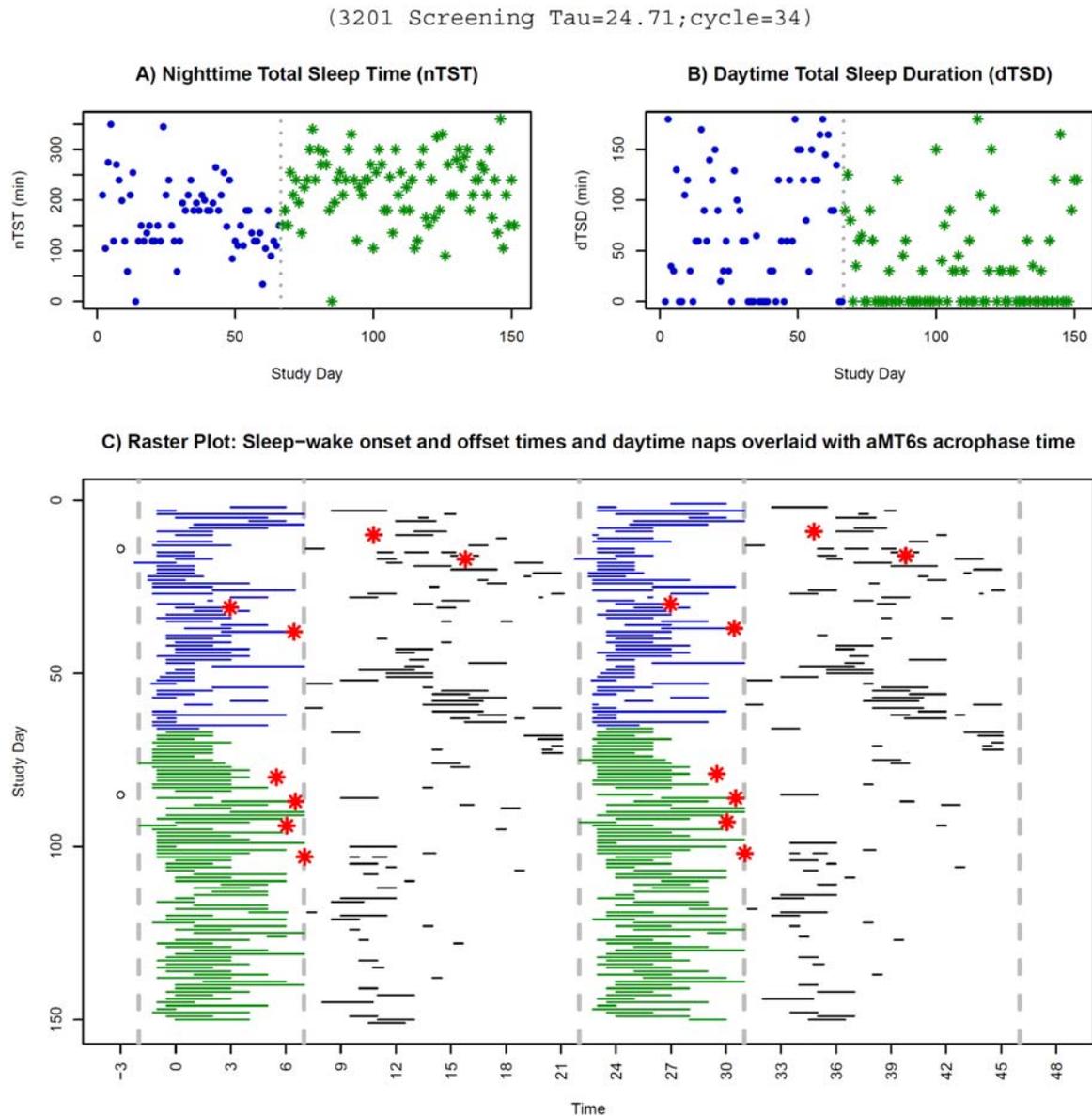
Nighttime total sleep (nTST) and daytime total nap duration are plotted for one individual in the top boxes and double plotted in the bottom raster plot. The color code is 1) royal blue - baseline screening, 2) bright green - treatment phase (3201), 3) dark green - tasimelteon run-in phase (3203), and 4) muted blue - randomized withdrawal phase (3203). Red stars represent the time of the aMT6s acrophase and the vertical hashed lines in the raster plot represent the scheduled bed time and wake-time. The first day of dosing in 3201 is represented in the top two boxes by the dashed vertical line, and by the color change of the nTST in the raster plot. The randomized withdrawal phase of 3203 is represented by the change from green to blue in the upper boxes and the dashed horizontal line in the raster plot.

Note: Gaps between Study 3201 and Study 3203 in the raster plot represent a gap in data collection. A gap on the raster plot could represent one or more of several scenarios: 1) the subject had collected the required 2.5 circadian cycles worth of sleep data in study 3201 in which they were still on study drug (tasimelteon or placebo), 2) the subject was on open label tasimelteon as part of the run in to study 3203, or 3) the subject was in between studies 3201 and 3203. For study 3203, subjects were on open-label tasimelteon during the first 6 weeks of the open-label run-in phase of 3203 and did not record sleep diary data. Subjects began collecting sleep diary data on day 42, the same week as urine collection for circadian entrainment assessment.

Source: NDA 205677, 5/31/13: Module 2.7.4 Summary of Clinical Efficacy, Table 17, page 86.

The effect of tasimelteon on the cyclical nature of Non-24 Hour Disorder is not clear in the graphical presentation of sleep diary in some subjects. For example, subject (b) (6) (see Figure below) was randomized to tasimelteon in Study 3201 and did become entrained. However, the effect on the cyclical nature of nighttime and daytime symptoms while on tasimelteon is not clear. There appears to be subtle progressive drifting of the daytime and nighttime sleep even on tasimelteon despite being entrained (stable acrophase / red stars).

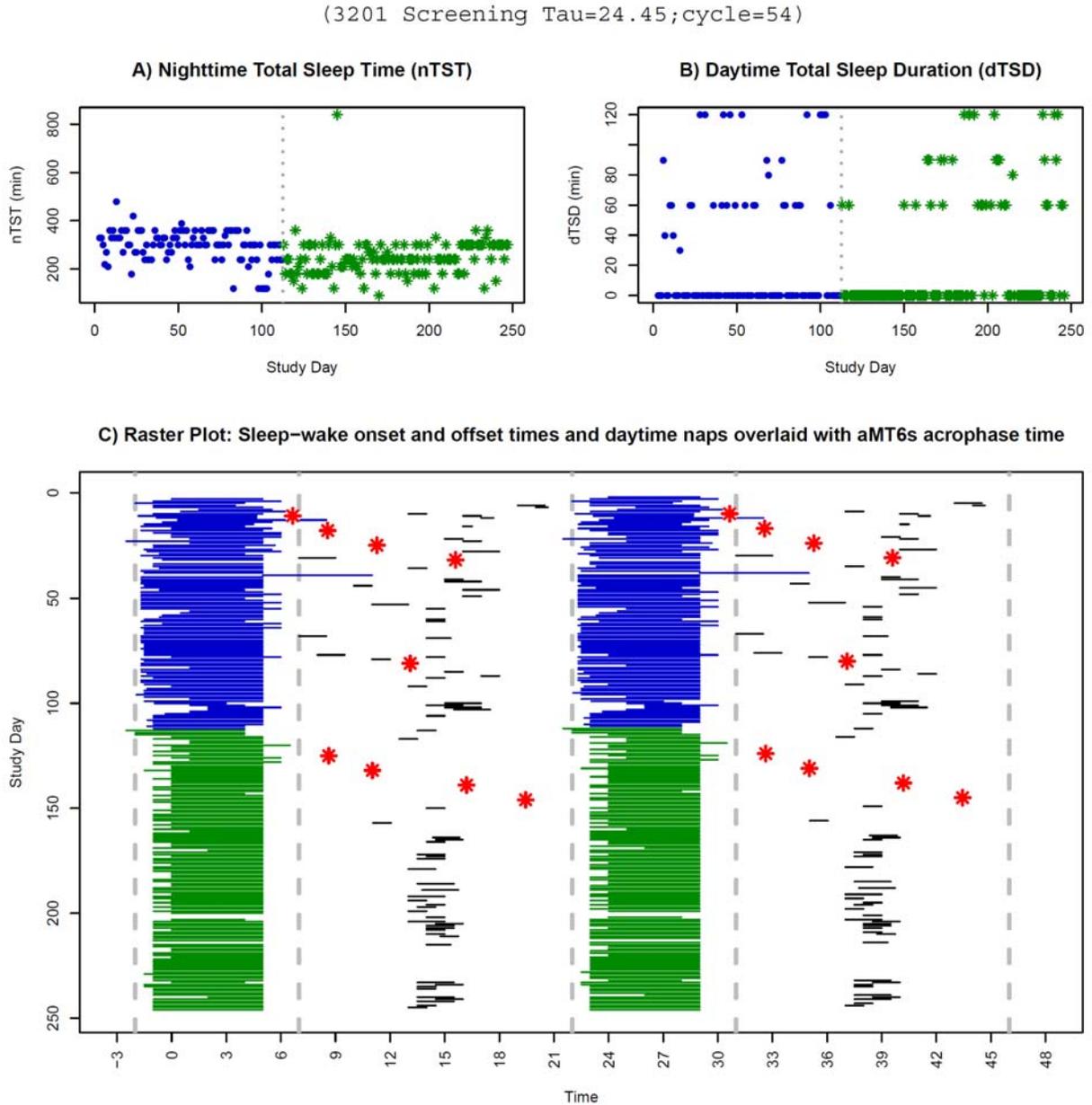
Figure 10: Graphic depiction of sleep diary data over time for Subject (b) (6) in Study 3201.



Source: NDA 205677, 5/31/13: Module 2.7.4 Summary of Clinical Efficacy – Appendix 2: Raster plots, IVRS Summary Report for (b) (6)

The following figure is the raster plot for subject (b) (6) who was randomized to tasimelteon in Study 3201. After beginning tasimelteon (green bars), this subject clearly did not entrain as evidenced by the drifting acrophase (red stars). In contrast, the subject appears to have had a beneficial stabilization of the nighttime sleep (incidentally, appears to be waking up at the same time on most days) and consolidation of the daytime naps on tasimelteon.

Figure 11: Graphic depiction of sleep diary data over time for Subject (b) (6) in Study 3201.



Source: NDA 205677, 5/31/13: Module 2.7.4 Summary of Clinical Efficacy – Appendix 2: Raster plots, IVRS Summary Report for (b) (6).

I reviewed the graphic representation of the sleep diary data for each individual subject in Studies 3201 and 3203. The visual assessment of benefit on the cyclical nature of the nighttime and daytime sleep using the graphical representation in an individual subject is very subjective. However, despite the subjective nature of such an assessment, the proportion of subjects (14/42; 33.3%) who appear to have had a positive effect on stabilizing the cyclical nighttime and daytime symptoms in the tasimelteon subjects was numerically higher than that in placebo subjects (4/42; 9.5%). In most of these subjects who appeared to have had a benefit, the benefit seems to begin approximately within the first 30 - 50 days after treatment with tasimelteon began.

Mid-point of Sleep Timing (MoST):

A description of MoST is provided in Section 6.1.1 'Methods' of this review. MoST score for an individual who is sleepy during the day but does not nap (possibly due to social/employment circumstances) will be higher (i.e., better) than another individual who takes a consolidated nap in the afternoon and otherwise remains functional during the rest of the day. Therefore, higher MoST scores do not necessarily translate to clinical benefit. Nevertheless, MoST can potentially evaluate an effect of tasimelteon on the periodic misalignments of the circadian period and the 24-hour clock. The mean change from baseline in MoST in both Studies 3201 and 3203 was statistically significant in favor of tasimelteon (see Sections 6.1.5 and 6.1.6 of this review).

Differences in nTST Between Maximum Alignment (In-Phase) and Maximum Misalignment (Out-of-Phase) in a Given Subject:

In Study 3201, the lengths of circadian cycle varied among the enrolled subjects. Circadian cycle length expressed as a percentage (actual time/circadian cycle length) is a potential means of comparing effects at a given point in a circadian cycle in one subject to a similar time point in another subject. For example, the time point at 50% circadian cycle time is when patients are expected to be most symptomatic since the endogenous circadian rhythm is most out-of-sync with the 24-hour day, and time points 0% or 100% are when there is synchronization. The Applicant was asked to conduct the following analyses using all available nTST data in the Randomization phase of Study 3201 (and the Study 3203 run-in phase for tasimelteon subjects who enrolled seamlessly into the run-in phase) for each subject randomized in Study 3201 (regardless of entrainment status).

For each randomized subject who was in the trial for at least 70% of the duration of his/her first circadian cycle in the randomization period in Study 3201, all available nTST data collected between the time points at 0% and 20% of the first circadian cycle was used to calculate the mean, and all available nTST data collected between the time points 50% to 70% of first circadian cycle to calculate the mean for this segment. The difference between these two means is a reflection of the most symptomatic phase after correcting for within subject most-likely-to-be asymptomatic period. Similar analysis was requested for subjects with a second circadian cycle in the randomized phase. The Applicant was asked to provide a summary of these means and differences for each individual subject by each cycle, and compare the mean difference between the treatment groups for the first cycle and then for the second cycle, using both ANCOVA and permutation ANCOVA t-test (baseline, site and treatment groups as covariates).

The above analyses are intended to evaluate the benefit when subjects are expected to be most misaligned (and, therefore, most symptomatic) and which also accounts for non-specific effects on insomnia, if any. In addition, data in individual subjects and group mean data over the first and second cycle can help evaluate an effect on cyclicity.

The Applicant notes that predictions of future timing of acrophase were made based on the timing of the observed acrophase during the measurement of τ which was performed during the screening period over approximately 4 successive weeks. However, this measurement was not precise enough to predict where the acrophase will be several weeks later, resulting in a very large error of estimating the future position of the acrophase. This suggests that using the available τ measurements to predict whether a patient is in-phase or out-of-phase at the time of randomization may result in some imprecise estimates of timing of “in-phase” for some patients. Therefore, the Applicant proposed an analysis that can provide insight into whether the treatment is corrective for the Non-24 cyclical pattern of the sleep-wake cycle, i.e., an analysis of the *absolute value* of |Diff (in – out)|, as this would represent the change between phases regardless of assignment. Reviewer’s comments: I agree that the absolute value of |Diff (in – out)| is appropriate since it would capture the effect on cyclicity regardless of whether subjects were randomized when they were In-Phase (endogenous clock aligned with the 24-hour clock) or Out-of-Phase.

The following two tables summarize the results for the difference between In-phase and Out-of-Phase for nTST and dTSD, respectively, for Cycle 1, Cycle 2 and Cycles 1+2 combined. As can be seen, the tasimelteon group had statistically significantly lower mean absolute value than the placebo group placebo group, indicating a significant benefit in stabilizing the cyclical pattern of nighttime and daytime symptoms in Non-24 Hour Disorder. The Sponsor also conducted a sensitivity analysis by not using the absolute value but instead removing from the analysis population individuals with highly negative Diff (in-out) values, as they would suggest incorrect phase estimation. These analyses also showed statistical significance in favor of tasimelteon (data reviewed but summary table not included in this review).

Table 15: Absolute Value of the Difference of nTST for In-phase and Out-of-phase

Cycle (N)	Placebo (Hour)	Tasimelteon (Hour)	Diff (Hour)	P-Value ^a	Permutation P-Value ^b
Cycle 1 (N= Placebo: 34; tasimelteon: 38)	1.46	0.52	0.94	0.0006	0.0002
Cycle 2 (N= Placebo: 32; tasimelteon: 37)	1.03	0.52	0.52	0.0082	0.0078
Cycle 1+2 (N= Placebo: 34; tasimelteon: 38)	1.15	0.43	0.72	0.0007	0.0003

^a P-value was based on analysis of variance model.

^b P-value was based on the permutation ANOVA t-test

Note: The mean differences between the in-phase segment and out-of-phase segment was analyzed in the Analysis population by an ANOVA model with the fixed effect of pooled site and treatment group, as well as by a permutation ANOVA t-test. The permutation ANOVA t-test was conducted through the MULTTEST procedure in SAS on the residuals from the ANOVA model with only the pooled site adjusted.

Table 16: Absolute Value of the Difference of *dTSD* for In-phase and Out-of-phase

Cycle (N)	Placebo (Hour)	Tasimelteon (Hour)	Diff (Hour)	P-Value ^a	Permutation P-Value ^b
Cycle 1 (N= Placebo: 34; tasimelteon: 38)	1.01	0.34	0.66	0.0070	0.0031
Cycle 2 (N = Placebo: 32; tasimelteon: 37)	0.66	0.26	0.40	0.0077	0.0065
Cycle 1+2 (N= Placebo: 34;tasimelteon: 38)	0.70	0.28	0.42	0.0211	0.0166

^a P-value was based on analysis of variance model.

^b P-value was based on the permutation ANOVA t-test

Note: The mean differences between the in-phase segment and out-of-phase segment was analyzed in the Analysis population by an ANOVA model with the fixed effect of pooled site and treatment group, as well as by a permutation ANOVA t-test. The permutation ANOVA t-test was conducted through the MULTTEST procedure in SAS on the residuals from the ANOVA model with only the pooled site adjusted.

Source: NDA 205677, 5/31/13: Amendment dated 10/15/13: Response to Information Request, 9/19/13; Table 1, page 5.

The above analyses were conducted in the Analysis Population, which was defined as all subjects in the ITT population that had at least 70% of one cycle of data reported during each of Pre-randomization *and* Randomization phases. However, the above analyses do not involve a change from baseline, and therefore, subjects with at least 70% of one cycle of data during the Randomization phase should be included in the analyses (there were 4 such subjects in the placebo group and 1 subject in the tasimelteon group). The Applicant was asked to perform analyses including these subjects such that the *new Analysis Population* will have 38 subjects in the placebo group and 39 subjects in the tasimelteon group (n = 77). These analyses of the Absolute Value of the Difference of nTST and dTSD for In-phase and Out-of-phase are shown in the following two tables for nTST and dTSD, respectively. The tasimelteon group had statistically significantly lower mean absolute value than the placebo group placebo group.

Table 17: Absolute Value of the Difference of *nTST* for In-phase and Out-of-phase in subjects with $\geq 70\%$ of cycle data post-randomization

Cycle (N)	Placebo (Hour)	Tasimelteon (Hour)	Diff (Hour)	P- Value ^a	Permutation P-Value ^b
Cycle 1 (N= Placebo: 38; tasimelteon: 39)	1.42	0.53	0.89	0.0007	0.0004
Cycle 2 (N= Placebo: 33; tasimelteon: 37)	1.00	0.52	0.49	0.0105	0.0087
Cycle 1+2 (N= Placebo: 38; tasimelteon: 39)	1.15	0.43	0.72	0.0004	0.0003

^a P-value was based on analysis of variance model.

^b P-value was based on the permutation ANOVA t-test

Source: NDA 205677, 5/31/13: Amendment dated 10/29/13: Response to Information Request, 10/24/13; Table 1, page 2.

Table 18: Absolute Value of the Difference of *dTSD* for In-phase and Out-of-phase in subjects with $\geq 70\%$ of cycle data post-randomization

Cycle (N)	Placebo (Hour)	Tasimelteon (Hour)	Diff (Hour)	P-Value ^a	Permutation P-Value ^b
Cycle 1 (N= Placebo: 38; tasimelteon: 39)	0.97	0.39	0.58	0.0149	0.0100
Cycle 2 (N= Placebo: 33; tasimelteon: 37)	0.64	0.29	0.35	0.0181	0.0151
Cycle 1+2 (N= Placebo: 38; tasimelteon: 39)	0.73	0.30	0.43	0.0181	0.0148

^a P-value was based on analysis of variance model.

^b P-value was based on the permutation ANOVA t-test

Source: NDA 205677, 5/31/13: Amendment dated 10/29/13: Response to Information Request, 10/24/13; Table 2, page 2.

The Applicant was also asked to perform analyses of the Absolute Value of the Difference of nTST and dTSD for In-phase and Out-of-phase on all subjects (n=42 in placebo and n=42 in the tasimelteon group), using available raw data in the 0-20% and 50-70% windows in Cycle 1 and Cycle 2 for those subjects who have < 70% data in the Randomization phase (subjects that did not have even one night/day data in these windows in a given cycle could be exclude). Only one subject had non-missing night/day data in 0-20% and 50-70% windows in cycle 1. Analysis performed after adding this subject showed that tasimelteon group had statistically significantly lower mean absolute value than the placebo group placebo group (data reviewed but not included in review).

In addition, the Applicant was asked to perform analyses of the Absolute Value of the Difference of nTST and dTSD for In-phase and Out-of-phase on all subjects in each treatment group (n=42 in placebo and n=42 in the tasimelteon group) using the following imputation methods for subjects with <70% data in the Randomization phase, i.e., for the 4 placebo subjects and 3 tasimelteon subjects.

- Impute the data for subjects with < 70% of data in the Randomization phase with mean of the 77 subjects in the new analysis population.
- Impute the data for subjects with <70% of data in the Randomization phase with mean of their respective treatment group mean (38 subjects in the placebo group and 39 subjects in the tasimelteon group).

These analyses also showed that the tasimelteon group had statistically significantly lower mean absolute value than the placebo group placebo group, indicating a significant benefit in stabilizing the cyclical pattern of nighttime and daytime symptoms in Non-24 Hour Disorder.

Reviewer's conclusions regarding an effect on cyclicity: The visual assessment of benefit on the cyclical nature of the nighttime and daytime sleep using the graphical representation in individual subjects over time (although such assessment is subjective in nature), the statistically significant effect favoring tasimelteon on MoST, and importantly, the statistically significant effect favoring tasimelteon on the absolute value of the difference of between In-phase and Out-of-Phase for cycle 1 and 2 post-randomization, indicate a specific effect of tasimelteon on the cyclical nature of Non-24 Hour Disorder.

7 Review of Safety

Safety Summary

Applicant's Conclusion Regarding Safety:

Based upon the overall safety data as well as the specific analyses performed by Study Group, tasimelteon is generally safe and well-tolerated in both the target population of totally blind individuals with non-24 Hour Disorder as well as a larger population who includes sighted and blind individuals, 18 years of age and older, including elderly patients up to 92 years of age. It is reasonable to conclude, based upon the overall safety data, that tasimelteon is safe and well tolerated and reasonably likely to pose a minimal safety risk to the indicated population. The large majority of adverse events will be mild to moderate in nature, and will occur within the first 30 days of therapy.

Reviewer's Conclusion Regarding Safety:

Across the entire safety database, there were no deaths, and there were few non-fatal serious adverse events. Other than, perhaps gastroenteritis, no treatment-emergent serious adverse event was experienced by more than one subject. The proportion of subjects who experienced any treatment-emergent adverse event that led to early termination was fairly even between treatment groups in the entire safety database. Treatment-emergent adverse events which 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 is not associated with adverse effects due to abrupt withdrawal as assessed by the Tyrer Benzodiazepine Withdrawal Symptoms Questionnaire based on safety data which are adequate for such an assessment. Similarly, tasimelteon is not associated with next-day residual effects as assessed by Digit Symbol Substitution Test, Visual Analog Scale (mood scale assessing sleepy/alert), and Karolinska Sleepiness Scale.

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

Tasimelteon is not associated with an adverse effect on suicidality as assessed by the Columbia Suicide Severity Rating Scale based on safety data which are adequate for such an assessment.

The following common treatment-emergent adverse events, defined as experienced by at least 3 subjects in the tasimelteon group and with a ≥ 2 -fold greater frequency than in placebo group, were identified in subjects with Non-24 Hour Disorder: 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 laboratory measures of liver injury, and available data is 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 is 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 available data which are sufficient for such a determination.

Tasimelteon does not have adverse effects on vital signs.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data from a total of 22 clinical studies were used in the Integrated Summary of Safety (ISS) to assess safety of tasimelteon (the Applicant uses the terms Summary of Clinical Safety and ISS interchangeably). These 22 studies include 14 Phase I studies, 2 Phase II studies and 6 Phase III studies (see Figure and Table in Section 5.1 ‘Tables of Studies/Clinical Trials’ of this review). Four studies (VP-VEC-162-3201, VP-VEC-162-3202, VP-VEC-162-3203 and VP-VEC-162-3204) were conducted in the target population – subjects with Non-24 Hour Disorder. Twenty of the 22 studies have been completed. The remaining two studies are open-label safety studies (VP-VEC-162-3202 and VP-VEC-162-3204) in subjects with Non-24 Hour Disorder which are ongoing. Interim database locks from both of these studies were conducted and safety data through the cut-off date of 11/30/12 was included in the integrated safety database submitted as part of this NDA.

7.1.2 Categorization of Adverse Events

Adverse events were defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related, consistent with 21CFR 312.32. Treatment-emergent adverse events were defined as those events which were newly occurring or worsening from baseline, and only events occurring after administration of at least 1 dose of study drug and within 3 days following cessation of the study drug were included. The definition of a serious adverse event was consistent with the regulatory definition (21CFR 312.32), and included those adverse events that were considered serious based on appropriate medical judgment. This definition was uniformly applied to all clinical studies in the safety database

The source of the safety data was the clinical trials conducted by the Applicant. All Phase I and II clinical studies, with the exception of Study 1108 (n = 82), were conducted in the United States. A total of 136 subjects were enrolled in Study 3201 (double-blind and open-label

extension) which was conducted in the United States (n = 124) and Germany (n = 12); 84 of 136 subjects were enrolled in the placebo-controlled double-blind segment and the remaining 52 were enrolled into the parallel open-label extension. Study 3203 (randomized withdrawal) was conducted in the United States. The open-label Study 3202 is being conducted in France, and the open-label Study 3204 is being conducted in the United States.

All adverse events were included in the pooled safety database, and datasets for the various pools regardless of seriousness or relationship to the investigational product. Adverse events included those spontaneously reported by subjects, those observed by the investigator, and clinically significant laboratory values, vital signs, ECGs or other standardized measurements. The clinical significance of these assessments was left entirely to the investigator's discretion. Guidance as to which laboratory values were potentially clinically notable was included in the study protocols. The above definition of an adverse event and method of collecting events was uniformly applied across all studies in the integrated safety database. When possible, symptoms were grouped together as a single syndrome or diagnosis.

All studies were re-coded for the pooled safety database from the original verbatim terms including those studies that were originally coded to MedDRA 14.1. Verbatim Terms were coded to Preferred Terms and the Primary System Organ Class (SOC). High Level Term and High Level Group Term were not included due to the low frequency of events. If Verbatim Terms contained more than one term or symptom, these were split into distinct codable terms.

I reviewed the appropriateness of coding. In the entire integrated safety database, there were a total of 1078 adverse events (treatment-emergent and non treatment-emergent) that were reported verbatim and which were coded into 464 Preferred Terms using the MedDRA 14.1 coding dictionary. I reviewed all these reported events for appropriateness and consistency of coding into the Preferred Terms and System Organ Class. I audited the Case Report Forms and narratives which were provided to see if the adverse events described in them were captured in the adverse event dataset. There were a few discrepancies in coding. For example, subject VP-VEC-162-COSET (b) (6) reported verbatim 'sprained left thumb as the result of a fall' which was coded to the preferred term 'ligament sprain' but not also to 'fall'. However, despite these few discrepancies, the coding of the verbatim terms to preferred terms was appropriate and should allow for reasonably accurate assessment of safety.

I reviewed the individual narratives and source documents (Case Report Forms, laboratory test reports, etc) for cases of death, nonfatal serious adverse events, adverse events leading to drop-out, and adverse events of special interest in order to determine if the event was coded to the preferred term correctly, to examine the onset/worsening of the event in the context of study drug exposure time line, to determine if there was a likely explanation for the event other than the study drug (i.e., another concomitant drug or illness), and finally, the outcome of dechallenge or, importantly, rechallenge.

Although clinical trials were not powered to detect statistically significant difference between treatment groups for individual adverse events (or combination of related adverse events), nonetheless, I calculated significance level for major safety analyses such as serious adverse events, adverse events of special interest, etc. Since the safety dataset in this application was

relatively small and the frequency of significant adverse events were rare (and therefore the asymptotic method unreliable), it is desirable to calculate a significance level based on the exact distribution of the test statistic which makes it possible to obtain an accurate p-value without relying on assumptions that the data may not meet. I used the StatXact® – a statistical package for exact nonparametric inference, of the base software Cytel Studio® 9 to calculate exact confidence intervals for proportions and ratio of proportions.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

As noted above, the Applicant converted the raw safety data from the 22 individual studies to the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) format which were then pooled together to create the ISS pooled database, from which the analysis datasets were generated.

The following Table summarizes the pooling of clinical studies into Pooled Study Groups in the ISS. A unique subject identifier was assigned to each individual in the ISS since subjects had the potential to enroll into more than one study (e.g., placebo-controlled study into open-label study). Subjects were treated uniquely in each Pooled Study Group except Pooled Study Group 3 where subjects were treated uniquely in each study of this Group. This was because subjects in Study 3203 were a subset of those screened and/or enrolled in Study 3201.

Table 19: Pooling of Study Groups in the integrated summary of safety

Pooled Study Group	Studies Included	Population Studied	Purpose of Group	Tasimelteon N	Placebo N
1	All studies	All subjects in all studies	Overall safety database	1,346	306
2	3201, 3104 & 004	Subjects with insomnia or Non-24	PC repeat dose efficacy studies	429	203
2.1	3201 & 3104	Subject with insomnia or Non-24, non-elderly studies	Non-elderly, PC efficacy studies	259	146
3	3201 & 3203	Subjects with Non-24	Target indication, PC studies	52	52
4	3201, 3202, 3203 & 3204 (placebo data not presented)	Subjects with Non-24	Target indication, all safety data in exposure subjects	183	N/A
5	Studies not included in Groups 2-4	Clinical Pharmacology and Healthy Volunteers	All studies not included in Groups 2-4	776	131

Source: NDA 205677, 5/31/13: Module 2.7.4 Summary of Clinical Safety; adapted from Tables 1 & 2, pp14-15.

All clinical studies were pooled into the **Pooled Study Group 1**. Pooling of all clinical studies in the development program would be useful to identify important safety events – serious events, those leading to early discontinuations, designated medical events, and rare but significant events, across the entire safety population. Placebo-controlled studies were pooled together to

allow for reliable estimation of incidence rates of treatment-emergent adverse events between treatment groups.

Pooled Study Group 2 (placebo-controlled pool) consisted of 3 placebo-controlled studies which enrolled subjects with primary insomnia or subjects with Non-24 Hour Disorder, and in which subjects were treated double-blind for at least 4 weeks: CN-116-004 (interchangeably referred to as Study 004 in this review), VP-VEC-162-3104 (interchangeably referred to as Study 3104 in this review), and Study 3201. The daily doses of tasimelteon evaluated in Study 004 were 1, 10 and 50 mg, in Study 3104 were 20 and 50 mg, and in Study 3201 was 20 mg. Thus, tasimelteon was categorized into <20 mg, 20 mg, 50 mg, and overall tasimelteon in the Pooled Study Group 2. Since Study 004 was a relatively large (n = 227) study which enrolled only elderly subjects (ages 65- 92 years), **Pooled Study Group 2.1** was provided to show placebo-controlled data for repeat dosing studies in non-elderly adult subjects (i.e., Pooled Study Group 2 without Study 004).

Study 3201 and Study 3203 had placebo-controlled, double-blind study phases. Data from these two studies were pooled (**Pooled Study Group 3**) to evaluate the safety profile in subjects with Non-24 Hour Disorder. This pool analyzed data only from the double-blind portions of each study, i.e., data from the Pre-Randomization Phase of Study 3201 and the Run-in Phase of Study 3203 were excluded. Thirteen subjects participated in the double-blind portions of both Study 3201 and Study 3203. As noted above, for the purposes of this pool only, each of the 13 subjects was counted separately by the study.

In the **Pooled Study Group 4**, safety data from Non-24 Hour Disorder subjects with exposure only to tasimelteon in Study 3201, Study 3202, Study 3203 and Study 3204 were pooled and analyzed longitudinally over time for each subject, and included all randomized and open-label treatment periods (data from subjects while they received placebo were not included). For each subject, the safety data was characterized from the beginning of the first dose of tasimelteon (regardless of which study resulted in first active exposure for that subject) and continuing throughout the subsequent active and open-label treatment periods for that individual subject. Some subjects had short breaks in tasimelteon exposure between study participation during which safety data was not systematically collected; therefore, the time during these breaks was ignored for the purpose of analyses in Pooled Study Group 4. Additionally, some subject had single-blind placebo treatment during 2 weeks of washout (early protocol versions of Study 3201), and/or received double-blind placebo treatment as part of the randomized withdrawal period of Study 3203; the data collected during these periods were also ignored for the purpose of analyses in Pooled Study Group 4.

All clinical pharmacology studies, Study 2101 and Study 3101 were pooled (**Pooled Study Group 5**). In the latter two studies, healthy volunteers were asked to sleep 5 hours prior to their usual bedtimes on 3 sequential nights or on a single night, respectively. In Pooled Study Group 5, tasimelteon treatment was categorized into ≤ 20 mg, 30mg – 50 mg, >50 mg, and overall tasimelteon.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Across the ISS, the safety populations were defined as all subjects treated with at least one dose of study medication. A total of 1,346 subjects received at least one dose of tasimelteon during the course of all 22 clinical studies. The following table summarizes subjects who received at least one dose of tasimelteon by dose category in different phases of drug development. A total of 437 healthy subjects and subjects with hepatic impairment or renal impairment received at least one dose of tasimelteon in Phase I studies. In Phase II/III studies, 909 healthy subjects and subjects with primary insomnia or Non-24 Hour Disorder received at least one dose of tasimelteon.

Table 20: Summary of all unique subjects who received at least one dose of tasimelteon in all clinical trials

Study Phase	Study Population	<20 mg	20 mg	> 20 mg	Any Dose
All	All subjects ^a	170	621	555	1,346
	All Phase I subjects	47	221	169	437
All Phase I Studies	Healthy Subjects	47	189	169	405
	Subjects with Hepatic Impairment	0	16	0	16
	Subjects with Renal Impairment	0	16	0	16
	All Phase II and Phase III subjects	123	400	386	909
All Phase II, III studies	Healthy subjects – Proof of concept of	9	8	14	31
	Healthy subjects – induced transient	0	100	208	308
	Subjects with insomnia/ primary	114	109	164	387
	Subjects with Non-24-Hour disorder	0	183	0	183

^aSubjects exposed to more than one dose level in different treatment periods and/or in different studies were counted only once and were counted in the highest dose category.

Note: The Applicant did not include subject VP-VEC-162-1108- (b) (6) in the ISS safety population because this subject did not receive either tasimelteon alone or placebo alone. The Applicant hard coded subject # VP-VEC-162-COSET- (b) (6) to not be a safety subject after determining that this subject returned all dispensed study medication without taking any dose, and was also not included. The pooled safety data excluded 1 Bristol-Myers-Squibb study (Study 005) in which 2 subjects received single doses of tasimelteon, but the study was discontinued due to corporate termination of the development program.

Source: NDA 205677, 5/31/13: Module 2.7.4 Summary of Clinical Safety, Table 3, pp 18-19.

The following table summarizes the number of unique subjects who received at least one dose of the proposed marketing dose (20 mg) by exposure interval. A total of 621 subjects received at least one dose of tasimelteon 20 mg. All subjects (n=149) with chronic tasimelteon exposures > 12 weeks were administered only the 20 mg dose (once a day). Furthermore, all chronic exposures > 12 weeks occurred only in subjects with the Non-24 Hour Disorder (n=149).

Subjects in the > 26 weeks and > 52 weeks in the Exposure Interval category are a subset of those in the > 12 weeks category.

Table 21: Summary of unique subjects who received at least one dose of 20 mg by duration (cumulative exposure) and interval (safety population)

		All Studies Combined ^a	Adult Insomnia Subjects ^b	Non-24-Hour Disorder Subjects		
				All	≤65 years	>65 years
Duration of Exposure (days)	N	621 ^a	109	183	164	19
	Mean (SD)	81.24 (143.42)	33.5 (5.57)	252.0 (167.44)	250.8 (164.15)	262.3 (198.37)
	Median	9.0	35.0	243.0	241.0	262.0
	Q1, Q3	1, 73	34, 35	111, 355	111.5, 353.5	87, 409
	Range	1 - 712	5 - 39	1 - 712	1 - 688	22 - 712
Exposure Interval, n (%)	> 12 weeks (84 days)	149 (24.0%)	0	149 (81.4%)	134 (81.7%)	15 (78.9%)
	> 26 weeks (182 days)	111 (17.9%)	0	111 (60.7%)	100 (60.9%)	11 (57.9%)
	> 52 weeks (364 days)	44 (7.1%)	0	44 (24.0%)	39 (23.8%)	5 (26.3%)

^aIncludes 221 subjects from Phase I studies.

^bElderly insomnia subjects were evaluated in Study 004, but the 20 mg dose group was not assessed in the study.

Note: Total cumulative dose is defined as the sum of doses over the total treatment period. Duration of Exposure period = (date of last dose of continuous tasimelteon exposure) - (date of first dose of tasimelteon continuous exposure) + 1. The sum of all individual exposure periods is presented. All gaps are allowed and no gap days are included in calculation. If gap days between exposure intervals are included, the mean exposure is 83.4 days (median = 9 days).

Source: NDA 205677, 5/31/13: Module 2.7.4 Summary of Clinical Safety, adapted from Table 5, p 20; Module 5.35.3 ISS – Integrated Summary of Tables; adapted from Tables 1.0.3.1 & 1.0.3.2.

Overall, 183 subjects with Non-24 Hour Disorder received tasimelteon 20 mg dose with a mean duration of exposure of 252 days (median = 243 days). As of the cut-off date of 11/30/12, **111 out these 183 subjects were treated for at least 6 months, and 44 treated for at least one year.**

Reviewer's comments: The safety exposures at the proposed marketing dose do not meet the minimum ICH E1 guideline of 100 subject exposures for ≥ 1 year and 300 subject exposures for ≥ 6 months for medicines intended for long-term treatment of non-life threatening conditions. The Applicant estimates prevalence of subjects with Non-24 Hour Disorder to be about 100,000 in the United States based on extrapolation from published literature. However, during drug development the Applicant stated that most of subjects who have this condition were unaware that they have it and that there was low awareness of this condition among healthcare providers, and noted difficulty in recruiting a reasonable number of patients to enroll in clinical studies. The Applicant also began a comprehensive outreach effort to identify and recruit totally blind

patients with N24HSWD to a patient registry. For these reasons, the size of the safety database is not unreasonable. During the pre-NDA meeting (2/21/13), the Agency agreed that the safety database was adequate to support filing.

7.2.2 Explorations for Dose Response

Only one dose – 20 mg, was evaluated in clinical studies of Non-24 Hour Disorder. The Applicant states that the selection of 20 mg dose in Non-24 Hour Disorder studies was based on the extrapolation of data from an in-vivo preclinical pharmacology model of chronic phase-shifting activity, human acute phase-shifting activity (see below), and accrued safety results. A preclinical tasimelteon study in rats showed chronobiotic efficacy at doses ranging from 1 to 5 mg/kg, equivalent to 10 - 50 mg dose range in a 70 kg subject.

An acute phase-shifting study in humans (Study 2101, see Section 5.3 ‘Discussion of Individual Studies/Clinical Trials’ of this review for a description of study design) demonstrated that tasimelteon induced a forward shift in Dim Light Melatonin Onset25%, LOQ5, on the first night of treatment in a dose-dependent manner (placebo= -0.48 ± 0.84 , tasimelteon 10mg= 0.18 ± 2.48 , tasimelteon 20 mg= -1.14 ± 0.46 , tasimelteon 50mg= -0.50 ± 0.32 , tasimelteon 100mg= -2.74 ± 1.95). DLMO25%, LOQ5s was defined as the time when melatonin production reached 25% of the maximum melatonin concentration, and samples below the limit of quantification (LOQ) of the melatonin assay were assigned 5 pg/ml.

Clinical Study 3101 (see Section 5.3 ‘Discussion of Individual Studies/Clinical Trials’ of this review for a description of study design) showed significant improvement in both LPS and WASO at 20 mg and 50 mg of tasimelteon compared to placebo (LPS = 21.5 min, $p = 0.001$ and 26.3 min, $p < 0.001$ for 20 and 50, respectively; WASO = 24.2 min, $p = 0.026$ and 33.7 min, $p = 0.002$, for 20 and 50, respectively).

The Applicant states that single oral doses of 1 mg to 300 mg were well tolerated by healthy subjects in previous clinical studies. In addition, administration of 1 mg to 150 mg of tasimelteon was also well tolerated by healthy volunteers for up to 28 consecutive days. Therefore, 20 mg was within the dose range with established safety margin. The Applicant hypothesized that for maximum efficacy the time of maximum plasma concentration of tasimelteon should coincide with the time that subjects go to bed. The peak C_{max} of tasimelteon is reached at 30-60 minutes. Consequently, the subjects were instructed to take the study medication 60 minutes prior to the target bedtime.

7.2.3 Special Animal and/or In Vitro Testing

Please refer to the review of non-clinical data.

7.2.4 Routine Clinical Testing

Routine clinical testing in the Phase II/III studies included collection of adverse events, physical signs, vital parameters, laboratory and electrocardiogram assessments. These are discussed in the relevant sections of this review.

7.2.5 Metabolic, Clearance, and Interaction Workup

The Applicant conducted pharmacokinetic studies to assess drug-drug interaction, discussed in Section 7.5.5 ‘Drug-Drug Interactions’ of this review. For additional details, please refer to the review of clinical pharmacology data.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Tasimelteon is a new molecular entity. However, there is at least one approved drug in the market with affinity for melatonin MT1 and MT2 receptors. For a discussion of these potential adverse events see Section 7.3.5 ‘Submission Specific Primary Safety Concerns’ of this review.

7.3 Major Safety Results

7.3.1 Deaths

There were no subjects who died during participation in clinical studies of tasimelteon.

7.3.2 Nonfatal Serious Adverse Events

Across all clinical studies, 16 subjects experienced non-fatal serious adverse events. Five of these subjects experienced serious adverse events either during the Screening Period (n=3) or after 3 days after last dose of study drug (n=2) and, therefore, were *not* treatment-emergent (see Table below). I reviewed the narratives and the source documents for these subjects and concur that these events were not treatment-emergent; however, the narratives for subjects who experienced serious adverse events after 3 days after last dose of study drug are provided below.

Table 22: Listing of *non* treatment-emergent serious adverse events across all clinical studies (safety population)

Study ID; Design; Study Population	Unique Subject Identifier	SAE Preferred Term
Study 004; RD, PC; Elderly subjects with primary insomnia	CN116-004- (b) (6)	Squamous cell carcinoma
Study 3201; RD, PC; Totally blind subjects with non-24 disorder	VP-VEC-162-COSET- (b) (6)	Acute lymphocytic leukemia*
	VP-VEC-162-COSET- (b) (6)	Cholecystitis
	VP-VEC-162-COSET- (b) (6)	Small intestinal obstruction
Study 3204; OL; Totally blind subjects with non-24 disorder	VP-VEC-162-3104- (b) (6)	Blood pressure increased*

RD = randomized; PC = placebo-controlled; OL = open-label; SAE = serious adverse event

*Serious adverse events occurred after 3 days after last dose of study drug, and therefore were not considered treatment-emergent. In subject VP-VEC-162-COSET (b) (6), the event was formally diagnosed about 9 days after the last dose of tasimelteon; see narrative in Section 7.3.4 of this review. In subject VP-VEC-162-3104 (b) (6) the event occurred 10 days after the last administration of tasimelteon; see narrative in this section of review.

Source: NDA 205677, 5/31/13; Module 2.7.4 Summary of Clinical Safety, Section 5.2; and Module 5.3.5.3 Data Analysis Data - Reviewer's analysis of ADAE and ADSL datasets.

The remaining 11 subjects experienced *treatment-emergent* serious adverse events. Across the safety database, a total of 10 (10/1346 = 0.00743; 95% CI: 0.00396 to 0.01330) subjects were exposed to tasimelteon and 1 (1/306 = 0.00327; 95% CI: 0.00017 to 0.01699) subject to placebo (see table below). The clinical narratives of these subjects are provided in the paragraphs below. Other than perhaps gastroenteritis, no treatment-emergent serious adverse event was experienced by more than one subject.

Table 23: Listing of *treatment-emergent* serious adverse events across all clinical studies (safety population)

Study ID; Design; Study Population	Unique Subject Identifier	SAE Preferred Term	Placebo N=306 n (%)	Tasimelteon* N=1346 n (%)	
All Studies		Subjects with any SAE	1 (0.3)	10 (0.7)	
Study 3104; RD, PC; Subjects with primary insomnia	VP-VEC-162-3104- (b) (6)	Hypertensive emergency	1 (0.3)	0	
		Dizziness	0	1 (0.07)	
Study 004; RD, PC; Elderly subjects with primary insomnia	CN116-004- (b) (6)	Electrocardiogram ST segment elevation	0	1 (0.07)	
		Gastritis [#]	0	1 (0.07)	
		Hypertension	0	1 (0.07)	
		Ventricular arrhythmia	0	1 (0.07)	
		VP-VEC-162-COSET- (b) (6)	Syncope	0	1 (0.07)
Study 3201; RD, PC; Totally blind subjects with non-24 disorder	VP-VEC-162-COSET- (b) (6)	Diverticulitis	0	1 (0.07)	
		VP-VEC-162-COSET- (b) (6)	Serotonin syndrome [^]	0	1 (0.07)
		VP-VEC-162-COSET- (b) (6)	Transient ischaemic attack	0	1 (0.07)
Study 3203; RD, WD; Totally blind subjects with non-24 disorder	VP-VEC-162-COSET- (b) (6)	Procedural pain [@]	0	1 (0.07)	
		VP-VEC-162-COSET- (b) (6)	Loss of	0	1 (0.07)

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	(b) (6)			
		consciousness		
	VP-VEC-162-COSET-	Coronary artery disease	0	1 (0.07)
Study 3204; OL; Totally blind subjects with non-24 disorder	(b) (6)			
	VP-VEC-162-COSET-	Gastroenteritis viral	0	1 (0.07)
	(b) (6)			
	VP-VEC-162-COSET-	Neoplasm	0	1 (0.07)
	(b) (6)			

RD = randomized; PC = placebo-controlled; WD = withdrawal; OL = open-label; SAE = serious adverse event
 *Subject #CN116-004-(b) (6) was exposed to tasimelteon 10 mg; all other subjects in the tasimelteon group were dosed with the 20 mg dose.
 #Subject #CN116-004-(b) (6) experienced five reported SAEs during one single episode; however, gastritis was the discharge diagnosis.
 ^Subject VP-VEC-162-COSET-(b) (6) experienced serotonin syndrome; event began on the day of the 3201 end-of-study visit which was also the first day of study 3203 (taking tasimelteon in both these studies); Table 36 of the ISS reflects these two studies, although the single event is counted once.
 @Subject #VP-VEC-162-COSET-(b) (6) experienced a worsening knee pain in both 3201 (placebo) and 3203 (tasimelteon); the event in Study 3201 led to knee replacement surgery (placebo was discontinued prior to surgery but subject not withdrawn from the study), and five days after the surgery; subject was rolled over into Study 3203 on tasimelteon, and 22 days later worsening of knee pain led to hospital visit (see narrative for details). In Table 36 of the ISS, this subject was counted twice.
 Source: NDA 205677, 5/31/13: Module 2.7.4 Summary of Clinical Safety, Section 5.2; and Module 5.3.5.3 Data Analysis Data - Reviewer's analysis of ADAE and ADSL datasets.

The mean age of subjects who reported any treatment-emergent serious adverse event was 52 years in the tasimelteon group versus 47 years in the placebo group. Two subjects were elderly (> 65 years; CN116-004-(b) (6) and VP-VEC-162-COSET-(b) (6)); all other subjects were ≤ 65 years. Most of the subjects in the tasimelteon group were female (7/10) and white (7/10). The mean (range) of Study Days to onset of serious adverse events was 106 (9 – 315) in the tasimelteon group compared to 27 in the one placebo subject.

The following table summarizes the incidences of subjects with any serious adverse events in Pooled Study Group 2 and 3. In the Pooled Study Group 2, there were 3 (3/429 = 0.00699; 95% CI: 0.0019 to 0.0197) subjects who experienced treatment-emergent serious adverse events compared to 1 (1/203 = 0.00493; 95% CI: 0.00025 to 0.02511) in the placebo group. In Pooled Study Group 3, the proportion (3.9%; 2/52) of subjects with any treatment-emergent serious adverse events (i.e., diverticulitis or syncope) is higher than that in the placebo group (0%); however, the number of subjects experiencing a serious adverse event is too small for meaningful inference.

Table 24: Treatment-emergent serious adverse events in Pooled Study Groups 2 and 3

Preferred Term	Pooled Study Group 2		Pooled Study Group 3	
	Tasimelteon N=429 n (%)	Placebo N=203 n (%)	Tasimelteon N=52 n (%)	Placebo N=52 n (%)
At least one serious adverse event	3^ (0.7)	1 (0.5)	2^ (3.9)	0
Diverticulitis	1 (0.2)	0	1 (1.9)	0
Dizziness*	1 (0.2)	0	0	0
Electrocardiogram ST segment* elevation	1 (0.2)	0	0	0

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Gastritis*	1 (0.2)	0	0	0
Hypertension*	1 (0.2)	0	0	0
Ventricular arrhythmia*	1 (0.2)	0	0	0
Hypertensive emergency	0	1 (0.5)	0	0
Syncope	1 (0.2)	0	1 (1.9)	0

All these 5 events were reported by one subject, CN116-004- (b) (6) VP-VEC-162-COSET- (b) (6) and VP-VEC-162-COSET- (b) (6) were counted in both Pooled Study Group 2 and Pooled Study Group 3.

Note: Subjects in Pooled Study Group 2: tasimelteon group - CN116-004- (b) (6) VP-VEC-162-COSET- (b) (6) and VP-VEC-162-COSET- (b) (6); placebo group - VP-VEC-162-3104 (b) (6)

Note: Subjects in Pooled Study Group 3: VP-VEC-162-COSET- (b) (6) and VP-VEC-162-COSET (b) (6)

Source: NDA 205677, 5/31/13: Module 5.3.5.3 Data Analysis Data - Reviewer's analysis of ADAE and ADSL.

The following are the narratives for subjects who reported treatment-emergent serious adverse events.

Subject #CN116-004- (b) (6) (gastritis): Subject was a (b) (6) with medical history of intermittent arrhythmia, (b) (6) and suicide attempt at (b) (6). Subject was randomized in Study 004 to tasimelteon 10 mg dose group. After taking tasimelteon 10 mg for 8 days, on Study Day 9 subject was admitted to a hospital for evaluation of nausea, loose stools, vomiting and dizziness; other events noted upon admission were ventricular arrhythmia, ST segment elevation on ECG and hypertension. A cardiologist was consulted to evaluate the ECG findings. Per Case Report Form, the cardiologist believed that the subject's symptoms were probably due to the **gastritis**, and thought that the ECG changes were due to hypertension but did not find ST elevation or other abnormalities. The subject was discharged the next day, and the event of gastritis was reported as resolved five days later. The last dose of tasimelteon was the day prior to hospital admission, and was not restarted. On Study Day 25, subject was discharged from the study. The Applicant assessed the event of gastritis as being not related to study drug, and the event of ventricular arrhythmia as also not being related to study drug (based on prior history of intermittent arrhythmia and cardiologist's assessment). Reviewer's comments: Given the presenting symptoms of nausea, loose stools, vomiting and dizziness, the diagnosis of *gastroenteritis* is more likely. I agree with the Applicant's assessment.

Subject #VP-VEC-162-COSET- (b) (6) (syncope): Subject was a (b) (6) with blindness resulting from glaucoma and a past medical history of hypertension, hyperlipidemia, insomnia, elevated creatine phosphokinase level, vertigo, and intermittent syncope. Subject was randomized in Study 3201 to tasimelteon 20 mg dose group. On Study Day 169, subject experienced a fainting spell (**syncope**) at the doctor's office during a blood draw and was subsequently admitted to hospital for observation, and study drug withheld. Subject was discharged on the second day (Study Day 171) and study medication resumed on the same day. Subject successfully completed Study 3201, and subsequently rolled over to Studies 3203 and 3204. Reviewer's comments: History of intermittent syncope provides an alternate explanation.

Subject #VP-VEC-162-COSET- (b) (6) (diverticulitis): Subject was a (b) (6) with blindness resulting from congenital glaucoma and a medical history of depression and intermittent constipation for which (b) (6) was on stool softeners. Subject was randomized in Study 3201 to tasimelteon 20 mg. On Study Day 142, after having no bowel movements for three days, subject presented to the emergency room with stomach pain. A CT Scan confirmed **diverticulitis**. Subject was treated with a seven day course of spektramox and a stool softener, and was discharged on the same day; the event was reported resolved on Study Day 149. Both the Investigator and the Applicant assessed this event as unrelated to study drug. Reviewer's

comments: the documented history of prior intermittent constipation on stool softeners confounds causality assessment.

Subject #VP-VEC-162-COSET- (b) (6) (serotonin syndrome): Subject was a (b) (6) with blindness resulting from microphthalmia and a medical history of migraine headaches, depression, tachycardia, (b) (6) and intermittent cardiac chest pain. Concomitant medications included lorazepam, duloxetine, metoprolol, sertraline, tramadol, paracetamol and naproxen. Subject was enrolled in the open-label extension of Study 3201 and began taking tasimelteon 20 mg. On Study Day 181 (i.e., the last day) of open-label extension of Study 3201 (same as Study Day 0 of Study 3203, i.e., rollover visit), subject reported “intermittent muscle spasms” that had begun on Study Day 133 of Study 3201 open-label extension. The investigator noted tremors in arms, legs as an ongoing adverse event in Study 3201 and also as an adverse event in Study 3203. On the evening of this same rollover visit (Study Day 181/0), subject presented to the emergency room with tremors in arms, legs. In the emergency room, subject’s heart rate was 145 and was given lorazepam, and then hospitalized. During hospitalization, it was discovered that subject was taking both duloxetine (disclosed at screening) and sertraline (started by a different provider during the study but not disclosed to the site investigator), and was diagnosed with **serotonin syndrome**. Sertraline was discontinued resulting in symptom resolution and was discharged from the hospital 2 days later. Tasimelteon was interrupted due to hospitalization for one day and was resumed on Study Day 183. The Applicant concluded that the serotonin syndrome resulted from taking both duloxetine and sertraline, additionally supported by resolution of symptoms after discontinuing sertaline, and that the event was unrelated to the study drug. Reviewer’s comments: I agree with the Applicant’s assessment.

Subject #VP-VEC-162-COSET- (b) (6) (transient ischaemic attack): Subject was a (b) (6) with blindness resulting from retinopathy of prematurity, a medical history of hypothyroidism and hypercholesterolemia, and without history of hypertension, diabetes or nicotine use. The Subject was enrolled in the open-label extension of Study 3201 and began tasimelteon 20 mg. On Study Day 43, subject presented with transitory difficulty speaking preceded by vertigo (not rotatory/ postural), autonomic symptoms, dizziness and thirst, and increased heart rate and blood pressure. Subject was hospitalized for evaluation. Evaluation showed no evidence of relevant source of arterial or cardiac embolism. In view of the reversible neurological deficits and negative laboratory evaluation, the final diagnosis was vertebrobasilar transitory ischemic attack (**transient ischaemic attack**). Subject was discharged from the hospital on Study Day 49. Tasimelteon treatment was interrupted on Study Day 43 and restarted on Study Day 46; however, tasimelteon was stopped on Study Day 64 due to a decision by the Applicant’s Chief Medical Officer (reason for this decision is not stated). The Applicant assessed this event as unrelated to the study medication. Reviewer’s comments: I agree with the Applicant’s assessment.

Subject #VP-VEC-162-COSET- (b) (6) (procedural pain): Subject was a (b) (6) with ocular trauma (left eye) and glaucoma (right eye) and a past medical history of arthritis and left knee replacement (approximately 3 years prior to randomization). Subject was randomized in Study 3201 to the placebo group. The subject reported worsening left knee arthritis on Study Day 47 at which time a repeat left knee replacement (knee arthroplasty) was scheduled for and performed on Study Day 167. Although placebo treatment (blinded) was discontinued prior to surgery, subject was not withdrawn from Study 3201 due to this event. Subject completed Study 3201 (Study Day 182) and was rolled over on the same day into Study 3203 (Study Day 0) and began Tasimelteon 20 mg. On Study Day 22 of Study 3203, subject reported worsening pain in

the knee for which (b) (6) presented to the emergency room. Investigations were unremarkable and subject was discharged on Study Day with (b) (6) home medications and cefalexin 500 mg every 8 hours and oxycocet 5/325 mg every 4 hours as needed for pain. The post-surgical left knee pain (**procedural pain**) was reported as resolved. No action was taken with the study drug.

Reviewer's comments: This event was unrelated to tasimelteon.

Subject #VP-VEC-162-COSET-(b) (6) in Study 3201 (also referred to as Subject #VP-VEC-162-3203-(b) (6) in Study 3203) (loss of consciousness due to opiate ingestion): Subject was a (b) (6) with blindness resulting from retinoblastoma leading to bilateral enucleation with prosthesis. Subject was enrolled in Study 3203 (screening failure in Study 3201) and was started on tasimelteon 20 mg. On Study Day 60, subject was seen by (b) (6) doctor and reported that (b) (6) sleep overall was stable and (b) (6) daytime sleepiness had improved. On Study Day 64 (b) (6) subject was found (b) (6) as minimally responsive, confused and moaning. Subject was taken to an emergency room where (b) (6) stated that (b) (6) became lightheaded the night before; however, subject was too lethargic to provide any further information, and was hospitalized. Subject had lesions on (b) (6) knees and ankles from the pressure of lying down in one position for a prolonged duration. A standard urine toxicology screen was positive for opiates but was negative for PCP, benzodiazepines, acetaminophen, methadone, amphetamines, methamphetamine, THC, and barbiturates. Laboratory results revealed evidence of rhabdomyolysis (CK >10,000 U/L). The final assessment of the event was **loss of consciousness (due to opiate ingestion)** based on toxicology results) in a left lateral position resulting in rhabdomyolysis with associated metabolic derangements and left peroneal nerve compression. Subject was discharged on Study Day 74 (b) (6)

(b) (6) Tasimelteon was permanently discontinued (last dose was the day prior to the event) and was not restarted. The Applicant concluded that the most likely explanation for these events was opioid-induced prolonged loss of consciousness and immobility, resulting in rhabdomyolysis, and that this event was not related to the study drug based on the fact that the subject had taken tasimelteon for 60 days without ill effect, had not dosed on the day of the event (event onset was in the evening prior to dosing) and considering that tasimelteon has a half-life of 90 minutes and does not accumulate in blood. Reviewer's comments: I agree with the Applicant's assessment.

Subject # VP-VEC-162-COSET-(b) (6) in Study 3201 (also referred to as #VP-VEC-162-3203-(b) (6) in Study 3203; #VP-VEC-162-3204-(b) (6) in Study 3204) (coronary artery disease): Subject was a (b) (6) with blindness resulting from glaucoma (left), retinopathy of prematurity (right) and a past medical history of myocardial infarction (status-post cardiac stent placement and later stent revision many years prior to randomization), diabetes, diabetic neuropathy, hypertension and hyperlipidemia. Subject was randomized into Study 3201 (tasimelteon 20 mg arm) and after completing this study (187 days of tasimelteon), entered the Run-In Phase of Study 3203 and continued to dose with tasimelteon 20 mg. After 288 days of cumulative exposure to tasimelteon 20 mg, subject enrolled in the open-label Study 3204 and continued dosing with tasimelteon 20 mg. On cumulative Study Day 385 (Study Day 97 for Study 3204), subject experienced "chest pain and shortness of breath while walking". Two days later, subject underwent coronary angiogram (95% lesion in right coronary artery) followed by cardiac stent placement the same day. On Study Day 388, the event was considered resolved and the subject was discharged from the hospital with a diagnosis of **coronary artery disease**. Study drug was continued uninterrupted. The Applicant and the Investigator assessed the event as unrelated to study drug. Reviewer's comments: I agree with the Applicant's assessment.

Subject #VP-VEC-162-COSET- (b) (6) (gastrointestinal viral infection): Subject was a (b) (6) with blindness resulting from retinopathy of prematurity and a past medical history of gastroesophageal reflux disease, fatty liver, asthma, hepatitis B and dyslipidemia. Subject was randomized into Study 3201 and began dosing with tasimelteon 20 mg. After completing Study 3201 (182 days of tasimelteon), subject entered the Run-In Phase of Study 3203 and continued dosing with tasimelteon 20 mg. After 301 days of cumulative exposure to tasimelteon 20 mg, subject sequentially enrolled in the open-label Study 3204 and continued dosing with tasimelteon 20 mg. On cumulative Study Day 309, subject experienced stomach pain, diarrhea, vomiting, fever of 101° F and chills. (b) (6) was hospitalized with a diagnosis of **gastrointestinal viral infection** which resolved by Study Day 311. Additional findings and treatment during this hospitalization included trace pleural effusion versus pleural thickening in the deep posterobasilar right costodiaphragmatic recess (CT thorax with contrast), and narrowed esophagus (by endoscopy, and thought to be due to chronic gastroesophageal reflux disease) resulting in esophageal dilation. Subject was discharged home on Study Day 313. Study drug was discontinued on Study Day 309 and restarted on Study Day 314. Reviewer's comments: This event was unrelated to tasimelteon.

Subject #VP-VEC-162-COSET- (b) (6) (soft tissue neoplasm): Subject was a (b) (6) with blindness resulting from congenital glaucoma and a past medical history of hypothyroidism. Subject was enrolled into the open label extension of Study 3201 and began dosing with tasimelteon 20 mg. After completing that study (182 days of treatment), subject enrolled into the open-label Study 3204 with no interruption in study drug and continued dosing with tasimelteon 20 mg. On cumulative Study Day 317, subject reported new onset of left foot pain and by Study Day 434 noted “sensing a mass in (b) (6) left foot when (b) (6) walked”. On cumulative Study Day 496 subject was hospitalized, and a solitary mass (fibroadipose tissue) was removed. The final diagnosis was left foot myopericytoma (MedDRA codes to “**soft tissue neoplasm**”). Subject was discharged from the hospital on Study Day 499. No action was taken with study drug. Reviewer's comments: This event was unrelated to tasimelteon.

Subject #VP-VEC-162-3104- (b) (6) (blood pressure increased): Subject was a (b) (6) with a history of primary insomnia who was randomized to tasimelteon 20 mg arm in Study 3104. Subject completed the study and received all 35 doses of tasimelteon. Ten days after (b) (6) last dose of double-blind medication, the subject returned to the site for evaluation of chest pain with radiating pain in the left arm. Blood pressure was elevated at 198/100 and 192/100 (repeat 20 minutes later), and an ECG did not reveal any clinically significant findings or changes from baseline. Subject was hospitalized for evaluation and discharged the following day when the chest pain resolved. Elevated blood pressure (coded as, **blood pressure increased**) was considered resolved by Study Day 52 when the subject started taking Toprol XL. The Principal Investigator felt the chest pain and radiating left arm pain were associated symptoms, likely due to elevated blood pressure. Reviewer's comments: This event is technically not treatment-emergent as it was reported 10 days after the last dose but the onset of the event is not clear.

Subject #VP-VEC-162-3104- (b) (6) (hypertensive emergency): Subject was a (b) (6) with no relevant medical history or concomitant medications. Subject was randomized in Study 3104 to the *placebo group*. On Study Day 26, subject was hospitalized for **hypertensive emergency** (BP 220/140). Subject was discharged the next day on antihypertensive medications. Subject was withdrawn from the study on Study Day 27. Reviewer's comments: subject was randomized to placebo.

Sponsor’s conclusion regarding serious adverse events: There was no apparent relationship in duration of these events or adverse event type and treatment group, however the low number of serious adverse events limited the ability to evaluate the duration of event by type or treatment group. No preferred term was reported more than once. There were no trends related to any demographic that could be identified among the serious adverse events in Study Groups 2 or 2.1.

Reviewer’s conclusions regarding treatment-emergent serious adverse events: In the placebo-controlled Pooled Study Group 2, the incidence of serious adverse events was fairly comparable between the treatment groups. Although a higher proportion of subjects taking tasimelteon reported treatment-emergent serious adverse events than those taking placebo in Pooled Study Group 3, the total number of subjects reporting any event was very small. In the overall safety population, other than perhaps gastroenteritis, no treatment-emergent serious adverse event was experienced by more than one subject.

7.3.3 Dropouts and/or Discontinuations

In entire safety database, there were 95 subjects (95/1346; 7.1%) in the overall tasimelteon group compared to 21 (21/306; 6.9%) who discontinued early, regardless of the reason for discontinuation. The following table is a summary of the disposition of all subjects in the safety population. As can be seen, the proportions of subjects with the most common reasons for early termination – ‘adverse event’ (whether or not considered treatment-emergent), ‘withdrawal by subject’ and ‘other’, were fairly even between the treatment groups.

Table 25: Disposition of all subjects in the safety database, Pooled Study Group 1

Parameter	Overall Tasimelteon (N=1346)	Placebo (N=306)
Final Subject Status, n (%)		
Completed	1136 (84.4%)	285 (93.1%)
Early Termination	95 (7.1%)	21 (6.9%)
Active	115 (8.5%)	0
Reason for Early Termination, n (%)		
Adverse Event	34 (2.5%)	7 (2.3%)
Withdrawal By Subject	20 (1.5%)	6 (2.0%)
Other	15 (1.1%)	2 (0.7%)
Protocol Deviation	7 (0.5%)	4 (1.3%)
Withdrawn Due To Screening Visit Lab Results	6 (0.4%)	0
Lack Of Efficacy	5 (0.4%)	1 (0.3%)
Lost To Follow-Up	3 (0.2%)	0
Unsatisfactory Therapeutic Effect	3 (0.2%)	1 (0.3%)
Did Not Satisfy Rand Withdrawal Inclusion Crit	2 (0.1%)	0

Note: Subjects who were active in ongoing studies at the time of interim data cut (11/30/12) were counted as 'Active';

Note: Subject is only counted in the primary reason for early termination.

Note: Adverse events included both treatment-emergent events and those that were not treatment-emergent. Two subjects (VP-VEC-162-1108- (b) (6) and VP-VEC-162-1108 (b) (6)) experienced adverse events that were not treatment-emergent but led to early termination.

Source: NDA 205677, 5/31/13: Module 5.35.3 ISS – Integrated Summary of Tables; adapted from Table 1.0.1.

Among the 20 tasimelteon subjects with the reason ‘withdrawal by subject’, for 11 (11/20; 55%) subjects no additional information regarding a specific reason for withdrawal was captured

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during the clinical trials. The reasons cited by the remaining 9 (9/20; 45%) subjects included: no longer interested in study participation, difficulty (work, frequent travel, long distance to study center, etc) complying with study visits, wanting to get pregnant, and trouble taking medication in capsule form.

Of the 15 tasimelteon subjects with the reason ‘other’, 7 (7/15; 46.7%) subjects were terminated early as the study they were participating in was closed (due to administrative reasons, the Applicant elected to close Study 3201 after these actively enrolled subjects had collected sufficient data during the Randomization Phase necessary for assessing the primary and secondary endpoints). The following were the ‘Other’ reasons for early withdrawal of the remaining 8 subjects: positive urine drug screen after rolling over in Study 3204, incarceration, ‘doubt concerning therapeutic effect’, personal reasons, taking prohibited medication, and information not captured.

Across the entire safety population (Pooled Group 1), 32 subjects (32/1346; 2.5%) in the tasimelteon group experienced *treatment-emergent* adverse events that led to early terminations versus 7 subjects (7/306; 2.3%) in the placebo group; the proportion of subjects in each treatment group appears fairly even. The following table summarizes the treatment-emergent adverse events in each individual subject that led to early discontinuations across the entire safety population. In this safety population, treatment-emergent adverse events which 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). These events are discussed further below in this section or in other relevant sections of this review.

Table 26: Listing of subjects with treatment-emergent adverse events leading to early termination across all safety population by treatment group, Pooled Study Group 1

Subject ID	Preferred Term	Verbatim Term	SAE	Dose
Tasimelteon Group				
VP-VEC-162-COSET- (b) (6)	Supraventricular extrasystoles	Ectopic supraventricular rhythm	No	20 mg
VP-VEC-162-COSET- (b) (6)	Tachycardia~*	Nocturnal tachycardia~	No	20 mg
VP-VEC-162-COSET- (b) (6)	Constipation	Constipation	No	20 mg
VP-VEC-162-2101- (b) (6)	Diarrhoea#	Diarrhea	No	10 mg
VP-VEC-162-3104- (b) (6)	Dyspepsia	Heartburn	No	50 mg
CN116-004 (b) (6)	Gastritis*	Gastritis	Yes	10 mg
VP-VEC-162-1104 (b) (6)	Vomiting#	Vomiting	No	100 mg
VP-VEC-162-COSET- (b) (6)	Fatigue	Fatigue	No	20 mg
CN116-004 (b) (6)	Local swelling	SL swelling RT neck	No	1 mg
VP-VEC-162- (b) (6)	Oedema peripheral	Edema of upper limbs	No	20 mg

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VP-VEC-162-COSET- (b) (6)	Cholestasis	Drug-induced cholestatis^	No	20 mg
VP-VEC-162-COSET- (b) (6)	ALT increased ^{&} ; AST increased; GGT increased	Increase of ALT; Increase of AST; Increase of GGT	No	20 mg
VP-VEC-162-3104- (b) (6)	Blood CK increased	Increased CPK	No	50 mg
VP-VEC-162-COSET- (b) (6)	Blood CK increased [#]	Intermittent elevated creatine kinase levels	No	20 mg
VP-VEC-162-COSET- (b) (6)	Hyperglycaemia [#]	Hyperglycemie	No	20 mg
CN116-004 (b) (6)	Dizziness	Dizziness	No	10 mg
VP-VEC-162-3104 (b) (6)	Headache [#]	Headache	No	20 mg
VP-VEC-162-COSET- (b) (6)	Loss of consciousness	Loss of consciousness	Yes	20 mg
CN116-004 (b) (6)	Somnolence [#]	Excessive daytime sleepiness	No	50 mg
VP-VEC-162-COSET- (b) (6)	Syncope	Fainting spell	No	20 mg
VP-VEC-162-COSET- (b) (6)	Transient ischaemic attack	Vertebrobasilar transitory ischemic attack	Yes	20 mg
CN116-004- (b) (6)	Disorientation [#]	Disorientation	No	1 mg
CN116-004 (b) (6)	Insomnia [#]	Increased insomnia	No	50 mg
VP-VEC-162-COSET- (b) (6)	Insomnia [#]	Worsened insomnia	No	20 mg
VP-VEC-162-COSET- (b) (6)	Middle insomnia [#]	Night awakening worsening	No	20 mg
VP-VEC-162-3104- (b) (6)	Nightmare [#]	Nightmares	No	20 mg
VP-VEC-162-COSET- (b) (6)	Nightmare	Nightmares	No	20 mg
VP-VEC-162-COSET- (b) (6)	Nightmare [#]	Nightmares	No	20 mg
VP-VEC-162-COSET- (b) (6)	Renal pain	Kidney pain	No	20 mg
CN116-002 (b) (6)	Rash	Rash	No	150 mg
CN116-004- (b) (6)	Rash	Rash	No	1 mg
VP-VEC-162- (b) (6)	Rash	Skin rash	No	20 mg
Placebo Group				
VP-VEC-162-COSET- (b) (6)	Deafness neurosensory	Worsening sensorineural hearing loss (right)	No	-
CN116-004 (b) (6)	Seasonal allergy [#]	Worsening of seasonal allergies	No	-
CN116-002 (b) (6)	ECG T wave abnormal	T wave changes	No	-
VP-VEC-162-COSET- (b) (6)	Joint swelling	Bilateral ankle swelling	No	-
VP-VEC-162-3104 (b) (6)	Affective disorder	Affective changes	No	-
CN116-004- (b) (6)	Nervousness	Nervous attack	No	-
VP-VEC-162-3104- (b) (6)	Hypertensive emergency [*]	Hypertensive emergency	Yes	-

Note: When multiple adverse events led to early discontinuation, one event was designated as the primary event which is reflected in this table (all events are included in the table below). *When multiple events led to early discontinuation, this event was designated as primary event in the Clinical Study Report. In subject CN116-004- (b) (6) cardiologist designated 'gastritis' as the primary diagnosis which is reflected in the Clinical Study Report.

[#]When multiple events led to early discontinuation, this event was designated as primary event by the Applicant's Medical Officer.

[~]Event was originally reported by the investigative site as nocturnal tachycardia but since the heart rate was not assessed at the time of this subjective experience, the Applicant determined that the term ‘palpitations’ was a more accurate description of the event.

[^]On 9/20/12, the Applicant combined the various reported symptoms into one diagnostic term “drug-induced cholestasis”.

[@]Placebo group includes subject #VP-VEC-162-COSET- (b) (6) who discontinued from Study 3201 because adverse event (worsening sensorineural hearing loss) needed treatment with a prohibited concomitant medication (oral steroids); this subject was enrolled in the open-label Study 3204 and remained active through the ISS cut-off date (11/30/12).

[&]These preferred terms were grouped together as ‘elevated liver function tests’

Source: NDA 205677, 5/31/13: Module 5.35.3 Appendix 3 – Discontinuations due to Adverse Events, adapted from Table 1, pages 1-6.

Pooled Study Group 1 included all clinical studies (pharmacokinetic, crossover, controlled and uncontrolled designs) and combined different study populations (healthy volunteers, subjects with insomnia, subjects with Non-24 Hour Disorder, etc), and had unequal exposures between the tasimelteon and placebo groups. Pooled Study Groups 2 and 3 allow for better estimation of incidence rates of adverse events for comparison between treatment groups (see below). Study groups 2 and 3 do not include subject #VP-VEC-162-COSET- (b) (6) with history of blindness (due developmental disorder), bilateral sensorineural hearing loss since birth and who was randomized to *placebo* arm in Study 3201; on Study Days 58, 78 and 165, subject experienced intermittent worsening of *sensorineural hearing loss*, for which he was usually prescribed oral steroids – a prohibited concomitant medication. Therefore, he was discontinued from Study 3201 but, subsequently, was enrolled in the open-label Study 3204 and remained active through the ISS cut-off date (11/30/12).

Pooled Study Group 2 consists of placebo-controlled studies of insomnia and Non-24 Hour Disorder. As can be seen from the Table below, the incidence of subjects experiencing any treatment-emergent adverse event leading to early discontinuation was fairly similar between the two treatment groups (3.3% in tasimelteon group versus 3.0% in the placebo group). Three preferred terms that led to early discontinuation were reported in two subjects: somnolence, insomnia, and nightmare (highlighted in the table below). These events are discussed further below in this section or other relevant sections of this review.

Table 27: Treatment-emergent adverse events leading to permanent discontinuation by Pooled Study Group 2 (placebo-controlled studies in insomnia and Non-24 Hour Disorder)

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System Organ Class Preferred Term	Tasimelteon			Overall (N=429)	Placebo (N=203)
	< 20 mg (N=114)	20 mg (N=151)	50 mg (N=164)		
Number (%) of Subjects with at least one TEAE	5 (4.4%)	5 (3.3%)	4 (2.4%)	14 (3.3%)	6 (3.0%)
Cardiac disorders	1 (0.9%)	1 (0.7%)	0	2 (0.5%)	0
Supraventricular extrasystoles	0	1 (0.7%)	0	1 (0.2%)	0
Ventricular arrhythmia	1 (0.9%)	0	0	1 (0.2%)	0
Ear and labyrinth disorders	0	0	0	0	1 (0.5%)
Deafness neurosensory	0	0	0	0	1 (0.5%)
Gastrointestinal disorders	1 (0.9%)	1 (0.7%)	2 (1.2%)	4 (0.9%)	0
Diarrhoea	0	0	1 (0.6%)	1 (0.2%)	0
Dyspepsia	0	0	1 (0.6%)	1 (0.2%)	0
Gastritis	1 (0.9%)	0	0	1 (0.2%)	0
Hypoesthesia oral	0	0	1 (0.6%)	1 (0.2%)	0
Vomiting	0	1 (0.7%)	0	1 (0.2%)	0
General disorders and administration site conditions	1 (0.9%)	0	0	1 (0.2%)	0
Local swelling	1 (0.9%)	0	0	1 (0.2%)	0
Immune system disorders	0	0	0	0	1 (0.5%)
Seasonal allergy	0	0	0	0	1 (0.5%)
Investigations	1 (0.9%)	0	1 (0.6%)	2 (0.5%)	0
Blood creatine phosphokinase increased	0	0	1 (0.6%)	1 (0.2%)	0
Electrocardiogram st segment elevation	1 (0.9%)	0	0	1 (0.2%)	0
Musculoskeletal and connective tissue disorders	0	0	0	0	1 (0.5%)
Joint swelling	0	0	0	0	1 (0.5%)
Nervous system disorders	2 (1.8%)	2 (1.3%)	2 (1.2%)	6 (1.4%)	0
Somnolence	0	0	2 (1.2%)	2 (0.5%)	0
Ataxia	1 (0.9%)	0	0	1 (0.2%)	0
Dizziness	1 (0.9%)	0	0	1 (0.2%)	0
Headache	0	1 (0.7%)	0	1 (0.2%)	0
Syncope	0	1 (0.7%)	0	1 (0.2%)	0
Psychiatric disorders	1 (0.9%)	3 (2.0%)	1 (0.6%)	5 (1.2%)	2 (1.0%)
Insomnia	0	1 (0.7%)	1 (0.6%)	2 (0.5%)	0
Nightmare	0	2 (1.3%)	0	2 (0.5%)	0
Anger	0	1 (0.7%)	0	1 (0.2%)	0
Confusional state	1 (0.9%)	0	0	1 (0.2%)	0
Depression	0	1 (0.7%)	0	1 (0.2%)	0
Disorientation	1 (0.9%)	0	0	1 (0.2%)	0
Affective disorder	0	0	0	0	1 (0.5%)
Nervousness	0	0	0	0	1 (0.5%)
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1 (0.5%)
Nasal congestion	0	0	0	0	1 (0.5%)
Skin and subcutaneous tissue disorders	1 (0.9%)	0	0	1 (0.2%)	0
Rash	1 (0.9%)	0	0	1 (0.2%)	0
Vascular disorders	0	0	0	0	1 (0.5%)
Hypertension	0	0	0	0	1 (0.5%)
Hypertensive emergency	0	0	0	0	1 (0.5%)

Note: When multiple adverse events led to early discontinuation, one event was designated as the primary event reflected in the table above; all events leading to discontinuation are included in this table.

Note: Placebo group excludes subject #VP-VEC-162-COSET (b) (6) who discontinued from Study 3201 because adverse event (worsening sensorineural hearing loss) needed treatment with a prohibited concomitant medication (oral steroids).

Note: Pooled Study Group 2 includes placebo-controlled Studies 004, 3104 and 3201

Note: A subject that reports an event coding (MedDRA Version 14.1) to the same System Organ Class or Preferred Term on more than one occasion is only counted one time for that SOC and PT using the event with the maximum severity.

Source: NDA 205677, 5/31/13: Module 5.3.5.3. Integrated Summary of Safety Tables, adapted from Table 2.0.5.2.2

Pooled Study Group 3 (placebo-controlled studies in Non-24 Hour Disorder, i.e., Study 3201 and data from randomized withdrawal phase of Study 3203) is a subset of Pooled Study Group 2. In Pooled Study Group 3, the incidence of subjects experiencing any treatment-emergent adverse event leading to early discontinuation in the tasimelteon group (3/52; 5.8%) appears numerically higher than in the placebo group (2/52; 3.8%), however, the absolute number of subjects in each treatment group is quite small limiting meaningful conclusions. There were no preferred terms leading to early discontinuation reported in more than one subject in this pooled group.

I reviewed the narratives and source documents that were provide for all the subjects who experienced adverse events that led to early discontinuations. In the following paragraphs, I summarize the narratives for selected treatment-emergent adverse events that led to early discontinuations that are not otherwise discussed elsewhere in this review. Most of the treatment-emergent adverse events that led to early withdrawal are discussed in other relevant sections of this review.

Subject #CN116-004- (b) (6) (daytime somnolence, insomnia): Subject was a (b) (6) with no significant past medical history, and who was randomized to tasimelteon 50 mg arm in Study 004. Concomitant medication was Premarin (estrogens conjugated). Subject took the first dose tasimelteon in the evening of Study Day 0, and on Study Day 2 reported moderate **daytime somnolence** and moderate increased insomnia (**insomnia**). The subject's last dose of tasimelteon was on Study Day 5, and was permanently discontinued from the study. No treatment was administered, and the events resolved spontaneously by Study Day 7. The Applicant states that worsening of daytime sleepiness ("somnolence") and pre-existing insomnia is expected within the first 14 days of initiation of tasimelteon, based upon the drug's mechanism of action, i.e., an indication of physiologic effect. Therefore, the Applicant concludes that the event is possibly related to study drug. Reviewer's comments: I agree with the Applicant's assessment.

Subject #VP-VEC-162-COSET- (b) (6) (insomnia): Subject was a (b) (6) with blindness resulting from congenital cataracts and a past medical history of insomnia, hypertension, coronary artery bypass surgery and Type 1 diabetes, and enrolled in Study 3201. After taking the first dose of tasimelteon 20 mg, subject reported worsening of his **insomnia, vomiting, nausea, headache** and 'dysgeusia' (this was the verbatim term used). The subject discontinued tasimelteon after the first dose. The insomnia resolved 2 days later and all other events resolved 1 day later. The subject was permanently discontinued on Study Day 6. The Applicant disagreed with the Investigator's assessment of relatedness of worsening insomnia to tasimelteon, reasoning that one single dose of study drug is insufficient evidence to determine whether worsening of the subject's existing insomnia is due to study drug or chance alone. Reviewer's comments: There is a temporal relationship between the events and tasimelteon exposure, and positive dechallenge.

Subject #VP-VEC-162-COSET- (b) (6) (asthenia headaches, night awakening worsening): A (b) (6) with a medical history of bilateral blindness secondary to retinal detachment and initial and middle insomnia was enrolled in the open-label Study 3202, and began taking tasimelteon 20 mg. The subject reported **headaches, night awakening worsening** and **asthenia** as beginning on the same day after taking tasimelteon. The subject initiated paracetamol 500 mg per day as needed on Study Day 1 for the treatment of headaches. At the Week 8 study visit (Study Day 56), the subject voluntarily withdrew from the study stating that the reason was the adverse events experienced. At this visit, the subject indicated that (b) (6) could not recall the date of last tasimelteon administration; therefore, the investigative site conservatively recorded the date of last dose as Study Day 55. The subject indicated that following the last tasimelteon administration, the adverse event of headaches and asthenia resolved with concurrent improvement of 'night awakening worsening'. Reviewer's comments: There is a temporal relationship between the events and tasimelteon exposure, and positive dechallenge.

Subject #CN116-004- (b) (6) (acute confusion, ataxia and disorientation): Subject was a (b) (6) with medical history of primary insomnia, acid reflux, hypertension, hypoglycemia, mild asthma, arthritis, and cholecystectomy who was randomized to tasimelteon 1

mg group in Study CN116-004 (primary insomnia in elderly subjects). Concomitant medications included hydrochlorothiazide, Zestril, Prevacid, Evista, multivitamins, vitamin E, vitamin C, beta-carotene, glucosamine with chondroitin, and Claritin. Subject experienced severe sweating (Study Days 9 and 10), and **acute confusion** (coded as confusional state), **ataxia and disorientation** on Study Day 10. Tasimelteon was permanently discontinued on Study Day 11, and these events were reported resolved by Study Day 13. Additionally, on Study Day 13 ST-T wave changes were noted on ECG which were deemed to be not clinically significant. The Applicant concludes that the events of acute confusion (confusional state), ataxia and disorientation were possibly related to the study drug. Reviewer's comments: I agree with the Applicant's assessment.

Reviewer's conclusion regarding treatment-emergent adverse events that led to early discontinuations: The proportion of subjects who experienced any treatment-emergent adverse event that led to early termination was fairly even between treatment groups in the entire safety database. Treatment-emergent adverse events which 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).

7.3.4 Significant Adverse Events

The Applicant identified 3 serious adverse events as being potentially relevant and 1 important medical event. The serious adverse events were: acute lymphocytic leukemia, loss of consciousness and serotonin syndrome. Cholestasis was the important medical event. The narratives for these events are either provided below or referred to the appropriate location.

Subject #VP-VEC-162-COSET- (b) (6) (acute lymphocytic leukemia, syncope): Subject was a (b) (6) with blindness resulting from retinoblastoma at age 8 (s/p bilateral enucleation) and a past medical history of hypothyroidism, removal of gall bladder polyps, malignant breast lump removal followed by radiation (11 years prior to randomization), benign fibroids and removal of benign colon polyps. Subject was randomized in Study 3201 to tasimelteon 20 mg dose group. Laboratory tests done on Study Day 0 (day of randomization) showed elevated liver enzymes (ALT 4x ULN; AST 2x ULN; bilirubin normal) and low platelet count (these tests were normal at Screening done about 104 days prior to randomization). Tasimelteon was withheld on Study Day 2. These tests were repeated locally, and after the primary care physician judged repeat test results as not clinically significant, tasimelteon was restarted on Study Day 14. On Study Day 18, subject reported an adverse event of **syncope**; tasimelteon was formally discontinued the next day, and subject was withdrawn from the trial on Study Day 20. During the follow-up period, subject experienced symptoms of nausea, dizziness, diarrhea, and shortness of breath (dyspnoea) for which (b) (6) was hospitalized. (b) (6) was diagnosed with acute lymphoblastic leukemia (**acute lymphocytic leukemia**) on Study Day 27. The Applicant concluded that this event was unrelated to study drug based on DNA sequencing of the retinoblastoma gene in this subject (b) (4) (b) (4) in the RB1 gene. This RB1 mutation (b) (4) is (b) (4)

(b) (4) The Applicant states that the loss of the retinoblastoma gene expression is common in patients with de novo acute lymphoblastic leukemia, suggesting that deletions of the retinoblastoma play a significant role in the pathogenesis of acute lymphoblastic leukemia. Reviewer's comments: The duration of exposure to tasimelteon was 19 days; however, manifestations and/or symptoms of the underlying condition were likely evident during screening, treatment or shortly after study drug discontinuation. The history of breast malignancy and the event of acute lymphocytic leukemia appear to be consistent with the notion that RB1 mutation is pathogenic and supports a genetic predisposition for the development of other malignancies including leukemias.

Subject # VP-VEC-162-COSET- (b) (6) (loss of consciousness and immobility due opioid toxicity): Subject was a (b) (6) with blindness who experienced prolonged **loss of consciousness and immobility due opioid toxicity**, resulting in rhabdomyolysis. This narrative is fully described in Section 7.3.2 'Nonfatal Serious Adverse Events' of this review. Reviewer's comments: As stated in the full narrative, opioid toxicity offers an alternate explanation.

Subject # VP-VEC-162-COSET- (b) (6): Subject was a (b) (6) with blindness who experienced **serotonin syndrome** as a result of concomitant administration of both duloxetine (a non-selective, serotonin & norepinephrine reuptake inhibitor) and sertraline (a selective serotonin reuptake inhibitor). This narrative is fully described in Section 7.3.2 'Nonfatal Serious Adverse Events' of this review. Reviewer's comments: As stated in the full narrative, tasimelteon and this event are unrelated.

Subject # VP-VEC-162-COSET- (b) (6) in Study 3204 (also referred to as VP-VEC-162-3201- (b) (6) in Study 3201): Subject was a (b) (6) experienced **drug-induced cholestasis** (was taking high dose of atorvastatin). This narrative is fully described in Section 7.4.2 'Laboratory Findings' of this review. Reviewer's comments: As stated in the full narrative, concomitant high dose of atorvastatin offers an alternate explanation for cholestasis.

7.3.5 Submission Specific Primary Safety Concerns

Tasimelteon is a new molecular entity. However, there is at least one approved drug (ramelteon) in the market with affinity for melatonin MT1 and MT2 receptors.

Endocrine effects:

Ramelteon is associated with a 4.9 µg/L (34% increase) change from baseline in mean serum prolactin level in women compared with -0.6 µg/L in placebo group in women. No differences between active- and placebo-treated groups occurred among men. Therefore the Agency recommended the Applicant to assess endocrine effects in the tasimelteon development program. Endocrine effects of tasimelteon are discussed in Section 7.4.2 'Laboratory Findings' of this review.

Next day residual effects:

Tasimelteon is not intended to treat insomnia. However, since tasimelteon is administered 1 hour before bedtime, I evaluated for next-day residual effects of tasimelteon.

Somnolence as a next day residual event is discussed in the next Section 7.4.1 ‘Common Adverse Events’ of this review. Somnolence is not a safety signal in non-elderly subjects with Non-24 Hour Disorder. However, elderly female subjects with insomnia taking tasimelteon have a higher incidence of somnolence compared to placebo control.

The Visual Analog Scale (VAS) and the Digit Symbol Substitution Test (DSST) were assessed in Study 001 (single ascending dose in healthy volunteers), Studies 2101 and 3101 (circadian rhythm effects in healthy volunteers), and Study 3104 (non-elderly subjects with insomnia). Additionally, the Karolinska Sleepiness Scale (KSS) was administered in Study 2101. With the exception of Study 001, these tests were administered prior to treatment and in the morning after treatment.

While these studies were not powered to detect treatment differences, there were no statistically significant differences between the placebo group and tasimelteon dose groups in the change from baseline in DSST scores, or in the change from baseline in VAS scores for any mood category, for in the change from baseline in KSS.

DSST is a subtest from the Wechsler Adult Intelligence Scale that requires speedy recording of symbols to measure psychomotor performance. It presents a code of 9 matched digits and symbols at the top of the test sheet. Subjects are required to substitute a symbol for a digit from this code, which is visible throughout the test. The number of correct items completed in 90 seconds is the score.

VAS is a self-rated scale designed to assess feelings, affect, and mood, and their changes. The scale has a neutral word at one end of a 100-mm line and a “mood” adjective at the other. The respondents indicate the point on the line that best describes how they are currently feeling. Subjects were instructed on how to complete the visual analog mood scale and were given a practice test at Screening Visit. Three mood scales were administered: Sad/Happy, Calm/Excited, and Sleepy/Alert.

KSS is a question to assess self-reported sleepiness. Subjects estimated how sleepy they felt at that time using a 9-point scale (1 = extremely awake and 9 =extremely sleepy – fighting to stay awake). In Study 2101, subjects were required to answer this question 6 times a day (every 3 hours).

The Tyrer Benzodiazepine Withdrawal Symptoms Questionnaire (BWSQ) was administered to assess the abrupt effects of tasimelteon in Studies 3104, 3201 and 3203. These results are discussed in Section 7.6.4 ‘Overdose, Drug Abuse Potential, Withdrawal and Rebound’ of this review. There were no significant differences observed between the means and medians in the treatment groups.

Reviewer’s conclusion: Tasimelteon is not associated with next-day residual effects as assessed by DSST, VAS and KSS, or with adverse effects due to abrupt withdrawal as assessed by the Tyrer BWSQ. Somnolence is not a safety signal in non-elderly adult subjects with Non-24 Hour Disorder or insomnia. However, elderly female subjects with insomnia taking tasimelteon have a higher incidence of somnolence compared to placebo control.

Class-labeled adverse events for insomnia drugs:

Approved drugs to treat insomnia are required to carry class-labeled adverse events: severe anaphylaxis and anaphylactoid reactions, abnormal thinking and behavioral changes including complex behaviors such as sleep driving with amnesia for the event. Even though tasimelteon is not intended to treat insomnia, I reviewed the reported adverse events for the potential for such events.

There was one subject #CN116-004- (b) (6), a (b) (6) with insomnia randomized to the tasimelteon 50 mg, who reported an event of ‘**sleepwalking**’ on Study Day 11 without recurring, dose was not discontinued, and subject went on to complete the study. Reviewer’s comments: additional information on this event is not available but it does not appear to be a typical complex behavior with amnesia.

Reviewer’s conclusion: Overall, I did not find adverse events that are suggestive of class-label for insomnia drugs.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In order to obtain an estimate of the overall incidence of subjects reporting any treatment-emergent adverse event for comparison between treatment groups across various phases of clinical development and different study populations, the relevant placebo-controlled clinical studies were combined and analyzed (see table below). As can be seen from this table, relative to a ≥ 2 -fold the incidence in the placebo group, there is a higher incidence of subjects reporting any treatment-emergent adverse event in the pooled < 20 mg tasimelteon dose group in healthy volunteers and elderly subjects with insomnia. Similarly, there was a higher incidence in healthy subjects with transient insomnia in the > 20 mg dose group. However, a consistent dose-relationship in the incidence of treatment-emergent adverse events was not present. This is discussed further in the sections below.

Table 28: Incidence of subjects reporting any treatment-emergent adverse event by study population: All placebo-controlled studies

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 Devanand Jillapalli, MD
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 Tasimelteon capsules

Study Population	Tasimelteon			Overall (N=838)	Placebo (N=344)
	< 20 mg (N=153)	20 mg (N=269)	> 20 mg (N=416)		
Pooled Phase I Studies	10 (6.5%)	0	15 (3.6%)	25 (3.0%)	11 (3.2%)
Healthy volunteers :Single dose	6 (3.9%)	0	8 (1.9%)	14 (1.7%)	5 (1.5%)
Healthy volunteers: Repeat dose	4 (2.6%)	0	7 (1.7%)	11 (1.3%)	6 (1.7%)
Phase II/III Studies	79 (51.6%)	99 (36.8%)	113 (27.2%)	291 (34.7%)	103 (29.9%)
Healthy subjects with transient insomnia	0	13 (4.8%)	29 (7.0%)	42 (5.0%)	11 (3.2%)
Adult subjects with insomnia	0	39 (14.5%)	35 (8.4%)	74 (8.8%)	32 (9.3%)
Elderly subjects with insomnia	71 (46.4%)	0	35 (8.4%)	106 (12.6%)	24 (7.0%)
N24HSWD	0	40 (14.9%)	0	40 (4.8%)	28 (8.1%)
Healthy subjects	8 (5.2%)	7 (2.6%)	14 (3.4%)	29 (3.5%)	8 (2.3%)

Note: Placebo-controlled studies included were: 001, 002, 004, 2101, 3101, 3104, 3201 and 3203.

Source: NDA 205677, 5/31/13: Module 5.35.3 ISS – Integrated Summary of Tables; adapted from Table 0.1.5.4

In the sections below, I review the common treatment-emergent adverse events in the pooled placebo-controlled study groups, and the pooled tasimelteon only subjects with Non-24 Hour Disorder (Pooled Study Group 4).

I used the MedDRA Adverse Event Diagnostic Service (MAED Service) developed by the Computational Science Center of the Agency's Center for Drug Evaluation and Research and JMP to analyze the AE datasets provided by the Applicant to compare the frequency of treatment-emergent adverse events between the tasimelteon and placebo groups in the pooled placebo-controlled study groups. I also compared my analyses of treatment-emergent adverse events with that of the applicant, and discuss significant differences if any.

The following table is a summary of System Organ Classes (SOC) containing treatment-emergent adverse events reported by at least 1.5% of subjects in the tasimelteon group and with a ≥ 2 -fold frequency than in placebo group in Pooled Study Group 2. There were two SOC's that met the above criteria: cardiac disorders and renal and urinary disorders. The preferred terms that were reported in each of these two SOC's are provided as foot notes to the table below. In the cardiac disorders SOC, with the exception of conduction disorder which was reported by two subjects, all events were reported by one subject each. No treatment-emergent adverse event reported in the renal and urinary disorders SOC was experienced by more than one subject.

Table 29: Summary of System Organ Class with any treatment-emergent adverse event reported by $\geq 1.5\%$ of subjects in the tasimelteon group and with a ≥ 2 -fold greater frequency than in placebo group in the Pooled Study Group 2

SOC	Tasimelteon N=429		Placebo N=203		RR	RR C.I. (lower bound)	RR C.I. (upper bound)
	n	%	n	%			
Cardiac disorders	9	2.1	0	0	9.014	0.527	154.116
Renal and urinary disorders	8	1.9	1	0.5	3.786	0.477	30.064

SOC = System Organ Class; RR = Relative risk (incidence in tasimelteon group / incidence in placebo group); CI = 95% confidence interval.

Note: Pooled Study Group 2 includes placebo-controlled studies 004, 3104 and 3201.

Cardiac disorders SOC: atrial fibrillations, conduction disorder, myocardial infarction, palpitations, sinus bradycardia, supraventricular extrasystoles, ventricular arrhythmia, and ventricular extrasystoles.

Renal and urinary disorders SOC: costovertebral angle tenderness, glycosuria, haematuria, incontinence, nephrolithiasis, polyuria, proteinuria, urinary tract inflammation, and urine abnormality.

Source: NDA 205677, 5/31/13: Module 5.3.5.3 Data Analysis Data - Reviewer's analysis of ADAE and ADSL datasets using MAED Service.

In the Pooled Study Group 5 (healthy volunteers in clinical pharmacology studies), the only preferred terms reported by at least 1% of subjects (i.e., at least 8 subjects) in the tasimelteon group and with a ≥ 2 -fold greater frequency than in placebo group were somnolence and dizziness.

In Pooled Study Group 2, there were 429 and 203 subjects at risk (i.e., the denominator) in the tasimelteon and placebo groups, respectively. Since the absolute number of subjects in each study group was relatively small, I used the following criteria to identify *commonly* occurring treatment-emergent adverse events: reported by at least 1% of subjects (i.e., at least 5 subjects) in the tasimelteon group and with a ≥ 2 -fold greater frequency than in placebo group (see table below). The assumption is that the incidence of the unselected adverse events (i.e., unselected by the above cutoff definition and not included in the following table) is higher in the placebo group by chance, and that there is no particular reason for the incidence to be lower in the tasimelteon group. As can be seen in this table, 'nightmare' and 'abnormal dreams' appear to be related; these events, somnolence, along with other events of interest are discussed in this and other relevant sections of this review.

Table 30: Summary of common treatment-emergent adverse events (reported by $\geq 1\%$ of subjects in the tasimelteon group and with a ≥ 2 -fold greater frequency than in placebo group) in the Pooled Study Group 2.

Preferred Term	Tasimelteon N=429		Placebo N=203		RR
	n	%	n	%	
Any TEAE	214	49.88	80	39.4	1.266
Somnolence	13	3.03	3	1.48	2.051
Dry mouth	10	2.33	1	0.49	4.732
Diarrhoea	10	2.33	2	0.99	2.366
Pain in extremity	7	1.63	0	0	7.116
Nightmare	6	1.4	0	0	6.167
Abnormal dreams	5	1.17	1	0.49	2.366
Dysgeusia	5	1.17	1	0.49	2.366
Nasal congestion*	5	1.17	1	0.49	2.366
Rhinorrhoea*	5	1.17	1	0.49	2.366

RR = Relative risk (incidence in tasimelteon group / incidence in placebo group); TEAE = treatment-emergent adverse event

Note: Pooled Study Group 2 includes placebo-controlled studies 004, 3104 and 3201.

*Incidence of rhinorrhea and nasal congestion combined: 9 (2.1%) subjects in tasimelteon group versus 2 (0.98%) in placebo group.

Source: NDA 205677, 5/31/13: Module 5.3.5.3 Data Analysis Data - Reviewer's analysis of ADAE and ADSL datasets using MAED Service.

As previously described, Pooled Study Group 2 included placebo-controlled Study 004 – a relatively large (n = 227) study in elderly subjects with primary insomnia. Therefore, Pooled Study Group 2.1 (a subset of Pooled Study Group 2), which included only Studies 3104 and 3201 (Study 004 was not included), was designed to provide placebo-controlled data for repeat dosing of tasimelteon in *non-elderly* adult subjects. A review of data from this pool (summary table not included in this review) showed that four events – urinary tract infection, alanine aminotransferase increased, nightmare and rhinorrhoea, were reported by at least 5 subjects in the tasimelteon group and with a ≥ 2 -fold greater frequency than in placebo group.

Pooled Study Group 3 combined data from the placebo-controlled Study 3201 (which was also included in Pooled Study Group 2) and placebo-controlled withdrawal phase of Study 3203. The purpose of this pool was to provide placebo-controlled data in subjects with Non-24 Hour Disorder. The following table is a summary of treatment-emergent adverse events experienced by at least 3 subjects (> 5%) in the tasimelteon group and with a ≥ 2 -fold greater frequency than in placebo group. The numbers of subjects experiencing common treatment-emergent adverse events other than ‘headache’ and ‘alanine aminotransferase increased’ are too small for meaningful between-treatment group comparison. The frequency of ‘headache’ and ‘alanine aminotransferase increased’ in the tasimelteon group of Pooled Study Group 3 is fairly similar to that in the pooled tasimelteon only long-term exposures in Non-24 Hour Disorder (Pooled Study Group 4).

Table 31: Summary of common treatment-emergent adverse events (reported by > 5% in the tasimelteon group and with a ≥ 2 -fold greater frequency than in placebo group) in the Pooled Study Group 3.

Preferred Term	Pooled Study Group 3				RR	Pooled Study Group 4	
	Tasimelteon N=52		Placebo N=52			Tasimelteon N=183	
	n	%	n	%		n	%
At least one TEAE	40	76.9	28	53.9	1.4	131	71.6
Headache	8	15.4	3	5.8	2.7	26	14.2
Alanine aminotransferase increased	5	9.6	2	3.9	2.5	10	5.5
Nightmare/abnormal dreams	4	7.7	0	0	-	10	5.5
Conduction disorder	3	5.8	0	0	-	3	1.6
Sleep disorder	3	5.8	0	0	-	3	1.6
Upper respiratory tract infection	3	5.8	0	0	-	7	3.8
Somnolence	3	5.8	1	1.9	3	5	2.7
Urinary tract infection	3	5.8	1	1.9	3	12	6.6

RR = Relative risk (incidence in tasimelteon group / incidence in placebo group); - relative risk could not be determined due to 0 events in the placebo group; TEAE = treatment-emergent adverse event.

Source: NDA 205677, 5/31/13: Module 5.3.5.3 Data Analysis Data - Reviewer’s analysis of ADAE and ADSL datasets using MAED Service.

Several adverse events were identified based on frequency of occurrence in the tasimelteon group and at a rate ≥ 2 -fold higher than that of the placebo group. These events are discussed in the following paragraphs.

Headache:

I reviewed the verbatim terms that were mapped to the preferred term ‘headache’, and conclude that the potential for under ascertainment is minimal (i.e., inclusion of ‘head discomfort’ identified one additional patient). The incidence of headache in the Pooled Study Groups 2, 3 and 4 is summarized in the following table. The frequency of headache in the tasimelteon subjects aged ≤ 65 years in Pooled Study Group 3 was > 2 -fold that in the placebo group. The incidence of headaches in the tasimelteon group in Pooled Study Group 3 is similar to that in the long-term follow-up Pooled Study Group 4. In Pooled Study Group 2, there were no significant differences between the incidences of headaches between the treatment groups; and there was no effect of dose on the incidence of headache (not shown in table below). Additionally in the Pooled Study Group 2, no significant differences in the incidence of headache were evident based on most categories of demographic characteristics; in a few of these categories (for example, age > 65 years in 20 mg dose, black race, etc) the subject numbers were too small to arrive at a meaningful conclusion. Further, in Pooled Study Group 2, the majority of headaches in both the tasimelteon and placebo groups (61% and 66.7%, respectively) began within the first 14 days of exposure; the median duration of headaches was 2 days in both treatment groups.

Table 32: Incidence of headache by pooled study group and age

Age	Study Group 3		Study Group 4	Study Group 2	
	Tasimelteon 20 mg	Placebo	Tasimelteon 20 mg	Tasimelteon Any Dose	Placebo
≤ 65	N=47	N=47	N=164	N=276	N=151
	7 (14.9%)	3 (6.4%)	22 (13.4%)	25 (9.1%)	11 (7.3%)
> 65	N=5	N=5	N=19	N=153	N=52
	1 (20%)	0	4 (21.1%)	16 (10.5%)	4 (7.7%)
Overall	N=52	N=52	N=183	N=429	N=203
	8 (15.4%)	3 (5.8%)	26 (14.2%)	41 (9.6%)	15 (7.4%)

Source: NDA 205677, 5/31/13: Module 5.35.3, Integrated Summary of Safety, Table 35, page 51.

Across the entire safety database, there were no headaches reported as a serious event. Two subjects experienced headache which led to early discontinuation (see narratives below).

Subject #VP-VEC-162-3104- (b) (6) (headache and nightmares): Subject was a (b) (6) with insomnia and no other relevant medical history or concomitant medications, and who was enrolled in Study 3104 (randomized to tasimelteon 20 mg arm). On Study Day 0, in the night after taking the first dose of tasimelteon, subject experienced **headache and nightmares**. The subject continued dosing with tasimelteon and the symptoms continued through study 6. When the subject reported these continuing adverse events on Study Day 7, the Investigator discontinued the subject from the study. No treatment was given for these events. The subject’s headaches and nightmares were considered resolved on study 7. The Applicant concludes that the

events of headache and nightmare are possibly related to study drug administration. Reviewer's comments: I agree with Applicant's assessment.

Subject #VP-VEC-162-COSET-(b) (6) headache): The narrative is located in Section 7.3.3 'Dropouts and/or Discontinuations' of this review. The subject reported headaches, night awakening worsening and asthenia as beginning on the same day after taking tasimelteon, and voluntarily withdrew from the study stating that the reason was the adverse events experienced. The subject indicated that following the last tasimelteon administration, the adverse event of headaches and asthenia resolved with concurrent improvement of 'night awakening worsening'. Reviewer's comments: There is a temporal relationship between the events and tasimelteon exposure, and positive dechallenge.

Applicant's conclusion regarding headaches: The headache events were not associated with additional adverse events or other safety issues and therefore, given all the available information regarding timing of headaches, it is reasonable to conclude that headache is not a safety signal.

Reviewer's conclusions regarding headaches: I agree with the Applicant's conclusion.

Somnolence:

I reviewed the verbatim terms that were mapped to the preferred term somnolence (under nervous system disorders SOC) and agree with the appropriateness of such coding. In addition, I reviewed all verbatim terms containing the term sleep, sedation, and all verbatim terms mapped to the preferred term sleep disorder (under psychiatric disorders SOC). Verbatim term 'sleeping' was coded to the preferred term 'sleep disorder' but unlike other verbatim terms mapped to 'sleep disorder' (for example, fitful sleep, nighttime sleep disrupted', etc), the verbatim term 'sleeping' could potentially be coded to 'somnolence'. There were 25 subjects who experienced the verbatim term 'sleeping'; all these 25 subjects were from one single Study CN116-003 – a Phase I randomized, parallel group, 2-period crossover pharmacokinetic study of single doses of tasimelteon 50 mg and placebo (administered in the *morning*), separated by a 7-day washout, in 40 healthy volunteers. The verbatim term 'sleeping' in this Phase I study likely represents pharmacological effects of the drug administered earlier in the morning (as opposed to residual adverse effects in the morning after drug administration the night before). One subject (VP-VEC-162-1108-(b) (6)) reported 'sedation' but this subject was already captured as reporting 'somnolence'.

The Applicant performed analyses of somnolence events by stratifying the timing of dosing, i.e., morning versus evening dosing. In the integrated safety database, the proportion of subjects who experienced somnolence was higher among subjects enrolled in Phase I studies who were dosed in the morning (23.8%) compared to subjects enrolled in studies where dosing was in the evening (2.8%). In the integrated *placebo-controlled* Phase I studies (i.e., Studies 001 and 002), among subjects who were dosed in the *morning*, 13 (13/36; 36.1%) subjects in the tasimelteon reported somnolence compared to 3 (3/12; 25%) subjects in the placebo group; among subjects dosed in the *evening*, one (1/24; 4.2%) of the tasimelteon subjects reported somnolence compared to none in the placebo group.

The following table summarizes the incidence of subjects who experienced somnolence in the Pooled Study Groups 2, 3 and 4. As can be seen, the incidence of somnolence in Pooled Study Group 2 was higher in the tasimelteon group compared to placebo group, driven by a higher frequency in elderly subjects. In Study 004 (elderly subjects with insomnia), 10 subjects (10/170; 5.9%) reported somnolence in the tasimelteon group compared to 1 subject (1/57; 1.8%) in the placebo group; within tasimelteon subjects, the proportion of subjects with any event in the 1 mg, 10 mg and 50 mg dose groups were 10.7% (6/56), 0% (0/58) and 7.1% (4/56), respectively. In contrast, in Study 3104 (non-elderly adults with insomnia) the incidence was fairly even between treatment groups (tasimelteon: 2/217; 0.9%; placebo: 1/104; 1%).

Table 33: Incidence of somnolence in Pooled Study Group 2, 3 and 4

Preferred Term	Pooled Study Group 2			Pooled Study Group 3			Pooled Study Group 4
	Tasimelteon N=429 n (%)	Placebo N=203 n (%)	RR	Tasimelteon N=52 n (%)	Placebo N=52 n (%)	RR	Tasimelteon N=183 n (%)
Somnolence	13* (3.0)	3* (1.5)	2	3* (5.8)	1* (1.9)	3	5 (2.7)

RR = Relative risk (incidence in tasimelteon group / incidence in placebo group)

*Two subjects (VP-VEC-162-COSET- (b) (6) tasimelteon; and VP-VEC-162-COSET (b) (6), placebo) were counted in both Pooled Study Group 2 and 3;

Source: NDA 205677, 5/31/13: Module 5.3.5.3 Data Analysis Data - Reviewer's analysis of ADAE and ADSL datasets using MAED Service.

The frequency of somnolence in Pooled Study Group 2 was higher (10/242; 4.1%) in female subjects with tasimelteon exposure than female subjects taking placebo (1/119; 0.8%), again driven by *elderly* female subjects in Study 004; the incidence in males was similar between treatment groups. In Study 004, 9 out of 11 elderly subjects who reported any event of somnolence were female (9/11; 81.8%). The proportion of *elderly female* subjects in Study 004 who reported any event of somnolence in placebo, 1 mg, 10 mg and 50 mg groups were 0% (0/34), 9.1% (3/33), 6.7% (2/30) and 12.1% (4/33), respectively. No significant differences in the incidence of somnolence were evident based on most other categories of demographic characteristics; in a few of these categories (for example, age > 65 years in 20 mg dose, black race, etc) the subject numbers were too small to arrive at a meaningful conclusion. Majority of somnolence events occurred within the first 7 days of treatment; and the median duration of somnolence in the tasimelteon and placebo groups were 11 and 34 days, respectively. The number of subjects experiencing somnolence in the Pooled Study Group 3 was also too small for meaningful inference. In Pooled Study Group 3, there were two *female* subjects with any event of somnolence, one in each treatment group: (b) (6) in the tasimelteon group, and a (b) (6) in the placebo group. The remaining two subjects were males, ages 40 and 45 years, and both in the tasimelteon group. (In the safety population of Study 3201, there were 35 female subjects with Non-24 Hour Disorder, randomized 18 to tasimelteon group and 17 to placebo group. Four of these 35 subjects (4/35; 11.4%) were > 65-years: 2 in the tasimelteon group and 2 in the placebo group.)

Across the entire safety database, there were no events of somnolence reported as a serious event. Two subjects experienced somnolence which led to early discontinuation (see narrative below).

Subject #CN116-004- (b) (6) (excessive daytime somnolence): Subject was a (b) (6) with primary insomnia who was randomized to tasimelteon 50 mg group in Study CN116-004 (study of primary insomnia in elderly subjects). Tasimelteon was interrupted between Study Days 4 - 6 due to gingival infection for which erythromycin was prescribed. Tasimelteon was resumed on Study Day 7. Subject experienced diarrhea between Study Days 6 - 8, and 20 - 21, and intermittent perioral numbness (coded as hypoaesthesia oral) between Study Days 19 - 23. On Study Day 14 subject reported severe **excessive daytime somnolence** (coded as somnolence). The last dose of tasimelteon was on Study Day 20, and subject was permanently discontinued from study on Study Day 21. Somnolence was reported resolved on Study Day 28. The Applicant concludes that the above events were possibly related to study medication. Reviewer's comments: I agree with the Applicant's assessment.

Subject #CN116-004- (b) (6) (daytime somnolence, increased insomnia): Subject was (b) (6) taking Premarin (estrogens conjugated) who was enrolled in Study CN116-004 and began taking tasimelteon 50 mg every evening. On Study Day 2, subject reported **daytime somnolence** (coded as somnolence) and **increased insomnia**. The subject's last dose of tasimelteon was on Study Day 5, and the subject was discontinued. No treatment was administered, and the events resolved on Study Day 7. The Applicant's assessment is as follows: "Worsening of daytime sleepiness ("somnolence") and pre-existing insomnia is expected within the first 14 days of initiation of tasimelteon, based upon the drug's mechanism of action. This is an indication of physiologic effect". The Applicant concluded that the event is possibly related to study drug. Reviewer's comments: I agree with the Applicant's assessment.

Applicant's conclusion regarding somnolence: The overall reporting of somnolence is primarily driven by study design. This analysis indicates that there is minimal evidence to suggest an Adverse Drug Reaction of somnolence associated with tasimelteon 20 mg. There is some evidence to indicate that somnolence may result from daytime dosing of tasimelteon. However, the indicated dose timing is one hour prior to bedtime. Therefore, based upon all of the available evidence, neither daytime somnolence nor residual daytime effects are expected to be a safety issue associated with tasimelteon at the recommended dose of 20 mg once per day 1 hour prior to bedtime.

Reviewer's conclusions regarding somnolence: I agree that somnolence is not a safety signal in non-elderly adult subjects with Non-24 Hour Disorder. However, elderly *female* subjects with insomnia taking tasimelteon have a higher incidence of somnolence compared to placebo control.

Dizziness, Syncope and Falls:

Dizziness:

I reviewed the verbatim terms that were mapped to the preferred term 'dizziness', and conclude that the potential for under ascertainment is minimal. Across the ISS safety database, there were

a total of 46 subjects who reported an event of dizziness: 29 of these subjects were receiving tasimelteon, and the remaining subjects received other medications (such as moxifloxacin or midazolam / ethanol / fluvoxamine in combination with tasimelteon). Among the above noted 29 subjects who reported dizziness while exposed to tasimelteon, the majority of subjects (25/29; 86.2%) were enrolled in the early-phase, pharmacokinetic studies when dosing was most often during the day. In Pooled Study Group 5 (pharmacokinetic studies), the incidence of dizziness in tasimelteon subjects is higher than that in placebo subjects (see table below); the incidence of dizziness does not appear to be dose-related.

Table 34: Incidence of treatment-emergent dizziness in the Pooled Study Group 5

Preferred Term	Tasimelteon			Overall N=776 n (%)	Placebo N=131 n (%)
	≤ 20 mg N=385 n (%)	30-50 mg N=161 n (%)	> 50 mg N=230 n (%)		
Dizziness	18 (4.7)	3 (1.9)	7 (3.0)	28 (3.6)	0

Note: Subjects excluded from above analyses were: 10 subjects in Study 1108 (additive effects of tasimelteon with ethanol consumption) - not treated with tasimelteon alone at the time of event. Other subjects were taking other medications at the time of event.

Source: NDA 205677, 5/31/13: Module 5.3.5.3 Data Analysis Data - Reviewer's analysis of ADAE and ADSL datasets.

The incidence of subjects reporting treatment-emergent dizziness was low and fairly even between the treatment groups in Pooled Study Groups 2 and 3 (see Table below). The number of subjects reporting dizziness in Pooled Study Group 2 was small limiting meaningful subgroup analyses based on demographic characteristics. The majority of dizziness events occurred within the first 7 days of the start of tasimelteon exposure.

Table 35: Incidence of treatment-emergent dizziness, syncope and fall in Pooled Study Groups 2, 3 and 4

Preferred Term	Pooled Study Group 2			Pooled Study Group 3			Pooled Study Group 4
	Tasimelteon N=429 n (%)	Placebo N=203 n (%)	RR	Tasimelteon N=52 n (%)	Placebo N=52 n (%)	RR	Tasimelteon N=183 n (%)
Dizziness	4 (0.9)	2 (1.0)	0.9	1 (1.9)	1 (1.9)	1	3 (1.6)
Syncope	2* (0.5)	0	-	2* (3.8)	0	-	2* (1.1)
Fall [^]	0	1 (0.5)	0	0	1 (1.9)	-	0

RR = Relative risk (incidence in tasimelteon group / incidence in placebo group)

-RR could not be calculated due to 0 events in the placebo group.

[^] VP-VEC-162-COSET- (b) (6) with tasimelteon exposure who reported verbatim 'sprained left thumb as the result of a fall' which was coded to the preferred term 'ligament sprain' but not also to 'fall' is not included.

*The same two subjects (VP-VEC-162-COSET- (b) (6) and VP-VEC-162-COSET- (b) (6)) were counted in these columns.

Subject #VP-VEC-162-1103 (b) (6) was not counted as this subject did not belong to Pooled Study Group 2.

Source: NDA 205677, 5/31/13: Module 5.3.5.3 Data Analysis Data - Reviewer's analysis of ADAE and ADSL datasets using MAED Service.

In the entire ISS safety database, one subject (CN116-004- (b) (6)) experienced a serious adverse event of dizziness as part of gastritis (narrative provided in Section 7.3.2 of this review). One subject (CN116-004- (b) (6)) reported treatment-emergent dizziness which led to withdrawal from study (see narrative).

Subject #CN116-004- (b) (6) (dizziness): Subject was (b) (6) with history of hypertension who was randomized to tasimelteon 10 mg arm in Study 004. Concomitant medications included zestril, hydrochlorozide, pilocarpine, Trusopt, timolol and vitamin supplements. On Study Day 1, subject reported **dizziness**; study medication was interrupted till Study Day 3. After study medication was resumed on Study Day 4, subject reported dizziness again. The subject was discontinued from the trial on Study Day 6. The subject had discontinued Norvasc (amlodipine) on her own two weeks before starting study medication because of ankle edema. The Applicant states that dizziness is a potential effect of abrupt discontinuation of amlodipine, and therefore, due to this confounding effect the cause of dizziness is unassessable in regards to relationship with study drug administration. Reviewer's comments: positive rechallenge favors a causal relationship between the event and tasimelteon.

Syncope:

In the entire safety database, there were three subjects – all with exposure to tasimelteon, who experienced treatment-emergent syncope (see narratives below).

Subject #VP-VEC-162-COSET- (b) (6) Subject with history of intermittent syncope experienced **syncope** on Study Day 169 (tasimelteon 20 mg) during a blood draw and was admitted to hospital for observation. This event was reported as a serious event. The narrative is located in Section 7.3.2 'Nonfatal Serious Adverse Events' of this review. Reviewer's comments: History of intermittent syncope provides an alternated explanation.

Subject #VP-VEC-162-COSET- (b) (6) See Section 7.3.4 'Significant Adverse Events' for full narrative. Briefly, subject was diagnosed to have acute lymphocytic leukemia on Study Day 27. On Study Day 18, subject reported an adverse event of **syncope**; tasimelteon was formally discontinued the next day, and subject was withdrawn from the trial on Study Day 20. Reviewer's comments: As discussed in the full narrative, the duration of exposure to tasimelteon was 19 days; however, manifestations and/or symptoms of underlying malignancy were likely evident during screening, treatment or shortly after study drug discontinuation (7 days after the event of syncope, subject experienced nausea, dizziness, diarrhea, and shortness of breath which led to hospitalization and diagnosis).

Subject #VP-VEC-162-1103 (b) (6): Subject was (b) (6) who was enrolled in Study 1103 (thorough QT study). Subject received tasimelteon 20 mg daily for 3 days; the next day, in the morning, subject experienced **syncope** which resolved spontaneously. No abnormalities in ECG were noted. Subject continued in the study and completed the study as planned. The Applicant states that given the short (90-minute) half-life of tasimelteon and the fact that tasimelteon does not accumulate in the bloodstream, it is unlikely that a dose of tasimelteon given at 08:21 AM on one day would result in an associated adverse event > 24 hours later; however, given the timeframe of the sequence of events, it is impossible to exclude tasimelteon in

association with this event of syncope. Reviewer's comments: I agree with the Applicant's assessment.

Falls:

In the entire safety database, there was one subject (VP-VEC-162-COSET-[REDACTED]^{(b) (6)}) who reported on Study Day 83 of *placebo* exposure a fall which was coded as 'fall'. However, there was one other subject (VP-VEC-162-COSET-[REDACTED]^{(b) (6)}) with *tasimelteon* exposure who reported verbatim 'sprained left thumb as the result of a fall' which was coded to the preferred term 'ligament sprain' but not also to 'fall'. These two subjects were one in each treatment group when they experienced treatment-emergent falls; these events were not reported as serious, and did not lead to early withdrawal from study.

Applicant's conclusion regarding dizziness, syncope and falls: Based on the low number and rate of dizziness events, and no clinically meaningful difference between the rate or type of events in the tasimelteon group compared to the placebo group in the indicated population or in the efficacy studies, it is reasonable to conclude that there is no discernible safety signal or trend present due to dizziness or related events associated with daily use of tasimelteon 20 mg.

Reviewer's conclusions regarding dizziness, syncope and falls: An excess of dizziness events in the tasimelteon group compared to placebo group was evident in healthy volunteers participating in pharmacokinetic studies in the context of day-time dosing in many of these early studies. There is no safety signal with regard to dizziness, syncope and falls in subjects with Non-24 Hour Disorder or insomnia when tasimelteon is dosed around bedtime.

Nightmare and abnormal dreams:

I reviewed the verbatim terms that were mapped to the preferred term 'nightmare' and 'abnormal dreams', and conclude that the potential for under ascertainment is minimal. Since these terms appear related, they were aggregated and analyzed. In the safety database, there were a total of 25 subjects with tasimelteon exposure who experienced either 'nightmare' and/or 'abnormal dreams'. In Pooled Study Group 5 (pharmacokinetic studies), the incidence of subjects reporting any of these events was fairly even between the treatment groups in (table not included in review). There was an excess of tasimelteon subjects reporting either event compared to placebo subjects in both Pooled Study Groups 2 and 3. These events were not dose-related based on data from Pooled Study Group 2 (data reviewed; table not included in review). These events appear to be more common in females (9/12; 75%). No significant differences in the incidence of these events were evident based on most other categories of demographic characteristics. These events occurred most frequently early after initiation of tasimelteon treatment, i.e., 6/11 (54.5%) occurring within the first 7 days of treatment and 9/11 (81.8%) occurring within the first 2 weeks.

Table 36: Incidence of treatment-emergent abnormal dreams or nightmare in Pooled Study Groups 2, 3 and 4

Preferred Term	Pooled Study Group 2			Pooled Study Group 3			Pooled Study Group 4
	Tasimelteon N=429 n (%)	Placebo N=203 n (%)	RR	Tasimelteon N=52 n (%)	Placebo N=52 n (%)	RR	Tasimelteon N=183 n (%)
Any event	11* (2.6)	1 (0.5)	5.2	4* (7.7)	0	-	10* (5.5)
Abnormal dreams	5 (1.2)	1 (0.5)	2.4	2 (3.8)	0	-	6 (3.3)
Nightmare	6 (1.4)	0	-	2 (3.8)	0	-	4 (2.2)

RR = Relative risk (incidence in tasimelteon group / incidence in placebo group)

-RR could not be calculated due to 0 events in the placebo group.

*The same four subjects (VP-VEC-162-COSET- (b) (6), VP-VEC-162-COSET- (b) (6), VP-VEC-162-COSET- (b) (6) and VP-VEC-162-COSET- (b) (6)) were counted in each of these columns.

Source: NDA 205677, 5/31/13: Module 5.3.5.3 Data Analysis Data - Reviewer's analysis of ADAE and ADSL datasets using MAED Service.

In the safety database, there were no events of abnormal dreams or nightmare that were reported as serious. There were three subjects who experienced these events which led to early termination from the trial (see narrative below). One subject (VP-VEC-162-COSET (b) (6)) randomized to tasimelteon 20 mg in Study 3201 withdrew early due to “subject reported an inability to commit to study visits due to their work schedule” and had a treatment-emergent nightmare that was ongoing at the time of early drop out.

Subject #VP-VEC-162-3104- (b) (6): Subject was (b) (6) with primary insomnia without other relevant medical history or concomitant medications. Subject was randomized to tasimelteon 20 mg. On Study Day 8, subject reported **depression, rage/anger, and nightmares**. Subject was discontinued from study due to these adverse events on Study Day 9; the last dose of tasimelteon was taken the night before. No treatment was given for these adverse events. All events were reported resolved three days after discontinuation of tasimelteon. Reviewer's comments: There is a temporal relationship between these events and tasimelteon, and a positive dechallenge.

Subject #VP-VEC-162-COSET (b) (6) Subject was (b) (6) with blindness resulting (b) (6) with a medical history of hypertension which was being treatment with hydrochlorothiazide. Subject was enrolled in the Open-Label Extension of Study 3201. On Study Day 9 after treatment with tasimelteon 20 mg began, subject reported onset of **intermittent and mild nightmares** which **became severe and continuous** by Study Day 27. Subject also reported thirst (Study Day 9) and mild headaches (Study Day 14). No treatment was given for these adverse events. Subject took the last dose of tasimelteon on Study Day 84 and was discontinued from the study. Nightmares were reported as resolved the next day (Study Day 85); mild headaches and thirst were ongoing at the time of permanent discontinuation. Reviewer's comments: There is a temporal relationship between nightmares and tasimelteon, and a positive dechallenge.

Subject #VP-VEC-162-COSET- (b) (6) Subject was (b) (6) with blindness resulting from congenital glaucoma and with a past medical history of migraines. Subject was enrolled into the Open-Label Extension of Study 3201 and began tasimelteon 20 mg treatment.

On Study Day 2, subject reported onset of **irritability and nightmares**. Tasimelteon treatment was discontinued on Study Day 15 and the irritability and nightmares resolved on the same day (not clear if the last dose was on the previous night). The subject was discontinued from the study on Study Day 29. Reviewer's comments: There is a temporal relationship between these events and tasimelteon, and a positive dechallenge.

Applicant's conclusion regarding abnormal dreams and nightmares: Based upon these findings, and given that these events are largely transient and mild in nature without sequelae, it is reasonable to conclude that "vivid or unusual dreams" are reasonably common with use of tasimelteon, and may be related to the mechanism of action of the drug.

Reviewer's conclusion regarding abnormal dreams and nightmares: I largely agree with the Applicant's assessment. However, some subjects experience these with sufficient severity as to discontinue early from the trials.

Rash:

I reviewed the verbatim terms that were coded to 'Skin and subcutaneous tissue disorders' SOC; included in this SOC were preferred term 'rash' (n = 12); 'urticaria' which was coded from 'hives (full body)' (n = 1); and 'dermatitis allergic' which was coded from the verbatim term 'rash (allergic reaction)' (n = 1). The verbatim terms, such as rash on wrist under actigraphy strap is appropriately coded to 'application site rash' under 'General disorders and administration site conditions'. The 'Immune system disorders' SOC contained mostly seasonal/environmental allergies, 'allergic reaction to trimethoprim/sulfamethoxazole' and 'allergic reaction to antibiotic' (none were serious events). In the safety database, there were 12 subjects who experienced the preferred terms 'rash' who were evenly distributed between the treatment groups (tasimelteon = 10/1346; 0.7%; placebo = 2/306; 0.7%). No subject experienced 'rash' as a serious event. There were three subjects who discontinued from a trial early due to 'rash' (see narratives below).

Subject #CN116-002- (b) (6) (rash): Subject was (b) (6) with no reported medical history and who was randomized to tasimelteon 150 mg in Study CN116-002. On Study Day 7, subject experienced a maculopapular pruritic **rash** on (b) (6) back and the back of (b) (6) head and neck. Subject was treated with calamine (Study Day 9 – 11) and diphenhydramine 25mg (Study Day 9 – 10). On Study Day 12, treatment was initiated with triamcinolone. The last dose of study medication was on Study Day 7. The rash improved following cessation of dosing and resolved on Study Day 20. Subject was permanently discharged from the study on Study Day 20. The Applicant concludes that this event is unassessable in its relationship to study drug administration due to the lack of available information. Reviewer's comments: There is a clear temporal relationship between tasimelteon and the onset of the event. However, triamcinolone was initiated about 5 days after onset of event. It is unknown whether it was started empirically or if there was evidence for fungal infection.

Subject #CN116-004 (b) (6) (rash): Subject was (b) (6) with a medical history of hypertension (on Norvasc 5 mg and Dyazide 25 mg) and an allergy to sulfa and aspirin who was randomized to tasimelteon 1 mg in Study 004 (primary insomnia in elderly subjects). On

Study Day 7, subject reported a mild **rash** which appeared on (b) (6) abdomen and back which worsened by Study Day 25. Subject took the last dose of tasimelteon on Study Day 27 and permanently discontinued from the trial on Study Day 35. On Study Day 38, the event of Rash was considered resolved. The subject had a TB test and hepatitis inoculation on the first day of double-blind treatment (Study Day 0). The Applicant concludes that the even of rash was possibly related to study drug. Reviewer's comments: I agree with the Applicant.

Subject #VP-VEC-162-1110- (b) (6) (rash): Subject was (b) (6) with a medical history of food and animal dander allergies and migraine headaches, who was enrolled into Group 1 of Study 1110 (drug interaction study with CYP3A4 and CYP2C8). Subject received the first dose of midazolam 10 mg on Study Day 1, and after a 2-day washout received a single dose of rosiglitazone 4 mg on Study Day 3. After a second 2-day washout, subject began dosing with tasimelteon 20 mg QD on Study Day 5. On Study Day 16 (Day 12 of tasimelteon dosing), subject reported a mild **rash** (beneath (b) (6) right eye, front of nose, medial right upper arm) that had begun four days earlier (Day 8 of tasimelteon dosing). When the rash did not improve with diphenhydramine given between Study Days 16 through 17, i.e., spread to axilla bilaterally, forehead, scalp and genitalia, the Investigator discontinued the subject. After skin scraping from the axilla performed at the study site was reported as "fungal elements observed", subject was administered oral terbinafine 250 mg QD from Study Day 17 through 30 (diphenhydramine was discontinued). During follow-up, subject also reported administration of topical Lamisil (terbinafine) BID from study 28 through 47. Subject reported rash as resolved on Study Day 55. The Applicant states that the diagnosis of fungal infection (skin scraping) and resolution of rash following administration of antifungal agent provide clear evidence of an alternate etiology. Therefore, the Applicant concludes that this event is unrelated to tasimelteon. Reviewer's comments: I agree with the Applicant's assessment.

Reviewer's conclusion regarding rash: Rash is not a safety signal associated with tasimelteon treatment.

7.4.2 Laboratory Findings

Of the 22 studies included in the integrated safety analysis, 21 studies were either single-site studies using a local laboratory or multi-site studies using a central laboratory; the exception was Study 1106 [pharmacokinetic study in subjects with renal impairment (n = 16) and healthy subjects (n = 16)]. The integrated safety datasets include both scheduled and unscheduled laboratory test results. All studies tested the same laboratory parameters, except for Study 004, which did not test for magnesium. The following laboratory tests were included in the integrated safety analyses:

Hematology: red blood cell (RBC) count, hemoglobin, hematocrit, platelets, and white blood cell (WBC) count with differential (absolute counts of neutrophils, lymphocytes, monocytes, eosinophils, basophils).

Chemistry: sodium, potassium chloride, magnesium, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, gamma glutamyl transferase (GGT), blood urea/blood urea nitrogen (BUN), creatinine, glucose, calcium, albumin, total cholesterol, phosphorus, lactate dehydrogenase (LDH), total protein, and uric acid.

Urinalysis: Urinalysis laboratory parameters assessed in the integrated analyses were casts, glucose and protein.

Endocrine: Endocrine tests were assessed in Study 3201; for a listing of these tests, please see the subsection on endocrine effects further below in this section of this review.

Laboratory test results were converted to Standard International units across all studies prior to creating the pooled integrated safety database. For the legacy studies, the laboratory test result values and reference ranges for each test in their respective original units were also provided in the laboratory dataset (along with the standardized units).

Laboratory data were included in the analysis if the sample was taken after the start of the active treatment period or within three days after the last dose of tasimelteon. If samples were taken on the date of a dose change in Phase I studies, then the sample was assigned to the previous dose for analysis (blood sampling was generally performed prior to dispensing medication). If multiple results were reported within given visit window, then the last available measurement reported for that visit was used in summaries of change from baseline by visit. An additional summary of the worst result, defined as maximum value of absolute change from baseline among the identified measurements within a visit window was also provided by treatment group.

I reviewed the Applicant's criteria for potentially clinically significant abnormalities (PCSA). The Applicant's criteria are reasonable.

Analyses focused on measures of central tendency:

I reviewed the change from baseline of laboratory values over time in the integrated safety database. There were no consistent trends over time in these laboratory test values including urinalyses between treatment groups in the placebo-controlled pooled groups of healthy volunteers and subjects with insomnia/Non-24 Hour Disorder.

Analyses focused on shifts from baseline:

In Pooled Study Group 5 (pharmacokinetic studies), there were excess of subjects in the < 20 mg tasimelteon group with shifts from normal at baseline to worst low values at on-treatment for the leukocyte count and erythrocyte count compared to the placebo group; the proportions were similar between the other dose groups and placebo group. The proportions were similar between treatment groups in the Pooled Study Group 2. For all other laboratory parameters, a review of shifts in laboratory test values from low, normal or high categories at baseline to similar categories on-treatment showed that the proportions of subjects experiencing these shifts were fairly similar between treatment groups in the placebo-controlled pooled groups of healthy

volunteers and subjects with insomnia/Non-24 Hour Disorder. No dose-related trends were evident.

Analyses focused on outliers:

The incidence of subjects experiencing a PCS abnormality for most laboratory tests was low and fairly similar between treatment groups. In the overall tasimelteon group, there were 5 (5/429; 1.2%) subjects who experienced ≥ 3 times the upper limit of normal in alanine aminotransferase compared to 1 (1/203; 0.5%) subject in the placebo group (see table below). These subjects are discussed in the ‘Assessment for the potential for drug-induced liver injury’ subsection below.

Table 37: Incidence of Potentially Clinically Significant Clinical Chemistry Test Abnormalities: placebo-controlled Pooled Study Group 2

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Parameter Criterion	Tasimelteon						Overall		Placebo	
	< 20 mg (N=114)		20 mg (N=151)		50 mg (N=164)		Overall (N=429)		Placebo (N=203)	
	M	n (%)	M	n (%)	M	n (%)	M	n (%)	M	n (%)
Alanine Aminotransferase (nkat/L) >= 3 x ULN	105	0	146	3 (2.1%)	154	2 (1.3%)	405	5 (1.2%)	190	1 (0.5%)
Alkaline Phosphatase (ukat/L) >= 3 x ULN	105	0	146	0	154	0	405	0	190	0
Aspartate Aminotransferase (ukat/L) >= 3 x ULN	105	0	146	0	154	1 (0.6%)	405	1 (0.2%)	190	0
Bilirubin (umol/L) >= 34.2 umol/L	105	0	146	0	154	1 (0.6%)	405	1 (0.2%)	190	1 (0.5%)

Note: Group 2 (Placebo-Controlled Pool) includes double-masked data from studies 004, 3104, and 3201.

Note: Baseline assessment was the last available assessment prior to time of the first dose. If there were multiple assessments collected at the same scheduled time, the average of those assessments was used.

Note: M = number of subjects with baseline and at least one post-baseline measurements of specified parameter.

Note: n = number of subjects with post-baseline measurement meeting specified criterion.

Note: % = (n/M)*100

Source: NDA 205677, 5/31/13; Module 5.3.5.3 Integrated Summary of Safety - Tables; Table 2.0.6.3.2, page 1/1.

Analyses focused on laboratory abnormalities reported as treatment-emergent adverse events:

Across the entire safety database, there was no laboratory abnormality that was reported as a treatment-emergent serious adverse event. The Applicant counted three subjects (excluded one subject, VP-VEC-162-COSET-^{(b)(6)}) with laboratory abnormalities leading to early drop out. The following is a listing of all four subjects (including the above noted subject) – all with exposure to tasimelteon, with laboratory abnormalities that led to early discontinuation:

- Subject #VP-VEC-162-3104-^{(b)(6)} (Study 3204): blood creatine phosphokinase increased.
- Subject # VP-VEC-162- COSET-^{(b)(6)} (Study 3202): alanine aminotransferase increased, aspartate aminotransferase increased and gamma glutamyl transferase increased (these terms were grouped as ‘elevated liver function tests’).
- Subject # VP-VEC-162-COSET-^{(b)(6)} (Study 3204): blood creatine phosphokinase increased.
- Subject # VP-VEC-162-COSET-^{(b)(6)} (Study 3204; subject also referred to as VP-VEC-162-3201-^{(b)(6)} in Study 3201): drug-induced cholestasis.

The following table is a summary of the common (≥ 3 subjects in overall tasimelteon group) laboratory abnormalities that were reported as treatment-emergent adverse events. The incidence of subjects reporting ‘blood creatine phosphokinase increased’ appears dose-related; however, the overall proportion of subjects is similar between treatment groups. The incidence of subjects reporting other laboratory abnormalities were fairly similar between the treatment groups.

Table 38: Common laboratory abnormalities (≥ 3 subjects in overall tasimelteon group) reported as treatment-emergent adverse events, placebo-controlled Pooled Study Group 2

Preferred Term	Tasimelteon				Placebo (N=203)
	< 20 mg (N=114)	20 mg (N=151)	50 mg (N=164)	Overall (N=429)	
Alanine aminotransferase increased	0	4 (2.6%)	3 (1.8%)	7 (1.6%)	2 (1.0%)
Blood creatine phosphokinase increased	0	1 (0.7%)	5 (3.0%)	6 (1.4%)	4 (2.0%)
Aspartate aminotransferase increased	0	3 (2.0%)	1 (0.6%)	4 (0.9%)	2 (1.0%)
Neutropenia	0	1 (0.7%)	3 (1.8%)	4 (0.9%)	1 (0.5%)
Blood glucose increased	1 (0.9%)	2 (1.3%)	0	3 (0.7%)	0

Source: NDA 205677, 5/31/13: Module 5.3.5.3 Integrated Summary of Safety; Appendix 7 Laboratory Assessments, Table 1, page 1.

In the subsections below, I discuss specific categories of laboratory tests based on excess of events in the tasimelteon group in the analyses of shifts from baseline, outliers, laboratory events reported as adverse events, or those that are specific to the application.

Assessment of the potential for severe drug-induced liver injury:

As noted above, in the entire safety database there was no subject who experienced a liver function test abnormality that was reported as a serious event. Two subjects (see narratives below) experienced elevation of liver transaminases that led to early drop out.

VP-VEC-162-COSET- (b) (6) (elevated ALT, AST, and GGT values): Subject was (b) (6) with a medical history of hypertension and bilateral blindness secondary to congenital glaucoma (left eye) and retinal detachment (right eye), and who enrolled in the open-label Study 3202. Subject was taking Hytacand (candesartan) for hypertension for several years prior to study enrollment. Laboratory tests at baseline visit (Study Day 0) showed **elevated ALT, AST, and GGT values** (see table below, and note that the reference range is in conventional units). These abnormal laboratory values were greater than > 2 times Upper Limit of Normal which was an exclusion criterion; however, the subject was enrolled into the study in error. The test results for these laboratory tests worsened by Study Day 70. The Investigator considered the values as critically high and discontinued tasimelteon treatment on Study Day 76. Repeat testing on Study Days 84 (unscheduled) and 112 (Early Termination Visit) showed abnormally high but declining values for these tests. Subject was followed by an outside treating physician whose overall assessment on Study Day 191 was that there was a slight improvement in the liver function tests

after the reduction of alcoholic beverages and that the assessments performed did not reveal any factor other than alcohol that was contributory to the elevated laboratory results. The Applicant concluded that this event was unrelated to Study Drug given the subject’s existing elevated hepatic enzyme results at enrollment, prior to initiation of Study Drug. Reviewer’s comments: Total bilirubin values were not abnormal at any time point. While abnormal liver injury tests at baseline confound causality assessment, the role of tasimelteon in worsening liver function can not be excluded.

Table 39: Liver function tests over time for Subject #VP-VEC-162-COSET- (b) (6)

Study Visit (Study Day)	AST (U/L)	ALT (U/L)	GGT (U/L)	Alkaline Phosphatase (U/L)	Total Bilirubin (mg/dL)
Laboratory Reference Range:	9-34	6-41	11-52	37 - 116	0.10 - 1.10
Screening (-56)	100	139	1329	63	0.62
Week1 (0)	96	109	1296	65	0.71
Week4 (28)	94	111	800	64	0.54
Week8 (70)	188	232	887	71	0.78
Unscheduled (84)	104	115	864	70	0.74
Early Term (112)	76	65	716	66	0.84

Source: Module 5.35.3 ISS – Integrated Summary of Safety, Appendix 3; Narrative for Subject #VP-VEC-162-COSET- (b) (6); adapted from Tables 1, and laboratory test results.

Subject # VP-VEC-162-COSET- (b) (6) in Study 3204 (also referred to as VP-VEC-162-3201- (b) (6) in Study 3201) (drug-induced cholestasis): Subject was (b) (6) with a past medical history of dyslipidemia, hypertension, diabetes and alcohol intake of less than 2 beers per week. Subject was enrolled in the open label extension of Study 3201; and on cumulative Study Day 278 rolled over into Study 3204 continuing with tasimelteon 20 mg. Concomitant medications at the time of the event included: atorvastatin (switched from simvastatin about 2 months prior to rollover into Study 3204), and the following medications for approximately 4 years prior to rollover into Study 3204: lisinopril, glipizide, atenolol, amlodipine, and metformin. All liver function tests were normal during Study 3201. On cumulative Study Day 323 (Study Day 45 for Study 3204) (b) (6) reportedly developed severe full body pruritus and loss of appetite. Subject was evaluated at an outside facility where his symptoms were attributed to a food allergy and was prescribed oral loratadine, hydroxyzine and topical triamcinolone. Liver enzymes and total bilirubin were abnormally elevated (see Table below). Hepatitis A, B and C serology and HIV were negative. Abdominal ultrasound and CT scan were not suggestive of a biliary/pancreatic process. On cumulative Study Day 343 (Study Day 65 in Study 3204), subject was evaluated by a Gastroenterologist who noted that the subject had been started on atorvastatin 40 mg per day (switched from simvastatin that (b) (6) had been taking for years) approximately 2 months prior to rollover into Study 3204, but subject had been mistakenly taking a double dose (80 mg) instead. The subject was discontinued from Study 3204 on cumulative Study Day 343 and both atorvastatin and tasimelteon were discontinued on cumulative Study Day 344. As can be seen from the Table below, by cumulative Study Day 404 total bilirubin had returned to normal and transaminases had decreased although still abnormal. This event was not considered as being serious. On 9/20/12, the Applicant combined the various reported symptoms into one diagnostic term “**drug-induced cholestasis**”. As of the cut-off date (11/30/12), the event was considered ongoing.

Table 40: Liver function tests over time for Subject #VP-VEC-162-COSET- (b) (6)

Parameter (Reference Range)	Study Day 259	Study Day 56/334*	Study Day 59/337*	Study Day 71/349*	Study Day 97/375*	Study Day 126/404*
ALT (<36 U/L)	25	531	412	311	179	150
AST (10-40 U/L)	22	286	189	304	-	92
Alkaline phosphatase (37-117 U/L)	111	-	1327	1006	621	473
Total Bilirubin (0.2-1.2 mg/dL)	1.1	2.9	1.9	1.7	1.1	0.86
Direct bilirubin (0-0.3 mg/dL)	-	1.2	0.9	0.8	-	-

Exposure in Study 3204 is provided first / followed by cumulative exposure in both Studies 3201 and 3204; includes a gap in treatment of 19 days. Additionally, subject was discontinued from Study 3204 on 7/19/12, i.e., Study Day 343.
 -Not provided/available

Source: Module 5.35.3 ISS – Integrated Summary of Safety, Appendix 3; Narrative for Subject #VP-VEC-162-COSET- (b) (6) in Study 3204 (also referred to as VP-VEC-162-3201 (b) (6) in Study 3201), and laboratory test results.

The Applicant states that based on pre-clinical and clinical pharmacology studies, tasimelteon does not inhibit the pathways for atorvastatin metabolism (CYP3A4), and in a study of hepatically-impaired subjects there was no clinical effect upon hepatic function and no requirement for tasimelteon dosage adjustment. The Applicant concludes that due to the hepatotoxic nature of the subject’s concomitant atorvastatin, his double-dosing of atorvastatin, and positive dechallenge, combined with the absence of clinical evidence of hepatotoxicity resulting from prior use of tasimelteon, it is unlikely that this event is related to tasimelteon and is instead due to the subject’s overdosage of atorvastatin. Reviewer’s comments: The approved dose range for Lipitor (atorvastatin) is 10 to 80 mg once daily. The Warnings and Precautions section of the label describes dose-related persistent elevations of transaminases (>3x ULN); the incidences of subjects with such elevations were 0.6% for the 40 mg dose and 2.3% for the 80 mg dose. One subject in clinical trials of Lipitor developed jaundice. Increases in liver function tests in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction (of Lipitor), drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Therefore, I conclude that concomitant high dose of atorvastatin offers an alternate explanation.

Rates of ALT elevation > 3 ULN between treatment groups:

An excess of subjects with ALT elevations > 3x ULN in the drug group compared to the control (placebo) group is believed to have a high sensitivity as a predictor of a potential for severe drug-induced liver injury; the specificity is, however, low. The following table is a summary of subjects with ALT elevations > 3x ULN in the placebo-controlled Pooled Study Groups 2 and 3 (I have also included incidences of subjects with elevations in AST, total bilirubin and alkaline phosphatase). While the proportion of these subjects in the overall tasimelteon group appears higher than the placebo group in either placebo-controlled Pooled Study Groups, the numbers of subjects are small and limit interpretation. The incidence in the Pooled Study Group 4 (tasimelteon only subjects with Non-24 Hour Disorder) is also appended to the table below; however, since most of the subjects in Pooled Study Group 4 are subjects from the ongoing open-label studies with long exposures, direct comparison of incidence in this group to those in the pooled Groups 2 and 3 is also limited. Furthermore, note that subjects in the tasimelteon arm

of Pooled Study Group 3 are also included in Pooled Study Group 4. All the subjects included in this table, as well other subjects who had significant ALT elevations but were not included in this table, are individually discussed in the paragraphs below.

Table 41: Incidence of subjects with ALT > 3x ULN in the Pooled Study Groups 2, 3 and 4.

Laboratory test	Pooled Study Group 2					Pooled Study Group 3		Pooled Study Group 4
	Tasimelteon <20 mg N=114 n (%)	Tasimelteon 20 mg N=151 n (%)	Tasimelteon 50 mg N=164 n (%)	Tasimelteon Overall N=429 n (%)	Placebo N=203 n (%)	Tasimelteon 20 mg N=52 n (%)	Placebo N=52 n (%)	Tasimelteon 20 mg N=183 n (%)
ALT	0	3 (2.0)*	2 (1.2)	5 (1.2)*	1 (0.5)	2 (3.8)*	1 (1.9)	8 (4.4)*
AST	0	0	1 (0.6)	1 (0.2)	0	0	0	5 (2.7)
Total bilirubin	0	0	1 (0.6)^	1 (0.2)^	1 (0.5)	0	1 (1.9)	0
Alkaline phosphatase	0	0	0	0	0	0	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Criteria for inclusion in the table: ALT, AST and alkaline phosphatase \geq 3xULN; total bilirubin \geq 2x ULN

*Two subjects (VP-VEC-162-COSET- (b) (6) and VP-VEC-162-COSET- (b) (6) are common to each of these columns.

^VP-VEC-162-3104 (b) (6): See narrative below. The total bilirubin at baseline was 1.8x ULN which increased further to 2.1x ULN by Study Day 37 (ALT remained normal throughout).

Source: NDA 205677, 5/31/13: Module 5.3.5.3 Data Analysis Data - Reviewer's analysis of ADLB and ADSL datasets.

Subject # VP-VEC-162-3104- (b) (6): Subject was (b) (6) with insomnia who enrolled in and completed Study 3104 after receiving tasimelteon 50 mg for 34 days. On Study Day 36 (two days after last dose), ALT was elevated to 3.5x ULN; by Study Day 53, ALT was within normal limits. AST was elevated to 1.6x ULN on Study Day 36 and was otherwise normal at all other time points. Total bilirubin and alkaline phosphatase remained normal throughout.

Subject #VP-VEC-162-3104 (b) (6): Subject was a (b) (6) with insomnia who enrolled in and completed Study 3104 after receiving tasimelteon 50 mg for 40 days. On Study Day 30, ALT and AST were increased to 3.2x and 3.4x ULN, respectively, but were reduced to normal by Study Day 43. Total bilirubin remained normal throughout. Alkaline phosphatase was mildly abnormal (1.1x ULN) at baseline, and remained mildly abnormal at all time points.

Subject #VP-VEC-162-3104 (b) (6) Subject was (b) (6) with insomnia who enrolled in and completed Study 3104 after receiving tasimelteon 50 mg for 36 days. Blood tests done on Study Day 38 (two days after last dose) showed 1.3x ULN elevation of ALT, which increased to 3.9x ULN by Study Day 43 and then down to 1.3x ULN of normal by Study Day 70. Other than 1.8x ULN elevation of AST at Study Day 43, AST, total bilirubin and alkaline phosphatase remained normal throughout. This subject was not counted in the above table by the Applicant since the ALT elevation occurred at day 43, i.e., 7 days after last dose (outside the 3-day window after the last dose).

Subject #VP-VEC-162-3104 (b) (6) Subject was (b) (6) with insomnia who enrolled in and completed Study 3104, i.e., received 35 days of treatment with tasimelteon 20 mg. Blood tests done on Study Day 37 (two days after the last dose) showed ALT elevation of 4x

ULN, followed by reversal to near normal (1.1 x ULN) by Study Day 54. AST, total bilirubin and alkaline phosphatase remained normal throughout.

Subject #VP-VEC-162-COSET- (b) (6): Subject was (b) (6) who sequentially enrolled in Study 3201, Study 3203 and Study 3204. During Study 3201, abnormal elevations of transaminases occurred at a single time point (Study Day 57): ALT and AST were up to 3.2x and 2.2x ULN, respectively. Total bilirubin and alkaline phosphatase were normal throughout Study 3201. Subsequently, all liver function tests were normal during Study 3203 and the ongoing open-label Study 3204.

Subject #VP-VEC-162-COSET- (b) (6): Subject was (b) (6) who enrolled in Study 3201 and after completing it enrolled in the ongoing open-label Study 3204. During screening ALT was elevated at 1.5x ULN (AST, total bilirubin and alkaline phosphatase were normal). Liver tests done on Study Day 1 (tasimelteon was scheduled to be taken that night at bedtime) showed further elevation of ALT to 4.7x ULN (AST was 2.3x ULN; total bilirubin and alkaline phosphatase were normal). After exposure to tasimelteon 20 mg began, ALT values fluctuated from normal to as high as 3.2x ULN (Study Day 115) in Study 3201; and in the ongoing open-label Study 3204, the last available ALT value was normal (Study Day 142). Total bilirubin and alkaline phosphatase remained normal throughout.

Subject #VP-VEC-162-COSET (b) (6): Subject was (b) (6) who was enrolled in the open-label extension of Study 3201. Subject was terminated early after 35 days of treatment with tasimelteon 20 mg due to a protocol deviation. At baseline, ALT was elevated 1.7x ULN (AST, total bilirubin and alkaline phosphatase were normal). On Study Day 32, ALT and AST were increased to 3.2x and 5.1x ULN, respectively. By Study Day 44, ALT value reduced to 1.5x ULN and AST was normal. Total bilirubin and alkaline phosphatase were normal at all time points.

Subject #VP-VEC-162-COSET- (b) (6) Subject was (b) (6) who sequentially enrolled in Study 3201 open-label extension and in the ongoing open-label Study 3204. Liver tests were normal at baseline. Subject had elevation of transaminases at one time-point (Study Day 54): ALT and AST were up to 3.3x and 2.2x ULN, respectively. In the ongoing open-label Study 3204, the liver transaminases have remained normal as of cumulative Study Day 351. Total bilirubin and alkaline phosphatase were normal at all time points.

Subject #VP-VEC-162-COSET- (b) (6) Subject was a (b) (6) who completed the open-label extension of Study 3201 and then enrolled in the run-in phase of Study 3203. At baseline, ALT and AST were elevated to 1.6x and 1.7x ULN, respectively (total bilirubin and alkaline phosphatase were normal). After tasimelteon exposure began, ALT values were mostly normal; however, on Study Day 183, ALT value increased to 3.2x ULN and AST to 2.5x ULN (total bilirubin and alkaline phosphatase were normal). In the run-in phase of Study 3203, the liver transaminases were normal (as of cumulative Study Day 211); total bilirubin and alkaline phosphatase were normal.

Subject #VP-VEC-162-COSET- (b) (6) Subject was (b) (6) who was sequentially enrolled in the open-label extension of Study 3201, run-in phase of Study 3203, and the ongoing open-label Study 3204. Liver function tests were normal at baseline. After approximately 85 days of tasimelteon exposure, liver transaminases values began to rise, and by Study Day 117 ALT and AST values increased to 3.2x and 4x ULN, respectively (total bilirubin

and alkaline phosphatase were normal). Liver function tests were normal during Study 3203 and in the ongoing open-label Study 3204 (as of cumulative Study Day 355).

Subject #VP-VEC-162-COSET- (b) (6): Subject was (b) (6) who completed the open-label extension of Study 3201 and then enrolled in the run-in phase of Study 3203 (was not randomized in this study). At screening, liver function tests were normal. Blood tests done on Study Day 1 (tasimelteon was scheduled to be begin that night at bedtime) showed ALT elevation of 1.6x ULN (AST, total bilirubin and alkaline phosphatase were normal). ALT continued to increase to 3.1x ULN (by Study Day 33) with concomitant elevation of AST (2.4x ULN). During Study 3201 and Study 3203, ALT and AST fluctuated between normal values to as high as 3.7x ULN and 2.8x ULN, respectively. The last available ALT value (cumulative Study Day 251) was 2.1x ULN (AST was normal). Total bilirubin and alkaline phosphatase were normal at all time points.

Subject #VP-VEC-162-COSET- (b) (6): Subject was (b) (6) who sequentially enrolled in the open-label extension of Study 3201 and the ongoing open-label Study 3204. Liver function tests were essentially normal during the 188 days of tasimelteon 20 mg exposure in Study 3201. After rolling over into the ongoing open-label Study 3204, ALT was elevated at one single time point (cumulative Study Day 273) to 3.2x ULN of normal (AST and total bilirubin were normal; and alkaline phosphatase was elevated to 1.5x ULN). As of cumulative Study Day 293 in the ongoing open-label Study 3204, all liver function tests were normal.

Subject #VP-VEC-162-COSET- (b) (6) Subject was (b) (6) who was enrolled in the open-label Study 3202. During screening, ALT and AST values were 3.4x and 2.9x ULN, respectively (total bilirubin and alkaline phosphatase were normal). After tasimelteon exposure began, ALT and AST values increased to as high as 5.7x and 5.5x ULN, respectively. As of the last available results (Study Day 113) in this ongoing study, ALT and AST values were 2.7x and 2.2x ULN, respectively. Total bilirubin and alkaline phosphatase were normal at all time points.

Subject #VP-VEC-162-COSET (b) (6) in Study 3204 (also referred to as VP-VEC-162-3201- (b) (6) in Study 3201: See narrative for this subject at the beginning of this subsection. This subject experienced elevated liver transaminases, total bilirubin and alkaline phosphatase in the context of concomitant use of high dose of atorvastatin; these events led to early discontinuation.

Subject #VP-VEC-162-3104- (b) (6): Subject was (b) (6) with insomnia, who enrolled in Study 3104 and completed 35 days of dosing with tasimelteon 50 mg. The total bilirubin at baseline was 1.8x ULN which increased further to 2.1x ULN by Study Day 37 (ALT remained normal throughout).

Subject #VP-VEC-162-COSET- (b) (6): Subject was (b) (6) randomized to *placebo* in Study 3201. Liver function tests were normal at baseline. ALT and AST increased to 3.2x and 2.4x ULN, respectively, by Study Day 114, and returned to normal thereafter. Alkaline phosphatase increased to 1.3x ULN on Study Day 121. Total bilirubin remained normal at all time points.

Marked elevations of ALT elevation up to 5x, 10x or 20x in treatment groups:

A more specific signal of the potential to cause severe drug-induced liver injury is a higher rate of more marked peak ALT elevations (5x, 10x, or 20x ULN). In the entire safety database, there

were no subjects with ALT elevations >10x ULN. There were three subjects who had ALT increases 5x ULN.

Subject #VP-VEC-162-COSET- (b) (6) This subject had abnormal ALT test results *at baseline* which worsened on-treatment leading to early dropout. See narrative at the beginning of this subsection. Reviewer's comments: abnormal ALT at baseline confounds assessment of causality.

Subject #VP-VEC-162-COSET- (b) (6): ALT and AST values were 3.4x and 2.9x ULN, respectively, during screening, and worsened on-treatment to as high as 5.7x and 5.5x ULN, respectively. See narrative in the above paragraphs. Reviewer's comments: abnormal ALT at screening confounds assessment of causality.

Subject #VP-VEC-162-COSET- (b) (6) in Study 3204 (also referred to as VP-VEC-162-3201- (b) (6) in Study 3201): See narrative for this subject at the beginning of this subsection. This subject experienced elevated liver transaminases, total bilirubin and alkaline phosphatase in the context of concomitant use of high dose of atorvastatin; these events led to early discontinuation. Reviewer's comments: concomitant use of high dose of atorvastatin offers an alternate explanation.

Subjects meeting criteria for Hy's law:

The most specific predictor of a drug's potential for severe hepatotoxicity is evidence of reduced overall liver function in one or more subjects, manifested by increased serum total bilirubin, in conjunction with ALT elevation, not explained by any other cause, together with an increased rate of ALT elevation in the overall study population compared to control. In the entire safety database, there were no subjects who met the criteria for Hy's Law, defined as $\geq 3x$ ULN for ALT or AST and $\geq 2x$ ULN bilirubin but without alkaline phosphatase $\geq 2x$ ULN, and without alternate reason. However, Subject #VP-VEC-162-COSET (b) (6) in Study 3204 (also referred to as VP-VEC-162-3201- (b) (6) in Study 3201) – who appears to have an alternative explanation (high dose of atorvastatin) and was discussed in the narrative at the beginning of this subsection, had concomitant elevations of $\geq 3x$ ULN for ALT and $\geq 2x$ ULN of total bilirubin and alkaline phosphatase.

Applicant's conclusion regarding the potential for drug-induced liver injury: It is reasonable to conclude there is no clinically meaningful evidence for drug-induced liver injury risk associated with tasimelteon treatment.

Reviewer's conclusion regarding the potential for drug-induced liver injury: Based on the safety data which are adequate, the potential for tasimelteon-induced liver injury is low.

Blood creatine phosphokinase:

Across the entire safety database, there was one subject who experienced elevation in blood creatine phosphokinase as part of a serious event. There were two subjects with increases in creatine phosphokinase which led to early discontinuation from the trial (see narratives below):

Subject #VP-VEC-162-COSET- (b) (6) in Study 3201 (also referred to as Subject #VP-VEC-162-3203- (b) (6) in Study 3203): Subject was (b) (6) with who experienced **loss of consciousness (due to opiate ingestion** based on toxicology results) with prolonged immobility resulting in rhabdomyolysis (CK >10,000 U/L). Subject was hospitalized. The narrative is located in Section 7.3.2 ‘Nonfatal serious adverse events’ of this review.

Subject #VP-VEC-162-3104 (b) (6) Subject was a (b) (6) with no relevant medical history or concomitant medications. Screening laboratory tests for Study VP-VEC-162-3104 showed elevated CPK level of 373 IU/L (normal range: 24-195) which the investigator considered as not clinically significant. The subject was randomized to the 50 mg of tasimelteon group and received four doses of tasimelteon after which the results for the laboratory tests done on Study Day 0 (baseline) were available. These results showed a clinically significantly **elevated CPK level of 915 IU/L** and the subject was discontinued from the study on Study Day 5. The last dose was taken the night on Study Day 4. Repeat testing on Study Day 7 showed CPK still elevated at 537 IU/L. The subject was otherwise asymptomatic. Reviewer’s comments: the event that led to discontinuation was unrelated to the study medication, i.e., not treatment-emergent.

Subject #VP-VEC-162-COSET- (b) (6) in Study 3201 (also referred to as VP-VEC-162- (b) (6) in Study 3204): Subject was (b) (6) with blindness (cause reported as unknown), history of musculoskeletal pain and a baseline elevation of CPK (1058 U/L; Reference range: 25-210 U/L). Subject was enrolled in the open-label Study 3204 and began taking tasimelteon 20 mg. Subject experienced **intermittent elevations of CPK levels** which ranged from 178 to 5,960 U/L (Study Days 0 – 6, 29, through 92). In addition, subject experienced elevated AST levels (103 U/L; Reference range: 9-34 U/L) on Study Day 85 that resolved upon retest on Study Day 92 (42 U/L); at baseline and Study Day 58, AST values were 29 and 21 U/L, respectively). As a result of these abnormalities, the subject was discontinued for precautionary reasons on Study Day 92. Reviewer’s comments: Ongoing musculoskeletal pain, baseline elevation of CPK, intermittent fluctuation and normalization of CPK while on tasimelteon confound causality assessment. However, the role of tasimelteon in worsening CPK can not be excluded. AST elevation was isolated occurrence at a single time-point; ALT and total bilirubin were not affected.

The incidence of subjects who had ‘blood creatine phosphokinase increased’ reported as a treatment-emergent adverse event in the placebo-controlled Pooled Study Group 2 is summarized in the above table. As previously stated, the incidence of subjects reporting ‘blood creatine phosphokinase increased’ appears dose-related; however, the overall proportion of subjects is similar between treatment groups.

Creatine phosphokinase was not measured in all clinical studies, and therefore was not included in the integrated analyses of laboratory data. In Study 3201, there was no consistent trend in the change from baseline in creatine phosphokinase values between treatment groups over time (through Study Day 196). The number of subjects with shifts in creatine phosphokinase from normal at baseline to high on-treatment was low and fairly even between treatment groups (1/40; 2.5% in tasimelteon versus in 2/39; 5.1% placebo). There were 7 (7/40; 17.5%) subjects in the tasimelteon group who experienced creatine phosphokinase values outside the normal high range in the randomization phase compared to 5 (5/39; 12.8%) in the placebo subjects.

Reviewer's comments regarding the creatine phosphokinase: Tasimelteon does not have an adverse effect on creatine phosphokinase.

Effects on endocrine function:

Since drugs with mechanisms of action similar to tasimelteon have adverse endocrine effects, the Agency recommended (6/26/09) the Applicant to assess those effects during the drug development program. Specifically, ramelteon – a melatonin receptor agonist at MT1 and MT2 receptors, when administered 16 mg (approved dose is 8 mg) daily for 6 months in subjects with chronic insomnia was associated with a 4.9 µg/L (34% increase) change from baseline in mean serum prolactin level in women compared with -0.6 µg/L in placebo group in women. No differences between active- and placebo-treated groups occurred among men.

Evaluation of effects on endocrine function was not evaluated during the early development phase; however, it was evaluated in Study 3201. In Study 3201, endocrine laboratory tests included serum total thyroxine (T4), free T4, thyroid stimulating hormone (TSH), triiodothyronine (T3), total testosterone, free testosterone, luteinizing Hormone (LH), follicle stimulating hormone (FSH), progesterone (in woman of child bearing potential), prolactin, and urinary cortisol secretion. These tests were performed at Study Days 0, 28, 56, 84, 112, 183, and 196. However, very few progesterone evaluations were made because very few females of child-bearing potential who were not already (at enrollment) using a hormonal form of contraception were enrolled in the study.

In Study 3201, there was no consistent trend in the change from baseline in T4, free T4, TSH, T3, total testosterone, free testosterone, prolactin, LH and FSH values between treatment groups over time (through Study Day 196). Additionally, the changes from baseline in prolactin values over time were comparable between tasimelteon-treated male and female subjects.

The number of subjects with shifts in T4, free T4, TSH, T3, total testosterone, free testosterone, prolactin, LH and FSH values from normal/low at baseline to high on-treatment, or normal/high at baseline to low on-treatment, were low and fairly even between treatment groups.

The numbers of subjects with endocrine parameters (other than prolactin) outside the normal range (low or high) during the randomization phase of Study 3201 were low and fairly even between treatment groups. For prolactin, there were 6 (6/39; 15.4%) tasimelteon subjects who had *low* values compared to 3 (3/36; 8.3%) placebo subjects; there were no clear differences in proportions between tasimelteon-treated male and female subjects. The proportion of subjects with *high* prolactin values was 10.3% (4/39) in the tasimelteon group and was comparable to that (4/36; 11.1%) in the placebo group. Reviewer's comments: I reviewed the prolactin values over time for each of these subjects with outlier values. In all of these subjects, the abnormal values were just above the upper value of the reference range or just below the lower value of the reference range, and occurred at one single time point on-treatment.

A review of treatment-emergent adverse events in the Endocrine Disorders, Metabolic and Nutrition Disorders, and Investigations SOCs revealed no event that was categorized as being

serious. There were two subjects (one in each treatment group) who experienced a relevant adverse event that led to withdrawal from trial (see narratives below).

Subject #VP-VEC-162-COSET- (b) (6) Subject was (b) (6) with a medical history of bilateral blindness secondary to ocular trauma, hypercholesterolemia, hypertension, and non-insulin dependent diabetes mellitus (NIDDM) about 12 years prior to enrollment being treated with gliclazide. Subject enrolled in the open-label Study 3202 (tasimelteon 20 mg QD). Pre-treatment blood glucose values were abnormal, ranging from 128 – 150 mg/dL (Reference range: 60 – 115 mg/dL). On-treatment blood glucose values were also abnormal (coded as **hyperglycemia**) and ranged from 187 – 208 mg/dL between Study Days 28 – 84. On Study Day 84, subject reported worsening of diabetes with polyuria and polydipsia which began about 5 days earlier. Subject was referred to a health care provider who advised the subject to discontinue the study. The subject was withdrawn from the study on Study Day 112 (blood glucose value on this day was 220 mg/dL); the last dose of tasimelteon was administered the previous evening. The adverse events were on-going at the time of study discontinuation. Reviewer’s comments: abnormal blood glucose values at pre-treatment time points confound causality assessment.

Subject #VP-VEC-162-COSET- (b) (6) Subject was (b) (6) with a medical history of deep vein thrombosis, pernicious anemia and diverticulitis who was randomized to **placebo** arm in Study 3201. During screening (prior to tasimelteon exposure), subject experienced dizziness resulting in a fall at multiple times. Subject was discontinued due to elevated free testosterone on Study Day 29.

In the entire safety database, there were 18 (18/1346; 1.3%) tasimelteon subjects who reported relevant treatment-emergent adverse events in the above SOCs compared to 3 (3/306; 1.0%) placebo subjects. The proportion of subjects with any endocrine-related adverse events, or hyperglycemia-related events (see footnote) is fairly similar between the treatment groups in Pooled Study Groups 2 and 3 (see table below). One tasimelteon subject (VP-VEC-162-COSET- (b) (6)) experienced three events (blood follicle stimulating hormone increased, blood luteinizing hormone increased, and blood prolactin decreased), and was counted once in each of the three tasimelteon columns in the table below. In this subject, the follicle stimulating hormone and luteinizing hormone were elevated at baseline and during on-treatment, and the decreased prolactin value (82 μ IU/mL; reference range: 86 – 324 μ IU/mL) was just one occurrence at Study Day 58 and was normal at all other time points. Another tasimelteon subject (VP-VEC-162-COSET- (b) (6)) experienced blood glucose increased, and was counted once in each of the three tasimelteon columns in the table.

Table 42: Summary of endocrine-related adverse events in Pooled Study Groups 2, 3 and 4

Preferred term	Pooled Study Group 2		Pooled Study Group 3		Pooled Study Group 4
	Tasimelteon N=429 n (%)	Placebo N=203 n (%)	Tasimelteon N=52 n (%)	Placebo N=52 n (%)	Tasimelteon N=183 n (%)
Any event	6 (1.4)	3 (1.5)	4 (7.7)	2 (3.8)	17 (9.3)
Blood follicle stimulating	1 (0.2)	0	1 (1.9)	0	1 (0.5)

Preferred term	Pooled Study Group 2		Pooled Study Group 3		Pooled Study Group 4
	Tasimelteon N=429 n (%)	Placebo N=203 n (%)	Tasimelteon N=52 n (%)	Placebo N=52 n (%)	Tasimelteon N=183 n (%)
hormone increased					
Blood glucose decreased	0	0	0	0	1 (0.5)
Blood glucose increased	3 (0.7)	0	1 (1.9)	0	3 (1.5)
Blood luteinising hormone increased	1 (0.2)	0	1 (1.9)	0	2 (1.0)
Blood prolactin decreased	1 (0.2)	1 (0.5)	1 (1.9)	1 (1.9)	1 (0.5)
Blood testosterone decreased	0	0	0	0	2 (1.0)
Blood testosterone free increased	0	1 (0.5)	0	1 (1.9)	0
Diabetes mellitus	0	0	0	0	2 (1.0)
Glucose tolerance impaired	0	0	0	0	1 (0.5)
Hyperglycaemia	0	1 (0.5)	0	0	2 (1.0)
Hypothyroidism	0	0	0	0	1 (0.5)
Polydipsia	0	0	0	0	1 (0.5)
Hyperglycemia-related terms*	3 (0.7)	1 (0.5)	1 (1.9)	0	9 (4.9)

*Hyperglycemia related terms: blood glucose increased, diabetes mellitus, glucose tolerance impaired, hyperglycaemia, and polydipsia.

Source: NDA 205677, 5/31/13: Module 5.3.5.3 Data Analysis Data - Reviewer's analysis of ADAE and ADSL datasets.

Applicant's conclusion regarding effects on endocrine laboratory parameters: There were no clinically notable individual laboratory results identified, and there were no clinically meaningful or persistent changes from baseline at any time point for any endocrine laboratory parameter.

Reviewer's conclusion regarding effects on endocrine laboratory parameters: Tasimelteon is not associated with an increase in prolactin values over time in either male or female subjects, and subjects with outlier values were due to isolated single reductions (just below the lower value of the reference range) or single elevations (just above the upper value of the reference range). The long-term effect of tasimelteon doses higher than 20 mg has not been evaluated.

Neutropenia and white blood cell count:

In Pooled Study Group 5 (pharmacokinetic studies), there were 14 (14/289; 4.8%) subjects in the < 20 mg tasimelteon group with shifts from normal at baseline to worst low results at on-treatment for the leukocyte count compared to 3 (3/123; 2.4%) in the placebo group; the proportions were similar between the other dose groups and placebo group. Similar excess of tasimelteon subjects with shifts in the leukocyte count was not evident in the Pooled Study Group 2. For neutrophils and lymphocytes, the proportions of subjects with shifts were similar between the treatment groups in the Pooled Study Groups 2 and 5. The incidence of subjects experiencing a PCS abnormality for these laboratory tests was low and fairly similar between treatment groups.

As can be seen from Table above, the incidences of subjects with neutropenia were 0.7%, 1.8% and 0.5% in the tasimelteon 20 mg, tasimelteon 50 mg, and placebo groups, respectively. Five of the four subjects were enrolled in Study 3104 (non-elderly adult subjects with insomnia); one subject is enrolled in the ongoing open-label Study 3204. The % neutrophils for the subjects in Study 3104 (reference range: 40.9% - 77%) were: 39.5%, 33.5%, 33.5%, 44.4%, and 40.8% (placebo). The on-treatment leukocyte count in the tasimelteon subjects remained either normal or was as low as $3.3 \times 10^9/L$ and in the placebo subject low at $3.1 \times 10^9/L$. Neutropenia was reported during 31 – 38 days after treatment with study drug in 5/6 tasimelteon subjects, and at Study Day 519 in the remaining tasimelteon subject. All five subjects completed Study 3104, and one subject remains enrolled in the ongoing open-label Study 3204.

In the entire safety database, there were no subjects who experienced any relevant treatment-emergent adverse event (see Table below for a listing of terms) as a serious adverse event or resulted in early termination from a trial. In the integrated safety database, there were 12 (12/1346; 0.9%) tasimelteon subjects who reported any relevant treatment-emergent adverse events compared to 3 (3/306; 1.0%) placebo subjects; the incidences were comparable between treatment groups.

Table 43: Summary of neutropenia- and leukocyte count-related treatment-emergent adverse events in Pooled Study Group 1

Preferred term	Tasimelteon	Placebo
	N=1346 n (%)	N=306 n (%)
Any event	12 (0.9)	3 (1.0)
Neutropenia	5 (0.4)	1 (0.3)
White blood cell count decreased	4 (0.3)	1 (0.3)
Neutrophil count decreased	2 (0.2)	1 (0.3)
White blood cell count increased	2 (0.2)	0
Leukocytosis	1 (0.1)	0
Neutrophil percentage decreased	1 (0.1)	0

Source: NDA 205677, 5/31/13: Module 5.3.5.3 Data Analysis Data - Reviewer's analysis of ADAE and ADSL datasets.

Reviewer's conclusion regarding effects on neutropenia and white blood cell count: Tasimelteon does not have an adverse effect on neutropenia and white blood cell count.

Hemoglobin and erythrocyte count:

In Pooled Study Group 5 (pharmacokinetic studies), there were 8 (8/267; 3.0%) subjects in the < 20 mg tasimelteon group with shifts from normal at baseline to worst low at on-treatment for the erythrocyte count compared to 1 (1/112; 0.9%) in the placebo group; the proportions were similar between the other dose groups and placebo group. Similar excess of tasimelteon subjects with shifts in the erythrocyte count was not evident in the Pooled Study Group 2. For hemoglobin, the proportions of subjects with shifts were similar between the treatment groups in

the Pooled Study Groups 2 and 5. The incidence of subjects experiencing a PCS abnormality for these laboratory tests was low and fairly similar between treatment groups.

In the entire safety database, there were no subjects who experienced any relevant treatment-emergent adverse event (see Table below for a listing of terms) as a serious adverse event or which led to early termination from a trial. In the integrated safety database, there were 23 (23/1346; 1.7%) tasimelton subjects who reported any relevant treatment-emergent adverse events compared to 3 (3/306; 1.0%) placebo subjects; the incidences were comparable between treatment groups.

Table 44: Summary of hemoglobin- and erythrocyte count-related treatment-emergent adverse events in Pooled Study Group 1

Preferred term	Tasimelton	Placebo
	N=1346 n (%)	N=306 n (%)
Any term	23 (1.7)	3 (1.0)
Haematocrit decreased	16 (1.2)	3 (1.0)
Haemoglobin decreased	10 (0.7)	2 (0.7)
Anaemia	4 (0.3)	0
Anisocytosis	1* (0.1)	0
Haematology test abnormal	1* (0.1)	0
Hypochromasia	1* (0.1)	0
Mean cell haemoglobin decreased	1* (0.1)	0
Mean cell volume decreased	1* (0.1)	0
Poikilocytosis	1* (0.1)	0
Polycythaemia	1* (0.1)	0
Red blood cell abnormality	1* (0.1)	0
Red blood cell microcytes present	1* (0.1)	0

*One subject VP-VEC-162-COSET (b) (6) reported the following events: anisocytosis, haematocrit decreased, haemoglobin decreased, hypochromasia, mean cell haemoglobin decreased, mean cell volume decreased, poikilocytosis, red blood cell abnormality, and red blood cell microcytes present.

Source: NDA 205677, 5/31/13: Module 5.3.5.3 Data Analysis Data - Reviewer's analysis of ADAE and ADSL datasets.

Reviewer's conclusion regarding effects on hemoglobin and erythrocyte count: Tasimelton does not have an adverse effect on hemoglobin and erythrocyte count.

Applicant's overall conclusion regarding effects on metabolic or endocrine laboratory parameters: There were no clinically significant changes in endocrine or metabolic laboratory parameters, nor were there any clinical complaints of adverse events that could be considered endocrine- or metabolic-related associated with any clinically meaningful changes in any endocrine parameter. Therefore, there is no evidence of any adverse effect on laboratory measures of endocrine function due to tasimelton use.

Reviewer's overall conclusion regarding effects on metabolic or endocrine laboratory parameters: Based on the available safety data, which is adequate, the potential for tasimelteon-induced liver injury is low. Tasimelteon does not adversely affect metabolic or endocrine laboratory parameters.

7.4.3 Vital Signs

The vital signs collected include systolic blood pressure (SBP), diastolic blood pressure (DBP), body temperature, body weight, Body Mass Index (BMI; based on height at screening) and heart rate. Blood pressures and pulse rates were measured in a standardized fashion (seated) for most studies. The legacy Study CN116-001 (single ascending dose in healthy volunteers) was the only study where vital signs were obtained in a non-standard manner.

All subjects who had a baseline and at least one follow-up vital sign measurement were included in the integrated analyses. If blood pressure and pulse were measured in different positions (sitting, standing, and/or supine) for different studies, each of these positions was summarized separately. If multiple results were reported within given visit windows, then the last available measurement reported for that visit was used in summaries of observed values and change from baseline by visit. Additional summary of the worst result, defined as maximum value of absolute change from baseline among the identified measurement within a visit window, across all visits were also presented by treatment group. Measurements reported within 3 days after the last dose of tasimelteon were included in the analysis.

The incidences of potentially clinically significant abnormalities (PCSA) for vital signs after the baseline through the end of treatment visit were summarized by treatment group for each parameter. The Applicant used the following criteria for identifying vital sign values as potentially clinically significant abnormalities (see table below).

Table 45: Criteria for Potentially Clinically Significant Vital Signs (Criteria I)

Systolic Blood Pressure	≥ 180 mmHg and an increase of ≥ 20 mmHg ≤ 90 mmHg and a decrease of ≥ 20 mmHg
Diastolic Blood Pressure	≥ 105 mmHg and an increase of ≥ 15 mmHg ≤ 50 mmHg and a decrease of ≥ 15 mmHg
Heart Rate	≥ 120 bpm and an increase of ≥ 15 bpm ≤ 50 mmHg and a decrease of ≥ 15 bpm
Oral Temperature	≥ 38.3 deg C and an increase of ≥ 1.1 deg C ≥ 101 deg F and an increase of ≥ 2.2 deg F
Body Weight	Change from baseline of $\geq 7\%$

Source: NDA 205677, 5/31/13: Module 5.3.5.3 Integrated Summary of Safety; Appendix 1 Statistical Analysis Plan, Table 10, page 41.

In this review, I will refer to the above criteria for PCSA as Criteria I. The above criteria for a given parameter combine a threshold value *and* a change from baseline value, and appear insensitive to detect subjects with outlier values. Therefore, the Agency proposed another criteria (see table below) and asked the Applicant to perform analyses of subjects with outlier values meeting these criteria. I will refer to these criteria for PCSA as Criteria II.

Table 46: Criteria for Potentially Clinically Significant Abnormalities for blood pressure and pulse rate (Criteria II)

<ul style="list-style-type: none">• Systolic BP<ul style="list-style-type: none">• ≥ 160 mm Hg• ≤ 90 mm Hg• Increase from baseline in systolic BP of 20 mm Hg• Decrease from baseline in systolic BP of 20 mm Hg• Diastolic BP<ul style="list-style-type: none">• ≥ 95 mm Hg• ≤ 50 mm Hg• Increase from baseline in diastolic BP of 15 mm Hg• Decrease from baseline in diastolic BP of 15 mm Hg• Pulse rate<ul style="list-style-type: none">• ≥ 110 bpm• ≤ 40 bpm• Increase from baseline in pulse rate of 20 bpm• Decrease from baseline in pulse rate of 20 bpm
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Source: Agency communication via email on 4/12/13.

Analyses focused on measures of central tendency:

I reviewed the change from baseline of vital sign parameter (heart rate, diastolic blood pressure, systolic blood pressure, weight and temperature) values over time in the integrated safety database. There were no consistent trends over time for these vital sign parameter values between treatment groups in the placebo-controlled pooled groups of healthy volunteers and subjects with insomnia/Non-24 Hour Disorder.

Analyses focused on outliers:

I reviewed incidence analyses of subjects with vital sign values meeting Criteria I or Criteria II.

In Pooled Study Group 5 (healthy volunteers/pharmacology studies), blood pressure and pulse were measured in different positions (sitting, standing, supine or semi-supine) for different early legacy studies. The incidence analyses of subjects with blood pressure and pulse PCSA were summarized for each of these positions. The pooled numbers of subjects for some of these positions were relatively small, and in several instances, even though the proportion of subjects with a PCSA in the overall tasimelteon group was higher than that in the placebo group, there was no clear dose-related trend within the tasimelteon dose groups, or trends in the direction of change (increase from baseline versus decrease from baseline, or below versus above a given threshold) for a given vital sign parameter. The following table summarizes the incidences of

subjects with outlier values meeting Criteria II for heart rate, systolic blood pressure and diastolic blood pressure. As can be seen, the proportion of subjects with ≥ 20 mmHg decrease from baseline in systolic blood pressure in the tasimelton group was higher compared to placebo group (highlighted). The incidences of subjects with PCSA for heart rate and diastolic blood pressure, and temperature and weight (reviewed but not included in the table below) was comparable between treatment groups.

Table 47: Incidence of subjects with PCSA in heart rate, systolic and diastolic blood pressure (Criteria II) in Pooled Study Group 5 (healthy volunteers/pharmacology studies)

Parameter Criterion	Tasimelton						Overall (N=776)		Placebo (N=131)	
	≤ 20 mg (N=385)		30-50 mg (N=161)		> 50 mg (N=230)		M	n (%)	M	n (%)
Heart Rate Sitting (bpm)										
≤ 40 bpm	127	0	102	0	132	0	361	0	103	0
≥ 110 bpm	127	1 (0.8%)	102	0	132	0	361	1 (0.3%)	103	0
Decrease from baseline ≥ 20 bpm	127	3 (2.4%)	102	4 (3.9%)	132	4 (3.0%)	361	11 (3.0%)	103	5 (4.9%)
Increase from baseline ≥ 20 bpm	127	9 (7.1%)	102	2 (2.0%)	132	3 (2.3%)	361	14 (3.9%)	103	4 (3.9%)
Systolic Blood Pressure Sitting (mmHg)										
≤ 90 mmHg	127	5 (3.9%)	102	0	132	3 (2.3%)	361	8 (2.2%)	103	3 (2.9%)
≥ 160 mmHg	127	0	102	0	132	0	361	0	103	0
Decrease from baseline ≥ 20 mmHg	127	8 (6.3%)	102	6 (5.9%)	132	12 (9.1%)	361	26 (7.2%)	103	2 (1.9%)
Increase from baseline ≥ 20 mmHg	127	4 (3.1%)	102	1 (1.0%)	132	1 (0.8%)	361	6 (1.7%)	103	0
Diastolic Blood Pressure Sitting (mmHg)										
≤ 50 mmHg	127	1 (0.8%)	102	0	132	1 (0.8%)	361	2 (0.6%)	103	0
≥ 95 mmHg	127	0	102	0	132	3 (2.3%)	361	3 (0.8%)	103	0
Decrease from baseline ≥ 15 mmHg	127	16 (12.6%)	102	5 (4.9%)	132	9 (6.8%)	361	30 (8.3%)	103	8 (7.8%)
Increase from baseline ≥ 15 mmHg	127	4 (3.1%)	102	2 (2.0%)	132	3 (2.3%)	361	9 (2.5%)	103	4 (3.9%)

Note: Pooled Study Group 5 (healthy volunteers/pharmacology studies) includes data from studies 001, 002, 003, 1101, 1102, 1103, 1104, 1105, 1106, 1107, 1108, 1110, 1111, 1112, 2101, and 3101.

Note: Baseline assessment was the last available assessment prior to time of the first dose. If there were multiple assessments collected at the same scheduled time, the average of these assessments was used.

Note: M = number of subjects with baseline and at least one post-baseline measurements of specified parameter.

Note: n = number of subjects with post-baseline measurement meeting specified criterion

Source: NDA 205677, 5/31/13: Module 2.7.4 Summary of Clinical Safety Tables; adapted from Table 5.0.7.2.1

In Pooled Study Group 2 (insomnia/Non-24 Hour Disorder studies), the incidences of subjects with PCSA for all vital sign parameters using Criteria II was comparable between treatment groups (data summary table not included in review). Using Criteria I, the proportion of subjects with systolic blood pressure ≤ 90 mmHg and a decrease of ≥ 20 mmHg from baseline in the overall tasimelton group (5/257; 1.9%) was higher compared to the placebo group (1/143; 0.7%); within tasimelton dose groups, the proportions for the < 20 mg, 20 mg and 50 mg dose groups were 0%, 2.7% and 0.9%, respectively.

Analyses focused on vital sign abnormalities or vital sign-related events as treatment-emergent adverse events:

Across the entire safety database, there was one subject (CN116-004-^{(b) (6)}) randomized to tasimelton who presented with nausea, loose stools, vomiting and dizziness, and hypertension was noted among other adverse events during the brief hospitalization; subject was diagnosed with gastritis and discharged the next day (narrative is located in Section 7.3.2 ‘Nonfatal Serious Adverse Events’) of this review. One other subject (VP-VEC-162-3104-^{(b) (6)}) in the placebo

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group experienced hypertensive emergency as a treatment-emergent serious adverse event. Note, syncope is discussed under a separate subheading in Section 7.4.1 ‘Common Adverse Events’ of this review.

There were no subjects who experienced vital sign-related adverse event which led to early termination from the trial.

There were few subjects in the safety database who experienced any vital sign abnormality or vital sign-related event as a treatment-emergent adverse event. The following table summarizes subjects with vital sign abnormalities reported as treatment-emergent adverse events in Pooled Study Groups 2 (insomnia and Non-24 Hour Disorder studies). The overall numbers of subjects and proportions were low and fairly comparable between treatment groups. In Pooled Study Group 3 (Non-24 Hour Disorder studies), vital sign-related adverse event was reported one each in a tasimelteon subject (hypotension) and a placebo subject (weight increased).

Almost all the reductions in systolic blood pressure values that met the PCSA criteria as noted above were sporadic, and most were not reported as treatment-emergent adverse events.

Table 48: Vital sign findings reported as treatment-emergent adverse events in Pooled Study Group 2

System Organ Class Preferred Term	Tasimelteon				Placebo (N=203)
	< 20 mg (N=114)	20 mg (N=151)	50 mg (N=164)	Overall (N=429)	
Number (%) of Subjects with at least one TEAE	71 (62.3%)	73 (48.3%)	70 (42.7%)	214 (49.9%)	80 (39.4%)
Sinus bradycardia	0	0	1 (0.6%)	1 (0.2%)	0
Pyrexia	0	0	1 (0.6%)	1 (0.2%)	0
Blood pressure increased	0	0	1 (0.6%)	1 (0.2%)	0
Pulse abnormal	0	0	0	0	1 (0.5%)
Weight increased	0	0	0	0	1 (0.5%)
Hypertension	2 (1.8%)	0	0	2 (0.5%)	1 (0.5%)
Hypotension	0	1 (0.7%)	0	1 (0.2%)	0
Hypertensive emergency	0	0	0	0	1 (0.5%)

Source: NDA 205677, 5/31/13: Module 5.35.3 ISS – Integrated Summary of Safety; Appendix 9.1 – Vital signs as treatment-emergent adverse events; Table 1.

Applicant's conclusion regarding vital signs: No major treatment group differences were observed in the incidence or type of vital signs abnormalities. There is no safety signal present.

Reviewer's conclusions regarding vital signs: I agree with the Applicant's conclusions.

7.4.4 Electrocardiograms (ECGs)

During the clinical development program, ECGs were read centrally for 7/22 studies (1103, 3101, 3104, 3201, 3202, 3203, and 3204). ECGs were assessed for clinically significant abnormalities. All subjects who had a pre-dose and at least one follow-up ECG measurement were included in the integrated analysis. ECGs done within 3 days after the last dose of tasimelteon were included in the analysis. If multiple results were reported within given visit window, then the last available measurement reported for that visit was used in summaries of observed values and change from baseline by visit. Additional summaries of the worst value and maximum change from baseline were also provided. Scheduled and unscheduled ECG assessments were included in the integrated analyses.

Electrocardiogram parameters in the integrated analysis were heart rate (HR), PR, QRS, and QT intervals (actual value and values corrected for heart rate). The QT interval values were corrected for heart rate using the following methods: QTcB (Bazett; $QTc = QT/RR^{1/2}$) and QTcF (Fredericia; $QTc = QT/RR^{1/3}$).

Incidence of potentially clinically significant ECG abnormalities were summarized by treatment and overall (based on the maximum increase from baseline for all post-Baseline visits up to and including Study End). The values for an ECG parameter were considered as an abnormal value if it met the given criteria at any time during the treatment visit. The criteria for potentially clinically significant ECG abnormalities are summarized in the following table.

Table 49: Criteria for Potentially Clinically Significant ECGs.

ECGs	Criterion	
	Low	High
PR	< 110 ms	> 210 ms
QRS	NA	>110 ms
QTc	< 350 ms	> 450 ms for males, > 470 ms for females. In addition, report all > 500 ms.
Heart Rate	< 50 bpm	> 100 bpm
QTc	Increase ≥ 30 ms relative to baseline	
QTc	Increase ≥ 60 ms relative to baseline	
Note: bpm = beats per minute; ms = millisecond.		

Source: NDA 205677, 5/31/13: Module 5.3.5.3 Integrated Summary of Safety; Appendix 1 Statistical Analysis Plan, Table 11, page 42.

Thorough QT study (Study 1103): Study 1103 was a randomized, double-blind, crossover trial to define the ECG effects of tasimelteon using a clinical (20 mg) and a suprathreshold dose (300 mg) compared to placebo and moxifloxacin (positive control) in 44 healthy men (n = 22) and women (n = 22). Each subject participated in all four treatment periods with a four-day washout between each treatment period in an inpatient setting. Subjects were randomly assigned to receive 20 mg of tasimelteon for three days, 300 mg of tasimelteon for three days, placebo for three days, or 400-mg moxifloxacin on Day 3. When enrolled in the moxifloxacin arm, subjects received placebo on Days 1 and 2 that was identical to the tasimelteon capsule, and received one

open-label 400-mg moxifloxacin tablet in the morning on Day 3. ECGs and plasma samples for pharmacokinetic analysis were assessed at baseline, and on Study Day 3 of each treatment period up to 24 hours (0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 18, and 23.5 hours after dosing). A time-matched analysis was conducted. Results are summarized in the following table. The QTcI and QTcF placebo-corrected mean change from baseline values for moxifloxacin were +9.4 msec. The QTcI mean changes from baseline placebo-corrected for the clinical and suprathapeutic doses of tasimelteon were +1 msec and –1 msec, respectively. For QTcF, these values were +1 msec and –1 msec, respectively. Please see review of this study by the QT Interdisciplinary Review Team.

Reviewer’s comments: The suprathapeutic dose of 300 mg appears adequate considering that it is 15-fold higher than the labeled 20 mg dose and the worst drug-drug interaction assessed (with fluvoxamine) resulted in a 6.5-fold increase in AUC. This thorough QT study is negative because the assay sensitivity was established and the upper bound of the 95% one-sided confidence interval for the largest time-matched placebo-corrected, baseline-subtracted mean effect of tasimelteon on the QTc interval excludes 10 ms.

Table 50: Placebo-corrected change from baseline by treatment – QTcI (msec)

Time (h)	VEC-162 20 mg		VEC-162 300 mg		Moxifloxacin 400 mg	
	Estimate ^a	Upper bound ^b	Estimate ^a	Upper bound ^b	Estimate ^a	Upper bound ^b
0.5	3.2	5.9	0.1	2.8	11.2	15.6
1	1.8	4.6	-0.2	2.5	13.6	18.1
2	5.1	7.9	2.1	4.9	16.0	20.4
3	1.8	4.6	-1.9	0.9	9.8	14.2
4	1.7	4.4	-0.5	2.2	13.0	17.4
5	0.7	3.5	-0.5	2.1	8.3	12.7
6	0.8	3.6	-0.1	2.6	9.3	13.7
8	0.1	2.9	0.3	3.1	6.7	11.2
10	2.3	5.0	1.0	3.7	10.2	14.6
12	0.0	2.7	1.0	3.7	9.7	14.1
14	-0.3	2.4	-1.0	1.7	5.4	9.9
18	-2.1	0.6	-0.9	1.8	7.6	12.0
23.5	-0.2	2.6	-3.4	-0.6	6.1	10.6

ANOVA = analysis of variance

^aMixed-model ANOVA is fit for placebo-corrected change from Baseline and includes terms for treatment, gender, time, and a time by treatment interaction.

^bUpper bound = upper 1-sided 95% ANOVA model based confidence limit. (Moxifloxacin is Bonferroni-corrected.)

Source: NDA 205677, 5/31/13: Module 5.3.4.1 – Study 1103 Study Report; adapted from Table 9, p 60.

Analyses focused on measures of central tendency:

I reviewed the change from baseline of ECG parameter (QTcB, QTcF, QT uncorrected interval, QRS duration, PR interval, and heart rate) values over time in the integrated safety database. There were no consistent trends over time for these ECG parameter values between treatment groups in the placebo-controlled pooled groups of healthy volunteers and subjects with insomnia/Non-24 Hour Disorder.

Analyses focused on outliers:

In the Pooled Study Group 5 (healthy volunteers/pharmacology studies), the incidences of subjects with PCS in all ECG parameters with few exceptions (QTc \geq 30 ms increase from baseline and \geq 210 PR interval duration) were fairly similar between tasimelteon dose groups and placebo group.

The incidences of subjects experiencing a PCS abnormality in \geq 30 ms increase from baseline in both QTcB (Bazett's correction) and QTcF (Fridericia's correction) were higher in the tasimelteon > 50 mg dose group compared to placebo subjects (highlighted in table below). However, the incidences in the tasimelteon > 50 mg dose group of Pooled Study Group 5 were driven by Study 1103 (thorough QT study) which was included in this pool. Specifically, there were 19 subjects in Study 1103 who met these criteria (given the cross-over study design, subjects meeting these criteria were conservatively assigned to the tasimelteon 300 mg group). After excluding these 19 subjects from Pooled Study Group 2, the incidences between tasimelteon > 50 mg dose group (7/187; 3.7%) and placebo group (5/131; 4.1%) were comparable.

There was one subject each in tasimelteon group and placebo group who met the criteria for \geq 60 ms increase from baseline in QTcB only (but not in QTcF). There were no subjects in Pooled Study Group 5 with > 500 ms (QTcB or QTcF).

The incidence of subjects with a PCS abnormality in \geq 210 ms PR interval was also higher in the tasimelteon > 50 mg dose group compared to placebo subjects (highlighted in table below). However, all the 6 subjects in the tasimelteon > 50 mg dose group were from Study 1103 (thorough QT study). After excluding these 6 subjects from Pooled Study Group 2, the incidences between tasimelteon > 50 mg dose group (0/187; 0%) and placebo group (1/131; 0.8%) were comparable.

Table 51: Incidence of potentially clinically significant ECG abnormalities in Pooled Study Group 5 (healthy volunteers/pharmacology studies)

Clinical Review
 Devanand Jillapalli, MD
 NDA 205677 (Priority)
 Tasimelteon capsules

Parameter Criterion	Tasimelteon						Overall		Placebo	
	<= 20 mg (N=385)		30-50 mg (N=161)		> 50 mg (N=230)		(N=776)		(N=131)	
	M	n (%)	M	n (%)	M	n (%)	M	n (%)	M	n (%)
Qteb - Bazett's Correction Formula (msec)										
< 350 ms	302	5 (1.7%)	153	4 (2.6%)	197	8 (4.1%)	652	17 (2.6%)	122	9 (7.4%)
≥ 350 ms	303	0	153	0	199	0	655	0	122	0
Increase ≥ 30 ms from baseline	304	12 (3.9%)	153	5 (3.3%)	199	26 (13.1%)	656	43 (6.6%)	122	5 (4.1%)
Increase ≥ 60 ms from baseline	304	0	153	0	199	1 (0.5%)	656	1 (0.2%)	122	1 (0.8%)
Male > 450 ms or Female > 470 ms	296	1 (0.3%)	151	1 (0.7%)	199	3 (1.5%)	646	5 (0.8%)	122	3 (2.5%)
Qtef - Fridericia's Correction Formula (msec)										
< 350 ms	273	0	101	1 (1.0%)	149	2 (1.3%)	523	3 (0.6%)	102	0
≥ 350 ms	272	0	101	0	149	0	522	0	102	0
Increase ≥ 30 ms from baseline	274	6 (2.2%)	101	1 (1.0%)	149	7 (4.7%)	524	14 (2.7%)	102	0
Increase ≥ 60 ms from baseline	274	0	101	0	149	0	524	0	102	0
Male > 450 ms or Female > 470 ms	270	0	101	0	149	0	520	0	102	0
Summary (Mean) Heart Rate (bpm)										
< 50 bpm	293	11 (3.8%)	151	8 (5.3%)	191	23 (12.0%)	635	42 (6.6%)	118	10 (8.5%)
≥ 50 bpm	298	0	153	0	198	1 (0.5%)	649	1 (0.2%)	122	0
Summary (Mean) Pr Duration (msec)										
< 110 ms	321	0	160	0	206	1 (0.5%)	687	1 (0.1%)	129	0
≥ 110 ms	318	2 (0.6%)	155	1 (0.6%)	205	6 (2.9%)	678	9 (1.3%)	130	1 (0.8%)
Summary (Mean) Qrs Duration (msec)										
> 110 ms	315	3 (1.0%)	155	0	162	1 (0.6%)	632	4 (0.6%)	129	0

Note: Pooled Study Group 5 (healthy volunteers/pharmacology studies) includes data from studies 001, 002, 003, 1101, 1102, 1103, 1104, 1105, 1106, 1107, 1108, 1110, 1111, 1112, 2101, and 3101.

Note: Baseline assessment was the last available assessment prior to time of the first dose. If there were multiple assessments collected at the same scheduled time, the average of these assessments was used.

Note: M = number of subjects who had parameter assessed during the randomization phase through 3 days after the last dose of study medication who did not have the specified abnormality at baseline.

Note: n = number of subjects meeting abnormality criterion at study endpoint or any time during the treatment visit, given it did not meet the criteria at the baseline.

Source: NDA 205677, 5/31/13: Module 2.7.4 Summary of Clinical Safety Tables; adapted from Table 5.0.8.2.

In the Pooled Study Group 2 (placebo-controlled studies in insomnia and Non-24 Hour Disorder), the incidences of subjects with PCS in all ECG parameters with one exception (≥ 210 PR interval duration) were fairly similar between tasimelteon dose groups and placebo group.

The incidences of subjects with a PCS abnormality in ≥ 210 ms PR interval were higher in the tasimelteon dose groups compared to placebo subjects (highlighted in table below); although the absolute numbers were small, there appears to be dose-relatedness. All subjects who met this criterion were from the insomnia studies (Study 004 and Study 3104); none were subjects with Non-24 Hour Disorder.

Table 52: Incidence of potentially clinically significant ECG abnormalities in Pooled Study Group 2 (studies of insomnia and Non-24 Hour Disorder)

Clinical Review
 Devanand Jillapalli, MD
 NDA 205677 (Priority)
 Tasimelton capsules

Parameter Criterion	Tasimelton						Overall		Placebo	
	< 20 mg (N=114)		20 mg (N=151)		50 mg (N=164)		(N=429)		(N=203)	
	M	n (%)	M	n (%)	M	n (%)	M	n (%)	M	n (%)
Qteb - Bazett's Correction Formula (msec)										
< 350 ms	105	1 (1.0%)	145	0	149	1 (0.7%)	399	2 (0.5%)	189	1 (0.5%)
> 500 ms	106	0	145	2 (1.4%)	151	0	402	2 (0.5%)	189	0
Increase >= 30 ms from baseline	106	8 (7.5%)	145	12 (8.3%)	151	7 (4.6%)	402	27 (6.7%)	189	11 (5.8%)
Increase >= 60 ms from baseline	106	0	145	0	151	0	402	0	189	0
Male > 450 ms or Female > 470 ms	106	0	140	4 (2.9%)	147	1 (0.7%)	393	5 (1.3%)	185	2 (1.1%)
Qtef - Fridericia's Correction Formula (msec)										
< 350 ms	105	1 (1.0%)	145	0	148	1 (0.7%)	398	2 (0.5%)	189	0
> 500 ms	106	0	145	1 (0.7%)	151	0	402	1 (0.2%)	189	0
Increase >= 30 ms from baseline	106	5 (4.7%)	145	10 (6.9%)	151	8 (5.3%)	402	23 (5.7%)	189	10 (5.3%)
Increase >= 60 ms from baseline	106	0	145	0	151	0	402	0	189	0
Male > 450 ms or Female > 470 ms	106	0	142	2 (1.4%)	149	0	397	2 (0.5%)	186	0
Summary (Mean) Heart Rate (bpm)										
< 50 bpm	105	1 (1.0%)	143	8 (5.6%)	150	5 (3.3%)	398	14 (3.5%)	187	13 (7.0%)
> 100 bpm	104	0	145	1 (0.7%)	150	1 (0.7%)	399	2 (0.5%)	189	1 (0.5%)
Summary (Mean) Pr Duration (msec)										
< 110 ms	102	0	144	0	148	0	394	0	189	0
>= 210 ms	100	2 (2.0%)	143	5 (3.5%)	141	6 (4.3%)	384	13 (3.4%)	183	1 (0.5%)
Summary (Mean) Qrs Duration (msec)										
> 110 ms	101	4 (4.0%)	143	4 (2.8%)	146	1 (0.7%)	390	9 (2.3%)	183	2 (1.1%)

Note: Pooled Study Group 2 includes data from studies 004, 3104 and 3201.

Note: Baseline assessment was the last available assessment prior to time of the first dose. If there were multiple assessments collected at the same scheduled time, the average of these assessments was used.

Note: M = number of subjects who had parameter assessed during the randomization phase through 3 days after the last dose of study medication who did not have the specified abnormality at baseline.

Note: n = number of subjects meeting abnormality criterion at study endpoint or any time during the treatment visit, given it did not meet the criteria at the baseline.

Source: NDA 205677, 5/31/13: Module 2.7.4 Summary of Clinical Safety Tables; adapted from Table 2.0.8.2.

Analyses focused on ECG abnormalities or Cardiac-related events as treatment-emergent adverse events:

Across the entire safety database, there were two subjects who experienced cardiac-related serious adverse events. The narratives for these subjects are provided in Section 7.3.2 'Nonfatal Serious Adverse Events' of this review.

Subject #CN116-004-(b) (6): Briefly, this subject was (b) (6) who was randomized to tasimelton 10 mg and was admitted on Study Day 9 to the hospital for nausea, loose stools and vomiting. **Ventricular arrhythmia and ST segment elevation** were noted at admission but during the hospitalization a cardiologist evaluated the subject and concluded that the subject had gastritis but did not find ST elevation or other abnormalities. Subject was discharged from the hospital the next day. The full narrative for this subject is provided in Section 7.3.2 'Nonfatal Serious Adverse Events' of this review. Reviewer's comments: These events are unrelated to tasimelton.

Subject #VP-VEC-162-COSET-(b) (6) Briefly, this subject was (b) (6) with history of myocardial infarction who experienced chest pain and shortness of breath (on cumulative Study Day 385 of tasimelton). Two days later, subject underwent coronary angiogram and stent placement. The event was coded as **coronary artery disease**. The full narrative for this subject is provided in Section 7.3.2 'Nonfatal Serious Adverse Events' of this review. Reviewer's comments: The prior history of myocardial infarction provides an alternate explanation for this event.

In the safety database, there were 5 subjects who experienced ECG abnormalities or cardiac-related treatment-emergent adverse events that led to early withdrawal from clinical trials.

Subject #CN116-004 (b) (6) The narrative for this subject is located in Section 7.3.3 'Dropouts and/or Discontinuation' of this review. Briefly, this subject was a (b) (6) with medical history of primary insomnia, acid reflux, hypertension and hypoglycemia, and concomitant medications including hydrochlorothiazide, Zestril, Prevacid, Evista and multivitamins. Tasimelteon 1 mg was permanently discontinued on Study Day 11 due to severe sweating, acute confusion, ataxia and disorientation (Study Days 9-10); these events were reported resolved by Study Day 13. On Study Day 13, **ST-T wave changes** were noted on ECG which were deemed to be not clinically significant. Reviewer's comments: The relationship between the ECG finding and tasimelteon is unlikely.

Subject #VP-VEC-162-2101 (b) (6) Subject was (b) (6) who was randomized to tasimelteon 10 mg dose group in Study 2101 (subjects in study were administered a total of 3 doses). On Study Day 0, ECG revealed a long R in Lead V-1, symmetric T wave inversion in V1-V3 and an S-T elevation in V3-V6 (coded as **abnormal EKG**); similar findings were noted at Screening (Study Day -49). The consulting cardiologist concluded that "that this was an atypical EKG but a normal variant of early repolarization". Subject was asymptomatic. However, next day, subject had abdominal pain and diarrhoea which led to permanent discontinuation on Study Day 2. Reviewer's comments: Occurrence of these ECG findings at Screening offers an alternate explanation.

Subject #VP-VEC-162-COSET (b) (6) (intraventricular conduction defect, ectopic supraventricular rhythm): Subject was (b) (6) with blindness resulting from cornea death, uveitis, dry eye and cataracts (left eye) and glaucoma (right eye) and a past medical history of decreased hemoglobin, hematocrit and platelet count. The subject was enrolled in Study 3201. ECG was normal at Screening and Study Day 0. On Study Day 29, ECG was noted to have some "new abnormalities" that were judged by the Investigator to be "not clinically significant"; subject was asymptomatic at that time. On Study Day 63, the subject was again asymptomatic but (b) (6) ECG indicated **intraventricular conduction defect** (coded as **conduction disorder**); subject was referred for cardiac workup to a clinic unaffiliated with the study. ECG done at a follow-up site visit on Study Day 83 demonstrated an **ectopic supraventricular rhythm**. Per Case Report Form, due to persistent ECG abnormalities, the Applicant and the Investigator at the site interrupted the study medication on Study Day 110; tasimelteon was permanently discontinued on Study Day 134. The Applicant states that this subject has been lost to follow-up after initiating a cardiac workup external to the site; medical records of this evaluation have not been made available to the site, and the event remains ongoing. The Applicant concludes that given the subject's history of low hematology laboratory measurements, a lack of clarity regarding a diagnosis of anemia prior to study enrollment, and the fact that the subject was lost to follow-up, it is unclear whether the subject's new finding of ectopic rhythm was related to study drug, (b) (6) history of low hematology measurements, or chance alone. Reviewer's comments: The above events were temporally associated with tasimelteon administration. A causal relationship between the event and tasimelteon cannot be excluded.

Subject #VP-VEC-162-COSET (b) (6) (palpitations): Subject was (b) (6) with a medical history of bilateral blindness secondary to retinoblastoma, and initial and middle insomnia. Subject was enrolled in Study 3202 and began open-label tasimelteon 20 mg treatment. Subject reported **palpitations** that woke him in the night on Study Day 45, and again on two additional nights intermittently the following week. Tasimelteon was permanently discontinued

on Study Day 52. The event was reported as resolved the next day, i.e., Study Day 53. ECG performed at Screening, and at Study Days 28, 56 and 105 (End of Study Visit) showed no abnormalities. The Investigator reported that the subject was not compliant with tasimelteon administration. This event was originally reported by the investigative site as *nocturnal tachycardia* but since the heart rate was not assessed at the time of this subjective experience, the Applicant states that the term ‘palpitations’ was a more accurate description of the event. The Applicant concluded that this event was unassessable in relationship to Study Drug and protocol. Reviewer’s comments: Palpitations were temporally associated with tasimelteon and there was a positive dechallenge. A causal relationship between the event and tasimelteon cannot be excluded.

Subject #CN116-002 (b)(6) Subject experienced **T wave changes** while on placebo treatment.

The following table summarizes subjects with ECG abnormalities or cardiac-related treatment-emergent adverse events in Pooled Study Groups 2, 3 and 4. In Pooled Study Group 2, there was an excess of subjects experiencing any event in the tasimelteon group (13/429; 3.0%) compared to the placebo group (0/203; 0%); within the tasimelteon pooled subjects, the proportion of subjects with any event in the < 20 mg, 20 mg and 50 mg groups were 4.4% (5/114), 2.0% (3/151) and 3.0% (5/164), respectively. Events reported by ≥ 2 subjects include ‘electrocardiogram ST-T change’, ‘atrial fibrillation’ and ‘conduction disorder’. Out of the 13 subjects who reported any event in Pooled Study Group 2, 8 (8/13; 62%) subjects were from Study 004 which randomized 227 elderly subjects (≥ 65 years) with insomnia (1:1:1:1) to tasimelteon 1, 10 or 50 mg, and placebo. These 8 elderly subjects – all in tasimelteon dose groups, reported a total of 9 events: atrial fibrillation, myocardial infarction, sinus bradycardia, ventricular arrhythmia, ST segment elevation, ventricular extrasystoles, ST-T change.

Table 53: Summary of subjects with ECG abnormalities or cardiac-related treatment-emergent adverse events in Pooled Study Groups 2, 3 and 4

Preferred terms	Pooled Study Group 2		Pooled Study Group 3		Pooled Study Group 4
	Tasimelteon N=429 n (%)	Placebo N=203 n (%)	Tasimelteon N=52 n (%)	Placebo N=52 n (%)	Tasimelteon N=183 n (%)
Any event	13 (3.0)	0	4 (7.7)	0	5 (2.7)
Electrocardiogram ST-T change~	3 (0.7)	0	0	0	0
Atrial fibrillation	2 (0.4)	0	0	0	0
Conduction disorder	2* (0.4)	0	3* (5.8)	0	3* (1.5)
Electrocardiogram ST segment elevation~	1 (0.2)	0	0	0	0
Electrocardiogram T wave inversion	1 (0.2)	0	0	0	0
Myocardial infarction	1 (0.2)	0	0	0	0
Palpitations	1^ (0.2)	0	1^ (1.9)	0	1^ (0.5)
Sinus bradycardia	1 (0.2)	0	0	0	0
Supraventricular	1 (0.2)	0	0	0	1 (0.5)

Preferred terms	Pooled Study Group 2		Pooled Study Group 3		Pooled Study Group 4
	Tasimelteon N=429 n (%)	Placebo N=203 n (%)	Tasimelteon N=52 n (%)	Placebo N=52 n (%)	Tasimelteon N=183 n (%)
extrasystoles					
Ventricular arrhythmia	1 (0.2)	0	0	0	0
Ventricular extrasystoles	1 (0.2)	0	0	0	0
Bundle branch block right	0	0	0	0	1 (0.5)
Coronary artery disease	0	0	0	0	1 (0.5)

Note: Two subjects (CN116-004- (b) (6) and VP-VEC-162-COSET- (b) (6)) in Pooled Study Group 2 experienced two events each. One subject (VP-VEC-162-COSET- (b) (6)) in Pooled Study Group 4 experienced 'conduction disorder', 'bundle branch block right', and coronary artery disease'.

Four elderly subjects (CN116-004- (b) (6), CN116-004- (b) (6), CN116-004- (b) (6) and CN116- (b) (6)) – all in Study 004, reported related terms Electrocardiogram ST-T change and Electrocardiogram ST segment elevation. VP-VEC-162-COSET- (b) (6) and VP-VEC-162-COSET- (b) (6) were counted in both Pooled Study Groups 2, 3 and 4. One additional subject (VP-VEC-162-COSET- (b) (6)) experienced conduction disorder while participating in the Run-in phase of Study 3203.

VP-VEC-162-COSET- (b) (6) was counted in Pooled Study Groups 2, 3 and 4.

Source: NDA 205677, 5/31/13: Module 5.3.5.3 Data Analysis Data - Reviewer's analysis of ADAE and ADSL datasets.

Four subjects (CN116-004- (b) (6), CN116-004- (b) (6), CN116-004- (b) (6) and CN116-004- (b) (6)) – all *elderly* subjects enrolled in Study 004 and randomized to tasimelteon, reported treatment-emergent adverse events that appear related, Electrocardiogram ST-T change and Electrocardiogram ST segment elevation. The narrative for CN116-004- (b) (6) is briefly discussed above. Three (3/114; 2.6%) of these 4 subjects were in tasimelteon < 20 mg group (1 mg and 10 mg) and the remaining subject (1/164; 0.6%) in the 50 mg group; none were in the 20 mg group (0/151).

Three subjects (VP-VEC-162-COSET- (b) (6), VP-VEC-162-COSET- (b) (6) and VP-VEC-162-COSET- (b) (6)) reported conduction disorder (verbatim: intraventricular conduction defect). All 3 subjects (b) (6) were diagnosed with Non-24 Hour Disorder, and were taking tasimelteon 20 mg dose; and the onset of events for each subject was on Study Days 64, 188 and 274. The narrative for subject VP-VEC-162-COSET- (b) (6) – who was withdrawn early from trial, is provided above in this section of review.

Two subjects (VP-VEC-162-3104- (b) (6) and CN116- (b) (6)) experienced atrial fibrillation. Subject VP-VEC-162-3104- (b) (6) was (b) (6) with insomnia enrolled in Study 3104 (tasimelteon 50 mg) who observed to have an asymptomatic episode of atrial fibrillation identified on ECG. ECGs at baseline and screening were normal. The finding resolved spontaneously. An ECG performed one week later was normal. Subject CN116-004- (b) (6) was (b) (6) with insomnia enrolled in Study 004 (tasimelteon 50 mg) who was reported to have atrial fibrillations at Study Day 30.

Effect on QT interval:

There were no consistent trends over time in the corrected QT interval values (QTcB or QTcF) between treatment groups in the placebo-controlled pooled groups of healthy volunteers and subjects with insomnia/Non-24 Hour Disorder.

QTc increase ≥ 30 ms from baseline or absolute QTc > 450 ms:

As noted above, in Pooled Study Group 5 (healthy volunteers/pharmacology studies), the incidences of subjects experiencing a PCS abnormality in ≥ 30 ms increase from baseline in both QTcB and QTcF were higher in the tasimelteon > 50 mg dose group compared to placebo subjects. However, these higher incidences were driven by Study 1103 (thorough QT study) which was included in this pool. Excluding the 19 subjects who were from Study 1103 ((given the cross-over study design, subjects meeting these criteria were conservatively assigned to the tasimelteon 300 mg group), the incidences between tasimelteon > 50 mg dose group (7/187; 3.7%) and placebo group (5/131; 4.1%) were comparable in Pooled Study Group 2.

In the Pooled Study Group 2 (placebo-controlled studies in insomnia and Non-24 Hour Disorder), the incidences of subjects with ≥ 30 ms increase from baseline in QTc (QTcB or QTcF) were fairly similar between tasimelteon dose groups and placebo group.

As can be seen from the tables above, the proportion of subjects with ≥ 30 ms increases from baseline in QT interval using Bazett's formula were higher compared to when using Fridericia's formula, although the proportions were comparable between tasimelteon and placebo groups for either formulae. The ICH E14 document, *The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* notes the following: "In general, however, Bazett's correction overcorrects at elevated heart rates and under corrects at heart rates below 60 beats per min and hence is not an ideal correction. Fridericia's correction is more accurate than Bazett's correction in subjects with such altered heart rates."

I reviewed the QTc values over time for individual subjects in the safety database with ≥ 30 ms increase from baseline or with absolute QTc values > 450 ms. In the vast majority of subjects, these abnormalities were isolated findings occurring only once on-treatment or were also abnormal at baseline. A few subjects had these abnormalities more than once but interspersed with normal values and without a clear sustained trend toward abnormality.

QTc increase ≥ 60 ms from baseline or absolute QTc > 500 ms:

Across the entire safety database, there was 1 tasimelteon subject (CN116-001-(b) (6)) with a QTcB increase from baseline of > 60 ms (see below). There were no subjects with a QTcF increase from baseline of > 60 ms.

Subject #CN116-001-(b) (6) This subject experienced a QTcB increase of > 60 ms (371 ms to 433 ms) at one single time point. ECG parameters (including QTc) were normal at all other time points and the subject was asymptomatic.

In the entire safety database, there were 3 subjects with QTc ≥ 500 ms. All subjects were on tasimelteon at the time of the event.

Subject #VP-VEC-162-COSET- (b) (6) This subject had a baseline QTcB of 498 ms, which rose to QTcB 501 ms (QTcF 499 ms) at a single measurement (on Study Day 85) during the course of the clinical study. QTc was ranged from 464 – 488 ms at all other time points up to the last available time, Study Day 164.

Subject #VP-VEC-162-COSET (b) (6) This subject with Non-24 Hour Disorder and history of implanted cardiac pacemaker and left bundle branch block was enrolled sequentially in Studies 3201, 3203 and 3204. He had a baseline QTcB and QTcF values of 513 ms and 499 ms, respectively, at Screening (Study Day -12). There was a QTcB measurement of QTcB 529 ms (QTcF 526 ms) on Study Day 30, which was based upon an incomplete ECG (only one lead recording throughout). Another QTcB elevation > 500 ms occurred on Study Day 405 (QTcB 506 ms). QTc was normal at all other time points including at the last available time point, Study Day 560 when the QTcB was 470 ms. This subject also had a history of left bundle branch block which confounds QTc interpretation.

Subject #VP-VEC-162- (b) (6): This subject was enrolled in Study 1106 (renal impairment). QTcB value was 524 ms at baseline, and remained above 500 ms on-treatment.

PR interval:

There were no consistent trends over time in PR interval values between treatment groups in the placebo-controlled pooled groups of healthy volunteers and subjects with insomnia/Non-24 Hour Disorder.

As noted above, in Pooled Study Group 2, the incidences of subjects with a PCS abnormality in ≥ 210 ms PR interval were higher in the tasimelteon dose groups compared to placebo subjects (highlighted in Table 52); although the absolute numbers were small, there appears to be dose-relatedness. All subjects who met this criterion were from the insomnia studies (Study 004 and Study 3104); none were subjects with Non-24 Hour Disorder. There were no differences in the incidence of subjects with ≥ 210 PR interval between treatment groups in Pooled Study Group 5 (healthy volunteers/pharmacology studies).

I reviewed the PR intervals over time for each individual subject with > 210 ms in the Pooled Study Group 2 (n = 14). Four subjects had PR interval > 210 ms at screening and at least at one time point during on-treatment (ranging from 211 – 215 ms); 2 of these subjects were in the 20 mg dose group and the other 2 in the 50 mg dose group. Nine subjects had normal PR interval at baseline and > 210 ms at one other time point on-treatment (ranging from 211 – 217 ms). One subject (CN116-004 (b) (6) – (b) (6) with insomnia in the tasimelteon 50 mg dose group, had a baseline PR interval value of 195 ms which increased by 71 ms (266 ms) at Week 4 (the only time point assessed on-treatment); this subject did not report any treatment-emergent adverse event.

Of the above 14 subjects, only 3 subjects (including the lone placebo subject) reported at least one treatment-emergent adverse event; none of these adverse events were related to cardiac SOC

or ECG or vital sign (heart rate). The remaining 11 subjects (including Subject #CN116-004-
(b) (6)) did not experience any treatment-emergent adverse event.

Applicant's conclusion regarding electrocardiogram assessments: There is no evidence of clinically meaningful ECG changes associated with tasimelteon use, a finding consistent with that found in the early phase thorough QT study, and the relative lack of reported adverse events during the clinical studies.

Reviewer's conclusion regarding electrocardiogram assessments: Although, there was an excess of adverse changes in ECG or cardiac-related adverse events in the tasimelteon group compared to placebo subjects in Pooled Study Group 2, there was no clear discernable safety signal. Overall, based on available data which appears adequate, the potential for an adverse effect of tasimelteon on cardiac repolarization is low.

7.4.5 Special Safety Studies/Clinical Trials

There are no special safety studies conducted that have not otherwise been discussed in other sections in this review.

7.4.6 Immunogenicity

Tasimelteon is not a therapeutic protein. A search of the adverse event dataset for hypersensitivity yielded the following terms.

- Subject VP-VEC-162-COSET-(b) (6) reported verbatim term 'allergic reaction to antibiotic' that was coded as 'drug hypersensitivity'.
- Subject VP-VEC-162-COSET-(b) (6) reported verbatim term 'allergic reaction to trimethoprim/sulfamethoxazole' coded as 'drug hypersensitivity'.
- Subject VP-VEC-162-1110-(b) (6) reported 'hives (full body)' which was coded as 'urticaria' during exposure to midazolam in Study 1110 (drug interaction study with CYP3A4 and CYP2C8 enzymes).
- Subjects CN116-004-00014-(b) (6) and CN116-004-(b) (6) reported verbatim terms 'environmental allergies' and 'allergies', respectively, that were coded as 'hypersensitivity'.

Please see Section 7.4.1 'Common Adverse Events' of this review for a discussion of 'rash' and related events.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In Phase I studies, single doses were administered to healthy volunteers up to 300 mg (Study CN116-001), and multiple doses (1, 10, 50, 150 mg and placebo) were administered for 28 days in healthy volunteers (Study CN116-002). As can be seen, there was no clear dose dependency for common treatment-emergent adverse events (see Table below) in Pooled Study Group 5 (pharmacokinetic studies).

Table 54: Summary of common treatment-emergent adverse events (reported by ≥ 5 subjects in the tasimelteon >50 mg group) in the Pooled Study Group 5.

Preferred term	Tasimelteon								Placebo N=131	
	Tasimelteon ≤ 20 mg N=385		Tasimelteon 30-50 mg N=161		Tasimelteon > 50 mg N=230		Tasimelteon Overall N=776			
	n	%	n	%	n	%	n	%	n	%
Any event	124	32.21	57	35.4	69	30.0	250	32.22	30	22.9
Somnolence	46	11.9	12	7.45	28	12.2	86	11.1	7	5.34
Headache	27	7.01	6	3.73	11	4.78	44	5.67	7	5.34
Nausea	13	3.38	4	2.48	8	3.48	25	3.22	6	4.58
Dizziness	18	4.68	3	1.86	7	3.04	28	3.61	0	0
Fatigue	7	1.82	0	0	6	2.61	13	1.68	2	1.53
Diarrhoea	2	0.52	2	1.24	5	2.17	9	1.16	1	0.76
Dyspepsia	0	0	1	0.62	5	2.17	6	0.77	0	0
Constipation	6	1.56	0	0	5	2.17	11	1.42	2	1.53

Source: NDA 205677, 5/31/13: Module 5.3.5.3 Data Analysis Data - Reviewer's analysis of ADAE and ADSL datasets.

As noted above, in Study CN116-002 multiple doses (1, 10, 50, 150 mg and placebo) were administered for 28 days in healthy volunteers. There was no apparent relationship between the incidence of treatment-emergent adverse events and tasimelteon dose (see Table below).

Table 55: All treatment-emergent adverse events by dose group in healthy volunteers (Study CN116-002)

Primary Term	Number (Percent) of Subjects				
	1mg N = 6	10mg N = 6	50mg N = 6	150mg N = 6	Placebo N = 8
Accidental Injury	0	1(16.7)	1(16.7)	0	1(12.5)
Asthenia	0	0	0	0	1(12.5)
Headache	1(16.7)	0	1(16.7)	1(16.7)	2(25.0)
Pain Abdomen	0	0	0	1(16.7)	2(25.0)
Abnormal ECG	0	0	0	0	1(12.5)
Constipation	2(33.3)	0	0	0	1(12.5)
Diarrhea	0	0	0	2(33.3)	1(12.5)
Eructation	0	0	0	1(16.7)	0
Flatulence	0	0	0	0	1(12.5)
Nausea	1(16.7)	0	0	0	1(12.5)
Stomatitis Aphthous	0	0	0	0	1(12.5)
Vomiting	0	0	0	0	1(12.5)
Myalgia	0	0	0	1(16.7)	1(12.5)
Abnormal Dream	1(16.7)	0	0	0	2(25.0)
Agitation	0	0	0	0	1(12.5)
Insomnia	1(16.7)	0	2(33.3)	0	2(25.0)
Somnolence	0	0	1(16.7)	0	0
URI	0	0	2(33.3)	0	0
Pruritus	0	0	0	0	1(12.5)
Rash	0	0	0	2(33.3)	0
Conjunctivitis	0	0	0	1 (16.7)	0

Source: NDA 205677, 5/31/13: Module 5.3.3.1 Healthy Subject PK studies; CN116-002 Study Report, Table 12.1.2, page 87.

In the placebo-controlled clinical studies of insomnia in the elderly subjects (Study CN116-004) and non-elderly subjects (Study 3104), multiple doses – 1, 10 and 50 mg in Study CN116-004 and 20 and 50 mg in Study 3204, were administered for 35 days (including single blind administration for 7 days in the elderly subjects). Only the 20 mg dose was used in clinical studies of subjects with Non-24 Hour Disorder. As can be seen in the Table below, the incidence of subjects experiencing ‘blood creatine phosphokinase’, ‘dysgeusia’, and ‘neutropenia’ appear somewhat dose related but the number of subjects experiencing these events is small limiting meaningful inference.

Table 56: Summary of common treatment-emergent adverse events (reported by ≥ 2 subjects in the tasimelteon 50 mg group) in the Pooled Study Group 2.

Preferred Term	Tasimelteon								Placebo (N=203)	
	1 mg (N=56)		10 mg (N=58)		20 mg (N=151)		50 mg (N=164)		n	(%)
	n	(%)	n	(%)	n	(%)	n	(%)		
Headache	5	8.93	5	8.62	18	11.92	13	7.93	15	7.39
Nasopharyngitis	6	10.71	8	13.79	6	3.97	8	4.88	13	6.4
Blood creatine phosphokinase increased	0	0	0	0	1	0.66	5	3.05	4	1.97
Somnolence	3	5.36	3	5.17	3	1.99	4	2.44	3	1.48
Dry mouth	2	3.57	2	3.45	2	1.32	4	2.44	1	0.49

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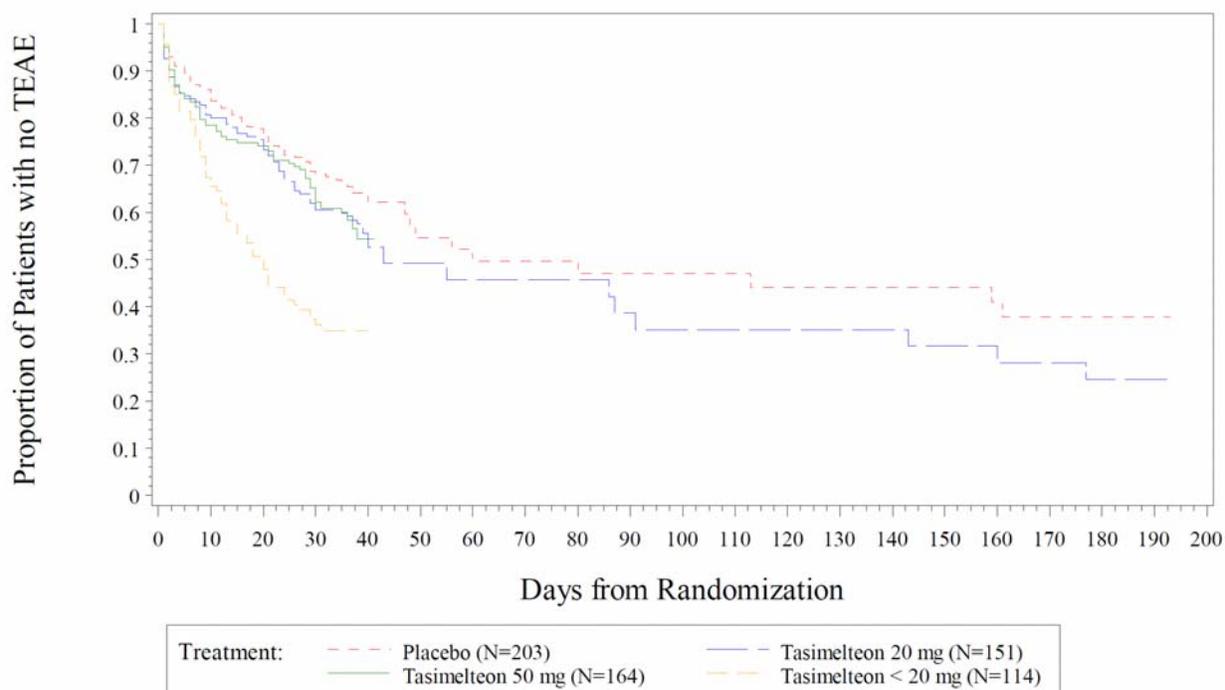
Dysgeusia	0	0	0	0	1	0.66	4	2.44	1	0.49
Dyspepsia	2	3.57	1	1.72	0	0	4	2.44	4	1.97
Alanine aminotransferase increased	0	0	0	0	4	2.65	3	1.83	2	0.99
Rhinorrhoea	0	0	0	0	2	1.32	3	1.83	1	0.49
Constipation	3	5.36	0	0	1	0.66	3	1.83	2	0.99
Neutropenia	0	0	0	0	1	0.66	3	1.83	1	0.49
Urinary tract infection	0	0	1	1.72	7	4.64	2	1.22	5	2.46
Upper respiratory tract infection	1	1.79	2	3.45	6	3.97	2	1.22	3	1.48
Diarrhoea	2	3.57	2	3.45	4	2.65	2	1.22	2	0.99
Nightmare	0	0	0	0	4	2.65	2	1.22	0	0
Nausea	0	0	3	5.17	3	1.99	2	1.22	6	2.96
Pain in extremity	1	1.79	1	1.72	3	1.99	2	1.22	0	0
Cough	2	3.57	1	1.72	2	1.32	2	1.22	4	1.97
Fatigue	1	1.79	0	0	2	1.32	2	1.22	2	0.99
Back pain	4	7.14	2	3.45	1	0.66	2	1.22	4	1.97
Insomnia	0	0	0	0	1	0.66	2	1.22	0	0
Nasal congestion	2	3.57	0	0	1	0.66	2	1.22	1	0.49
Hypersensitivity	0	0	1	1.72	0	0	2	1.22	0	0
Atrial fibrillation	0	0	0	0	0	0	2	1.22	0	0

Source: NDA 205677, 5/31/13: Module 5.3.5.3 Data Analysis Data - Reviewer's analysis of ADAE and ADSL

7.5.2 Time Dependency for Adverse Events

The Kaplan-Meier analysis of time to any treatment-emergent adverse event in Pooled Study Group 2 is summarized in the following Figure. The majority of treatment-emergent adverse events tend to occur within the first 40 days of exposure to study drug.

Figure 12: Kaplan-Meier analysis of time to any treatment-emergent adverse event in Pooled Study Group 2.



Note: Studies 004 and 3104 included in Pooled Study Group 2 (and in which tasimelton doses other than 20 mg were used) were of short duration (28 & 35 days, respectively).

Source: NDA 205677, 5/31/13: Module 5.35.3 ISS – Integrated Summary of Figures; Figure 2.0.1.

7.5.3 Drug-Demographic Interactions

Very few differences in the incidence of common treatment-emergent adverse events were evident based on demographic characteristics; these are discussed in Section 7.4.1 ‘Common Adverse Events’ of this review. In a few of the demographic categories (for example, age > 65 years in 20 mg dose, black race, etc) the subject numbers were too small for meaningful inference.

7.5.4 Drug-Disease Interactions

Study 1105 in subjects with mild or moderate hepatic impairment showed that exposure (AUC) to tasimelton after a single 20 mg dose was increased by 43% and 90%, respectively; increase in C_{max} was about 20% in both mild and moderate hepatic impairment. Tasimelton has not been studied in patients with severe hepatic impairment.

In Study 1106, exposure to tasimelton in subjects with severe renal impairment or end stage renal disease had inconsistent results after a single dose of 20 mg. Compared to matched controls, severe renal impairment subjects had, on average, a lower CL/F with a geometric mean ratio of 71%. In contrast, end stage renal disease subjects, had a comparable arithmetic mean

CL/F with a geometric mean ratio of 98%, and comparable mean plasma concentrations and arithmetic mean values for C_{max} and AUC. The Applicant states that this inconsistency may be a consequence of the variability intrinsic with small numbers of subjects per group rather than a true difference.

The Applicant concludes that considering the highly favorable safety and tolerability profile of tasimelteon (i.e. doses up to at least 300 mg are well tolerated, and nonclinical data showed that chronic dosing of tasimelteon did not result in any relevant toxicological findings at the expected therapeutic dose), no dose adjustment is deemed necessary for these special populations.

Reviewer's comments: The clinical pharmacology review team recommends tasimelteon dose reduction with moderate hepatic insufficiency.

7.5.5 Drug-Drug Interactions

CYP1A2 and CYP3A4 are the major isozymes involved in the metabolism of tasimelteon.

In Study 1111, inhibition of CYP1A2 by treatment with fluvoxamine resulted in an 85% decrease in tasimelteon clearance leading to a 6.5-fold increase in exposure. The Applicant concludes that the observed exposure effects are not considered clinically relevant; however, caution should be used when tasimelteon is given together with strong CYP1A2 inhibitors such as fluvoxamine.

Studies 1107 and 1112 show that the exposures to tasimelteon and its main metabolites are affected by the induction of CYP1A2 (e.g. cigarette smoking) and/ or CYP3A4 and other CYPs (e.g. rifampin). Cigarette smoking, and thus induction of CYP1A2, decreased exposure (AUC) by approximately 40%. Rifampin, a strong CYP3A4 and moderate CYP2C19/2C9 inducer, reduced the exposure to tasimelteon by approximately 90%. The Applicant concludes that a dose increase should be considered in patients who are concomitantly treated with drugs that are strong inducers of CYP3A4 or in patients that smoke.

Reviewer's comments: The clinical pharmacology review team recommends contraindicating concomitant administration of moderate and strong CYP1A2 inhibitors, and moderate and strong CYP3A4 inducers.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Across the clinical studies, there was one subject (VP-VEC-162-COSET [REDACTED]^{(b) (6)}) who was diagnosed with acute lymphoblastic leukemia (narrative is located in Section 7.3.4 'Significant

Adverse Events' of this review. One other subject (VP-VEC-162-COSET-^{(b) (6)} reported basal cell carcinoma in the forehead. There were no other reports of malignancy.

7.6.2 Human Reproduction and Pregnancy Data

Safety and effectiveness of tasimelteon has not been established in pregnant or lactating women.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of tasimelteon in pediatric and adolescent subjects below the age of 18 years has not been established. On 1/19/10, the Agency granted orphan-drug designation of tasimelteon for Non-24 Hour Disorder in blind individuals without light perception. Therefore, pursuant to the Pediatric Research Equity Act, a submission of a pediatric assessment is not required for an application to market a product for an orphan-designated indication.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Two nonclinical studies were conducted with tasimelteon to evaluate the potential abuse liability with oral or intra venous administration. The Applicant concludes that these drug-discrimination and self administration studies indicate there is no evidence that tasimelteon has abuse potential. During the meeting between the Applicant and the Agency (10/28/11), the Agency agreed that a human abuse potential study would not be needed if the above nonclinical studies did not demonstrate a signal.

The Tyrer Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) was administered in Studies 3104, 3201, and 3203. This self-reported questionnaire was developed to assess the symptoms experienced during withdrawal from benzodiazepines. Since a questionnaire specific to drugs used to treat disorders of circadian rhythm has not been developed, the Applicant considered the BWSQ as the most appropriate tool for assessment of withdrawal. The questionnaire consists of 20 symptoms and each symptom is rated from 0 to 2. Thus, the score ranges from 0 to 40; high scores indicating presence of symptoms.

In Study 3104 (non-elderly adult subjects with insomnia), BWSQ was used to evaluate the effects of abrupt discontinuation of tasimelteon 20 and 50 mg relative to placebo after 5 weeks of treatment. The statistics for Study Days 30 (during double-blind evaluation period, i.e., baseline) and 37 (during placebo washout period) in BWSQ score are summarized in the table below. During the placebo washout period (Study Day 37), subjects in all three treatment arms reported fewer BWSQ symptoms compared to baseline (Study Day 30). The Applicant concluded that abrupt discontinuation of tasimelteon (20 mg and 50 mg) does not appear to cause the types of

withdrawal symptoms experienced with benzodiazepines in pharmacologically dependent subjects.

Table 57: Summary of withdrawal effects as evaluated by BWSQ in Study 3104

Parameter	VEC-162 20 mg N=108	VEC-162 50 mg N=109	Placebo N=104
Day 30 (Baseline)			
n	99	97	94
Mean	1.6	1.2	1.0
SD	3.4	2.1	2.0
Median	0.0	0.0	0.0
Minimum	0	0	0
Maximum	18	8	10
Day 37			
n	100	96	95
Mean	0.9	0.8	0.5
SD	2.6	1.5	1.3
Median	0.0	0.0	0.0
Minimum	0	0	0
Maximum	15	7	6

SD = Standard deviation.

Source: NDA 205677, 5/31/13: Module 5.3.3.1 - 3104 Study Report; Table 33, page 143.

In Study 3201, BWSQ was administered during the 2-week placebo wash-out period following 6 months of treatment in some subjects who were enrolled under earlier versions of the US protocol, i.e., earlier than US Version 6 (8/8/11) and German-specific protocol. The questionnaire was administered to 11 subjects in 3201. The Applicant concludes that no differences were observed between treatment groups in Study 3201, with the BWSQ scores ranging from 0 to 1 for the placebo group and 0 to 2 for the tasimelteon group in 3201; with a maximum possible score of 40, these low scores indicate that there were no withdrawal symptoms present in either treatment group.

In Study 3203, the BWSQ was administered after at least 3 months of open-label tasimelteon treatment during the randomized withdrawal phase. The questionnaire was administered to 20 subjects in 3203. No differences were observed between the means and medians in the treatment groups (see table below).

Table 58: Summary of withdrawal effects as evaluated by BWSQ in Study 3203

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Visit Statistic	Placebo (N=10)			VEC-162 20 mg (N=10)		
	Day 0	Visit	Change	Day 0	Visit	Change
Day 0						
N'		10			10	
Mean		0.1			0.4	
SD		0.32			0.97	
Minimum		0			0	
Median		0.0			0.0	
Maximum		1			3	
Day 1						
N'	9	9	9	10	10	10
Mean	0.1	0.0	-0.1	0.4	0.3	-0.1
SD	0.33	0.00	0.33	0.97	0.67	0.32
Minimum	0	0	-1	0	0	-1
Median	0.0	0.0	0.0	0.0	0.0	0.0
Maximum	1	0	0	3	2	0
Day 2						
N'	10	10	10	10	10	10
Mean	0.1	0.0	-0.1	0.4	1.1	0.7
SD	0.32	0.00	0.32	0.97	2.81	2.67
Minimum	0	0	-1	0	0	-2
Median	0.0	0.0	0.0	0.0	0.0	0.0
Maximum	1	0	0	3	9	8
Day 7						
N'	10	10	10	10	10	10
Mean	0.1	0.0	-0.1	0.4	0.1	-0.3
SD	0.32	0.00	0.32	0.97	0.32	0.67
Minimum	0	0	-1	0	0	-2
Median	0.0	0.0	0.0	0.0	0.0	0.0
Maximum	1	0	0	3	1	0
Day 14						
N'	10	10	10	10	10	10
Mean	0.1	0.1	0.0	0.4	0.0	-0.4
SD	0.32	0.32	0.47	0.97	0.00	0.97
Minimum	0	0	-1	0	0	-3
Median	0.0	0.0	0.0	0.0	0.0	0.0
Maximum	1	1	1	3	0	0

SD = Standard deviation.

Source: NDA 205677, 5/31/13: Module 5.3.3.1 - 3203 Study Report; adapted from Table 14.3.5.1.

Reviewer's conclusion: There are no adverse effects due to abrupt withdrawal of tasimelteon as assessed by the Tyrer BWSQ.

7.7.5 Suicidality Assessments

Prospective assessment of suicidality using the Columbia Suicide Severity Rating Scale (C-SSRS) was made in Studies 3201, 3202, 3203, 3204 and phase I studies that were initiated after the Agency's request to do so (1106, 1108, 1111, and 1112). The C-SSRS was a semi-structured clinical interview designed to systematically assess and track suicidal adverse events (behavior and ideation, and completed suicides). For Studies 3201 and 3203, the C-SSRS was assessed through a phone system. If the result was positive, then a paper version of C-SSRS was administered in the site. In this case, only the data from the paper version was used into the analysis. For Phase I studies (1106, 1108, 1111, and 1112 only), the paper version was administered.

In Pooled Study Group 5 (healthy volunteer and clinical pharmacology studies) all subjects, regardless of treatment, reported 'no' to all baseline and post-baseline C-SSRS questions.

In Pooled Study Group 3 (Non-24 studies, placebo-controlled phases only), 4 subjects (3 in the placebo group and 1 in the tasimelteon group) had any suicidal ideation during the clinical studies, and none had suicidal behavior during the study (see table below). The Applicant notes that in Pooled Study Group 4 (tasimelteon only group in Non-24 Hour Disorder), 3 subjects demonstrated treatment-emergent suicidal ideation, but these reports were considered low-risk in nature (per the score system) and there was no emergence of any serious suicidal ideation or behavior in long-term safety follow-up of tasimelteon-treated subjects. The Applicant concludes that the results of the C-SSRS suggest that there is no evidence of risk due to suicidal ideations or behavior associated with tasimelteon 20 mg.

Table 59: Summary of suicide related adverse events during the randomized phase of Study 3201

Parameter	Placebo (N=42) n/N' (%)	Tasimelteon (N=42) n/N' (%)
Suicidal ideation (score of 1-5)	3/39 (7.7)	1/40 (2.5)
1. Wish to be dead	2/39 (5.1)	1/40 (2.5)
2. Non-specific active suicidal thoughts	2/39 (5.1)	1/40 (2.5)
3. Active suicidal ideation with any methods (no plan) without intent to act	0	0
4. Active suicidal ideation with some intent to act, without specific plan	0	0
5. Active suicidal ideation with specific plan and intent	0	0
Suicidal behavior (score of 6-10)	0	0
6. Preparatory acts or behavior	0	0
7. Aborted suicide attempt	0	0
8. Interrupted suicide attempt	0	0
9. Non-fatal suicide attempt	0	0
10. Completed suicide	0	0
Suicidal ideation or behavior (score of 1-10)	3/39 (7.7)	1/40 (2.5)

N' = number of patients who had event assessed during the randomization phase through 3 days after the last dose of study drug; n = number of patients with event.

Source: NDA 205677, 5/31/13: Module 5.3.3.1 - 3201 Study Report; Table 33, page 116.

Reviewer's conclusion: Based on data which appear adequate, tasimelteon is not associated with an adverse effect on suicidality as assessed by the C-SSRS.

7.7 Additional Submissions

There were amendments to the original NDA, many in response to requests from reviewers for additional information or additional analyses. These were reviewed and discussed in the relevant sections of this review.

120-day Safety Update: On 9/30/13, the Applicant submitted the 120-day Safety Update which covered safety information for subjects in the two ongoing, long-term open-label studies (Study 3202 and Study 3204) from the period 12/1/12 to 7/10/13. The studies are ongoing and the databases are not locked.

Subject Disposition:

- **Study 3202:** During the above noted interval, 1 additional subject enrolled in this study, 4 subjects discontinued from the study (adverse event, n=1; lost to follow-up, n=2; unsatisfactory therapeutic effect, n=1), and 28 subjects are actively participating in the study.
- **Study 3204:** During the above noted period, 5 subjects enrolled in this study (none were treatment-naïve at the time of enrollment), 6 subjects discontinued from the study (adverse event, n=1; lost to follow up, n=1; sponsor request, n=1; withdrew consent, n=2; other, n=1), and 79 subjects are actively participating in the study.

Extent of Exposure:

The following table summarizes the exposures in subjects with Non-24 Hour Disorder as of the cut-off date of 7/10/13. As noted above, one treatment-naïve subject initiated dosing in the interval period. As of 7/10/13, 93 subjects with Non-24 Hour Disorder were treated for at least one year.

Table 60: Exposures in Non-24 Hour Disorder through interim safety reporting period

Exposure Interval	As of 30 Nov 2012	As of 10 July 2013	Additional Exposures
>= 1 day	183	184	1
>12 weeks (84 days)	149	163	14
>26 weeks (182 days)	111	139	28
>52 weeks (364 days)	44	93	49

Source: NDA 205677, 5/31/13: Amendment dated 9/30/13: 120-day Safety Update; Table 3, page 5.

Deaths: There were no deaths reported during the reporting period.

Non-fatal serious adverse events: A total of 5 subjects reported non-fatal serious adverse events during the reporting period. The narratives for these subjects are provided below.

VP-VEC-162-COSET- (b) (6) Subject is (b) (6) with a past medical history of HIV positive status (2007), GERD, hyperlipidemia, hypertension, pre-diabetes, blindness (due to gunshot wound) who enrolled into Study 3204. On Study Day 98 of tasimelteon therapy, subject experienced symptoms of chest wall burning, productive cough and malaise. Three days later (Study Day 101), subject was on a bus for eight hours and upon exiting the bus, (b) (6) felt faint, and (b) (6) was admitted to the hospital. On Study Day 103 (b) (6) was diagnosed with

elevated blood glucose and **community-acquired pneumonia** both of which were reported resolved on Study Days 105 and 107, respectively. Per sponsor discretion, the subject discontinued study medication on Study Day 138 and completed early termination procedures. The Investigator and Applicant conclude that the events were unrelated to study drug. Reviewer's comments: I agree with the Applicant's conclusion.

VP-VEC-162-COSET- (b) (6) The subject is (b) (6), with a past medical history of type II diabetes and GERD enrolled in Study 3204. On Day 205 of tasimelteon therapy, (b) (6) experienced **difficulty breathing** during renovations to (b) (6) apartment complex and was subsequently hospitalized the same day, at which time study drug was interrupted. (b) (6) recovered and was discharged on Study Day 212. Study drug re-start date has not yet been specified. The investigator assessed the event to be not related to the protocol and unrelated to study drug. Reviewer's comments: Clinical findings during hospitalization, laboratory/radiology testing, concomitant medications, and discharge diagnosis are not provided. Occurrence of the event during renovations to the apartment is confounding.

VP-VEC-162-COSET- (b) (6) The subject is (b) (6) with a past medical history of retinopathy of prematurity, GERD, osteoporosis, and dyslipidemia. On Study Day 406 of tasimelteon therapy, subject noted dyspnea on exertion and palpitations with one flight of stairs, with worsening and dry cough. On Study Day 414, the subject experienced breathing difficulty, and was evaluated by (b) (6) primary physician who ordered various unspecified blood and urine testing. On Study Day 420 a lung biopsy was performed, and the subject was subsequently diagnosed with **scleroderma** on Study Day 422 by a rheumatologist. Treatment medications included prednisone, mycophenolate twice daily and oxygen. The investigator considered the scleroderma as a medically significant event, and subject continues to take study drug uninterrupted. Reviewer's comments: Scleroderma provides an alternate explanation.

VP-VEC-162-COSET- (b) (6) The subject is (b) (6) with a relevant medical history for meningioma since 1990, bilateral retinoblastoma in 1984 (status post bilateral enucleation in 1984), asthma, and GERD. On Study Day 175 of tasimelteon therapy, subject underwent **surgery for the meningioma**. Study drug was re-started on Study Day 252. The investigator assessed the event to be not related to study drug. Reviewer's comments: I agree with the assessment.

VP-VEC-162-COSET- (b) (6) The subject is (b) (6) with a medical history of Behcet's syndrome. On Study Day 57 of tasimelteon therapy, the subject felt dizzy and weak at the train station following (b) (6) site visit, and she was taken to the local hospital, where (b) (6) was diagnosed with **hypoglycemia** which required hospitalization. The subject has no prior history of diabetes or a family history of diabetes. After appropriate treatment, the event was considered resolved the same day. The subject restarted study drug therapy on Study Day 64. The investigator assessed the event to be unrelated to study drug. Reviewer's comments: I agree with the assessment.

Adverse events leading to early withdrawal: Two subjects permanently discontinued from the study due to an adverse event during the reporting period.

VP-VEC-162-COSET- (b) (6) Subject is (b) (6) who enrolled in the open-label Study 3202. On Study Day 898 (b) (6) withdrew permanently from the study due to the adverse events of "**senile dementia**" and "**worsening balance disorder**". The onset of these events was

documented as beginning on Study Day 834. The events were considered ongoing at the end-of-study visit. The events were considered unrelated to study medication. Reviewer's comments: I agree with the assessment.

VP-VEC-162-COSET- (b) (6) Subject is (b) (6) who enrolled in the open-label Study 3204. On Study Day 392, subject discontinued permanently due to **jaw pain** and **back pain**. The onset of these events was documented as beginning on Study Day 354, and the date of last dose was Study Day 357. The events were considered ongoing at the end-of-study visit. The events were considered unrelated to study medication. Reviewer's comments: I agree with the assessment.

Applicant's conclusion regarding the 120-day Safety Update: Given the available additional long-term safety data, there is no evidence of any newly learned information that materially impacts safety.

Reviewer's conclusion regarding the 120-day Safety Update: I agree with the Applicant's conclusion.

8 Postmarket Experience

Tasimelteon has not been marketed in any country including in the United States.

9 Appendices

9.1 Literature Review/References

Bjorvatn B and Pallesen S. A practical approach to circadian rhythm sleep disorders *Sleep Medicine* 2009;13:47-60.

Circadian rhythm sleep disorders. In: Hauri PJ (Task Force Chair). *The International Classification of Sleep Disorders* 2nd Ed. Westchester, Illinois: American Academy of Sleep Medicine, 2005:126-130.

Lewy AJ, et al. Capturing the circadian rhythms of free-running blind people with 0.5 mg melatonin *Brain Research* 2001;918:96-100.

Sack RL, et al. Entrainment of free-running circadian rhythms by melatonin in blind people *NJEM* 2000;343:1070-1077.

Skene DJ and Arendt J. Circadian rhythm sleep disorders in the blind and their treatment with melatonin *Sleep Medicine* 2007;8:651-655.

Zisapel N. Circadian rhythm sleep disorders *CNS Drugs* 2001;15(4):311-328.

9.2 Labeling Recommendations

Labeling recommendations are provided in separate document.

9.3 Advisory Committee Meeting

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

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

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/s/

DEVANAND JILLAPALLI
11/29/2013

RONALD H FARKAS
12/18/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2: Study 3203 Indication: Treatment of Non-24 Hour Disorder				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.				No prior agreement
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?				Prior agreement with the Division of Neurology Products
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?				Orphan indication
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?				
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Devanand Jillapalli, MD	7/30/13
Reviewing Medical Officer	Date
Ronald Farkas, MD, PhD	7/30/13
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEVANAND JILLAPALLI
07/30/2013

RONALD H FARKAS
07/30/2013