EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 April 2015
EMA/CHMP/601383/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Hetlioz

International non-proprietary name: tasimelteon

Procedure No. EMEA/H/C/003870/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Hetlioz
Applicant:	Vanda Pharmaceuticals Ltd. Liberty House 222 Regent Street London, W1B 5TR United Kingdom
Active substance:	tasimelteon
International Nonproprietary Name/Common Name:	tasimelteon
Pharmaco-therapeutic group (ATC Code):	Psycholeptics, melatonin receptor agonists (N05CH03)
Therapeutic indication:	Hetlioz is indicated for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24) in totally blind adults.
Pharmaceutical form:	Capsule, hard
Strength:	20 mg
Route of administration:	Oral use
Packaging:	bottle (HDPE)
Package size:	30 capsules

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List of abbreviations

ADR	Adverse Drug Reaction	
AE	Adverse Event	
ALT	Alanine aminotransferase	
aMT6s	urinary 6-sulfatoxymelatonin	
ANCOVA	analysis of covariance	
AST	aspartate aminotransferase	
AUS	area under the plasma concentration-time curve	
AUC0-24	AUC from time 0 to 24 hours	
AUC0-inf	AUC from time 0 extrapolated to infinity	
BCS	Biopharmaceutical Classification System	
BMI	Body Mass Index	
CEP	Certificate of Suitability	
CGI-C	Clinical Global Impression of Change	
CHMP	Committee for Medicinal Products for Human Use	
Cmax	maximum observed plasma concentration	
Cmin	minimum observed serum concentration	
CYP	cytochrome P-450	
DSC	Differential scanning calorimetry	
dTSD	Day time Total Sleep Duration	
EC	European Commission	
EEA	European Economic Area	
EU	European Union	
GC	Gas chromatography	
GCP	Good Clinical Practice	
GMP	Good Manufacturing Practice	
HDPE	High Density Polyethylene	
HPLC	High-performance liquid chromatography	
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use	
ICP-MS	Inductively coupled plasma mass spectrometry	
ITT	Intent to treat	
IR	Infrared	
KF	Karl Fischer titration	
LC-MS	Liquid Chromatography coupled with Mass Spectrometry	
LDPE	Low Density Polyethylene	
LOD	Limit of Detection	
LOQ	Limit of Quantification	
LQ-nTST	Lower Quartile of nTST MoST	Midpoint of Sleep Timing
n/a	not applicable	
Non-24	Non-24-Hour Sleep-Wake Disorder	
N24CRS	Non-24 Clinical Response Scale	
nTST	Night-time Total Sleep Time	
PhEur	European Pharmacopoeia	
PIL	Patient Information LeafletPIP	Paediatric Investigation Plan

PK	Pharmacokinetic
PP	polypropylene
Pre-SQ	Pre-Sleep Questionnaire
PVC	polyvinyl chloride
RH	relative humidity
SAE	Serious Adverse Event
SCN	suprachiasmatic nucleus
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
Tmax	time at maximum concentration
UQ-dTSD	Upper Quartile of dTSD
UV	Ultraviolet
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Vanda Pharmaceuticals Ltd. submitted on 1 May 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Hetlioz, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 October 2013.

Hetlioz was designated as an orphan medicinal product EU/3/10/841 on 23 February 2011. Hetlioz was designated as an orphan medicinal product in the following indication: treatment of Non-24-Hour Sleep-Wake Disorders in blind people with no light perception.

The applicant applied for the following indication: treatment of Non-24-Hour Sleep-Wake Disorder (Non-24) in the totally blind.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Hetlioz as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that tasimelteon was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0141/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001531-PIP01-13 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity:

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance tasimelteon contained in the above medicinal product to be considered as a new active substance in itself, claiming that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Hetlioz was given a Marketing Authorisation in the United States on 31 January 2014.

1.2. Manufacturers

Manufacturer(s) responsible for batch release

FDC International Limited
Unit 6 Fulcrum 1, Solent Business Park, Solent Way, Whiteley, Fareham, Hampshire, PO15 7FE, United Kingdom

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Rapporteur: Greg Markey

Co-Rapporteur: David Lyons

- The application was received by the EMA on 1 May 2014.
- The procedure started on 28 May 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 August 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 August 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 11 September 2014
- During the meeting on 25 September 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 September 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 December 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 2 February 2015.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 12 February 2015
- During the CHMP meeting on 26 February 2015, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.

- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 March 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 31 March 2015.
- PRAC RMP Advice and assessment overview, adopted on 10 April 2015
- During the meeting on 23 April 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Hetlioz.

2. Scientific discussion

2.1. Introduction

2.2. Problem statement

Non-24-Hour Sleep-Wake Disorder (Non-24) is a serious, debilitating, chronic disorder that occurs when individuals are unable to synchronize their endogenous circadian clock to the 24-hour light-dark cycle. The majority of reported cases of Non-24 occur in blind patients with no conscious perception of light. As a result of light information failing to reach the suprachiasmatic nucleus (SCN) to synchronize the clock and its outputs, the pacemaker may revert to its endogenous non-24-hour period. The result of this lack of entrainment is the gradual shifting of the endogenous rhythm as compared to the social/environmental 24-hour clock. The progressive shifting of the rhythm also produces a cyclical remission during which alignment will be achieved every 1 to 16 months depending on the period of the endogenous clock.

In Non-24, the timing of physiology and behaviour that is controlled by the circadian system (e.g. the timing of melatonin and cortisol production, the core body temperature rhythm, metabolic processes, the sleep-wake cycle, and alertness and performance patterns) becomes desynchronized from the 24-hour day, which has serious consequences on the daily functioning of the patient. Non-24 is associated with significant clinical symptoms which are often mistakenly diagnosed as related to insomnia, rather than as a result of a non-entrained circadian clock, often leading to inappropriate therapeutic interventions. For some totally blind individuals, the sleeplessness and daytime somnolence that result from being non-entrained have profound impacts on their social and occupational lives and can be considered the most disabling aspects of their blindness. The ultimate goal in treating individuals with Non-24 is to entrain their circadian clock with the 24-hour day so that the timing of their physiology and behaviour is synchronized appropriately with the 24-hour social day.

Onset of Non-24 can occur at any age, from birth onward, and usually coincides with or follows shortly after the total loss of light perception or loss or surgical removal of the eyes. The risk of developing Non-24 ultimately depends on the risk of complete loss of circadian photoreceptive function rather than on the cause of blindness; any ocular disorder which abolishes light-dark input to the circadian pacemaker and prevents entrainment to the light-dark cycle can lead to Non-24. Eye disorders that damage the ganglion cell layer (e.g., glaucoma), affect the optic nerve (e.g., retinopathy of prematurity), or cause removal of the eye entirely (e.g., retinoblastoma, trauma) are more likely to result in total blindness, prevent circadian entrainment, and therefore increase the likelihood of Non-24.

Non-24 should be suspected in any totally blind individual who presents with a chronic history of a severe sleep-wake disorder. More than half and as many as seventy percent of the totally blind patients are expected to have Non-24, making the disorder one of the most prevalent conditions among the totally blind with an estimated prevalence of 1.5 to 2.2 persons per 10,000 in the EU Community. (8-10) 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 EU. There is currently no other approved treatment for Non-24 in the EU.

2.3. About the product

Tasimelteon is a circadian regulator that resets the master body clock in the suprachiasmatic nucleus (SCN). Tasimelteon is a Dual Melatonin Receptor Agonist (DMRA) with selective agonist activity at the MT1 and MT2 receptors believed to act in the SCN. 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.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as hard capsules containing 20 mg of tasimelteon as active substance.

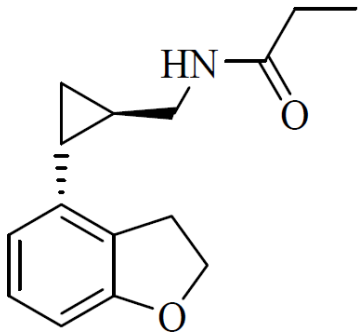
Other ingredients of the capsule core are: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate. Ingredients of the hard capsule shell are: gelatin, titanium dioxide, brilliant blue FCF, erythrosine, orange yellow S (E110). Ingredients of the printing ink are: shellac, propylene glycol, sodium hydroxide, povidone K17, and titanium dioxide.

The product is available in high density polyethylene (HDPE) bottle containing 30 hard capsules with polypropylene child-resistant closures containing polypropylene resin induction seals. Each bottle also contains a 1.5-g silica gel desiccant canister and polyester dunnage. Single HDPE bottle is provided in paperboard carton.

2.4.2. Active Substance

General information

The chemical name of tasimelteon is (1R, 2R)-N-[2-(2,3-dihydrobenzofuran-4-yl)cyclopropylmethyl] propanamide and has the following structure:



The chemical structure of tasimelteon has been adequately demonstrated by elemental analysis, IR and UV absorption spectroscopy, ^{1}H, ^{13}C, and COSY (Correlation Spectroscopy) nuclear magnetic resonance spectroscopy, heteronuclear multiple quantum coherence and heteronuclear multiple bond correlation, and mass spectrometry (MS, including MS/MS). Single-crystal X-ray diffraction analysis was used additionally in order to determine the molecular structure, solid state conformation, and relative and absolute stereo configuration of tasimelteon.

Tasimelteon is a white to off-white crystalline powder, it is non hygroscopic, soluble in water across relevant pH values and freely soluble in alcohols, cyclohexane, and acetonitrile. Conducted *in vivo* studies demonstrate that tasimelteon is highly permeable substance. Photostability testing and testing on stress conditions demonstrated that the active substance degrades in light.

Tasimelteon exhibits stereoisomerism due to the presence of two chiral centres. Active substance is manufactured as a single, trans-1R,2R isomer. Enantiomeric purity is controlled routinely during manufacture of active substance intermediates by chiral HPLC/specific optical rotation and additionally controlled in the active substance. Stability data indicates tasimelteon is isomerically stable.

Polymorphism has been observed in polymorphic screening studies for tasimelteon and two forms have been identified. The thermodynamically more stable form has been chosen for development and the manufacturing process consistently yields active substance of single, desired polymorphic form. It was demonstrated that milling of the active substance does not affect polymorphic form. Polymorphism is additionally controlled in active substance release and shelf-life specifications using X-ray powder diffraction analysis.

Manufacture, characterisation and process controls

The active substance intended for the proposed commercial process is obtained from a single manufacturer. During the development, two additional manufacturers of active substance were used. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

Tasimelteon is synthesized in nine main steps using linear synthesis and using commercially available well-defined starting materials with acceptable specifications. Three intermediates are isolated for control of active substance quality including stereochemical control. The active substance is isolated by slow recrystallisation or precipitation of tasimelteon from an ethanol/water mixture which ensures the formation of desired polymorphic form. Up to two additional, optional recrystallisations may be performed for unmilled tasimelteon to ensure that milled tasimelteon active substance is of high purity. Seed crystals complying with active substance specifications can be used optionally. Active substance is jet milled (micronised) to reduce and control particle size, which is critical in finished product performance with regards to content uniformity and dissolution.

The active substance is not sterile, and therefore process validation data is not required. However, the validation results of three consecutive validation batches at the proposed commercial manufacturing site were provided.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The active substance is packaged in double low density polyethylene bags each closed with a twist tie inside a sealed polyethylene terephthalate/aluminium/LDPE bag. A silica desiccant is placed inside the aluminium bag.

The aluminium bag is finally placed inside a 6-L paper drum with matching paper lid. The materials chosen for the packaging comply with the EC directive 2002/72/EC and EC 10/2011 and are suitable to protect the active substance from moisture and light. Each batch of polyethylene bags is tested prior to use. The secondary packaging is suitable to protect the active substance during transportation and storage.

Specification

The active substance specification includes tests for appearance, identity (IR, specific rotation, chiral HPLC), melting point (Ph. Eur., DSC), sulfated ash (Ph. Eur.), heavy metals (Ph. Eur.), elemental impurities (ICP-MS), loss on drying (Ph. Eur.), water content (KF), assay (HPLC), purity (HPLC), chiral purity (HPLC), related substances (HPLC), residual solvents (GC), polymorphic form (XRPD), particle size (laser diffraction), and microbial limits (Ph. Eur.). The specifications for potentially genotoxic impurities are well below the Threshold of Toxicological Concern (TTC) as established in the Guideline on the Limits of Genotoxic Impurities.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data (n=16, commercial scale) of the active substance from the proposed manufacturer were provided. Batch analysis data from two additional manufacturers used for manufacturing pre-clinical and clinical batches were provided as supporting information. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on 10 commercial scale batches of unmilled and 8 commercial scale batches of milled active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 24 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on 2 batches. Results of stress studies under acidic, alkaline, oxidation, photolysis, heat, and heat in solution conditions were also provided on one batch.

The following parameters were tested: appearance, identity (IR, chiral HPLC), loss on drying (Ph. Eur.), water content (KF), assay (HPLC), purity (HPLC), chiral purity (HPLC), related substances (HPLC), polymorphic form (XRPD), particle size (laser diffraction), and microbial limits (Ph. Eur.). The analytical methods used were the same as for release and were stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable when stored in the original package. All tested parameters were within the specifications. The stability results justify the proposed retest period in the proposed container.

2.4.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The proposed commercial finished product formulation of tasimelteon is Size 1, dark blue opaque, hard gelatin capsules printed with “VANDA 20 mg” in white, containing 20 mg of tasimelteon per capsule.

The aim of pharmaceutical development was to develop a stable immediate release solid dosage form for oral use, providing high bioavailability of the active substance. Tasimelteon is classified as highly soluble and highly permeable substance according to BCS classification system.

The key attributes of the active substance affecting finished product quality are compatibility of active substance with excipients, water content, solubility, permeability, particle size, agglomeration, polymorphism, and

stability. Dissolution is the main parameter that can influence the *in vivo* performance of the finished product. The discriminatory power of the dissolution method has been demonstrated.

Agglomeration of the active substance on storage has been noticed. The impact of agglomeration on the quality of the active substance has been investigated and the agglomerates have been found not to affect the crystal form or chemical stability of the active substance. However, the manufacturing process of the finished product includes controls to minimise agglomeration including a hold time of 12 weeks for the milled active substance. Specification limits for both active substance agglomerates and particle size of active substance, anhydrous lactose and microcrystalline cellulose have been set to ensure the quality of the finished product.

A screening study on the binary mixes of the active substance and excipients, stored at elevated temperature and humidity was performed. In summary, the active substance showed good compatibility with the excipients tested.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The formulation used during clinical studies is the same as that intended for marketing.

The primary packaging is HDPE bottle. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of six main steps: five mixing steps and encapsulation. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. It has been demonstrated that there is no interconversion of polymorphic form of active substance during the finished product manufacturing process. The in-process controls are adequate for this type of manufacturing process for hard capsules.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification (UV, HPLC), assay (HPLC), content uniformity (HPLC), related substances (HPLC), dissolution (HPLC), disintegration (Ph. Eur.), water content (KF), and microbial limits (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Batch analysis results are provided for 3 commercial scale batches used for the validation of manufacturing process. A number of additional supporting batch analysis results have been provided, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications through traditional final product release testing.

Stability of the product

Stability data of 3 commercial scale batches of finished product stored under long term conditions for 24 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay (HPLC), related substances (HPLC), dissolution (HPLC), disintegration (Ph. Eur.), water content (KF), and microbial limits (Ph. Eur.). The analytical procedures used are stability indicating. Stability results show that no significant changes of the physical or chemical characteristics have been observed in the tested batches.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

Due to sensitivity of the active substance to light, a storage precaution to store the finished product in the original container, keeping the bottle tightly closed in order to protect from moisture and light is included in section 6.4 of the SmPC.

In-use stability study data had been provided as the product is packaged in a multi-dose container, supporting proposed in-use shelf life for the proposed packaging.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.5. Non-clinical aspects

2.5.1. Introduction

The nonclinical pharmacology programme for tasimelteon consisted of pharmacodynamic studies; in vitro assays and in vivo and ex vivo studies in rat. Safety pharmacology studies were performed in vitro and in vivo to evaluate the potential cardiovascular effects of tasimelteon. Pharmacokinetic studies were performed to determine ADME and drug-drug interaction potential. The nonclinical toxicology programme consisted of 35 studies including acute and repeated dose studies, genotoxicity assays, carcinogenicity studies, and the evaluation of reproductive and developmental toxicity. Local tolerance and abuse liability studies were also conducted.

All pivotal toxicity studies and the majority of other studies were conducted in accordance with GLP.

2.5.2. Pharmacology

Primary pharmacodynamic studies

In radioligand binding studies tasimelteon showed potent inhibition of 2-[^{125}I]iodomelatonin binding at the MT1 and MT2 receptors, with a Ki of 0.35 nM and 0.17 nM, respectively. In a dose-response assay tasimelteon inhibited forskolin-stimulated cAMP accumulation with a pEC_{50} ~9 nM. In two separate screens, using 63 and 170 different targets at 10 and 100 µM, and 170 different receptors at 10 µM tasimelteon, there were no interactions identified as significant (50% inhibition at 10 µM). A number of receptors showed potential for binding with IC_{50} concentrations in the low nanomolar range. Given the expected clinical C_{MAX} is about 1 µM, and tasimelteon is highly protein bound, these secondary binding interactions do not appear to be clinically relevant. Overall the in vitro assays support the characterisation of tasimelteon as a potent, specific agonist at the MT1 and MT2 receptors.

The affinity and potency of the metabolites M3, M9, M11, M12, M13, and M14 were determined in a series of radioligand binding assays. Each metabolite showed some inhibitory response at the MT1 and MT2, although at least one order of magnitude lower than that of tasimelteon. Based on IC_{50} and K_i, the rank order of potency for human melatonin receptors MT1 and MT2 was tasimelteon followed by M13, M14, M11, M12 and M9, with consistent higher potency for the MT2 receptor. The data suggest that although there is a potential for pharmacological inhibition of the MT1/2 receptors by the circulating metabolites, significant interaction is not expected at clinically relevant concentrations. Binding assays for 163 non-related targets did not identify significant activity with any of the metabolites tested, and do not indicate a potential for clinically relevant interactions.

In an ex vivo study to evaluate the chronobiotic efficacy of tasimelteon, a dose of 5 mg/kg (s.c. injection) was shown to shift the peak of the suprachiasmatic nuclei (SCN) electrical activity rhythm of rats after 2 days in a reversed light-dark cycle, similarly to melatonin (1 mg/kg). A lower dose of tasimelteon (1 mg/kg) had no effect in this model.

Two independent in vivo studies showed also that, upon chronic administration (1.0 or 5.0 mg/kg s.c.) in rats showing "free running" circadian rhythms in constant darkness, tasimelteon was able to shift the onset of running-wheel activity (Study 52274), and was able to entrain it (Study 52273).

Secondary pharmacodynamic studies

Two studies were conducted to assess the vasoconstrictor properties of tasimelteon, and to compare them to that of melatonin, which has previously been shown to modulate vascular smooth muscle tone and in particular to induce vasoconstriction of rat caudal and cerebral arteries, and human coronary arteries.

Tasimelteon produced vasoconstrictive effects in isolated rat caudal artery, which was predicted based on the distribution of melatonin binding sites in the rat caudal arteries. Based on EC50 and Emax values, tasimelteon was less potent and efficacious than melatonin. In isolated rat anterior cerebral arteries, tasimelteon showed some vasoconstrictive effects, with less maximal constriction, roughly 500-fold less potently than melatonin. The studies were consistent with the known distribution of melatonin receptors in the vasculature, and the expected pharmacology of an MT receptor agonist. The findings also correlated with the observed increased mean arterial blood pressure seen in cardiovascular safety pharmacology studies in anaesthetised dogs.

Safety pharmacology programme

Specific studies were conducted to assess the effect of tasimelteon on the cardiovascular system but no dedicated central nervous system or respiratory system safety studies were conducted in animals.

The studies are summarised in Table 1 below.

Table 1: Summary of safety pharmacology studies with tasimelteon

Study/ Organ Systems Evaluated	**GLP**	**Species / Strain/number**	**Doses (mg/kg)**	**Noteworthy Findings**
070227.WBO Cardiovascular	Yes	Human Embryonic Kidney Cells	NA	The 100 µM concentration (highest soluble concentration tested) of tasimelteon which produces14% inhibition of the hERG current is almost 100 fold greater than the average C_{max} of the 20 mg/day therapeutic dose.
070228.WBO Cardiovascular	Yes	Rabbit (NZW) Cardiac Purkinje Fibers	Nominal 1, 10 and 100 µM	Tasimelteon does not prolong action potential repolarization in isolated rabbit Purkinje fibers.
52199 Cardiovascular	No	Anesthetized Beagle Dog 3 Male	Cumulative dose of 0.1, 0.3, 1.0 And 3.0 mg/kg IV. Each dose monitored for 30 min.	Tasimelteon produced a small decrease in MABP (14%) and HR (17%) at 3 mg/kg compared to vehicle response. A similar decrease in HR was observed in separate experiments involving repeated administration of vehicle alone in anesthetized dogs.

	Conscious Mongrel Dog 3 Male	Vehicle, tasimelteon (1 and 3 mg/kg), and melatonin (1 and 3 mg/kg) IV Hemodynamics recorded for 90 min.	There was no significant change in MABP or HR as compared to vehicle when tasimelteon or melatonin was administered. ECG analysis shows no effect on QRS width and QT or PR interval for either the tasimelteon or melatonin treated dogs as compared to vehicle.

Two in vitro studies were conducted to assess the effect of tasimelteon on the hERG potassium channel current in human embryonic kidney cells (Study 070227.WBO) and on action potentials in rabbit cardiac Purkinje fibres (Study 070228.WBO). Results show a lack of noteworthy inhibitory effect of tasimelteon on hERG potassium current and generally the absence of prolonged action potential repolarisation in isolated rabbit Purkinje fibres, at concentrations significantly higher than the average human maximum plasma concentration (Cmax = 238 ng/mL, Day 20 in clinical Study VP-VEC-162-1110) observed at the 20 mg/day therapeutic dose. Based on the reported human Cmax, changes in the action potential duration observed at the highest concentration tested of 100 µM (~24.5 µg/mL), equate to ~100 times higher than the average human Cmax.

Following intravenous administration, tasimelteon (3 mg/kg) was shown to produce a 14% reduction in mean arterial blood pressure (MABP) in anesthetised dogs. The applicant has determined that the human equivalent dose of 1.7 mg/kg is comparable to the 3 mg administered to dogs i.v. This dose corresponds to an oral dose of 267 mg hence would 16x higher than the proposed human oral dose of 20 mg daily. Therefore the in terms of clinical significance of the 14% reduction in MABP seen in dogs; an adequate human safety margin can be applied. This is supported further by the reported absence of reported fluctuations in blood pressure outside of the normal range in the clinic thus far.

In conscious dogs, there were no change ($p > 0.05$) from the vehicle response in MABP or HR for either tasimelteon or the melatonin treated dogs. ECG analysis showed no effect on QRS width, PR or QT interval for any treatment group as compared to the vehicle group

Pharmacodynamic drug interactions

No specific animal studies have been undertaken to assess potential pharmacodynamics drug interaction. However since tasimelteon demonstrated full agonist activity at both receptors MT1 and MT2 and no appreciable affinity for over 160 other pharmacologically relevant receptors, the CHMP accepted the absence of further studies.

2.5.3. Pharmacokinetics

The pharmacokinetics of tasimelteon was investigated in vitro and in vivo studies with mice (CD-1), rats (Sprague-Dawley (SD) and Long Evans), rabbits (New Zealand white (NZW)), and monkeys (cynomolgus). Seven single dose pharmacokinetic studies were performed in rats and monkeys, and four repeat-dose pharmacokinetic studies were conducted in mice, rats and rabbits. The metabolites of tasimelteon were determined in vitro and in vivo. A tissue distribution study was performed in rats by using [14C]-tasimelteon.

Following single dose oral administration of tasimelteon in rats and monkeys, absorption was generally rapid, with maximal plasma concentration reached within 1-2 hours. Oral bioavailability was estimated at 92.8%, 58.5% and 100% (in rats) and 11.7 ± 8.2% in monkeys. After a single i.v. dose to rats, plasma drug concentrations exhibited a monoexponential decline with an elimination half-life of 0.24 hour; the plasma AUC value was 1.84 mg•h/L; and the values of clearance and apparent volume of distribution (steady state) were 45.2 mL/min•kg and 0.99 L/kg, respectively. The mean brain/plasma concentration ratio was 0.9 at 20 minutes. Dose proportional increases in AUC and Cmax were reported in mice given oral doses of active (100 to 600 mg/kg). The levels of both parameters on Day 1 were approximately 2 to 4 times greater than those on Day 29, suggesting that possible hepatic enzyme induction may have occurred. Exposure increased non-proportionally in rats (including pregnant rats). Plasma drug concentrations in females were generally greater than those in the males. Tasimelteon was moderately bound to proteins in human and animal serum and the binding was concentration dependent.

Drug-related radioactivity was shown to be widely distributed to tissues in rats following a single dose. The highest drug concentrations were observed in the plasma, liver, kidneys, and gastrointestinal system. The long half-life of radioactivity in the eyes (126 hours) and longer half-life in pigmented skin (15.4 hours) versus non-pigmented skin (7.6 hours) suggest binding of [^{14}C]-tasimelteon associated activity to melanin.

Metabolic products in human were similar to those in monkey, including 8 metabolites (H1 to H8); except for H2, a minor metabolite, all other metabolites were also found in the mice and rats. The most abundant metabolites in vivo were M9, M12, and M13, and the other main metabolites were M3, M11, and M14. M9 was identified as a phenol-carboxylic acid derivative of tasimelteon. M11 was proposed to be hydroxy-phenol tasimelteon and M8 was identified as a glucuronide of M11. M12 and M14 were determined as α and β-isomers of 7-hydroxy tasimelteon. M13 was identified as 8-hydroxy tasimelteon and M1 was identified as 8-O-glucuronide of tasimelteon. Glucuronidation was the major phase II metabolic route.

The extent and route of excretion was determined in rats and monkeys. In both species, elimination of drug related material was predominantly in the urine (57% - 75% and 79% - 83% in rats and monkey, respectively). Faecal elimination was greater in rats (~21% - 24%) than monkeys (3% - 4%). In both species elimination of tasimelteon was rapid, with over 90% of radioactivity recovered in rats and 86% 89% in monkeys, 24 hours after oral administration. Elimination was near complete in rats and monkeys by 72 and 168 hours, respectively.

The excretion of tasimelteon into milk has not been investigated. CHMP has accepted the absence of such data and an adequate warning was included in the SmPC.

Pharmacokinetic drug interaction

The potential of drug interaction with tasimelteon or with its metabolites was investigated in eight in vitro studies of human enzymes and transporters; an ex vivo study was also conducted to evaluate tasimelteon as an inducer of liver microsomal cytochrome P450 and UDP glucuronosyltransferase expression in rats. No in vivo studies were conducted. Results indicated that a low potential for inhibition of human CYP enzymes at the therapeutic dose. However, Tasimelteon appears to be an inducer of multiple CYP450 enzymes in rats and CYP3A4/5 and CYP2C8 in humans. No induction potential by the parent or major metabolites M9. M12 and M13 of CYP1A2 and CYP 2B6 enzymes was apparent. Furthermore there appears to be no interaction potential with the uptake transporters OATP1B1, OATP1B3, OCT2, OAT1, and OAT3 or interactions at concentrations at least 6 times higher than the average human maximum plasma concentration at the 20 mg therapeutic dose suggesting little or no likelihood of in vivo inhibition. Tasimelteon and its metabolites do not appear to be substrates for P-gp, OATP1B1 or OATP1B3 transporters nor do they appear to inhibit the Breast Cancer Resistance Protein (BCRP), the Bile Salt Export Pump (BSEP), or P-gp.

2.5.4. Toxicology

Single dose toxicity

In an acute study in mice, one male administered 1750 mg/kg died following a number of clinical signs of toxicity. The 1750 mg/kg dose also was associated with tonic convulsions, hypoactivity, inappropriate locomotion, and ataxia shortly after dosing. In two rat studies, the highest doses of 400 and 1750 mg/kg did not cause mortality. Clinical signs included ptosis at ≥ 400 mg/kg, and ataxia, impaired respiration and loss of righting reflex at 1750 mg/kg. In a non-GLP compliant dose range finding study in cynomolgus monkeys no mortality was seen up to the highest dose of 200 mg/kg. Clinical signs of salivation were seen in males ≥ 50 mg/kg, and emesis was seen in one female at 100 and 150 mg/kg. In all species, doses which produced clinical signs generally caused minimal decreases in food consumption and/or body weight gain. Overall, clinical signs were limited to highly supratherapeutic doses and the studies do not indicate tasimelteon to cause acute systemic toxicity.

Repeat dose toxicity

Table below shows major findings observed in repeat-dose toxicology studies.

Table 2: Summary of repeat-dose studies performed with tasimelteon.

Study ID	Species /Sex/No /Group	Dose/Route (mg/kg/day)	Duration	NOAEL (mg/kg/day)	Major findings
Non-Pivotal Studies					
98352 **GLP**	CD-1 mice 10 M/F TK: 18 M/F	25, 100, 400, 800 (↓ to 600 on Day 2) Oral	13 weeks	100	Mortality in 9 mice at 800 mg/kg (2 test, 9 TK) Clinical signs: Labored breathing, prostration at ≥ 400 mg/kg Clinical pathology: Minimal ↑ total protein and albumin, males at ≥ 400 mg/kg Necropsy: Dose related ↑ liver weights at ≥ 400 mg/kg Histopathology: Hepatocellular hypertrophy at ≥ 400 mg/kg TK: Greater than proportional increase in systemic exposures (AUC). No gender differences. NOEL C_{max} 3,303/2,011 ng/mL in M/F NOEL AUC 26,892/32,698 ng/mL in M/F
97306 **Non-GLP**	SD rat 5 M/F	0, 50, 100, 200, 400	2 weeks	50	No mortality/clinical signs Cholesterol at ≥ 100 mg/kg, ↑ serum glucose, triglycerides at ≥ 200 mg/kg; ↑ total protein, globulins and ↓ albumin/globulin ratio, ↑ calcium, ↓ sodium at 400 mg/kg

					Necropsy: ↑ liver weights at ≥ 100 mg/kg, ↑ liver size at ≥ 200 mg/kg Histopathology: Hepatocellular hypertrophy at ≥ 100 mg/kg; ↑ hepatocellular mitoses at 400 mg/kg, hyaline droplet accumulation proximal renal tubules (M) at ≥ 100 mg/kg, TK: Exposure at each dose was verified NOEL AUC 1,178/4,083 ng/mL in M/F
97326 **GLP**	Cyn monkey 1 M/F	0, 25, 50, 100, 175	1 week	50	Mortality: None Clinical signs: Emesis, salivation, ↓ FC, BW loss at 175 mg/kg Clinical pathology: ↓ serum chloride, ↑ glucose, ↑ alanine aminotransferase at ≥ 100 mg/kg; ↑ triglycerides, ↓ phosphorus, ↓ sodium, ↑ fibrinogen at 175 mg/kg
TAJ0014 **GLP**	SD rat 3 M/F	25, 100, 250, 500 Oral	4 weeks	N/A	Mortality: none Clinical signs: at 500 mg/kg: underactivity, coolness to touch, partially closed eyelids and unsteady gait in both sexes with irregular breathing, piloerection, abnormal gait and uncoordinated unsteady gait also seen in one female TK: systemic exposures to tasimelteon and metabolites M3, M9, M12, M13, and M14 identified in males and females with no evidence of accumulation of parent or metabolites except M9 and M13 at the highest dose
Pivotal Studies					
97331-52295 **GLP**	SD rat 15 M/F	0, 25, 100, 400 Oral gavage (100% PEG 400)	1 month	25	Mortality: 1 400 mg/day F euthanized; Moribund, signs of dehydration Clinical signs: hypoactivity, ptosis, ↓ food consumption in 400 mg/kg F Clin Chemistry: ↑ riticulocytes in F, ↑ absolute neutrophils in M at 400 mg/kg. ↑ cholesterol ≥ 25 mg/kg (F); ↑ triglycerides ≥ 100 mg/kg (F); ↑ total protein, albumin, globulins, ALT, calcium, potassium, ↓ urea nitrogen and creatinine, ↑ urine volume, ↓ urine specific gravity in M and/or F at 400 mg/kg Necropsy: ↑ liver weight and/or size at ≥ 100 mg/kg; ↑ kidney weight (M), adrenal and heart weights (F) at 400 mg/kg Histopathology: Hepatocellular hypertrophy at ≥ 100 mg/kg; increased severity hyaline droplets in renal tubules

					(M) at ≥ 100 mg/kg. All findings reversed except partially reversed cholesterol at ≤ 100 mg/kg and the hyaline droplet change TK: systemic exposures dose proportional; female exposures greater than males (1.5 – 4 fold); exposures decreased with repeat dosing NOEL C_{max} 843/3606 ng/mL in M/F NOEL AUC 2468/10196 ng/mL in M/F
TAJ0007	SD rat 20 M/F	0, 5, 50, 500 Oral	26 weeks	5	Mortality: 1 F, Day 3 given 500 mg/kg Clinical signs: at 500 mg/kg; Convulsions, hypoactivity, laboured respiration, ataxia, loss of righting reflex, extension of the limbs, recumbency, tremors; more severe in females. ↓ weight gain in males overall; ↑ weight gain in females at 500 mg/kg Clinical pathology: 500 and 50 mg/kg: ↓ RBC indices, ↑ neutrophils/WBCs; ↑ platelets, effects on coagulation parameters; changes in liver and kidney serum chemistry; ↑ triglycerides, cholesterol, and glucose; ↓ sodium and chloride, ↑ calcium; ↑ total protein from ↑ albumin and globulins; ↑ urine volume and protein, ↓ specific gravity Necropsy: large livers and increased liver weights at 500 and 50 mg/kg. ↑ kidney, heart, adrenal, and spleen weights mainly at 500 mg/kg Histopathology: 500 or 50 mg/kg. Centrilobular hepatocellular hypertrophy, increased incidence and/or severity of chronic progressive nephropathy in males and females, increased hemosiderosis and extramedullary hematopoiesis in females TK: systemic exposure increased in dose-related manner and greater in females. Exposures decreased with repeated dosing at 50 and 500 mg/kg NOEL C_{max} 304/805 ng/mL in M/F NOEL AUC 670/1458 ng/mL in M/F
97655	Cynomolgus Macaque 3 M/F	0, 15, 45, 125 Nasogastric intubation	1 month	15	Mortality: none Clinical signs: none Clinical pathology: none Necropsy: ↑ liver size at 125 mg/kg; ↑liver weights at ≥ 45 mg/kg; ↓ spleen weight at 125 mg/kg Histopathology: none

					TK: systemic exposures [AUC (TAU)] increased in a greater than dose proportional manner. Generally greater exposures in males (1.2 to 1.9 fold)
057-005 (98353)	Cynomolgus Macaque 7 M/F	0, 3, 20, 150 Nasogastric intubation	1 year	N/A	Mortality: none compound related Clinical signs: ↓ appetite and ↑salivation at ≥ 20 mg/kg; ↓ BW gain, ↓ activity, ↑ emesis, and convulsions at 150 mg/kg. One male prostration, ataxia at 3 mg/kg Clinical pathology: ↓ erythron mass parameters, ↑ ALT, GGT at 150 mg/kg Necropsy: ↑ liver size and weights at 150 mg/kg Histopathology: possible ↓ in ovarian CLs at 150 mg/kg TK: dose-related greater than proportional systemic exposures, no gender differences, decreased exposures with multiple doses

In summary clinical signs seen across species, generally at exposures many times those achieved at the anticipated therapeutic dose, included laboured breathing, prostration, hypoactivity, ataxia, ptosis, tremors, and convulsions. Food consumption and appetite were decreased in some studies with decreased body weight gains, although body weight gains were increased in female rats given 500 mg/kg of tasimelteon for 6 months. Clinical pathology parameters affected included decreases in erythron parameters and slight changes in liver and kidney serum chemistry in rats and monkeys. In rats there were also increases in neutrophils, WBCs, reticulocytes, platelets; changes in coagulation parameters; increases in cholesterol, triglycerides, and glucose; changes in serum electrolytes; and increased urine volume with decreases in urine specific gravity. The spleen was a target organ in rodents, with increased spleen weight correlating with incidence and severity of hemosiderosis and extramedullary hematopoiesis. The CHMP considered the splenic findings to be a compensatory effect secondary to the altered haematology parameters, and given adequate safety margins and the absence of clinical correlation, they were not considered a relevant clinical risk.

Increased liver size and weights were common pathology findings in both non-clinical species used in the pivotal general toxicity repeat-dose studies (rats and monkeys), which was correlated with hepatocellular hypertrophy in the rat. In rats there was also a treatment-related increased incidence and/or severity of chronic progressive nephropathy. The CPN is known to be a common incidence in rats which is increased following chemical exposure and the safety margins from the human are sufficient (23-fold). The CHMP agreed with the Applicant that as the pathogenesis of CPN in rats is distinct from human nephropathy, the findings are not considered predictive of human toxicity.

Genotoxicity

Submitted genotoxicity studies are summarised in the table below.

Table 3: Genotoxicity studies with tasimelteon and the metabolite M11

Type of test/study ID/GLP	**Test system**	**Concentrations/ Concentration range/ Metabolising system**	**Results Positive/negative/equivocal**
Gene mutations in bacteria (study 96742 **Non-GLP**)	Salmonella strains TA98, TA100	1 – 5,000 µg/plate +/- S9	Negative +/- S9 in TA100 Positive – S9 in TA98 Negative following re-te4st
Gene mutations in bacteria (study 97679 **GLP**)	Salmonella strains TA98, TA100, TA1535, TA1537 Escherichia coli strain WP2 uvrA	312.5 – 5,000 µg/plate +/- S9	Negative +/- S9 Cytoxotoxicity demonstrated at 5000 µg/plate
Chromosomal aberrations in vitro (Study 97680 **GLP**)	Cultured human lymphocytes	24 h: 25 - 200 µg/mL -S9 5 h: 100 – 800 µg/ml + S9	No ↑ chromosome aberration under any condition. Dose-dependent ↓ in mitotic indices 45% at 200 µg/mL +S9, 24% at 800 µg/mL – S9
Chromosomal aberrations in vivo (97331-52270 **GLP**)	Mouse, micronuclei in bone marrow	25, 100, 400 mg/kg/day oral gavage	No significant increase in MN-PCEs No positive control
Gene mutations in bacteria with metabolite M11 (study UNN0003 **GLP**)	Salmonella strains TA98, TA100, TA1535, TA1537 Escherichia coli strain WP2 uvrA	8 – 5,000 µg/plate +/- S9 TA1537 (1.6 – 5000 µg/plate)	Negative +/- S9 in pre-incubation and incorporation assays
Gene mutations with metabolite M11 in mammalian cells (UNN0004 **GLP)**	CHO-cells, HGPRT-locus	Up to 1,800 µg/mL+ S9 1,500 µg/mL - S9	+S9: ↑ chromosome aberrations at ≥ 1,500 µg/mL ↑ polyploidy ≥ 50 µg/mL -S9: Negative for chromosome aberrations ↑ polyploidy

In vitro studies concluded that tasimelteon was not mutagenic or clastogenic (Study 96742; Study 97679; Study 97680). M11 had no mutagenic potential in a bacterial reverse mutation assay (Study UNN0003), and was equivocally clastogenic at high concentrations in the presence of S-9 mix in an in vitro cytogenetic test (Study UNN0004).

In vivo tasimelteon was not genotoxic to rat bone marrow cells at doses of up to 400 mg/kg administered for one month (Study 97331-52295). Toxicokinetic evaluation was performed in this study confirming adequate drug exposure at multiples of the expected human exposure at the proposed therapeutic dose.

Carcinogenicity

Two 24-month carcinogenicity studies were conducted to evaluate the potential carcinogenicity of orally administered tasimelteon in mice and rats. The design and major findings of each study are described in table 4.

Table 4: Summary of carcinogenicity studies with tasimelteon

Study ID /GLP	Species/No.	Dose (mg/kg)	AUC Week 26 (Ng.h/ml)	Major findings
TAJ0002 **GLP**	CD-1 Mouse 66/sex/ group	30 100 300	6,500/5,850 22,100/16,400 88,300/61,400	No treatment-related neoplastic findings Non-neoplastic: ↑ hepatocyte hypertrophy ≥100 mg/kg M, 300 mg/kg F NOAEL 100 mg/kg
TAJ0001 **GLP**	SD rats 65/sex/ group	20 100 250	6,520/9,900 38,800/42,000 52,500/101,000	Neoplastic: Dose-related ↑ hepatocellular adenoma Isolated hepatocellular carcinoma 100 mg/kg M ↑ endometrial adenocarcinoma and squamous cell carcinoma in uterus at 250 mg/kg Non-neoplastic: Centrilobular hepatocyte hypertrophy ≥20mg/kg Bile duct hyperplasia ≥ 100 mg/kg Regenerative hyperplasia, cystic degeneration, Centrilobular hepatocyte vacuolation in M ≥100 mg/kg Pigment in hepatocytes and ↓ incidence of basophilic foci in F >+ 100 mg/kg Renal cortical tubular pigments in all F ↑ Ovarian cysts ≥ 100 mg/kg, ↑ epithelial hyperplasia/keratinisation at 250 mg/kg NOAEL 20 mg/kg

Two-year carcinogenicity studies showed that tasimelteon was not associated with tumour development in mice. In rats there was a treatment related increase in hepatocellular adenoma, which was significant in males at 250 mg/kg and females at ≥100 mg/kg. Additional non-neoplastic liver findings included centrilobular hypertrophy at ≥100 mg/kg, regenerative hyperplasia, cystic degeneration in males at ≥100 mg/kg, and bile duct hyperplasia, hepatocyte pigmentation and basophilic foci in females at ≥ 100 mg/kg. The NOEL for hepatocellular adenoma was 20 mg/kg, which provides a 17 fold margin of safety at the proposed clinical dose to 20 mg/day. Given that tasimelteon was shown to be a phenobarbitol-type inducer of CYP2B1/2 in rats in vivo, and in the absence of genotoxic effects, the tumourigenic effects are consistent with rodent-specific tumourigenicity secondary to hepatic enzyme induction.

At 250 mg/kg there were increased incidences of uterine tumours (endometrial adenocarcinoma and squamous cell carcinoma) and other non-neoplastic female reproductive tract changes which suggested a species-specific effect of unknown etiology in aging female rats, as similar findings were not seen in the associated mouse carcinogenicity study (Study TAJ0002).

Reproduction Toxicity

A summary of the pivotal reproductive toxicity studies submitted, including relevant findings, is provided in the table below.

Table 5: Summary of reproductive and developmental toxicity studies in rats and rabbits.

Study type/ Study ID / GLP	Species; No/sex/ group	Route & dose (mg/kg)	Dosing period	NOAEL (mg/kg)	Major findings
Fertility and EED study **TAJ0008 (99009) GLP**	SD rats 25/sex/ group	0, 5, 50, 500 Oral	M: 4 weeks pre-mate F: 2 weeks pre-mate, 7 days post mate	Male Fertility: 500 Female fertility: 50 F1: 500	Mortality: 3F at 500 mg/kg w/ clinical signs of lethargy, dehydrated skin, changes in faecal output. 4M and 2F euthanized, attributed to intubation. Clinical Signs: perioral and/or periocular substances and coat changes due to lack of grooming, ↓ BWG at 500 mg/kg Fertility parameters: ↑ extended estrous phases and irregular cycles at ≥ 50 mg/kg. Mating performance unaffected; ↓ female fertility when treated males were paired with treated females at ≥ 50 mg/kg. No effects on the numbers of corpora lutea, litter size and embryo-fetal viability.
Dose-range finding Embryo-fœtal development study **98046**	SD rat 8F	0, 62.5, 125, 250, 500 Oral gavage	GD6-15	Fetal: 500 Maternal: N/A	Mortality: None Clinical Signs: Brown perinasal substance and soft and/or reduced faeces at 500 mg/kg. Mild to moderate ↓ in maternal body weight gain at ≥125 mg/kg and in food consumption in dams given 500 mg/kg. Maternal and litter observations at Cesarean-Sectioning: None Fetal observations: None Necropsy: None
Pivotal Embryo-fœtal development study **99005 GLP**	SD rat 22F	0, 5, 50, 500 mg/kg	GD6-15	Fetal: 500 Maternal: 50	Mortality: 1F at 500 mg/kg euthanized with perioral and/or periocular substances reduced and/or soft faeces; poorly groomed hair coat. Clinical signs: perioral and/or periocular substances, reduced faeces, poor grooming, ↓ motor activity, and ataxia, ↓ BW/BWG, FC at 500 mg/kg Necropsy: No gross necropsy findings; all 13 *in utero* embryos present appeared normal.
Dose-range finding Embryo-fœtal development study **98052**	NZ White Rabbit 6F	0, 37.5, 75, 150, 300	GD7-19	Fetal: 150 Maternal: 75	Mortality: None Clinical Signs: ↓ in maternal body weight gain at 300 mg/kg and in food consumption at ≥150 mg/kg. Maternal and litter observations at Cesarian-Sectioning: Mild ↓ in mean fetal body weight at 300 mg/kg. Fetal observations: None Necropsy: None
Pivotal Embryo-fœtal development study **99001**	NZ White Rabbit 20F	0, 5, 30, 200 Oral Gavage	GD7-19	Fetal: 30 Maternal: 30	Mortality: None Clinical Signs: ↑ abortions at 200 mg/kg. Soft/reduced/absent faeces at 200 mg/kg ↓ BWG and FC at 200 mg/kg Maternal observations: decr BWG and food consumpt at 200 mg/kg

					Fetal observations: ↓ fetal BW at 200 mg/kg. ↑ incompletely ossified pubes.
Supplementary PK study **Study TAJ0016** **GLP**	NZ White Rabbit 4F	200 mg/kg Oral gavage	GD6-19	N/A	Cmax and AUC_8 in pregnant females lower on GD19 than those values after a single dose. The mean accumulation ratio, was 0.42, indicating that no accumulation occurred. Extent of systemic exposure to metabolite M11 were similar on GD19 to values after a single dose. M11 AUC at GD19 1,470 ng.h/mL (10 fold clinical AUC)
Dose-range finding peri & postnatal development study **TAJ0015** **GLP**	SD rat 6F	0, 50, 150, 450 Oral gavage	D6 post mating to D10 lactation		Mortality: None Clinical Signs: At 450 mg/kg: Underactivity, unsteady, partially closed eyelids; ↓ FC and BWG days 6-14; marginally longer gestation length; ↓ mean bodyweights and body weight gain in male and female offspring. At 150 mg/kg: underactivity; ↓ FC; slight decrease bodyweights male and female offspring. Clinical Pathology: None Necropsy: None
Pivotal peri & postnatal development study **Study TAJ0017** **GLP**	SD rat 22F	0, 50, 150, 450 Oral gavage	D6 post mating to D20 lactation	F0 Fem: 150 F1 Males: 150 F1 Fem: 150	Mortality: No F0 deaths Clinical Signs: ↓ activity and unsteady gait ≥ 150 mg/kg/day, partially closed eyelids at 450 mg/kg. 1F at 450 mg/kg has convulsion on lactation D15. ↓ BWG and FC at 450 mg/kg from GD6-20, and at 150 mg/kg from GD6-10. F1: ↑ gestation length ≥ 50 mg/kg ↑ birth weight and growth to weaning, Lower growth and longer righting reflex at 450 mg/kg ↓ BW at all doses. F1 males showed learning defecit at day 32, at 450 mg/kg No effect on fertility/litter size for F1. No macroscopic findings.

BW: Body weight; BWG: Body weight gain; FC: Food consumption

Reproductive and developmental toxicity studies showed that oestrous cycles were prolonged in rats treated with high doses of tasimelteon, with no effect on mating performance or male fertility, with only a marginal effect on female fertility. Tasimelteon administration was not associated with malformations and did not cause selective embryo-fetal toxicity in rats or in rabbits. Offspring of female rats treated with high doses of tasimelteon had a birth weight marginally low and bodyweight significantly low by weaning; in these animals the mean age of achievement of surface righting and air righting was slightly higher, and these animals were significantly lighter than controls and showed minor changes in the timing of sexual development but with no effect on fertility. Taken together, these results indicate that overall tasimelteon had limited effects on reproductive function and embryo/fetal development at clinically relevant exposures. These results and precautions for use in pregnant and breast-feeding women have been reflected in appropriate sections of the SmPC.

Toxicokinetic data

The results of the toxicokinetic evaluation of tasimelteon and its major human metabolites in the oral repeated dose toxicity studies conducted in the rat and monkey are presented in the tables below.

Table 6: Exposure in pivotal repeat-dose toxicity studies

Study ID	Daily Dose (mg/kg)	C_{max} (ng/mL)		Animal AUC (ng.h/ml)		Animal:Human AUC Exposure Multiple	
		♂	♀	♂	♀	♀	♀
4 week rat study 97331-52295	**25**	**843**	**3,606**	**2,468**	**10,196**	**6**	**28**
	100	1,755	6,730	10,085	44,807	27	123
	400	5,291	11,628	35,345	137,835	97	379
6 month rat study TAJ000798348	**5**	**304**	**805**	**670**	**1,458**	**2**	**4**
	50	2,603	10,053	8,435	34,176	23	94
	500	7,577	16,761	70,085	158,164	193	436
1 month monkey study 97655	**15**	**3,210**	**2,038**	**5,968**	**3,504**	**16**	**10**
	45	5,906	7,038	19,759	21,630	54	60
	125	22,240	13,812	101,040	86,509	278	238
12 month monkey study 057-005 98353	**3**	**181**	**222**	**384**	**352**	**1**	**1**
	20	2,886	2,619	12,792	6,281	35	17
	150	17,164	20,258	145,199	139,243	400	384

NOAEL dose in bold

Table 7: Estimated metabolite levels in rats estimated from metabolite/tasimelteon AUC ratios in Study TAJ0014

Dose		Tasimelteon	M9 ratio	M9	M12 ratio	M12	M13 ratio	M13	M3 ratio	M3
1 rat month study										
25 mg/kg	M	2,468	0.25	617	2.14	5,282	0.03	74	0.29	716
	F	10,196	0.28	2,855	4.21	42,925	0.01	102	0.25	2,549
100 mg/kg	M	10,085	0.32	3,227	2.51	25,313	0.03	303	0.58	5,849
	F	44,807	0.12	5,377	2.45	109,777	0.02	896	0.26	11,650
400 mg/kg	M	35,345	0.29	10,250	2.02	71,397	0.06	2,121	0.78	27,569
	F	137,835	0.16	22,054	1.75	241,211	0.03	4,135	0.64	88,214
6 month rat study										
50 mg/kg	M	8,435	0.30	2,531	2.40	20,244	0.03	253	0.78	6,579
	F	34,176	0.14	4,785	2.60	88,858	0.02	684	0.39	13,329
500 mg/kg	M	70,085	0.27	18,923	1.92	134,563	0.06	4,205	0.75	52,564
	F	158,164	0.16	25,306	1.70	268,879	0.04	6,327	0.67	105,970

Toxicokinetics groups were analyzed in all pivotal repeat-dose studies. Tasimelteon was measurable at all doses throughout the study period, and safety margins are calculated based on AUC values determined in a clinical pharmacology study.

Given that tasimelteon treatment in rodents results in enzyme hepatic induction, there is a potential for alterations in the metabolite profile in long term studies. Therefore, the CHMP asked the Applicant to justify the absence of toxicokinetic analysis of metabolites in the pivotal toxicity studies. To address the absent data, a specific 4 week pharmacokinetic study was performed, and these data were used to extrapolate exposure levels in the chronic studies. The treatment doses chosen for the study are sufficient to cover the doses used in the long-term studies. The Applicant considered the metabolite profile at 4 weeks to be representative of the long term studies because decreased tasimelteon exposure seen at 28 days indicated hepatic induction has already occurred at this point, accumulation was minimal at 28 days and levels of parent drug were similar at weeks 4 and week 26, indicating steady state was reached by 4 weeks.

The data indicate that levels of parent drug are consistent at the end of the 4 week PK study and the chronic toxicity studies. The data do not provide direct evidence that the profile of metabolites, and the relative fraction of each metabolite, is equivalent at the end of the chronic study. However, the CHMP agreed that it is reasonable to assume that if significantly increased activity of enzymes involved in tasimelteon metabolism were to occur in the long term studies, this would be reflected by decreased levels of circulating parent drug. Moreover, since the safety margins for the majority of metabolites is large, the NOAEL doses would allow for small changes in the metabolite profile without posing a safety concern. Therefore the CHMP agreed that the absence of TK data for the metabolites of tasimelteon in the long term studies is acceptable.

Local Tolerance

Two studies were conducted to evaluate the local tolerance of tasimelteon. In a bovine corneal opacity and permeability assay (Study 99AB38.350); tasimelteon was classified as a mild irritant. In a skin sensitisation assay using guinea pigs (Study BMY 378/993273/SS), tasimelteon showed no evidence of inducing skin sensitivity.

Phototoxicity

A study was conducted to determine the molar extinction coefficient for tasimelteon and its main metabolites (Study VCR-TMI-121012). No other specific non-clinical photosafety testing was conducted.

A spectroscopic scan between 290 and 700 nm has demonstrated that tasimelteon absorbs light at 290 nm which would trigger the need for specific photoxicity testing in accordance with ICH guidance. However, tasimelteon was also shown to have a Molar Extinction Coefficient (MEC) of 689.41 L/mol/cm (Study VCR-TMI-121012). Molecules with an MEC less than 1000 L mol-1 cm-1 are deemed less of a photosafety risk since this low level of light absorption is unlikely to prove harmful

Metabolites M3, M12 and M14 were reported to have MEC values that exceeded 1,000 L/mol/cm at the absorption wavelength of 290 nm. In the single dose distribution study (Study 178/214778/003) a long half-life of radioactivity in the eyes (126 hours) and longer half-life in pigmented skin (15.4 hours) versus non-pigmented skin (7.6 hours) was reported (suggesting binding of [14C]-tasimelteon associated activity to melanin).

In the absence of specific phototoxicity studies with the metabolites, the Applicant has conducted further analyses and data reviews to assess this potential risk. However, the non-clinical concern regarding the phototoxic potential of tasimelteon and its metabolites M3, M12 and M14 was not regarded resolved by the CHMP. To avoid the need for protective measures during therapeutic use of tasimelteon the phototoxic potential of tasimelteon and its metabolites the CHMP has recommended that this concern will be investigated as a Post-approval measure (PAM).

Other toxicity studies

Dependency

The dependence studies do not indicate that tasimelteon has stimulus effects similar to the midazolam training cue in a drug discrimination study (Study 8260770), nor did self-administered tasimelteon act as a reinforcer similar to midazolam (Study 8260771). With extrapolation from oral and i.v. toxicokinetics studies in rats, the exposures achieved for tasimelteon and most metabolites in the abuse liability studies were at parity or multiples of the exposures anticipated in humans at the therapeutic dose. These results indicate a lack of potential for abuse liability, consistent with the selective receptor binding profile of tasimelteon.

2.5.5. Ecotoxicity/environmental risk assessment

The applicant has submitted an ERA based on the EMEA/CHMP/SWP/4447/00 guideline. Tasimelteon PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Therefore tasimelteon is not expected to pose a risk to the environment.

The log Kow value was determined in a study, which was in line with OECD 107, by the flask shake method.

Based on the data presented below, both Log Kow and PEC values indicate that bioaccumulation in the food of aquatic organisms is unlikely, and that the use of tasimelteon is well below the PEC risk threshold value. Therefore, the CHMP was of the opinion that the use of tasimelteon for the treatment of Non-24 in totally blind persons is unlikely to have a significant impact on the environment and no Phase II Environmental Fate and Effects Analyses are warranted.

Table 8 Summary of main study results

Substance (INN/Invented Name): tasimelteon			
CAS-number (if available): 609799-22-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	2.44	Potential PBT N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.44	not B
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)		µg/L	> 0.01 threshold N
Other concerns (e.g. chemical			None

class)			

2.5.6. Discussion on non-clinical aspects

Nonclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Results from a series of in vitro and in vivo pharmacology studies support the rationale for the development of tasimelteon for the proposed indication due to the highly specific receptor interaction with only human MT1 and MT2 and chronobiotic effects demonstrated ex vivo and in vivo.

The potential for hERG inhibition by the major metabolites of tasimelteon has not been investigated. The applicant explained that there was no appreciable affinity for the hERG ion channel by the major metabolites. The CHMP agreed that the absence of affinity for this channel in vitro supports the decision to not conduct specific studies. Further reassurance was provided by in vivo animal and human data. In particular, there was a lack of electrocardiographic findings in the One-Year Oral Toxicity Study in monkeys, where toxicokinetic analyses demonstrated significant clinical safety margins at the highest dose tested for human metabolites M9, M12, and M13. Furthermore there has been no significant cardiac safety signals in the clinical programme; including the thorough QTc study where dose levels up to 300 mg have been administered allowing exposure levels of major metabolites up to 15x the Cmax levels expected at the proposed therapeutic dose.

The absence of a GLP-compliant in vivo cardiovascular safety study in line with ICH 7A was justified by the fact that this study was performed prior to the publication of ICH 7A, and was therefore in line with regulatory requirements at the time. Although the study was not GLP-compliant, the CHMP was of the opinion that the study was performed adequately and the conclusions of the study are reliable.

With the exception of studies on the cardiovascular system, no other specific non-clinical safety pharmacology studies were conducted. To justify the absence of respiratory and CNS safety pharmacology studies, the applicant has outlined the clinical safety profile with respect to both organ systems. In 23 clinical studies there were no adverse respiratory events. CNS effects have been established clinically following treatment in ~1000 patients for CNS indications. Effects included psychomotor effects, suicidality, dizziness and withdrawal symptoms. Given the well-established clinical safety profile in respiratory and CNS systems, the CHMP has agreed that further non-clinical safety studies would not significantly add to the safety information for tasimelteon, and their absence was acceptable.

In the absence of specific phototoxicity studies with the metabolites, the Applicant has conducted further analyses and data reviews to assess this potential risk. However, the non-clinical concern regarding the phototoxic potential of tasimelteon and its metabolites M3, M12 and M14 is not regarded resolved by the CHMP for the following reasons:

1.) The Applicant attributes the long half-life of tasimelteon, which was determined in the eyes and skin of rats after single drug administration (mass-balance study 178/214778/003), to an incorrect overestimation due to the limited animal numbers. The Applicant disregarded the possibility that low animal numbers might even lead to an underestimation of the actual half-life. In fact, the unchanged concentration of tasimelteon at the 72 h and 168 h time points indicates drug accumulation and the limited data set does not allow to conclude, if accumulation of tasimelteon is 2.5-fold, 8-fold or even higher. Hence, it remains the responsibility of the Applicant to clarify these equivocal results by an adequately performed repeated-dose pharmacokinetic study as noted earlier in this procedure and in the current OC by reference to the pertinent ICH S3B requirements (CPMP/ICH/385/95).

2.) The assumption of the Applicant that the ratio of tasimelteon and its metabolites, which was determined after repeated administration in plasma, will remain the same in tissues is purely hypothetical and not substantiated by appropriate experimental data. Consequently, this hypothesis is rejected for the human risk assessment and drug accumulation in eyes and skin must be expected.

3.) The absence of adverse ocular and skin events in long-term repeated-dose toxicity studies is not reassuring to exclude any human risk during therapeutic use, because the artificial light conditions in animal facilities do neither cover exposure and intensity in the range of natural sunlight irrespective of a 12 h light/dark cycle (see Hayes. Principles and Methods of Toxicology; 5th ed. 2008; Informa Healthcare Inc., USA: 1070-1071), nor at the maximum absorption of tasimelteon (290 nm). Likewise, the light conditions in clinical trial facilities do not reflect natural sunlight exposure. Therefore, ICH guidelines do not recommend the evaluation of the phototoxic potential of a compound as part of standard toxicity studies, but in dedicated investigations.

4.) The possibility of drug elimination during the normal life-cycle of keratinocytes is regarded irrelevant to exclude a phototoxic hazard, because this argument does not apply to the eyes and would instead abrogate any phototoxicity testing independent of the tiered approach outlined in the prevailing ICH S10 guideline.

In conclusion, unless negated by further experimental data, tasimelteon is regarded to fulfil the general criteria of the ICH S10 guideline, that necessitate further evaluation of its phototoxic potential. In order to resolve this concern and to avoid the need for protective measures during therapeutic use of tasimelteon, a repetition of the MEC value determination and a repeated-dose pharmacokinetic study to determine the distribution of tasimelteon and its metabolites to light-exposed tissues was deemed necessary as PAM.

Tasimelteon was not genotoxic in the standard battery of genotoxicity studies in line with ICH S2B. The metabolite M11 was negative in the Ames test but in the mammalian assay increased the number of aberrant chromosomes at high doses of ≥ 1,500 µg/mL, in the presence of S-9. This concentration is roughly 30,000 fold greater than the expected clinical C_{max} at 20 mg/day. Metabolite M11 was also shown to be a metabolite in mouse, so it can be assumed that mice were exposed to M11 in the in vivo genotoxicity assay. Thus, given the very high concentration in the in vitro assay, and the absence of increased multinucleated polychromatic erythrocytes in the in vivo assay, the metabolite M11 is not considered to present a genotoxic risk.

The applicant has provided a detailed discussion of the maternal and foetal findings in the rabbit EFD study. The increased embryo-foetal loss occurred at maternal doses of 200 mg/kg/day, which was maternally toxic. There was sufficient justification to show that the abortive effect is secondary to maternal toxicity, therefore the applicant's conclusion was supported by the CHMP. Considering the large margin of safety from the 200 mg/kg dose in rabbits, and the absence of foetal loss at non-maternally toxic doses, the CHMP agreed that these findings do not present a specific clinical safety concern to pregnancy.

The applicant asserted that the delayed ossification observed in this study was linked to foetal growth rates, and was not indicative of a permanent teratogenic effect. The delay in ossification was not considered to persist in the post-natal period. As post-natal development was not studied in rabbits, the recovery cannot be determined, and the mechanism underlying the finding was not elucidated. However the CHMP accepted that delayed ossification is a common finding, and given that the finding only occurred at the 200 mg/kg tasimelteon dose, the risk to the foetus can be considered in the context of the large safety margin from the clinical dose. Therefore the risk of delayed ossification occurring clinically is negligible.

The absence of antigenicity testing was justified by the Applicant, stating that antigenicity studies are typically conducted for biotechnology derived products. As tasimelteon is a small molecule, there were no findings in the toxicology studies to warrant specific studies, and there was no evidence of antigenic responses in the clinical

safety database, specific antigenicity studies were not deemed necessary. This justification was accepted by the CHMP.

No immunotoxicity studies have been conducted. This is supported by the CHMP since the data (haematology, clinical chemistry, gross pathology, organ weights and histology) generated from the numerous repeat dose toxicity studies both in rat and monkey demonstrate no evidence that the immune system was a target organ of toxicity of tasimelteon.

Studies conducted to determine local tolerance and dependence potential did not identify any relevant toxicities. The dependence studies were not GLP-complaint as required by guideline EMEA/CHMP/SWP/94227/2004. However, as they were of a sufficient standard in terms of design, execution and data control, the CHMP did not consider the lack of GLP-compliance to impact the findings of the studies.

Finally, there are no issues in relation to the impurity profile of the drug substance or drug product from a non-clinical perspective.

2.5.7. Conclusion on the non-clinical aspects

In conclusion the non-clinical data provided were considered sufficient, together with additional measure as specified earlier, to support this dossier.

2.6. Clinical aspects

2.6.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted, wholly or in part, outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Table 9 Tabular overview of clinical studies

Type of Study	**Study Identifier**	**Objective(s) of the Study**	**Test Product(s);** **Dosage Regimen:** **Route of Administration**	**Number of Subjects**	**Duration of Treatment**	**Study Status;** **Type of Report**
Safety, PK and PD	CN116-001	Safety and Tolerability, PK and PD	Tasimelteon/PBO 1, 3, 10, 30, 100, 300 mg capsules; single dose; oral	Total = 48	Single dose PBO lead-in followed by Single dose	Complete; Full
Safety, PK and PD	CN116-002	Short-term; Safety and Tolerability, PK and PD	Tasimelteon/PBO 1, 10, 50, 150 mg capsule; multiple dose; once daily; oral	Total = 32	Single dose PBO lead-in followed by 28 days	Complete; Full

Type of Study	Study Identifier	Objective(s) of the Study	Test Product(s); Dosage Regimen: Route of Administration	Number of Subjects	Duration of Treatment	Study Status; Type of Report
Safety, PK and PD	CN116-003	Comparison of PK across populations (age and gender); Safety and Tolerability; PD	Tasimelteon/PBO 50 mg capsule; single doses; oral	Total = 40	Single doses, separated by 7 day wash-out	Complete; Abbreviated
Efficacy and Safety	CN116-004	Short-term, Efficacy and Safety	Tasimelteon/PBO 1, 10 and 50 mg capsules; single doses; oral	Total = 227	28 days followed by 1 week placebo	Complete; Abbreviated
Efficacy	CN116-005	Single Dose Efficacy	Tasimelteon/PBO 1, 10 and 50 mg capsules; single doses; oral	Total = 3	Single doses, separated by at least 7 day wash-out	Terminated; Abbreviated
PK	VP-VEC-162-1101	Assess AME; Safety and Tolerability	Tasimelteon; 100 mg (100 µCi) [^{14}C]- tasimelteon solution; single dose; oral	Total = 6	Single dose	Complete; Full
PK	VP-VEC-162-1102	Assess Food Effect on PK; Safety and Tolerability	Tasimelteon 100 mg capsule; single doses; oral	Total = 26	2 single doses (1 Fasted; 1 Fed), separated by 7 day wash-out	Complete; Full
Thorough QT	VP-VEC-162-1103	Effects on QT interval; Safety and Tolerability	Tasimelteon/PBO 20 and 300 mg capsules and moxifloxacin (positive-control) 400 mg tablet; multiple dose; once daily; oral	Total = 44	3 days followed by 4 day wash-out	Complete; Full
PK	VP-VEC-162-1104	PK interaction with midazolam; Safety and Tolerability	Tasimelteon 100 mg capsule and midazolam 10 mg syrup; once daily; oral	Total = 24	7 days tasimelteon, 2 single doses midazolam	Complete; Full
PK	VP-VEC-162-1105	Effect of hepatic impairment on PK , Safety and Tolerability	Tasimelteon 20 mg capsule; single dose; oral	Total = 29	Single dose	Complete; Full
PK	VP-VEC-162-1106	Effect of renal impairment on PK; Safety and Tolerability	Tasimelteon 20 mg capsule, single dose; oral	Total = 32	Single dose	Complete; Full
PK and Safety	VP-VEC-162-1107	Assess smoking status, age, gender, weight, and BMI on PK, Safety and Tolerability	Tasimelteon 20 mg capsule; single dose; oral	Total = 60	Single dose	Complete; Full
PK and PD	VP-VEC-162-1108	PK/PD interactions with ethanol; Safety and Tolerability	Tasimelteon/tasimelteon PBO/ ethanol/ ethanol/PBO; 20 mg capsule and 0.6 g/kg (female) or 0.7 g/kg (male) ethanol liquid given in 4 combinations; single doses; oral	Total = 28	2 single doses of tasimelteon and ethanol in combination with each other and placebo	Complete; Full
PK	VP-VEC-162-1110	Assess impact on CYP450 3A4 and 2C8; Safety and Tolerability	Tasimelteon 20 mg capsule, midazolam 10 mg oral syrup and rosiglitazone 4 mg tablet; once daily; multiple doses; oral	Total = 24	16 days tasimelteon, 2 single doses of midazolam and rosiglitazone	Complete; Full
PK	VP-VEC-162-1111	Assess impact of combination treatment of a CYP1A2 inhibitor on PK parameters; Safety and Tolerability	Tasimelteon 5 mg capsule, alone and in combination with fluvoxamine 50 mg tablet; single doses; oral	Total = 24	2 single doses tasimelteon, 7 days fluvoxamine	Complete; Full

Type of Study	Study Identifier	Objective(s) of the Study	Test Product(s); Dosage Regimen: Route of Administration	Number of Subjects	Duration of Treatment	Study Status; Type of Report
PK	VP-VEC-162-1112	Assess impact of combination treatment of a CYP3A4 inhibitor and CYP3A4 inducer on PK parameters; Safety and Tolerability	Tasimelteon 20 mg capsule, alone and in combination with ketoconazole 200 mg tablet x 2 (Cohort 1) or rifampin 300 mg capsule x 2 (Cohort 2); single doses; oral	Total = 48	2 single doses tasimelteon, Cohort 1 = 5 days ketoconazole Cohort 2 = 10 days rifampin	Complete; Full
Efficacy and Safety	VP-VEC-162-2101	Efficacy; Dose comparison; PK; Safety and Tolerability	Tasimelteon/PBO10, 20, 50 and 100 mg capsules; daily dose; oral	Total = 39	3 days	Complete; Full
Efficacy and Safety	VP-VEC-162-2301	Efficacy, Safety and Tolerability	Tasimelteon/PBO 20 mg capsules; daily dose; oral	Total = 507	Double-Masked Phase 8 weeks Open-Label Phase: 52 weeks	Double-Masked Phase Complete, Full Open-Label Phase: Complete, Abbreviated
Efficacy and Safety	VP-VEC-162-3101	Efficacy; Dose comparison; Safety	Tasimelteon/PBO 20, 50 and 100 mg capsules; single dose; oral	Total = 412	Single dose	Complete; Full
Efficacy and Safety	VP-VEC-162-3104	Short-term, Efficacy, Dose comparison; Safety	Tasimelteon/PBO 20 and 50 mg capsules; once daily; oral	Total = 322	35 days followed by a 1 night single blind placebo washout	Complete; Full
Efficacy and Safety	VP-VEC-162-3201 (SET)	Long-term, Efficacy; Safety	Tasimelteon/PBO 20 mg capsules; once daily; oral	Total = 84	26 weeks randomized; 26 weeks open-label	Complete; Full
Safety	VP-VEC-162-3202	Long-term, Safety;	Tasimelteon 20 mg capsules; once daily; oral	Total = 140 planned	52 weeks followed by a 3 year optional sub-study	Ongoing; Interim
Efficacy and Safety	VP-VEC-162-3203 (RESET)	Assess maintenance effect post-withdrawal; Safety	Tasimelteon/PBO 20 mg capsules; once daily; oral	Total = 20	20-24 weeks	Complete; Full
Safety	VP-VEC-162-3204	Long-term, Safety	Tasimelteon 20 mg capsules; once daily; oral	Total = 200 planned	2 years	Ongoing; Interim
BA and PK	VP-VEC-162-4101	Determine Absolute Bioavailability; Safety and Tolerability	Tasimelteon 20 mg capsules/ Tasimelteon 2 mg IV	Total = 14	Two single doses, separated by 5 (± 2) days wash-out	Complete; Full

2.6.2. Pharmacokinetics

The tasimelteon development program included fourteen phase I clinical pharmacology studies.

Absorption

Tasimelteon is absorbed rapidly, with median peak concentration (Tmax) occurring at approximately 0.5 hours after fasted oral administration. Total oral absorption of tasimelteon is at least 80.4% and the mean absolute

bioavailability is 38%. In study VP-VEC-162-1102 administration of tasimelteon with a high fat/high calorie meal resulted in a reduction of Cmax by 44%. The median Tmax increased from 0.75 hours under fasted conditions to 2.5 hours under fed conditions. AUC (0-t) and AUC (inf) were comparable under fed and fasted conditions, 108.57% and 106.54%, respectively, and 90% confidence intervals contained within the 80% to 125% equivalence window.

Based on these results it has been recommended in the SmPC that tasimelteon should be administered without food.

Distribution

The apparent volume of distribution at steady state of tasimelteon in young healthy subjects ranged from 58.5 to 125.9 litres. At therapeutic concentrations, tasimelteon is about 88.6 - 90.1% protein bound. Renal impairment does not affect the protein binding of tasimelteon.

Elimination

Tasimelteon is extensively metabolised. Following oral administration of radiolabeled tasimelteon, <1% of the unchanged parent drug was detectable in the urine. The main route of elimination of tasimelteon and its metabolites in humans is through the kidney, with biliary excretion to feces contributing for a minor portion. Mean recovery of total radioactivity in urine was 80.4% and 3.72% was recovered in feces resulting in a mean recovery of 84.1% (Study 1101).

Metabolism

When administered orally, tasimelteon undergoes a rapid metabolism through the CYP450 system at the gastrointestinal level and in the liver. Eight metabolites have been characterized — M1, M3, M8, M9, M11, M12, M13, and M14. All were present in plasma and M1, M3, M8, and M9 were present in urine.

Metabolism of tasimelteon consists primarily of oxidation at multiple sites and oxidative dealkylation resulting in opening of the dihydrofuran ring followed by further oxidation to give a carboxylic acid. From in vitro studies it was found that tasimelteon is mainly metabolized by CYP1A2 and CYP3A4, with minimal contribution from CYP1A1, CYP2C9/19, and CYP2D6, however the in vivo contribution of various enzyme pathways is uncertain, particularly the relative importance of CYP1A2 and CYP2C19.

Phenolic glucuronidation is the major phase II metabolic route.

Dose proportionality and time dependencies

- **Dose proportionality**

The dose proportionality of tasimelteon following a single oral dose between 1-300 mg was evaluated in healthy volunteers (BMS Study 001). Following a single 1-, 3-, 10-, 30-, 100-, 300- mg dose of tasimelteon, the estimated geometric means for AUC(inf) for the tasimelteon were in the following ratios, 1:1.5:7.9:13.5:66.9:210.5 suggesting an increase less than proportionally to dose. Excluding the 1 mg dose, the geometric means for AUC(inf) were in the following ratios: 1:5.3:9.1:45.0:141.5 suggesting dose proportionality and linearity over the dose range of 3- to 300-mg.

- **Time dependency**

Study VEC-162-1110 evaluated the multiple dose pharmacokinetics of tasimelteon and main metabolites (M9, M11, M12, M13, and M14), including the time to steady-state, during administration of 20 mg once daily for 16 days (Study Days 5-20) in twenty-four (24) healthy male and female subjects. The pharmacokinetics of tasimelteon did not change with continued daily dosing. This was also true for tasimelteon metabolites.

Special populations

Mild and moderate hepatic impairment resulted in minimal increases in exposure at a dose of 20 mg – approximately 2-fold for the parent, less for the metabolites. Tasimelteon was not studied in patients with severe hepatic impairment.

Exposure to tasimelteon in subjects with severe renal impairment (SRI) or end stage renal disease (ESRD) had inconsistent results after a single dose of 20 mg. Compared to matched controls, SRI patients had, on average, a lower CL/F with a geometric mean ratio (GMR) of 70.52%. In contrast, ESRD patients, had a comparable arithmetic mean CL/F with a GMR of 97.82%, and comparable mean plasma concentrations and arithmetic mean values for Cmax and AUC(inf).

Population PK analyses was conducted for four studies (Study 1105, Study 1106, Study 1107, and Study 1110) with orally administered tasimelteon to evaluate the effect of gender on the PK profile of tasimelteon. In this analysis, gender did not affect the apparent clearance of tasimelteon. Similarly, race and ethnicity were not found to affect the apparent clearance of tasimelteon in any of the analyses done.

From the Population PK analysis results, elderly subjects had an apparent clearance of 20% less than young adults. In contrast, study 1107 didn't show any difference. CHMP agreed that this discrepancy is related to the overall variability of Tasimelteon PK more than the age. Therefore, no dose adjustment in the elderly is recommended in the SmPC.

Two independent analyses, a multivariate statistical analysis of PK parameters based on non-compartmental analysis and a compartmental model-based population PK analysis, concluded that increasing BMI was associated with a decrease in the apparent clearance of tasimelteon whereas no other metric of body size affected apparent clearance. This effect is probably due to the known decrease in CYP1A2 activity with increased BMI. Due to the overall inter-subject variability of tasimelteon, contributions to this variability by these factors, if present, were judged to be not clinically meaningful. Therefore, no dose adjustment has been found necessary based on BMI.

Pharmacokinetic interaction studies

Effect of tasimelteon on other drugs

In vitro data suggested that tasimelteon had the potential to induce the activity of CYP3A4/5 and CYP2C8. This was examined in 2 clinical studies, Study 1104 and Study 1110, in which a single 10 mg oral dose of midazolam (a CYP3A4 substrate) was administered alone and then after tasimelteon 100 mg QD × 7 days and 20 mg QD × 14 days, respectively. Additionally, Study 1110 investigated the effect of tasimelteon on a single dose of rosiglitazone (a CYP2C8 substrate) given concomitantly after tasimelteon 20 mg × 16 days. The mean PK parameters for midazolam and 1-OH-midazolam (major metabolite of midazolam) after administration alone were comparable between the two studies suggesting consistency between the 2 studies with respect to the 2 probe drugs. Administration of tasimelteon 100 mg once daily for 7 days resulted in a trend toward a decrease in the exposure to midazolam that was not statistically significant. While there was also a trend toward a decrease in midazolam exposure after administration of 20 mg once daily for 14 days the difference was again not statistically significant.

The mean values for Cmax, AUC (0-t), and AUC(inf) of midazolam, 1-OH-midazolam, and rosiglitazone were comparable when given alone or in combination with tasimelteon after multiple dosing. Tasimelteon therefore does not appear to have the potential for in vivo induction of either CYP3A4/5 or CYP2C8.

Effects of other drugs on tasimelteon

The results of drug-drug interactions studies are summarised in the Table 10 below.

Table 10 Impact of other drugs on tasimelteon pharmacokinetics

Study No.	Dose Route Formulation	Subjects No. (M/F) Type	DDI Pharmacokinetics Parameter	Geometric Mean Ratio (%)*	
				Estimate	Estimate
1112	20 mg Oral Capsule	24 (12/12) Healthy Volunteer	**Ketoconazole Interaction**		
			CL/F	64.95	58.12 → 72.60
			C_{max}	133.06	116.73 → 151.68
			$AUC_{(0-t)}$	161.14	141.49 → 183.53
			$AUC_{(inf)}$	153.95	137.75 → 172.07
1112	20 mg Oral Capsule	24 (12/12) Healthy Volunteer	**Rifampin Interaction**		
			CL/F	930.50	723.47 → 1,196.77
			C_{max}	17.22	13.29 → 22.31
			$AUC_{(0-t)}$	10.48	8.11 → 13.55
			$AUC_{(inf)}$	10.75	8.36 → 13.82
1111	5 mg Oral Capsule	24 (17/7) Healthy Volunteer	**Fluvoxamine Interaction**		
			CL/F	15.31	12.35 → 18.97
			C_{max}	232.74	202.63 → 267.33
			$AUC_{(0-t)}$	651.06	524.43 → 808.28
			$AUC_{(inf)}$	653.36	527.12 → 809.82
1108	20 mg Oral Capsule	28 (20/8) Healthy Volunteer	**Ethanol Interaction**		
			C_{max}	125.89	105.08 → 150.81
			$AUC_{(0-t)}$	112.22	85.87 → 146.67
			$AUC_{(inf)}$	111.53	85.08 → 146.20

*Based on analysis of natural log-transformed parameters.
Source Data: 1112 Clinical Study Report Table 15; 1111 Clinical Study Report Table 14; 1108 Clinical Study Report Table 12.

Consistent with the major role of CYP1A2 in the metabolism of tasimelteon, administration of fluvoxamine and the subsequent inhibition of CYP1A2, and CYP2C19 resulted in a decrease in the mean CL/F and an increase in exposure as measured by AUC(inf) with a geometric mean ratio (GMR) of 653.36% (90% CI: 527.12% to 809.82%). Conversely, induction of CYP1A2 by cigarette smoking increased the mean CL/F compared to non-smokers with a GMR, smokers-to-non-smokers, of 166.27% (90% CI: 119.87% to 230.64%). Administration of ketoconazole and the subsequent inhibition of CYP3A4 resulted in a decrease in the mean CL/F with a GMR, tasimelteon alone-to-tasimelteon + ketoconazole, of 64.95% (90% CI: 58.12% to 72.60%) (Table 16). The decrease in CL/F resulted in an increase in exposure as measured by AUC(inf) with a GMR of 153.95%

(90% CI: 137.75% to 172.07%). Conversely, administration of rifampin and the subsequent induction of CYP3A4,CYP2C9, and CYP2C19 resulted in substantial increases in the mean CL/F, with a GMR, tasimelteon alone-to-tasimelteon + rifampin, of 930.50% (90% CI: 723.47% to 1,196.77%). The increase in CL/F resulted in a decrease in exposure as measured by AUC(inf) with a GMR of 10.75% (90% CI:8.36% to 13.82%)

Administration of tasimelteon 20 mg QD for 16 days did not produce any clinically significant changes in the Tmax, Cmax, or AUC of rosiglitazone (CYP2C8 substrate) after oral administration of 4 mg. This indicates that there is no induction of CYP2C8 by tasimelteon at this dose.

Pharmacokinetics using human biomaterials

A preliminary in vitro study (Study BMS-10Nov97) was conducted to determine whether tasimelteon can be metabolized by specific cDNA-derived cytochrome P450 isoenzymes. The CYP450-mediated metabolism of tasimelteon was then investigated in human liver microsomes (Study XBL08639) and in recombinant CYP enzyme systems (Study XBL08639), by monitoring the formation of five main metabolites (M9, M11, M12, M13, and M14) with and without selective CYP450 chemical inhibitors. CYP1A2 and CYP3A4 are the major isozymes involved in the metabolism of tasimelteon. CYP1A1, CYP2C9/19, and CYP2D6 also minimally contribute to the metabolism of tasimelteon.

Tasimelteon and Metabolites as Cytochrome P450 Inhibitors

The potential for tasimelteon and its most abundant human metabolites (M9, M12 and M13) to inhibit, in vitro, the major CYP enzymes in human liver microsomes — CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 was investigated in Study XT12A024, Study XT065016 and Study XT135015. Based on the results of these studies tasimelteon and its most abundant metabolites are unlikely to cause clinically relevant inhibition of any of the major CYPs in humans (i.e., CYP1A2, 2B6, 2C8, 2C9, 2C19 or 3A4/5) at the therapeutic dose.

Tasimelteon and Metabolites as Cytochrome P450 Inducers

The effect of treating primary cultures of human hepatocytes with tasimelteon on the mRNA expression of several microsomal CYP450 enzymes — CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5— was investigated in vitro in Study XT063014. The data from this study suggested that tasimelteon had the potential to induce the activity of CYP3A4/5 and CYP2C8.

The effects of treating cultured human hepatocytes with tasimelteon and its most abundant metabolites, M9, M12, and M13, on the expression of CYP1A2 and 2B6 enzymes were investigated in vitro in Study XT123078. In this study, the ability of tasimelteon's most abundant metabolites to induce CYP1A2 in vitro was also evaluated. Results showed that neither tasimelteon nor its most abundant metabolites appear to induce CYP1A2 or CYP2B6, except at high concentrations well above the average human maximum plasma concentrations at the 20 mg therapeutic dose .

Tasimelteon and Metabolites as Transporter Inhibitors or Substrates

Tasimelteon and its most abundant metabolites showed either no interaction potential with the uptake transporters OATP1B1, OATP1B3, OCT2, OAT1, and OAT3 or interactions at concentrations at least 6 times higher than the average human maximum plasma concentration at the 20 mg therapeutic dose suggesting little or no likelihood of in vivo inhibition. Tasimelteon and its metabolites do not appear to be substrates for P-gp, OATP1B1 or OATP1B3 transporters nor do they appear to inhibit BCRP, BSEP, or P-gp (Study 10VNDAP1R1,

Solvo 12700, and XT138089). Therefore, the CHMP agreed that further evaluation of the potential for tasimelteon to interact with these transporters (P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OCT2, OAT1 and OAT3) is not warranted.

2.6.3. Pharmacodynamics

Mechanism of action

Tasimelteon is a circadian regulator that resets the master body clock in the suprachiasmatic nucleus (SCN) of the hypothalamus. This activity is believed to be mediated by the affinity of tasimelteon to the MT1 and MT2 receptors in the SCN. Tasimelteon main metabolites (i.e. M3, M9, M11, M12, M13 and M14) also bind to the melatonin receptors but with less affinity than the parent.

Primary and secondary pharmacology

The results of the Proof of Concept study (VP-VEC-162-2101) showed that tasimelteon induced a forward shift in DLMO25% and LOQ5 on the first night of treatment. Disruption of sleep efficiency, REM polarity and wake after sleep onset (WASO) caused by phase advance also improved.

Study CN116-001 studied the safety, tolerance, pharmacokinetic and pharmacodynamics of single doses of tasimelteon in healthy subjects whilst study CN116-002 was conducted to study the safety, tolerance, pharmacokinetics and pharmacodynamics of multiple doses of tasimelteon in healthy subjects. The results suggested that tasimelteon has some sleep promoting effect without affecting daytime functioning. No change was noted in the psychometric variables between the treatment and placebo group.

Study VP-VEC-162-1108 studied the pharmacodynamics and pharmacokinetics interactions of tasimelteon and ethanol. With the exceptions of visual-motor –processing speed (number of symbols completed within a given time on the DSST, administration of tasimelteon alone did not have any significant effects on subjective measures, sustained attention, cognition, balance, or psychomotor performance. The combination of Tasimelteon + ethanol did no significantly differ from ethanol alone.

The results of the QTc study 1103 demonstrated that tasimelteon has no potential to affect cardiac repolarization. No effects were recorded on heart rate, PR or QRS interval duration or cardiac morphology.

2.6.4. Discussion on clinical pharmacology

The PK characteristics of tasimelteon are highly variable amongst individuals. Intrinsic factors that might influence the PK variability of tasimelteon include age, gender, and body composition. Due to the overall inter-subject variability of tasimelteon, contributions to this variability by these factors, if present, are probably small and not clinically meaningful. Therefore, no dose adjustment is necessary based on age, gender, or body max index.

Mild and moderate hepatic impairment resulted in minimal increases in exposure at a dose of 20 mg — approximately 2-fold for the parent, less for the metabolites. Based on the observed inter-subject variability in the PK parameter of tasimelteon and taking into account the therapeutic margin of tasimelteon (i.e., doses up to at least 300 mg are well tolerated), the CHMP was of the opinion this increased exposure is not clinically relevant and dose adjustment is not necessary in patients with mild or moderate hepatic impairment.

Tasimelteon has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) therefore caution was recommended when prescribing it to patients with severe hepatic impairment.

The inconsistent results of renal impairment study have been judged to be related to the intrinsic variability. Considering the overall favourable 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 was deemed necessary for these special populations.

Theoretically, the tasimelteon pharmacokinetics of healthy subjects should be similar to that of Non-24 patients as Non-24 patients have interrupted biorhythms but typically do not present with any other particular variables that would affect the overall PK differences seen in healthy subjects. The CHMP agreed that the pharmacokinetics of tasimelteon would be expected to be similar between Non-24 patients and the healthy subjects.

The exposures to tasimelteon and its main metabolites are affected by the induction of CYP1A2 (e.g. smoking) and/ or CYP3A4 and other CYPs. Rifampin, a strong CYP3A4 and moderate CYP2C19/2C9 inducer with little/no effect on CYP1A2, reduced the exposure to tasimelteon by approximately 90% (Study 1112). Therefore, the concomitant use of rifampin and other strong CYP3A4 and moderate CYP2C19/2C9 inducers with tasimelteon should be avoided.

Co-administration with fluvoxamine, which inhibits CYP1A2 and CYP2C9/19, resulted in an 85% decrease in tasimelteon clearance leading to a 6.5-fold increase in exposure. Similarly, tasimelteon exposure increased by approximately 54% when given concomitantly with a strong CYP3A4 inhibitor, ketoconazole.

While it was claimed by the applicant that CYP1A2 is the major enzyme involved in the metabolism of tasimelteon, this was inconsistent with the results of the rifampin interaction study; the effect was much larger than could be explained by induction of CYP3A4, representing only 30% of drug elimination. As CYP1A2 is not induced by rifampin, there is uncertainty regarding the quantitative importance of CYP2C19 and 1A2 in vivo. While it is accepted that the maximum extent of interaction has been defined (6.5-fold increase in AUC), lower, but still important exposure increases cannot be ruled out without clarification of the relative contributions of CYP1A2 and CYP2C19. Therefore, the CHMP requested additional in vitro and in vivo studies in order to mitigate the risk of drug-drug interactions. These studies will be conducted as post-approval measures. Appropriate wording advising caution has been included in the SmPC, until this uncertainty is resolved with additional study data.

2.6.5. Conclusions on clinical pharmacology

A number of uncertainties have been identified by the CHMP regarding unanticipated drug-drug interactions due to inadequate understanding of the quantitative contribution of the enzymes responsible for the elimination of tasimelteon. These issues are to be investigated post approval.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

1. The applicant should perform *in vitro* investigations of which enzymes are catalysing the main elimination pathways using incubations of the drug with: 1) human liver microsomes with and without enzyme specific inhibitors/antibodies and 2) recombinant CYP enzymes. Both studies should be conducted according to the current Guideline on the Investigations of Drug Interactions (CPMP/EWP/560/95/Rev.1), using clinically

relevant concentrations under linear conditions and monitoring metabolite formation. The applicant should submit the study protocol for review prior to study start.

2. The applicant should provide a pooled analysis of all genotype data collected during the phase 1 study programme and relationship to apparent drug clearance. In addition, the Company should add a series of columns to the table in 2.7.6 Synopses of Individual Studies: including one column for genotypes investigated and a second column to highlight any reasons why the genotype data could not be investigated retrospectively. In addition, the applicant should submit a plan for retrospective analysis of 2C19 and other genotypes of phase 1 study samples or provide a justification as to why this information cannot be obtained or is unnecessary.

3. Unless otherwise justified, the applicant should conduct a retrospective analysis of phase 1 study samples to determine 2C19 and other genotypes and conduct an analysis of relationship to apparent drug clearance, pooling data across studies.

4. Depending on the results of the additional in vitro studies and additional in vivo data/analyses, the applicant should perform additional *in vivo* studies such as (1) a new study of tasimelteon in extensive and poor CYP2C19 metabolisers, (2) a new PK study of tasimelteon that includes markers of CYP1A2, 3A4 and 2C19 metabolism, (3) a new DDI study with a strong CYP2C19 inhibitor, such as fluconazole and/or (4) any other approach deemed to be informative. The applicant should submit the study protocol(s) for review prior to study start or provide a justification as to why additional in vivo studies are unnecessary. Once the study programme is complete (even in the case that no new *in vivo* study is conducted), the applicant should provide an updated mass balance scheme that shows clearly the quantitative importance of different enzymatic pathways according to the cumulative excretion of all entities following a particular pathway and integrating the data derived from the recently conducted absolute bioavailability study.

2.7. Clinical efficacy

Introduction

The clinical development of tasimelteon included 2 dose-finding clinical studies (VP-VEC-162-2101 and VP-VEC-162-3101) and 2 pivotal efficacy trials (VP-VEC-162-3201 (SET) and VP-VEC-162-3203 (RESET).

2.7.1. Dose response studies

The selection of 20 mg as the dose used in the phase III clinical studies was based on two dose-finding clinical studies and supported by the non-clinical .

Study VP-VEC-162-2101 was a randomized, double-blind, parallel, placebo-controlled, in-patient study in a light controlled time isolation sleep facility that assessed the safety and efficacy of four oral doses of tasimelteon (10-, 20-, 50-, and 100 mg) compared to placebo. Subject's sleep schedule was abruptly advanced by 5 hours, a protocol which severely disrupts circadian rhythms including those of melatonin and the sleep-wake cycle. Circadian rhythms, sleep parameters, and subject alertness were assessed during an 8-day inpatient stay.

When compared to placebo, patients treated with Tasimelteon showed a phase advance shift in the secretion of endogenous melatonin on the first night of treatment when compared to baseline. The effect on melatonin secretion as measured by Dim Light Melatonin Onset-DLMO was dose-dependent (placebo=0.48+- 0.84 hours, tasimelteon 10mg=0.18+-2.48 hours, tasimelteon 20mg=-1.14+-0.46hours; tasimelteon 50mg=-0.50+-0.32

hours, tasimelteon 100mg=-2.74-+1.95 hours). Tasimelteon was also able to reduce the disruption in full night sleep efficiency in a dose-related manner. The 20mg dose was the minimum dose that separated from placebo.

Study VP-VEC-162-3101 was a multicentre, randomized, double-blind, placebo-controlled, parallel-group study to investigate the efficacy and safety of single oral doses of tasimelteon (20, 50, and 100 mg) and matching placebo in healthy male and female subjects with induced transient insomnia. Transient insomnia was induced via a combination of stress inducement (by first night in a sleep laboratory) and via circadian rhythm disruption (by a 5-hour bedtime advance).

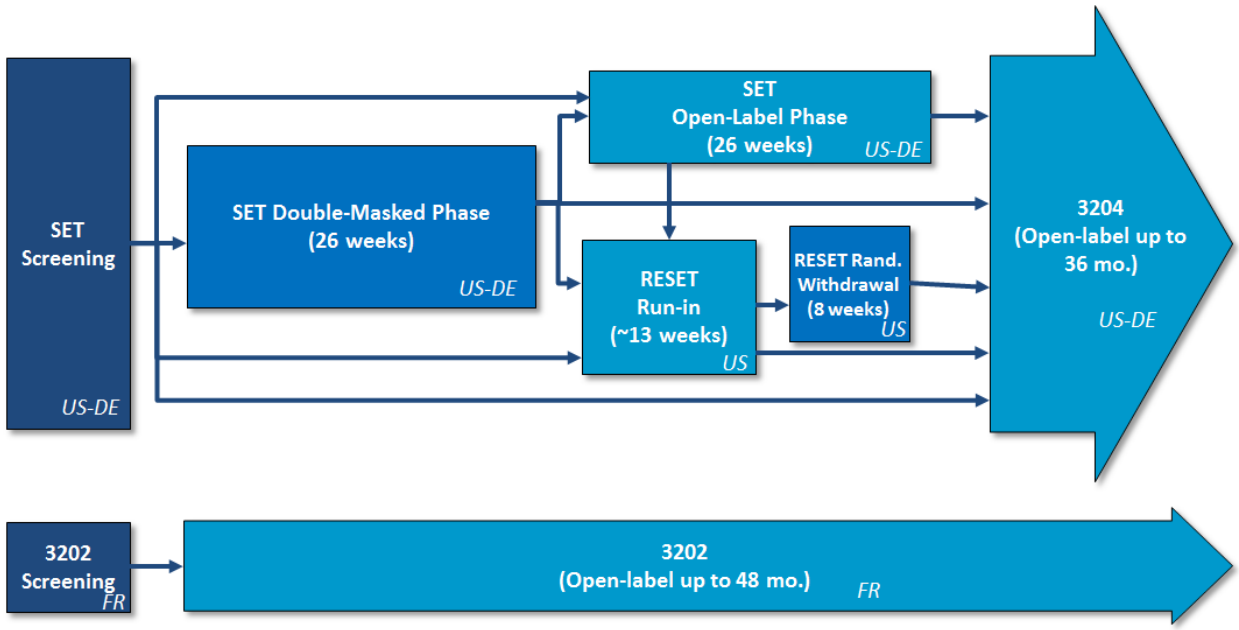
This study showed significant improvement in both objective latency to persistent sleep (LPS) and wake after sleep onset (WASO) at 20 mg and 50mg of tasimelteon.

The CHMP agreed with the selection of the 20mg for the main studies.

2.7.2. Main studies

The efficacy of tasimelteon in the treatment of Non-24-Hour Sleep-Wake Disorder in totally blind individuals was investigated in two randomized double-blinded, placebo-controlled, multicenter, parallel-group trials (VP-VEC-162-3201 (SET) and VP-VEC-162-3203 (RESET). VP-VEC-162 3202 was an open-label safety study.

The diagrammatic overview of the Phase 3 studies is presented in the Figure below.



Introduction

An individual who is entrained to the 24-hour day/night has a circadian period of 24.0 hours. Patients with Non-24 have circadian periods greater than 24.0 hours or in very rare cases less than 24.0 hours.

The time taken to complete one cycle of a circadian rhythm is defined as the circadian period (τ). A fixed point within a single cycle is termed the phase and is usually measured from the peak (maximum) or trough

(minimum) of the rhythm. The peak of a rhythm is fitted using a sine function is termed the acrophase. The circadian period is therefore defined as the duration of time between one phase and the next.

In the pivotal studies, the measurement of urinary melatonin metabolite, aMT6s has been used as a circadian marker for patients in the home environment.

The circadian period was used as an inclusion criterion for participation in SET and RESET and was also the measure for the primary endpoints (entrained or not entrained) in both studies.

Table 11: Definitions of Entrained and Not Entrained

Condition	Definition
Inclusion criterion for SET (aMT6s)	$\tau \geq 24.25$ hours with the lower bound of the 95% CI > 24.0 hours and the upper bound < 24.9 hours
SET primary endpoint (entrainment definition)	$\tau < 24.1$ hours with a 95% CI that includes 24.0 hours
Inclusion criterion for RESET Run-in Phase	$\tau \geq 24.1$ hours and a lower bound of the 95% CI > 24.0 hours during SET screening
Inclusion criterion for RESET Randomization Phase	$\tau < 24.1$ hours and a 95% CI that includes 24.0 hours during the RESET Run-in Phase
RESET primary endpoint (non-entrainment definition)	$\tau \geq 24.1$ hours or a lower bound of the 95% CI $>$ 24.0 hours

VP-VEC-162-3201 (SET): Multicentre, randomised, double-masked, placebo-controlled, parallel study designed to evaluate the efficacy and safety of 20mg of tasimelteon versus placebo in patients suffering from Non-24.

Methods

Study participants

Adult male and female patients in good physical health with non-entrained circadian rhythms (circadian period (τ) length of ≥ 24.25 hours and the lower bound of 95% CI > 24.0 hours and the upper bound of 95% CI < 24.9 hours) were eligible for inclusion in this study. Subjects had to have no perception of light and diagnosis of non-24 determined by history and urinary aMT6s demonstrated by a progressive delay of the aMT6s acrophase time. Subjects could not be pregnant, nursing, or planning pregnancy within the projected duration of the study. Subjects of reproductive potential had to agree to remain abstinent or use two acceptable methods of birth control during the study.

Subjects could not have had a probable diagnosis of a current sleep disorder other than Non-24 that was the primary cause of the sleep disturbance and history (within the 12 months prior to screening) of uncontrolled psychiatric disorders. Subjects who took non-steroidal anti-inflammatory drugs (NSAIDs) daily and would not interrupt their use for the 48-hour urine collections were also excluded.

Patients who had a τ >24.0 and met all entry criteria but that were ineligible for the Randomization Phase due to their τ value were given the opportunity to participate in the Open-Label Extension Phase. During this phase, patients received open-label 20 mg tasimelteon for 26 weeks.

Treatments

Patients were randomized to receive placebo or tasimelteon 20 mg every night for 6 months of treatment. Entrainment of urinary aMT6s and cortisol was assessed via a series of urinary measurements during screening and post-randomization during month 1 and for a subset of patients at month 7 (during the run-in for RESET study).

For maximum efficacy, the applicant hypothesized that the time of maximum plasma concentration of tasimelteon should coincide with the time that subjects go to bed. The peak Cmax of tasimelteon is reached at .25 to 2 hours consequently; the patients were instructed to take the study medication 60 minutes prior to bedtime.

Objectives

The primary objective of this study was to determine the efficacy of tasimelteon in patients with Non-24 as measured by the proportion of entrainment. A step-down objective was to determine the efficacy of tasimelteon in patients with Non-24 as measured by the proportion of patients with a clinical response.

Clinical response was defined as the coincident demonstration of:

1. Entrainment of the 6-sulfatoxymelatonin (aMT6s) rhythm and
2. A score of ≥3 on the Non-24 Clinical Response Scale (N24CRS).

The key secondary objectives were the following:

1. To determine the efficacy of tasimelteon in patients with Non-24 as measured by the proportion of responders with a combined sleep/wake response for night-time sleep duration and daytime sleep duration defined as:
   a) Increase of 90 minutes or greater in the lower quartile of nights of subjective night time total sleep time (LQ-nTST) and
   b) Decrease of 90 minutes or greater in the upper quartile of days of subjective day time sleep duration (UQ-dTSD).
2. To determine the efficacy of tasimelteon in patients with Non-24 as measured by the proportion of entrainment as assessed by urinary cortisol.

N24CRS is a 4-item scale that includes Lower Quartile of Night-time Total Sleep Time (LQ-nTST), Upper Quartile of Day time Total Sleep Duration (UQ-dTSD), Midpoint of Sleep Timing (MoST) and Clinical Global Impression of Change (CGI-C) assessments. Each assessment on the scale is scored as a 1 or 0 depending on whether the pre-specified threshold is achieved or not, as defined in Table 12. The score for each assessment is summed with a range of 0-4. The thresholds for each of the four parameters that make up the N24CRS are clinically meaningful (e.g. 45 minute improvements).

Table 12: Non-24 Clinical Response Scale Components

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 Day 112 and Day 183 compared to baseline

Night-time Total Sleep Time (nTST)

Patients 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. The patients were instructed to call the Interactive Voice Recording System (IVRS) and answer the Post Sleep Questionnaire (PSQ) questions no later than 1 hour after their scheduled awakening. The measure of nTST is a subjective patient-reported outcome and a well-accepted measure of total night-time sleep.

Lower Quartile of nTST (LQ-nTST)

LQ-nTST enriches for the worst night analysis reflective of the cyclical nature of Non-24. LQnTST is highly correlated with circadian phase, and is clinically meaningful as it is a direct reflection of the amount of night-time sleep when patients are suffering the most. Patients suffering from Non-24 may have trouble sleeping as a result of their circadian sleep cycle being out of synchrony with the 24-hour clock. This misalignment generally leads to intervals of poor sleep followed by intervals of good sleep.

Day time Total Sleep Duration (dTSD)

The Pre-Sleep Questionnaire (Pre-SQ) was used in SET and RESET to assess the number of daytime sleep episodes and the total amount of daytime sleep duration (dTSD). Daytime sleep was defined as any sleep event that lasted for > 5 minutes and that occurred after their predefined wake-time and prior to the patient's scheduled dosing time. Patients were instructed to call the IVRS in the evening no later than 15 minutes after their daily dosing time to report all of the day time sleep that occurred that day.

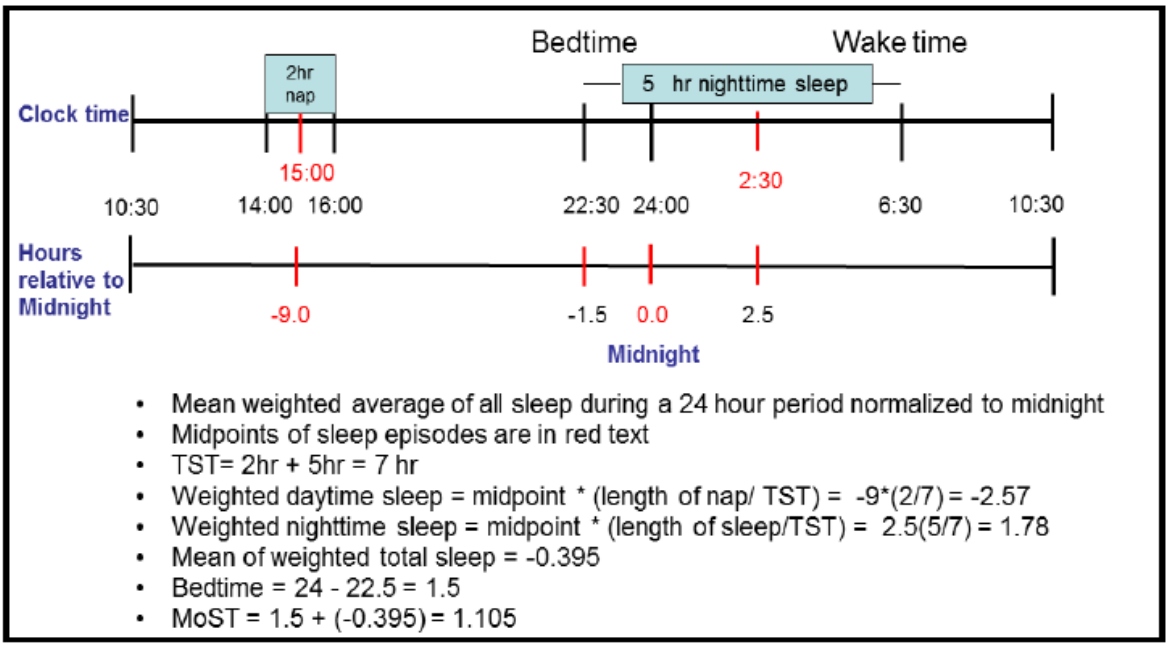
Upper Quartile of dTSD (UQ-dTSD)

UQ-dTSD enriches for the worst day analysis reflective of the cyclical nature of Non-24. UQ-dTSD is highly correlated with circadian phase and it is clinically meaningful as it is a direct reflection of the amount of daytime sleep when patients are suffering the most. During the periods when Non-24 patients' circadian rhythms are out-of-phase with the 24-hour light-dark cycle, the patient may experience a very strong circadian drive to sleep during the day regardless of the amount of sleep they had the night before. During other phases the patient may not experience daytime sleep episodes at all.

Midpoint of Sleep Timing (MoST)

Non-24 patients frequently present with complaints of sleep timing problems (e.g. trouble sleeping at night and excessive daytime sleepiness and daytime sleeping). Non-24 patients typically get the same amount of sleep on average every day; it may just be displaced on days when they are out-of-phase compared to days when they are in-phase.

While LQ-nTST and UQ-dTSD measure daytime and night-time sleep separately, MoST measures the average weighted midpoint of sleep reflecting both the timing and consolidation of sleep over a 24-hour period. MoST endpoint measures the average timing of sleep relative to an individual's desired period of night-time sleep over at least one circadian period. MoST measurement for a calendar day was derived from the Total Sleep Time (TST) 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.



Outcomes/endpoints

The primary efficacy endpoints were the following:

- The entrainment of the circadian melatonin rhythm as measured by urinary aMT6s

and

- (a step-down endpoint): The Clinical Response rate corresponding to individuals who had both:

1. Entrainment of the aMT6s rhythm and

2. A score of ≥3 on the N24CRS.

The key secondary efficacy endpoints were the following:

- The proportion of responders with a combined sleep/wake response for nighttime sleep duration and daytime sleep duration defined as:

1. Increase of 90 minutes or greater in LQ-nTST and

2. Decrease of 90 minutes or greater in UQ-dTSD.

- The entrainment of the circadian rhythm as measured by urinary cortisol.

Sample size

Eighty-four patients were randomised to receive tasimelteon (42 patients) or placebo (42 patients).

Randomisation

A randomisation list was prepared prior to the start of patient screening. The list contained blocks of size 4, i.e., each block of 4 treatments contained 2 from each treatment group in a random order. Randomisation was centrally performed through the IVRS system and was not stratified by study site.

Blinding (masking)

The patients and the medical staff were not aware of which treatment was administered. Data remained masked until database lock, at which time the randomization schedule was released for the purposes of assessment of drug safety and efficacy. All pre- and post-randomization τ calculations were conducted prior to database lock.

Statistical methods

The primary endpoints were analysed by Barnard's exact test, followed by a sensitivity analysis with Fisher's exact test. The continuous efficacy endpoints were analysed using an analysis of covariance model (ANCOVA). The primary efficacy analysis was based on the Intent-to-Treat (ITT) population.

Sensitivity analyses were conducted to verify the results of the step-down endpoint (Clinical Response). The first analysis had threshold scores of > 2 for the N24CRS. The second and the third were conducted for individuals (regardless of entrainment status) with a N24CRS score of >3 and > 2, respectively. The last one was conducted for responders who are entrained in the randomization phase and that also have a N24CRS score of >3.

No inferential statistics were produced for the analysis of data collected during the open-label extension.

Intent-to-Treat (ITT) Population included all subjects randomised into the study that have τ calculated post-randomisation.

Analysis Population included all subjects in the ITT population that have at least 70% of one circadian cycle of nTST data reported during each of screening and post-randomisation. The number of non-missing days of nTST data during each of screening and post-randomisation must have been be at least equal to the number of days that make up 70% of one circadian cycle.

The Safety Population included all subjects randomised into the study who receive at least one dose of study medication.

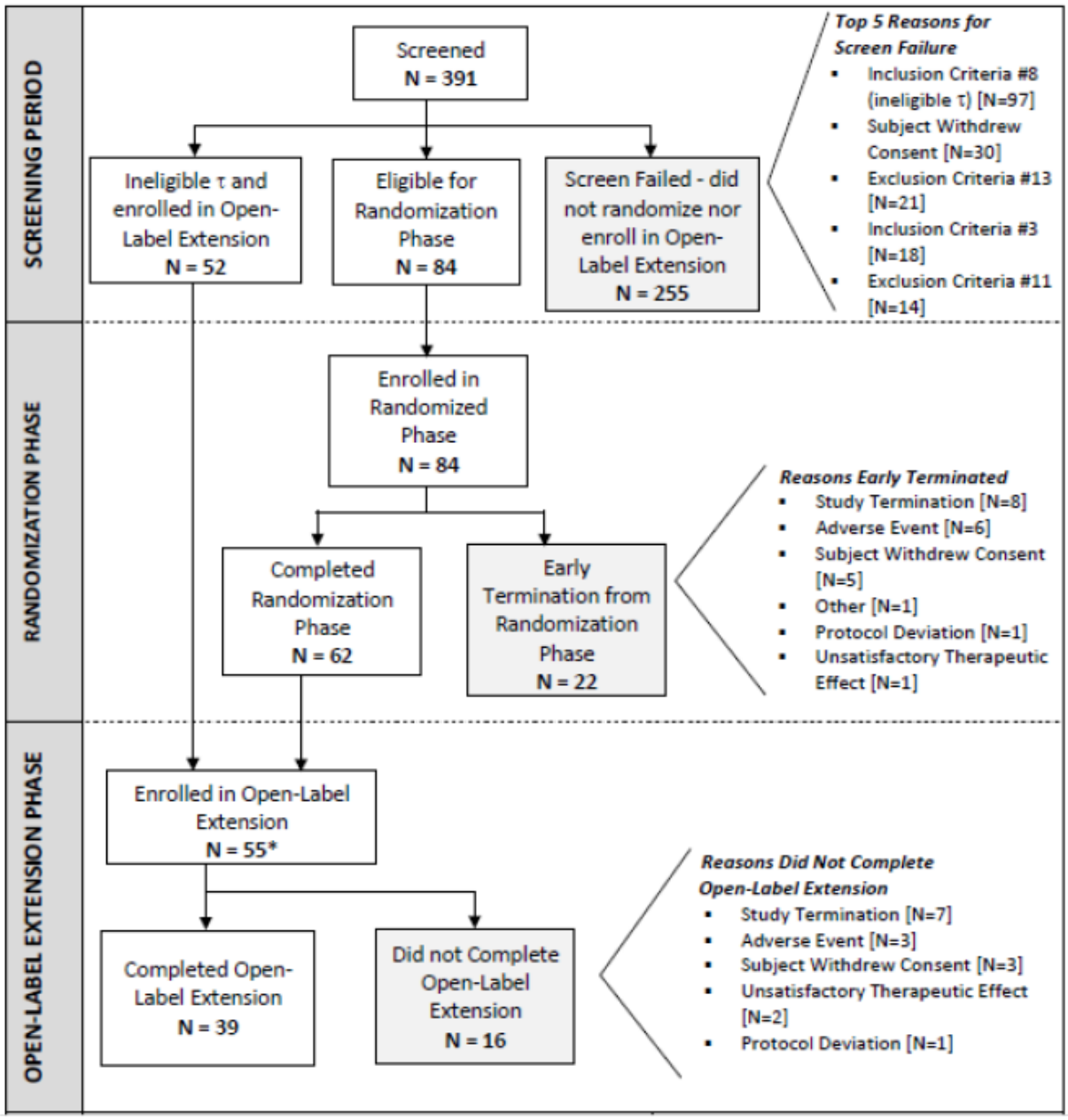
The ITT population was utilised for all circadian rhythm related outcomes: the primary endpoint of entrainment, the cortisol entrainment endpoint, and the aMT6s baseline secretion rate analyses, and the circadian analyte

analyses. The Analysis Population was used for analysis of all other endpoints including the step-down primary and all other efficacy analyses.

Analyses of data collected during the open-label extension included all subjects enrolled that have received at least one dose of study medication.

Results

Participant flow



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

Recruitment

The first subject enrolled on 25 August 2010 and the study was completed on 29 October 2012.

The study was conducted in 33 investigative sites in the US (n=27) and Germany (n=6).

Conduct of the study

The country-specific protocol for Germany also allowed for an Open-label Extension that followed the Randomisation Phase.

The original protocol was amended 11 times. None of the changes in any of the amendments negatively impacted subject safety or integrity of the data collected during the course of the study.

Baseline data

There were 49 males and 35 females in the study. The mean age was 50.7 years with a range of 23 to 74 years. The majority of patients were White (83.3%) and not Hispanic or Latino (96.4%).

The mean BMI was 27.95 kg/m2. Overall, the mean LQ-nTST, UQ-dTSD, nTST, and dTSD at screening were 3.2 h, 2.4 h, 5.3 h, and 0.9 h, respectively. The mean τ values as measured by urinary aMT6s and cortisol were 24.47 h and 24.45 h, respectively.

Numbers analysed

For the double-blind phase, a total of 78 subjects were analysed for efficacy (Intent-to-Treat population) and 84 subjects were analysed for safety (Safety population).

Outcomes and estimation

The summary of results of SET study is presented in the Table 13 below.

Table 13: Summary of Primary Efficacy Endpoints (ITT and Analysis Populations)

Category Statistic	Placebo n (%)	Tasimelteon 20 mg n (%)	P-value[1]	P-value[2]
Primary analysis	(N=38)	(N=40)		
Entrainment rate (aMT6s)[3]	1 (2.6)	8 (20.0)	0.0171	0.0291
Primary step-down analysis	(N=34)	(N=38)		
Entrainment and N24CRS ≥3[4,5]	0 (0.0)	9 (23.7)	0.0028	0.0025
Sensitivity analyses	(N=34)	(N=38)		
Entrainment in Study 3201 and N24CRS ≥3[5]	0 (0.0)	5 (13.2)	0.0286	0.0558
Entrainment and N24CRS ≥2[4,5]	0 (0.0)	11 (28.9)	0.0006	0.0005
N24CRS ≥3[5]	1 (2.9)	11 (28.9)	0.0031	0.0036
N24CRS ≥2[5]	7 (20.6)	22 (57.9)	0.0014	0.0017

[1] P-value was based on Barnard's Exact Test, two-sided.
[2] P-value was based on Fisher's Exact Test, two-sided.
[3] Entrainment was defined as having a post-baseline τ value <24.1 and a 95% CI that included 24.0. Results were based on the ITT Population from Study 3201 only.
[4] Entrainment was defined as having a post-baseline τ value <24.1 and a 95% CI that included 24.0. For patients 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 patient did not become entrained in Study 3201 but did become entrained during the screening phase of Study 3203. Results were based on the Analysis Population.
[5] Non-24 Clinical Response Scale was a 4-item scale that included LQ-nTST, UQ-dTSD, MoST, and CGI-C assessments. Each assessment was scored as 1 or 0 depending on whether the subtype responder was achieved.

The proportion of Non-24 patients who were entrained after tasimelteon treatment was statistically significantly greater than the proportion of patients who were entrained after placebo treatment (% difference = 17.4; p = 0.0171).

The proportion of patients who were entrained (aMT6s) and had a clinical response rate (N24CRS) ≥3 after tasimelteon treatment was statistically significantly greater than the proportion of patients who were entrained and had a clinical response rate ≥3 after placebo treatment.

Secondary Analyses

Table 14 presents a summary of the results of the secondary efficacy endpoints. Tasimelteon was statistically significantly superior to placebo for entrainment (measured by cortisol) and all but one of the sleep/wake parameters.

Table 14: Summary of Secondary Efficacy Endpoints (ITT and Analysis Populations)

Category Statistic	Placebo	Tasimelteon 20 mg	Treatment Difference (Tasimelteon minus Placebo)	P-value
LQ-nTST and UQ-dTSD ≥45 min, n (%)[1,2]	3 (8.8)	12 (31.6)	22.8	0.0177
LQ-nTST and UQ-dTSD ≥90 min, n (%)[1,2]	1 (2.9)	5 (13.2)	10.2	0.1312
Entrainment rate (cortisol), n (%)[1,3,4]	1 (2.6)	7 (17.5)	14.9	0.0313
Entrained and ≥45 minute improvement in LQ-nTST, n (%)[1,2,3]	0 (0.0)	10 (26.3)	26.3	0.0013
LQ-nTST, LS mean hours (LS mean minutes)[5]	0.28 (17.08)	0.95 (56.80)	0.66 (39.71)	0.0055
Entrained and ≥45 minute improvement in UQ-dTSD, n (%)[1,2,3]	0 (0.0)	11 (28.9)	28.9	0.0006
UQ-dTSD, LS mean hours (LS mean minutes)[5]	-0.30 (-17.87)	-0.77 (46.48)	-0.48 (-28.61)	0.0050
Entrained and ≥30 min improvement in MoST and SD ≤2.0 hours, n (%)[1,2,3]	0 (0.0)	8 (21.1)	21.1	0.0046
MoST, LS mean hours (LS mean minutes)[5]	0.24 (14.48)	0.58 (35.00)	0.34 (20.52)	0.0123
Entrained and ≤2.0 in average CGI-C, n (%)[1,2,3]	0 (0.0)	7 (19.4)	19.4	0.0078
CGI-C (LS mean)[6]	3.4	2.6	-0.8	0.0093

[1] P-value was based on Barnard's Exact Test, two-sided.
[2] Results for LQ-nTST, UQ-dTSD, MoST, and CGI-C assessments were based on the Analysis Population where 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.
[3] Entrainment was defined as having a post-baseline τ value <24.1 and a 95% CI that included 24.0. For patients 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 patient did not become entrained in Study 3201 but did become entrained during the screening phase of Study 3203.
[4] Results were based on the ITT Population where N=38 in the placebo group and N=40 in the tasimelteon group.
[5] P-value was based on analysis of covariance model.
[6] P-value was based on analysis of variance model.

Ancillary analyses
Subgroup Analyses

The subgroup factors, gender, race, age (<50 and ≥ 50), smoking status, with/without concomitant beta-blocker medications, and BMI (BMI<25, 25≤ BMI <30, and BMI ≥ 30), were explored to assess the impact on the primary endpoint and the key secondary endpoints. Treatment group differences were then evaluated within each subgroup.

The results were generally consistent pointing towards a treatment effect in most subgroups. However two subgroups did not seem to benefit from treatment. These were the subjects receiving concomitant beta-blocker

medication, where 0 out of 8 subjects on active entrained, and those with a BMI >= 30, where 0 out of the 14 subjects on tasimelteon entrained.

Post hoc Entrainment Rate Analysis

To better estimate tasimelteon entrainment rate, the entrainment status for all patients randomised in Study 3201 was assessed using circadian period assessments from all available time points. This included assessments conducted in the screening phase for Study 3203 for patients who continued directly from Study 3201 into Study 3203. Patients were excluded from the entrainment rate calculation if 1) they did not have a minimum of 2 aMT6s cosinor fit with $p<0.05$ for the τ calculation during randomization; 2) they had a τ >24.75 h; or 3) they had concomitant use of β-adrenoreceptor antagonists. Individuals with a Study 3201 baseline τ >24.75 were excluded based on peer-reviewed publications that suggested that these individuals may not entrain with standard melatonin agonist treatment regimens. Beta-1-blockers block sympathetic signalling to the pineal gland, resulting in suppression of night-time levels of melatonin. Consequently, patients with concomitant beta blocker usages were identified as a subpopulation for analysis and were excluded from this *post hoc* assessment. Under this assessment of entrainment, 54% (15/28) of the tasimelteon-treated patients achieved entrainment during the evaluation.

Maintenance of effect

<u>Study VP-VEC-162-3203-(</u>RESET) Multi-centre, randomised withdrawal, double-masked, placebo-controlled, parallel-group study designed to evaluate the long-term maintenance effect and safety of 20 mg of tasimelteon versus placebo in patients with Non-24.

Methods

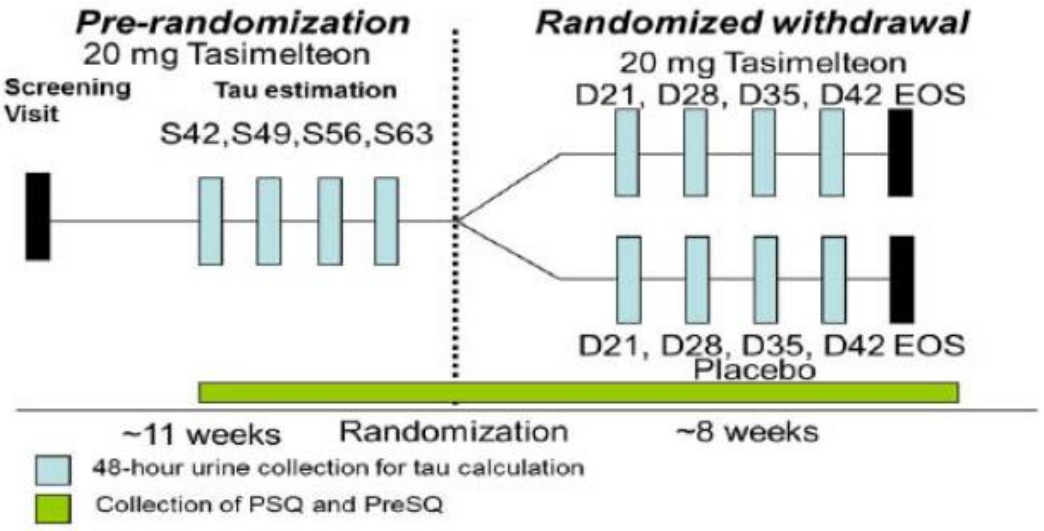
Study Participants

Patients who met the entrance criteria and who had previously participated in, or were screened for, Study 3201 (SET) were eligible to participate.

The inclusion criteria for the RESET run-in- phase was a non-entrained circadian rhythm (τ > 24.1 hours and a 95% CI > 24.0 hours). To be enrolled in the randomized withdrawal phase patients had to have responded to tasimelteon treatment during the run-in phase as measured by aMT6s, $\tau \leq 24.1$ hours and a 95% CI that included 24.0 hours.

The study had 2 phases: a Pre-Randomisation Phase (consisting of an Open-label tasimelteon Run-in Phase [approximately 6 weeks] and a τ Estimation Phase [approximately 6 weeks]), and a Randomised Withdrawal Phase (8 weeks).

Figure 1: Study Design



EOS = End of study visit; PreSQ = Pre-Sleep Questionnaire; PSQ = Post-Sleep Questionnaire.
Source: Study Protocol (Appendix 16.1.1)

Treatments

During the tasimelteon Run-in Phase, all patients who met the eligibility criteria were treated with 20 mg/day of tasimelteon for 6 weeks. Patients were instructed to take their medication one hour prior to their defined bedtime at the same time every day. During the τ Estimation Phase, all patients continued to receive 20 mg tasimelteon once daily.

Patients whose aMT6s τ values after the open label phase indicated entrainment to a 24-hour clock were randomised to receive either placebo or 20 mg tasimelteon one hour before bedtime at the same time every day for 8 weeks during the Randomised Withdrawal Phase.

Objectives

The primary objective of this study was to demonstrate the maintenance of effect of tasimelteon to entrain circadian rhythms in patients with Non-24 as measured by urinary 6-sulfatoxymelatonin (aMT6s).

The secondary objectives of this study were the following:

- To demonstrate the maintenance of effect of tasimelteon to treat Non-24 as measured by the time to relapse, with relapse defined as a 45 minute or greater decrement in the weekly average subjective night-time total sleep time (nTST) compared to the Run-in-Phase;
- To demonstrate the maintenance of effect of tasimelteon to entrain circadian rhythms in patients with Non-24 as assessed by urinary cortisol;
- To demonstrate the maintenance of effect of tasimelteon in patients with Non-24 as measured by the proportion of patients with non-entrainment and an average of 30 minutes or greater decrement of nTST compared to the Run-in Phase;
- To demonstrate the maintenance of effect of tasimelteon on subjective nTST in patients with Non-24, as assessed by the change from the Run-in Phase in the average nTST;

- To demonstrate the maintenance of effect of tasimelteon on subjective nTST in patients with Non-24 as assessed by the change from the Run-in Phase in the lower quartile of days of nTST (LQ-nTST);
- To demonstrate the maintenance of effect of tasimelteon on subjective daytime total sleep duration (dTSD) in patients with Non-24, as assessed by the change from the Run-in Phase in the average dTSD;
- To demonstrate the maintenance of effect of tasimelteon on subjective dTSD in patients with Non-24, as assessed by the change from the Run-in Phase in the upper quartile of days of dTSD (UQ-dTSD);
- To demonstrate the maintenance of effect of tasimelteon on the midpoint of sleep time (MoST); and
- To assess symptoms of withdrawal after a minimum of 3 months of tasimelteon treatment assessed by the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ).

Outcomes/endpoints

The primary efficacy endpoint was defined as the proportion of patients who become non-entrained to a 24-hour day after randomisation to tasimelteon or placebo as measured by urinary 6-ulfatoxymelatonin (aMT6s). Non-entrainment is defined as a τ value $\geq$ 24.1 or the lower bound of 95% CI > 24.0.

The secondary efficacy endpoints were as follows:

- Time to relapse with relapse defined as a 45 minute or greater decrement in the weekly average of nTST
- The proportion of non-entrainment of the circadian rhythm as measured by cortisol
- Proportion of patients that are non-entrained and have an average of 30 minutes or greater decrement of subjective nighttime total sleep time (nTST) compared to the Run-in Phase
- The change in average nTST
- The change in average LQ-nTST
- The change in average dTSD
- The change in average UQ-dTSD
- The change in average MoST

Sample size

Approximately 20 patients were planned to be randomized at a ratio of 1:1 to receive tasimelteon (20 mg/day) or placebo during the Randomized Withdrawal Phase.

Randomisation

A randomisation list was prepared prior to the start of subject screening. The list contained blocks of size 4, i.e., each block of 4 treatments contained 2 from each treatment group in a random order. Randomisation was centrally performed through the IVRS system and was not stratified by study site.

Blinding (masking)

The patients and the medical staff were not aware of which treatment was administered. Data remained masked until database lock, at which time the randomization schedule was released for the purposes of assessment of drug safety and efficacy.

Statistical methods

The primary endpoint was analysed using Barnard's exact test. Fisher's exact test was used as the sensitivity analysis method. The difference of the proportion of people with "non-entrained" circadian rhythms in each treatment group, the 95% CI, as well as the p-value of the unconditional test, was to be presented in a summary table.

Circadian cycle time to first relapse event was analysed via the Kaplan-Meier method and an unstratified log-rank test for treatment group comparison. Circadian cycle time is based on an individual's tau, a person with τ= 25 has a 24 day circadian cycle compared to a person with a τ = 24.5 who has a 48 day circadian cycle. Fifty percent of one circadian cycle would then be 12 days and 24 days respectively for the example above. Subjects who did not meet the criteria for a relapse event (i.e. a 45 minute decrement in their nTST) during the Randomised Withdrawal phase were censored at the cycle time of the discontinuation or completion of the study. A similar analysis, including the KM plot, was also done with actual calendar time to first relapse.

The cortisol non-entrainment, as well as patients who are non-entrained as measured by aMT6s and have an average of 30 minutes or greater decrement of subjective night-time total sleep time (nTST) compared to the Run-in Phase, was summarised and analysed in the same manner of the primary endpoint in the ITT population.

For the continuous efficacy variables, descriptive statistics were presented by treatment groups. 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 as a covariate. These analyses were conducted in the ITT Population.

The Intent-to-Treat Population included all subjects randomised into the study that have τ calculated post-randomisation.

Results

Recruitment

This study started on 15 September 2011 and completed on 28 November 2012.

Conduct of the study

The original protocol was amended 3 times. None of the changes in any of the amendments negatively impacted subject safety or integrity of the data collected during the course of the study.

Baseline data

There were 12 males and 8 females in the Randomised Withdrawal phase. The mean age was 52.1 years. The mean BMI was 29.10 kg/m2. The mean LQ-nTST, UQ-dTSD, nTST, and dTSD during the run-in phase were 4.717 h, 1.290 h, 6.255 h, and 0.503 h, respectively.

Numbers analysed

Of the 58 patients who were screened for this study, one patient failed screening and was not enrolled in the Run-in Phase. A total of 57 patients received tasimelteon during the Run-in Phase; 37 of those patients failed the Run-in Phase and were not enrolled in the Randomised Withdrawal Phase. The most common reason for Run-in failure was that patients did not meet the inclusion criteria for the Randomised Withdrawal Phase: 24 (41.4%) patients. An equal number of patients were randomized into each treatment group of the Randomised

Withdrawal Phase: 10 patients in the placebo group and 10 patients in the tasimelteon group. All randomised patients completed the Randomised Withdrawal Phase.

Outcomes and estimation

A statistically significant difference (70.0%; p = 0.0026) was observed between patients treated with Tasimelteon (10%). who became non-entrained and placebo treated patients (80%). The primary efficacy endpoint has been demonstrated.

During the withdrawal randomisation phase, the difference in proportion of patients who became non-entrained (cortisol) after tasimelteon was statistically significantly lower than the proportion of Non-24 patients who became non-entrained after placebo treatment (% difference = -60.0; p = 0.0118 [Barnard's Exact Test], p = 0.0230 [Fisher's Exact Test]).

Statistically significant differences between tasimelteon treated and placebo treated patients were also observed in the nTST, dTSD and MoST.

The detailed results of the RESET study are presented in the Tables 15 and 16 below.

Table 15: Summary of Primary Efficacy Endpoint (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

[1] P-value was based on Barnard's Exact Test, two-sided.
[2] P-value was based on Fisher's Exact Test, two-sided.
[3] Not entrained was defined as having a post-baseline τ value ≥24.1 or the lower bound of the 95% CI >24.0.
[4] This analysis excluded one patient who was randomized to the placebo arm of Study 3201 and was subsequently categorized as entrained.

Table 16: Summary of Secondary Efficacy Endpoints (ITT Population)

Category Statistic	Placebo (N=10)	Tasimelteon 20 mg (N=10)	Treatment Difference (Tasimelteon minus Placebo)	P-value
Circadian time to first relapse[1] (median days)[2]	24.7	NE	NA	0.0907
Actual time to first relapse[1] (median weeks)[2]	4.0	NE	NA	0.1481
Circadian time to first relapse (alternate definition)[3] (median)[2]	32.4	NE	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

[1] Time to relapse with relapse defined as a 45 minute or greater decrement in the weekly average of nTST compared to the Run-in Phase.
[2] Log-rank p-value was based on Kaplan-Meier.
[3] Time to relapse with relapse defined as a 60 minute or greater decrement in the weekly average of nTST compared to the Run-in Phase.
[4] Not entrained was defined as having a post-baseline τ value ≥24.1 or the lower bound of the 95% CI >24.0.
[5] P-value was based on Barnard's Exact Test, two-sided.
[6] P-value was based on analysis of covariance model.

Summary of Efficacy for trial SET

Title: A Phase III, multicentre, randomised, double-masked, placebo-controlled, parallel study designed to evaluate the efficacy and safety of 20mg of tasimelteon versus placebo in patients suffering from Non-24.			
Study identifier	VP-VEC-162-3201		
Design	The study began with a Pre-Randomisation Phase and was followed by either a Randomisation Phase or an Open-Label Extension Phase. Eligible patients at US sites could participate in the Randomisation Phase or the Open-Label Extension Phase depending on their circadian period (τ) length; eligible patients at sites in Germany could participate in the Randomisation Phase followed by the Open-Label Extension Phase after completing the washout segment or could directly enter the Open-Label Extension Phase depending on their τ**.**		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		26 weeks not applicable Not applicable, separate extension study (RESET)
Hypothesis	Superiority		
Treatments groups	Tasimelteon 20mg		1 tablet once a day(approximately one hour prior bedtime) Duration: 26 weeks Randomised , N 42
	placebo		1 tablet once a day(approximately one hour prior bedtime) Duration: 26 weeks Randomised , N 42
Endpoints and definitions	Primary endpoints		-The entrainment of the circadian melatonin rhythm as measured by urinary aMT6s -(a step-down objective): The Clinical Response rate corresponding to individuals who had both: 1. Entrainment of the aMT6s rhythm and 2. A score of ≥3 on the N24CRS.

	Secondary endpoints		· The proportion of responders with a combined sleep/wake response for nighttime sleep duration and daytime sleep duration defined as: 1. Increase of 90 minutes or greater in LQ-nTST and 2. Decrease of 90 minutes or greater in UQ-dTSD. · The entrainment of the circadian rhythm as measured by urinary cortisol.

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	**Intent-to-Treat (ITT) Population:** included all subjects randomised into the study that have τ calculated post-randomisation. **Analysis Population:** included all subjects in the ITT population that have at least 70% of one circadian cycle of nTST data reported during each of screening and post-randomisation.			
Descriptive statistics and estimate variability		**Placebo**	**Tasimelteon**	**1.P-value was** based on Barnard's Exact Test, two-sided. **2 P-value was** based on Fisher's Exact Test, two-sided.
	Number of subject	38(90.5%)	40(95.2%)	
	Primary endpoints			
	Entrainment rate (aMT6s)	1(2.6%)	8(20.0%)	0.0171 0.0291
	Entrainment and N24CRS ≥3	0(0.0%)	9(23.7%)	0.0028 0.0025
	Secondary endpoints	**Placebo**	**Tasimelteon**	**P-Value**
	LQ-nTST and UQ-dTSD ≥90 min, n (%)[1]	1 (2.9)	5 (13.2)	0.1312
	Entrainment rate (cortisol),	0 (0.0)	10 (26.3)	0.0313

	LQ-nTST and UQ-dTSD ≥45 min, n (%)	3 (8.8)	12 (31.6)	0.0177
	Entrained and ≥45 minute improvement in LQ-nTST, n (%)	0 (0.0)	10 (26.3)	0.0013
	LQ-nTST, LS mean hours (LS mean minutes)	0.28 (17.08)	0.95 (56.80)	0.0055
	Entrained and ≥45 minute improvement in UQ-dTSD, n (%)	0 (0.0)	11 (28.9)	0.0006
	UQ-dTSD, LS mean hours (LS mean minutes)	-0.30 (-17.87)	-0.77 (-46.48)	0.0050
	Entrained and ≥30 min improvement in MoST and SD ≤2.0 hours, n (%)	0 (0.0)	8 (21.1)	0.0046
	MoST, LS mean hours (LS mean minutes)	0.24 (14.48)	0.58 (35.00)	0.0123
	Entrained and ≤2.0 in average CGI-C, n(%)	0 (0.0)	7 (19.4)	0.0078
	CGI-C (LS mean)	0 (0.0)	7 (19.4)	0.0093

Analysis performed across trials (pooled analyses and meta-analysis)
Analyses of entrainment at month 7 in a subset of patients who moved from SET study into the run-in period for the subsequent RESET study demonstrated that 59% of patients entrained by month 7.

The combined data from SET and RESET demonstrated that entrainment response is maintained with continued tasimelteon treatment and has been confirmed in patients treated for 9 months. The analysis of individual entrainment status for each circadian rhythm assessment for all subjects who entrained during the Non-24 development program in either SET or RESET showed that entrainment occurs at month 1 for some patients and may take more than one month of treatment for other patients. Eight individuals treated with tasimelteon were entrained when assessed at month 1 in SET study. Four of these patients participated in RESET and all 4 continued to be entrained at month 7. Two of these 4 were randomized to continue tasimelteon treatment and both continued to be entrained at month 9. In total there were 9 individuals who had entrainment assessed after 9 months of tasimelteon treatment and 8/9 were entrained, demonstrating duration of entrainment response. Six individuals were not entrained at Month 1 but were entrained when measured at Month 7.

Clinical studies in special populations
No safety and efficacy studies have been performed in special populations. Given the proposed therapeutic indication, this was acceptable.

2.7.3. Discussion on clinical efficacy

Design and conduct of clinical studies
The ability of tasimelteon to entrain the master body clock in Non-24 was investigated in two randomized double-masked, placebo-controlled, multicenter, parallel-group trials, which were designed to provide evidence of short-term efficacy (SET study) and the maintenance of effect (RESET). The CHMP agreed that the design of the trials was appropriate. As there is no other authorised treatment for Non-24, the CHMP agreed that placebo was an appropriate comparator.

The N24CRS scale was designed by the applicant to be a specific and clinically meaningful measure of efficacy for treating Non-24 and was accepted by the CHMP for this purpose. Entrainment of circadian rhythm was measured by a urinary melatonin metabolite, aMT6s and was declared to be the primary endpoint for both studies.

The measurements of the urinary aMT6s, and of urinary cortisol for patients in the home environment are well established and accepted measurements of the circadian pacemaker. The pattern of production of aMT6s in both plasma and urine reproduces the pattern of measurable melatonin secretion. Peak urinary aMT6s production normally occurs 3.5 hours before wake time and peak plasma melatonin normally occurs 6 hours before wake time. Measurement of salivary and plasma melatonin rhythms is normally done in a study centre but in the pivotal trials it was done at home environment to reflect real-world conditions and to minimize the burden on the patients. The CHMP endorsed this choice of endpoint.

No discussion on Quality of Life improvement has been provided and no formal QoL measurements have been developed. However, the applicant stated that the global functioning was measured via clinician and patient reported outcomes. The absence of a formal QoL assessment was justified by the lack of approved scales for assessment of quality of life in blind people. The Applicant is planning to conduct a QoL assessment in the ongoing 3202 study and in the paediatric population. The results of the Clinical Global Impression of Change (CGI-C) from the SET study and CGI-C, Patient Impression of Change (PGI-C) and nigh-time and daytime sleep

from the RESET study show a significant improvement in the global functions. This explanation was accepted by the CHMP.

Efficacy data and additional analyses

In SET, tasimelteon entrained circadian rhythms at month 1 at a significantly higher rate than placebo as measured by aMT6s and cortisol (20% vs. 2.6 % [p= 0.0171] and 17.5% vs 2.6% [p= 0.0313] respectively). Analyses of entrainment at month 7 in a subset of patients who moved directly into RESET study demonstrated that 59% of treated patients entrained by month 7, indicating that response to treatment may take weeks or months for some patients to respond.

Tasimelteon has demonstrated superiority to placebo in both studies and most secondary endpoints also point towards a beneficial effect. However the response rates in most endpoints are around 20%, so only a minority of subjects seem to benefit from treatment. The study population was selected based on the circadian period (τ) length and excluded subjects unlikely to benefit from Tasimelteon. Treatment was then started at the optimum point in their circadian phase to optimise treatment response.

The N24CRS scale and scoring has been created by the applicant its clinical relevance required further clarification. The CHMP requested the Applicant to calculate response rates to the individual components of the N24CRS scale for all subjects in the ITT population.

The presented analyses demonstrated that the proportions of responders were higher in the tasimelteon group compared to the placebo group in all clinical components, thereby easing concerns that the overall N24CRS response may not have extended to all individual components. It was also reassuring that a treatment effect was still apparent when the whole ITT population is analysed, rather than only looking at those entrained.

The mean and median values for the continuous endpoints have also been presented and suggest a skewed distribution. The applicant therefore carried out a permutation ANCOVA t-test on the residuals from the protocol-specified ANCOVA model with the treatment term excluded. Results from this non-parametric analysis also demonstrate statistical superiority of tasimelteon when compared to placebo.

In the SET pivotal efficacy study, initiation of dosing was attempted to coincide with when the patient was predicted to be "in-phase". This was not proposed in clinical practice because it requires 24 hour urine collections but the CHMP noted that it may lead to less efficient entrainment. The applicant provided further discussion on this topic. The CHMP agreed that it would be very challenging logistically to the patient and physician to initiate treatment at a time when a patient will be "in-phase". The applicant also stated that due to the lack of evidence in the tasimelteon development program for improved efficacy when treatment is initiated in-phase versus without regard to phase, prescribing instructions should not require treatment initiation when patients are in-phase. The CHMP agreed that the entrainment rate irrespective of phase is acceptable, particularly in view of the benign safety profile of tasimelteon.

The CHMP noted that, in theory, the endpoints of entrainment and response could have been reached briefly during the study for the patient to be counted positive for the endpoint. The applicant was asked to provide individual data for time to entrain and/or respond and duration of entrainment and/or response. The analysis of the combined data from SET and RESET demonstrated that entrainment response is maintained with continued tasimelteon treatment and has been confirmed in patients treated for 9 months. It has been confirmed that entrainment is solid rather than fleeting.

As only 20% of patients became entrained in Study 3201, the CHMP has asked the Applicant to analyse if there were any physical and or psychosocial predictors of entrainment/response. In the SET study (3201) the primary

endpoint of entrainment was measured at one month and 20% of patients were responders. However, the applicant stated that it is likely that this is an underestimate of the true rate of entrainment and that an adequate trial of tasimelteon treatment requires more than one month of treatment for some patients, as demonstrated in RESET study. This has been accepted by the CHMP. The CHMP also acknowledged that the database was too small to identify factors which might be associated with success or failure by means of formal analysis. Consequently, there are no clinical pointers to patients who might be expected to respond well or poorly to tasimelteon. The CHMP endorsed applicant's recommendation that the physicians should evaluate patient response to tasimelteon 3 months after initiating treatment utilizing a clinician interview to assess their sleep-wake response and overall functioning.

The lack of efficacy observed in the SET study with concomitant beta-1-blockers administration, was attributed to their action to block sympathetic signalling to the pineal gland, resulting in suppression of night-time levels of melatonin. The CHMP agreed with this justification and an appropriate warning was included in the SmPC. The CHMP questioned if BMI ≥ 30 kg/m2 can be considered to be a risk for non-response as a result of different PK profile in this population. However, the Applicant has demonstrated that the PK of these patients does not have lower initial concentration due to a larger volume of distribution and that individuals with a BMI ≥ 30 kg/m2 do entrain. While no patients with a BMI ≥ 30 kg/m2 entrained in SET study, 36.4% did in RESET during the run-in phase, and no difference could be detected among BMI categories. The CHMP accepted this explanation.

The CHMP agreed with the applicant's recommendation in the SmPC that tasimelteon should preferably be dosed at the same time every day because of its circadian entrainment characteristics. It has been acknowledged that normal circadian entrainment requires exposure to a consistent 24 hour time cue and inconsistent timing of dose can result in loss of entrainment.

2.7.4. Conclusions on the clinical efficacy

The SET and RESET studies demonstrated the ability of tasimelteon to entrain the master body clock in patients with Non-24, and the RESET demonstrated that continued daily dosing of tasimelteon is necessary to maintain entrainment. Both studies have demonstrated the superiority of Tasimelteon over placebo.

2.8. Clinical safety

Patient exposure

The Applicant has provided safety data from fourteen Phase I studies, two Phase II studies and six Phase III studies. The safety data up to October 2013 was included in the safety database.

Study Phase	Study Population	<20 mg	20 mg	> 20 mg	Any Dose
All	All subjects[a]	170	622	555	1347
All Phase I Studies	All Phase I subjects	47	221	169	437
	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, III studies	All Phase II and Phase III subjects	123	401	386	910
	Healthy subjects – Proof of concept of circadian regulation	9	8	14	31
	Healthy subjects – induced transient insomnia	0	100	208	308
	Insomnia/ Primary Insomnia	114	109	164	387
	Non-24-Hour Sleep-wake disorder	0	184	0	184

[a] Subjects exposed to more than one dose level in different periods or studies are counted in the highest category
Source: ISS Tables 1.0.3.2, 4.0.3.2; 1105 CSR Post text table 14.1.1; 1106 CSR Post text table 14.1-1a

The applicant further grouped the exposed population as follows.

Study Group	Population Studied	Purpose of Group	Tasimelteon N	Placebo N
1	All subjects	Overall safety database	1,347	306
2	Subjects with insomnia or Non-24	Placebo-controlled phases in repeated dosing efficacy studies	429	203
2.1	Subjects with insomnia or Non-24, non-elderly studies	Non-elderly, placebo-controlled phases in efficacy studies	259	146
3	Patients with Non-24	Target indication, placebo-controlled	52	52
4	Patients with Non-24	Target indication, all safety data in exposed patients	184	N/A
5	Clinical Pharmacology and Healthy Volunteers	Safety data in all other studies	776	131

Source data: Module 2.7.4, Table 2

Following the CHMP request, the applicant has provided combined overall safety data from the entire population exposed to the medication including those in research for other indications and post-marketing data. The

applicant has also been asked to provide a summary of the length of exposure, including the length of treatment with < 20 mg, 20 mg, and >20 mg doses.

Adverse events

The AEs were classified using MedDRA dictionary. The events were assessed for severity and relationship to study medication by the investigators.

The most frequently reported adverse events in tasimelteon-treated patients across multiple study groups occurring more frequently than in placebo-treated subjects were headache, somnolence, and nightmares or unusual dreams.

The table 17 below shows a summary of adverse events (except euphoric mood, and the addition of nightmares), which are considered as having a reasonable plausibility of causality based on comparative incidence in the clinical trials and evaluation of causality from individual case reports. Consequently, they were listed in the SmPC as adverse drug reactions.

Table 17: Select Adverse Events reported in the entire exposed population with a relatedness frequency greater than 50%

System Organ Class	Preferred Term	Tasimelteon (n=1772)				Placebo (n=387)	
		Adverse Event Reported		Related	% Related	Adverse Event Reported	
Ear and Labyrinth Disorders	Tinnitus	7	0.4%	4	57%	0	0.0%
Gastrointestinal Disorders	Dry Mouth	36	2.0%	34	94%	4	1.0%
	Dyspepsia	30	1.7%	17	57%	4	1.0%
	Nausea	70	4.0%	46	66%	13	3.4%
General Disorders and Administration Site Conditions	Fatigue	44	2.5%	39	89%	6	1.6%
	Feeling Abnormal	8	0.5%	8	100%	0	0.0%
Investigations	Alanine Aminotransferase Increased	19	1.1%	13	68%	0	0.0%
	Aspartate Aminotransferase Increased	13	0.7%	8	62%	0	0.0%
	Gamma-Glutamyltransferase Increased	8	0.5%	6	75%	0	0.0%
Nervous System Disorders	Dizziness	55	3.1%	45	82%	4	1.0%
	Dysgeusia	11	0.6%	7	64%	0	0.0%
	Headache	184	10.4%	128	70%	27	7.0%
	Somnolence	153	8.6%	149	97%	15	3.9%
Psychiatric Disorders	Abnormal Dreams	25	1.4%	23	92%	4	1.0%
	Euphoric Mood	14	0.8%	14	100%	0	0.0%
	Insomnia	22	1.2%	14	64%	1	0.3%
	Sleep Disorder	35	2.0%	33	94%	3	0.8%
Renal And Urinary Disorders	Pollakiuria	9	0.5%	5	56%	0	0.0%

Serious adverse event/deaths/other significant events

There were no recorded deaths in the course of the clinical trials included in the safety database.

For all studies, 21 (21/1,654, 1.3%) subjects experienced serious adverse events. Of these, 19 were reported in the tasimelteon group. Treatment-emergent SAEs were reported in 15 (1.1%) tasimelteon-treated subjects and 2 placebo subjects (<1.0%).

Of the 21 subjects reporting serious adverse events, none of these events are considered to be related to study medication by the applicant. There was no specific trend observed in incidence of SAEs.

4 SAEs (rhabdomyolysis, cholestasis, Acute Lymphocytic Leukaemia and serotonin syndrome) were designated as important although described as not related by the applicant.

Laboratory findings

The clinical laboratory data include measurements in patients from all study Groups. Blood samples for haematology and serum biochemistry were taken at baseline and reassessed during and at the end of treatment. Overall, tasimelteon has no clinically meaningful effect on any haematology, biochemistry or urinalysis parameters.

There were no laboratory value based clinical safety signals identifiable from the clinical studies, apart from ALT increase of >3x ULN after exposure to tasimelteon, which was reported in 19 of 1772 clinical trial subjects.

Safety in special populations

Elderly

A total of 251 subjects > 65 years of age participated in this clinical development program. Dry mouth, nasopharyngitis, back pain, and somnolence were reported as TEAEs with higher incidence in tasimelteon-treated elderly subjects than in tasimelteon-treated non-elderly subjects. It is of interest that nightmares and unusual dreams have not been recorded in the elderly group.

Paediatric Patients

The safety and effectiveness of tasimelteon in paediatric and adolescent patients below the age of 18 has not been established.

The European Medicines Agency (EMA) has waived the obligation to submit the results of studies with tasimelteon in the following subsets of the paediatric population in Non-24 in the totally blind: preterm and/or term newborn infants (0-27 days) and infants and toddlers (28 days to 23 months). The EMA has deferred the obligation to submit the results of studies with tasimelteon in the following subsets of the paediatric population in Non-24 in the totally bind: children (2 to 11 years); adolescents (12 to 18 years).

Hepatic Impairment

Please see section on Pharmacokinetics.

Renal Impairment

Please see section on Pharmacokinetics.

Pregnancy and Lactation

Safety and effectiveness of tasimelteon has not been established in pregnant or lactating women.

Safety related to drug-drug interactions and other interactions

Please see section on Pharmacokinetics.

Immunological events

There were 23 subjects with potential immunological events. Of those only 3 are cases of environmental and nasal allergies. There were also further 2 reports of urticaria. One event occurred in Study VP-VEC-162-1110, in a subject receiving active comparator (midazolam) to which the event was attributed, and the other event occurred in VP-VEC-162-COSET, in a subject who was receiving placebo treatment and was taking the

concomitant medication of terbinafine, to which the event was attributed. The remaining 18 events were various cases of skin rash occurring at higher frequency in placebo subjects than in tasimelteon treated subjects.

No immunological safety signal was identified.

Discontinuation due to adverse events

In all subjects in all studies, the overall discontinuation rate for any reason was 7.8% in the tasimelteon group compared with 6.9% for the placebo group. The most common reason for discontinuation in both (placebo and active) groups was AE.

Table 18: Treatment-emergent Adverse Events Leading to Permanent Discontinuation of Trial Medication by study population sub-group

Study Group	Number (%) of Subjects with at least one TEAE leading to discontinuation	
	Tasimelteon Any Dose	Placebo
Group 1	34 (2.5%)	7 (2.3%)[a]
Group 2	14 (3.3%)	6 (3.0%)
Group 3	3 (5.8%)	2 (3.8%)
Group 4	19 (10.3%)	NA
Group 5	4 (0.5%)	1 (0.8%)

[a] includes subject VP-VEC-162-COSET[redacted]. The subject discontinued from SET because AE needed treatment with a prohibited concomitant medication. Subject was enrolled in Study 3204 (open label safety study) and remained active through the ISS data cut-off. .

Source: ISS Listing 1.0.2, ISS Table 2.0.5.2.2, ISS Table 3.0.5.2.2, ISS Table 4.0.5.2.2, and ISS Table 5.0.5.2.2, and subject narratives

In Study Group 3, there were no significant differences in the overall discontinuation rate due to AEs in the tasimelteon group (3/52, 5.8%) compared to the placebo group (2/52, 3.8%).

In Group 4, 19/184 subjects (10.3%) discontinued due to treatment-emergent AEs. This rate was higher than the rate of 5.8% in Study Group 3. These difference have been explained by the extended open-label phase in SET, and the longer follow-up period in the long-term safety studies (3202 and 3204) compared to the primary efficacy studies (SET and RESET).

Post marketing experience

The aggregate safety reports with post-authorisation data through 31 October 2014 as submitted to the US Food and Drug Administration were provided by the applicant. No new safety data or problems have been identified in clinical practice.

2.8.1. Discussion on clinical safety

An analysis of the adverse events experienced in the total clinical trial population did not reveal any new safety risks and was consistent with the safety profile established in patients with Non-24.

Euphoric mood was further examined by the Applicant and the vast majority of reports occurred with ethanol use during the ethanol interaction drug trial (VP-VEC-162-1108). Therefore, the CHMP considered that euphoric mood was not having a reasonable possibility for a causal relationship to tasimelteon and therefore is not included in the SmPC. In addition, due to the similarity between nightmares and abnormal dreams, nightmare was also considered to have a reasonable possibility for a causal relationship between the medicinal product and the adverse event and therefore was included in the SmPC.

The applicant has been asked by the CHMP to elaborate on the pharmacodynamic mechanisms and clinical implications of nightmares and unusual dreams. Primary and expanded safety analyses revealed that abnormal dreams and nightmares were largely transient and mild in nature without clinical sequelae and could be reported at any time after treatment initiation. The potential mechanism of this effect is not fully known or understood; however, this effect is likely related to tasimelteon's action to normalize REM stage sleep accumulation and resultant increased REM episodes with longer sleep episodes.

The CHMP agreed that the single report of rhabdomyolysis does not indicate a safety concern related to the use of tasimelteon nor a relationship to a change in sleep architecture resulting from tasimelteon use. No information obtained from clinical trials to date indicated that the use of tasimelteon results in disturbance of the sleep architecture, disruptive sleep behaviours nor parasomnias. The CHMP was of the opinion, that while the recorded events cannot be seen as a safety signal, it is necessary to address the possibility of such events being rare but related. The regular pharmacovigilance activities are expected to address the potential risks.

The CHMP has also asked the Applicant to summarise information on effect of tasimelteon withdrawal on circadian rhythms and to justify with the clinical evidence whether this presents a safety concern. The RESET study showed that entrainment is maintained only by continued dosing with Tasimelteon and that withdrawal from it brings the patients back to their original circadian rhythm. There does not appear to be physical or mental dependence to tasimelteon that results in "withdrawal" symptoms as typically observed with drugs like anti-depressants or opioids. The benzodiazepine withdrawal symptom questionnaire (BWSQ) administered in Study 3104, SET and RESET evaluated for drug withdrawal, and overall, there were no reported instances of withdrawal effects following discontinuation of tasimelteon, even when safety was evaluated up to 30 days post-treatment. There were also no indications of a worsening of insomnia symptoms compared to baseline, or a rebound insomnia effect, upon withdrawal of tasimelteon treatment. Based upon all the available data, the CHMP concluded that there is no evidence of withdrawal symptoms or abuse liability associated with tasimelteon use or its discontinuation.

The applicant has investigated cardiac safety in a separate study conducted in healthy volunteers. Results from this study and the recorded events overall do not raise any specific cardiac safety concerns.

2.8.2. Conclusions on the clinical safety

Based on the available data, there are no safety signals that would preclude granting of a marketing authorisation.

2.9. Pharmacovigilance

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC. The applicant's pharmacovigilance system summary

includes a reference to the location where the pharmacovigilance system master file for the medicinal product is kept and provides proof that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC.

2.10. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.1 is acceptable pending some minor changes. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 2.2 with the following content:

Safety concerns

Summary of safety concerns	
Important Identified Risk	▪ Elevated ALT
Important potential risks	▪ Nightmares and abnormal dreams ▪ Changes in prolactin levels
Missing information	▪ Use in individuals less than 18 years of age ▪ Use in pregnant and breast feeding women ▪ Use in elderly ▪ Long term use ▪ Off label use

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
VP-VEC-162-3202 Phase III study Open-label safety study of a 1-year 20 mg dose regimen of tasimelteon for the treatment of Non-24-hour	**Primary** The primary objective of this study is to characterize the effect of tasimelteon, 20 mg/night for 52 weeks, on standard measures of	Long term safety	Ongoing	Dec 2016 (planned)

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Sleep-Wake Disorder (N24HSWD) in blind individuals with no light perception Category 3	patients' safety			
VP-VEC-162-3204 Phase III study An extension open-label safety study of a 24-month 20 mg dose regimen of tasimelteon for the treatment of Non-24-hour Sleep-Wake Disorder (N24HSWD) in blind individuals with no light perception who have enrolled in other Tasimelteon clinical trials. Category 3	**Primary** The primary objective of this study is to characterise the effect of tasimelteon, 20 mg/night for 24 months, on standard measures of subject safety	Long term safety	Ongoing	May 2015 (planned)
VP-VEC-162-4203 Phase III Totally blind paediatric patients diagnosed with Non-24 who demonstrated to respond to tasimelteon treatment after an 11 week open-label treatment period	To establish the maintenance effect of tasimelteon and the minimum dose required for long-term therapy.	Use in patients under 18 years of age	Planned	To be determined

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
will be enrolled into a placebo controlled study. Category 3				
VP-VEC-162-4204 Totally blind paediatric patients diagnosed with Non-24 will be invited to enrol in a 2 year open label tasimelteon safety study. Patients will be treated with the paediatric-adjusted equivalent dose based upon the 20-mg adult dose. Category 3	This study will assess the safety of long-term treatment with tasimelteon in paediatric patients, with a special focus on assessing the effects of tasimelteon on sexual maturity/puberty.	Use in patients under 18 years of age	Planned	To be determined
VEC-162-MEC NonClinical Study Molecular Extension Coefficient of tasimelteon Category3	**Primary** Determine the MEC value of tasimelteon	Photosafety	Planned	Jul 2015 (planned)
VEC-162-3T3 NRU-PT NonClinical Study Neutral Red Uptake Phototoxicity Assay of tasimelteon and metabolites M3, M12, and M14	**Primary** Assess the phototoxicity potential of tasimelteon and metabolites M3, M12 and M14	Photosafety	Planned	Sep 2015 (planned)

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Category 3				
In Vitro Study Preclinical Study Cytochrome P450 Reaction Phenotyping in Recombinant CYP Enzymes Category 3	**Primary** To characterize the cytochrome P450 enzymes responsible for the formation of the prominent metabolites	Potential drug interactions	Planned	Dec 2015 (planned)
In Vitro Study Preclinical Study Cytochrome P450 Reaction Phenotyping in Human Liver Microsomes Category 3	**Primary** To characterize the cytochrome P450 enzymes responsible for the formation of the prominent metabolites	Potential drug interactions	Planned	Dec 2015 (planned)
Pool Analysis of Phase 1 Study Samples Compilation and Analysis of Available Data Pharmacogenetic Pooled Analysis Study to evaluate the contribution of CYP2C19 enzyme Category 3	**Primary** To evaluate the contribution of CYP2C19 enzyme on the apparent clearance of tasimelteon	Potential drug interactions	Planned	Aug 2015 (planned)

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Retrospective Analysis of Phase 1 Study Samples Retrospective Pool Analysis Pharmacogenetic Retrospective Pooled Analysis Study to evaluate the contribution of CYP2C19 enzyme Category 3	**Primary** To evaluate the contribution of CYP2C19 enzyme on the apparent clearance of tasimelteon	Potential drug interaction	Planned	Oct 2015 (planned)
DDI Study Phase IV Study An open-label study to evaluate the single-dose pharmacokinetics of tasimelteon alone and in combination with a CYP2C19 inhibitor, omeprazole, in healthy volunteer Category 3	**Primary** To evaluate the single-dose pharmacokinetics of tasimelteon 20 mg alone and in combination with a CYP2C19 inhibitor, omeprazole, at steady state	Drug-drug interaction	Planned	Dec 2016 (planned)

Risk minimisation measures

Safety concern	***Routine risk minimisation measures***	***Additional risk minimisation measures***
Elevated ALT (Identified risk)	***Text in SmPC*** ***Prescription only medicine***	***None***
Nightmares and abnormal dreams (Potential risk)	***Text in SmPC*** ***Prescription only medicine***	***None***
Changes in prolactin levels (Potential risk)	***Prescription only medicine***	***None***
Use in patients under 18 years of age (Missing Information)	***Text in SmPC*** ***Prescription only medicine***	***None***
Use in elderly (Missing Information)	***Text in SmPC*** ***Prescription only medicine***	***None***
Use in Pregnancy and Breast-feeding (Missing Information)	***Text in SmPC*** ***Prescription only medicine***	***None***
Long term use (Missing Information)	***Prescription only medicine***	***None***
Off label use (Missing	***Text in SmPC***	***None***

Safety concern	***Routine risk minimisation measures***	***Additional risk minimisation measures***
Information)	***Prescription only medicine***	

2.11. Product information

2.11.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

Benefits

Beneficial effects
The SET and RESET studies demonstrated the ability of tasimelteon to entrain the master body clock in patients with Non-24-Hour Sleep-Wake Disorder, and the RESET demonstrated that continued daily dosing of tasimelteon is necessary to maintain entrainment. Both studies have demonstrated the superiority of Tasimelteon over placebo.

The primary endpoints were achieved for SET and RESET and most secondary endpoints also showed a beneficial effect. The overall response rates in most endpoints was around 20%. In the post-hoc analysis, patients with concomitant beta-blocker and with a τ >24.75 were excluded from the analysis. Under this assessment the response rate of entrainment of the tasimelteon-treated patients achieved 54%. Analyses of entrainment in RESET study at month 7 in a subset of patients demonstrated that 59% of treated patients entrained by month 7, indicating that response to treatment may take weeks or months for some patients to respond. This late response suggests that time to response may be influenced by the individual's endogenous cycle length and the point in the cycle during which dose is initiated.

The SET and RESET studies showed significant improvement compared to placebo both in increasing nighttime sleep and decreasing daytime sleep duration. Compared to placebo, treatment with tasimelteon resulted in a greater improvement in post-randomisation Clinical Global Impression of Change (CGI-C) scores which reflects the general social, occupational and health functioning of the patient.

Uncertainty in the knowledge about the beneficial effects

In SET study, patients with a circadian period (τ) length whose upper bound of 95% CI exceeded 24.9 hours were excluded from the randomisation, as they were not expected to benefit from treatment. In the RESET study, the population was also selected based on the circadian period (τ) length and excluded subjects unlikely

to benefit from tasimelteon. Treatment was then started at the optimum point in their circadian phase to optimise treatment response. Therefore, it is possible that the response rate in the general non-24 population may be lower than observed in the clinical trials.

Subgroup analyses in SET study were only conducted for the entrainment endpoints. The results were generally consistent pointing towards a treatment effect in most subgroups. The CHMP acknowledged that the clinical trials database was too small to identify factors which might be associated with success or failure by means of formal analysis. The SET and RESET statistical analysis plans did not pre-specify analyses of predicators of tasimelteon response. Consequently, there are no clinical pointers to patients who might be expected to respond well or poorly to tasimelteon. The CHMP endorsed applicant's recommendation that the physicians should evaluate patient response to tasimelteon 3 months after initiating treatment utilizing a clinician interview to assess their sleep-wake response and overall functioning.

Risks

Unfavourable effects

Based on the available data, no serious toxicity has been identified so far. Tasimelteon does not seem to cause any clinically significant changes in vital signs and ECG. There were no laboratory value based clinical safety signals identifiable from the clinical studies, apart from ALT increase of >3x ULN after exposure to tasimelteon, which was reported in 19 of 1772 clinical trial subjects.

The most frequent adverse events recorded which were found to be related to the study medication were: Headache, Somnolence and Nightmares/Unusual Dreams.

Uncertainty in the knowledge about the unfavourable effects

There is still some uncertainty regarding quantitative importance of enzyme pathways for which the applicant has been requested to conduct a series of *in vitro* and *in vivo* studies and analysis of the available genotype information as post–approval commitment in order to further elucidate the contribution of different enzyme pathways and better inform the SmPC regarding the risk of drug-drug interactions.

Further non-clinical evaluation of Tasimelteon phototoxic potential is also required as post-approval measure.

Safety and effectiveness of tasimelteon has not been established in pregnant or lactating women.

Benefit-risk balance

Importance of favourable and unfavourable effects

Tasimelteon is a melatonin analogue, a member of a class of medicinal products generally considered to have a benign safety profile. Like other members of the class, it is well tolerated and appears to be clinically safe.

In consideration of the fact that Non-24-Hour Sleep-Wake Disorder is an orphan and debilitating condition and tasimelteon causes only few mild side effects, a response rate of 20% is still considered important for the patients who would benefit from this treatment. In the post-hoc analysis of the subpopulation most likely to benefit from the treatment, the rate of entrainment of the tasimelteon-treated patients achieved 54%. The increased response of entrainment (59%) at month 7 in the subset of patients who moved directly from SET into RESET study indicates that an even better response can be expected with time.

Benefit-risk balance
The CHMP considers benefit-risk balance of tasimelteon in the treatment of Non-24 sleep-wake disorder to be positive.

Discussion on the benefit-risk balance

For some totally visually impaired individuals, the sleeplessness and daytime somnolence that result from being non-entrained have profound impacts on their social and occupational lives. Despite the severity of the disorder there is no other approved treatment for Non-24 sleep-wake disorder in the EU.

As the adverse effects identified so far are mild and reversible, even modest benefit is judged to be sufficient to outweigh the risks.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Hetlioz in the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24) in totally blind adults and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to complete post-authorisation measures**

Not applicable

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that tasimelteon is qualified as a new active substance.