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# Safety profile of tasimelteon, a melatonin $MT_1$ and $MT_2$ receptor agonist: pooled safety analyses from six clinical studies

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EXPERT OPINION





# Safety profile of tasimelteon, a melatonin $MT_1$ and $MT_2$ receptor agonist: pooled safety analyses from six clinical studies

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***Introduction:*** Tasimelteon, a novel circadian regulator, is the first product for the treatment of Non-24-hour Sleep-Wake Disorder (Non-24) approved by either the FDA or the European Medicines Agency (EMA). Tasimelteon is a potent and specific melatonin ($MT_1$ and $MT_2$) receptor agonist with 2 – 4 times greater affinity for the $MT_2$ receptor.

***Methods:*** Safety was assessed in two controlled and two open-label studies in blind individuals with Non-24 and in two controlled studies of primary insomnia. Periodic assessments included collection of adverse events (AEs), laboratory testing, electrocardiograms (ECGs), vital sign monitoring, physical examinations and assessment for the potential for suicide. One study included additional assessments for endocrine function.

***Results:*** A total of 184 blind individuals with Non-24 received tasimelteon nightly with a median exposure > 1 year. In placebo-controlled studies, 387 patients with insomnia and 42 patients with Non-24 received tasimelteon nightly for 4 – 26 weeks. The total patient years exposure for the six studies assessed here is 258.64 patient years. Discontinuations due to AEs were similar across treatment groups. Overall in the clinical studies described here, AEs attributable to tasimelteon treatment were headache, diarrhea, dry mouth, alanine aminotransferase increased, somnolence, dizziness and nightmare/abnormal dreams. There were no clinically significant differences in treatment group with ECGs, vital signs, withdrawal, endocrine function and suicidality assessments.

***Conclusion:*** Long-term tasimelteon administration was safe and well-tolerated. This is supported by placebo-controlled data in both Non-24 and insomnia patients.

**Keywords:** blindness, circadian, melatonin receptor agonist, non-24-h sleep-wake disorder, safety, tasimelteon

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## 1. Introduction

The circadian regulator, tasimelteon (Hetlioz®, Vanda Pharmaceuticals) is a melatonin receptor agonist approved by the US FDA and the European Medicines Agency (EMA) for the treatment of Non-24-hour Sleep-Wake Disorder. Tasimelteon specifically binds with high affinity to the $MT_1$ and $MT_2$ melatonin receptors (with 2 – 4 times greater affinity for the $MT_2$ receptor), which are thought to be involved in the control of circadian rhythms [1].

A complete toxicology program was conducted as part of the drug development of tasimelteon including assessments of acute toxicity, repeat-dose toxicity,

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genotoxicity, carcinogenicity, reproductive and developmental toxicity and phototoxicity studies. The results of these studies are beyond the scope of this introduction, but the overall conclusion of the totality of the data is that the nonclinical toxicological assessment supports tasimelteon's use at therapeutic doses.

Tasimelteon is rapidly and consistently absorbed, with a mean absolute bioavailability of 38% [2]. Tasimelteon is extensively metabolized with CYP1A2 and CYP3A4 being the major isozymes involved in the metabolism of tasimelteon [3]. Clinical studies demonstrated that tasimelteon does not affect the pharmacokinetics of other drugs. Specifically drug–-drug interaction studies were conducted to examine the effect of tasimelteon on CYP3A4 and CYP2C8 substrates, midazolam and rosiglitazone, respectively. Both of these studies demonstrated that tasimelteon does not induce either CYP3A4 or CYP2C8 (Prescribing Information). Clinical studies demonstrated that concomitant use of strong CYP1A2 inhibitors like fluvoxamine increase tasimelteon exposure and strong CYP3A4 inducers like rifampin decrease exposure of tasimelteon [3]. An additional drug–drug interaction study was conducted with ethanol, and while there was a trend for additive effects on psychomotor performance tests, they were not clinically significant and none were seen on memory tasks (Prescribing information).

Tasimelteon was shown to entrain the circadian clock of totally blind individuals with Non-24, induce clinically meaningful improvements in sleep and functioning, and maintain these effects in the SET (Safety and Efficacy of Tasimelteon) and RESET (Randomized-withdrawal Study of the Efficacy and Safety of Tasimelteon) studies [4]. Tasimelteon also demonstrated the ability to phase advance circadian rhythms in a lab based study in healthy volunteers following an abrupt 5 h advance in sleep schedule, enabling subjects to fall asleep faster [1,5].

Intrinsic circadian rhythms including hormone production, temperature and metabolic regulation, and sleep-wake cycles are important for normal physiological and behavioral functioning. These rhythms are spontaneously generated by an endogenous oscillator in the suprachiasmatic nuclei (SCN) [6,7]. The major environmental time cue that synchronizes (entrains) this pacemaker to the Earth's 24-h day is the light-dark cycle, detected and transmitted to the SCN by the eyes via specialized photosensitive retinal ganglion cells. In most totally blind individuals, circadian photoreception is abolished, and patients suffer from non-entrained circadian rhythms with a disorder known as Non-24-h Sleep-Wake Disorder (Non-24) [8].

Non-24 is defined in the International Classification of Sleep Disorders – Third Edition (ICSD-3) [9] and in the American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5) [10] as a circadian rhythm sleep-wake disorder in which endogenous circadian rhythms are not synchronized to the external 24-h day and patients experience a consistent daily drift in sleep-wake propensity usually to later times each day. Patients present with a chronic sleep complaint that may include severely disrupted nighttime sleep and forced daytime sleep episodes which may occur with a cyclical pattern. As a result of this severe disruption of the sleep-wake timing, patients experience severe impairment in social and occupational functioning given the inability to schedule activities to a 24-h day.

Non-24 is an orphan disease with a very distinct etiology from insomnia [11-13]. There are approximately 1,300,000 blind people in the US [14], and approximately 130,000 of these have no light perception [15]. The prevalence of Non-24 in totally blind individuals is 50 – 70% [16]. According to the European portal for rare diseases (Orphanet), the prevalence rate of Non-24 (Hypernychthemeral syndrome, ORPHA number 73267) is estimated to be 18.5 per 100,000 individuals in the European Union (EU) or roughly 94,000 individuals within the EU. As a result, these individuals suffer from periodic insomnia and daytime sleepiness [15,17-20]. For some totally blind individuals, the sleeplessness and daytime fatigue that accompany this chronic sleep disturbance have profound impact on their social and occupational lives and are considered the most disabling aspect of their blindness [20]. Poor sleep as the result of Non-24 may have an important impact on physical and mental health. Recent research has indeed concentrated on how sleep is important for cognition, memory consolidation, energy balance, cardiovascular regulation and immunity [21-25]. Insufficient sleep has been associated with obesity, type-2 diabetes, hypertension, depression, cognition deficit and accidents [26-31].

The etiology and cyclical relapsing and remitting sleep-wake problem correlating to the individual's endogenous circadian pacemaker distinguish Non-24 from insomnia. Unlike Non-24 which is primarily caused by an inability to sense the daily light-dark cycle necessary to regulate the circadian pacemaker, the etiology of insomnia is multifactorial. Patients with insomnia may have trouble falling asleep, maintaining sleep or awakening earlier than desired or they may experience all these. Typically, their symptoms do not have a recurring and relapsing cyclical pattern. Patients suffering from either insomnia or Non-24 may experience excessive daytime sleepiness. Daytime naps are very common in most patients with Non-24 and occur in a lesser percentage of insomnia patients. Patients with Non-24 are often misdiagnosed with insomnia primarily due to the ubiquitousness of insomnia and the lack of disease awareness of Non-24 in healthcare providers and patients. A Non-24 diagnosis should be considered when a person with no light perception presents with sleep-wake complaints given the high prevalence of Non-24 among totally blind individuals [15,16,18-20].

In considering the safety profile of tasimelteon, the profile of compounds with similar mechanisms of action may be relevant. There are four commercially available melatonin receptor agonists, two of which are approved by the FDA (tasimelteon and ramelteon) and three by the EMA

(tasimelteon, agomelatine and prolonged release melatonin). Overall as a class, melatonin agonists are typically safe and well tolerated where studied. Safety findings unique to the individual therapeutics are compared and contrasted in detail in the Discussion. Significant findings are reproductive effects including decreased testosterone and increased prolactin levels associated with ramelteon, and cases of liver injury, including hepatic failure, elevations of liver enzymes, hepatitis and jaundice in patients treated with agomelatine. Melatonin is classified as a food supplement in the US and has the least characterized safety profile of any other approved treatment.

The goal of this manuscript is to describe the safety profile of tasimelteon from multiple studies in Non-24 or insomnia patients. As Non-24 is a chronic disorder, which requires chronic treatment, there is a need to make available a comprehensive safety assessment for the only approved treatment in the US and EU.

## 2. Patients and methods

While the tasimelteon studies in Non-24 patients are the largest placebo-controlled studies conducted in this rare disorder, in the interest of having an expanded population for the evaluation of safety, this analysis has been extended to include data from insomnia patients treated with tasimelteon. This is done with the understanding that such a method may not be ideal because some safety signals may be population specific.

The safety data presented herein are derived from six clinical studies of tasimelteon conducted in the US and Europe (**Table 1**). Four studies were conducted in patients with Non-24 in the US, Germany and France including: two efficacy studies (SET and RESET) and two long-term, open-label safety studies (3202 and 3204). This has been supplemented with two additional studies (004 and 3104) that were placebo-controlled US studies conducted in patients with primary insomnia. Study design, duration of treatment, dosing regimen and study population are described in **Table 2**. Additional details of the study designs are available in the supplementary materials. Patients enrolled in SET if eligible were allowed to enroll in RESET, or 3204. Similarly patients who enrolled into RESET were allowed to enroll into 3204 (**Figure 1**). Pooled analysis data include all data from the completed studies (SET, RESET, 004 and 3104) and interim data (as of 31 October 2013) from the two studies that were ongoing at the time this manuscript was prepared (3202 and 3204).

All studies were approved by central and local Institutional Review Boards or Ethics Committees and conducted in accordance with Good Clinical Practice (GCP) as required by the US FDA, the German Federal Institute for Drugs and Medical Devices (SET and 3204), the French National Agency for Medicines and Health Products Safety (3202), and the Declaration of Helsinki. All patients provided written informed consent.

### 2.1 Study population

Non-24 patients aged 18 – 75 years who reported complete absence of light perception and problems within the past 3 months of falling asleep, staying asleep, waking-up too early, daytime napping, excessive daytime sleepiness and/or cyclical periods of good sleep followed by periods of bad sleep were enrolled in SET, RESET, 3202 and 3204. For inclusion in SET, RESET and 3204 patients must have had a Non-24 circadian rhythm as measured by urinary 6-sulfatoxy melatonin. The most common causes of blindness within the Non-24 patients enrolled were retinopathy of prematurity (27%), congenital glaucoma (16%), ocular trauma (15%), glaucoma (12%) and retinoblastoma (11%). Insomnia patients were aged 18 – 64 (Study 3104) and 65 – 92 years (Study 004) and met diagnostic criteria for primary insomnia as defined in DSM-IV [10]. All protocols required the discontinuance of hypnotics, anxiolytics and prescription or over-the-counter sleep aids prior to enrollment.

As placebo-controlled data in the Non-24 population is relatively limited, two overlapping populations were defined to assess the safety and tolerability of tasimelteon. The Non-24 analysis population includes longitudinal safety data from all Non-24 subjects receiving tasimelteon, and the placebo-controlled analysis population includes placebo-controlled data for subjects with Non-24 as well as elderly and non-elderly patients with insomnia.

#### *2.1.1 Non-24 analysis population*

The longitudinal safety data derived from all Non-24 subjects receiving tasimelteon in any controlled or open-label study or combination of studies (N = 184 tasimelteon treated) includes subjects participating in Studies SET, RESET, 3202 and 3204. For each patient, the safety data are characterized from the first dose of tasimelteon through the last dose of tasimelteon treatment, including treatments in subsequent studies. With the exception of reporting adverse events (AEs) within the windows defined, any gaps between tasimelteon treatment periods such as gaps between participation in studies or during placebo-washout periods are excluded from this analysis. Exposure data for this population is reported as the sum of all individual treatment periods.

#### *2.1.2 Placebo-controlled analysis population*

The largest placebo-controlled dataset for analysis of tasimelteon includes patients from clinical trials conducted in Non-24 as well as elderly and non-elderly patients with insomnia (SET, 004 and 3104). This group was evaluated to increase the number of unique tasimelteon exposures in controlled studies due to the quantitative limitations of the target population. This analysis population consists of a pool of placebo-controlled studies with 26 weeks of dosing in Non-24 patients and at least 4 weeks of dosing in Insomnia patients. This population includes 429 patients.

**Table 1. Listing of pooled clinical studies for the assessment of tasimelteon safety.**

| Study ID (clinicaltrials.gov ID) | Objective(s) of the study | Study design and type of control | Safety assessments (conducted monthly) | Test product(s)* | Total number of subjects‡ | Patient population | Treatment duration |
|---|---|---|---|---|---|---|---|
| *Non-24-h population* | | | | | | | |
| SET (NCT01163032, EudraCT 2011-000281-35) | Efficacy and safety | Randomized, double-masked, placebo-controlled, parallel; additional open-label extension | AEs, hematology, chemistry, urinalysis, endocrine, ECG, withdrawal, and suicidal ideation and behavior | Tasimelteon 20 mg/PBO 1 h prior to a fixed bedtime | Total = 84 20 mg = 42; PBO = 42; 20 mg OLE = 52 | Totally blind with Non-24 (18 – 75 yrs) | 26 weeks randomized; 26 weeks open-label |
| RESET (NCT01430754) | Maintenance of efficacy and safety | Randomized withdrawal | AEs, hematology, chemistry, urinalysis, ECG, withdrawal§, and suicidal ideation and behavior | Tasimelteon 20 mg/PBO 1 h prior to a fixed bedtime | Total = 20 20 mg = 10; PBO = 10 | Totally blind with Non-24 (≥ 18 yrs) | 12-week open-label run-in followed by 8 week randomized withdrawal |
| 3202 (NCT0121878, EudraCT 2010-020912-12) | Long-term safety | Open-label | AEs, hematology, chemistry, urinalysis, ECG, and suicidal ideation and behavior | Tasimelteon 20 mg 1 h prior to a fixed bedtime | Total = 48 at time of interim database lock 20 mg = 48 | Totally blind with Non-24 (18 – 75 yrs) | 52 weeks followed by a 3-year optional sub-study |
| 3204 (NCT01429116, EudraCT 2011-004520-35) | Long-term safety | Open-label | AEs, hematology, chemistry, urinalysis, ECG, and suicidal ideation and behavior | Tasimelteon 20 mg 1 h prior to a fixed bedtime | Total = 86 at time of interim database lock 20 mg = 86 | Totally blind with Non-24 (≥ 18 yrs) | 2 years |
| *Primary insomnia population* | | | | | | | |
| CN116-004¶ | Efficacy and safety | Randomized, double-masked, placebo-controlled, crossover | AEs, hematology, chemistry, urinalysis, ECG | Tasimelteon 1, 10, and 50 mg/PBO At bedtime | Total = 227 1 mg = 56; 10 mg = 58; 50 mg = 56; PBO = 57 | Elderly with primary insomnia (≥ 65 years) | 28 days followed by 1-week placebo |
| 3104 (NCT00548340) | Efficacy | Randomized, double-masked, placebo-controlled, parallel | AEs, hematology, chemistry, urinalysis, ECG, and withdrawal§ | Tasimelteon 20 and 50 mg/PBO ½ h prior to bedtime | Total = 322 20 mg = 109 50 mg = 109 PBO = 104 | Primary insomnia (18 – 64 yrs) | 35 days followed by 1 night placebo |

*Non-24 patients had the opportunity to participate in up to 3 of the following studies; SET, RESET and 3204 (**Figure 1**). All the patients enrolled in 3202, 004 and 3104 were unique. A total of 184 unique patients with Non-24 participated in SET, RESET, 3204 and 3202. In this table, each patient is counted within each study enrolled.

‡Withdrawal was assessed following cessation of tasimelteon treatment in RESET (after 12 weeks of treatment) and in 3104 (after 35 days of treatment).

§Study 004 completed on 15-Mar-1999 and was not registered on ClinicalTrials.gov;

The route of administration in all studies was oral capsules administered once daily 30 or 60 min prior to bedtime;

AE: Adverse event assessment; ECG: 12-lead resting electrocardiogram; OLE: Open-label extension; PBO: Placebo; withdrawal: Assessment for symptoms of withdrawal using the Benzodiazapene Withdrawal Symptom Questionnaire (BWSQ). Suicidal ideation and behavior was assessed using the Columbia Suicidality Severity Rating Scale (C-SSRS).

**Table 2. Summary of subjects who received at least one dose of tasimelteon by analysis population.**

| Duration of exposure | Overall 1 – 50 mg | Non-24 analysis population 20 mg | Combined placebo-controlled analysis population 1 – 50 mg |
|---|---|---|---|
| ≥ 1 day | 571 | 184 | 429 |
| > 12 weeks | 163 | 163 | 38 |
| > 26 weeks | 139 | 139 | 24 |
| > 52 weeks | 111 | 111 | 0 |

The Non-24 analysis population includes 184 unique Non-24 patients from SET, RESET, 3202 and 3204. The combined placebo-controlled population includes Non-24 subjects (SET study) and insomnia subjects (studies 004 and 3104). The 42 subjects receiving tasimelteon in the SET study are included in both analysis populations.

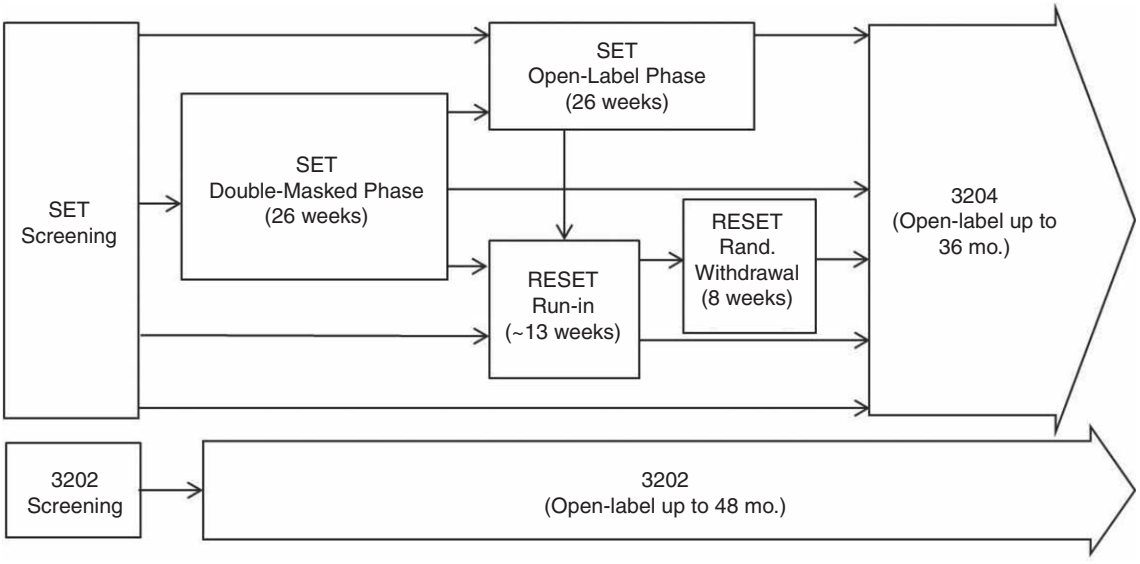


**Figure 1. Flow chart.**
Patients entered the open-label safety study, 3204, from SET (after screening or study completion) and from RESET(after the Run-in or study completion). RESET: Randomized-withdrawal study of the efficacy and safety of tasimelteon; SET: Safety and efficacy of tasimelteon.



## 2.2 Safety assessments

The safety and tolerability profile of tasimelteon was evaluated using reported AEs, serious adverse events (SAEs), vital signs, laboratory measurements including hematology, chemistry and urinalysis, endocrine measurements, electrocardiograms (ECGs), Benzodiazepine Withdrawal Symptom Questionnaire and the Columbia Suicide Severity Rating Scale (CSSRS). Safety assessments in all studies were scheduled every 30 days or less for the first 3 months of treatment, every 60 days or less for the next 3 months and every 90 days or less for the last 6 months of the first year of treatment. Following the first year of continuous exposure, safety assessments were scheduled every 6 months.

### *2.2.1 Adverse events*

AEs were defined as any untoward medical occurrence temporally associated with the use of tasimelteon, whether or not considered drug related, and were recorded throughout the study period for all studies. AE rates were based on events that occurred on or after the first day of treatment and within 3 days after the last dose of study medication. AEs were coded using the Medical Dictionary of Regulatory Activities (MedDRA) version 14.1 and were classified by MedDRA System Organ Class (SOC) and preferred term (MedDRA® trademark is owned by IFPMA on behalf of the International Classification of Harmonization) [32]. SAEs were defined as any AE that resulted in death, considered life-threatening by the investigator, resulted in hospitalization or prolongation of existing hospitalization, resulted in congenital anomaly or birth defect, persistent or significant disability, or is otherwise considered an Important Medical Event requiring medical or surgical intervention to prevent a more serious outcome. SAEs were reported through 30 days following the last study visit for all studies.

### *2.2.2 Physicals, vital signs and laboratory assessments*

Changes in physical exam findings, vital signs and laboratory assessments were assessed in all studies. Vital sign assessments

included systolic and diastolic blood pressure, heart rate, respiratory rate, temperature and body weight. Clinical laboratory assessments included hematology and chemistry panels as well as urinalysis. All studies used CLIA-certified central laboratories. Laboratory sample collection, handling, testing and reporting procedures were consistent with GCP and Good Clinical Laboratory Practice. Changes and abnormalities considered clinically significant by the investigator were reported as AEs and vital signs and laboratory assessments were reviewed in aggregate for trends. The Supplementary Materials describe the assessment methods and thresholds utilized to determine potential clinical significance.

#### 2.2.2.1 *Endocrine assessments*

A thorough evaluation of endocrine parameters was performed in the SET study to assess the effect of tasimelteon on the thyroid and reproductive axes. Endocrine testing included total T4, free T4, thyroid-stimulating hormone (TSH), T3 and prolactin, in both males and females. Progesterone was also assessed in females. Total testosterone, free testosterone, luteinizing hormone and follicle-stimulating hormone were also studied in males.

#### 2.2.3 *Electrocardiograms*

Resting 12-lead ECGs were performed in all studies. ECGs were read centrally in SET, RESET, 3202, 3204 and 3104 and read by the Investigator in 004. Abnormalities were assessed by study investigators for clinical significance in all studies. Additionally, ECG wave parameters were collected in all studies, and pooled parameters are presented.

#### 2.2.4 *Columbia suicide severity rating scale*

The C-SSRS is a semi-structured clinical interview designed to systematically assess and identify suicidal AEs (behavior and ideation, and completed suicides) [33]. The C-SSRS was assessed through a phone system. If the results were positive, then a paper version of C-SSRS was administered at the site. In these instances, only the data from the paper version was used for the analysis. C-SSRS was evaluated in SET, RESET, 3202 and 3204.

### 2.3 Statistical analyses

As Non-24 patients had the potential to enroll in more than one study, the Non-24 analysis population includes safety data from all Non-24 patients receiving at least one dose of tasimelteon in any placebo-controlled or open-label study or combination of studies. The flow of patients within the program is presented in **Figure 1**.

Safety data from individual studies was standardized into a tabular format and pooled. Analysis datasets were then generated from the pooled tabular data to support the programmed tables, listings and figures.

## 3. Results

### 3.1 Exposure

**Table 1** gives details on 571 unique subjects who were treated with at least one dose of tasimelteon in at least one of the six studies. The total patient years of exposure for 004, 3104, SET, RESET, 3202 and 3204 combined is 258.64. A total of 184 (unique subjects) totally blind individuals with Non-24 received doses of tasimelteon 20 mg 1 h before bedtime with a mean duration of exposure of 449.2 days (median = 448.5 days). Of these 184 patients, 139 were treated for at least 6 months, 111 were treated for at least 1 year and 36 patients were treated for at least 2 years. One hundred and twenty-six patients (76.1%) completed and/or remained active on open-label treatment. Of the 58 patients who discontinued study treatment: 19 patients stopped due to at least one AE (10.3%).

In the placebo-controlled analysis population study (SET, 004 and 3104), 632 unique patients were studied and 88.8% (561/632) completed the treatment protocol. Eighty-four of the subjects (SET) in the pooled placebo-controlled analysis group are also part of pooled for the Non-24 patient analysis group. Of the 632 patients in the placebo-controlled analysis population, 429 received nightly doses of tasimelteon with a mean duration of exposure of 43.5 days (median = 34.0 days) and 203 received placebo. AE was the most common reason for early discontinuation; however, there was no difference in discontinuation rates from AEs between tasimelteon 20 mg (3.3%) and placebo-treated patients (3.0%).

### 3.2 Demographics

**Table 3** summarizes the demographic data of the safety population. On average patients were in their sixth decade of life. The Non-24 population had slightly more males than females and the placebo-controlled analysis population had more females than males.

### 3.3 Adverse events

There were no deaths in the tasimelteon clinical development program.

SAEs were reported in 3/429 (0.7%) tasimelteon-treated and 2/203 (1.0%) placebo-treated patients in the placebo-controlled studies. SAEs in tasimelteon-treated patients included gastritis, syncope and diverticulitis. All events were considered as unrelated to tasimelteon administration.

AEs in the placebo-controlled analysis population with a frequency of 2% or more and at least twice as high on tasimelteon than on placebo are reported in **Table 4**. These events were somnolence, nightmare or abnormal dreams, diarrhea and dry mouth (**Table 4**). Of these events, somnolence, diarrhea and dry mouth were reported with higher frequency in tasimelteon-treated elderly (> 65 years of age) subjects than in tasimelteon-treated non-elderly subjects suggesting that

**Table 3. Demographic characteristics by analysis population.**

| | Non-24 | Combined placebo-controlled | |
|---|---|---|---|
| | Tasimelteon 20 mg | Tasimelteon 1 – 50 mg | Placebo |
| | n = 184 | n = 429 | n = 203 |
| *Age* | | | |
| 18 – 65 (%) | 89.7 | 64.3 | 74.4 |
| > 65 years (%) | 10.3 | 35.7 | 25.6 |
| Mean (yrs) | 51.4 | 54.7 | 52.1 |
| Range (yrs) | 21 – 75 | 20 – 92 | 18 – 87 |
| *Gender* | | | |
| Male (%) | 61.4 | 43.6 | 41.4 |
| Female (%) | 38.6 | 56.4 | 58.6 |
| *Race* | | | |
| Black (%) | 12.0 | 15.2 | 19.2 |
| White (%) | 84.2 | 83.0 | 79.3 |
| Other (%) | 3.8 | 1.9 | 1.5 |
| BMI (kg/m$^2$): Mean | 28.09 | 26.89 | 26.39 |

BMI: Body mass index.

**Table 4. Adverse events in the combined placebo-controlled population by age.**

| | Age group | | | | | |
|---|---|---|---|---|---|---|
| | All patients | | > 65 years | | ≤ 65 years | |
| Event | Tasimelteon 1 – 50 mg (N = 429) | Placebo (N = 203) | Tasimelteon 1 – 50 mg (N = 153) | Placebo (N = 52) | Tasimelteon 1 – 50 mg (N = 276) | Placebo (N = 151) |
| Somnolence | 3.0% | 1.5% | 4.6% | 1.9% | 2.2% | 1.3% |
| Nightmares or abnormal dreams | 2.6% | 0.5% | 0.0% | 0.0% | 4.0% | 0.7% |
| Diarrhea | 2.3% | 1.0% | 2.6% | 0.0% | 2.2% | 1.3% |
| Dry mouth | 2.3% | 0.5% | 3.9% | 0.0% | 1.4% | 0.7% |

Adverse events with an incidence in all patients of 2% or more and at least twice as high on tasimelteon than on placebo are included. The combined placebo-controlled analysis population includes Non-24 patients (SET study) and insomnia patients (studies 004 and 3104). All patients enrolled in study 004 were > 65 years of age and all patients enrolled in 3104 were ≤ 65 years of age. SET patients are included in both age groups.

the incidence of these events may increase with age. Nightmare or abnormal dreams was not reported in elderly subjects. Somnolence, nightmare or abnormal dreams, diarrhea and dry mouth were reported by tasimelteon-treated patients in placebo-controlled insomnia studies and in the placebo-controlled Non-24 study. Somnolence and diarrhea were reported with similar frequencies in tasimelteon and placebo-treated Non-24 patients, suggesting that these events may have a higher association with tasimelteon use in insomnia than in Non-24. Insomnia (2/429, 0.5%) was the most commonly reported AE leading to discontinuation for tasimelteon-treated subjects in this safety analysis population.

A total of 14/184 (7.6%) SAEs were reported in Non-24 patients receiving tasimelteon. The System Organ Classes of the SAEs reported were nervous system disorders (n = 4), infections and infestations (n = 3), neoplasm (n = 2), cardiac disorders (n = 1), injury, poisoning, and procedural complications (n = 1), metabolism and nutrition disorders (n = 1), musculoskeletal and connective tissue disorders (n = 1), respiratory, thoracic and mediastinal disorders (n = 1). All events were considered unrelated to tasimelteon treatment.

In the Non-24 population, headache and nasopharyngitis were the most commonly reported AEs occurring in 27/184 (14.7%) and 26/184 (14.1%) of patients respectively. Urinary tract infection, increased alanine aminotransferase, arthralgia, and nightmare/abnormal dreams were also reported by > 5% of all tasimelteon-treated Non-24 patients. Event rates are displayed in **Table 5**. In all Non-24 patients, 19 patients (10.3%) discontinued treatment due to an AE. Nightmare or abnormal dreams were the most frequently reported event leading to discontinuation with a frequency of 1.1%. Sixty-seven percent of headache and 19% of nasopharyngitis reports occurred within the first 60 days of treatment. Of nightmare or abnormal dream events reported, 100% occurred within the first 60 days of treatment, and 90% were reported within the first 14 days. Overall in the clinical studies described here, AEs attributable to tasimelteon treatment that were very common (occurring at a rate ≥ 1/10)

**Table 5. Adverse events in the non-24 analysis population.**

| Event | Tasimelteon 20 mg (n = 184) |
|---|---|
| Headache | 14.7% |
| Nasopharyngitis | 14.1% |
| Urinary tract infection | 7.1% |
| Alanine aminotransferase increased | 6.5% |
| Arthralgia | 6.5% |
| Nightmares or abnormal dreams | 5.5% |

Adverse events with an incidence of 5% or more are included.
The Non-24 analysis population includes 184 unique patients from SET, RESET, 3202 and 3204.



were headache, and events considered common (occurring at a rate ≥ 1/100) were diarrhea, dry mouth, increased alanine aminotransferase, somnolence, dizziness and nightmare/abnormal dreams. Events considered less common (occurring at a rate ≥ 1/1,000) or uncommon (occurring at a rate ≥ 1/10,000) cannot be calculated at this time due to sample size constraints.

### 3.4 Laboratory assessments

Tabular results are presented in supplement.

#### *3.4.1 Hematology*

Among all Non-24 subjects treated with tasimelteon, there were a total of 32 potentially clinically significant abnormalities in hematology measures. In the placebo-controlled population, there were a total of 18 potentially clinically significant hematology test abnormalities in the tasimelteon-treated group and 14 in the placebo group.

#### *3.4.2 Biochemistry*

In the Non-24 analysis population, there were 18 potentially clinically significant laboratory test abnormalities. In the placebo-controlled population, there were 11 and 4 in the tasimelteon-treated and placebo groups, respectively.

##### *3.4.2.1 Assessment of liver function*

Liver function were evaluated with hepatic transaminases using guideline ranges of 3x Upper Limit of Normal (ULN), 5x ULN, 10x ULN and 20x ULN as recommended by FDA's Premarket Evaluation of Drug-Induced Liver Injury (DILI) (39). No subjects met the criteria for Hy's Law, ≥ 3x ULN for alanine aminotransferase (ALT) or aspartate aminotransferase (AST) and ≥ 2x ULN for bilirubin.

Fifteen subjects experienced elevated hepatic transaminase (s) ≥ 3x ULN with exposure to tasimelteon. Two of these 15 subjects had a single elevation of hepatic transaminase ≥ 5x ULN. Both subjects had elevated transaminases at baseline greater than 1.4x ULN and improved within 42 days to a level below their pre-exposure level upon discontinuation of tasimelteon.

Twelve additional subjects had single elevations in ALT and/or AST ≥ 3x ULN and < 5x ULN. Five of these 12 subjects started with ALT/AST levels above the normal range prior to tasimelteon exposure. All five subjects had their elevation in ALT or AST levels fall to levels below their pre-exposure levels within 28 days, including two without discontinuation of tasimelteon.

Seven subjects had single elevations with all prior ALT/AST evaluations being normal. Most of these elevations to ≥ 3x ULN occurred between days 30 and 60 of tasimelteon use. Five of these seven subjects normalized without discontinuation of tasimelteon use; one normalized with discontinuation, and one subject did not have follow up labs to analyze progression.

The last subject experienced multiple hepatic transaminase elevations ≥ 3x ULN but had pre-existing abnormal ALT and AST levels at baseline and continued to have fluctuations in ALT and AST with periods of improvement and decline without modification in tasimelteon use.

Based on the lack of higher elevations of hepatic transaminase elevations (≥ 10x ULN), a high portion of abnormal hepatic enzymes being a single elevation in hepatic transaminase levels with spontaneous resolution despite continued use of tasimelteon, and no clinical indications of a chronic hepatic injury or insult, it is reasonable to conclude that there is no clinically meaningful evidence of a significant DILI risk associated with tasimelteon use.

##### *3.4.2.2 Endocrine assessments*

A summary of post-baseline thyroid axis parameters outside of the reference range are displayed in **Table 6**. The only parameter which varied between treatment groups was TSH for which 11.8% of tasimelteon-treated and 19.4% of placebo-treated patients demonstrated values higher than the reference range. **Table** 7 presents the number of post-baseline values outside of the reference range for reproductive axis parameters. Parameters with treatment group differences included prolactin with values below the reference range reported for 15% of tasimelteon-treated males and 0% of placebo-treated males and values above the reference range reported for 5.9% of tasimelteon-treated females and 13.3% of placebo-treated females. Luteinizing hormone with values above the reference range was reported in 5.3% of tasimelteon-treated males and 20% of placebo-treated males. Of the three tasimelteon-treated males with low prolactin values, one was considered clinically significant but unrelated. The other two were not considered as clinically significant.

#### *3.4.3 Urinalysis*

There were no clinically relevant differences in changes from baseline for any urinalysis analyse, and there was no clinically meaningful difference between tasimelteon-treated subjects and placebo-treated subjects in shift from baseline to worst possible value during treatment for any urinalysis analyze in either analysis population.

**Table 6. Subjects with post-randomization endocrine laboratory values outside of the reference range - thyroid axis (SET study).**

| Laboratory parameter | Tasimelteon 20 mg (n = 42) | Placebo (n = 42) |
|---|---|---|
| T4 (< 66 nmol/l) | 1/37 | 1/34 |
| T4 (> 181 nmol/l) | 0/37 | 0/34 |
| Free T4 (< 12 pmol/l) | 1/36 | 0/35 |
| Free T4 (> 21.9 pmol/l) | 0/36 | 1/35 |
| Thyroid-stimulating hormone (TSH) (< 0.40 mIU/l) | 0/34 | 0/31 |
| TSH (> 4.00 mIU/l) | 4/34 | 6/31 |
| T3 (< 1.23 nmol/l) | 1/39 | 1/35 |
| T3 (> 3.07 nmol/l) | 1/39 | 0/35 |

Subjects with out-of-range values prior to randomization are excluded.
Endocrine assessments were not performed in RESET, 004, 3104, 3202 and 3204.
IU: International units; T3: Triiodothyronine; T4: Thyroxine.

**Table 7. Subjects with post-randomization endocrine laboratory results outside of the reference range – reproductive axis (SET Study).**

| | Males | | Females | |
|---|---|---|---|---|
| | Tasimelteon 20 mg (n = 24) | Placebo (n = 25) | Tasimelteon 20 mg (n = 18) | Placebo (n = 17) |
| Prolactin (< 86 mIU/l [males]; < 102 mIU/l [females]) | 3/20 | 0/19 | 3/17 | 2/15 |
| Prolactin (> 324 mIU/l [males]; > 496 mIU/l [females]) | 2/20 | 2/19 | 1/17 | 2/15 |
| Follicle-stimulating hormone (< 1.6 IU/l) | 0/17 | 0/19 | n/a | n/a |
| Follicle-stimulating hormone (> 11.0 IU/l) | 1/17 | 0/19 | n/a | n/a |
| Luteinizing hormone (< 1.7 IU/l) | 0/19 | 1/20 | n/a | n/a |
| Luteinizing hormone (> 8.6 IU/l) | 1/19 | 4/20 | n/a | n/a |
| Progesterone (< 0.10 nmol/l) | n/a | n/a | 0/3 | 0/4 |
| Progesterone (> 85.9 nmol/l) | n/a | n/a | 0/3 | 1/4 |
| Free testosterone (< 5.6 pg/ml) | 2/21 | 3/19 | n/a | n/a |
| Free testosterone (> 27.0 pg/ml) | 0/21 | 0/19 | n/a | n/a |
| Total testosterone (< 9.37nmol/l) | 3/21 | 4/18 | n/a | n/a |
| Total testosterone (> 37.13 nmol/l) | 0/21 | 1/18 | n/a | n/a |

Subjects with out-of-range values prior to randomization are excluded.
Endocrine assessments were not performed in RESET, 004, 3104, 3202 and 3204.
IU: International units.



### 3.5 Electrocardiograms (ECGs)

In the placebo-controlled pool, there were no clinically meaningful differences between treatment groups in ECG parameter changes from baseline (**Table 8**). These findings were consistent with a thorough QT study conducted with doses of tasimelteon up to 300 mg.

### 3.6 Suicidality and potential for abuse or withdrawal

**Table 9** displays the suicide-related events reported during CSSRS assessments. All seven suicide-related events reported in the long-term safety population were also present at baseline at the same value. There is no evidence of suicidality-related thoughts or behaviors associated with the use of tasimelteon. Additionally, tasimelteon demonstrated no evidence for the potential of withdrawal or abuse following its abrupt discontinuation [1].

## 4. Discussion

The aim of this publication is to provide integrated safety data from the use of tasimelteon, a novel circadian regulator indicated for the treatment of Non-24 disorder [1,5].

It is indeed true that Non-24 disorder is relatively poorly known amongst patients and medical care providers, even if its pathophysiology is well known, based on the absence of stimulation of the biological clock by light via the retino-

**Table 8. ECG parameter changes from baseline by safety analysis population.**

| | Placebo-controlled* | | Non-24 |
|---|---|---|---|
| **Parameter** | **Tasimelteon 20 mg (n = 429)** | **Placebo (n = 203)** | **Tasimelteon 20 mg (n = 184)** |
| QTcb – Bazett's correction formula (ms) | -1.2 | -3.8 | -6.6 |
| QTcf – Fridericia's correction formula (ms) | 2.4 | -0.1 | -4.7 |
| Heart rate (b.p.m.) | -3.6 | -3.8 | 1.6 |
| PR duration (ms) | 2.1 | 1.9 | 1.7 |
| QRS duration (ms) | -0.4 | -1.0 | 1.2 |
| QT duration – uncorrected (ms) | 9.1 | 8.9 | -3.5 |

*The combined placebo-controlled analysis population includes Non-24 patients (SET study) and insomnia patients (studies 004 and 3104).
The maximum change from baseline at any post-baseline visit is used for each subject.
b.p.m.: Beats per minute; ms: Millisecond.

**Table 9. Summary of suicide related events by safety analysis population.**

| | SET Study | | All Non-24 |
|---|---|---|---|
| **Parameter** | **Tasimelteon 20 mg (n = 42)** | **Placebo (n = 42)** | **Tasimelteon 20 mg (n = 184)** |
| Suicidal Ideation | 1 (2.4%) | 3 (7.1%) | 7 (3.8%) |
| Wish to be dead | 1 (2.4%) | 2 (4.8%) | 7 (3.8%) |
| Non-specific active suicidal thoughts | 1 (2.4%) | 2 (4.8%) | 2 (1.1%) |

Suicidality was assessed using the Columbia Suicidality Severity Rating Scale (C-SSRS).
SET: Safety and efficacy of tasimelteon.



hypothalamus visual tracts. However, there have been relatively few studies conducted in humans to identify the symptoms of this disorder [15,20,34]. According to the ICSD-3, "the severity of individual sleep-wake symptoms can be variable. Starting with the asymptomatic period when the individual's endogenous rhythm is aligned to the external environment and required sleep-wakes times, sleep latency will gradually increase and the individual will complain of sleep-onset insomnia" Studies investigating the treatment of Non-24 by melatonin agonists are even rarer (28 – 35, 41 – 43). To our knowledge, no studies have been devoted to systematically assess AEs, vital signs, laboratory measurements, endocrine measurements, ECGs, potential for withdrawal and suicidality of melatonin or melatonin agonist in Non-24 patients only. We believe that this well-controlled comprehensive assessment of tasimelteon in studies totaling more than 1100 patients with exposures for greater than one year including more than 100 Non-24 patients is important. Furthermore, tasimelteon demonstrates no evidence for the potential of withdrawal or abuse following its abrupt discontinuation [1].

People with blindness may be considered vulnerable due to their visual disability. Therefore, it seems of particular interest to assess whether a treatment may be deleterious to their safety (as for every disease), since sleep and alertness may be modified by the treatment and may have by themselves an impact on the risk of mistake or accident.

As shown in **Table 5**, somnolence was in our analysis reported more frequently in the tasimelteon-treated group compared to the placebo-controlled analysis population. Somnolence is, however, an expected and desired outcome of tasimelteon given its mechanism of action and nighttime dosing and sleepiness has been reported as a normal effect of melatonin in previous studies [30,32,34]. However, a rate of 3% of patients experiencing somnolence does not seem too high, compared to studies in the general population of New York and California that report a prevalence of sleepiness of 19.5% with moderate excessive sleepiness and 11.0% with severe excessive sleepiness [35]. Notably, nightmare or abnormal dreams occurred frequently in tasimelteon-treated patients within both analysis populations and is considered an adverse drug reaction expected to occur in a small percentage of individuals treated with tasimelteon. While the mechanism of this effect is not fully known, it is likely related to the mechanism of action of tasimelteon and its effect to normalize REM stage sleep accumulation, with more REM episodes occurring during the later stages of a sleep episode The occurrence of abnormal dreams and nightmares were transient and mild in nature without sequelae arguing against a mechanism like rebound wakefulness which would not be expected to resolve. Such patients, especially those with prolonged disruption of sleep patterns such as Non-24 patients, are more likely to both enter sleep and wake up in close temporal proximity to a REM episode and are therefore more likely to remember and report their dream content [5].

Based on documented reports of safety made after each adverse effect, the three serious AEs reported were quoted by

investigators as not related to tasimelteon. Our analysis also shows that tasimelteon was safe and well-tolerated in Non-24 patients as well as in an expanded safety population comprised of Non-24 and insomnia patients. The incidence of AEs associated with tasimelteon use is largely limited to common and non-severe symptoms. In the Non-24 analysis population, 6.5% of subjects experienced elevated alanine aminotransferase. This abnormality did not appear commonly in the placebo-controlled population. There is no other evidence of adverse effects on laboratory parameters, vital signs, or ECGs. Tasimelteon is not associated with next-day effects, or suicidal ideation or behavior.

Beyond tasimelteon, there are no other approved treatments for the treatment Non-24.

Overall as a class, melatonin agonists are typically safe and well tolerated where studied, although none have as desirable a profile as tasimelteon. Melatonin is classified as a food supplement in the US and is not regulated by the FDA or EMA. It is available in hundreds of formulations and has not been approved to prevent or treat any disease or condition. As a non-FDA approved supplement, there are no well-controlled, large-scale or long-term clinical trials to assess its maintenance of effect, safety, side-effect profile or drug–drug interactions [36]. In addition, studies of dozens of the available preparations have shown significant variability in potency, purity, dissolvability and safety between lots and brands [37-39].

Several other melatonin receptors agonists (ramelteon, circadin and agomelatine) have been launched and approved by the FDA and/or the EMA in the last years with a labelling for insomnia or depression [40].

- Ramelteon is indicated for the treatment of insomnia characterized by difficulty with sleep onset in the US [41]. Precautions and warnings while taking ramelteon include the potential for abnormal thinking, behavioral changes, complex behaviors including sleep-driving and hallucinations, worsening of depression or suicidal thinking may occur, there may also be potential impairment of activities requiring complex mental alertness such as operating machinery or driving a motor vehicle after ingesting the drug. Reproductive effects include decreased testosterone and increased prolactin levels. The most common adverse reactions (≥ 3% and more common than with placebo) are somnolence, dizziness, fatigue, nausea and exacerbated insomnia.
- Circadin is a prolonged-release formulation of melatonin approved by the EMA for the short-term treatment of primary insomnia characterized by poor quality of sleep in patients over 55 years of age. It has a moderate influence on the ability to drive and use machines and it may cause drowsiness. The most common adverse reactions were headache, nasopharyngitis, back pain and arthralgia.
- Agomelatine is a melatonin agonist coupled with a 5-$HT_{2C}$ receptor antagonist indicated for the treatment of major depressive episodes by the EMA. According to the Summary of Product Characteristics (SmPC) cases of liver injury, including hepatic failure (few cases were exceptionally reported with fatal outcome or liver transplantation in patients with hepatic risk factors), elevations of liver enzymes exceeding 10 times ULN, hepatitis and jaundice have been reported in patients treated with agomelatine in the post-marketing setting. The pattern of damage is predominantly hepatocellular with serum transaminases which usually return to normal levels on cessation of agomelatine. The most common adverse reactions were nausea and dizziness.

It is noteworthy that the liver injury observed with agomelatine does not appear to be shared by other members of the class of compounds, and that importantly the reproductive effects from ramelteon treatment on prolactin and testosterone levels have not been observed with tasimelteon treatment. Prolactin and testosterone levels were not examined in people treated with circadin, agomelatine or melatonin. A conclusion about the class of compounds effects on reproductive hormones cannot be determined at this time. Overall the overlapping AEs for the class of melatonin agonists include somnolence nausea, dizziness and headache.

## 5. Conclusion

Non-24 is a serious and rare circadian rhythm sleep-wake disorder that predominantly affects totally blind patients. The epidemiology and disease progression of Non-24 have not been extensively studied because of the rarity of the disorder. Currently, very little is known about the long-term consequences of Non-24 disorder and whether there are any changes over time. Tasimelteon a circadian regulator has been approved for the treatment of Non-24. Placebo-controlled and open-label studies in Non-24 patients as well as insomnia patients have demonstrated that it is safe and well tolerated in long-term treatment. Currently, there is one ongoing long-term, open-label safety study with tasimelteon 20 mg in Non-24 patients, which provides the opportunity to perform future evaluations to gain a better understanding of very long-term treatment with tasimelteon. We hope that the safety evaluations described help the community of research in providing knowledge on this rare disease and its treatment.

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## Declaration of interest

D Leger has received funding or has been the main investigator in studies sponsored by SANOFI-AVENTIS, MERCK, VANDA, ACTELION, BIOPROJET, PHILIPS, RESMED, VITALAIRE in the last 5 years. He has been principal investigator in the 3202 study and he received fees and compensation for performing these surveys. He declares having access to all safety reports and documents made during the survey. MF Vecchierini has been the main investigator in a study sponsored by RESMED and a co-investigator in studies sponsored by VANDA, MERCK and BIOPROJET. She has been a co-investigator in the 3202 study and has received fees for this study. P Ogrizek received fees for being a co-investigator in the 3202 study sponsored by VANDA and has been invited by UCB and VITALAIRE to attend international congresses in the last 5 years. M-A Quera-Salva has received funding or has been the main investigator in studies sponsored by SERVIER, VANDA, ACTELION, BIOPROJET, PHILIPS, ASSOCIATION Française contre les Myopathies, Les Gueules casés, Fondation Vinci pour une conduite responsible. Has received consulting fees from servier and vanda. C Perry and MA Dressman are employees of Vanda Pharmaceuticals. The research reported in this manuscript was funded by Vanda Pharmaceuticals and Bristol Myers Squibb. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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