

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205677Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

BIOPHARMACEUTICS REVIEW - ADDENDUM Office of New Drug Quality Assessment			
Application No.:	NDA 205-677	Reviewer: Kareen Riviere, Ph.D.	
Submission Dates:	5/31/13; 8/20/13; 10/10/13; 10/25/13		
Division:	DNP	Team Leader: Angelica Dorantes, Ph.D.	
Applicant:	Vanda Pharmaceuticals	Acting Supervisor: Richard Lostritto, Ph.D.	
Trade Name:	Hetlioz (tasimelteon) Capsules	Date Assigned:	6/4/13
Generic Name:	Tasimelteon	Date of Review:	12/4/13
Indication:	Treatment of Non-24-Hour Disorder in the totally blind	Type of Submission: 505(b)(1) New Drug Application	
Formulation/strengths:	IR Capsule/ 20 mg		
Route of Administration:	Oral		
<p>SYNOPSIS:</p> <p>This document is an Addendum to the original Biopharmaceutics review by Dr. Kareen Riviere dated October 30, 2013 in DARRTS. In Dr. Riviere's original review it was concluded that tasimelteon drug substance is (b) (4) soluble and the proposed drug product is (b) (4) however, the final ONDQA and OCP joint Reviewers recommendation for the BCS Class I designation of tasimelteon drug substance was pending, because the Clinical Pharmacology reviewer, Dr. Jagan Parepally, had not yet determined whether the drug substance could be classified as (b) (4) permeable.</p> <p>On November 8, 2013, Dr. Parepally's Clinical Pharmacology review was entered in DARRTS. In his review, Dr. Parepally determined that the current available permeability data are inconclusive for tasimelteon to be considered as a (b) (4) permeable drug due to of the following deficiencies:</p> <ul style="list-style-type: none"> In the mass-balance study, about 84% of the radiolabel dose was recovered from urine, and feces, which is less than the threshold (90%) recommended by the BCS guidance. Tasimelteon is metabolized extensively. The overall AUC of tasimelteon in plasma is approximately 10-15 times lower when compared to total radioactivity. The sponsor did not provide evidence that tasimelteon is absorbed (b) (4) <p>In conclusion, although the provided data demonstrated that tasimelteon drug substance is (b) (4) soluble and the proposed drug product is (b) (4) based on OCP's assessment stating that tasimelteon is (b) (4) in simulated gastric and simulated intestinal fluids but it is not a (b) (4) permeable drug, the Applicant's request for a BCS-Class I classification for tasimelteon is not fully supported and therefore is not acceptable. Note that only those BCS requests that are fully supported are submitted to the CDER's BCS Committee for the final official BCS-Class I assessment and recommendation.</p> <p>RECOMMENDATION:</p> <p>The provided permeability data does not support the Applicant's request and therefore a BCS Class I designation has not been granted for tasimelteon drug substance/Hetlioz drug product. Note that this BCS recommendation does not have any impact on the approvability of NDA 205-677. Thus, Hetlioz (tasimelteon) capsules, 20 mg is still recommended for approval from a Biopharmaceutics standpoint.</p> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><u>Kareen Riviere, Ph.D.</u> Biopharmaceutics Reviewer Office of New Drug Quality Assessment</p> </div> <div style="width: 45%;"> <p><u>Angelica Dorantes, Ph.D.</u> Biopharmaceutics Team Leader Office of New Drug Quality Assessment</p> </div> </div> <p>cc: Dr. Richard Lostritto</p>			

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/s/

KAREEN RIVIERE
12/04/2013

ANGELICA DORANTES
12/04/2013

CLINICAL PHARMACOLOGY REVIEW

NDA:	205677
Brand Name:	Hetlio
Generic Name:	Tasimelteon, VEC-162, BMS-214778
Dosage Form & Strength:	Capsule (20 mg)
Indication:	Treatment of totally blind patients with Non-24-Hour Disorder (Non-24)
Applicant:	Vanda Pharmaceuticals
Submission:	505(b)(1), Priority
Submission Date:	5/31/2013
OND Division:	OND-1/Division of Neurology Drug Products
OCP Divisions:	Clinical Pharmacology DCP-1
Primary Reviewer:	Jagan Mohan Parepally, Ph.D.,
Team Leader:	Angela Men, M.D., Ph.D.
Pharmacogenomics (PG) reviewer:	Robert Schuck, Pharm.D., Ph.D.
PG Secondary Reviewer:	Michael Pacanowski, Pharm.D., M.P.H.

The OCP office level briefing was held on Friday, October 11, 2013.

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1. Executive Summary

The sponsor is seeking the approval of Hetlioz (tasimelteon, VEC-162) for the treatment of totally blind patients with a circadian rhythm (Non-24) disorder. Tasimelteon is a circadian regulator, which presumed to act through activation of melatonin MT1 and MT2 receptors. The proposed dosing regimen is 20 mg per day taken orally approximately same time prior to bedtime every night.

To support the approval of the application, the sponsor conducted a single Phase 2 and two placebo-controlled efficacy studies in subjects with Non-24 Disorder and the clinical pharmacology program consisted of single and multiple-dose studies, mass-balance and metabolic characterization study, thorough QT study and studies evaluating effect of intrinsic and extrinsic factors on tasimelteon.

The pharmacokinetics of tasimelteon is linear following single ascending doses ranging from 3 to 300 mg and multiple doses ranging from 1 to 50 mg. The time to peak concentration of tasimelteon ranges from 0.5 to 3 hours under fasting condition and the mean elimination half-life ranges 1.3 - 2.6 hours. CYP1A2 and CYP3A4 are the major isozymes involved in the metabolism of tasimelteon. Drug interaction studies with CYP1A2 inhibitor, fluvoxamine and CYP3A4 inducer, rifampin resulted in 6.5 fold increase and 90% decrease in tasimelteon exposure respectively. CYP1A1, CYP2C9/19, and CYP2D6 also minimally contribute to tasimelteon metabolism. In women, the mean overall exposure of tasimelteon was approximately 32% higher when compared to males. In the elderly subjects, AUC increased by about 2 fold when compared to the young. Cigarette smoking resulted in increased clearance of tasimelteon and decreased exposure about 40%. Subjects with severe renal impairment had a 30% lower clearance when compared to healthy subjects. The AUC of tasimelteon increased 43% and 110% in patients with mild and moderate hepatic impairment, respectively. The selection of 20 mg used in the phase III clinical studies for the Non-24 indication was based on two dose-finding clinical studies (Study 2101 and 3101) of chronic phase-shifting/ entrainment activity. Tasimelteon should be avoided in subjects taking strong CYP1A2 inhibitors and CYP3A4 inducers. Increase in tasimelteon dose may be needed in smokers.

1.1 Recommendation

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 1 (OCP/DCP-1) has reviewed the submission and finds NDA 205677 acceptable from an OCP perspective provided that an agreement is reached between the Sponsor and the Agency regarding the revised labeling language.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Pharmacokinetics

The PK of tasimelteon is essentially dose-proportional over the range of 3-300 mg following single dose administration and over the range of 1-50 mg following multiple dose administration qhs (bedtime every day) for 28 consecutive days. Dose-linearity following tasimelteon administration up to 300 mg was demonstrated. The tasimelteon PK parameters displayed high inter-individual variability.

Absorption:

Tasimelteon is absorbed with T_{max} ranging from 0.5 to 3 hours after single- or multiple-dose administration under fasting conditions. As determined by mass-balance study, total urinary recovery of tasimelteon and metabolites is 80.4%. Food delayed the absorption by approximately 1.75 hours and reduced C_{max} by 44% without a change in overall exposure (AUC).

Tasimelteon shows (b) (4) apparent permeability, P_{app} values of (b) (4) (apical to basolateral) and (b) (4) (basolateral to apical) (b) (4) determined in the Caco-2 cell model system. The overall AUC of tasimelteon in plasma is approximately 10-15 times lower when compared to total radioactivity. From the available information in the NDA, it cannot be confirmed that tasimelteon is absorbed in its (b) (4) form in humans.

Distribution:

The apparent volume of distribution at steady state ranges from 56 - 126 L in young healthy subjects. At therapeutic concentrations, tasimelteon is about ~ 90% bound to proteins.

Metabolism:

Tasimelteon is extensively metabolized by CYP enzymes in the liver. CYP1A2 and CYP3A4 are the major isozymes involved in the metabolism and CYP1A1, CYP2D6, CYP2C19, and CYP2C9 play a minor role. Phenolic glucuronidation is the major phase II metabolic route. The major metabolites formed include M12, M13, M9, M11 and M14. These metabolites are eliminated at similar rate when compared to tasimelteon. The parent to metabolite exposure ratio is 1.6, 0.96, 0.92, 0.38 and 0.05 for M12, M13, M9, M11 and M14 respectively. Metabolite M12, M14 and M9 are inactive. M13 (parent to metabolite ratio, 0.96) is approximately 13-times lower in potency at MT1 and MT2 receptors. M11 (parent to metabolite ratio, 0.38) is approximately 800-times lower in potency at MT1 and 50 times lower at MT2 receptors.

Elimination:

The major route of elimination of tasimelteon is excretion in urine. Mass balance studies show a mean recovery of 84.1% of the administered dose, out of which 80.4% of total radioactivity is excreted in urine and approximately 3.7% in feces. Less than 1% of the dose is excreted in urine as the parent compound. The elimination half-life (t_{1/2}) ranges from 1.3 to 2.6 hrs.

Dose-Response Relationships:

There is no dose-response relationship established. A 20 mg dose was studied in both pivotal phase 3 studies VP-VEC-162-3201 and VP-VEC-162-3203. The selection of 20 mg as the dose used in the phase III clinical studies for the Non-24 indication is based on two dose-finding clinical studies (Study 2101 and 3101) of chronic phase-shifting/ entrainment activity.

Study 2101 was a placebo controlled, lab-based, dose-finding, PK, PD study of 10, 20, 50, and 100 mg of tasimelteon. This study demonstrated tasimelteon's ability to phase advance circadian rhythms on the first night of treatment in a dose dependent manner as measured by melatonin.

The results show that 20 mg tasimelteon was the lowest dose that was numerically separated from placebo on inducing melatonin secretion. In this study, healthy subjects were kept in the time isolation unit for seven days and were asked to initiate sleep 5 hours prior to their scheduled sleep time.

Study 3101 used a 5-hour circadian challenge to induce transient insomnia in 412 healthy subjects. This study showed significant improvement in both objective latency to persistent sleep (LPS) and wake after sleep onset (WASO) at 20 mg and 50 mg of tasimelteon but not the 100 mg.

Note: There was no apparent dose-safety relationship identified in clinical trials. There were 2 (2/52) serious adverse events (SAEs) in tasimelteon group in phase 3 study. Overall there were 10 SAEs in the entire data base; most of the adverse events were mild to moderate in nature.

Intrinsic Factors:

Age, gender or BMI:

In women, the mean overall AUC of tasimelteon was approximately 32% higher and C_{max} was about 60% higher when compared to males. In elderly subjects, the mean C_{max} and AUC increased by about 2 fold when compared to the young. Clearance of tasimelteon was inversely related to BMI (see details in section 2.3.1). Due to the well tolerated safety profile of tasimelteon, there is no dose adjustment for the female and the elderly.

Renal Impairment:

The effect of renal impairment was evaluated in subjects with severe renal impairment including subjects on dialysis compared to healthy subjects with normal renal function. Subjects with severe renal impairment had a 30% lower clearance when compared to healthy subjects. However, mean clearance in subjects with end stage renal disease (ESRD) was comparable to that of healthy subjects. These results may be due to small sample size. All the PK parameters were characterized by wide 90% CIs. No dose adjustment is needed for renal impaired patients.

Hepatic Impairment:

The effect of hepatic impairment on tasimelteon PK was evaluated in subjects with mild or moderate hepatic impairment compared to healthy subjects with normal hepatic function in an open-label, single-dose, parallel-group study including 32 subjects. The AUC of tasimelteon increased 43% and 110% in patients with mild and moderate hepatic impairment respectively. C_{max} increased by about 20% in both mild and moderate hepatic impairment when compared to healthy subjects. No dose adjustment is necessary for subjects with mild and moderate hepatic impairment. The effect of severe hepatic impairment on tasimelteon PK was not evaluated. Tasimelteon is not recommended in patients with severe hepatic impairment.

Extrinsic Factors:

Drug-Drug Interaction (DDI)

In vitro studies:

Tasimelteon and its most abundant human metabolites M9, M12, and M13 are unlikely to cause inhibition on the following CYP enzymes, CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4/5, and transporters OATP1B1, OATP1B3, OAT1, BCRP, OCT2 and OAT3 at the therapeutic concentration.

Tasimelteon and its metabolites M9, M12, and M13 are neither P-gp substrates nor inhibitors. They are not actively transported by OATP1B1 and OATP1B3. Tasimelteon shows (b) (4) apparent permeability with P_{app} values of (b) (4) (apical to basolateral) and (b) (4) (basolateral to apical) (b) (4) determined in the Caco-2 cell model system.

The induction potential on CYP450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5) was assessed by evaluating mRNA expression of several microsomal preparations following treatment of primary cultures of human hepatocytes with tasimelteon. The results indicate that tasimelteon had the potential to induce the activity of CYP3A4/5 and CYP2C8.

Effect of co-administered drugs and alcohol on tasimelteon:

- Inhibition of CYP1A2: Fluvoxamine 50 mg QD for 6 days resulted in an 85% decrease in tasimelteon CL/F leading to a 6.5-fold increase in AUC and 2.5 fold increase in Cmax. Coadministration of strong CYP1A2 inhibitors should be avoided.
- Inhibition of CYP3A4: Ketoconazole increased the Cmax and AUC of tasimelteon 33% and 53% respectively. No dose adjustment necessary when tasimelteon is administered with CYP3A4 inhibitors.
- Induction of CYP3A4: Rifampin, a strong CYP3A4 and moderate CYP2C8, CYP2C9/2C19 inducer, decreased the exposure of tasimelteon by approximately 90%. Decrease in exposure to tasimelteon in the presence of rifampin may reduce the efficacy and is not recommended to be co-administered.
- Alcohol increased tasimelteon exposure ranging from 10% to 25%. PD parameters evaluated on subjective measures, or on sustained attention, cognition, balance or psychomotor performance in this study did not show any additive trend. Most of the impairments on PD measures were related to ethanol and not to the addition of tasimelteon.

Effect of smoking on tasimelteon exposure

Cigarette smoking (CYP1A2 induction) increased the clearance of tasimelteon and decreased AUC by approximately 40%. Decrease in exposure to tasimelteon in smokers may reduce the efficacy. Increase in tasimelteon dose may be needed in smokers.

Effect of tasimelteon on co-administered drugs:

The in vitro studies suggested that tasimelteon had the potential to induce the activity of CYP3A4/5 and CYP2C8. Daily administration of tasimelteon 20 mg for 14 days did not significantly change the AUC of midazolam and 1-OH midazolam. Similarly, there was no change in 1-OH midazolam Cmax although there was a relatively small increase (13%) in midazolam Cmax. Tasimelteon 20 mg administered daily for 16 days did not significantly change the plasma concentrations and mean pharmacokinetic parameters of rosiglitazone.

Food Effect

When tasimelteon was administered with high fat, high calorie meal, the extent of absorption, [AUC(inf)] was comparable under both fed and fasted conditions with geometric mean ratios of 108% and 106%, respectively. 90% confidence intervals were within the 80% to 125%. However, Cmax was reduced by 44% and the median Tmax was delayed from 0.75 hours to 2.5 hours. Tasimelteon is taken preferably without food.

Jagan Mohan Parepally, Ph.D.
Reviewer, Neurology Drug Products
DCP-1, Office of Clinical Pharmacology

Concurrence: Angela Men, M.D., Ph.D.
Team Leader, Neurology Drug Products
Office of Clinical Pharmacology

cc: HFD-120 NDA 205677
 CSO/C Micheloski
 HFD-860 /DDD DCP-1/R. Uppoor
 /DD DCP-1/M. Mehta

2. Question Based Review

2.1 General Attributes

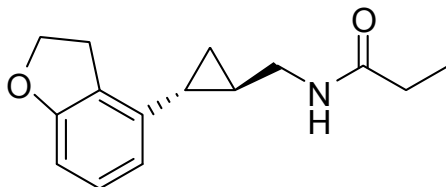
2.1.1 What are therapeutic indication(s) and the proposed mechanisms of action of Tasimelteon?

Tasimelteon is proposed for treatment of totally blind patients with Non-24-Hour Disorder (Non-24). Non-24 is a circadian rhythm disorder characterized by the inability to entrain (synchronize) the master body clock with the 24-hour day-night cycle. Patients with Non-24 have prolonged periods of misalignment of circadian rhythms, including the timing of melatonin and cortisol secretion and the sleep-wake cycle, which are associated with significant impairments in social and occupational functioning, or marked subjective distress.

The presumed mechanism of action i.e., circadian regulation by tasimelteon is mediated through activation of melatonin MT1 and MT2 receptors.

2.1.2 What are the highlights of physico-chemical properties of the drug substance?

Tasimelteon, the active ingredient of Hetlioz is chemically known as (1R, 2R)-N-[2-(2, 3-Dihydrobenzofuran-4-yl)cyclopropylmethyl]propanamide containing two chiral centers. The compound is produced as the (1R-trans)-enantiomer, with molecular formula $C_{15}H_{19}NO_2$, and molecular weight 245.32. The structural formula is provided in the Figure below. The only available strength of Hetlioz is 20 mg.



2.1.3 What are the proposed dosage(s) and route(s) of administration?

The sponsor proposes 20 mg per day taken orally before bedtime preferably at the same time every night.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor conducted 14 clinical pharmacology and biopharmaceutics studies, including single-dose and multiple dose studies in healthy subjects, renal and hepatic impaired patients. The efficacy and safety of 20 mg tasimelteon was supported by two Phase 2 studies and two pivotal efficacy studies in totally blind Non-24 disorder patients.

Study	Objective(s) of the Study	Study Design and Type of Control	Number of Subjects	Duration of Treatment
CN116-001	Safety and Tolerability, PK and PD	Randomized, double-blind, sequential, escalating dose design, placebo- controlled study	Total = 48 (36 tasimelteon and 12 PBO)	Single dose PBO lead-in followed by Single dose
CN116-002	Short-term; Safety and Tolerability, PK and PD	Randomized, double-blind, sequential, escalating dose, controlled study	Total = 32 (24 tasimelteon and 8 PBO)	Single dose PBO lead-in followed by 28 days
CN116-003	Comparison of PK across populations (age and gender); Safety and Tolerability; PD	Randomized, double-blind, placebo- controlled, parallel- group, 2 period crossover	Total = 40	Single doses, separated by 7 day wash-out
VP-VEC-162-1101	Assess AME; Safety and Tolerability	Open-Label	Total = 6	Single dose
VP-VEC-162-1102	Assess Food Effect on PK; Safety and Tolerability	Randomized, open-label, 2 period, 2 sequence, crossover	Total = 26	2 single doses (1 Fasted; 1 Fed), separated by 7 day washout
VP-VEC-162-1103	Effects on QT interval; Safety and Tolerability	Randomized, double-blind, placebo- and positive-controlled, 4 period, crossover	Total = 44	3 days followed by 4 day wash-out
VP-VEC-162-1104	PK interaction with midazolam; Safety and Tolerability	Open-label, single-sequence	Total = 24	7 days tasimelteon, 2 single doses midazolam
VP-VEC-162-1105	Effect of hepatic impairment on PK , Safety and Tolerability	Open-label, parallel- group	Total = 29	Single dose
VP-VEC-162-1106	Effect of renal impairment on PK; Safety and	Open-label, parallel- group	Total = 32	Single dose
VP-VEC-162-1107	Assess smoking status, age, gender, weight, and BMI on PK,	Open-label, parallel- group	Total = 60	Single dose

VP-VEC-162-1108	PK/PD interactions with Ethanol; Safety and Tolerability	Randomized, double-masked, 4 period crossover	Total = 28	2 single doses of tasimelteon and ethanol in combination with each other and
VP-VEC-162-1110	Assess impact on CYP450 3A4 and 2C8; Safety and Tolerability	Open-label, single sequence	Total = 24	16 days tasimelteon, 2 single doses of midazolam and rosiglitazone
VP-VEC-162-1111	Assess impact of combination treatment of a CYP1A2 inhibitor on PK parameters;	Open-label, single sequence	Total = 24	2 single doses tasimelteon, 7 days fluvoxamine
VP-VEC-162-1112	Assess impact of combination treatment of a CYP3A4 Inhibitor and CYP3A4 Inducer on PK parameters; Safety and Tolerability	Open-label, single sequence, 2 cohorts	Total = 48	2 single doses tasimelteon, Cohort 1 = 5 days ketoconazole Cohort 2 = 10 days rifampin
Phase 2 Studies				
VP-VEC-162-2101	Efficacy; Dose comparison; PK; Safety and Tolerability	Randomized, double-blind, placebo- controlled, parallel-study	Total = 39 (31 tasimelteon and 8	3 days
VP-VEC-162-3101	Efficacy; Dose comparison; Safety	Randomized, double-blind, placebo- controlled, parallel-study	Total = 412 (309 tasimelteon and 103 PBO)	Single dose

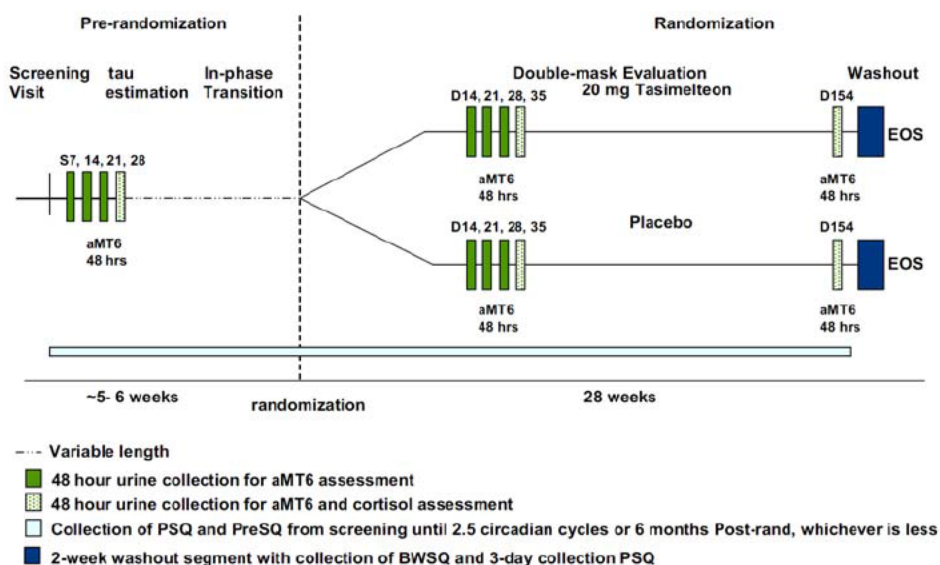
Phase 3 Studies

Two pivotal phase 3 studies were conducted for marketing approval of tasimelteon including VP-VEC-162-3201 (SET) and VP-VEC-162-3203 (RESET).

VP-VEC-162-3201 (SET)

This was a randomized, double-masked, placebo-controlled, parallel-study conducted to assess entrainment rate and clinical response following treatment with tasimelteon. At the pre-randomization, 136 subjects were included, out of which conducted in 84 blind subjects with Non-24 hour disorder were randomized to either placebo or treatment group for 28 weeks. Sixty two subjects completed the study. The following schematic represents the study design.

Study Design



The responder rate in this study was approximately 20%-25%. Following table represents clinical response parameters and ANCOVA results evaluated in this study.

Endpoint	ANCOVA (p value)
LQ-nTST	0.0515
UQ-dTSD	0.0097
MoST	0.0284
nTST	0.1296
dTSD	0.192
CGIC	0.0086

LQ-nTST: lower quartile of nights of subjective nighttime total sleep time

UQ-dTSD: upper quartile of days of subjective daytime sleep duration

MoST: midpoint of sleep timing

nTST: nighttime total sleep time

dTSD: days of subjective daytime sleep duration

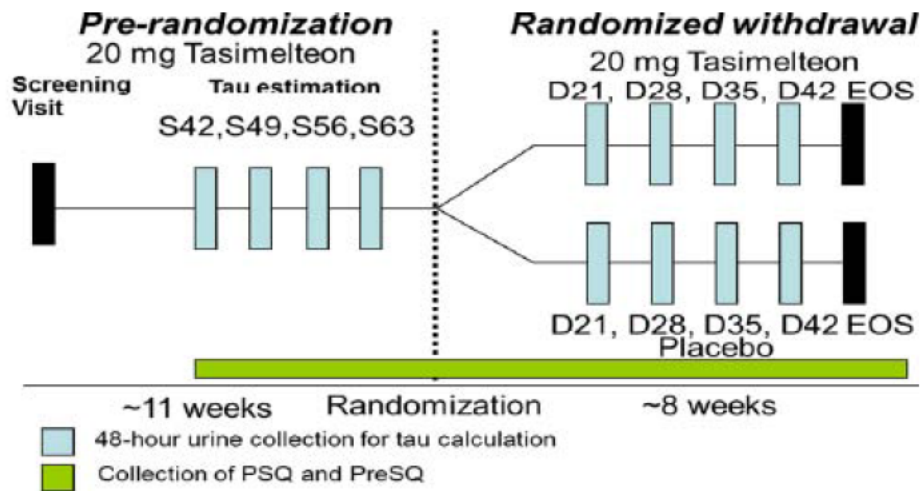
CGIC: Clinical Global Impression-Change

VP-VEC-162-3203 (RESET)

This study was a randomized, withdrawal, placebo-controlled, parallel-study. In this study subjects with Non-24 hour disorder who were treated with tasimelteon for 6 months were randomized to placebo or treatment for 8 weeks to evaluate maintenance effects mainly

entrainment rate and clinical response of tasimelteon conducted in 20 subjects. The following schematic represents the study design.

Study Design



Following table represents clinical response parameters and ANCOVA results evaluated in this study.

Endpoint	ANCOVA (p value)
LQ-nTST	0.0233
UQ-dTSD	0.0266
MoST	0.0108
nTST	0.1315
dTSD	0.0547

LQ-nTST: lower quartile of nights of subjective nighttime total sleep time
UQ-dTSD: upper quartile of days of subjective daytime sleep duration
MoST: midpoint of sleep timing
nTST: nighttime total sleep time
dTSD: days of subjective daytime sleep duration

2.2.2 Is there a biomarker for estimating entrainment of circadian rhythms? Can the biomarker be used to predict the clinical responses?

Non-24 is a circadian rhythm disorder characterized by the inability to entrain (synchronize) the master body clock with the 24-hour day-night cycle. Patients with Non-24 have periods of misalignment of circadian rhythms measured by melatonin and cortisol which are associated with significant impairments in the sleep and wake cycle.

The sponsor proposed to use the biomarker, urinary 6-sulfatoxymelatonin (aMT6s) for the proportion of entrainment and non-entrainment of the circadian melatonin rhythm. Literature suggests that peak urinary aMT6s production normally occurs 3.5 hours before wake time, albeit with a wide range in the normal population, while peak plasma melatonin normally occurs 6 hours before wake time. However, according to the Agency, aMT6s is a biomarker not well-enough understood in Non-24 disorder to take the place of clinically meaningful endpoints. The Agency disagreed with the sponsor in use of biomarker aMT6s as a primary efficacy end-point.

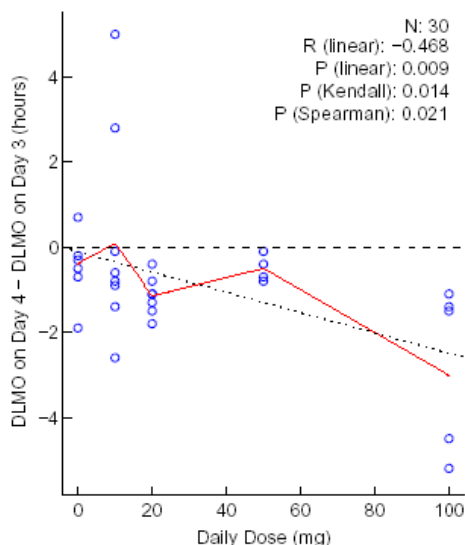
2.2.3 Dose-Response

2.2.3.1. Is there any significant dose-response relationship? And does the relationship support the proposed dosing regimen?

There is no dose-response (clinical endpoints for efficacy and safety) relationship established as only one dose, 20 mg, was studied in both pivotal phase 3 studies VP-VEC-162-3201 and VP-VEC-162-3203. The selection of 20 mg as the dose used in the phase III clinical studies for the Non-24 indication is based on two dose-finding clinical studies (Study 2101 and 3101) of chronic phase-shifting/ entrainment activity.

Study 2101 demonstrated tasimelteon's ability to phase advance circadian rhythms on the first night of treatment in a dose dependent manner as measured by melatonin (see figure below). Melatonin secretion was dose-dependent. The results showed that 20 mg tasimelteon was the lowest dose that numerically separated from placebo. In this study, healthy subjects were kept in the time isolation unit for seven days and were asked to initiate sleep 5 hours prior to their scheduled sleep time.

Change in DLMO_{25%}, LOQ₅ between night 4 and night 3 by dose



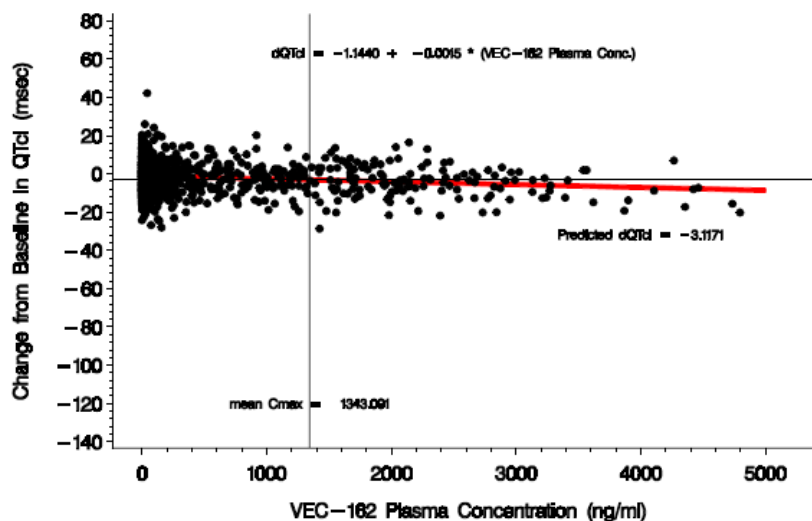
Study 3101 used a 5-hour circadian challenge to induce transient insomnia in 412 healthy subjects. This study showed significant improvement in both objective latency to persistent sleep (LPS) and wake after sleep onset (WASO) at 20 mg and 50 mg of tasimelteon but not at 100 mg [LPS=21.5 min, $p<0.001$ and 26.3 min, $p<0.001$, 22.8 min, $p<0.001$ for 20, 50, and 100 mg

respectively; WASO= 24.2 min, p=0.017, 33.7 min, p=0.001, and 17.4 min, p=0.081 for 20, 50, and 100 mg respectively.]

2.2.3.2 Does this drug prolong the QT or QTc interval?

No, tasimelteon did not produce a significant QTc prolongation effect (see figure below) in healthy subjects who received tasimelteon 20 mg and 300 mg (supratherapeutic dose).

Figure: QTcI Change from Baseline versus VEC-162 Concentration



2.2.4 What are the PK characteristics of the drug and its major metabolite?

Tasimelteon is absorbed with median T_{max} ranging from 0.5 to 3 hours. Tasimelteon is extensively metabolized by CYP1A2 and CYP3A4 and CYP1A1, CYP2C9/19, and CYP2D6 minimally contribute to tasimelteon metabolism. The observed mean elimination half-life is 1.32 hours. The mean terminal elimination half-life of the main metabolites ranges from 1.26 to 3.67. The pharmacokinetics of tasimelteon is linear following single ascending doses ranging from 3 mg to 300 mg and multiple doses ranging from 1 mg to 50 mg.

2.2.4.1 What are the single and multiple dose PK parameters?

PK characteristics of tasimelteon following single and multiple dose administration was evaluated in several studies, CN116-001, CN116-002, CN116-003, VP-VEC-162-1101, VP-VEC-162-1102 and VP-VEC-162-110.

Tasimelteon is absorbed with a median T_{max} of 0.5 hrs (ranging from 0.5 to 3 hours) following single- or multiple-dose administrations. Tasimelteon PK parameters, C_{max} and AUC, are essentially dose-proportionality in the 3-300 mg range following single dose and in the 1-50 mg range following multiple dose administrations. An average (\pm SD) tasimelteon C_{max} is 235 ± 128 ng/mL occurred at a median T_{max} of 0.50 hours (range 0.25 -2.00 hours), and AUC average (\pm SD) is 411.4 ± 327.8 h*ng/mL. T_{max} , is variable and dependent on the food intake with high-

fat, high calorie meal. The median T_{max} was about 2.25-hours. The accumulation index at steady state ranged from 1.22 to 2.22. The tasimelteon exposure profiles displayed high inter-individual variability. The elimination half-life (t_{1/2}) ranges from 1.3 to 3.05 hrs.

Following table illustrates PK parameters of tasimelteon and its main metabolites calculated from studies VP-VEC-162-1105, 1106, 1107, 1110, and 1112 in healthy volunteers (n=115)

	Parameter	Units	N	Arithmetic Mean	SD	Minimum	Median	Maximum
Tasimelteon	C _{max}	ng/mL	115	234.9	127.7	40.18	214.8	838.1
	T _{max}	h	115	0.569	0.233	0.250	0.500	2.000
	AUC	h*ng/ml	115	411.4	327.8	55.67	344.9	2,102
	T _{1/2}	h	115	1.32	0.431	0.648	1.26	3.05
M3	C _{max}	ng/mL	32	133.19	52.72	43.64	129.46	243.87
	T _{max}	h	32	0.658	0.201	0.500	0.500	1.050
	AUC	h*ng/ml	16	220.4	62.32	90.06	233.7	312.3
	T _{1/2}	h	16	3.67	2.22	1.32	2.77	9.74
M9	C _{max}	ng/mL	115	238.7	96.7	47.43	229.3	675.6
	T _{max}	h	115	0.690	0.251	0.250	0.750	2.00
	AUC	h*ng/ml	115	379.4	105.8	182.1	359.7	718.6
	T _{1/2}	h	115	1.41	0.405	0.703	1.33	3.02
M11	C _{max}	ng/mL	115	49.52	16.31	20.05	49.92	92.49
	T _{max}	h	115	1.10	0.389	0.500	1.000	3.000
	AUC	h*ng/ml	103	155.8	64.04	51.84	155.80	342.0
	T _{1/2}	h	103	2.02	0.632	0.782	1.91	3.94
M12	C _{max}	ng/mL	115	96.48	28.40	31.21	94.19	173.08
	T _{max}	h	115	1.38	0.958	0.250	1.00	6.00
	AUC	h*ng/ml	115	655.2	349.7	155.2	594.6	2,095
	T _{1/2}	h	115	3.33	1.32	1.36	3.11	8.54
M13	C _{max}	ng/mL	115	288.8	93.92	90.82	285.7	616.3
	T _{max}	h	115	0.585	0.242	0.250	0.500	2.00
	AUC	h*ng/ml	115	393.7	138.7	151.6	372.8	926.7
	T _{1/2}	h	115	1.26	0.480	0.439	1.19	3.01
M14	C _{max}	ng/mL	115	6.427	3.337	1.467	5.646	19.12
	T _{max}	h	115	0.820	0.512	0.250	0.750	3.00

	AUC	h*ng/ml	107	21.98	20.10	3.770	15.29	105.0
	T½	h	107	1.98	1.02	0.493	1.77	6.34

2.2.4.2 What are the characteristics of drug absorption?

Tasimelteon is absorbed with a Tmax ranging from 0.5 to 3 hours after single- or multiple-dose administration under fasting conditions. Following administration of tasimelteon (single 100 mg dose) with high-fat, high calorie meal, the Cmax was 44% lower than that when given in a fasted state. Median Tmax was delayed by approximately 1.75 hours. However, the overall AUC was not affected.

Tasimelteon shows (b) (4) in vitro apparent permeability with Papp values of (b) (4) (apical to basolateral) and (b) (4) (basolateral to apical) (b) (4) determined in the Caco-2 cell model system. Tasimelteon is stable in simulated gastric fluid and simulated intestinal fluid for 3 hours. The overall AUC of tasimelteon in plasma is approximately 10-15 times lower when compared to total radioactivity. From the available information in the NDA, it cannot be confirmed that tasimelteon is absorbed in its (b) (4) form in humans.

2.2.4.3 What are the characteristics of drug distribution?

The apparent volume of distribution at steady state in the young healthy subjects ranges from 56 - 126 L. At therapeutic concentrations, tasimelteon is about 89% - 90% bound to proteins.

2.2.4.4 What are the characteristics of drug metabolism?

Tasimelteon is extensively metabolized by CYP enzymes in the liver. CYP1A2 and CYP3A4 are the major isozymes involved in the metabolism and CYP1A1, CYP2D6, CYP2C19, and CYP2C9 play a minor role. Phenolic glucuronidation is the major phase II metabolic route. The major metabolites formed include M12, M13, M9, M11 and M14. These metabolites are eliminated at similar rate when compared to tasimelteon. The parent to metabolite AUC ratio is 1.6, 0.96, 0.92, 0.38 and 0.05 respectively.

Metabolite M12 is inactive, shows higher parent to metabolite ratio (1.6). M13 (parent to metabolite ratio, 0.92) is approximately 13-times lower in potency at MT1 and MT2 receptors. M11 (parent to metabolite ratio, 0.38) is approximately 800-times lower in potency at MT1 and 50 times lower at MT2 receptors as shown in the table below. Following table indicates activities of tasimelteon and its major metabolites at MT1 and MT2 receptors.

Potency of tasimelteon and metabolites M9, M11, and M13 for human melatonin MT1 and MT2 receptors

Compound	IC ₅₀ ^a (nM)	K _i ^a (nM)
MT₁ receptor		
Tasimelteon	0.586 ± 0.025	0.304 ± 0.013
M13	7.69 ± 0.416	4 ± 0.216
M11	481 ± 0.047	250 ± 0.024
M9	2,260 ± 0.346	1,180 ± 0.179
MT₂ receptor		
Tasimelteon	0.133 ± 0.014	0.0692 ± 0.007
M13	1.78 ± 0.430	0.922 ± 0.224
M11	6.63 ± 1.28	3.44 ± 0.663
M9	139 ± 0.005	71.9 ± 0.003

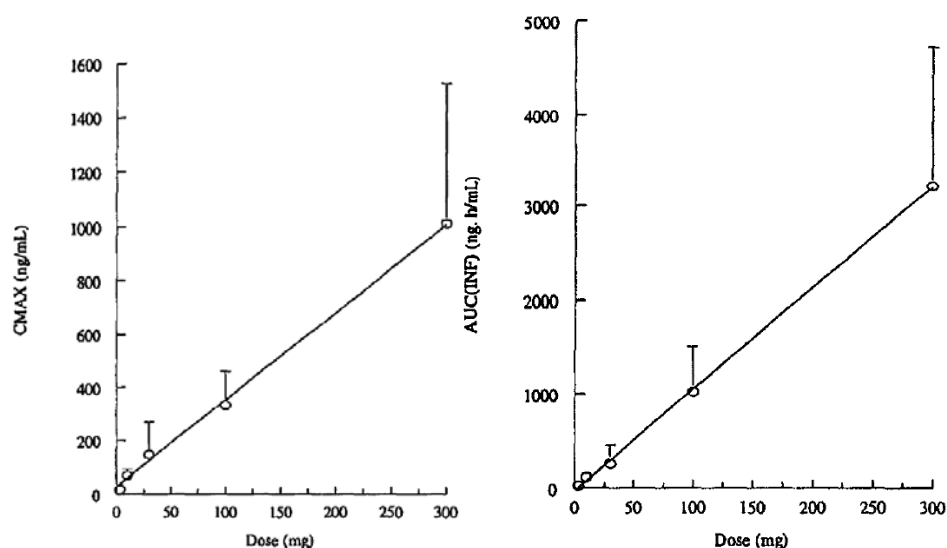
2.2.4.5 What are the characteristics of drug elimination?

The major elimination route of tasimelteon is excretion in urine. Mass balance studies show a mean recovery of 84.1% of the administered dose, out of which 80.4% of total radioactivity was excreted in urine and approximately 3.72% in feces. Less than 1% of the dose was excreted in urine as the parent compound. The elimination half-life ($t_{1/2}$) ranged from 1.3 to 2.6 hrs.

2.2.4.6 Based on tasimelteon PK parameters, what is the degree of linearity in the dose-concentration relationship?

Tasimelteon PK parameters increase in an essentially dose proportional manner (figures below) over the range of 3-300 mg and 1-50 mg, following single-dose and multiple-dose, respectively. The maximum concentration (C_{max}) and AUC show high inter-individual variability. However, in multiple dose study AUC(τ) increase more than proportionally from 50 to 150 mg. The half-life of tasimelteon is approximately 2 hours. Steady state is achieved by Day 15. The accumulation index at steady state ranged from 1.22 to 2.22.

Mean (SD) PK Parameters C_{max} and AUC(inf) Following Single Dose Levels of 3 to 300 mg.



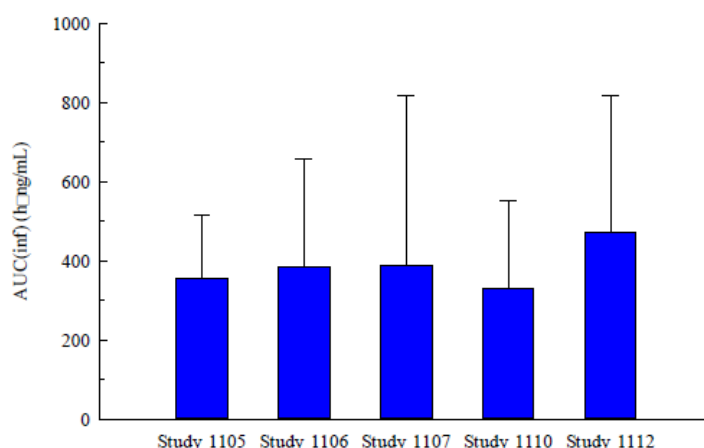
2.2.4.7 How does the PK of tasimelteon in healthy subjects compare to that in patients?

It is unknown. PK samples were not collected in the Non-24 population due to the difficulty of nighttime sample collection that would interfere with the measurement of key study endpoints.

2.2.4.8 What is the inter-subject variability of PK parameters in healthy subjects and patients?

The PK parameters inter-subject variability of tasimelteon and its main metabolites are generally moderate to high. The mean inter-subject variability of C_{max} and AUC is approximately in the range of 54 to 80% in single and multiple dose studies. The mean estimate of inter-subject variability of T_{max} and T_{1/2} ranges from 32% to 41%. Following figure represents the AUC of tasimelteon following 20 mg dose from five studies (total n=115).

In studies including subjects with renal and hepatic impairment, the inter-subject variability was up to 3 fold when compared to that of healthy controls. The apparent factors contributing to the inter-subject variability were gender, age and BMI.



2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on efficacy or safety of tasimelteon?

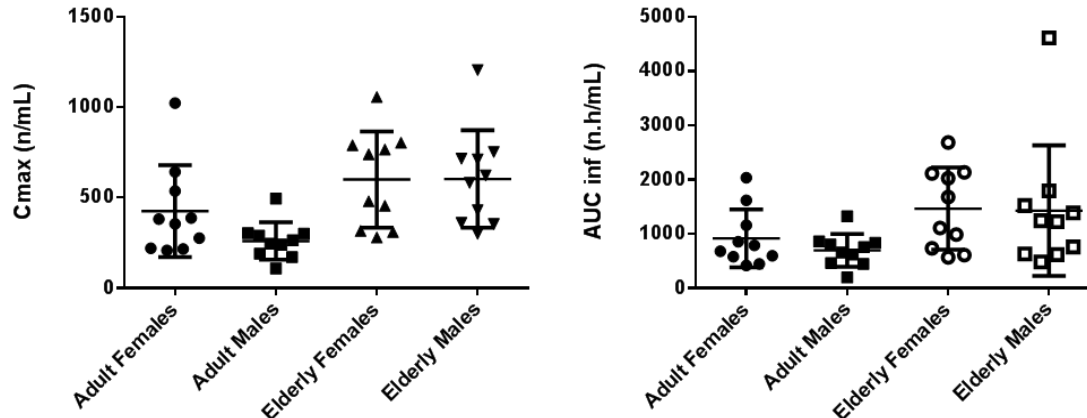
The influence of intrinsic factors such as age and gender on PK of tasimelteon was evaluated in study CNN116-003. The influence of age and BMI on PK of tasimelteon was evaluated in Study 1107. In women, the mean exposure of tasimelteon was approximately 20-30% higher when compared to males. In elderly subjects, C_{max} and AUC increased by about 2 fold when compared to the young as shown in the table below.

Summary of pharmacokinetic parameters for tasimelteon after oral administration of single 50 mg dose to young and elderly healthy male and female subjects

Parameter	Gender	
	Males	Females

Age		
Young		
C _{max} (ng/mL)	261 ± 104 (10)	426 ± 254 (10)
T _{max} (h)	1.00 (10) [0.50 - 2.00]	0.88 (10) [0.50 - 1.00]
AUC(inf) (h×ng/mL)	697 ± 303 (10)	920 ± 534 (10)
t _{1/2} (h)	2.79 ± 1.81 (10)	3.44 ± 2.11 (10)
Elderly		
C _{max} (ng/mL)	604 ± 269 (10)	601 ± 266 (10)
T _{max} (h)	0.50 (10) [0.50 - 1.00]	0.75 (10) [0.50 - 1.00]
AUC(inf)(h×ng/mL)	1,429 ± 1,200 (10)	1,466 ± 755 (10)
t _{1/2} (h)	2.99 ± 1.34 (10)	3.30 ± 0.52 (10)

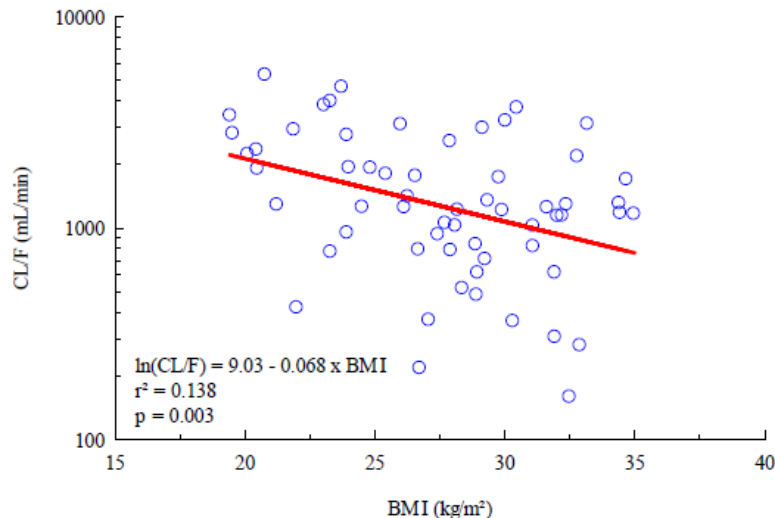
Following figure illustrates individual distribution of C_{max} and AUC_{inf} along with mean and standard deviation.



Note: One of the subjects (#24) elderly males) had unusually high C_{max} and AUC. The reason for high tasimelteon levels in this subject is not clearly understood. This subject did not have adverse events. During the course of clinical development, 153 total subjects > 65 years of age were treated with tasimelteon in placebo-controlled studies in doses ranging from 1 mg to 50 mg per day for 4-26 weeks. In two Phase 3 studies 5/52 subjects were in tasimelteon treatment group. The adverse event profile of these subjects is similar to the overall adverse event profile in pivotal Phase 3 studies in blind subjects with Non-24. No dose adjustment for tasimelteon is recommended for individuals older than 65 years of age or for females.

The clearance of tasimelteon is inversely related to BMI as shown in the figure below.

Relationship between Tasimelteon CL/F and BMI after Oral Administration of Single 20 mg doses of Tasimelteon to Young and Elderly Non-Smokers (Study 1107).

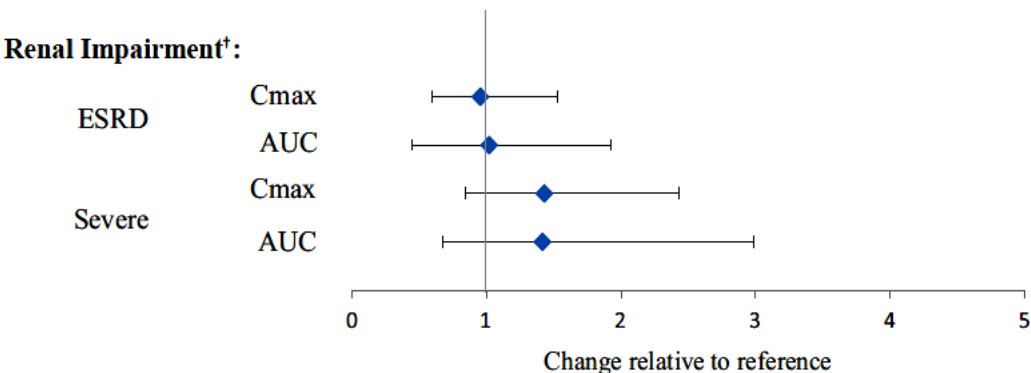


Approximately two fold decrease in CL/F is observed among the subjects with about two fold change in BMI. No dose adjustment for tasimelteon is recommended for obese subjects.

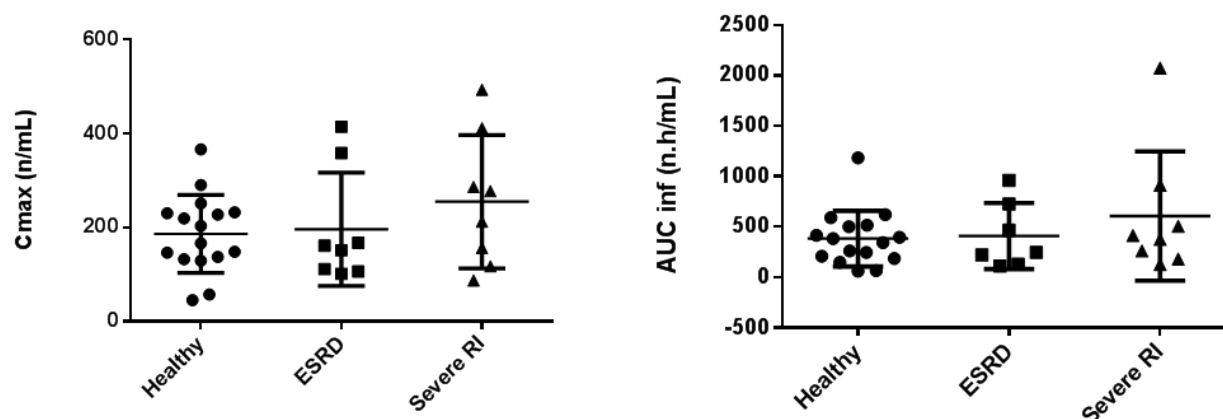
2.3.1.1 Renal impairment

The effect of renal impairment is evaluated using 20 mg tasimelteon in subjects with severe renal impairment including subjects on dialysis compared to healthy subjects with normal renal function in study VP-VEC-162-1106 (n=32). Subjects with severe renal impairment had a 30% lower a clearance when compared to that of healthy subjects. However, mean clearance in subjects with ESRD was comparable to that of healthy subjects. All the PK parameters were characterized by wide 90% CIs as shown in the figure below.

Impact of renal impairment on tasimelteon pharmacokinetics



Following figure illustrates individual distribution of C_{max} and AUC_{inf} along with mean and standard deviation.



Note: One of the subjects (b) (6) in severe renal impairment group had unusually high AUC. The reason for high tasimelteon levels in this subject is not clearly understood. There were no SAEs, severe AEs, or discontinuations during the study. There were no clinically significant changes in chemistry, hematology, ECG, and physical examinations following dosing with tasimelteon for subjects in any of the renal function groups.

Metabolite M13 showed approximately 20% decrease in geometric mean exposure in ESRD patients when compared to the matched controls. Severely impaired subjects have similar exposure compared to the matched controls characterized by wide confidence intervals as shown in the table below.

Statistical Comparison of Pharmacokinetic Parameters for Metabolite M13 After Oral Administration of Single 20 mg Doses of Tasimelteon to Subjects with ESRD, Subjects with Severe Impairment, and Matched Controls.

Parameter	ESRD vs. Matched Controls			Severe Impairment vs. Matched Controls		
	Geometric Mean Ratio (%)*			Geometric Mean Ratio (%)*		
	Estimate	90% Confidence Interval		Estimate	90% Confidence Interval	
C _{max}	109.88	80.46	→	150.05	107.92	63.79 → 182.56
AUC(0-t)	102.27	79.61	→	131.37	97.61	65.32 → 145.86
AUC(inf)	102.06	79.30	→	131.35	98.02	65.82 → 145.98
t _{1/2}	106.77	66.91	→	170.37	132.26	94.53 → 185.04

*Based on analysis of natural log-transformed parameters.

Metabolite M11 showed approximately 80% increase in geometric mean exposure in ESRD patients when compared to matched controls. Severely impaired subjects have similar exposure compared to the matched controls characterized by wide confidence intervals as shown in the table below.

Statistical Comparison of Pharmacokinetic Parameters for Metabolite M11 After Oral Administration of Single 20 mg Doses of Tasimelteon to Subjects with ESRD, Subjects with Severe Impairment, and Matched Controls.

Parameter	ESRD vs. Matched Controls			Severe Impairment vs. Matched Controls		
	Geometric Mean Ratio (%)*			Geometric Mean Ratio (%)*		
	Estimate	90% Confidence Interval		Estimate	90% Confidence Interval	
C _{max}	119.32	104.41	→ 136.36	97.10	69.09	→ 136.45
AUC(0-t)	136.70	101.94	→ 183.30	114.48	73.66	→ 177.91
AUC(inf)	180.12	124.74	→ 260.11	97.13	65.18	→ 144.73
t _{1/2}	392.09	199.69	→ 769.87	187.79	110.84	→ 318.16

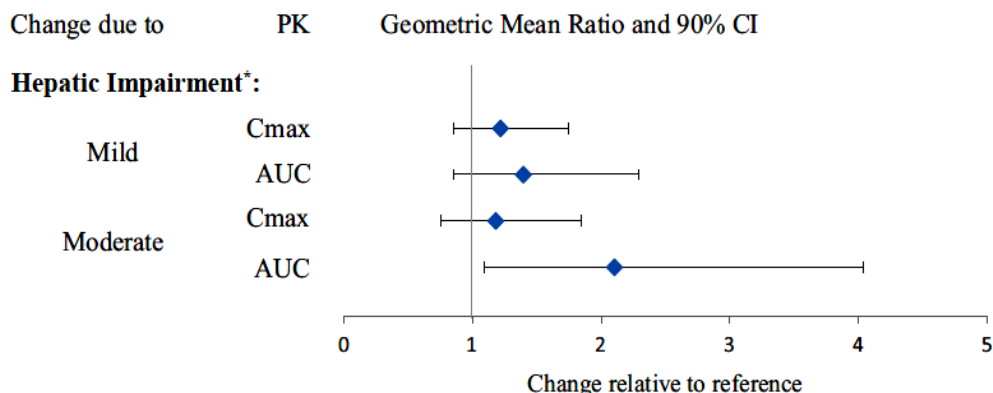
*Based on analysis of natural log-transformed parameters.

There was no apparent dose-safety relationship identified in clinical trials. There were 2 (2/52) serious adverse events (SAEs) in tasimelteon group in phase 3 study. Overall there were ten SAEs in the entire data base; most of the adverse events were mild to moderate in nature. In single ascending dose and multiple ascending dose studies tasimelteon was tolerated upto 300 mg and 150 mg respectively without any SAEs. No dose adjustment is indicated for exposure increases related to renal impairment.

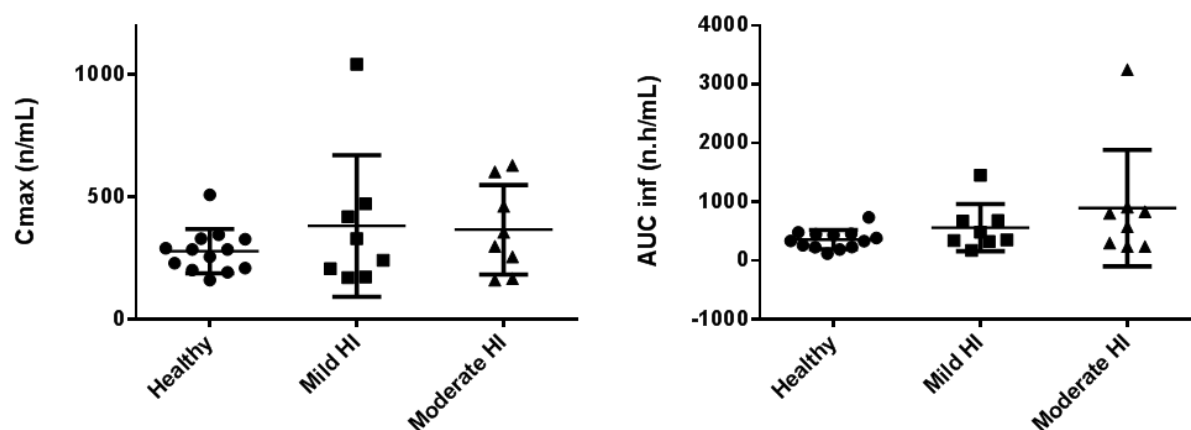
2.3.1.2 Hepatic Impairment

The effect of hepatic impairment on tasimelteon PK was evaluated in subjects with mild or moderate hepatic impairment in an open-label, single-dose, parallel-group study including 32 subjects in Study VP-VEC-162-1105. The AUC of tasimelteon increased by 43% and 110% in patients with mild and moderate HI respectively and C_{max} increased by about 20% in both mild and moderate HI when compared to healthy subjects.

Impact of hepatic impairment on tasimelteon pharmacokinetics



Following figure illustrates individual distribution of C_{max} and AUC_{inf} along with mean and standard deviation.



Note: One of the subjects (b) (6) in moderate hepatic impairment group had unusually high AUC. The reason for high tasimelteon levels in this subject is not clearly understood. This subject did not have adverse events.

Metabolite M13 ratio was 7% to 28% lower when compared to the matched controls in mild HI subjects. The Cmax was approximately 60% lower and AUC was approximately 30% lower in subjects with moderate HI. All the PK parameters were characterized by wide confidence intervals as shown in the table below.

Statistical comparison of pharmacokinetic parameters for M13 after oral administration of 20 mg of tasimelteon to subjects with mild or moderate hepatic impairment and healthy matched controls

Parameter	Geometric Mean Ratio (%)*	
	Estimate	90% Confidence Interval
Mild Hepatic Impairment vs. Matched Controls		
Cmax	72.24	55.20 → 94.54
AUC(inf)	93.92	72.91 → 120.97
t½	117.22	93.89 → 146.34
Moderate Hepatic Impairment vs. Matched Controls		
Cmax	39.69	29.57 → 53.28
AUC(inf)	70.73	53.23 → 93.98
t½	133.87	99.93 → 179.33

Metabolite M11 ratio for PK parameters was similar when compared to matched controls in mild HI subjects. However, Cmax was approximately 36% lower and AUC was approximately 11% lower in subjects with moderate HI. All the PK parameters were characterized by wide confidence intervals as shown in the table below.

Statistical comparison of pharmacokinetic parameters for M11 after oral administration of 20 mg of tasimelteon to subjects with mild or moderate hepatic impairment and healthy matched controls

Parameter	Geometric Mean Ratio (%)*	
	Estimate	90% Confidence Interval
Mild Hepatic Impairment vs. Matched Controls		
C _{max}	90.38	70.03 → 116.65
AUC(inf)	100.65	70.21 → 144.28
t _{1/2}	101.10	82.03 → 124.60
Moderate Hepatic Impairment vs. Matched Controls		
C _{max}	64.56	50.41 → 82.69
AUC(inf)	89.61	61.07 → 131.50
t _{1/2}	116.53	86.43 → 157.13

No dose adjustment is necessary for subjects with mild and moderate hepatic impairment. The effect of severe hepatic impairment on tasimelteon PK is not evaluated. Tasimelteon is not recommended in patients with severe hepatic impairment.

2.3.2 Is there a potential impact of genetic variation in drug metabolizing enzymes on tasimelteon exposure and whether additional pharmacogenetic studies are indicated on the basis of these results?

The applicant evaluated associations between CYP2D6, CYP1A2, CYP2C9, and CYP2C19 genotype and exposure of tasimelteon in four healthy subject studies (n=112). CYP1A2, CYP2C9 and CYP2C19 genotype were not associated with tasimelteon exposure in any study. In VP-VEC-162-1102, CYP2D6 poor metabolizers had significantly lower AUC and longer t_{1/2} compared to extensive metabolizers. This unexpected finding (based on in vitro data) was not replicated in two additional studies (CNN116-001 or CNN116-002), which found no association between CYP2D6 genotype and tasimelteon PK. The applicant suggests that CYP2D6 generates a metabolite that subsequently inhibits tasimelteon metabolism; however, no data are provided to support this hypothesis. Given the lack of a significant exposure-response relationship for efficacy or safety endpoints the high PK variability is not likely to be clinically significant at the proposed doses. Additional gene-drug or drug-drug interaction studies do not appear to be indicated on the basis of these findings.

2.4 Extrinsic Factors

2.4.1 Is the drug and/or the major metabolite a substrate, inhibitor or inducer of CYP enzymes on an in vitro basis?

Metabolism by CYP: The in vitro data indicates that tasimelteon is mainly metabolized by CYP1A2 and CYP3A4 with minor contribution from CYP1A1, CYP2C9/19, and CYP2D6.

Inhibition potential: The potential for tasimelteon and its most abundant human metabolites to inhibit, the major CYP enzymes in human liver microsomes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 was investigated in studies (b) (4) 12A024, (b) (4) 065016 and (b) (4) 135015. Study results indicate that tasimelteon and its most abundant metabolites are unlikely to cause inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19 or 3A4/5 at the therapeutic dose.

Induction potential:

Potential for induction of CYP450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5) was assessed by evaluating mRNA expression of several microsomal preparations following treatment of primary cultures of human hepatocytes with tasimelteon in Study (b) (4) 063014. The results indicate that tasimelteon had the potential to induce the activity of CYP3A4/5 and CYP2C8.

2.4.2 Is the drug and/or the major metabolite a substrate and/or an inhibitor of P-glycoprotein transport processes or any other transporter system?

The inhibition potential of tasimelteon and its major metabolites towards major transporters including human OATP1B1, OATP1B3, OCT2, OAT1 and OAT3 uptake transporters and the human BCRP efflux transporters was evaluated in Study 12700. Tasimelteon and its metabolites M9, M12, and M13 were not actively transported by OATP1B1 and OATP1B3. Tasimelteon and its metabolites have low likelihood of in vivo inhibition of transporters, OATP1B1, OATP1B3, OAT1, BCRP, OCT2 and OAT3 at therapeutic concentrations.

The P-gp inhibition potential of tasimelteon and its major metabolites was evaluated using the Caco-2 assay (Study 10VNDAP1R1). The bidirectional transport of the P-gp substrate digoxin in the presence cyclosporine (inhibitor for P-gp), tasimelteon and metabolites M9, M12 and M13 was measured. Tasimelteon and its major metabolites are neither P-gp substrates nor inhibitors at the nominal concentrations of 0.6 µM and 60 µM of tasimelteon and 0.5 µM to 5 µM nominal concentrations of metabolites.

2.4.3 Are there any in vivo drug-drug interaction studies that indicate the exposures alone and/or exposure-response relationships are different when drugs are co-administered? If yes, is there a need for dosage adjustment?

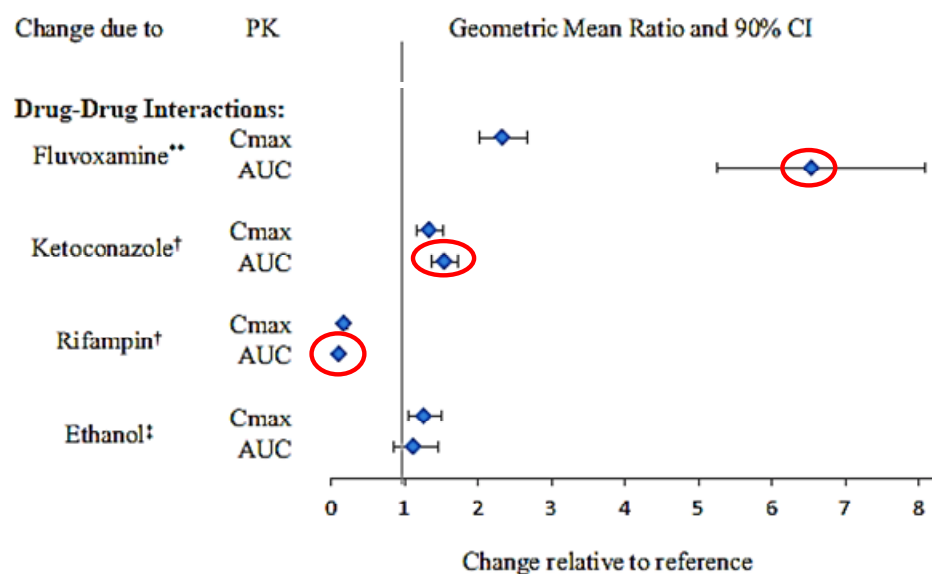
2.4.3.1 Effect of co-administered drugs on tasimelteon

The effect of coadministration of CYP1A2 inhibitor, fluvoxamine was evaluated in Study VP-VEC-162-1111. This study was an open-label, single-sequence study in healthy subjects conducted to evaluate the single-dose pharmacokinetics of tasimelteon alone and in combination with a fluvoxamine at steady-state. Inhibition of CYP1A2 by treatment with fluvoxamine 50 mg QD for 6 days resulted in an 85% decrease in tasimelteon CL/F leading to a 6.5-fold increase in AUC and 2.5 fold increase in C_{max}. There was a 2-fold increase in tasimelteon half-life. Co-administration of moderate to strong CYP1A2 inhibitors should be avoided when using tasimelteon.

The effect of co-administration of strong CYP3A4 inhibitor, ketoconazole and CYP3A4 inducer, rifampin was evaluated in Study VP-VEC-162-1112. When administered in combination with ketoconazole the C_{max} and AUC of tasimelteon increased by 33% and 53% respectively. Tasimelteon is tolerated upto 300 mg in single ascending dose and upto 150 mg in a multiple ascending dose tolerability studies. There was no clear dose-safety relationship and most of the adverse events were mild to moderate. Therefore, no dose adjustment is necessary for increase in exposure when tasimelteon is coadministered with ketoconazole. When administered in combination with rifampin, a strong CYP3A4 and moderate CYP2C8, CYP2C9/2C19 inducer, the overall AUC of tasimelteon was reduced by approximately 90%. Decrease in exposure to tasimelteon in the presence of rifampin may reduce the efficacy. Therefore, co-administration of tasimelteon with rifampin or strong CYP3A4 inducers should be avoided.

Pharmacokinetic and pharmacodynamic interaction of tasimelteon and ethanol was evaluated (VP-VEC-162-1108) in healthy subjects. Coadministration of tasimelteon with alcohol resulted in relatively small increase in exposure (AUC_{0-inf}, AUC_{0-t}, and C_{max}) to tasimelteon. The magnitude of increase in exposure ranged from 10% to 25%. PD parameters evaluated on subjective measures, or on sustained attention, cognition, balance or psychomotor performance in this study did not show any trend. Most of the impairments on PD measures were related to ethanol and not due to the addition of tasimelteon. Following figure summarizes the effect of coadministration of drugs on the PK of tasimelteon.

Impact of other drugs on tasimelteon pharmacokinetics

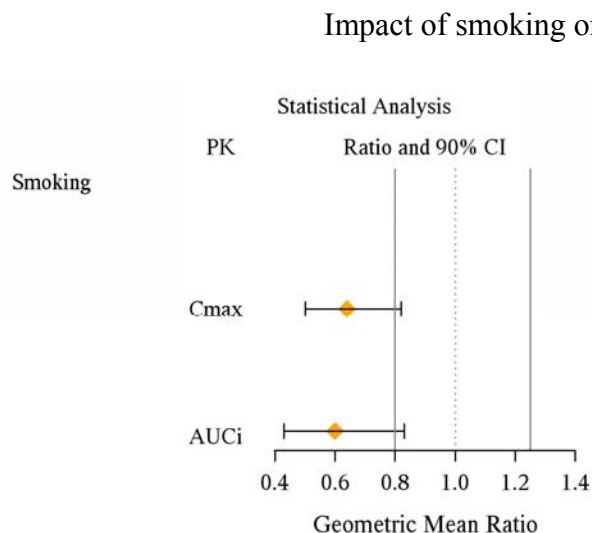


No dose adjustment is needed in subjects taking alcohol.

2.4.3.2 Effect of smoking on tasimelteon exposure

Tasimelteon is mainly metabolized by CYP1A2 and CYP3A4. The levels of CYP1A2 are higher in smokers due to induction. The effect of smoking on tasimelteon exposure was evaluated in a single-dose, parallel group study VP-VEC-162-1107. Cigarette smoking resulting in induction of CYP1A2, increased the clearance of tasimelteon and decreased exposure about 40%, which may

decrease the efficacy. Following figure represents geometric mean ratios for C_{max} and AUC, and 90% confidence intervals outside the 80% to 125%. Dose of tasimelteon may need to be increased for smokers.



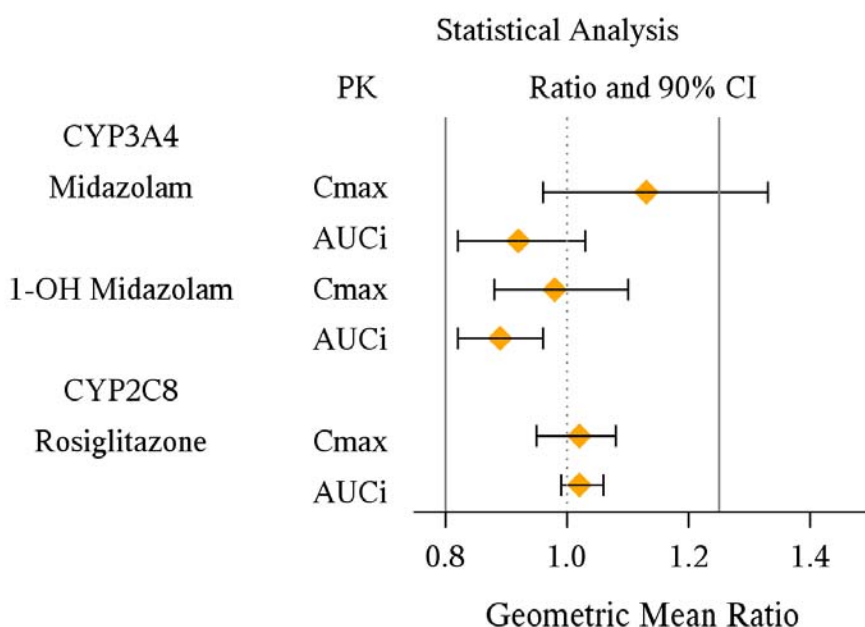
2.4.3.3 Effect of tasimelteon on co-administered drugs

The in vitro studies suggested that tasimelteon had the potential to induce the activity of CYP3A4/5 and CYP2C8. The effect of tasimelteon on CYP3A4 and CYP2C8 activity at steady state was evaluated using midazolam and rosiglitazone as markers respectively in a clinical study VP-VEC-162-1110.

Tasimelteon 20 mg daily administration for 14 days did not significantly change the overall AUC of midazolam and 1-OH midazolam. Similarly there was no change in 1-OH midazolam C_{max}. There was a relatively small increase (13%) in midazolam C_{max}. Tasimelteon 20 mg administered daily for 16 days did not significantly change the plasma concentrations and mean pharmacokinetic parameters of rosiglitazone.

Following figure summarizes the effect of tasimelteon on the PK of co-administered drugs

Impact of tasimelteon on pharmacokinetics of other drugs



2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug?

The Sponsor submitted information requesting formal BCS classification for tasimelteon. Absolute bioavailability was not determined for tasimelteon. The apparent permeability of tasimelteon as measured using Caco2 assay for AP to BL was (b) (4). The apparent permeability for BL to AP was (b) (4). The assay was conducted using (b) (4) permeability markers. The Caco2 assay was validated (b) (4). In vitro permeability of tasimelteon is approximately (b) (4). Tasimelteon is (b) (4) in simulated gastric fluid and simulated intestinal fluid for (b) (4). Based on the solubility data, the drug can be classified as (b) (4) soluble. But the current available permeability data are inconclusive for tasimelteon to be considered as (b) (4) permeable drug because of the following deficiencies.

- In the mass-balance study, about 84% of the radiolabel dose was recovered from urine, and feces, which is less than the threshold (90%) recommended by the BCS guidance.
- Tasimelteon is metabolized extensively. The overall AUC of tasimelteon in plasma is approximately 10-15 times lower when compared to total radioactivity. The sponsor did not provide evidence that tasimelteon is absorbed (b) (4).

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation and the formulation used in clinical trials?

Relative bioavailability study is not necessary as the formulation used in clinical trials is same as to-be-marketed formulation.

2.5.3. What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

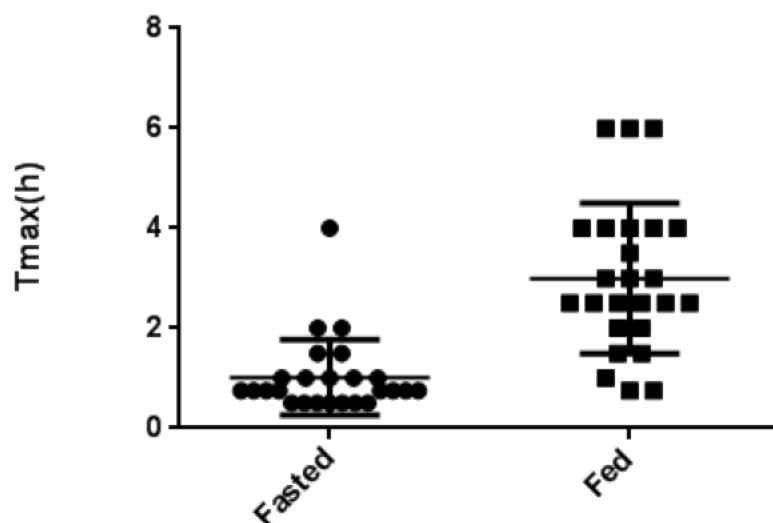
The effect of food on BA of tasimelteon was evaluated in a single-dose, randomized, cross-over study with a standard high fat diet (>50% of calories derived from fat, VP-VEC-162-1102).

When tasimelteon was administered with high fat, high calorie meal, the extent of absorption, AUC(0-t) and AUC(inf) was comparable under both fed and fasted conditions with geometric mean ratios of 108% and 106%, respectively, and 90% confidence intervals were within the 80% to 125%. However, C_{max} was reduced by 44% and the T_{max} was delayed from 0.75 hours to 2.5 hours (table below). It is recommended that tasimelteon should be taken without food preferably before bedtime and at approximately the same time every day for maximum efficacy.

Summary of Pharmacokinetic Parameters for VEC-162 after Single Oral 100 mg Doses Under Fasted and Fed Conditions

Parameter ^a	Fed	Fasted
C _{max} (ng/mL)	445 ±255 (25)	786 ±432 (25)
T _{max} (h)	2.50 (25) [0.75 – 6.00]	0.75 (25) [0.50 – 4.00]
AUC(0-t) (h·ng/mL)	2276 ±1444 (25)	2120 ±1401 (25)
AUC(inf) (h·ng/mL)	2304 ±1471 (24)	2269 ±1468 (21)
λ _z (h ⁻¹)	0.3749 ±0.1279 (24)	0.2871 ±0.1010 (21)
t _{1/2} (h)	2.06 ±0.70 (24)	2.75 ±1.09 (21)

Following figure shows individual median T_{max} distribution along with mean and standard deviation under fasted and fed conditions.



Note:

This study was conducted using 100 mg tasimelteon dose in healthy subjects. The two capsule strengths 20 mg and 100 mg are (b) (4). Dose linearity was demonstrated for tasimelteon upto 300 mg in single dose study. Dissolution profiles for 20 mg and 100 mg capsules are similar.

2.6 Analytical section

2.6.1 What analytical methods were used to determine drug and metabolite concentrations and were these analytical assay methods adequately validated?

Validated LC/MS/MS methods were used to quantitate tasimelteon and its metabolites in plasma. Summary of bioanalytical assay validation for tasimelteon and its active metabolites M13 and M11 are provided in the tables below.

Parameter	Tasimelteon
Method	LC/MS/MS
LLOQ	0.1 ng/mL
Linear range	0.1, 0.3, 1, 3, 10, 30, 60, and 100 ng/mL
QC samples	0.1, 0.3, 45, and 90 ng/mL
QC Inter-day accuracy and precision	%Bias -7.0 to 3.1 %CV 4.7 to 7.5.
QC Intra-day accuracy and precision	%Bias -6.0 to 6.0 %CV 1.6 to 3.2
Freeze-thaw stability	5 cycles

Bench-top stability at RT	19 hours
Auto sample stability at RT	138 hours
Long-term stability in K3EDTA human plasma	43 Days at -20°C
Stock solution stability at -20 °C	175 days at -20°C
Selectivity	<20% LLOQ for analyte <5% for internal standard
Dilution Integrity	500 ng/mL diluted to 100-fold

Metabolite M13

Analyte Name	M13
Internal Standard (IS)	M13- <i>d</i> ₃
Analytical Method Type	LC-MS/MS
Extraction Method	Liquid-liquid
QC Concentrations	0.1, 0.3, 45, and 90 ng/mL
Standard Curve Concentrations	0.1, 0.3, 1, 3, 10, 30, 75, and 100 ng/mL
Lower Limit Of Quantitation	0.1 ng/mL
Upper Limit Of Quantitation	100 ng/mL
Average Recovery of Drug (%)	70.5
Average Recovery of Internal Standard (%)	71.1
QC Intraday Precision Range (%CV)	3.2 to 11.9
QC Intraday Accuracy Range (%RE)	-17.0 to 1.0
QC Interday Precision Range (%CV)	4.0 to 11.8
QC Interday Accuracy Range (%RE)	-7.0 to -2.8
Stock Solution Solvent	Methanol
Master Stock Solution Stability in Methanol	280 Days at -20 C
Master Stock Solution Stability in Methanol	8 Hours at Room Temperature
Reinjection Reproducibility in Processed Samples	138 Hours at 4 C
Interference Tests for Fluvoxamine, Paroxetine, and Repaglinide	No interference from co-administered drugs to M13
Benchtop Stability in Plasma	19 Hours at Room Temperature
Freeze/Thaw Stability in Plasma	5 Cycles at -70 C
Long-term Storage Stability in Plasma	96 Days at -20 C 96 Days at -70 C
Dilution Integrity	500 ng/mL diluted 50-fold
Selectivity	≤20.0% LLOQ for analyte; ≤ 5.0% for IS

Metabolite M11

Analyte Name	M11
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Internal Standard (IS)	M11- <i>d</i> ₃
Analytical Method Type	LC-MS/MS
Extraction Method	Liquid-liquid
QC Concentrations	0.1, 0.3, 45, and 90 ng/mL
Standard Curve Concentrations	0.1, 0.3, 1, 3, 10, 30, 75, and 100 ng/mL
Lower Limit Of Quantitation	0.1 ng/mL
Upper Limit Of Quantitation	100 ng/mL
Average Recovery of Drug (%)	86.0
Average Recovery of Internal Standard (%)	86.3
QC Intraday Precision Range (%CV)	1.4 to 11.6
QC Intraday Accuracy Range (%RE)	-10.0 to -2.0
QC Interday Precision Range (%CV)	2.4 to 7.6
QC Interday Accuracy Range (%RE)	-8.0 to -2.3
Stock Solution Solvent	Methanol
Master Stock Solution Stability in Methanol	280 Days at -20 C
Master Stock Solution Stability in Methanol	8 Hours at Room Temperature
Reinjection Reproducibility in Processed Samples	138 Hours at 4 C
Interference Tests for Fluvoxamine, Paroxetine, and Repaglinide	No interference from co-administered drugs to M11
Benchtop Stability in Plasma	19 Hours at Room Temperature
Freeze/Thaw Stability in Plasma	5 Cycles at -70 C
Long-term Storage Stability in Plasma	96 Days at -20 C 96 Days at -70 C
Dilution Integrity	500 ng/mL diluted 50-fold
Selectivity	≤ 20.0% LLOQ for analyte; ≤ 5.0% for IS

3. Detailed Labeling Recommendations

Labeling recommendation to be sent to the Sponsor:

The following describes the proposed changes: the underlined text is the proposed change to the label language; the ~~Strikethrough-text~~ is recommendation for deletion from the perspective of OCP.

2. DOSAGE AND ADMINISTRATION

(b) (4)

The recommended dose of [TRADENAME] is 20 mg per day taken (b) (4) - before bedtime, (b) (4) at the same time every night. (b) (4)

7. DRUG INTERACTIONS

7.1

(b) (4)

(b) (4)

8. USE IN SPECIFIC POPULATIONS

8.5. Geriatric use

(b) (4)



8.6. Hepatic Impairment

(b) (4)

(b) (4) -Dose adjustment is not necessary in patients with mild or moderate hepatic impairment. [TRADENAME] has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, [TRADENAME] is not recommended in patients with severe hepatic impairment.

(b) (4)

12. CLINICAL PHARMACOLOGY

12.3. Pharmacokinetics

(b) (4)

(b) (4) The pharmacokinetics of [TRADENAME] is linear over doses ranging from (b) (4) 3 to 300 mg. The pharmacokinetics of [TRADENAME] and its metabolites did not change with repeated daily dosing.

(b) (4)

(b) (4)

Absorption

(b) (4) -The peak concentration (T_{max}) of tasimelteon occurred (b) (4) approximately 0.5 (b) (4) to 3 hours after fasted oral administration. (b) (4)

When administered with a high-fat meal, the C_{max} (b) (4) -of tasimelteon (b) (4) was 44% lower than when given in a fasted state (b) (4) the (b) (4) median T_{max} was (b) (4) delayed by approximately 1.75 hours. (b) (4)

(b) (4) Therefore, [TRADENAME] (b) (4) -should be taken (b) (4) without food.

Distribution

The apparent oral volume of distribution at steady state of tasimelteon (b) (4) -in young healthy subjects is approximately 56 - 126 L. At therapeutic concentrations, tasimelteon (b) (4) -is about (b) (4) 90 (b) (4) % bound to proteins (b) (4)

Metabolism

Tasimelteon is extensively metabolized. Metabolism of tasimelteon (b) (4) -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. CYP1A2 and CYP3A4 are the major isozymes involved in the metabolism of tasimelteon (b) (4).

(b) (4)
Phenolic glucuronidation is the major phase II metabolic route.

(b) (4)
(b) (4) Metabolite (b) (4) shows 13 fold less activity at melatonin receptors (b) (4)
(b) (4) compared to tasimelteon. (b) (4)

(b) (4) Elimination

Following oral administration of radiolabeled [TRADENAME], 80 (b) (4) % of total radioactivity was excreted in urine and approximately (b) (4) % in feces, resulting in a mean recovery of 84 (b) (4) %. Less than 1% of the dose was excreted in urine as the parent compound.

The observed mean elimination half-life for tasimelteon is 1.3 (b) (4) ± 0.4 (b) (4) hours. The mean terminal elimination half-life ± standard deviation of the main metabolites ranges from 1.26 ± 0.48 to 3.67 ± 2.22.

Repeated once daily dosing with [TRADENAME] does not result in PK parameter changes or significant accumulation (b) (4) of tasimelteon (b) (4).

Elderly:

In elderly subjects, tasimelteon exposure (b) (4) increased by approximately 2 fold (b) (4)
when compared to adults. (b) (4)

Gender (b) (4)

In women, the mean overall exposure of tasimelteon (b) (4) was approximately 20-30% higher when compared to males (b) (4)

Race (b) (4)

The effect of race on exposure of [TRADENAME] was not evaluated.

(b) (4)

Renal Impairment

The pharmacokinetic (b) (4) of tasimelteon (b) (4) (b) (4) (b) (4) a 20 mg dose to eight subjects with severe renal impairment (estimated glomerular filtration rate (eGFR) ≤ 29 mL/min/1.73m²), eight subjects with end-stage renal disease (ESRD) (eGFR < 15 mL/min/1.73m²) requiring hemodialysis and sixteen healthy matched controls. There was no apparent relationship between [TRADENAME] CL/F and renal function as measured by either estimated creatinine clearance (b) (4) or eGFR. Subjects with severe renal impairment had a 30% lower a clearance and -clearance in subjects with ESRD was comparable to that of healthy subjects. No dose adjustment is necessary for renal impaired patients.

Hepatic Impairment

The pharmacokinetics profile of 20 mg (b) (4) [TRADENAME] in eight patients with mild hepatic impairment (Child-Pugh Score ≥ 5 and ≤ 6 points) (b) (4) eight patients with moderate hepatic impairment (Child-Pugh Score ≥ 7 and ≤ 9 points) was compared to (b) (4) 13 healthy matched controls. (b) (4) Tasimelteon exposure (b) (4) -was increased less than (b) (4) 2-fold in subjects with moderate hepatic impairment (b) (4)

No dose adjustment is needed for mild and moderate hepatic impaired patients. [TRADENAME] has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). (b) (4) is not recommended in patients (b) (4)

Drug Interaction Studies

Effect of Other Drugs on (b) (4) [TRADENAME]

Drugs that inhibit CYP1A2 and CYP3A4 are expected to alter the metabolism of [TRADENAME].

Fluvoxamine (strong CYP1A2 inhibitor): When fluvoxamine 50 mg/day was administered for 6 days prior to single-dose co-administration of 5 mg [TRADENAME] and 50 mg fluvoxamine, the AUC_{0-inf} for tasimelteon (b) (4) increased approximately 7-fold, and the C_{max} (b) (4) increased approximately 2-fold, (b) (4)

Ketoconazole (strong CYP3A4 inhibitor): tasimelteon (b) (4) exposure (b) (4) increased by approximately (b) (4) % when (b) (4) administered on the fifth day of ketoconazole 400 mg per day (b) (4)

Rifampin (strong CYP3A4 and moderate CYP2C19 inducer): Administration of rifampin 600 mg once daily for 11 days resulted in (b) (4) decrease in exposure by approximately (b) (4) % (b) (4)
Efficacy may be reduced when [TRADENAME] is used in combination with strong CYP3A4 inducers such as rifampin. (b) (4)

Effect of Alcohol on [TRADENAME]

(b) (4)

Effect of [TRADENAME] on (b) (4) Other Drugs

(b) (4)

Midazolam (CYP3A4 substrate): Administration of [TRADENAME] 20 mg (b) (4) for 14 days did not produce any significant changes in the T_{max} , C_{max} , or AUC of midazolam or 1-OH midazolam (b) (4)
This indicates that there is no induction of CYP3A4 by [TRADENAME] at this dose.

Rosiglitazone (CYP2C8 substrate): Administration of [TRADENAME] 20 mg (b) (4) for 16 days did not produce any significant changes in the T_{max} , C_{max} , or AUC of rosiglitazone after oral administration of 4 mg. This indicates that there is no induction of CYP2C8 by [TRADENAME] at this dose.

4. Appendices

4.1 Consult Reviews

**OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS AND TARGETED THERAPY GROUP REVIEW**

NDA/BLA Number	205677
Submission Date	6/18/2013
Applicant Name	Vanda Pharmaceuticals Inc.
Generic Name	Tasimelteon
Proposed Indication	Treatment of non-24-hour disorder in the totally blind
Primary Reviewer	Robert Schuck, Pharm.D., Ph.D.
Secondary Reviewer	Michael Pacanowski, Pharm.D., M.P.H.

1 Background

The current submission is a NDA for tasimelteon, a dual melatonin receptor agonist (MT₁ and MT₂), for the treatment of non-24 hour disorder in the totally blind. Non-24-hour disorder is a condition that results in a circadian rhythm of greater than 24 hours. By activating the MT₁ and MT₂ melatonin receptors in the suprachiasmatic nuclei, tasimelteon is purported to synchronize the circadian rhythm to a 24-hour day.

Clinical pharmacology studies showed high intersubject variability in tasimelteon pharmacokinetics (PK). In vitro studies demonstrated that tasimelteon is primarily metabolized by CYP1A2 and CYP3A4; CYP1A1, CYP2C9, CYP2C19, and CYP2D6 contribute to a lesser extent. As such, the impact of CYP2D6, CYP1A2, CYP2C9, and CYP2C19 genotype on tasimelteon PK was evaluated in phase 1 studies. CYP2D6 genotype was associated with tasimelteon PK; however, this association was not consistent across studies.

The purpose of this review is to evaluate the potential impact of genetic variation in drug metabolizing enzymes on tasimelteon exposure and whether labeling or additional pharmacogenetic studies are indicated on the basis of these results.

2 Submission Contents Related to Genomics

The applicant conducted 14 phase 1 clinical pharmacology studies, four of which evaluated the association between CYP genotypes and tasimelteon PK (Table 1). Genotyping results were included within each individual study report.

Table 1: Studies evaluating associations between cytochrome P450 genotype and PK.

Study	N	Objective	Genes Assessed	Dose/ Regimen
VP-VEC-162-1101*	6	Mass Balance	CYP2D6, CYP1A2, CYP2C9	100 mg single dose
VP-VEC-162-1102	26	Food Effect	CYP2D6, CYP1A2, CYP2C9, CYP2C19	100 mg single dose (fasted)
CNN116-001	48	Single Ascending Dose	CYP2D6	1-300 mg
CNN116-002	32	Multiple Ascending Dose	CYP2D6	1-150 mg daily for 28 days

*The applicant noted insufficient representation of the different genotypes to conduct the planned genetic analysis.

Genotyping of CYP2D6 and CYP2C19 was performed using the Roche AmpliChip CYP450 test, CYP2C9*2, CYP2C9*3, and CYP1A2*1F were genotyped using Tag-It.

*Reviewer comments: The Roche AmpliChip is FDA-cleared for CYP450 genotype testing. Phenotype assignment was not specified. However, the parameterization offered by AmpliChip is generally acceptable. Analytical performance information was submitted for the CYP1A2*1F polymorphism, but not the CYP2C9*2 or CYP2C9*3 polymorphisms; however, genotype frequencies appear consistent with those reported in the literature.*

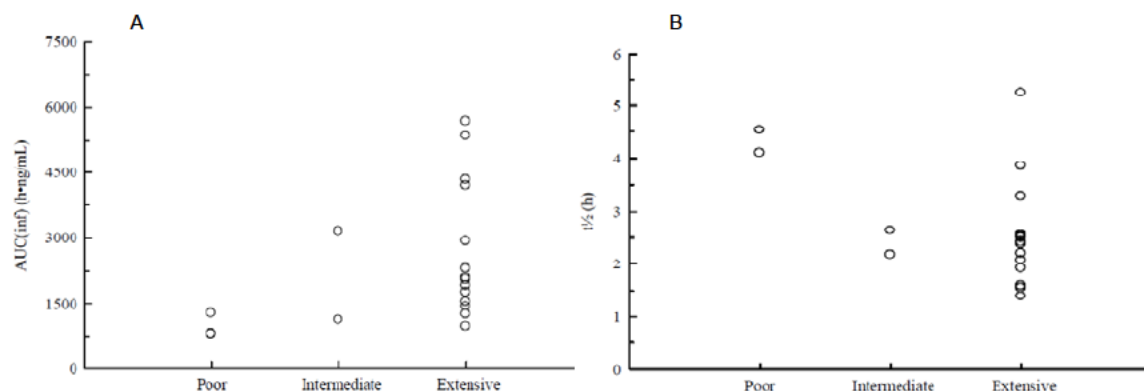
3 Key Questions and Summary of Findings

3.1 Do genetic polymorphisms in CYP2D6, CYP1A2, CYP2C9, or CYP2C19 affect tasimelteon PK?

3.1.1 Pertinent positive findings

Study VP-VEC-162-1102 evaluated food effects on tasimelteon PK in 26 healthy subjects. PK parameters were analyzed by CYP2D6, CYP1A2, CYP2C9, and CYP2C19 genotype. Findings from this study demonstrated that CYP2D6 genotype was significantly associated with AUC (Figure 1A, $p=0.0477$) and $t_{1/2}$ (Figure 1B, $p=0.0243$), which was driven by lower exposure in poor metabolizers ($n=3$). In addition, a trend toward lower C_{max} was observed in poor metabolizers compared to extensive metabolizers ($p=0.0570$).

Figure 1. Individual Subject VEC-162 AUC (A) and $t_{1/2}$ (B) by CYP2D6 Genotype After a Single Oral 100 mg Dose Under Fasted Conditions.



Reviewer comment: In vitro data suggests that CYP2D6 poor metabolizers should have higher AUC and C_{max} compared to extensive metabolizers, which is in contrast to these findings. The sponsor proposes that CYP2D6 might generate a metabolite that inhibits metabolism of tasimelteon by a different drug metabolizing enzyme.

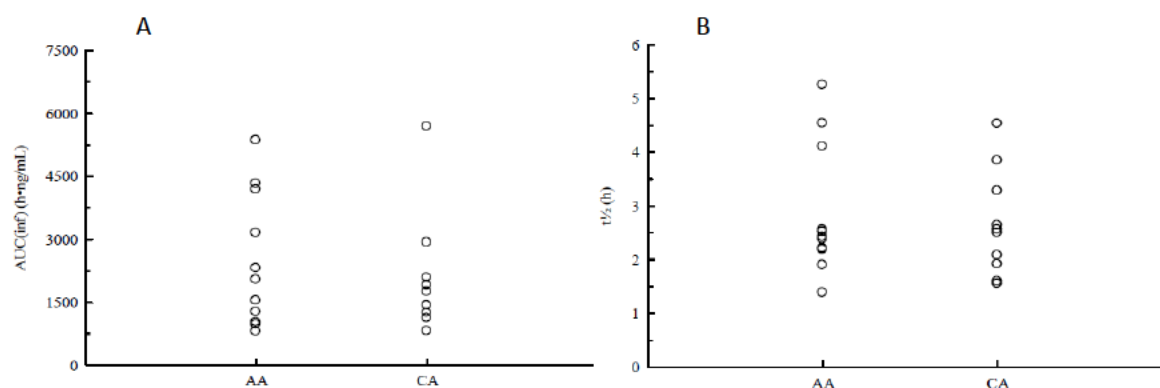
Study CNN116-001 evaluated single ascending doses in 48 healthy subjects, and study CNN116-002 evaluated multiple ascending doses in 32 healthy subjects. No genotype effects on tasimelteon PK were observed in either study. One individual with two null CYP2D6 alleles had

oral clearance of tasimelteon that was at least 2-fold higher than any other individual, but metabolism was potentially confounded by smoking in that subject (i.e., induction of CYP1A2).

3.1.2 Pertinent negative findings

The VP-VEC-162-1102 study also demonstrated that there was not a significant association between CYP1A2*1F genotype and tasimelteon AUC (Figure 2A) or $t_{1/2}$ (Figure 2B). The lack of an association between CYP1A2*1F genotype and tasimelteon PK is notable because 1) CYP1A2 is the main enzyme responsible for metabolism of tasimelteon, 2) fluvoxamine (a strong CYP1A2 inhibitor) co-administration resulted in a 6.5-fold increase in tasimelteon exposure (VP-VEC-162-1111), and 3) smoking (an inducer of CYP1A2) resulted in a 40% decrease in tasimelteon exposure (VP-VEC-162-1107). Similar to the lack of an association between CYP1A2 genotype and tasimelteon exposure, CYP2C9 (*2 and *3) genotype was not associated with tasimelteon PK; all subjects were CYP2C19 extensive metabolizers so no PK analysis was performed.

Figure 2. Individual Subject VEC-162 AUC (A) and $t_{1/2}$ (B) by CYP21A2*1F Genotype After a Single Oral 100 mg Dose Under Fasted Conditions.



Reviewer Comment: We were unable to assess the potential interaction between smoking and CYP1A2 genotype status due to the absence of a study with both genotype data and smoking status data.

Summary and Conclusions

The applicant evaluated associations between CYP2D6, CYP1A2, CYP2C9, and CYP2C19 genotype and exposure to tasimelteon in four healthy subject studies (n=112). CYP1A2, CYP2C9 and CYP2C19 genotype were not associated with tasimelteon exposure in any study. In VP-VEC-162-1102, CYP2D6 poor metabolizers had significantly lower AUC and longer $t_{1/2}$ compared to extensive metabolizers. This unexpected finding (based on in vitro data) was not replicated in two additional studies (CNN116-001 or CNN116-002), which found no association between CYP2D6 genotype and tasimelteon PK. The applicant suggests that CYP2D6 generates a metabolite that subsequently inhibits tasimelteon metabolism; however, no data are provided to support this hypothesis. Given the lack of a significant exposure-response relationship for

efficacy or safety endpoints the high PK variability is not likely to be clinically significant at the proposed doses. Additional gene-drug or drug-drug interaction studies do not appear to be indicated on the basis of these findings.

Recommendations

The submission is acceptable from a Genomics and Targeted Therapy Group perspective. Additional gene-drug or drug-drug interaction studies do not appear to be indicated on the basis of these findings.

Post-marketing studies

None.

Label Recommendations

None.

APPEARS THIS WAY ON ORIGINAL

4.2 Individual Study Reviews

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1.1 CNN116-001: Safety, Tolerance, Pharmacokinetics and Pharmacodynamics of Single Doses of BMS-214778 in Healthy Subjects

Objectives:

To evaluate pharmacokinetics, safety and tolerability profile of single oral doses of BMS-214778 (tasimelteon) in healthy subjects. An additional objective was the assessment of the effects of BMS-214778 on core body temperature, subjective sedation and cognition.

Study Design	This study was a randomized, double-blind, sequential, escalating dose design, placebo controlled study.																	
Study Population	Healthy male Age: 18-42 years BMI: 20 to 30 kg/m ² . Forty eight subjects were enrolled and 48 completed the study. Doses 1, 3, 10, 30, 100 and 300 mg BMS-214778 administered orally in 6 groups of 8 healthy subjects (48 subjects).																	
Sampling:	Blood samples for the determination of VEC-162 in plasma were taken for each subject at pre-dose and 1, 2, 4, 8, 12, 24 and 48 hours post-dosing.																	
Analysis	The plasma samples were analyzed for the concentration of tasimelteon by using LC-MS/MS method. The lower limit of quantification (LLOQ) was 0.1 ng/mL for tasimelteon.																	
	<table><tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr><tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>0.5, 50, and 80 ng/mL</td><td>0.1, 0.25, 1, 10, 30, 70 and 100 ng/mL</td></tr><tr><td>Between Batch Precision (%CV)</td><td>0.9% to 2.9%</td><td>1.0 to 7.5</td></tr><tr><td>Between Batch Accuracy (%RE)</td><td>-9.0% to 5.7%.</td><td>-12.2 to 5.2</td></tr><tr><td>Linearity</td><td colspan="2">Weighted linear equation (1/X²), mean r= 0.995</td></tr></table>	Parameter	Quality Control Samples	Standard Curve Samples	Quality Control or Standard Curve Concentration (ng/mL)	0.5, 50, and 80 ng/mL	0.1, 0.25, 1, 10, 30, 70 and 100 ng/mL	Between Batch Precision (%CV)	0.9% to 2.9%	1.0 to 7.5	Between Batch Accuracy (%RE)	-9.0% to 5.7%.	-12.2 to 5.2	Linearity	Weighted linear equation (1/X ²), mean r= 0.995			
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Linearity	Weighted linear equation (1/X ²), mean r= 0.995																	

	<table> <tr> <td>Linear Range (ng/mL)</td><td>0.1 to 100 ng/mL</td></tr> <tr> <td>Sensitivity (LLOQ, ng/mL)</td><td>0.1 ng/mL</td></tr> </table>	Linear Range (ng/mL)	0.1 to 100 ng/mL	Sensitivity (LLOQ, ng/mL)	0.1 ng/mL
Linear Range (ng/mL)	0.1 to 100 ng/mL				
Sensitivity (LLOQ, ng/mL)	0.1 ng/mL				
PK Assessments	Serial blood samples were collected prior to and for 48 hr post-dosing for the determination of BMS-214778 plasma pharmacokinetics. A cumulative urine sample was collected for 24 hr post-dose for the determination of BMS-214778 eliminated in the urine. The pharmacokinetic parameters C_{max} , T_{max} , AUC_{0-t} , $AUC_{(0-inf)}$, apparent volume of distribution, CL, t_{lag} and $t_{1/2}$ were calculated from the plasma concentration-time data using noncompartmental analysis.				
Safety Assessments	All adverse events recorded during the study were listed and tabulated by treatment, body system and primary term. Any serious adverse event was identified. All laboratory abnormalities meeting predefined criteria were listed and tabulated by treatment and laboratory test.				
Statistical Methods	Observed values of each of the pharmacokinetic parameters were plotted against dose. Summary statistics were tabulated by dose level: geometric means, coefficients of variation, minima and maxima for C_{max} (the maximum observed plasma concentration) and $AUC_{(inf)}$ (the area under the plasma concentration-time curve from zero time extrapolated to infinity); medians, minima and maxima for T_{max} ; means, standard deviations, minima and maxima for $t_{1/2}$ (the plasma terminal half-life) and UR(%) (BMS-214778 recovered in the urine from 0-24 hrs). No formal hypothesis testing of dose proportionality was performed. Summary statistics (means, standard deviations, medians, minima and maxima) were tabulated by dose level and time point for each of the pharmacodynamic variables and their respective changes from baseline (Study Day -1).				

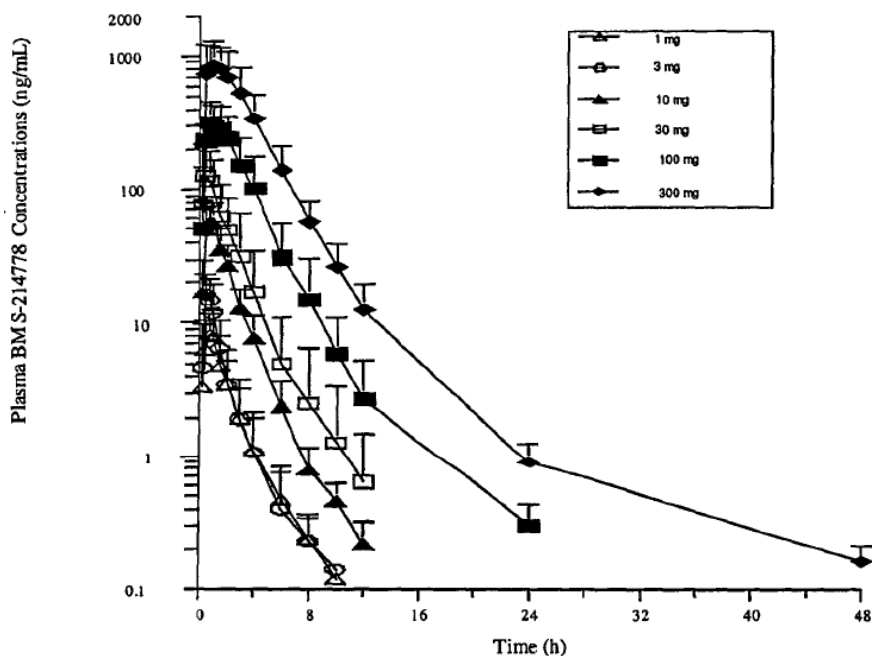
Pharmacodynamic Data Set

The pharmacodynamic data set consisted of all available data from subjects who received study drug (active or placebo) and for whom data were available. Core body temperature (CBT) and the following psychometric test results were summarized for Analog Mood Scales (Tension, Depression, Anger, Fatigue and Confusion), and Digit Symbol Substitution Test (DSST) (sec/digit).

RESULTS:

Following figure illustrates PK profile of tasimelteon following single ascending doses upto 300 mg.

Mean (SD) Plasma Concentration-Time Profiles of BMS-214778 Following Single Oral Doses to Healthy Subjects in Study CN116-001 (N=6 per Dose Group)

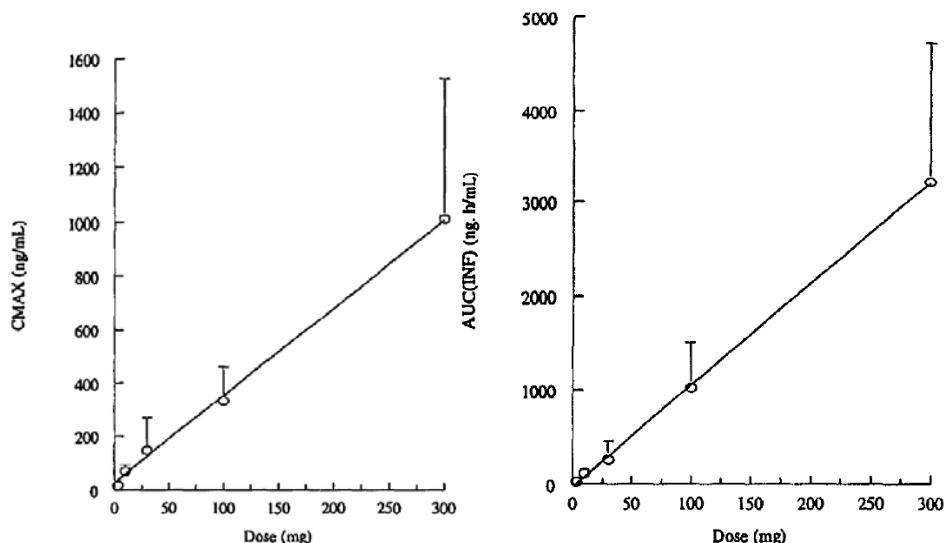


Following table summarizes PK parameters of tasimelteon following single ascending doses upto 300 mg.

Pharmacokinetic parameters for BMS-214778 are summarized in the table below:

Parameter		Dose					
		1 mg	3mg	10mg	30mg	100mg	300mg
C _{max} (ng/mL)	Geo. Mean (C.V.)	8.3 (46.5%)	15.6 (43.6%)	66.6 (32.3%)	103.5 (83.5%)	312.8 (37.2%)	900.5 (51.3%)
AUC(inf) (ng.h/mL)	Geo. Mean (C.V.)	14.0 (61.5%)	20.8 (60.4%)	110.8 (33.5%)	188.9 (76.9%)	935.3 (47.2%)	2943.2 (45.8%)
T _{max} (hr)	Median (Min,Max)	0.50 (0.5,1.0)	0.63 (0.5,1.0)	0.75 (0.5,1.0)	0.75 (0.25,1.0)	1.25 (0.75,1.5)	1.00 (0.5,1.5)
T _{1/2} (hr)	Mean (S.D.)	1.11 (0.26)	1.48 (1.03)	1.95 (0.96)	1.95 (0.86)	4.8 (1.65)	5.07 (1.52)
UR (%)	Mean (S.D.)	0.42 (0.33)	0.80 (0.42)	0.43 (0.33)	0.44 (0.30)	0.21 (0.09)	0.25 (0.08)

Mean (SD) Peak Plasma Concentrations (C_{max}) of BMS-214778 and the Area Under the Plasma Concentration Time Curve Extrapolated to Infinity (AUC(inf)) as a Function of Increment in the Dose Levels for Doses of 3 to 300 mg.



Pharmacodynamic Results:

PD parameters were evaluated -for exploratory purposes'. There were also no apparent treatment-related trends in psychometric test scores or core body temperature. Changes from baseline were small and similar to those in the placebo group.

For all of the psychometric variables, the mean changes from baseline within a treatment group were small and similar to those in the placebo group.

Safety Results

Number (Percent) of Subjects Reporting Treatment-Emergent Adverse Events

Adverse Event	Number (Percent) of Subjects						
	1 mg (N = 6)	3 mg (N = 6)	10 mg (N = 6)	30 mg (N = 6)	100 mg (N = 6)	300 mg (N = 6)	Placebo (N = 12)
Dizziness Postural	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)
Constipation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (8.3)
Somnolence	0 (0)	2 (33.3)	4 (66.7)	2 (33.3)	2 (33.3)	3 (50.0)	2 (16.7)

CONCLUSIONS:

- The pharmacokinetics of tasimelteon appeared to be essentially dose-proportional over the dose range of 3 mg to 300 mg characterized by large variability. Peak concentrations of tasimelteon were achieved with a Tmax of 0.5 to 1 hr. The terminal half-life was approximately 5 hr.
- There were no apparent treatment-related trends in pharmacodynamic variables tested.

- The primary treatment-emergent adverse event following morning administration was sleepiness. Mild postural hypotension and mild constipation were also reported. There were no Serious Adverse Events or discontinuations due to adverse events in this study.

1.2 CNN116-002: Safety, Tolerance, Pharmacokinetics and Pharmacodynamics of Multiple Doses of BMS-214778 in Healthy Subjects: Protocol CN116-002

Objectives:

- To assess the safety and tolerability profile of 1 to 150 mg BMS-214778 administered orally qhs (bedtime every day) for 28 consecutive days.
- To evaluate the single dose and steady state pharmacokinetics of BMS-214778.
- To assess effects on core body temperature and subjective sedation. In addition, the effects of BMS-214778 on dim light melatonin onset were assessed and data were collected on luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone (T) in healthy male subjects.

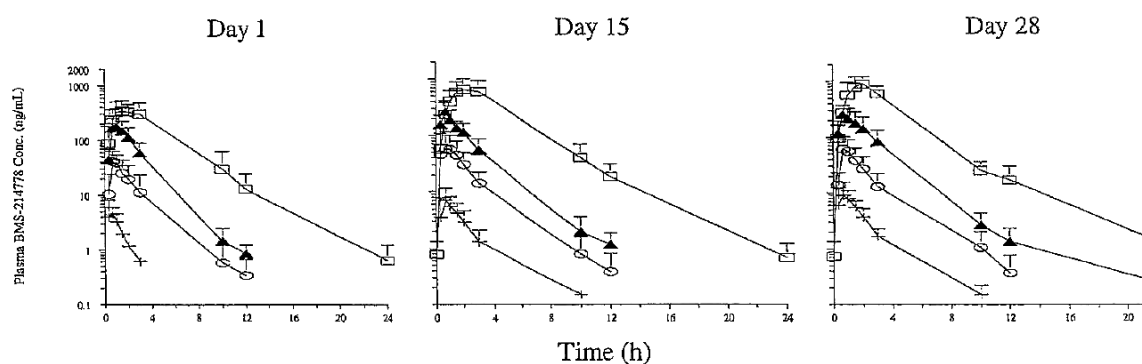
Study Design	This randomized, double-blind, sequential, escalating dose, placebo controlled study assessed the safety profile, tolerance, pharmacokinetics and pharmacodynamics of 1, 10, 50 and 150 mg BMS-214778 administered orally qhs for 28 days in 4 groups of 8 healthy subjects (32 subjects), all men.																							
Study Population	Healthy male Age: 18-50 years BMI: 18 to 35 kg/m ² . Thirty two subjects were enrolled and 30 completed the study																							
Sampling:	Blood samples for the determination of VEC-162 in plasma were taken for each subject before dosing and 20, 40 min, 1, 1.5, 2, 3, 10, 12 and 24 hours after dosing on days 1 and 28. On days 2 and 13, 14, 15, 26 and 27 samples were collected prior to dosing.																							
Analysis	<div>The plasma samples were analyzed for the concentration of tasimelteon by using LC-MS/MS method. The lower limit of quantification (LLOQ) was 0.1 ng/mL for tasimelteon.</div> <table><tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr><tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>0.5, 50, and 80 ng/mL</td><td>0.1, 0.25, 1, 10, 30, 70 and 100 ng/mL</td></tr><tr><td>Between Batch Precision (%CV)</td><td>1.5% to 4.5%</td><td>0.6 to 7.5</td></tr><tr><td>Between Batch Accuracy (%RE)</td><td>-10.8% to 9.0%.</td><td>-6.3 to 11.7</td></tr><tr><td>Linearity</td><td colspan="2">Weighted linear equation (1/X²), mean r= 0.995</td></tr><tr><td>Linear Range (ng/mL)</td><td colspan="2">0.1 to 100 ng/mL</td></tr><tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">0.1 ng/mL</td></tr></table>			Parameter	Quality Control Samples	Standard Curve Samples	Quality Control or Standard Curve Concentration (ng/mL)	0.5, 50, and 80 ng/mL	0.1, 0.25, 1, 10, 30, 70 and 100 ng/mL	Between Batch Precision (%CV)	1.5% to 4.5%	0.6 to 7.5	Between Batch Accuracy (%RE)	-10.8% to 9.0%.	-6.3 to 11.7	Linearity	Weighted linear equation (1/X ²), mean r= 0.995		Linear Range (ng/mL)	0.1 to 100 ng/mL		Sensitivity (LLOQ, ng/mL)	0.1 ng/mL	
Parameter	Quality Control Samples	Standard Curve Samples																						
Quality Control or Standard Curve Concentration (ng/mL)	0.5, 50, and 80 ng/mL	0.1, 0.25, 1, 10, 30, 70 and 100 ng/mL																						
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Linearity	Weighted linear equation (1/X ²), mean r= 0.995																							
Linear Range (ng/mL)	0.1 to 100 ng/mL																							
Sensitivity (LLOQ, ng/mL)	0.1 ng/mL																							
PK	Serial blood samples were collected following administration of BMS-214778																							

Assessments	on Days 1, 15 and 28. Blood samples for BMS-214778 C _{min} (trough concentration) determinations were taken on Days 13, 14, 26 and 27. The pharmacokinetic parameters C _{max} , T _{max} , AUC _{tau} , AUC _{inf} , apparent volume of distribution, CL, t _{lag} and t _{1/2} were calculated from the plasma concentration-time data using noncompartmental analysis.
PD Assessments	The pharmacodynamic variables evaluated include core body temperature, subjective sedation (Analogue Mood Scales test), dim light melatonin onset (determined from salivary melatonin measurements).
Safety Assessments	Safety assessments included physical examinations, vital signs (systolic/diastolic blood pressure, pulse rate, respiration rate, and oral body temperature), clinical laboratory tests (hematology, chemistry, and urinalysis), 12-lead electrocardiograms, and reported or observed adverse events.
Statistical Methods	<p>Summary statistics were tabulated by dose level and study day: geometric means, coefficients of variation, C_{min}, C_{max}, AUC_(inf), AUC_(tau); medians, minima and maxima for T_{max}; means, standard deviations, minima and maxima for the others. The general dependencies of C_{max} and AUC_(tau) on dose were explored by comparing the increasing ratios of the doses to the corresponding ratios of the dose level geometric means. Ninety-five percent (95%) confidence intervals were constructed for the mean AI. No formal hypothesis testing dose proportionality was performed.</p> <p>Pharmacodynamic Data: Summary statistics (means, standard deviations, medians, minima and maxima) were tabulated by dose level, study day and measure time for each of the pharmacodynamic variables and their respective changes from baseline (Study Day -1). For core body temperature data, intervals pre-dose and hourly (60 minute) post-dose were formed, and core body temperatures were averaged over these intervals for each subject. These hourly means were used in the calculation of summary statistics. The first time at which a minimum CBT measure was observed was tabulated and summarized. This value was captured prior to the formation of the hourly CBT intervals.</p>

RESULTS:

Following figure illustrates PK profile of tasimelteon following multiple ascending doses upto 150 mg.

Mean (SD) Plasma Concentration-Time Profiles of BMS-214778 on Days 1, 15 and 28 Following Single Daily Oral Doses of 1 mg (+), 10 mg (O), 50 mg (▲) or 150 mg (□) of BMS-214778



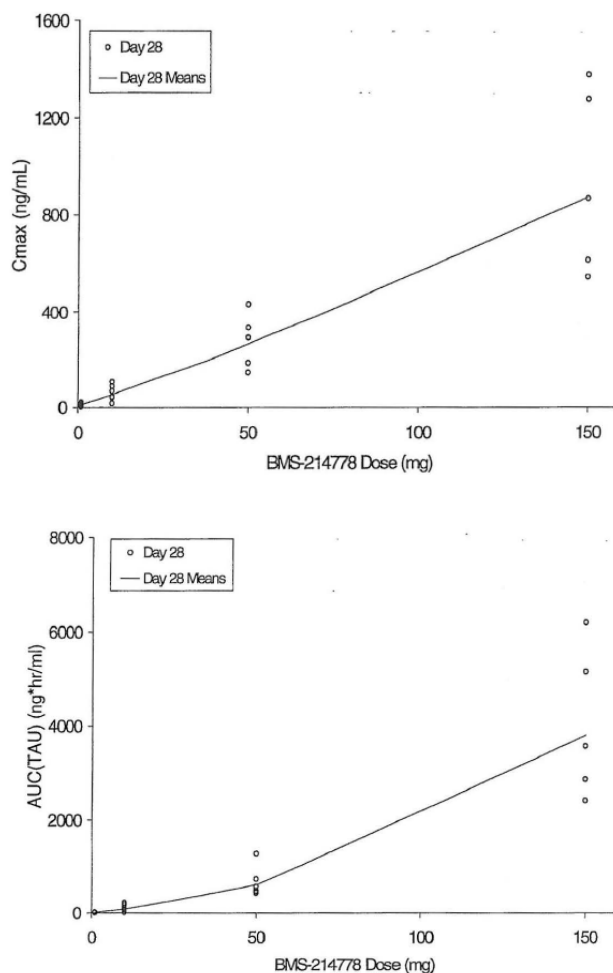
Following table summarizes PK parameters of tasimelteon following multiple ascending doses 1 mg to 150 mg (qhs).

Mean VEC-162 pharmacokinetic parameters are presented in the table below

Parameter	Statistic	Dose	Study Day		
			Day 1	Day 15	Day 28
C _{max} (ng/mL)	Geo. Mean (C.V.)	1	5 (55)	7 (49)	12 (43)
		10	33 (58)	48 (81)	51 (54)
		50	173 (49)	256 (41)	261 (37)
		150	394 (41)	652 (48)	873 (40)
AUC(tau) (ng•h/mL)	Geo. Mean (C.V.)	1	8 (19)	12 (48)	17 (25)
		10	59 (80)	98 (78)	96 (64)
		50	426 (50)	519 (36)	611 (50)
		150	1823 (47)	3243 (54)	3797 (39)
T _{max} (h)	Median (Min, Max)	1	0.67 (0.33, 1.00)	0.67 (0.33, 1.50)	0.67 (0.33, 1.50)
		10	0.67 (0.67, 1.00)	1.00 (0.67, 2.00)	0.83 (0.67, 1.00)
		50	1.00 (0.67, 1.50)	0.67 (0.67, 1.50)	0.67 (0.67, 1.00)
		150	2.25 (1.00, 3.00)	2.00 (1.50, 3.00)	2.00 (1.50, 2.00)
T-half (h)	Mean (S.D.)	1	1.75 (1.35)	1.64 (1.33)	1.49 (1.12)
		10	1.29 (0.39)	1.44 (0.34)	1.44 (0.40)
		50	2.37 (1.52)	2.38 (1.45)	2.57 (1.69)
		150	2.78 (0.51)	2.38 (0.17)	2.63 (0.52)

Dose (mg)	AUC(TAU) Accumulation Index Geometric Mean (95% Confidence Intervals)			
		Day 15		Day 28
1	1.59	(1.14, 2.21)	2.22	(1.66, 2.96)
10	1.66	(0.98, 2.82)	1.63	(1.20, 2.22)
50	1.22	(0.94, 1.58)	1.43	(1.10, 1.86)
150	1.80	(1.43, 2.27)	2.11	(1.46, 3.05)

Individual and Mean C_{max} and AUC(tau) Values of BMS-214778 Versus Dose Administered on Day 28



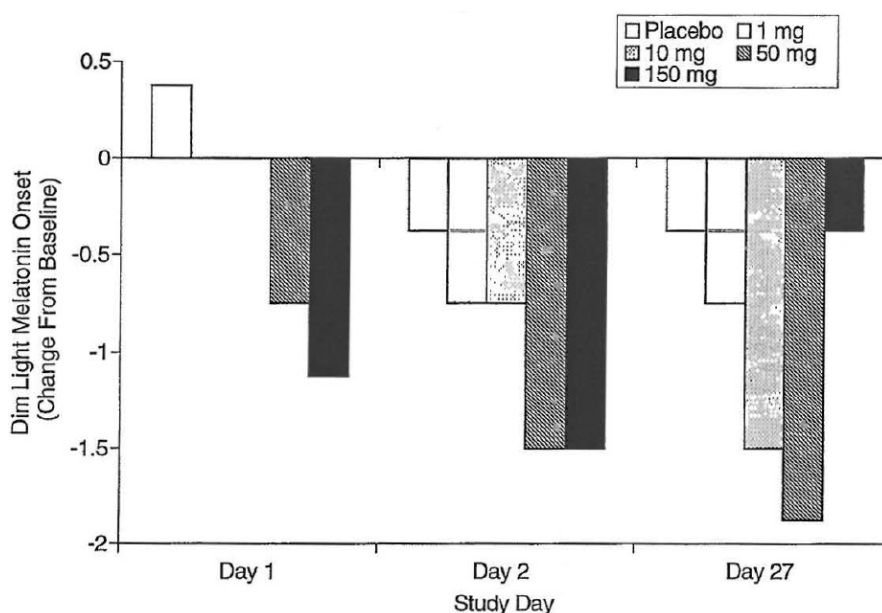
PHARMACODYNAMIC RESULTS:

A greater decrease in core body temperature over time was observed in the BMS-214778 treated groups compared to placebo.

The tasimelteon treated subjects tended to have an earlier occurrence of minimum temperature relative to baseline compared to placebo treated subjects. The other PD measures did not show any apparent trend.

Greater increases in salivary melatonin concentrations were observed in the BMS-214778 treated groups compared to placebo. For the earliest times at which salivary melatonin concentrations exceeded or were equal to 3.0 pg/mL (Dim Light Melatonin Onset, or DLMO), the BMS-214778 treated subjects tended to have an earlier occurrence relative to baseline compared to placebo treated subjects.

Median Time of Dim Light Melatonin Onset during Evening Administration of 1, 10, 50 or 150 mg BMS-214778 or Placebo for 28 Consecutive Days



CONCLUSIONS:

- The C_{max} values appeared to increase essentially proportional to the dose upto 150 mg. AUC(τ) appeared to increase approximately proportionally to dose up to 50 mg and more than proportionally from 50 to 150 mg. The half-life was approximately 2 h. Steady state was achieved by Day 15.
- The accumulation index at steady state ranged from 1.22 to 2.22.
- Salivary melatonin concentrations increased with increase in tasimelteon doses when compared to placebo. Dim Light Melatonin Onset was earlier in tasimelteon treated subjects in most cases relative to baseline when compared to placebo treated subjects.

1.3 CNN116-003: Comparison of the Pharmacokinetics of Single-Doses of BMS-214778 in Young and Elderly Subjects

Objectives:

To assess the effects of age and gender on the pharmacokinetics of a single oral dose of 50 mg BMS-214778. The second objective was to assess the safety and tolerance profile of BMS-214778 in young and elderly healthy subjects of both sexes. The third objective was to assess the effects of a single dose of BMS-214778 on subjective sleepiness and cognition in young and elderly subjects of both sexes.

Study Design	This was a double-blind, placebo-controlled, parallel group, 2 period crossover study designed to assess the effects of age and gender on the pharmacokinetics, safety and tolerability profile and pharmacodynamics of a single oral dose of 50 mg BMS-214778. Administration of the 2 treatments was separated by 7 days.																							
Study Population	Healthy: Adult male and female and elderly male and female Ten (10) subjects were enrolled into each of the following 4 parallel groups: healthy young men, age 18 to 45 years; healthy young women, age 18 to 45 years; healthy elderly men, age 65 years or older; and healthy elderly women, age 65 years or older. BMI: 18 to 35 kg/m ² . Forty subjects were enrolled and 40 completed the study																							
Sampling:	A 7-ml venous blood sample was obtained in a K3EDTA tube for plasma for pharmacokinetic analysis at the times relative to study drug administration on Day 1 of Study Periods 1 and 2 at predose and at 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 hours after dosing.																							
Analysis	<div>The plasma samples were analyzed for the concentration of tasimelteon by using LC-MS/MS method. The lower limit of quantification (LLOQ) was 0.1 ng/mL for tasimelteon.</div> <table><tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr><tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>0.5, 50, 80 and 500 ng/mL</td><td>0.1, 0.25, 1, 10, 30, 70 and 100 ng/mL</td></tr><tr><td>Between Batch Precision (%CV)</td><td>3.3% to 4.9%</td><td>1.9 to 4.0</td></tr><tr><td>Between Batch Accuracy (%RE)</td><td>-2.1% to 1.0%.</td><td>-5.7 to 5.1</td></tr><tr><td>Linearity</td><td colspan="2">Weighted linear equation (1/X²), mean r= 0.998</td></tr><tr><td>Linear Range (ng/mL)</td><td colspan="2">0.1 to 100 ng/mL</td></tr><tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">0.1 ng/mL</td></tr></table>			Parameter	Quality Control Samples	Standard Curve Samples	Quality Control or Standard Curve Concentration (ng/mL)	0.5, 50, 80 and 500 ng/mL	0.1, 0.25, 1, 10, 30, 70 and 100 ng/mL	Between Batch Precision (%CV)	3.3% to 4.9%	1.9 to 4.0	Between Batch Accuracy (%RE)	-2.1% to 1.0%.	-5.7 to 5.1	Linearity	Weighted linear equation (1/X ²), mean r= 0.998		Linear Range (ng/mL)	0.1 to 100 ng/mL		Sensitivity (LLOQ, ng/mL)	0.1 ng/mL	
Parameter	Quality Control Samples	Standard Curve Samples																						
Quality Control or Standard Curve Concentration (ng/mL)	0.5, 50, 80 and 500 ng/mL	0.1, 0.25, 1, 10, 30, 70 and 100 ng/mL																						
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Linearity	Weighted linear equation (1/X ²), mean r= 0.998																							
Linear Range (ng/mL)	0.1 to 100 ng/mL																							
Sensitivity (LLOQ, ng/mL)	0.1 ng/mL																							
PK Assessments	The pharmacokinetic parameters C _{max} , T _{max} , AUC _{0-t} , AUC _(0-inf) , apparent volume of distribution, CL, t _{lag} and t _{1/2} were calculated from the plasma concentration-time data using noncompartmental analysis.																							
Statistical Methods	Comparison of the pharmacokinetic parameters C _{max} and AUC _(inf) for tasimelteon between gender and age group was done using an analysis of variance (ANOVA) model with gender, age group, and gender × age group as																							

	the classification variables, using the natural logarithms of the data. Confidence intervals (CI) (90%) were constructed for the geometric mean ratios (GMR) male-to-female and young-to-elderly of both parameters using the log transformed data and the two one-sided t-tests procedure. The GMRs and CIs were exponentiated back to the original scale.
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RESULTS:

Following table summarizes PK parameters of tasimelteon following single 50 mg dose in young and elderly subjects.

Summary of pharmacokinetic parameters for tasimelteon after oral administration of single 50 mg doses to young and elderly healthy male and female subjects.

Parameter*	Gender	
	Males	Females
Age		
Young		
C _{max} (ng/mL)	261 ± 104 (10)	426 ± 254 (10)
T _{max} (h)	1.00 (10) [0.50 - 2.00]	0.88 (10) [0.50 - 1.00]
AUC(inf) (h×ng/mL)	697 ± 303 (10)	920 ± 534 (10)
t _{1/2} (h)	2.79 ± 1.81 (10)	3.44 ± 2.11 (10)
Elderly		
C _{max} (ng/mL)	604 ± 269 (10)	601 ± 266 (10)
T _{max} (h)	0.50 (10) [0.50 - 1.00]	0.75 (10) [0.50 - 1.00]
AUC(inf)(h×ng/mL)	1,429 ± 1,200 (10)	1,466 ± 755 (10)
t _{1/2} (h)	2.99 ± 1.34 (10)	3.30 ± 0.52 (10)

* Arithmetic mean ± standard deviation (N) except T_{max} for which the median (N) is reported

Following table summarizes statistical comparisons of tasimelteon PK parameters.!

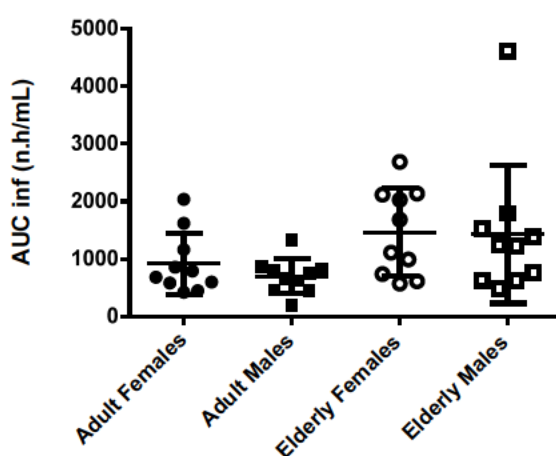
Statistical comparison of pharmacokinetic parameters for tasimelteon after oral administration of single 50 mg doses to young and elderly healthy male and female subjects.

Parameter	Geometric Mean Ratio (%)	
	Estimate	90% Confidence Interval

Males vs Females				
C _{max}	81.52	63.78	-	104.20
AUC(inf)	83.58	61.65	-	113.32
Elderly vs. Young				
C _{max}	182.55	142.82	-	233.34
AUC(inf)	169.94	125.34	-	230.40

Note: Arithmetic mean comparisons show greater differences in mean PK parameters when compared to geometric means because of large variability in PK parameters.

Following figure illustrates frequency distribution data for males and females



CONCLUSIONS:

- The C_{max} and AUC were about 63% and 32% higher respectively in young females when compared to young males.
- There were no apparent difference was seen between elderly males and elderly females.
- The C_{max} and AUC was higher in elderly subjects when compared to young subjects by approximately 2-fold respectively.

1.4 VP-VEC-162-1101: A Phase I, Open Label, Single-Center Study of the Absorption, Metabolism and Excretion of VEC-162 in Healthy Male Subjects

Objectives:

- To investigate the absorption, metabolic profile and excretion of [^{14}C]-VEC-162 in healthy male subjects following a single oral administration of 100 mg VEC-162 labeled with approximately 100 μCi of ^{14}C .
- To identify and characterize the metabolite profile of [^{14}C]-VEC-162 in humans.

Study Design	This was an open-label, 9-day, inpatient, single-center study. Six healthy male subjects were enrolled. CYP2C9, CYP2D6, and CYP1A2 genotyping samples were collected for all subjects																																		
Study Population	Healthy males Age: 18-50 years BMI: 18 to 35 kg/m^2 . Six subjects were enrolled and 6 completed the study																																		
Sampling:	<p>Blood samples for the determination of VEC-162 in plasma were taken for each subject before dosing and 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 8, 16, 24, 48, 72, 96, 120, 144 and 168 hours after dosing.</p> <p>Pooled urine samples were collected for 0-6, 6-12, 12- 24, 24-48, 48-72, 72-96, 96-120, 120- 144, 144-168, 168-192 hours to determine concentration of tasimelteon and total radioactivity.</p>																																		
Analysis	<p>The plasma samples were analyzed for the concentration of tasimelteon by using LC-MS/MS method. The lower limit of quantification (LLOQ) was 0.1 ng/mL for tasimelteon.</p> <table border="1"> <thead> <tr> <th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr> </thead> <tbody> <tr> <td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>0.3, 45, and 90 ng/mL</td><td>0.1, 0.3, 1, 3, 10, 30, 60 and 100 ng/mL</td></tr> <tr> <td>Between Batch Precision (%CV)</td><td>5.9 to 11.6</td><td>3.0 to 12.4</td></tr> <tr> <td>Between Batch Accuracy (%RE)</td><td>-8.0 to -2.9</td><td>-2.7 to 2.4</td></tr> <tr> <td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean $r=0.991$</td></tr> <tr> <td>Linear Range (ng/mL)</td><td colspan="2">0.1 to 100 ng/mL</td></tr> <tr> <td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">0.1 ng/mL</td></tr> </tbody> </table> <p>The urine samples were analyzed for the concentration of tasimelteon by using LC-MS/MS method. The lower limit of quantification (LLOQ) was 0.1 ng/mL for tasimelteon.</p> <table border="1"> <thead> <tr> <th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr> </thead> <tbody> <tr> <td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>3, 45, and 90 ng/mL</td><td>1, 3, 10, 30, 60, 80 and 100 ng/mL</td></tr> <tr> <td>Between Batch Accuracy (%RE)</td><td>-8.0 to -2.9</td><td>-6.4 to 4.5</td></tr> <tr> <td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean $r=0.998$</td></tr> </tbody> </table>		Parameter	Quality Control Samples	Standard Curve Samples	Quality Control or Standard Curve Concentration (ng/mL)	0.3, 45, and 90 ng/mL	0.1, 0.3, 1, 3, 10, 30, 60 and 100 ng/mL	Between Batch Precision (%CV)	5.9 to 11.6	3.0 to 12.4	Between Batch Accuracy (%RE)	-8.0 to -2.9	-2.7 to 2.4	Linearity	Weighted linear equation ($1/X^2$), mean $r=0.991$		Linear Range (ng/mL)	0.1 to 100 ng/mL		Sensitivity (LLOQ, ng/mL)	0.1 ng/mL		Parameter	Quality Control Samples	Standard Curve Samples	Quality Control or Standard Curve Concentration (ng/mL)	3, 45, and 90 ng/mL	1, 3, 10, 30, 60, 80 and 100 ng/mL	Between Batch Accuracy (%RE)	-8.0 to -2.9	-6.4 to 4.5	Linearity	Weighted linear equation ($1/X^2$), mean $r=0.998$	
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	Linear Range (ng/mL)	0.1 to 100 ng/mL
	Sensitivity (LLOQ, ng/mL)	0.1 ng/mL
PK Assessments	<p>Serial PK blood samples were drawn predose and postdose through discharge. All urine and feces were collected during the study and analyzed for total radioactivity.</p> <p>Metabolite Radioprofiling and Identification: Metabolite elucidation /identification was performed in plasma, urine, and feces. Plasma and urine samples were each pooled for metabolic profiling. Metabolites were identified in all 3 matrices. Metabolic profiles for plasma and/or urine samples were generated for individual subjects and for pooled samples.</p>	
Safety Assessments	<p>Safety assessments included physical examinations, vital signs (systolic/diastolic blood pressure, pulse rate, respiration rate, and oral body temperature), clinical laboratory tests (hematology, chemistry, and urinalysis), 12-lead electrocardiograms, and reported or observed adverse events.</p>	
Statistical Methods	<p>The pharmacokinetic parameters C_{max}, T_{max}, AUC_{0-t}, AUC(0-inf), apparent volume of distribution, CL, t_{lag} and t_{1/2} were calculated from the plasma concentration-time data using noncompartmental analysis.</p> <p>The urine and feces, collected during the course of the study were analyzed for total radioactivity.</p>	

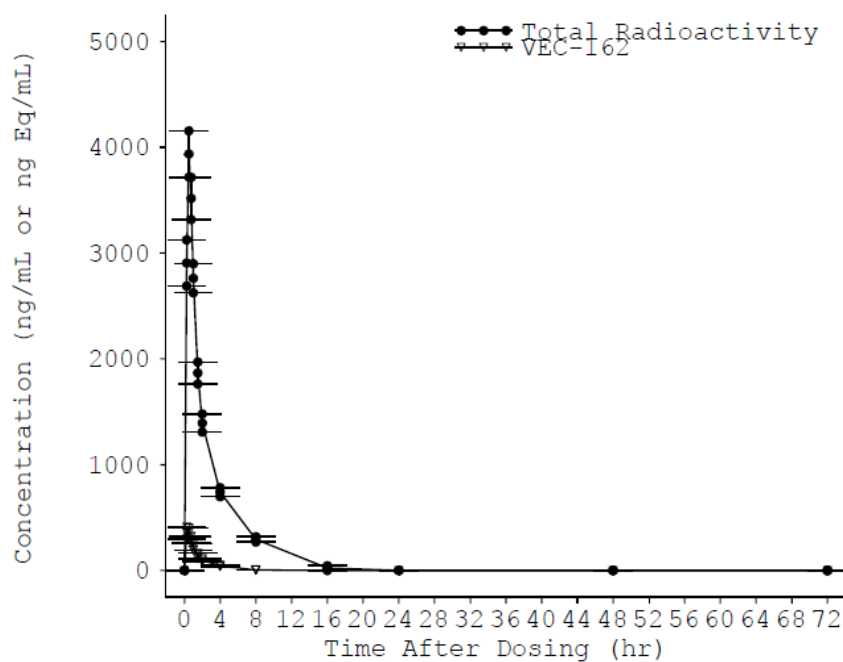
RESULTS:

A summary of mean PK parameters for VEC-162 in plasma, and total radioactivity in plasma and whole blood, is presented below.

Summary of mean (SD) a pharmacokinetic parameters in plasma and whole blood

Parameter	Units ^b	Plasma	Plasma	Whole Blood
		VEC-162	Total Radioactivity	Total Radioactivity
C _{max}	(ng/mL)	390 (120)	3987 (493)	2385 (412)
T _{max}	(hr)	0.500 (0.250, 0.500)	0.500 (0.250, 0.750)	0.500 (0.500, 0.500)
AUC _{0-t}	(ng•hr/mL)	686 (241)	9462 (1523)	6082 (718)
AUC _{0-∞}	(ng•hr/mL)	689 (241)	10516 (1451)	6787 (811)
T _{1/2}	(hr)	1.35 (0.335)	3.00 (0.746)	2.44 (0.290)
λ _z	(1/hr)	0.540 (0.124)	0.241 (0.0489)	0.288 (0.0375)
CL/F	(L/hr)	166 (73.1)	9.64 (1.14)	14.9 (1.61)

Mean Plasma Concentration versus Time Profile for VEC-162 and Total Radioactivity



A summary of mean recovery parameters for VEC-162 in urine and total radioactivity in urine and feces is presented below.

Table: Summary of mean (SD) pharmacokinetic parameters in urine and feces

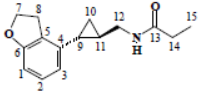
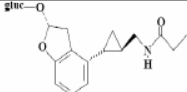
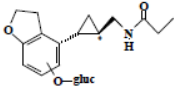
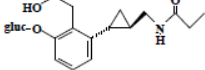
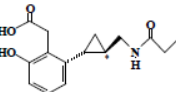
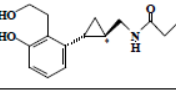
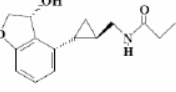
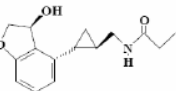
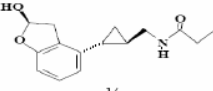
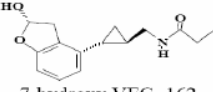
Parameter	Units	Urine	Urine	Feces	Urine+Feces
		VEC-162	Total Radioactivity	Total Radioactivity	Total Radioactivity
Ue	mg	0.0298 (0.0214)	80.7 (6.3)	NA	NA
% Recovered ^a	%	0.0298 (0.0214)	80.4 (6.4)	3.72 (0.62)	84.1 (5.8)

Metabolite Radioprofiling and Identification:

In addition to the unchanged tasimelteon, 8 metabolites were identified. M3 was characterized as an aryl glucuronide of phenolic VEC-162. M9 was identified as a phenol-carboxylic acid derivative of VEC-162. M11 was proposed to be hydroxy-phenol VEC-162. M8 was identified a glucuronide of M11. M12 and M14 were α and β -isomers of 7-hydroxy VEC-162. M13 was identified as 8-hydroxy VEC 16. M1 was identified as 8-O-glucuronide of VEC-162.

The major metabolic routes of VEC-162 in humans were oxidation at multiple sites and oxidative dealkylation resulting opening of the furan ring (O-dealkylation), followed by further oxidation to give carboxylic acid. Glucuronidation was the major Phase II metabolic route.

Summary of [¹⁴C]-VEC-162 and Metabolites in Human Plasma, Urine, and Feces

Metabolite Code ^a	Proposed Structure	MW (Da)	R _t (min)	Plasma (%AUC)	Excreta (%Dose) ^b		
					Urine (0 to 72 hour)	Feces (0 to 120 hour)	Total
VEC-162		245	~69	8.22	ND	0.04	0.04
M1 (M1)		437	~29	3.24	3.69	ND	3.69
M3		437	~32	7.80	12.53	ND	12.53
M8 (M2)		439	~39	3.46	4.87	ND	4.87
M9 (H1)		277	~41	19.79	29.69	0.85	30.54
M11		263	~54	3.56	ND	ND	ND
M12 (H4)		261	~55	3.94	ND	ND	ND
M14 (H6)	 8-hydroxy VEC-162	261	~58	7.13	ND	ND	ND
M13 (H5)	 and/or  7-hydroxy VEC-162	261	~56	14.55	ND	ND	ND

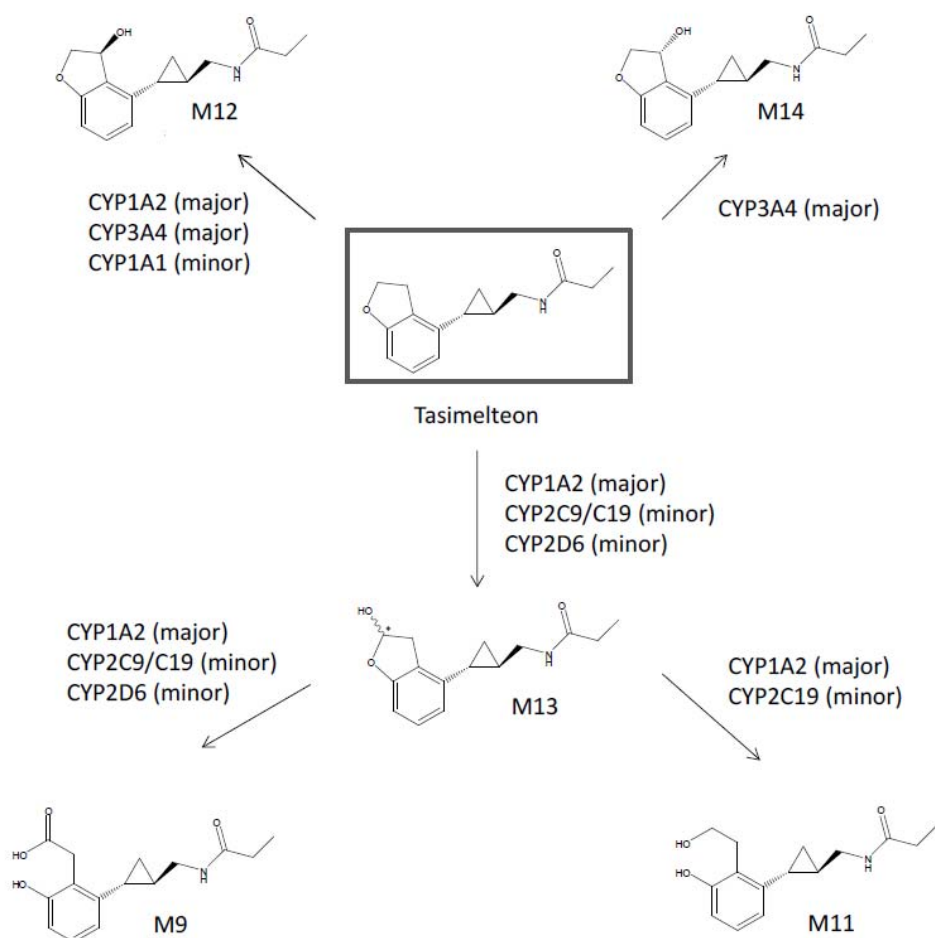
^a Codes in parenthesis were reported in a previous in vitro and vivo metabolism study of [¹⁴C]-VEC-162 with monkeys.

^b Mean percent of the dose in urine and feces.

ND = not detected; R_t: HPLC retention time, from HPLC Method 1.

Plasma AUC values for total radioactivity were higher than those for whole blood, indicating no uptake of total radioactivity into red blood cells.

Proposed metabolic pathway for tasimelteon based on human liver microsomes studies



CONCLUSIONS:

- Recovery of total radioactivity in urine and feces combined was 84.1%.
- Plasma exposure to tasimelteon (as measured by C_{max} and AUC values) was 10- to 15-fold lower than exposure to total radioactivity.
- Tasimelteon is highly metabolized following absorption after oral administration. Less than 1% of the administered tasimelteon dose was recovered unchanged in urine.

1.5 ***VP-VEC-162-1103: A double-blind, randomized, crossover trial to define the ECG effects of VEC-162 using a clinical and a supratherapeutic dose compared to placebo and moxifloxacin (a positive control) in healthy men and women: a thorough ECG trial.***

Objectives:

- To characterize the effect of 20 and 300 mg/day of VEC-162 on QT intervals in healthy volunteers

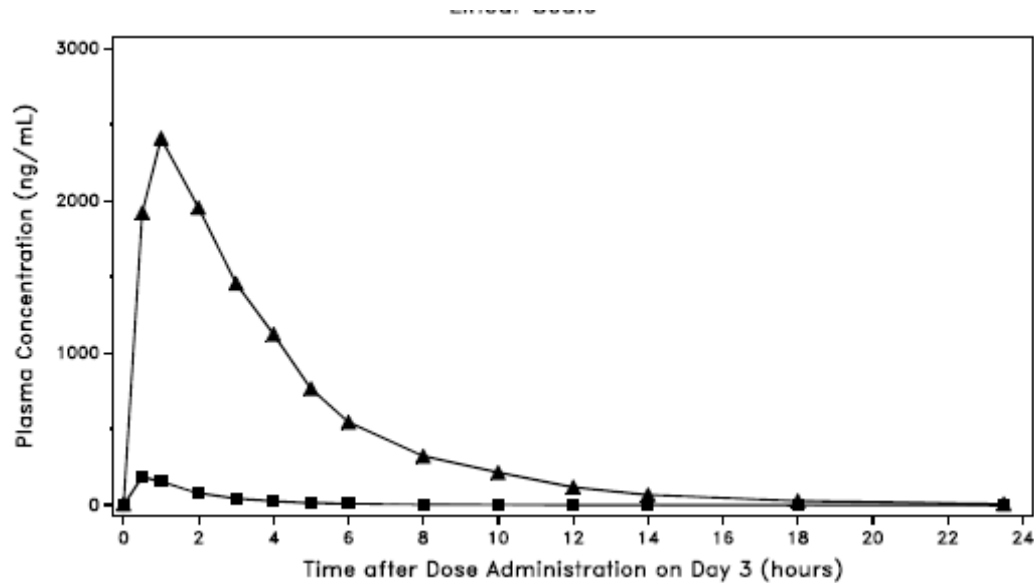
- To assess the pharmacokinetic-pharmacodynamic (PK/PD) relationship between plasma concentrations of VEC-162 and its effect, if any, on electrocardiogram (ECG) parameters

Study Design	This was a 4-period, randomized, double-blind (except for the use of moxifloxacin), multiple-dose, crossover study in healthy men and women. Forty-four subjects were enrolled with the intention that at least 40 subjects complete the study.																							
Study Population	Healthy male and female subjects (22 females, 22 males) Age: 18-45 years BMI: 18 to 35 kg/m ² .																							
Sampling:	Blood samples for the determination of VEC-162 in plasma were taken for each subject on Day 3 of each treatment period. The PK plasma samples were collected after the last ECG replicate for that time point before dosing (trough level) and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 18 and 23.5 hours after dosing																							
Analysis	<div>The plasma samples were analyzed for the concentration of tasimelteon by using LC-MS/MS method. The lower limit of quantification (LLOQ) was 0.1 ng/mL for tasimelteon.</div> <table><tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr><tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>0.3, 45, and 90 ng/mL</td><td>0.1, 0.3, 1, 3, 10, 30, 60 and 100 ng/mL</td></tr><tr><td>Between Batch Precision (%CV)</td><td>10.8 to 6.9</td><td>4.9 to 6.3</td></tr><tr><td>Between Batch Accuracy (%RE)</td><td>-4.7 to -1.6</td><td>-4.0 to 2.3</td></tr><tr><td>Linearity</td><td colspan="2">Weighted linear equation (1/X²), mean r= 0.996</td></tr><tr><td>Linear Range (ng/mL)</td><td colspan="2">0.1 to 100 ng/mL</td></tr><tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">0.1 ng/mL</td></tr></table>			Parameter	Quality Control Samples	Standard Curve Samples	Quality Control or Standard Curve Concentration (ng/mL)	0.3, 45, and 90 ng/mL	0.1, 0.3, 1, 3, 10, 30, 60 and 100 ng/mL	Between Batch Precision (%CV)	10.8 to 6.9	4.9 to 6.3	Between Batch Accuracy (%RE)	-4.7 to -1.6	-4.0 to 2.3	Linearity	Weighted linear equation (1/X ²), mean r= 0.996		Linear Range (ng/mL)	0.1 to 100 ng/mL		Sensitivity (LLOQ, ng/mL)	0.1 ng/mL	
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Sensitivity (LLOQ, ng/mL)	0.1 ng/mL																							
PK Assessments	The pharmacokinetic parameters C _{max} , T _{max} , AUC _{0-t} , AUC _(0-inf) , apparent volume of distribution, CL, t _{lag} and t _{1/2} were calculated from the plasma concentration-time data using noncompartmental analysis.																							
Safety Assessments	The safety of VEC-162 was assessed by: adverse events (AEs), clinical laboratory tests, vital signs, physical examinations, and single, standard, digital 12-lead ECGs.																							
Statistical Methods	The safety population consisted of all subjects who received at least one dose of any study treatment. The PK population included all subjects who received at least one VEC-162 treatment and had evaluable PK data. The PD (ECG) population consisted of all subjects who received at least one dose of any study treatment and had evaluable ECG data. Descriptive statistics included the number of subjects, mean, standard deviation, median, minimum, and maximum. Percentages were calculated using the number of subjects within each treatment as the denominator. Summary tables present descriptive statistics and/or frequency by treatment. Descriptive statistics were calculated for age, weight, height, and body mass index. Frequency counts were tabulated for gender, race, and ethnicity.																							

RESULTS:

Following figure illustrates PK profile of tasimelteon in healthy subjects following 20 mg and 300 mg dose.

Mean Plasma Concentrations of VEC-162 versus Time by Treatment



Mean Pharmacokinetic Parameters for VEC-162 by Treatment

Pharmacokinetic parameter (units)	20 mg (N = 43)		300 mg (N = 43)	
	n		n	
AUC _{0-t} (ng·h/mL)	43	396.4 (182.3)	43	10609.8 (5780.2)
AUC _{0-tau} (ng·h/mL)	43	396.8 (182.3)	43	10609.8 (5780.2)
AUC _{0-inf} (ng·h/mL)	30	438.5 (177.0)	43	10641.4 (5841.7)
C _{max} (ng/mL)	43	194.6 (82.7)	43	2491.5 (1058.3)
T _{max} (h) ^a	43	0.58 (0.58, 1.08)	43	1.08 (0.58, 3.08)
T _{1/2} (h)	30	2.34 (1.48)	43	2.68 (0.85)
CL/F (L/h)	43	64.4 (37.1)	43	39.9 (28.0)
V _d /F (L)	30	172.2 (121.6)	43	162.3 (151.9)

PHARMACOKINETIC RESULTS:

Following daily oral dosing for three days, mean AUCs and C_{max} of VEC-162 increased with increasing the dose from 20 mg/day to 300 mg/day for three days. The increase was greater than dose proportional for AUCs, while C_{max} appeared to increase proportionally with increasing dose. The apparent clearance was lower in the 300-mg dose group.

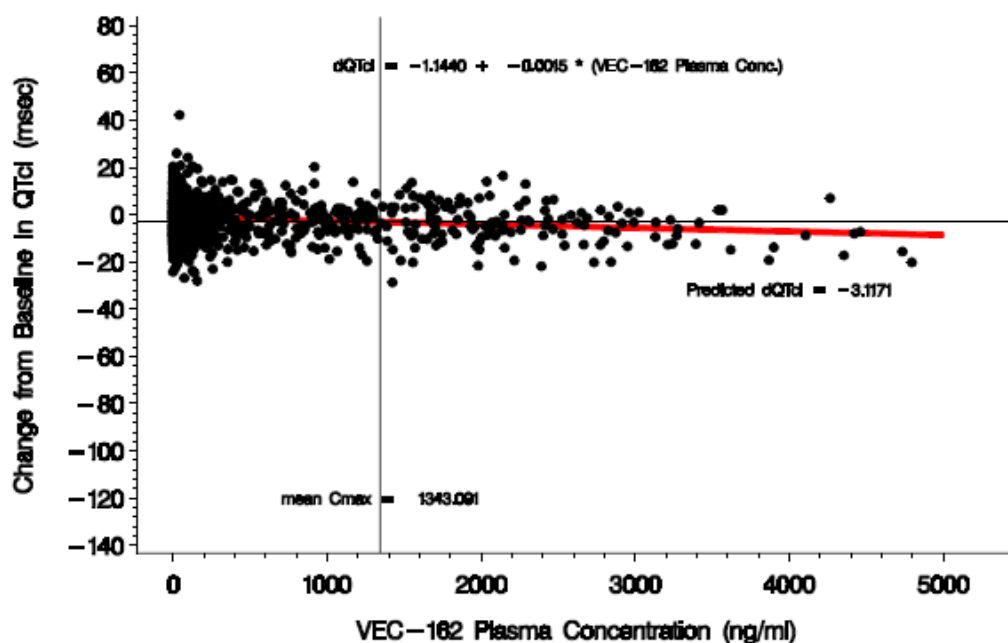
T_{max} reached approximately 0.6 hours to 1.1 hours after dosing. The mean half-life for both doses ranged from 2.3 hours to 2.7 hours.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIP

The PK/PD model showed the slopes for QTcI and QTcF were negative (-0.0015 for both). The predicted QTc and QTcF changes at C_{max} resulted in negative slopes (-3.1171 and -3.0999, respectively).

The data shows that tasimelteon did not produce a significant QTc prolongation effect in healthy subjects who received 20 mg and 300 mg tasimelteon (supratherapeutic dose).

Figure: QTcI Change From Baseline Versus VEC-162 Concentration



Note: A separate review of QTc data with respect to tasimelteon concentrations will be reviewed as a part of QT-IRT review.

CONCLUSIONS:

- The increase in tasimelteon overall (AUC) exposure from 20 mg to 300 mg was not dose-proportional. The mean C_{max} concentration increase was less than proportional for 20 mg and 300 mg.

- The apparent clearance was lower in the 300-mg dose group. The mean half-life ranged from 2.3 hours to 2.7 hours.

1.6 VP-VEC-162-1106: An Open-Label, Single-Dose, Parallel-Group Study to Compare the Pharmacokinetics of Tasimelteon in Subjects with Renal Impairment With That in Matched Control Subjects with Relatively Normal Renal Function

Objectives:

Primary:

To assess plasma concentrations and pharmacokinetics (PK) of tasimelteon in subjects with severe renal impairment including subjects on dialysis compared to healthy subjects with normal renal function.

Secondary:

- To assess plasma concentrations, PK and the percent protein binding of tasimelteon Metabolites M3, M9, M11, M12, M13, and M14 in subjects with severe renal impairment including subjects on dialysis compared to healthy subjects with normal renal function.
- To assess the effects of hemodialysis on the PK of tasimelteon and its metabolites.
- To assess the safety and tolerability of a single 20-mg oral dose of tasimelteon.

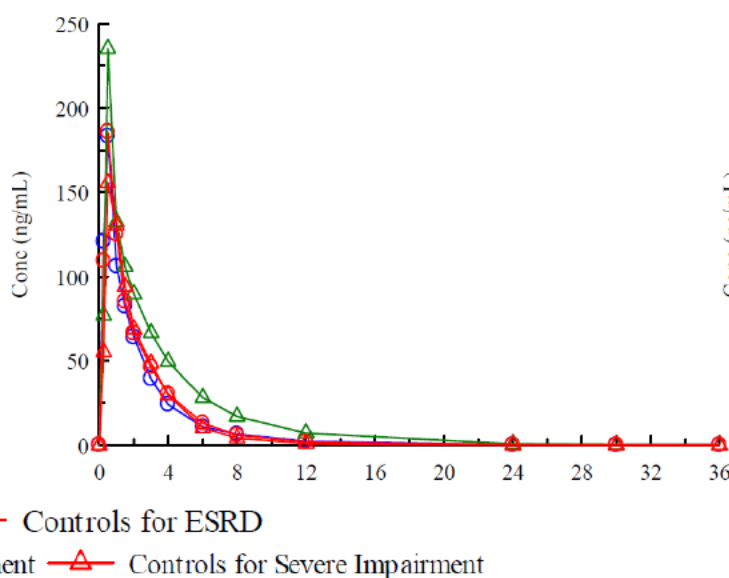
Study Design	This study was an open-label, parallel-group design. Thirty-two subjects were enrolled in 3 groups: <ul style="list-style-type: none">• Group 1 consisted of 8 subjects with end stage renal disease (ESRD) requiring dialysis;• Group 2 consisted of 8 subjects with severe (Stage 4) renal impairment;• Group 3 consisted of 16 healthy subjects with normal renal function matched by gender, age, body mass index (BMI), and smoking status to Groups 1 or 2.		
Study Population	Healthy subjects and patients with renal impairment (22 male and 10 female) Age: 18-79 years BMI: 18 to 40 kg/m ² . Thirty two subjects were enrolled and 32 completed the study.		
Sampling:	Plasma PK samples were collected at pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, and 36 hours after dosing. At the 0.5 and 3 hours post-dose blood draw, an additional 3 mL of blood was collected for protein binding measurements.		
Analysis	The plasma samples were analyzed for the concentration of tasimelteon by using LC-MS/MS method. The lower limit of quantification (LLOQ) was 0.3 ng/mL for tasimelteon.		
	Parameter	Quality Control Samples	Standard Curve Samples

		Quality Control or Standard Curve Concentration (ng/mL)	0.9, 135, and 270 ng/mL	0.3, 0.9, 3, 9, 30, 90, 225 and 300 ng/mL	
		Between Batch Precision (%CV)	2.6% to 4.3%	2.3 to 5.6	
		Between Batch Accuracy (%RE)	-9.3% to 4.3%	-9.3 to 4.7	
		Linearity	Weighted linear equation (1/X ²), mean r=0.998		
		Linear Range (ng/mL)	0.3 to 300 ng/mL		
		Sensitivity (LLOQ, ng/mL)	0.3 ng/mL		
PK Assessments	The pharmacokinetic parameters C _{max} , T _{max} , AUC _{0-t} , AUC _(0-inf) , apparent volume of distribution, CL, t _{lag} and t _{1/2} were calculated from the plasma concentration-time data using noncompartmental analysis. Comparison of the pharmacokinetic parameters was done by analysis of variance.				
Safety Assessments	Safety was assessed by adverse event (AE) and serious adverse event (SAE) monitoring, changes in clinical laboratory parameters that were relevant to safety. Influence of trial medication on vital signs and electrocardiogram (ECG) parameters.				
Statistical Methods	Pharmacokinetic: Comparison of the pharmacokinetic parameters C _{max} , AUC(0-t), AUC(inf), and t _{1/2} for tasimelteon and metabolites and CL/F and V _z /F for tasimelteon between groups - ESRD and matching controls or severe impairment and matching controls - was done using an analysis of variance (ANOVA) model with renal function group as the classification variable, using the natural logarithms of the data. Confidence intervals (CI) (90%) were constructed for the ratios of ESRD-to-control or severe impairment-to-control subjects of all applicable parameters using the log transformed data and the two one-sided t-tests procedure. The point estimates and CIs were exponentiated back to the original scale. Relationships between individual subject tasimelteon CL/F and Creatinine Clearance and between the individual subject tasimelteon CL/F and estimated glomerular filtration rate were examined graphically for subjects with ESRD, subjects with severe impairment, and matched controls. Individual subject tasimelteon t _{1/2} was also examined by renal function group.				

RESULTS:

Following figure illustrates PK profile of tasimelteon in healthy subjects and in subjects with renal impairment.

Mean Plasma Concentrations of Tasimelteon After Oral Administration of Single 20 Mg Doses of Tasimelteon to Subjects with ESRD, Subjects with Severe Impairment, and Matched Controls



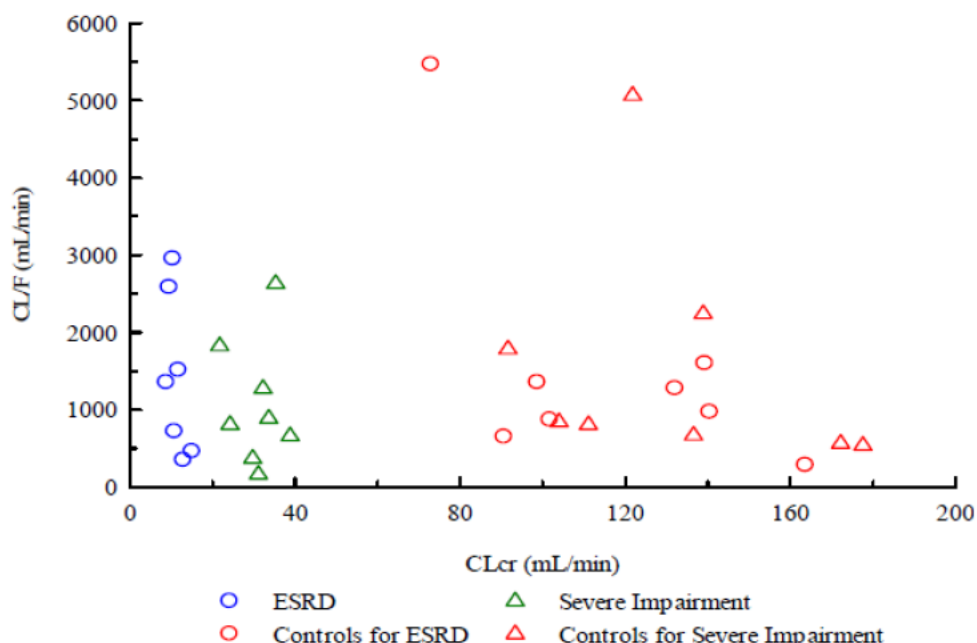
Summary of Pharmacokinetic Parameters for Tasimelteon after Oral Administration of Single 20 mg Doses of Tasimelteon to Subjects with ESRD, Subjects with Severe Impairment, and Matched Controls.

Parameter*	ESRD		Severe Impairment	
	Patients	Controls	Patients	Controls
C _{max} (ng/mL)	197 ± 121 (8)	197 ± 75.8 (8)	255 ± 142 (8)	176 ± 93.3 (8)
T _{max} (h)	0.50 (8)	0.50 (8)	0.50 (8)	0.50 (8)
AUC(0-t) (h,ng/mL)	373 ± 316 (8)	399 ± 344 (8)	605 ± 640 (8)	364 ± 209 (8)
AUC(inf) (h,ng/mL)	409 ± 326 (7)	401 ± 344 (8)	607 ± 641 (8)	366 ± 209 (8)
λ _z (1/h)	0.2934 ± 0.2196 (7)	0.5617 ± 0.2009 (8)	0.3517 ± 0.1446 (8)	0.5302 ± 0.1471 (8)
t _{1/2} (h)	3.40 ± 1.77 (7)	1.39 ± 0.53 (8)	2.32 ± 1.01 (8)	1.42 ± 0.49 (8)
CL/F (mL/min)	1,417 ± 1,024 (7)	1,556 ± 1633 (8)	1,075 ± 814 (8)	1,561 ± 1,545 (8)
V _z /F (L)	399 ± 430 (7)	149 ± 101 (8)	188 ± 149 (8)	161 ± 113 (8)

Statistical Comparison of Pharmacokinetic Parameters for Tasimelteon after Oral Administration of Single 20 Mg Doses of Tasimelteon to Subjects with ESRD, Subjects with Severe Impairment, and Matched Controls.

Parameter	ESRD vs. Matched Controls				Severe Impairment vs. Matched Controls			
	Geometric Mean Ratio (%)*				Geometric Mean Ratio (%)*			
	Estimate	90% Confidence Interval			Estimate	90% Confidence Interval		
C _{max}	95.66	59.94	→	152.69	143.22	84.47	→	242.83
AUC(0-t)	92.61	44.43	→	193.03	141.97	67.28	→	299.57
AUC(inf)	102.23	47.45	→	220.29	141.80	67.36	→	298.49
t _{1/2}	221.54	137.07	→	358.04	157.19	112.84	→	218.96
CL/F	97.82	45.40	→	210.77	70.52	33.50	→	148.45
V _z /F	216.70	107.56	→	436.55	110.85	60.86	→	201.90

Relationship Between the Individual Subject Tasimelteon CL/F and Creatinine Clearance After Oral Administration of Single 20 Mg Doses of Tasimelteon to Subjects with ESRD, Subjects with Severe Impairment, and Matched Controls.



The mean protein binding for tasimelteon in this study was 89.7% in ESRD patients, 90.0% in patients with severe impairment and 88.6% and 90.1% for the respective matched healthy controls.

Metabolite M12

Parameter*	ESRD		Severe Impairment	
	Patients	Controls	Patients	Controls
C _{max} (ng/mL)	91.0 ± 29.6 (8)	96.7 ± 27.6 (8)	120 ± 68.3 (8)	85.4 ± 16.7 (8)
T _{max} (h)	1.25 (8)	1.25 (8)	1.25 (8)	1.25 (8)
AUC(0-t) (hxng/mL)	572 ± 319 (8)	649 ± 243 (8)	934 ± 670 (8)	605 ± 211 (8)
AUC(inf) (hxng/mL)	583 ± 330 (8)	653 ± 245 (8)	969 ± 734 (8)	609 ± 211 (8)
2z (1/h)	0.2259 ± 0.1331 (8)	0.2344 ± 0.1188 (8)	0.1781 ± 0.0726 (8)	0.2252 ± 0.0921
t _{1/2} (h)	4.08 ± 2.12 (8)	3.45 ± 1.29 (8)	4.54 ± 1.98 (8)	3.46 ± 1.08 (8)

Statistical Comparison of Pharmacokinetic Parameters for Metabolite M12 After Oral Administration of Single 20 mg Doses of Tasimelteon to Subjects with ESRD, Subjects with Severe Impairment, and Matched Controls.

Parameter	ESRD vs. Matched Controls				Severe Impairment vs. Matched Controls			
	Geometric Mean Ratio*				Geometric Mean Ratio*			
	Estimate	90% Confidence Interval			Estimate	90% Confidence Interval		
C _{max}	93.30	70.96	→	122.67	127.86	92.10	→	177.53
AUC(0-t)	82.64	54.43	→	125.45	138.10	88.80	→	214.75
AUC(inf)	83.49	54.87	→	127.04	139.81	89.01	→	219.62
t _{1/2}	110.58	70.80	→	172.73	127.83	90.29	→	180.98

Metabolite M13

Summary of Pharmacokinetic Parameters for Metabolite M13 After Oral Administration of Single 20 mg Doses of Tasimelteon to Subjects with ESRD, Subjects with Severe Impairment, and Matched Controls.

Parameter*	ESRD		Severe Impairment	
	Patients	Controls	Patients	Controls
C _{max} (ng/mL)	235 ± 70.7 (8)	218 ± 80.3 (8)	292 ± 172 (8)	239 ± 89.7 (8)
T _{max} (h)	0.50 (8)	0.50 (8)	0.50 (8)	0.75 (8)
AUC(0-t) (h×ng/mL)	304 ± 88.3 (8)	295 ± 71.1 (8)	377 ± 178 (8)	366 ± 141 (8)
AUC(inf) (h×ng/mL)	308 ± 90.8 (8)	299 ± 71.5 (8)	382 ± 180 (8)	370 ± 142 (8)
λ _z (1/h)	0.6286 ± 0.3243 (8)	0.6743 ± 0.4024 (8)	0.4301 ± 0.1421 (8)	0.5743 ± 0.2483 (8)
t _{1/2} (h)	1.41 ± 0.73 (8)	1.31 ± 0.64 (8)	1.83 ± 0.82 (8)	1.37 ± 0.50 (8)

*Arithmetic mean ± standard deviation (N) except T_{max} for which the median (N) is reported.

Statistical Comparison of Pharmacokinetic Parameters for Metabolite M13 After Oral Administration of Single 20 mg Doses of Tasimelteon to Subjects with ESRD, Subjects with Severe Impairment, and Matched Controls.

Parameter	ESRD vs. Matched Controls				Severe Impairment vs. Matched Controls			
	Geometric Mean Ratio (%)*				Geometric Mean Ratio (%)*			
	Estimate	90% Confidence Interval			Estimate	90% Confidence Interval		
C _{max}	109.88	80.46	→	150.05	107.92	63.79	→	182.56
AUC(0-t)	102.27	79.61	→	131.37	97.61	65.32	→	145.86
AUC(inf)	102.06	79.30	→	131.35	98.02	65.82	→	145.98
t _{1/2}	106.77	66.91	→	170.37	132.26	94.53	→	185.04

*Based on analysis of natural log-transformed parameters.

Metabolite M9

Summary of Pharmacokinetic Parameters for Metabolite M9 After Oral Administration of Single 20 mg Doses of Tasimelteon to Subjects with ESRD, Subjects with Severe Impairment, and Matched Controls.

Parameter*	ESRD		Severe Impairment	
	Patients	Controls	Patients	Controls
C _{max} (ng/mL)	375 ± 104 (8)	194 ± 104 (8)	313 ± 122 (8)	167 ± 50.8 (8)
T _{max} (h)	1.75 (8)	0.50 (8)	1.00 (8)	0.75 (8)
AUC(0-t) (h×ng/mL)	3,335 ± 608 (8)	312 ± 91.7 (8)	1,427 ± 497 (8)	301 ± 44.9 (8)
AUC(inf) (h×ng/mL)	3,599 ± 686 (8)	318 ± 91.5 (8)	1,443 ± 496 (8)	305 ± 45.7 (8)
λ _z (1/h)	0.0746 ± 0.0248 (8)	0.5123 ± 0.1776 (8)	0.2343 ± 0.0878 (8)	0.4841 ± 0.1363 (8)
t _{1/2} (h)	9.92 ± 2.21 (8)	1.51 ± 0.56 (8)	3.32 ± 1.15 (8)	1.53 ± 0.41 (8)

Statistical Comparison of Pharmacokinetic Parameters for Metabolite M9 After Oral Administration of Single 20 mg Doses of Tasimelteon to Subjects with ESRD, Subjects with Severe Impairment, and Matched Controls.

Parameter	ESRD vs. Matched Controls				Severe Impairment vs. Matched Controls			
	Geometric Mean Ratio (%)*				Geometric Mean Ratio (%)*			
	Estimate	90% Confidence Interval			Estimate	90% Confidence Interval		
C _{max}	222.40	141.63	→	349.24	182.85	133.60	→	250.27
AUC(0-t)	1,099.36	878.50	→	1,375.76	455.97	362.42	→	573.68
AUC(inf)	1,160.92	930.63	→	1,448.20	455.35	362.60	→	571.84
t _{1/2}	676.04	512.51	→	891.76	212.24	159.54	→	282.36

Metabolite M11

Summary of Pharmacokinetic Parameters for Metabolite M11 After Oral Administration of Single 20 mg Doses of Tasimelteon to Subjects with ESRD, Subjects with Severe Impairment, and Matched Controls.

Parameter*	ESRD		Severe Impairment	
	Patients	Controls	Patients	Controls
C _{max} (ng/mL)	35.9 ± 5.53 (8)	30.0 ± 4.19 (8)	39.5 ± 17.4 (8)	40.1 ± 14.7 (8)
T _{max} (h)	1.50 (8)	1.00 (8)	1.00 (8)	1.25 (8)
AUC(0-t) (h×ng/mL)	131 ± 46.7 (8)	94.3 ± 27.2 (8)	160 ± 110 (8)	128 ± 57.3 (8)
AUC(inf) (h×ng/mL)	175 ± 31.2 (4)	101 ± 32.5 (6)	128 ± 53.1 (7)	133 ± 61.9 (7)
λ _z (1/h)	0.1269 ± 0.0974 (4)	0.4296 ± 0.2063 (6)	0.2452 ± 0.1829 (7)	0.3835 ± 0.1142 (7)
t _{1/2} (h)	8.38 ± 6.09 (4)	1.83 ± 0.57 (6)	4.35 ± 2.98 (7)	1.96 ± 0.61 (7)

*Arithmetic mean ± standard deviation (N) except T_{max} for which the median (N) is reported.

Statistical Comparison of Pharmacokinetic Parameters for Metabolite M11 After Oral Administration of Single 20 mg Doses of Tasimelteon to Subjects with ESRD, Subjects with Severe Impairment, and Matched Controls.

Parameter	ESRD vs. Matched Controls				Severe Impairment vs. Matched Controls			
	Geometric Mean Ratio (%)*				Geometric Mean Ratio (%)*			
	Estimate	90% Confidence Interval			Estimate	90% Confidence Interval		
C _{max}	119.32	104.41	→	136.36	97.10	69.09	→	136.45
AUC(0-t)	136.70	101.94	→	183.30	114.48	73.66	→	177.91
AUC(inf)	180.12	124.74	→	260.11	97.13	65.18	→	144.73
t _{1/2}	392.09	199.69	→	769.87	187.79	110.84	→	318.16

*Based on analysis of natural log-transformed parameters.

Metabolite M14

Summary of Pharmacokinetic Parameters for Metabolite M14 After Oral Administration of Single 20 mg Doses of Tasimelteon to Subjects with ESRD, Subjects with Severe Impairment, and Matched Controls.

Parameter*	ESRD		Severe Impairment	
	Patients	Controls	Patients	Controls
C _{max} (ng/mL)	5.17 ± 1.58 (8)	5.27 ± 3.32 (8)	7.04 ± 3.17 (8)	4.15 ± 2.12 (8)
T _{max} (h)	0.52 (8)	0.50 (8)	0.50 (8)	1.00 (8)
AUC(0-t) (h×ng/mL)	15.4 ± 12.0 (8)	14.7 ± 9.83 (8)	27.7 ± 23.1 (8)	13.7 ± 10.5 (8)
AUC(inf) (h×ng/mL)	18.7 ± 14.0 (7)	19.5 ± 14.1 (6)	30.1 ± 24.4 (8)	15.4 ± 11.0 (8)
λ _z (1/h)	0.4648 ± 0.2057 (7)	0.5427 ± 0.4438 (6)	0.2977 ± 0.1578 (8)	0.3684 ± 0.1481 (8)
t _{1/2} (h)	1.89 ± 1.11 (7)	2.07 ± 1.66 (6)	3.08 ± 1.90 (8)	2.11 ± 0.67 (8)

*Arithmetic mean ± standard deviation (N) except T_{max} for which the median (N) is reported.

Statistical Comparison of Pharmacokinetic Parameters for Metabolite M14 After Oral Administration of single 20 mg Doses of Tasimelteon to Subjects with ESRD, Subjects with Severe Impairment, and Matched Controls.

Parameter	ESRD vs. Matched Controls				Severe Impairment vs. Matched Controls			
	Geometric Mean Ratio (%)*				Geometric Mean Ratio (%)*			
	Estimate	90% Confidence Interval			Estimate	90% Confidence Interval		
C _{max}	109.09	69.89	→	170.28	177.47	118.51	→	265.78
AUC(0-t)	105.03	55.97	→	197.11	202.28	109.78	→	372.73
AUC(inf)	100.67	48.52	→	208.86	190.61	106.09	→	342.46
t _{1/2}	101.97	53.34	→	194.95	132.95	87.37	→	202.30

*Based on analysis of natural log-transformed parameters.

Metabolite M3

Summary of Pharmacokinetic Parameters for Metabolite M3 After Oral Administration of Single 20 mg Doses of Tasimelteon to Subjects with ESRD, Subjects with Severe Impairment, and Matched Controls.

Parameter*	ESRD		Severe Impairment	
	Patients	Controls	Patients	Controls
C _{max} (ng/mL)	250 ± 118 (8)	140 ± 62.0 (8)	220 ± 64.9 (8)	122 ± 54.7 (8)
T _{max} (h)	3.50 (8)	0.50 (8)	1.00 (8)	0.75 (8)
AUC(0-t) (h×ng/mL)	3,301 ± 1,535 (8)	256 ± 80.6 (8)	2,089 ± 1,536 (8)	215 ± 55.2 (8)
AUC(inf) (h×ng/mL)	2,590 (1)	243 ± 71.0 (4)	2,278 ± 1,915 (8)	226 ± 58.8 (7)
λ _z (1/h)	0.0560 (1)	0.1909 ± 0.0919 (4)	0.1115 ± 0.0335 (8)	0.2662 ± 0.0745 (7)
t _{1/2} (h)	12.4 (1)	4.79 ± 3.37 (4)	6.97 ± 3.02 (8)	2.80 ± 0.86 (7)

*Arithmetic mean ± standard deviation (N) except T_{max} for which the median (N) is reported.

Statistical Comparison of Pharmacokinetic Parameters for Metabolite M3 After Oral Administration of Single 20 mg Doses of Tasimelteon to Subjects with ESRD, Subjects with Severe Impairment, and Matched Controls.

Parameter	ESRD vs. Matched Controls			Severe Impairment vs. Matched Controls		
	Geometric Mean Ratio (%)*			Geometric Mean Ratio (%)*		
	Estimate	90% Confidence Interval		Estimate	90% Confidence Interval	
C _{max}	174.24	107.00	→	283.74	192.30	133.32 → 277.39
AUC(0-t)	1,207.05	826.49	→	1,762.85	826.63	527.55 → 1,295.28
AUC(inf)	1,102.32	501.86	→	2,421.19	823.88	490.01 → 1,385.24
t _{1/2}	302.04	59.69	→	1,528.25	242.32	179.04 → 327.96

*Based on analysis of natural log-transformed parameters.

Metabolites M3 and M9 are dialyzable. Tasimelteon, M11, M12, and M14 are dialyzable but to a lesser extent. However M13 was not removed by hemodialysis.

There were no changes in plasma protein binding in RI subjects when compared to healthy controls. Renal impairment does not affect the protein binding of tasimelteon, M9, M11, M12, and M13.

Reviewer's Comment: The difference between ESRD subjects and subjects with severe renal impairment ~~may be a~~ may be due to small sample size.

CONCLUSIONS:

- Subjects with severe impairment had, on average, a 30% lower CL/F.
- Subjects with ESRD had a comparable CL/F with a GMR of 97.8%. Mean plasma concentrations and arithmetic mean values for C_{max} and AUC (inf) were comparable with a large variability characterized by wide 90% CIs.
- Plasma protein binding in severe RI patients and ESRD patients was similar to matched controls.

1.7 ***VP-VEC-162-1105: An Open-Label, Single-Dose, Parallel-Group Study to Compare the Pharmacokinetics of Tasimelteon in Subjects with Mild or Moderate Hepatic Impairment with that in Matched Healthy Control Subjects.***

Objectives:

To assess plasma concentrations and pharmacokinetics (PK) of tasimelteon and its major metabolites in subjects with mild or moderate hepatic impairment compared to healthy subjects with normal hepatic function.

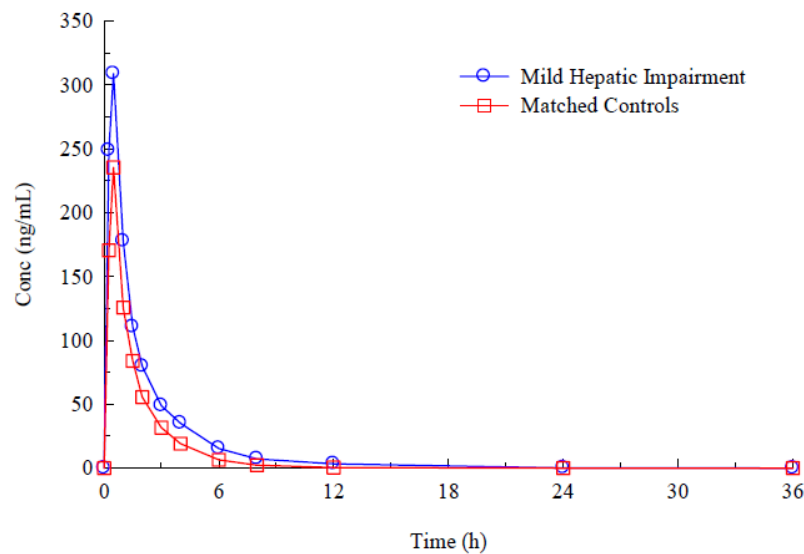
Study Design	The study employed an open-label, parallel-group design. Twenty-nine subjects were enrolled in 3 groups: Group 1 consisted of 8 subjects with mild hepatic impairment; Group 2 consisted of 8 subjects with moderate hepatic impairment; and Group 3 consisted of 13 healthy subjects matched by gender, age, smoking status, and body mass index (BMI), to Groups 1 and/or 2.																							
Study Population	Healthy subjects and patients with hepatic impairment (23 male and 6 female) Age: 45-62 years BMI: 18 to 35 kg/m ² . Thirty two subjects were enrolled and 32 completed the study.																							
Sampling:	Plasma PK samples were collected at predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 36 hours after dosing.																							
Analysis	<div>The plasma samples were analyzed for the concentration of tasimelteon by using LC-MS/MS method. The lower limit of quantification (LLOQ) was 0.3 ng/mL for tasimelteon.</div> <table><tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr><tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>0.9, 135, and 270 ng/mL</td><td>0.3, 0.9, 3, 9, 30, 90, 225 and 300 ng/mL</td></tr><tr><td>Between Batch Precision (%CV)</td><td>2.3% to 11.4%</td><td>1.9 to 4.0</td></tr><tr><td>Between Batch Accuracy (%RE)</td><td>-6.4% to 3.2%.</td><td>-5.7 to 5.1</td></tr><tr><td>Linearity</td><td colspan="2">Weighted linear equation (1/X²), mean r= 0.998</td></tr><tr><td>Linear Range (ng/mL)</td><td colspan="2">0.3 to 300 ng/mL</td></tr><tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">0.3 ng/mL</td></tr></table>			Parameter	Quality Control Samples	Standard Curve Samples	Quality Control or Standard Curve Concentration (ng/mL)	0.9, 135, and 270 ng/mL	0.3, 0.9, 3, 9, 30, 90, 225 and 300 ng/mL	Between Batch Precision (%CV)	2.3% to 11.4%	1.9 to 4.0	Between Batch Accuracy (%RE)	-6.4% to 3.2%.	-5.7 to 5.1	Linearity	Weighted linear equation (1/X ²), mean r= 0.998		Linear Range (ng/mL)	0.3 to 300 ng/mL		Sensitivity (LLOQ, ng/mL)	0.3 ng/mL	
Parameter	Quality Control Samples	Standard Curve Samples																						
Quality Control or Standard Curve Concentration (ng/mL)	0.9, 135, and 270 ng/mL	0.3, 0.9, 3, 9, 30, 90, 225 and 300 ng/mL																						
Between Batch Precision (%CV)	2.3% to 11.4%	1.9 to 4.0																						
Between Batch Accuracy (%RE)	-6.4% to 3.2%.	-5.7 to 5.1																						
Linearity	Weighted linear equation (1/X ²), mean r= 0.998																							
Linear Range (ng/mL)	0.3 to 300 ng/mL																							
Sensitivity (LLOQ, ng/mL)	0.3 ng/mL																							
PK Assessments	The pharmacokinetic parameters C _{max} , T _{max} , AUC _{0-t} , AUC _(0-inf) , apparent volume of distribution, CL, t _{lag} and t _{1/2} were calculated from the plasma concentration-time data using noncompartmental analysis. Comparison of the pharmacokinetic parameters was done by analysis of variance.																							
Safety Assessments	Safety was assessed by adverse event (AE) and serious adverse event (SAE) monitoring. Changes in clinical laboratory parameters that were relevant to safety. Influence of trial medication on vital signs and electrocardiogram (ECG) parameters.																							

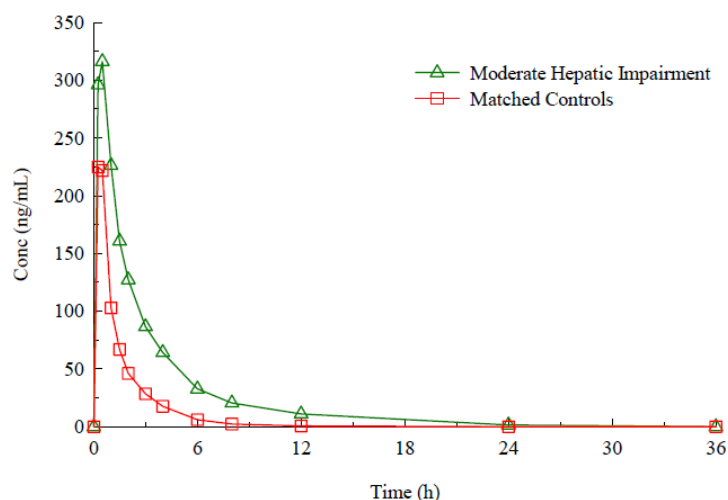
Statistical Methods	<p>Pharmacokinetic:</p> <p>Plasma concentration-time data for tasimelteon, M9, M11, M12, M13, and M14 were presented in descriptive summary tables, individual listings, mean profile plots, and individual profile plots, on linear and semi-logarithmic axes. Semi-logarithmic graphs of individual subject concentration versus time include a line segment indicating the range of data used to estimate the elimination rate constant. Descriptive statistics (number of nonmissing observations [n], arithmetic mean, standard deviation [SD], coefficient of variation [CV%], geometric mean, geometric CV, median, minimum, and maximum) were presented for plasma concentrations. Below quantifiable limit (BQL) concentrations were treated as zero for descriptive statistics. Mean concentrations that were BQL were presented as BQL, and the SD and CV% were reported as not applicable. Descriptive summaries of PK parameters include n, arithmetic mean, SD, CV%, median, minimum and maximum values. The Tmax was summarized only with n, mean, SD, CV%, median, minimum, and maximum.</p>
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RESULTS:

Following figure illustrates PK profile of tasimelteon in healthy subjects and in subjects with hepatic impairment.

Arithmetic Mean Plasma Concentrations of Tasimelteon After Oral Administration of 20 mg Tasimelteon to Subjects With Mild (top panel) or Moderate Hepatic Impairment (bottom panel) and Healthy Matched Controls





Summary of pharmacokinetic parameters for tasimelteon after oral administration of 20 mg of tasimelteon to subjects with mild or moderate hepatic impairment and healthy matched controls.

Parameter*	Mild Hepatic Impairment		Moderate Hepatic Impairment	
	Patients	Controls	Patients	Controls
Cmax (ng/mL)	366 ± 182 (8)	272 ± 58.8 (8)	381 ± 289 (8)	284 ± 109.8 (8)
Tmax (h)	0.50 (8) [0.25 – 1.00]	0.50 (8) [0.25 – 1.00]	0.50 (8) [0.25 – 1.00]	0.38 (8) [0.25 – 0.58]
AUC(0-t) (h×ng/mL)	556 ± 400 (8)	357 ± 124 (8)	880 ± 966 (8)	332 ± 195 (8)
AUC(inf) (h×ng/mL)	560 ± 401 (8)	358 ± 124 (8)	893 ± 990 (8)	334 ± 195 (8)
λ_z (h ⁻¹)	0.4593 ± 0.2679 (8)	0.5523 ± 0.1265 (8)	0.3819 ± 0.1732 (8)	0.5556 ± 0.1442 (8)
t1/2 (h)	1.84 ± 0.73 (8)	1.31 ± 0.27 (8)	2.17 ± 1.07 (8)	1.32 ± 0.34 (8)
CL/F (mL/min)	850 ± 521 (8)	1,128 ± 709 (8)	721 ± 505 (8)	1,318 ± 744 (8)
Vz/F (L)	118 ± 58.5 (8)	117 ± 44.1 (8)	107 ± 58.3 (8)	137 ± 51.6 (8)

Statistical comparison of pharmacokinetic parameters for tasimelteon after oral administration of 20 mg of tasimelteon to subjects with mild or moderate hepatic impairment and healthy matched controls-

Statistical comparison of pharmacokinetic parameters for tasimelteon after oral administration of 20 mg of tasimelteon to subjects with mild or moderate hepatic impairment and healthy matched controls.

Parameter	Geometric Mean Ratio (%)*	
	Estimate	90% Confidence Interval
Mild Hepatic Impairment vs. Matched Controls		
C _{max}	122.12	85.43 → 174.55
AUC(inf)	139.79	85.34 → 229.00
CL/F	71.54	43.67 → 117.19
V _z /F	94.31	64.63 → 137.62
t _{1/2}	131.83	94.91 → 183.12
Moderate Hepatic Impairment vs. Matched Controls		
C _{max}	118.25	75.67 → 184.78
AUC(inf)	210.55	109.76 → 403.86
CL/F	47.50	24.76 → 91.10
V _z /F	73.26	47.51 → 112.97
t _{1/2}	154.24	111.39 → 213.57

Metabolite M12

Summary of pharmacokinetic parameters for Metabolite M12 after oral administration of 20 mg of tasimelteon to subjects with mild or moderate hepatic impairment and healthy matched controls.

Parameter*	Mild Hepatic Impairment		Moderate Hepatic Impairment	
	Patients	Controls	Patients	Controls
C _{max} (ng/mL)	136 ± 28.3 (8)	96.4 ± 24.8 (8)	89.0 ± 29.4 (8)	118 ± 29.3 (8)
T _{max} (h)	1.00 (8) [0.50 – 3.00]	1.00 (8) [0.25 – 1.50]	2.00 (8) [0.50 – 4.00]	0.50 (8) [0.25 – 1.00]
AUC(0-t) (h×ng/mL)	1,059 ± 506 (8)	616 ± 161 (8)	854 ± 504 (8)	631 ± 174 (8)
AUC(inf) (h×ng/mL)	1,079 ± 521 (8)	623 ± 165 (8)	693 ± 171 (7)	637 ± 177 (8)
λ _z (h ⁻¹)	0.2194 ± 0.1066 (8)	0.2193 ± 0.0719 (8)	0.2175 ± 0.0854 (7)	0.2422 ± 0.0845 (8)
t _{1/2} (h)	3.78 ± 1.62 (8)	3.36 ± 0.72 (8)	3.60 ± 1.27 (7)	3.14 ± 0.95 (8)

Statistical comparison of pharmacokinetic parameters for Metabolite M12 after oral administration of 20 mg of tasimelteon to subjects with mild or moderate hepatic impairment and

healthy matched controls:-

Parameter	Geometric Mean Ratio (%)*	
	Estimate	90% Confidence Interval
Mild Hepatic Impairment vs. Matched Controls		
C _{max}	132.28	108.55 → 161.19
AUC(inf)	160.81	123.64 → 209.14
t _{1/2}	109.35	83.37 → 143.43
Moderate Hepatic Impairment vs. Matched Controls		
C _{max}	83.85	66.40 → 105.87
AUC(inf)	111.01	91.78 → 134.26
t _{1/2}	106.95	83.20 → 137.48

Metabolite M13

Summary of pharmacokinetic parameters for Metabolite M13 after oral administration of 20 mg of tasimelteon to subjects with mild or moderate hepatic impairment and healthy matched controls.

Parameter*	Mild Hepatic Impairment		Moderate Hepatic Impairment	
	Patients	Controls	Patients	Controls
C _{max} (ng/mL)	255 ± 83.2 (8)	331 ± 76.8 (8)	143 ± 53.6 (8)	381 ± 137 (8)
T _{max} (h)	0.50 (8) [0.25 – 1.00]	0.50 (8) [0.25 – 1.00]	0.50 (8) [0.50 – 1.00]	0.50 (8) [0.25 – 0.58]
AUC(0-t) (h×ng/mL)	372 ± 129 (8)	380 ± 104 (8)	291 ± 155 (8)	388 ± 142 (8)
AUC(inf) (h×ng/mL)	377 ± 132 (8)	384 ± 105 (8)	297 ± 158 (8)	393 ± 144 (8)
λ _z (h ⁻¹)	0.5247 ± 0.1934 (8)	0.6096 ± 0.1425 (8)	0.4912 ± 0.2628 (8)	0.6066 ± 0.1552 (8)
t _{1/2} (h)	1.50 ± 0.61 (8)	1.18 ± 0.23 (8)	1.85 ± 1.14 (8)	1.20 ± 0.27 (8)

Statistical comparison of pharmacokinetic parameters for Metabolite M13 after oral administration of 20 mg of tasimelteon to subjects with mild or moderate hepatic impairment and healthy matched controls:-

Parameter	Geometric Mean Ratio (%)*	
	Estimate	90% Confidence Interval
Mild Hepatic Impairment vs. Matched Controls		
C _{max}	72.24	55.20 → 94.54
AUC(inf)	93.92	72.91 → 120.97
t _{1/2}	117.22	93.89 → 146.34
Moderate Hepatic Impairment vs. Matched Controls		
C _{max}	39.69	29.57 → 53.28
AUC(inf)	70.73	53.23 → 93.98
t _{1/2}	133.87	99.93 → 179.33

Metabolite M14

Summary of pharmacokinetic parameters for Metabolite M14 after oral administration of 20 mg of tasimelteon to subjects with mild or moderate hepatic impairment and healthy matched controls.

Parameter*	Mild Hepatic Impairment		Moderate Hepatic Impairment	
	Patients	Controls	Patients	Controls
C _{max} (ng/mL)	6.45 ± 4.95 (8)	7.64 ± 1.91 (8)	6.60 ± 4.62 (8)	8.36 ± 3.23 (8)
T _{max} (h)	0.75 (8) [0.25 – 1.00]	0.50 (8) [0.25 – 1.00]	1.00 (8) [0.50 – 3.00]	0.50 (8) [0.25 – 1.00]
AUC(0-t) (h×ng/mL)	20.6 ± 19.9 (8)	17.8 ± 6.18 (8)	44.3 ± 72.3 (8)	17.4 ± 12.9 (8)
AUC(inf) (h×ng/mL)	22.9 ± 22.0 (8)	19.3 ± 6.69 (8)	64.5 ± 92.5 (6)	18.8 ± 12.7 (8)
λ _z (h ⁻¹)	0.4363 ± 0.1645 (8)	0.4601 ± 0.1402 (8)	0.3109 ± 0.1963 (6)	0.4879 ± 0.1542 (8)
t _{1/2} (h)	1.91 ± 1.05 (8)	1.60 ± 0.36 (8)	3.25 ± 2.52 (6)	1.54 ± 0.44 (8)

Statistical comparison of pharmacokinetic parameters for Metabolite M14 after oral administration of 20 mg of tasimelteon to subjects with mild or moderate hepatic impairment and

healthy matched controls:

Parameter	Geometric Mean Ratio (%)*	
	Estimate	90% Confidence Interval
Mild Hepatic Impairment vs. Matched Controls		
C _{max}	68.38	44.31 → 105.51
AUC(inf)	86.82	50.21 → 150.11
t _{1/2}	110.50	84.49 → 144.52
Moderate Hepatic Impairment vs. Matched Controls		
C _{max}	72.43	47.55 → 110.32
AUC(inf)	200.47	107.59 → 373.53
t _{1/2}	170.29	118.15 → 245.45

Metabolite M9

Summary of pharmacokinetic parameters for Metabolite M9 after oral administration of 20 mg of tasimelteon to subjects with mild or moderate hepatic impairment and healthy matched controls.

Parameter*	Mild Hepatic Impairment		Moderate Hepatic Impairment	
	Patients	Controls	Patients	Controls
C _{max} (ng/mL)	178 ± 103 (8)	221 ± 70.5 (8)	116 ± 60.9 (8)	262 ± 91.3 (8)
T _{max} (h)	0.75 (8) [0.50 – 1.00]	0.50 (8) [0.50 – 1.00]	0.75 (8) [0.50 – 1.00]	0.50 (8) [0.25 – 1.00]
AUC(0-t) (h×ng/mL)	283 ± 121 (8)	349 ± 95.5 (8)	279 ± 108 (8)	350 ± 109 (8)
AUC(inf) (h×ng/mL)	287 ± 121 (8)	354 ± 96.8 (8)	285 ± 112 (8)	355 ± 112 (8)
λ _z (h ⁻¹)	0.4850 ± 0.1626 (8)	0.5904 ± 0.1126 (8)	0.4097 ± 0.1660 (8)	0.5802 ± 0.1272 (8)
t _{1/2} (h)	1.60 ± 0.60 (8)	1.21 ± 0.21 (8)	2.07 ± 1.23 (8)	1.25 ± 0.28 (8)

Statistical comparison of pharmacokinetic parameters for Metabolite M9 after oral administration of 20 mg of tasimelteon to subjects with mild or moderate hepatic impairment and healthy matched controls:

Parameter	Geometric Mean Ratio (%)*	
	Estimate	90% Confidence Interval
Mild Hepatic Impairment vs. Matched Controls		
C _{max}	69.09	50.27 → 94.94
AUC(inf)	77.55	60.49 → 99.43
t _{1/2}	121.56	98.91 → 149.38
Moderate Hepatic Impairment vs. Matched Controls		
C _{max}	45.68	33.45 → 62.38
AUC(inf)	77.22	60.25 → 98.97
t _{1/2}	148.73	115.41 → 191.65

Metabolite M11

Summary of pharmacokinetic parameters for Metabolite M11 after oral administration of 20 mg of tasimeleone to subjects with mild or moderate hepatic impairment and healthy matched controls.

!

Parameter*	Mild Hepatic Impairment		Moderate Hepatic Impairment	
	Patients	Controls	Patients	Controls
C _{max} (ng/mL)	44.7 ± 12.8 (8)	48.8 ± 16.8 (8)	31.7 ± 09.1 (8)	49.3 ± 18.5 (8)
T _{max} (h)	1.00 (8) [0.50 – 1.50]	1.00 (8) [0.50 – 1.50]	1.50 (8) [0.50 – 3.00]	0.75 (8) [0.50 – 1.00]
AUC(0-t) (h×ng/mL)	143 ± 53.5 (8)	144 ± 63.2 (8)	136 ± 89.0 (8)	133 ± 60.8 (8)
AUC(inf) (h×ng/mL)	148 ± 61.2 (7)	153 ± 66.0 (7)	141 ± 94.3 (8)	135 ± 61.2 (8)
λ _z (h ⁻¹)	0.4389 ± 0.1646 (7)	0.4378 ± 0.0912 (7)	0.4080 ± 0.1990 (8)	0.4264 ± 0.0796 (8)
t _{1/2} (h)	1.75 ± 0.56 (7)	1.64 ± 0.29 (7)	2.23 ± 1.45 (8)	1.67 ± 0.28 (8)

Statistical comparison of pharmacokinetic parameters for Metabolite M11 after oral administration of 20 mg of tasimeleone to subjects with mild or moderate hepatic impairment and healthy matched controls:-

Parameter	Geometric Mean Ratio (%)*	
	Estimate	90% Confidence Interval
Mild Hepatic Impairment vs. Matched Controls		
C _{max}	90.38	70.03 → 116.65
AUC(inf)	100.65	70.21 → 144.28
t _{1/2}	101.10	82.03 → 124.60
Moderate Hepatic Impairment vs. Matched Controls		
C _{max}	64.56	50.41 → 82.69
AUC(inf)	89.61	61.07 → 131.50
t _{1/2}	116.53	86.43 → 157.13

Note: Based on IC₅₀ and K_i, the rank order of potency for human melatonin receptors MT1 and MT2 was tasimelteon followed by M13, M11 and M9, with consistent higher potency for MT2.

Potency of tasimelteon and metabolites M9, M11, and M13 for human melatonin MT1 and MT2 receptors

Compound	IC ₅₀ ^a (nM)	K _i ^a (nM)
MT₁ receptor		
Tasimelteon	0.586 ± 0.025	0.304 ± 0.013
M13	7.69 ± 0.416	4 ± 0.216
M11	481 ± 0.047	250 ± 0.024
M9	2,260 ± 0.346	1,180 ± 0.179
MT₂ receptor		
Tasimelteon	0.133 ± 0.014	0.0692 ± 0.007
M13	1.78 ± 0.430	0.922 ± 0.224
M11	6.63 ± 1.28	3.44 ± 0.663
M9	139 ± 0.005	71.9 ± 0.003

MT1 receptor: The potency of M13 compared to tasimelteon was 13 fold lower, M11 was 820 fold lower.

MT2 receptor: The potency of M13 compared to tasimelteon was 13 fold lower, M11 was 50 fold lower and M9 was a 1000 fold lower.

CONCLUSIONS:

- The overall ~~exposure~~ (AUC) of tasimelteon increased by 43% and 90% in patients with mild and moderate HI respectively. Whereas, increase in C_{max} was about 20% in both mild and moderate HI when compared to healthy subjects.
- The overall ~~exposure~~ (AUC) to metabolites (M9, M11 and M13) of tasimelteon decreased in mild and moderate HI by 6% to 30%. With an exception to Metabolite 14, where-in AUC increased by 2 fold in moderate HI.
- The maximum concentration of tasimelteon metabolites (M9, M11, M13 and M14) (C_{max}) decreased in mild and moderate HI by 10% to 60%. With an exception to Metabolite 14, the AUC increase was 2 fold in moderate HI.

1.8 VP-VEC-162-1111: An open-label, single-sequence study in healthy subjects to evaluate the single-dose pharmacokinetics of

tasimelteon alone and in combination with a CYP1A2 inhibitor, fluvoxamine.

Objectives:

- To evaluate the single-dose pharmacokinetics (PK) of tasimelteon 5 mg alone and in combination with a CYP1A2 inhibitor, fluvoxamine, at steady state.
- To evaluate the single-dose pharmacokinetics of tasimelteon metabolites (M9, M11, M12, M13, and M14) alone and in combination with a CYP1A2 inhibitor, fluvoxamine, at steady state.

Study Design	This was an open-label, single-sequence study conducted at one site.																										
Study Population	Healthy male and female subjects Age: 18-55 years BMI: 18 to 35 kg/m ² . Twenty four subjects were enrolled and 24 completed the study.																										
Duration of Treatment	A single-sequence of the following treatments: <ul style="list-style-type: none">• Single oral dose of tasimelteon 5 mg on Day 1• Six days of fluvoxamine 50 mg daily (QD) (Days 2- 7)• Single doses of tasimelteon 5 mg and fluvoxamine 50 mg on Day 8																										
Sampling:	Blood samples for determining drug concentration of tasimelteon and its metabolites were obtained for each subject as follows: Days 1 and 6: Pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 7, 8, 10, 12 and 24 hours post-dose Day 8 Pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 7, 8, 12 and 24 hours post-dose																										
Analysis	<p>The plasma samples were analyzed for the concentration of tasimelteon by using LC-MS/MS method. The lower limit of quantification (LLOQ) was 0.3 ng/mL for tasimelteon.</p> <table><tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr><tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>0.9, 135, and 270 ng/mL</td><td>0.3, 0.9, 3, 9, 30, 90, 225 and 300 ng/mL</td></tr><tr><td>Between Batch Precision (%CV)</td><td>1.6 to 2.6</td><td>2.9 to 4.3</td></tr><tr><td>Between Batch Accuracy (%RE)</td><td>2.5 to 3.9</td><td>-2.9 to 4.1</td></tr><tr><td>Linearity</td><td colspan="2">Weighted linear equation (1/X²), mean r= 0.998</td></tr><tr><td>Linear Range (ng/mL)</td><td colspan="2">0.3 to 300 ng/mL</td></tr><tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">0.3 ng/mL</td></tr></table> <p>The plasma samples were analyzed for the concentration of fluvoxamine by using LC-MS/MS method. The lower limit of quantification (LLOQ) was 0.3 ng/mL for fluvoxamine.</p> <table><tr><th>Parameter</th><th>Quality Control</th><th>Standard Curve</th></tr></table>			Parameter	Quality Control Samples	Standard Curve Samples	Quality Control or Standard Curve Concentration (ng/mL)	0.9, 135, and 270 ng/mL	0.3, 0.9, 3, 9, 30, 90, 225 and 300 ng/mL	Between Batch Precision (%CV)	1.6 to 2.6	2.9 to 4.3	Between Batch Accuracy (%RE)	2.5 to 3.9	-2.9 to 4.1	Linearity	Weighted linear equation (1/X ²), mean r= 0.998		Linear Range (ng/mL)	0.3 to 300 ng/mL		Sensitivity (LLOQ, ng/mL)	0.3 ng/mL		Parameter	Quality Control	Standard Curve
Parameter	Quality Control Samples	Standard Curve Samples																									
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Sensitivity (LLOQ, ng/mL)	0.3 ng/mL																										
Parameter	Quality Control	Standard Curve																									

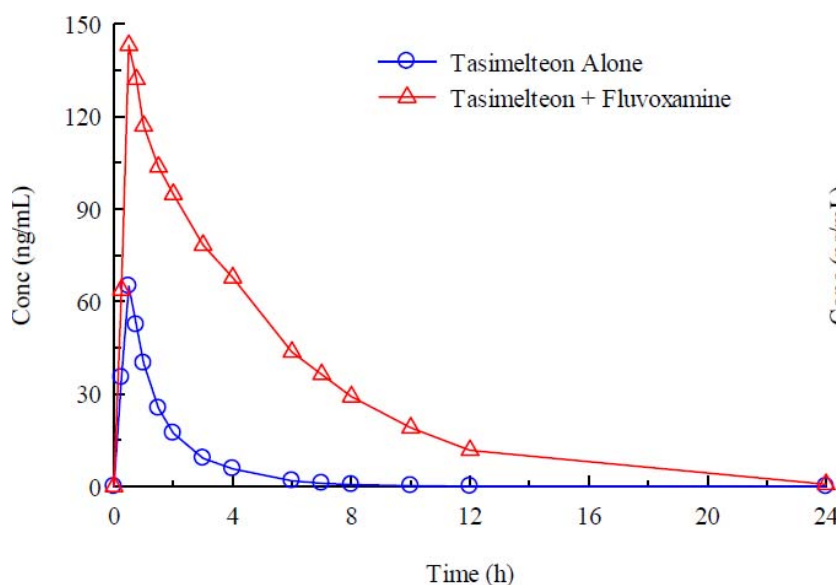
			Samples	Samples	
		Quality Control or Standard Curve Concentration (ng/mL)	0.5, 1.5, 75 and 375 ng/mL	0.5, 1, 5, 25, 50 100, 400 and 500 ng/mL	
		Between Batch Precision (%CV)	4.1 to 16	1.0 to 7.3	
		Between Batch Accuracy (%RE)	-3.8 to 5.2	-4.5 to 4.7	
		Linearity	Weighted linear equation (1/X ²), mean r= 0.997		
		Linear Range (ng/mL)	0.5 to 500 ng/mL		
		Sensitivity (LLOQ, ng/mL)	0.5 ng/mL		
PK Assessments	The pharmacokinetic parameters C _{max} , T _{max} , AUC ₀₋₁₂ , AUC _(0-inf) , apparent volume of distribution, CL, t _{lag} and t _{1/2} were calculated from the plasma concentration-time data using noncompartmental analysis. Comparison of the pharmacokinetic parameters was done by analysis of variance. Confidence intervals (CI) (90%) were constructed for the ratios of tasimelteon + fluvoxamine-to-tasimelteon alone of all applicable parameters using the log transformed data and the two one-sided t-tests procedure. The point estimates and CIs were exponentiated back to the original scale.				
Safety Assessments	Adverse event (AE) and serious adverse event (SAE) monitoring, <ul style="list-style-type: none">• Changes in clinical laboratory parameters that were relevant to safety• Influence of trial medication on vital signs and electrocardiogram (ECG) parameters• The Columbia-Suicide Severity Rating Scale (C-SSRS) was used to assess suicidal behavior and ideation.				
Statistical Methods	Pharmacokinetic: The 90% confidence intervals (CI) of the geometric mean ratio of AUC _{0-∞} and C _{max} values between the 2 treatments were calculated. The log-transformed data was analyzed using an analysis of variance model with factors for sequence, subjects within sequence, period, and treatment groups. The sequence effects were tested using the intersubject variation and differences between periods or treatments were compared using intrasubject variation estimated from the analysis of variance model.				

Note: Because of expected increase in exposure in the presence of fluvoxamine, tasimelteon dose evaluated in this study is 4 fold lower compared to the proposed prescription dose (20 mg). The pharmacokinetics of tasimelteon were dose-proportional and linear over the dose range of 3 mg to 300 mg.

RESULTS:

Following figure depicts PK profile of tasimelteon after oral administration of single 5 mg doses of tasimelteon alone and after dosing with fluvoxamine 50 mg QD × 6 days

Figure: Mean Plasma Concentrations of Tasimelteon After Oral Administration of Single 5 mg Doses of Tasimelteon Alone and After Dosing with Fluvoxamine 50 mg QD × 6 days



Following table represents PK parameters of tasimelteon alone or in combination with fluvoxamine.

Summary of Pharmacokinetic Parameters for Tasimelteon After Oral Administration of Single 5 mg Doses of Tasimelteon Alone and After Dosing With Fluvoxamine 50 mg QD × 6 Days

Parameter*	Treatment	
	Tasimelteon 5 mg	Tasimelteon 5 mg + Fluvoxamine 50 mg
C_{max} (ng/mL)	68.0 ± 28.9 (24)	155 ± 51.1 (24)
T_{max} (h)	0.50 (24)	0.50 (24)
$AUC_{(0-t)}$ (h · ng/mL)	101 ± 61.4 (24)	692 ± 400 (24)
$AUC_{(inf)}$ (h · ng/mL)	102 ± 61.5 (24)	701 ± 402 (24)
λ_z (1/h)	0.5987 ± 0.1098 (24)	0.2888 ± 0.0825 (24)
$t_{1/2}$ (h)	1.20 ± 0.22 (24)	2.59 ± 0.71 (24)
CL/F (mL/min)	1,093 ± 555 (24)	189 ± 155 (24)
Vz/F (L)	107 ± 48.1 (24)	36.0 ± 21.8 (24)

Statistical Comparison of Pharmacokinetic Parameters for Tasimelteon After Oral Administration of Single 5 mg Doses of Tasimelteon Alone and After Dosing with Fluvoxamine 50 mg QD × 6 Days

Parameter*	Geometric Mean Ratio (%)*	
	Estimate	90% Confidence Interval

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
t _{1/2}	211.82	194.07, 231.21
CL/F	15.31	12.35, 18.97
V _z /F	32.42	27.36, 38.41

Note: Fluvoxamine in addition to strongly inhibiting CYP1A2, fluvoxamine also strongly inhibits CYP2C19 and weakly inhibits CYP2C8, CYP2C9, and CYP3A4.

Metabolite M12

Summary of Pharmacokinetic Parameters for Metabolite M12 After Oral Administration of Single 5 mg Doses of Tasimelteon Alone and After Dosing With Fluvoxamine 50 mg QD x 6 Days

Parameter	Treatment	
	Tasimelteon 5 mg	Tasimelteon 5 mg + Fluvoxamine 50 mg
C _{max} (ng/mL)	31.0 ± 7.23 (24)	30.8 ± 17.6 (24)
T _{max} (h)	0.88 (24)	3.00 (24)
AUC _(0-t) (h · ng/mL)	183 ± 86.8 (24)	392 ± 86.1 (24)
AUC _(inf) (h · ng/mL)	189 ± 90.8 (23)	435 ± 109.3 (19)
λ _z (1/h)	0.2524 ± 0.0749 (23)	0.1220 ± 0.0579 (19)
t _{1/2} (h)	3.03 ± 1.02 (23)	7.03 ± 3.27 (19)

Statistical Comparison of Pharmacokinetic Parameters for Metabolite M12 After Oral Administration of Single 5 mg Doses of Tasimelteon Alone and After Dosing With Fluvoxamine 50 mg QD X 6 Days

Parameter	Geometric Mean Ratio (%)	
	Estimate	90% Confidence Interval
C _{max}	92.74	81.10, 106.05
AUC _(0-t)	229.24	205.19, 256.10
AUC _(inf)	274.81	251.47, 300.31
t _{1/2}	241.02	201.62, 288.12

Metabolite 13

Summary of Pharmacokinetic Parameters for Metabolite M13 After Oral Administration of Single 5 mg Doses of Tasimelteon Alone and After Dosing With Fluvoxamine 50 mg QD X 6 Days

Parameter	Treatment	
	Tasimelteon 5 mg	Tasimelteon 5 mg + Fluvoxamine 50 mg
C _{max} (ng/mL)	87.5 ± 24.4 (24)	63.6 ± 24.6 (24)
T _{max} (h)	0.50 (24)	0.50 (24)
AUC _(0-t) (h · ng/mL)	104 ± 32.4 (24)	117 ± 28.7 (24)
AUC _(inf) (h · ng/mL)	106 ± 32.6 (24)	133 ± 32.9 (22)
λ _z (1/h)	0.7517 ± 0.2146 (24)	0.2172 ± 0.0693 (22)
t _{1/2} (h)	1.00 ± 0.30 (24)	3.51 ± 1.18 (22)

Statistical Comparison of Pharmacokinetic Parameters for Metabolite M13 Oral Administration of Single 5 mg Doses of Tasimelteon Alone and After Dosing With Fluvoxamine 50 mg QD X 6 Days

Parameter	Geometric Mean Ratio (%)	
	Estimate	90% Confidence Interval
C _{max}	69.31	59.43, 80.84
AUC _(0-t)	114.40	107.12, 122.18
AUC _(inf)	125.05	118.94, 131.47
t _{1/2}	349.81	322.81, 379.06

Metabolite 9

Summary of Pharmacokinetic Parameters for Metabolite M9 After Oral Administration of Single 5 mg Doses of Tasimelteon Alone and After Dosing With Fluvoxamine 50 mg QD X 6 Days

Parameter	Treatment	
	Tasimelteon 5 mg	Tasimelteon 5 mg + Fluvoxamine 50 mg
C _{max} (ng/mL)	67.6 ± 19.1 (24)	47.4 ± 24.2 (24)
T _{max} (h)	0.50 (24)	0.75 (24)

AUC _(0-t) (h · ng/mL)	102 ± 30.0 (24)	113 ± 27.1 (24)
AUC _(inf) (h · ng/mL)	104 ± 30.0 (24)	126 ± 29.6 (23)
λ _Z (1/h)	0.6465 ± 0.1748 (24)	0.2034 ± 0.0720 (23)
t _{1/2} (h)	1.14 ± 0.29 (24)	3.83 ± 1.34 (23)

Statistical Comparison of Pharmacokinetic Parameters for Metabolite M9 After Oral Administration of Single 5 mg Doses of Tasimelteon Alone and After Dosing with Fluvoxamine 50 mg QD X 6 Days

Parameter	Geometric Mean Ratio (%)	
	Estimate	90% Confidence Interval
C _{max}	64.94	56.21, 75.01
AUC _(0-t)	113.05	105.47, 121.16
AUC _(inf)	122.56	115.33, 130.24
t _{1/2}	328.02	294.95, 364.79

Metabolite 11

Summary of Pharmacokinetic Parameters for Metabolite M11 After Oral Administration of Single 5 mg Doses of Tasimelteon Alone and After Dosing With Fluvoxamine 50 mg QD × 6 Days

Parameter*	Treatment	
	Tasimelteon 5 mg	Tasimelteon 5 mg+ Fluvoxamine 50 mg
C _{max} (ng/mL)	15.8 ± 5.40 (24)	11.0 ± 3.94 (24)
T _{max} (h)	1.00 (24)	1.00 (24)
AUC _(0-t) (h · ng/mL)	44.0 ± 16.9 (24)	49.9 ± 17.2 (24)
AUC _(inf) (h · ng/mL)	44.5 ± 17.2 (23)	55.8 ± 18.3 (24)
λ _Z (1/h)	0.4713 ± 0.1380 (23)	0.1906 ± 0.0756 (24)
t _{1/2} (h)	1.61 ± 0.55 (23)	4.14 ± 1.44 (24)

Statistical Comparison of Pharmacokinetic Parameters for Metabolite M11 After Oral Administration of Single 5 mg Doses of Tasimelteon Alone and After Dosing With Fluvoxamine 50 mg QD × 6 Days

Parameter	Geometric Mean Ratio (%)	
	Estimate	90% Confidence Interval
C _{max}	68.71	61.38, 76.93

AUC _(0-t)	115.01	106.96, 123.66
AUC _(inf)	16.03	118.24, 134.33
t _{1/2}	248.35	215.41, 286.32

Metabolite 14

Summary of Pharmacokinetic Parameters for Metabolite M14 After Oral Administration of Single 5 mg Doses of Tasimelteon Alone and After Dosing With Fluvoxamine 50 mg QD X 6 Days

Parameter	Treatment	
	Tasimelteon 5 mg	Tasimelteon 5 mg + Fluvoxamine 50 mg
C _{max} (ng/mL)	1.20 ± 0.40 (23)	3.20 ± 1.49 (24)
T _{max} (h)	0.75 (23)	4.00 (24)
AUC _(0-t) (h · ng/mL)	2.67 ± 1.83 (23)	37.8 ± 26.1 (24)
AUC _(inf) (h · ng/mL)	4.54 ± 2.39 (17)	42.6 ± 27.3 (22)
λ _z (1/h)	0.3691 ± 0.1447 (17)	0.1620 ± 0.0669 (22)
t _{1/2} (h)	2.18 ± 0.97 (17)	4.98 ± 1.89 (22)

Statistical Comparison of Pharmacokinetic Parameters for Metabolite M14 After Oral Administration of Single 5 mg Doses of Tasimelteon Alone and After Dosing With Fluvoxamine 50 mg QD x 6 Days

Parameter	Geometric Mean Ratio (%)	
	Estimate	90% Confidence Interval
C _{max}	264.58	227.03, 308.34
AUC _(0-t)	1500.19	1119.93, 2009.55
AUC _(inf)	944.73	684.71, 1303.49
t _{1/2}	243.34	188.00, 314.99

Metabolite 3

Summary of Pharmacokinetic Parameters for Metabolite M3 After Oral Administration of Single 5 mg Doses of Tasimelteon Alone and After Dosing With Fluvoxamine 50 mg QD × 6 Days

Parameter*	Treatment	
	Tasimelteon 5 mg	Tasimelteon 5 mg + Fluvoxamine 50 mg
C _{max} (ng/mL)	37.7 ± 10.1 (24)	27.0 ± 15.8 (24)
T _{max} (h)	0.50 (24)	0.50 (24)
AUC _(0-t) (h · ng/mL)	55.3 ± 15.2 (24)	49.4 ± 11.2 (24)
AUC _(inf) (h · ng/mL)	58.7 ± 18.2 (15)	54.0 ± 10.9 (24)
λ _z (1/h)	0.2667 ± 0.1431 (15)	0.1729 ± 0.0734 (24)
t _{1/2} (h)	3.35 ± 1.88 (15)	4.56 ± 1.47 (24)

Statistical Comparison of Pharmacokinetic Parameters for Metabolite M3 After Oral Administration of single 5 mg Doses of Tasimelteon Alone and After Dosing With Fluvoxamine 50 mg QD × 6 Days

Parameter	Geometric Mean Ratio (%)	
	Estimate	90% Confidence Interval
C _{max}	62.53	50.58, 77.31
AUC _(0-t)	90.14	84.06, 96.66
AUC _(inf)	97.69	88.99, 107.24
t _{1/2}	154.31	125.64, 189.53

CONCLUSIONS:

- Inhibition of CYP1A2 by treatment with fluvoxamine 50 mg QD × 6 days resulted in an 85% decrease in tasimelteon CL/F leading to a 6.5-fold increase in exposure. There was a 2-fold increase in t_{1/2}.
- There was about 3-fold increase in exposure to Metabolite M12, and a 25% increase in Metabolite M13 which are formed from tasimelteon by CYP1A2.
- There were relatively small changes in exposure to Metabolites M9 and M11, formed from M13 by CYP1A2.
- There was about 9.5-fold increase in exposure to Metabolite M14.

1.9 VP-VEC-162-1112: An open-label, single-sequence study in two cohorts of healthy subjects to evaluate the single-dose pharmacokinetics of tasimelteon alone and in combination with a CYP3A4 inhibitor, ketoconazole, or a CYP3A4 inducer, rifampin.

Objectives:

- To evaluate the single-dose pharmacokinetics of tasimelteon 20 mg alone and in combination with a CYP3A4 inhibitor (ketoconazole) or CYP3A4 inducer (rifampin), at steady state.
- To evaluate the single-dose pharmacokinetics of tasimelteon metabolites (M9, M11, M12, M13, and M14) alone and in combination with a CYP3A4 inhibitor or inducer, at steady state.

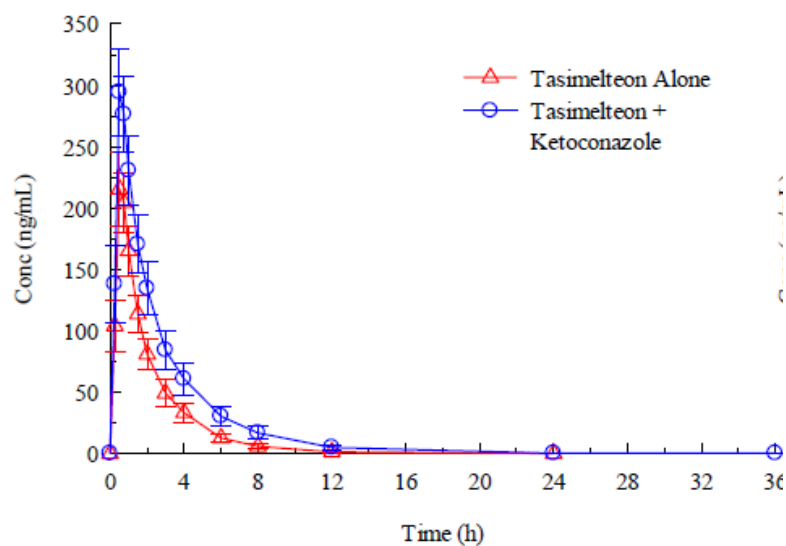
Study Design	This study was an open-label, single-sequence study conducted at one site. In one Cohort of 24 subjects, the potential effect of administration of a potent CYP3A4 inhibitor, ketoconazole, on tasimelteon’s pharmacokinetics was evaluated. In the second Cohort of 24 healthy volunteers, the potential effect of administration of a potent CYP3A4 inducer, rifampin, on tasimelteon’s pharmacokinetics was evaluated.								
Study Population	Healthy male and female subjects Age: 18-55 years BMI: 18 to 35 kg/m ² . Forty eight subjects were and 47 completed the study.								
Duration of Treatment	Cohort 1 Single oral dose of tasimelteon 20 mg on Day 1 Four days of ketoconazole 400 mg QD (Days 2- 5) <ul style="list-style-type: none">• Single doses of tasimelteon 20 mg and ketoconazole 400 mg on Day 6 Cohort 2 <ul style="list-style-type: none">• Single oral dose of tasimelteon 20 mg on Day 1!!• Ten days of rifampin 600 mg QD (Days 2- 11)• Single dose of tasimelteon 20 mg on Day 12								
Sampling:	Blood samples for determining drug concentration of tasimelteon and its metabolites were obtained for each subject as follows: Cohort 1: Days 1 and 6: Pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post-dose Days 2 and 7: 24 hours post- dose Day 7: 36 hours post-dose Cohort 2: Days 1 and 12: Pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post-dose Days 2 and 13: 24 hours post-dose Days 13: 36 hours post-dose								
Analysis	The plasma samples were analyzed for the concentration of tasimelteon by using LC-MS/MS method. The lower limit of quantification (LLOQ) was 0.3 ng/mL for tasimelteon. <table><tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr><tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>0.9, 135, and 270 ng/mL</td><td>0.3, 0.9, 3, 9, 30, 90, 225 and 300 ng/mL</td></tr></table>			Parameter	Quality Control Samples	Standard Curve Samples	Quality Control or Standard Curve Concentration (ng/mL)	0.9, 135, and 270 ng/mL	0.3, 0.9, 3, 9, 30, 90, 225 and 300 ng/mL
Parameter	Quality Control Samples	Standard Curve Samples							
Quality Control or Standard Curve Concentration (ng/mL)	0.9, 135, and 270 ng/mL	0.3, 0.9, 3, 9, 30, 90, 225 and 300 ng/mL							

		Between Batch Precision (%CV)	2.6 to 3.9	1.9 to 3.3	
		Between Batch Accuracy (%RE)	-1.5 to 3.7	-4.9 to 5.1	
		Linearity	Weighted linear equation (1/X ²), mean r=0.997		
		Linear Range (ng/mL)	0.3 to 300 ng/mL		
		Sensitivity (LLOQ, ng/mL)	0.3 ng/mL		
PK Assessments	The pharmacokinetic parameters C _{max} , T _{max} , AUC ₀₋₁₂ , AUC _(0-inf) , apparent volume of distribution, CL, t _{lag} and t _{1/2} were calculated from the plasma concentration-time data using noncompartmental analysis. <ul style="list-style-type: none">• Plasma concentrations and pharmacokinetic parameters of tasimelteon were compared when given alone and in combination with a CYP3A4 inhibitor, ketoconazole, at steady state.• Plasma concentrations and pharmacokinetic parameters of tasimelteon were compared when given alone and in combination with a CYP3A4 inducer, rifampin, at steady state.• Plasma concentrations and pharmacokinetic parameters of tasimelteon metabolites M9, M11, M12, M13, and M14 were compared when given alone and in combination with a CYP3A4 inhibitor, ketoconazole and CYP3A4 inducer, rifampin, at steady state.				
Safety Assessments	Adverse event (AE) and serious adverse event (SAE) monitoring, physical examination and weight, vital signs measurement, clinical laboratory analysis (hematology, blood chemistry, coagulation [PT, PTT], urinalysis, beta-2 microglobulin, microalbumin), 12-lead electrocardiogram (ECG).				
Statistical Methods	Pharmacokinetic: The 90% confidence intervals (CI) of the geometric mean ratio of AUC _{0-∞} and C _{max} values between the 2 treatments were calculated. The log-transformed data was analyzed using an analysis of variance model with factors for sequence, subjects within sequence, period, and treatment groups. The sequence effects were tested using the intersubject variation and differences between periods or treatments were compared using intrasubject variation estimated from the analysis of variance model.				

RESULTS:

Following figure depicts PK profile of tasimelteon after oral administration of single 20 mg doses of tasimelteon alone and after dosing with ketoconazole 400 mg.

Figure: Mean Plasma Concentrations of Tasimelteon After Oral Administration of Single 20 mg Doses of Tasimelteon Alone and After Dosing With Ketoconazole 400 mg QD for 5 Days



Following figure depicts PK profile of tasimelteon after oral administration of single 20 mg doses of tasimelteon alone and after dosing with rifampin 600 mg.

Mean Plasma Concentrations of Tasimelteon After Oral Administration of Single 20 mg Doses of Tasimelteon Alone and After Dosing With Rifampin 600 mg QD for 10 Days

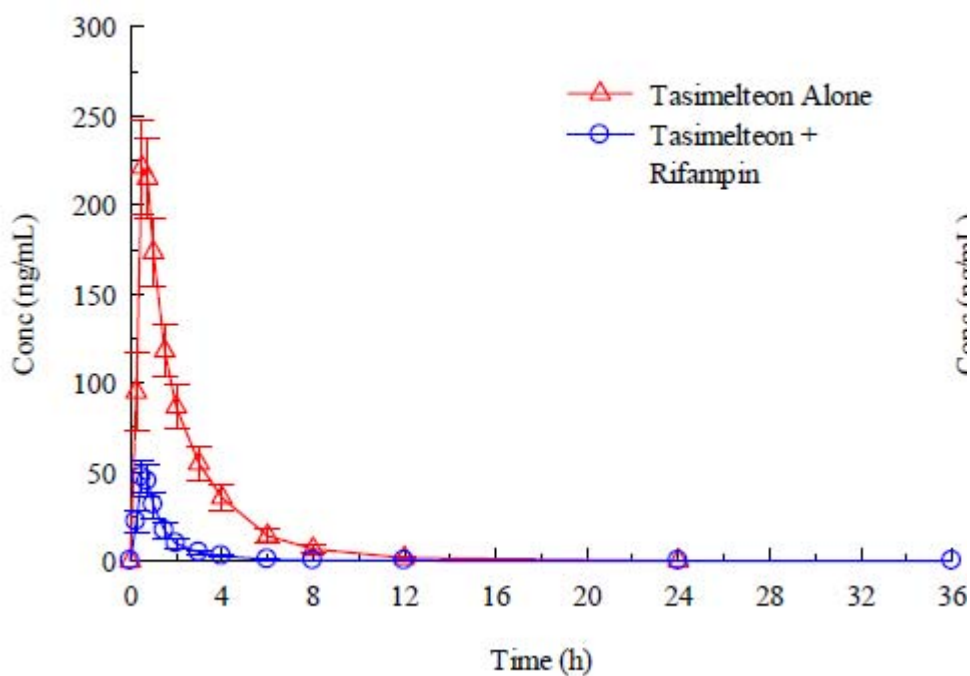


Table: Summary of Pharmacokinetic Parameters for Tasimelteon After Oral Administration of Single 20 mg Doses of Tasimelteon Alone and After Dosing With Ketoconazole 400 mg QD for 5 Days or Rifampin 600 mg QD for 10 Days

Parameter*	Cohort 1		Cohort 2	
	Alone (Day 1)	+ Ketoconazole (Day 6)	Alone (Day 1)	+ Rifampin (Day 12)
C _{max} (ng/mL)	243 ± 129 (24)	337 ± 188 (24)	240 ± 119 (24)	54.7 ± 49.4 (24)
T _{max} (h)	0.50 (24) [0.25 – 2.00]	0.50 (24) [0.25 – 2.00]	0.63 (24) [0.50 – 1.00]	0.50 (23) [0.25 – 0.75]
AUC(0-t) (h·ng/mL)	453 ± 350 (24)	767 ± 617 (24)	481 ± 340 (24)	66.2 ± 71.7 (23)
AUC(inf) (h·ng/mL)	457 ± 356 (24)	662 ± 562 (21)	484 ± 342 (24)	67.3 ± 72.0 (23)
λ _z (1/h)	0.5868 ± 0.2034 (24)	0.4566 ± 0.1635 (21)	0.5045 ± 0.1266 (24)	0.6497 ± 0.2087 (23)
t _{1/2} (h)	1.31 ± 0.42 (24)	1.88 ± 1.38 (21)	1.48 ± 0.46 (24)	1.07 ± 0.27 (23)
CL/F (ml/min)	307 ± 225 (24)	227 ± 191 (21)	288 ± 292 (24)	3493 ± 4702 (23)
V _z /F (L)	29.7 ± 16.8 (24)	35.7 ± 49.7 (21)	31.5 ± 23.4 (24)	258 ± 258 (23)

* Arithmetic mean ± standard deviation (N) except T_{max} for which the median (N) is reported.

Following table summarizes statistical analysis conducted on PK parameters of tasimelteon.!

Table: Statistical Comparison of Pharmacokinetic Parameters for Tasimelteon After Oral Administration of Single 20 mg Doses of Tasimelteon Alone and After Dosing With Ketoconazole 400 mg QD for 5 Days or Rifampin 600 mg QD for 10 Days

Parameter*	Geometric Mean Ratio(%)*			
	Cohort 1		Cohort 2	
	Estimate	90% Confidence Interval	Estimate	90% Confidence Interval
C _{max}	133.06	116.73 - 151.68	17.22	13.29 - 22.31
AUC(0-t)	161.14	141.49 - 183.53	10.48	8.11 - 13.55
AUC(inf)	153.95	137.75 - 172.07	10.75	8.36 - 13.82
t _{1/2}	134.29	110.53 - 163.15	72.66	67.56 - 78.13
CL/F	64.95	58.12 - 72.60	930.50	723.47 - 1196.77
V _z /F	87.23	72.82 - 104.48	676.05	528.79 - 864.33

* Arithmetic mean ± standard deviation (N) except T_{max} for which the median (N) is reported.

Metabolite M14

Table: Summary of Pharmacokinetic Parameters for Metabolite M14 After Oral Administration of Single 20 mg Doses of Tasimelteon Alone and After Dosing With Ketoconazole 400 mg QD for 5 Days or Rifampin 600 mg QD for 10 Days

Parameter*	Cohort 1		Cohort 2	
	Alone (Day 1)	+ Ketoconazole (Day 6)	Alone (Day 1)	+ Rifampin (Day 12)
C _{max} (ng/mL)	6.70 ± 3.47 (24)	2.12 ± 1.04 (24)	6.17 ± 3.83 (24)	16.2 ± 8.48 (22)
T _{max} (h)	0.75 (24) [0.25 – 3.00]	0.75 (24) [0.25 – 8.12]	0.93 (24) [0.50 – 2.00]	0.50 (23) [0.25 – 1.50]
AUC(0-t) (h·ng/mL)	22.7 ± 20.6 (24)	12.5 ± 13.0 (24)	24.9 ± 24.0 (24)	27.2 ± 21.4 (23)
AUC(inf) (h·ng/mL)	22.5 ± 21.5 (21)	13.7 ± 14.8 (14)	26.5 ± 25.7 (22)	28.1 ± 21.6 (23)
λ _z (1/h)	0.3922 ± 0.1514 (21)	0.2306 ± 0.0974 (14)	0.3406 ± 0.1377 (22)	0.7615 ± 0.2272 (23)
t _{1/2} (h)	2.05 ± 0.85 (21)	3.60 ± 1.59 (14)	2.44 ± 1.21 (22)	0.99 ± 0.28 (23)

* Arithmetic mean ± standard deviation (N) except T_{max} for which the median (N) is reported.

Table: Statistical Comparison of Pharmacokinetic Parameters for Metabolite M14 After Oral Administration of Single 20 mg Doses of Tasimelteon Alone and After Dosing With Ketoconazole 400 mg QD for 5 Days or Rifampin 600 mg QD for 10 Days

Parameter	Geometric Mean Ratio (%)			
	Cohort 1		Cohort 2	
	Estimate	90% Confidence Interval	Estimate	90% Confidence Interval
C _{max}	32.66	27.10 → 39.36	270.14	227.87 → 320.25
AUC(0-t)	46.86	38.45 → 57.11	119.94	101.17 → 142.19
AUC(inf)	55.36	43.12 → 71.08	115.22	96.46 → 137.62
t _{1/2}	180.19	146.83 → 221.13	41.96	37.98 → 46.36

Metabolite M12

Summary of Pharmacokinetic Parameters for Metabolite M12 After Oral Administration of Single 20 mg Doses of Tasimelteon Alone and After Dosing With Ketoconazole 400 mg QD for 5 Days or Rifampin 600 mg QD for 10 Days

Parameter	Cohort 1		Cohort 2	
	Alone (Day 1)	+ Ketoconazole (Day 6)	Alone (Day 1)	+ Rifampin (Day 12)
C _{max} (ng/mL)	89.0 ± 30.1 (24)	97.2 ± 27.7 (24)	86.3 ± 23.3 (24)	49.9 ± 23.9 (23)

T _{max} (h)	1.50 (24) [0.25 – 4.00]	2.00 (24) [0.75 – 8.00]	1.50 (24) [0.50 – 4.00]	0.75 (23) [0.25 – 1.50]
AUC(0-t) (h·ng/mL)	654 ± 389 (24)	1044 ± 586 (24)	657 ± 324 (24)	133 ± 110 (23)
AUC(inf) (h·ng/mL)	678 ± 419 (24)	1067 ± 611 (24)	683 ± 364 (24)	124 ± 100 (22)
λ _z (1/h)	0.2270 ± 0.0772 (24)	0.1676 ± 0.0531 (24)	0.2154 ± 0.0755 (24)	0.5635 ± 0.1368 (22)
t _{1/2} (h)	3.43 ± 1.25 (24)	4.69 ± 1.62 (24)	3.65 ± 1.46 (24)	1.31 ± 0.35 (22)

Statistical Comparison of Pharmacokinetic Parameters for Metabolite M12 After Oral Administration of Single 20 mg Doses of Tasimelteon Alone and After Dosing With Ketoconazole 400 mg QD for 5 Days

Parameter	Geometric Mean Ratio (%)			
	Cohort 1		Cohort 2	
	Estimate	90% Confidence Interval	Estimate	90% Confidence Interval
C _{max}	111.94	103.80 → 120.72	53.37	47.43 → 60.06
AUC(0-t)	162.35	150.96 → 174.61	17.16	14.98 → 19.65
AUC(inf)	160.79	148.99 → 173.54	16.65	14.59 → 18.99
t _{1/2}	134.42	124.58 → 145.03	37.62	34.65 → 40.85

Metabolite M13

Summary of Pharmacokinetic Parameters for Metabolite M13 After Oral Administration of Single 20 mg Doses of Tasimelteon Alone and After Dosing With Ketoconazole 400 mg QD for 5 Days or Rifampin 600 mg QD for 10 Days

Parameter	Cohort 1		Cohort 2	
	Alone (Day 1)	+ Ketoconazole (Day 6)	Alone (Day 1)	+ Rifampin (Day 12)
C _{max} (ng/mL)	298 ± 73.7 (24)	251 ± 85.7 (24)	279 ± 93.9 (24)	339 ± 148 (23)
T _{max} (h)	0.50 (24) [0.25 – 2.00]	0.50 (24) [0.25 – 2.00]	0.75 (24) [0.50 – 1.00]	0.50 (23) [0.25 – 1.00]
AUC(0-t) (h·ng/mL)	437 ± 152 (24)	428 ± 155 (24)	442 ± 168 (24)	317 ± 134 (23)
AUC(inf) (h·ng/mL)	441 ± 153 (24)	427 ± 157 (23)	448 ± 168 (24)	320 ± 135 (23)
λ _z (1/h)	0.6169 ± 0.2401 (24)	0.5295 ± 0.2418 (23)	0.5585 ± 0.2008 (24)	0.9623 ± 0.3803 (23)
t _{1/2} (h)	1.28 ± 0.46 (24)	1.54 ± 0.63 (23)	1.41 ± 0.56 (24)	0.86 ± 0.38 (23)

Statistical Comparison of Pharmacokinetic Parameters for Metabolite M13 After Oral Administration of Single 20 mg Doses of Tasimelteon Alone and After Dosing With Ketoconazole 400 mg QD for 5 Days or Rifampin 600 mg QD for 10 Days

Parameter	Geometric Mean Ratio (%)			
	Cohort 1		Cohort 2	
	Estimate	90% Confidence Interval	Estimate	90% Confidence Interval
C _{max}	82.29	72.93 → 92.86	118.05	102.86 → 135.48
AUC(0-t)	97.53	93.86 → 101.36	70.82	64.07 → 78.28
AUC(inf)	97.74	94.05 → 101.56	70.44	63.80 → 77.77
t _{1/2}	116.88	110.90 → 123.18	58.73	51.67 → 66.75

Metabolite M9

Summary of Pharmacokinetic Parameters for Metabolite M9 After Oral Administration of Single 20 mg Doses of Tasimelteon Alone and After Dosing With Ketoconazole 400 mg QD for 5 Days or Rifampin 600 mg QD for 10 Days

Parameter	Cohort 1		Cohort 2	
	Alone (Day 1)	+ Ketoconazole (Day 6)	Alone (Day 1)	+ Rifampin (Day 12)
C _{max} (ng/mL)	228 ± 88.1 (24)	182 ± 49.2 (24)	211 ± 70.3 (24)	372 ± 109 (23)
T _{max} (h)	0.75 (24) [0.25 – 2.00]	0.75 (24) [0.50 – 2.00]	0.75 (24) [0.50 – 1.03]	0.50 (23) [0.25 – 1.00]
AUC(0-t) (h·ng/mL)	360 ± 88.6 (24)	362 ± 110 (24)	388 ± 112 (24)	362 ± 91.4 (23)
AUC(inf) (h·ng/mL)	365 ± 89.1 (24)	371 ± 119 (24)	395 ± 113 (24)	365 ± 91.8 (23)
λ _z (1/h)	0.5134 ± 0.1274 (24)	0.4215 ± 0.1489 (24)	0.4846 ± 0.1149 (24)	0.6019 ± 0.0848 (23)
t _{1/2} (h)	1.43 ± 0.36 (24)	2.00 ± 1.39 (24)	1.52 ± 0.42 (24)	1.17 ± 0.17 (23)

Statistical Comparison of Pharmacokinetic Parameters for Metabolite M9 After Oral Administration of Single 20 mg Doses of Tasimelteon Alone and After Dosing With Ketoconazole 400 mg QD for 5 Days or Rifampin 600 mg QD for 10 Days

Parameter	Geometric Mean Ratio (%)			
	Cohort 1		Cohort 2	
	Estimate	90% Confidence Interval	Estimate	90% Confidence Interval
C _{max}	82.17	72.77 → 92.79	157.92	139.57 → 178.67
AUC(0-t)	99.58	96.14 → 103.15	95.30	91.81 → 98.92

AUC _(inf)	100.59	97.03 → 104.29	94.53	91.07 → 98.13
t _{1/2}	127.49	110.57 → 147.00	77.93	70.48 → 86.16

Metabolite M11

Summary of Pharmacokinetics Parameters for Metabolite M11 After Oral Administration of Single 20 mg Doses of Tasimelteon Alone and After Dosing With Ketoconazole 400 mg QD for 5 Days or Rifampin 600 mg QD for 10 Days

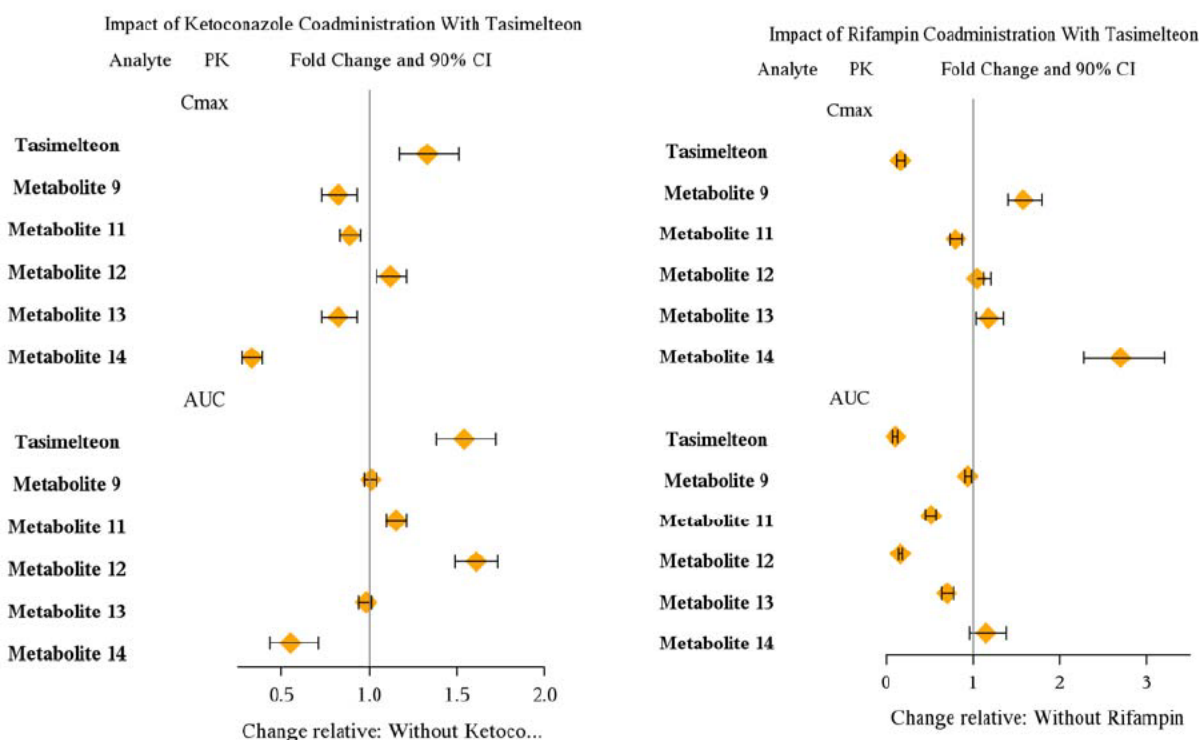
Parameter*	Cohort 1		Cohort 2	
	Alone (Day 1)	+ Ketoconazole (Day 6)	Alone (Day 1)	+ Rifampin (Day 12)
C _{max} (ng/mL)	51.6 ± 13.4 (24)	45.9 ± 12.8 (24)	48.9 ± 15.0 (24)	39.8 ± 15.4 (23)
T _{max} (h)	1.00 (24) [0.50 – 3.00]	1.50 (24) [0.75 – 2.00]	1.27 (24) [0.75 – 2.00]	0.75 (23) [0.25 – 1.50]
AUC _(0-t) (h·ng/mL)	160 ± 65.8 (24)	189 ± 82.2 (24)	164 ± 66.6 (24)	84.0 ± 37.0 (23)
AUC _(inf) (h·ng/mL)	167 ± 65.8 (23)	196 ± 86.3 (21)	167 ± 67.1 (24)	81.4 ± 36.6 (17)
λ _z (1/h)	0.3293 ± 0.0802 (23)	0.2969 ± 0.1091 (21)	0.3564 ± 0.0926 (24)	0.3087 ± 0.1272 (17)
t _{1/2} (h)	2.21 ± 0.47 (23)	2.84 ± 1.79 (21)	2.08 ± 0.59 (24)	2.82 ± 1.78 (17)

* Arithmetic mean ± standard deviation (N) except T_{max} for which the median (N) is reported.

Table: Statistical Comparison of Pharmacokinetic Parameters for Metabolite M11 After Oral Administration of Single 20 mg Doses of Tasimelteon Alone and After Dosing With Ketoconazole 400 mg QD for 5 Days or Rifampin 600 mg QD for 10 Days

Parameter*	Geometric Mean Ratio (%)			
	Cohort 1		Cohort 2	
	Estimate	90% Confidence Interval	Estimate	90% Confidence Interval
C _{max}	88.89	82.69 → 95.56	80.11	73.14 → 87.76
AUC _(0-t)	117.36	112.30 → 122.65	50.65	45.85 → 55.96
AUC _(inf)	115.41	109.95 → 121.15	51.92	46.40 → 58.10
t _{1/2}	105.09	93.74 → 117.82	127.16	102.67 → 157.48

Forest plot showing impact of concomitant administration of ketoconazole (left) and rifampin (right) with tasimelteon.



Discussion

The major metabolites M12, M13, M9, M11 and M14 are eliminated at similar rate when compared to tasimelteon. The parent to metabolite ratio is 1.6, 0.96, 0.92, 0.38 and 0.05 [for M12, M13, M9, M11 and M14](#) ,respectively.

Metabolite M12, which shows higher parent to metabolite ratio (1.6), is inactive. M13 (parent to metabolite ratio, 0.92) is approximately 13-times lower in potency at MT1 and MT2 receptors. M11 (parent to metabolite ratio, 0.38) is approximately 800-times lower in potency at MT1 and 50 times lower at MT2 receptors as shown in the table below. Following table indicates activities of tasimelteon and its major active metabolites at MT1 and MT2 receptors.

Potency of tasimelteon and metabolites M9, M11, and M13 for human melatonin MT1 and MT2 receptors

Compound	IC ₅₀ ^a (nM)	K _i ^a (nM)
MT₁ receptor		
Tasimelteon	0.586 ± 0.025	0.304 ± 0.013
M13	7.69 ± 0.416	4 ± 0.216
M11	481 ± 0.047	250 ± 0.024
M9	2,260 ± 0.346	1,180 ± 0.179
MT₂ receptor		
Tasimelteon	0.133 ± 0.014	0.0692 ± 0.007
M13	1.78 ± 0.430	0.922 ± 0.224
M11	6.63 ± 1.28	3.44 ± 0.663
M9	139 ± 0.005	71.9 ± 0.003

Reviewer's Comment: The potency of the major metabolites is much lower when compared to parent for most of the metabolites. Moreover, parent to metabolite ratio are similar or lower for most active metabolites. Change in concentration of the M13, which is most active, does not contribute to overall activity and impact of rifampin on tasimelteon.

Tasimelteon is tolerated upto 300 mg in single ascending dose and upto 150 mg in multiple ascending dose tolerability studies, no dose adjustment is necessary for increase in exposure (approximately 50%) when tasimelteon is coadministered with ketoconazole.

Reviewer's Comment: The sponsor's rationale appears reasonable. Labeling statements should be discussed with Clinical Division for the assessment of safety data including treatment related AE's.

CONCLUSIONS:

- The Cmax and AUC of tasimelteon increased by 33% and 53% respectively in the presence of ketoconazole, a strong inhibitor of CYP3A4.
- Rifampin, a strong CYP3A4 and moderate CYP2C19 inducer, reduced the Cmax and AUC of tasimelteon by approximately 90%.
- Decrease in exposure to tasimelteon in the presence of rifampin may reduce the efficacy when tasimelteon is concomitantly used with strong CYP enzyme inducers such as rifampin.

1.10 VP-VEC-162-1108: A randomized, double-mask, four period crossover study in healthy subjects to evaluate the pharmacodynamic and pharmacokinetic interactions of tasimelteon and ethanol

Objectives:

- To assess the effect of 20 mg tasimelteon on sustained attention test, cognition, postural stability and motor control alone and in combination with ethanol;

- To assess the effect of 20 mg tasimelteon on subjective ethanol-related effects such as intoxication, dizziness, and drowsiness;
- To evaluate the single-dose pharmacokinetics (PK), safety and tolerability of 20 mg tasimelteon and ethanol alone and in combination

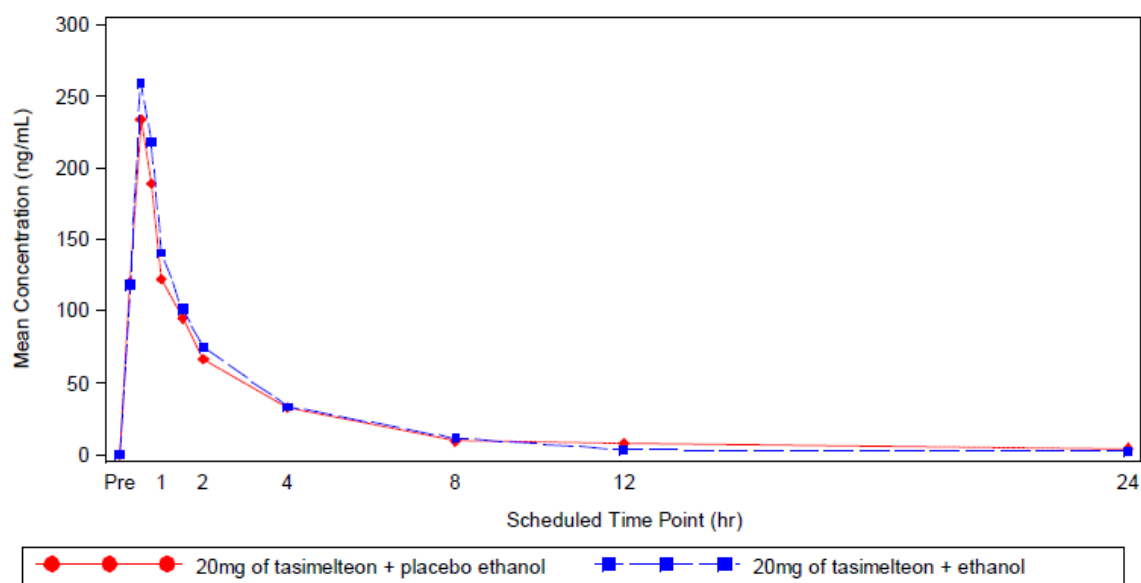
Study Design	<p>This was a single-center, randomized, double-masked, 4-period crossover study conducted in healthy subjects to evaluate the pharmacodynamic (PD) and PK interactions of tasimelteon and ethanol.</p> <p>The study consisted of a qualification period and 4 treatment periods: Qualification Period: Single oral dose of 0.6 g/kg (females) or 0.7 g/kg (males) of ethanol.</p> <p>Treatment Period:</p> <ul style="list-style-type: none">• 20 mg tasimelteon + placebo ethanol (with about 1 mL supernatant of ethanol),• 0.6 g/kg (female) or 0.7 g/kg (male) ethanol + placebo tasimelteon,• 20 mg tasimelteon + 0.6 g/kg (female) or 0.7 g/kg (male) ethanol, Placebo tasimelteon + placebo ethanol (with about 1 mL supernatant of ethanol).																					
Study Population	<p>Healthy male and female subjects</p> <p>Age: 19-75 years</p> <p>BMI: 18 to 35 kg/m².</p> <p>Twenty eight subjects were enrolled and 25 completed the study</p>																					
Sampling:	<p>Blood samples for the determination of tasimelteon and ethanol in plasma were taken for each subject before dosing and 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 8, 12 and 24 hours after dosing</p>																					
Analysis	<p>The plasma samples were analyzed for the concentration of tasimelteon by using LC-MS/MS method. The lower limit of quantification (LLOQ) was 0.3 ng/mL for tasimelteon.</p> <table><tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr><tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>0.9, 135, and 270 ng/mL</td><td>0.3, 0.9, 3, 9, 30, 90, 225 and 300 ng/mL</td></tr><tr><td>Between Batch Precision (%CV)</td><td>2.0 to 6.0</td><td>1.6 to 6.0</td></tr><tr><td>Between Batch Accuracy (%RE)</td><td>-6.7 to 0.7</td><td>-4.4 to 3.3</td></tr><tr><td>Linearity</td><td colspan="2">Weighted linear equation (1/X²), mean r= 0.998</td></tr><tr><td>Linear Range (ng/mL)</td><td colspan="2">0.3 to 300 ng/mL</td></tr><tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">0.3 ng/mL</td></tr></table>	Parameter	Quality Control Samples	Standard Curve Samples	Quality Control or Standard Curve Concentration (ng/mL)	0.9, 135, and 270 ng/mL	0.3, 0.9, 3, 9, 30, 90, 225 and 300 ng/mL	Between Batch Precision (%CV)	2.0 to 6.0	1.6 to 6.0	Between Batch Accuracy (%RE)	-6.7 to 0.7	-4.4 to 3.3	Linearity	Weighted linear equation (1/X ²), mean r= 0.998		Linear Range (ng/mL)	0.3 to 300 ng/mL		Sensitivity (LLOQ, ng/mL)	0.3 ng/mL	
Parameter	Quality Control Samples	Standard Curve Samples																				
Quality Control or Standard Curve Concentration (ng/mL)	0.9, 135, and 270 ng/mL	0.3, 0.9, 3, 9, 30, 90, 225 and 300 ng/mL																				
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Linear Range (ng/mL)	0.3 to 300 ng/mL																					
Sensitivity (LLOQ, ng/mL)	0.3 ng/mL																					
PK Assessments	<p>The pharmacokinetic parameters C_{max}, T_{max}, AUC_{0-t}, AUC_(0-inf), apparent volume of distribution, CL, t_{lag} and t_{1/2} were calculated from the plasma concentration-time data using noncompartmental analysis. Plasma concentrations and PK parameters of tasimelteon, metabolites M9, M11, M12, M13, and M14, and ethanol were compared among the 4 different groups.</p>																					
PD	<p>Peak change from pre-dose in Digit Vigilance (DV) • Peak change from pre-</p>																					

Assessments	dose in Digit Symbol Substitution Test (DSST) • Peak change from pre-dose in Hopkins Verbal Learning Test- Revised (HVLT-R) • Peak change from pre-dose in Divided Attention Test (DAT) • Peak change from pre-dose in Balance Platform Test • Peak change from pre-dose in Choice Reaction Time (CRT) • Peak change from pre-dose in Visual Analog Scales (VASS)
Safety Assessments	Subjective tolerability from spontaneous reporting of adverse events (AEs) • Changes in laboratory parameters that were relevant to safety • Influence of trial medication on vital signs and electrocardiogram (ECG) parameters • The Columbia Suicide Severity Rating Scale assessed suicidal behavior and ideation
Statistical Methods	<p>Pharmacokinetics: Plasma concentration data for tasimelteon and ethanol were summarized using descriptive statistics (arithmetic mean, standard deviation [SD], and coefficient of variation [CV]; geometric mean and CV; and median, minimum, and maximum).</p> <p>Pharmacodynamics: For each PD variable, descriptive and graphical data were presented for each time point. Peak change from baseline (either maximum [CFBmax] or minimum [CFBmin] effect, depending on the variable) were also calculated and summarized using standard descriptive statistics. CFBmax or CFBmin for each variable was analyzed inferentially using a mixed-effect model with fixed effects for treatment, period, and sequence and subject nested within sequence as a random effect. The least squares means for CFBmax/CFBmin were calculated for each treatment condition. Least squares mean differences and 95% confidence intervals (CI) for the differences were calculated for the following comparisons: • Ethanol alone vs. placebo • Ethanol alone vs. tasimelteon + ethanol • Tasimelteon alone vs. placebo • Tasimelteon alone vs. tasimelteon + ethanol</p>

RESULTS:

Following figure depicts PK profile of tasimelteon after oral administration of single 20 mg doses of tasimelteon alone and when coadministered with ethanol.

Plasma Tasimelteon Mean Concentration Curves (ng/mL)



Mean (%CV) Pharmacokinetic Parameters of Tasimelteon - Tasimelteon Alone and In Combination with Ethanol

	Treatment A (Tasimelteon Alone) (N = 26)	Treatment C (Tasimelteon + Ethanol) (N = 25)	Contrasts (Differences) Treatment C (Tasimelteon + Ethanol) vs. Treatment A (Tasimelteon Alone)			
			Least Squares Mean (SE)	90% CI	P-value	Estimated Ratio % (90% CI for Ratio)
C _{max} (ng/mL)	39.74 (30.52)	51.98 (64.56)	0.27 (0.06)	(0.17- 0.37)	<0.001	130.70 (118.50– 144.15)
T _{max} (h)	1.43 (0.62–4.42)	1.47 (0.50–4.38)	—	—	—	—
AUC _{0-t} (h*ng/mL)	138.9 (43.87)	197.4 (85.93)	0.27 (0.14)	(0.03– 0.50)	0.065	130.71 (103.22– 165.51)
AUC _{0-inf} (h*ng/mL)	142.6 (44.70)	207.4 (70.49)	0.30 (0.13)	(0.08– 0.53)	0.030	135.53 (108.18– 169.80)
T _{1/2} (h)	1.72 (0.86–4.58)	1.73 (0.32–13.38)	—	—	—	—
X _z (1/h)	0.42 (30.11)	0.45 (68.55)	—	—	—	—

Metabolite M9

Mean (%CV) Pharmacokinetic Parameters of M9 - Tasimelteon Alone and In combination with Ethanol (PK Population)

	Treatment A (Tasimelteon Alone) (N = 26 ^a)	Treatment C (Tasimelteon + Ethanol) (N = 25 ^a)	Contrasts (Differences) Treatment C (Tasimelteon + Ethanol) vs. Treatment A (Tasimelteon Alone)			
			Least Squares Mean (SE)	90% CI	P-value	Estimated Ratio % (90% CI for Ratio)
C _{max} (ng/mL)	157.5 (30.80)	34.92 (68.21)	-1.50 (0.08)	(-1.64 – -1.36)	<0.001	22.39 (19.49–25.73)
T _{max b} (h)	0.89 (0.50– 4.42)	0.98 (0.50– 8.35)	—	—	—	—
AUC _{0-t} (h*ng/mL)	330.7 (34.41)	112.5 (81.98)	-1.17 (0.16)	(-1.44 – -0.89)	<0.001	31.10 (23.63–40.93)
AUC _{0-inf} (h*ng/mL)	355.9 (41.07)	114.9 (74.87)	-1.17 (0.17)	(-1.45 – -0.89)	<0.001	30.99 (23.39–41.06)
T _{1/2} (h)	1.37 (0.85– 8.06)	2.21 (0.40– 4.14)	—	—	—	—
λ _z (1/h)	0.52 (47.93)	0.41 (49.71)	—	—	—	—

Metabolite M11

Mean (%CV) Pharmacokinetic Parameters of M11 - Tasimelteon Alone and In Combination with Ethanol (PK Population)

	Treatment A (Tasimelteon Alone) (N = 26)	Treatment C (Tasimelteon + Ethanol) (N = 25 ^a)	Contrasts (Differences) Treatment C (Tasimelteon + Ethanol) vs. Treatment A (Tasimelteon Alone)			
			Least Squares Mean (SE)	90% CI	P-value	Estimated Ratio % (90% CI for Ratio)
C _{max} (ng/mL)	39.74 (30.52)	51.98 (64.56)	0.27 (0.06)	(0.17–0.37)	<0.001	130.70 (118.50– 144.15)
T _{max} (h)	1.43 (0.62– 4.42)	1.47 (0.50– 4.38)	—	—	—	—

AUC _{0-t} (h*ng/mL)	138.9 (43.87)	197.4 (85.93)	0.27 (0.14)	(0.03–0.50)	0.065	130.71 (103.22– 165.51)
AUC _{0-inf} (h*ng/mL)	142.6 (44.70)	207.4 (70.49)	0.30 (0.13)	(0.08–0.53)	0.030	135.53 (108.18– 169.80)
T _{1/2} (h)	1.72 (0.86– 4.58)	1.73 (0.32– 13.38)	—	—	—	—
X _z (1/h)	0.42 (30.11)	0.45 (68.55)	—	—	—	—

Metabolite M13

Mean (%CV) Pharmacokinetic Parameters of M13 - Tasimelteon Alone and In Combination with Ethanol (PK Population)

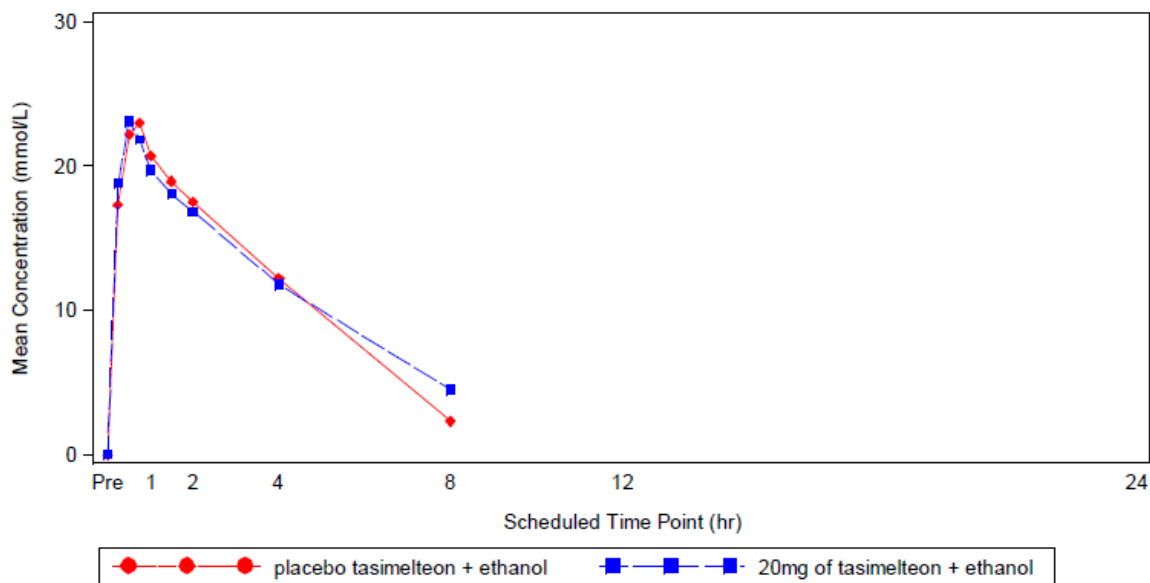
	Treatment A (Tasimelteon Alone) (N = 26)	Treatment C (Tasimelteon + Ethanol) (N = 25)	Contrasts (Differences) Treatment C (Tasimelteon + Ethanol) vs. Treatment A			
			Least Squares Mean (SE)	90% CI	P- value	Estimated Ratio % (90% CI for Ratio)
C _{max} (ng/mL)	257.9 (32.33)	300.6 (64.19)	0.19 (0.07)	(0.06–0.31)	0.020	120.33 (106.08– 136.48)
T _{max a} (h)	0.53 (0.48–4.38)	0.92 (0.25–	—	—	—	—
AUC _{0-t} (h*ng/mL)	505.5 (50.38)	673.3 (68.05)	0.29 (0.16)	(0.02–0.56)	0.077	134.03 (102.28– 175.64)
AUC _{0-inf} (h*ng/mL)	513.4 (50.24)	680.8 (67.56)	0.29 (0.16)	(0.016–0.56)	0.083	133.37 (101.63– 175.02)
T _{1/2} ^a (h)	1.27 (0.70–3.44)	1.19 (0.39– 2.16)	—	—	—	—
X _z (1/h)	0.61 (42.16)	0.65 (31.16)	—	—	—	—

Metabolite M14

Mean (%CV) Pharmacokinetic Parameters of M14 - Tasimelteon Alone and In combination with Ethanol (PK Population)

	Treatment A (Tasimelteon Alone) (N = 26)	Treatment C (Tasimelteon + Ethanol) (N = 25)	Contrasts (Differences) Treatment C (Tasimelteon + Ethanol) vs. Treatment A (Tasimelteon Alone)			
			Least Squares Mean (SE)	90% CI	P-value	Estimated Ratio % (90% CI for Ratio)
C _{max} (ng/mL)	4.07 (38.99)	4.01 (77.02)	-0.10 (0.09)	(-0.25–0.05)	0.254	90.36 (77.86–104.86)
T _{max b} (h)	0.92 (0.50–4.42)	1.08 (0.48–8.35)	—	—	—	—
AUC _{0-t} (h*ng/mL)	16.52 (76.85)	16.88 (151.0)	-0.18 (0.17)	(-0.47–0.11)	0.297	83.47 (62.44–111.58)
AUC _{0-inf} (h*ng/mL)	20.06 (80.45)	21.21 (92.02)	0.08 (0.09)	(-0.08–0.24)	0.410	108.10 (92.15–126.80)
T _{1/2^b} (h)	2.15 (0.81–6.72)	2.28 (0.73–6.81)	—	—	—	—
X _z (1/h)	0.37 (58.05)	0.35 (48.76)	—	—	—	—

Plasma Ethanol Mean Concentration Curves (ng/mL)



Mean (%CV) Pharmacokinetic Parameters of Ethanol - Ethanol Alone and In Combination with Tasimelteon (PK Population)

	Treatment B (Ethanol Alone) (N = 27)	Treatment C (Tasimelteon + Ethanol) (N = 25)	Contrasts (Differences)			
			Treatment C (Tasimelteon + Ethanol) vs. Treatment B (Ethanol Alone)			
			Least Squares Mean (SE)	90% CI	P-value	Estimated Ratio % (90% CI for Ratio)
C _{max} (mmol/L)	24.74 (16.49)	25.49 (24.31)	0.02 (0.04)	(-0.05–0.08)	0.652	101.67 (95.55– 108.18)
T _{max b} (h)	0.72 (0.42–1.68)	0.67 (0.42– 2.85)	—	—	—	—
AUC _{0-t} (h*mmol/L)	83.22 (17.05)	79.68 (19.14)	-0.06 (0.04)	(-0.12–0.00)	0.108	94.27 (88.73– 100.15)
AUC _{0-inf} (h*mmol/L)	140.9 (23.35)	156.4 (38.35)	0.01 (0.07)	(-0.10–0.12)	0.896	100.86 (90.23– 112.74)
T _{1/2} ^b (h)	3.44 (1.29–6.73)	3.68 (1.49– 16.51)	—	—	—	—
X _z (1/h)	0.23 (38.91)	0.20 (47.46)	—	—	—	—

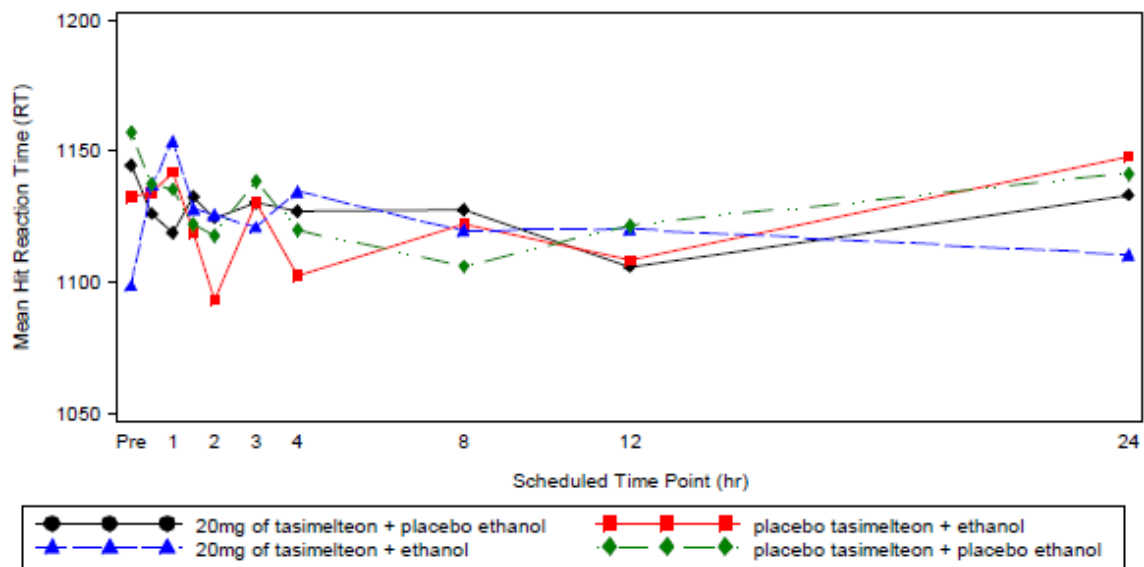
Pharmacokinetic Summary

- Ethanol 0.6 g/kg (female) or 0.7 g/kg (male) had no effect on the PK profile of tasimelteon. The 90% CIs for the ratio between tasimelteon alone and in combination with ethanol were not within 80%-125% range for all PK parameters (AUC_{0-inf}, AUC_{0-t}, and C_{max}). The magnitude of increase in exposure ranged from approximately 30% to 25%.
- Exposure to the metabolite M9 was significantly lower in the presence of ethanol and the magnitude of decrease in exposure ranged from approximately 70%–75% in the presence of ethanol. Exposure to the metabolite M12 and M14 was relatively small in the presence of ethanol.
- Exposure to the metabolites M11 and M13 was significantly higher in the presence of ethanol and the magnitudes of increase in exposure ranged from approximately 30% to 35% and 20% to 35%, respectively.
- Tasimelteon 20 mg had no effect on the PK profile of ethanol.

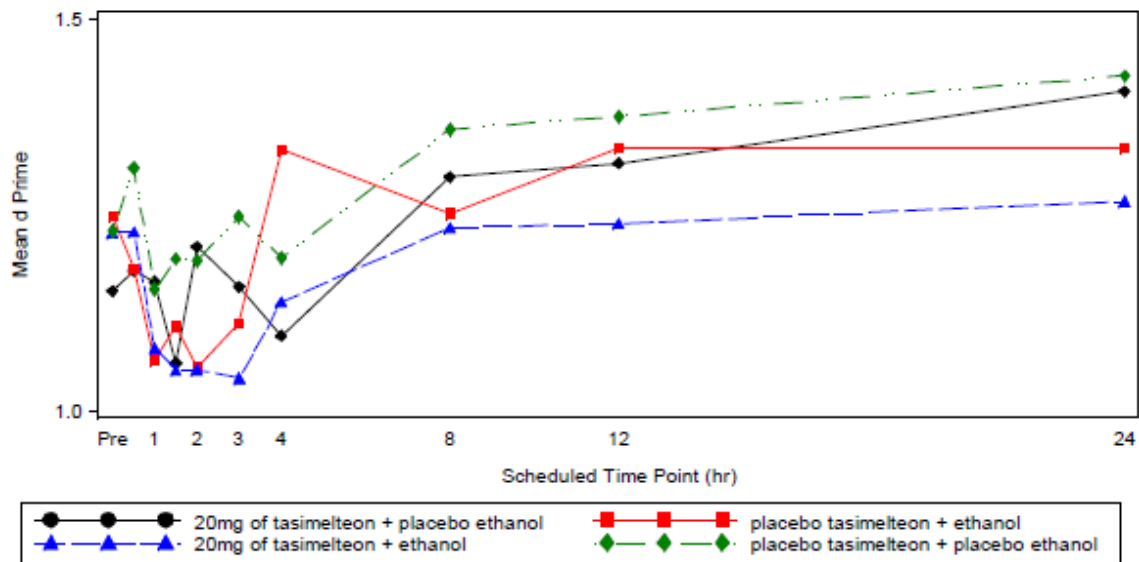
Pharmacodynamic Results

There was no trend in PD parameters evaluated (see below) when tasimelteon was concomitantly administered with ethanol. Most of the impairments on PD measures were related to ethanol and not to the addition of tasimelteon as shown in figure below.

Mean Hit Reaction Time – DV

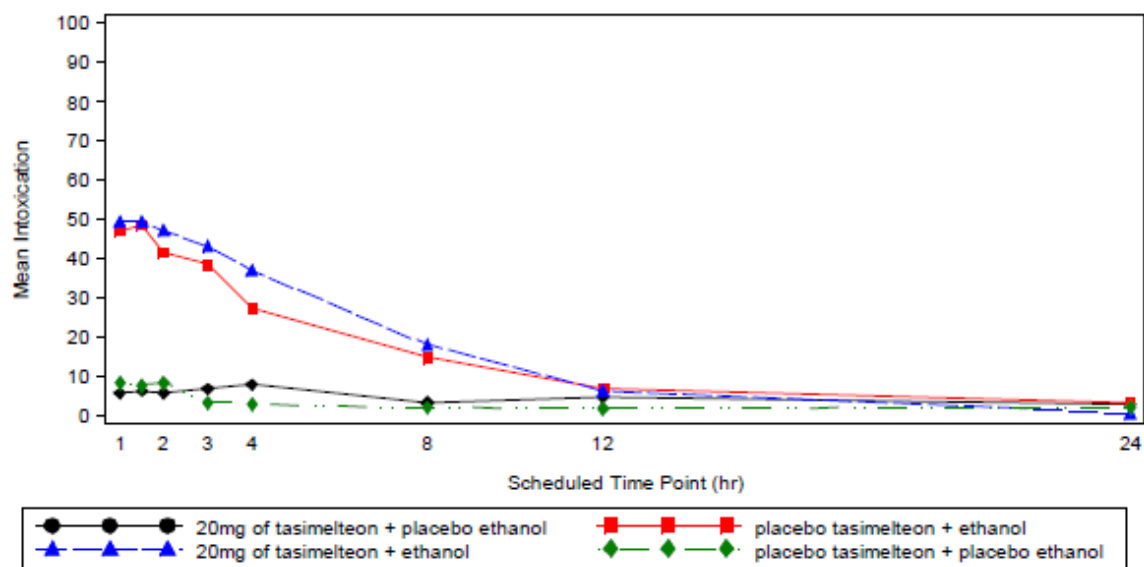


Mean d Prime – DV

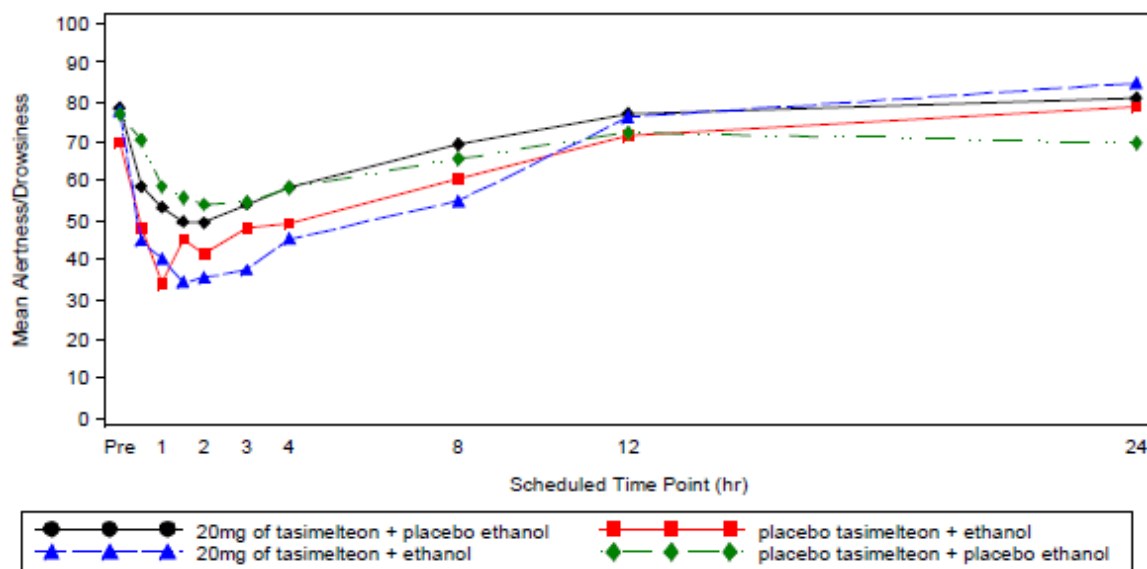


DV = digit vigilance

Mean Intoxication VAS Scores Over Time

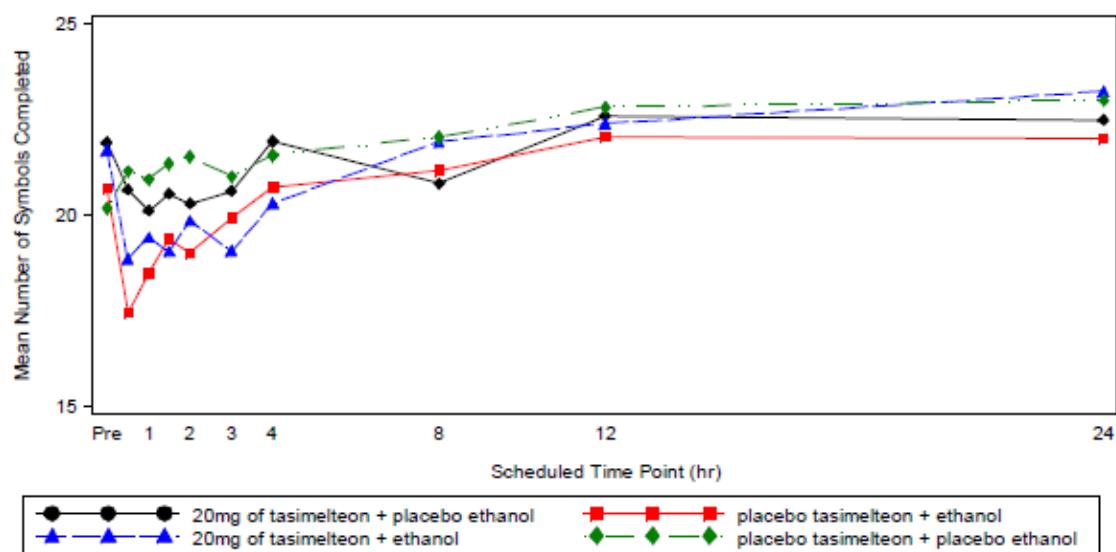


Mean Alertness/Drowsiness VAS Scores Over Time (PD Population)



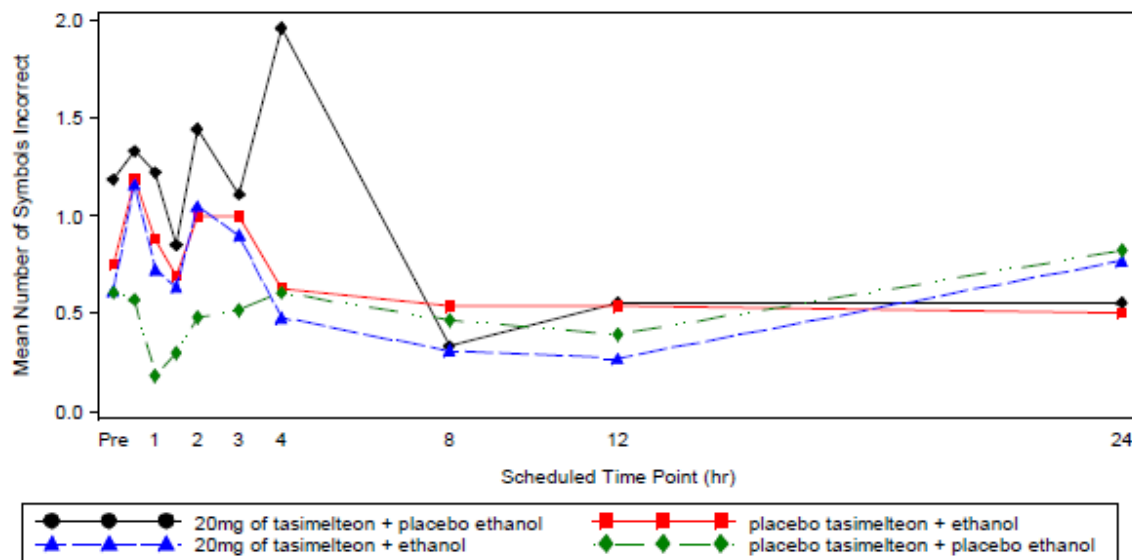
Digit Symbol Substitution Test (DSST)

Mean Number of Symbols Completed Over Time – DSST



DSST = digit symbol substitution test

Mean Number of Incorrect Symbols Over Time – DSST



CONCLUSIONS:

- Concomitant administration of ethanol resulted in relatively small increase in exposure (AUC_{0-inf}, AUC_{0-t}, and C_{max}) to tasimelteon. The magnitude of increase in exposure ranged from 10% to 25%.
- Tasimelteon 20 mg had no effect on the PK profile of ethanol.
- Pharmacodynamic parameters evaluated on subjective measures, or on sustained attention, cognition, balance or psychomotor performance in this study did not show

any trend when tasimelteon was concomitantly administered with ethanol. Most of the impairments on PD measures were related to ethanol and not to the addition of tasimelteon.

1.11 VP-VEC-162-1107: An open-label, single dose, parallel group study to assess the effect of smoking status, age and body size on the pharmacokinetics, safety, and tolerability of tasimelteon in healthy volunteers.

Objectives:

Primary:

- To assess plasma concentrations and pharmacokinetics of tasimelteon in subjects who smoke compared to subjects who do not smoke.
- To assess the effect of weight, body mass index (BMI), and age on the pharmacokinetic profile of tasimelteon.

Secondary:

- To assess effect of smoking, weight, BMI, and age on the pharmacokinetic profile of tasimelteon metabolites (M9, M11, M12, M13, and M14).
- To assess the safety and tolerability of a single 20-mg oral dose of tasimelteon.

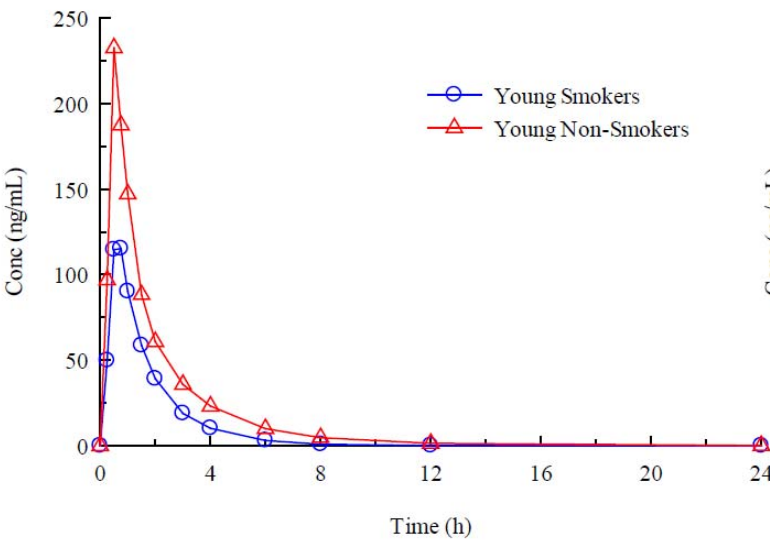
Study Design	This was an open-label, parallel-group design study. Sixty (60) healthy subjects were enrolled into the study.
Study Population	<p>Part 1</p> <p>Group 1: Twenty-four (24) male and female subjects between the ages of 18 and 55 years of age, inclusive, who smoked at least 10 tobacco cigarettes per day for at least 6 months prior to Screening and had a positive test for cotinine at Screening and Baseline.</p> <p>a. 8 underweight/normal [BMI \leq24.99], b. 8 overweight [BMI 25.00 to 29.99], and c. 8 obese [BMI \geq 30.00])</p> <p>Group 2: Twenty-four (24) male and female subjects between 18 and 55 years of age, inclusive, who had not consumed tobacco for 6 months before the start of the study and were similar in the distribution of the matching variables (gender, age (\pm10 years), and BMI category (underweight/normal, overweight and obese)) to Group 1.</p> <p>Part 2</p> <p>Group 3: Twelve (12) non-smoker subjects over 65 years of age were enrolled into the study.</p> <p>An approximately equal number of male and female volunteers were enrolled into each study group.</p>
Sampling:	Plasma PK samples were collected at pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4,

	6, 8, 12, and 24 hours after dosing.																					
Analysis	<p>The plasma samples were analyzed for the concentration of tasimelteon by using LC-MS/MS method. The lower limit of quantification (LLOQ) was 0.3 ng/mL for tasimelteon.</p> <table><tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr><tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>0.9, 135, and 270 ng/mL</td><td>0.3, 0.9, 3, 9, 30, 90, 225 and 300 ng/mL</td></tr><tr><td>Between Batch Precision (%CV)</td><td>1.9% to 3.3%</td><td>1.5 to 4.3</td></tr><tr><td>Between Batch Accuracy (%RE)</td><td>-5.7% to 5.0%.</td><td>-3.7 to 4.0</td></tr><tr><td>Linearity</td><td colspan="2">Weighted linear equation (1/X²), mean r= 0.996</td></tr><tr><td>Linear Range (ng/mL)</td><td colspan="2">0.3 to 300 ng/mL</td></tr><tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">0.3 ng/mL</td></tr></table>	Parameter	Quality Control Samples	Standard Curve Samples	Quality Control or Standard Curve Concentration (ng/mL)	0.9, 135, and 270 ng/mL	0.3, 0.9, 3, 9, 30, 90, 225 and 300 ng/mL	Between Batch Precision (%CV)	1.9% to 3.3%	1.5 to 4.3	Between Batch Accuracy (%RE)	-5.7% to 5.0%.	-3.7 to 4.0	Linearity	Weighted linear equation (1/X ²), mean r= 0.996		Linear Range (ng/mL)	0.3 to 300 ng/mL		Sensitivity (LLOQ, ng/mL)	0.3 ng/mL	
Parameter	Quality Control Samples	Standard Curve Samples																				
Quality Control or Standard Curve Concentration (ng/mL)	0.9, 135, and 270 ng/mL	0.3, 0.9, 3, 9, 30, 90, 225 and 300 ng/mL																				
Between Batch Precision (%CV)	1.9% to 3.3%	1.5 to 4.3																				
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Linearity	Weighted linear equation (1/X ²), mean r= 0.996																					
Linear Range (ng/mL)	0.3 to 300 ng/mL																					
Sensitivity (LLOQ, ng/mL)	0.3 ng/mL																					
PK Assessments	<p>The pharmacokinetic parameters C_{max}, T_{max}, AUC₀₋₁₂, AUC_(0-inf), apparent volume of distribution, CL, t_{lag} and t_{1/2} were calculated from the plasma concentration-time data using noncompartmental analysis. Comparison of the pharmacokinetic parameters was done by analysis of variance.</p> <p>Plasma concentrations and PK parameters of tasimelteon were compared between subjects who were current smokers and matched controls that did not smoke. Plasma concentrations and PK parameters of tasimelteon were also compared amongst subjects with different BMIs and ages.</p> <p>Secondary Endpoints</p> <ul style="list-style-type: none">• Plasma concentrations and PK parameters of tasimelteon metabolites M3 (Groups 1A, 1B, 2A, and 2B only), M9, M11, M12, M13, and M14 were compared between subjects who were current smokers and match controls that did not smoke.• Plasma concentrations and PK parameters of tasimelteon metabolites M9, M11, M12, M13, and M14 were compared amongst subjects with different BMIs and ages.																					
Safety Assessments	Safety was assessed by adverse event (AE) and serious adverse event (SAE) monitoring. Changes in clinical laboratory parameters that were relevant to safety. Influence of trial medication on vital signs and electrocardiogram (ECG) parameters.																					
Statistical Methods	<p>Pharmacokinetic:</p> <p>The effects of gender, smoking, age, and BMI were also examined using the data from all subjects in the study by a stepwise general linear models approach. For tasimelteon, the parameters examined were CL/F, Vz/F, and t_{1/2}; for the metabolites, the parameters examined were AUC(inf) and t_{1/2}. Parameters were natural log-transformed prior to the stepwise analysis.</p>																					

RESULTS:

Following figure depicts PK profile of tasimelteon in young smokers and young non-smokers.

Mean Plasma Concentrations of Tasimelteon after Oral Administration of Single 20 mg Doses of Tasimelteon to Young Smokers and Young Non-Smokers

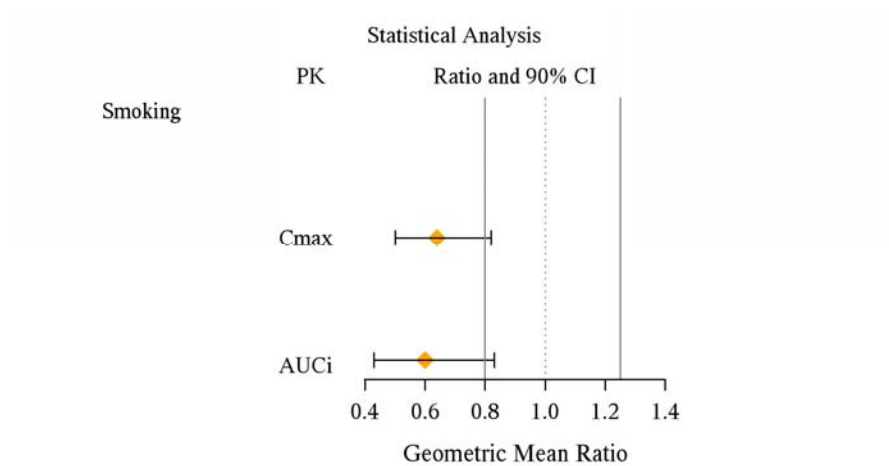


Following Table Summarizes PK Parameters of of Tasimelteon after Oral Administration of Single 20 mg Doses of Tasimelteon to Young Smokers and Young Non-Smokers.

Parameter*	Young Smokers	Young Non-Smokers
Cmax (ng/mL)	136 ± 59.5 (24)	239 ± 177 (24)
Tmax (h)	0.75 (24)	0.50 (24)
AUC(0-t) (h×ng/mL)	204 ± 151 (24)	386 ± 427 (24)
AUC(inf) (h×ng/mL)	205 ± 152 (24)	389 ± 429 (24)
λz (1/h)	0.7208 ± 0.1234 (24)	0.6433 ± 0.1737 (24)
t1/2(h)	0.99 ± 0.18 (24)	1.18 ± 0.46 (24)
CL/F (mL/min)	2,290 ± 1,232 (24)	1,482 ± 1,008 (24)
Vz/F (L)	189 ± 94.2 (24)	133 ± 83.0 (24)

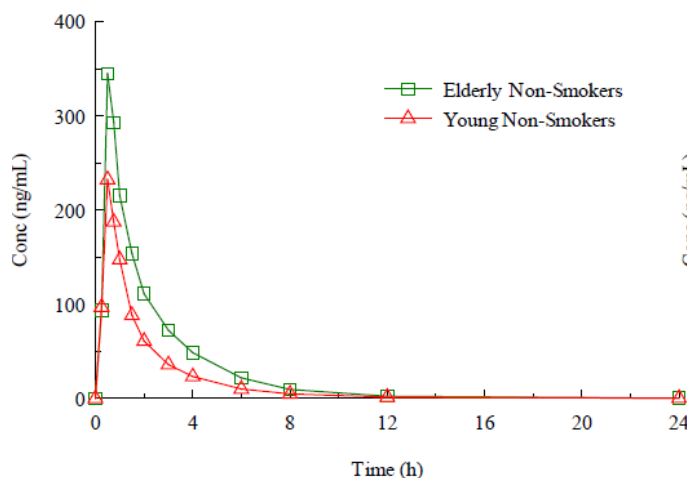
Following figure depicts [the](#) impact of smoking on tasimelteon Cmax and AUC.

Impact of smoking on tasimelteon



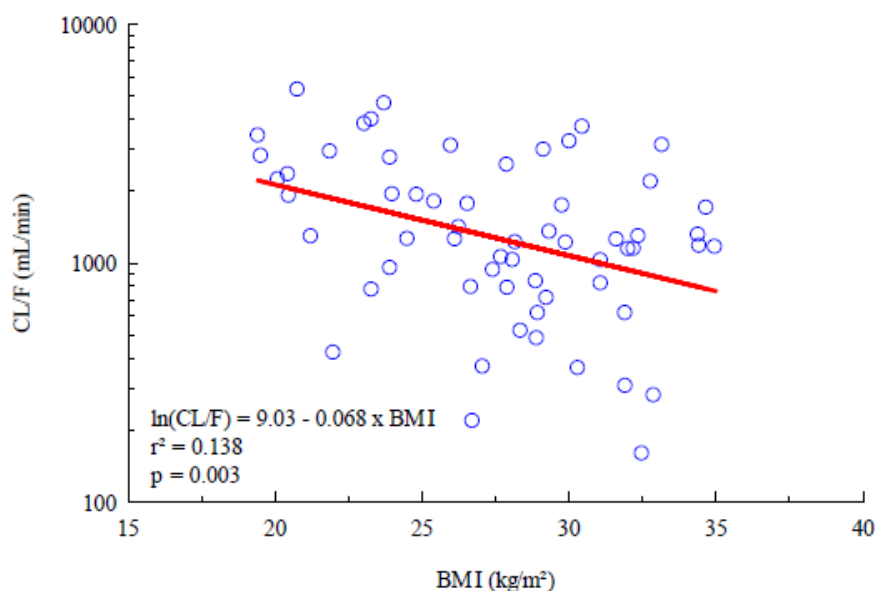
Following figure depicts PK profile of tasimelteon in young and elderly non-smokers.

Mean Plasma Concentrations of Tasimelteon after Oral Administration of Single 20 mg Doses of Tasimelteon to Young and Elderly Non-Smokers



Following figure depicts relationship between tasimelteon clearance and BMI.

Relationship between Tasimelteon CL/F and BMI after Oral Administration of Single 20 mg doses of Tasimelteon to Young and Elderly Non-Smokers.



Summary of Pharmacokinetic Parameters for Tasimelteon after Oral Administration of Single 20 mg Doses of Tasimelteon to Young and Elderly Non-Smokers:

Parameter*	Elderly Non-Smokers	Young Non-Smokers
Cmax (ng/mL)	365 ± 211 (12)	239 ± 177 (24)
Tmax (h)	0.50 (12)	0.50 (24)
AUC(0-t) (h×ng/mL)	649 ± 399 (12)	386 ± 427 (24)
AUC(inf) (h×ng/mL)	653 ± 402 (12)	389 ± 429 (24)
λ _z (1/h)	0.4562 ± 0.0963 (12)	0.6433 ± 0.1737 (24)
t _{1/2} (h)	1.59 ± 0.40 (12)	1.18 ± 0.46 (24)
CL/F (mL/min)	737 ± 471 (12)	1,482 ± 1,008 (24)
Vz/F (L)	92.8 ± 50.9 (12)	133 ± 83.0 (24)

CONCLUSIONS:

- Cigarette smoking resulting in induction of CYP1A2, increased the clearance of tasimelteon and decreased exposure about 40%.
- The clearance of tasimelteon is inversely related to age and BMI.

1.12 VP-VEC-162-1110: An open-label, single-sequence study to assess the effect of multiple doses of tasimelteon on the cytochrome P450 3A4 and 2C8 enzymes using midazolam and rosiglitazone as substrates in healthy subjects.

Objectives:

To characterize the effect of repeat 20 mg tasimelteon dosing on CYP3A4 and CYP2C8 activity at steady state. Midazolam and rosiglitazone were used as markers for CYP3A4 and CYP2C8 activity respectively.

Study Design	This was an open-label, single-sequence study conducted at one site. Approximately 24 subjects were enrolled in this study.																												
Study Population	Healthy male and female subjects Age: 18-55 years BMI: 18 to 35 kg/m ² . Twenty four subjects were enrolled and 24 completed the study.																												
Duration of Treatment	A single-sequence of the following treatments: <ul style="list-style-type: none"> • Single oral dose of midazolam 10 mg on Day 1 • Single oral dose of rosiglitazone 4 mg on Day 3 • Tasimelteon 20 mg QD for 13 days on Days 5-17 • Single oral doses of tasimelteon 20 mg and midazolam 10 mg on Day 18 • Single oral doses of tasimelteon 20 mg on Day 19 • Single oral doses of tasimelteon 20 mg and rosiglitazone 4 mg on Day 20. 																												
Sampling:	Blood samples for determining drug concentration of midazolam, tasimelteon and its metabolite were obtained for each subject as follows: Days 1 and 18: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post-dose Blood samples for determining drug concentration of rosiglitazone, tasimelteon were obtained for each subject as follows: Days 3 and 20: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post-dose Predose tasimelteon concentrations were determined on days 5, 8, 11, 14.																												
Analysis	<p>The plasma samples were analyzed for the concentration of tasimelteon by using LC-MS/MS method. The lower limit of quantification (LLOQ) was 0.3 ng/mL for tasimelteon.</p> <table border="1"> <thead> <tr> <th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr> </thead> <tbody> <tr> <td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>0.9, 135, and 270 ng/mL</td><td>0.3, 0.9, 3, 9, 30, 90, 225 and 300 ng/mL</td></tr> <tr> <td>Between Batch Precision (%CV)</td><td>2.3% to 11.4%</td><td>1.9 to 4.0</td></tr> <tr> <td>Between Batch Accuracy (%RE)</td><td>-6.4% to 3.2%.</td><td>-5.7 to 5.1</td></tr> <tr> <td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r= 0.998</td></tr> <tr> <td>Linear Range (ng/mL)</td><td colspan="2">0.3 to 300 ng/mL</td></tr> <tr> <td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">0.3 ng/mL</td></tr> </tbody> </table> <p>The plasma samples were analyzed for the concentration of midazolam and 1-OH midazolam by using LC-MS/MS method.</p> <p>Midazolam</p> <table border="1"> <thead> <tr> <th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr> </thead> <tbody> <tr> <td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>0.3, 5, 30, and 75 ng/mL</td><td>0.1, 0.2, 0.5, 1.5, 5, 15, 40, 80 and 100</td></tr> </tbody> </table>		Parameter	Quality Control Samples	Standard Curve Samples	Quality Control or Standard Curve Concentration (ng/mL)	0.9, 135, and 270 ng/mL	0.3, 0.9, 3, 9, 30, 90, 225 and 300 ng/mL	Between Batch Precision (%CV)	2.3% to 11.4%	1.9 to 4.0	Between Batch Accuracy (%RE)	-6.4% to 3.2%.	-5.7 to 5.1	Linearity	Weighted linear equation ($1/X^2$), mean r= 0.998		Linear Range (ng/mL)	0.3 to 300 ng/mL		Sensitivity (LLOQ, ng/mL)	0.3 ng/mL		Parameter	Quality Control Samples	Standard Curve Samples	Quality Control or Standard Curve Concentration (ng/mL)	0.3, 5, 30, and 75 ng/mL	0.1, 0.2, 0.5, 1.5, 5, 15, 40, 80 and 100
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			ng/mL	
	Between Batch Precision (%CV)	3.4% to 5.9%	3.1 to 6.6	
	Between Batch Accuracy (%RE)	-4.0% to 2.7%.	-7.0 to 3.4	
	Linearity	Weighted linear equation (1/X ²), mean r=0.997		
	Linear Range (ng/mL)	0.1 to 100 ng/mL		
	Sensitivity (LLOQ, ng/mL)	0.1 ng/mL		
	1-OH midazolam			
	Parameter	Quality Control Samples	Standard Curve Samples	
	Quality Control or Standard Curve Concentration (ng/mL)	0.3, 5, 30, and 75 ng/mL	0.1, 0.2, 0.5, 1.5, 5, 15, 40, 80 and 100 ng/mL	
	Between Batch Precision (%CV)	2.0% to 4.4%	1.0 to 7.3	
	Between Batch Accuracy (%RE)	-1.3% to 2.3%.	-4.5 to 4.7	
	Linearity	Weighted linear equation (1/X ²), mean r=0.997		
	Linear Range (ng/mL)	0.1 to 100 ng/mL		
	Sensitivity (LLOQ, ng/mL)	0.1 ng/mL		
PK Assessments	The pharmacokinetic parameters C _{max} , T _{max} , AUC _(0-inf) , apparent volume of distribution, CL, t _{lag} and t _{1/2} were calculated from the plasma concentration-time data using noncompartmental analysis. Comparison of the pharmacokinetic parameters was done by analysis of variance. <ul style="list-style-type: none">Plasma concentrations and pharmacokinetic parameters of midazolam were compared between Day 1 and Day 18.Plasma concentrations and pharmacokinetic parameters of rosiglitazone were compared between Day 3 and Day 20.!Plasma concentrations and pharmacokinetic parameters of tasimelteon and tasimelteon metabolites M9, M11, M12, M13, and M14, at Days 5, 8, 11, 14 (Group 1 only), and Days 17 and 19 (Groups 1 and 2).			
Safety Assessments	Safety of multiple oral doses of 20 mg of tasimelteon alone and in combination with 10 mg of midazolam as measured by adverse event (AE) and serious adverse event (SAE) monitoring. Changes in clinical laboratory parameters that were relevant to safety. Influence of trial medication on vital signs and electrocardiogram (ECG) parameters			
Statistical Methods	Pharmacokinetic: The 90% confidence intervals (CI) of the geometric mean ratio of AUC _{0-∞} and C _{max} values between the 2 treatments were calculated. The log-transformed data was analyzed using an analysis of variance model with factors for sequence, subjects within sequence, period, and treatment groups. The sequence effects were tested using the intersubject variation and differences between periods or treatments were compared using intrasubject variation estimated from the analysis of variance model.			

Following figure represents PK profile of midazolam alone or in combination with tasimelteon.

Figure 1 is a line graph showing the plasma concentration (ng/mL) of midazolam over 24 hours for two groups: Day 1 - Midazolam Alone (red line with triangles) and Day 18 - Midazolam + Tasimelteon (blue line with circles). The Y-axis represents Concentration (ng/mL) from 0 to 60, and the X-axis represents Time (h) from 0 to 24. Both groups show a rapid decline in concentration, with the Day 18 group reaching a lower concentration faster than the Day 1 group.

Time (h)	Day 1 - Midazolam Alone (ng/mL)	Day 18 - Midazolam + Tasimelteon (ng/mL)
0	0	0
0.5	48	52
1	42	35
2	25	22
3	16	14
4	11	10
6	5	5
8	3	3
12	1	1
24	0.5	0.5

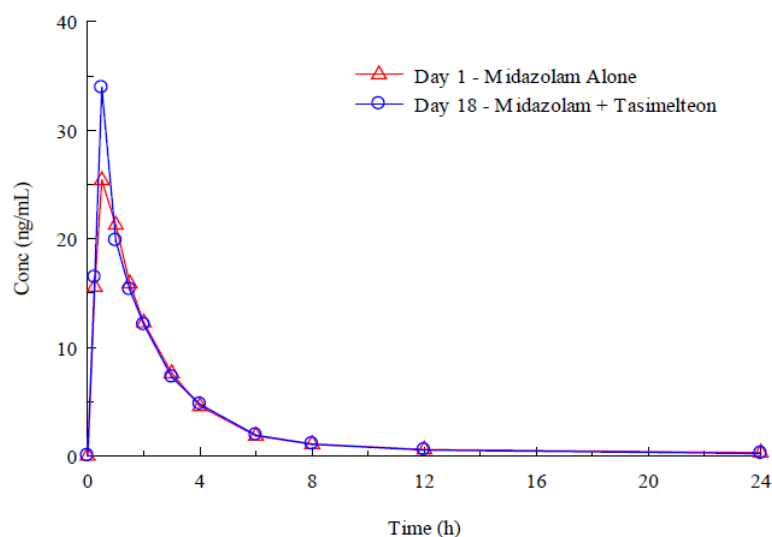
Summary of pharmacokinetic parameters for midazolam after oral administration of 10 mg alone and after dosing with tasimelteon 20 mg QD for 14 days:

Parameter*	Day 1 Midazolam Alone	Day 18 Midazolam + Tasemelteon
C _{max} (ng/mL)	59.3 ± 23.5 (23)	55.8 ± 13.9 (23)
T _{max} (h)	0.50 (23) [0.25 – 1.00]	0.50 (23) [0.25 – 1.00]
AUC(0-t) (h x ng/mL)	152 ± 37.8 (23)	135 ± 38.8 (23)
AUC(inf) (h x ng/mL)	155 ± 39.4 (23)	139 ± 39.9 (23)
λ _z (h ⁻¹)	0.1454 ± 0.0561 (23)	0.1405 ± 0.0443 (23)
t _{1/2} (h)	5.25 ± 1.47 (23)	5.36 ± 1.57 (23)

Statistical comparison of pharmacokinetic parameters for midazolam after oral administration of 10 mg alone and after dosing with tasimelteon 20 mg QD for 14 days:

Parameter	Geometric Mean Ratio (%)*	
	Estimate	90% Confidence Interval
Midazolam + Tasimelteon vs. Midazolam Alone		
C _{max}	113.40	96.44 → 133.34
AUC(0-t)	100.94	93.34 → 109.15
AUC(inf)	92.07	82.03 → 103.35

Mean plasma concentrations of 1-OH-midazolam after oral administration of 10 mg alone and after dosing with tasimelteon 20 mg QD x 14 days



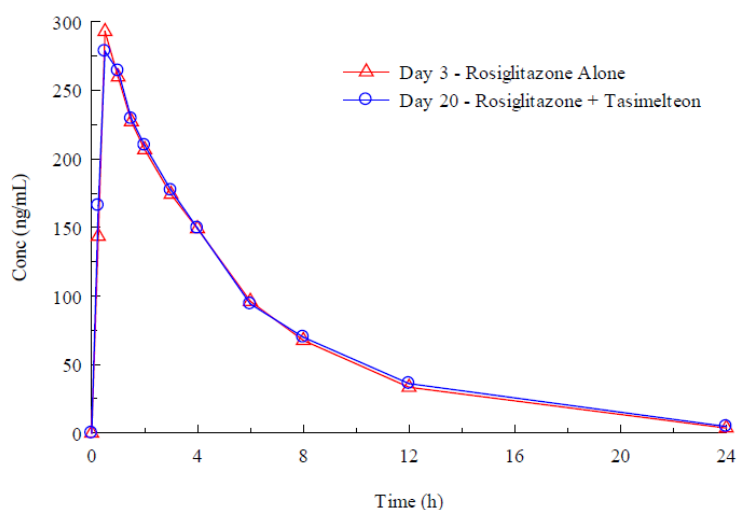
Statistical comparison of pharmacokinetic parameters for 1-OH-midazolam after oral administration of 10 mg alone and after dosing with tasimelteon 20 mg QD for 14 days:

Parameter	Geometric Mean Ratio (%)*	
	Estimate	90% Confidence Interval
Midazolam + Tasimelteon vs. Midazolam Alone		
C _{max}	98.17	87.70 → 109.88
AUC(0-t)	88.79	81.80 → 96.37
AUC(inf)	88.96	81.99 → 96.52

Rosiglitazone

Following figure represents PK profile of rosiglitazone alone and in combination with tasimelteon.

Mean plasma concentrations of rosiglitazone after oral administration of 4 mg alone and after dosing with tasimelteon 20 mg QD x 16 days.



Following table represents PK parameters of rosiglitazone alone or in combination with tasimelteon.

Summary of pharmacokinetic parameters for rosiglitazone after oral administration of 4 mg alone and after dosing with tasimelteon 20 mg QD for 16 days:-

Parameter*	Day 3 Rosiglitazone Alone	Day 20 Rosiglitazone + Tasimelteon
C _{max} (ng/mL)	310 ± 85.2 (23)	314.1 ± 85.0 (23)
T _{max} (h)	0.50 (23) [0.25 – 3.00]	0.50 (23) [0.25 – 4.00]
AUC(0-t) (h × ng/mL)	1,582 ± 347 (23)	1,638 ± 421 (23)
AUC(inf) (h × ng/mL)	1,638 ± 352 (23)	1,691 ± 427 (23)
λ _z (h ⁻¹)	0.1910 ± 0.0339 (23)	0.1816 ± 0.0336 (23)
t _{1/2} (h)	3.75 ± 0.76 (23)	3.96 ± 0.85 (23)

Statistical comparison of pharmacokinetic parameters for rosiglitazone after oral administration of 4 mg alone and after dosing with tasimelteon 20 mg QD for 16 days:-

Parameter	Geometric Mean Ratio (%)*		
	Estimate	90% Confidence Interval	
Rosiglitazone + Tasimelteon vs. Rosiglitazone Alone			
Cmax	101.66	95.51	→ 108.20
AUC(0-t)	102.73	99.07	→ 106.52
AUC(inf)	102.53	99.55	→ 105.59

Summary of pharmacokinetic parameters for tasimelteon on Days 18 and 20 after oral administration of 20 mg QD (Day 5 through Day 20).

Parameter*	Day 18	Day 20
C _{max} (ng/mL)	207 ± 133 (23)	238 ± 126 (23)
T _{max} (h)	0.50 (23)	0.50 (23)
AUC(0-t) (h×ng/mL)	360 ± 226 (23)	341 ± 211 (23)
AUC(24) (h×ng/mL)	360 ± 226 (23)	363 ± 207 (21)
λ _z (h ⁻¹)	0.6039 ± 0.1878 (23)	0.5659 ± 0.1605 (21)
t _{1/2} (h)	1.26 ± 0.39 (23)	1.31 ± 0.33 (21)

Metabolite M9

Summary of pharmacokinetic parameters for Metabolite M9 on Days 18 and 20 after oral administration of 20 mg QD (Day 5 through Day 20).

Parameter*	Day 18	Day 20
C _{max} (ng/mL)	232 ± 83.9 (23)	285 ± 134 (23)
T _{max} (h)	0.50 (23)	0.50 (23)
AUC(0-t) (h×ng/mL)	426 ± 122 (23)	422 ± 135 (23)
AUC(24) (h×ng/mL)	426 ± 122 (23)	423 ± 135 (23)
λ _z (h ⁻¹)	0.5267 ± 0.1154 (23)	0.4841 ± 0.0858 (23)
t _{1/2} (h)	1.38 ± 0.31 (23)	1.47 ± 0.25 (23)

Metabolite M11

Summary of pharmacokinetic parameters for Metabolite M11 on Days 18 and 20 after oral administration of 20 mg QD (Day 5 through Day 20).

Parameter*	Day 18	Day 20
C _{max} (ng/mL)	49.5 ± 19.1 (23)	50.0 ± 15.7 (23)
T _{max} (h)	1.02 (23)	1.00 (23)
AUC(0-t) (h×ng/mL)	154 ± 63.0 (23)	146 ± 62.6 (23)
AUC(24) (h×ng/mL)	149 ± 63.4 (20)	145 ± 63.5 (20)
λ _z (h ⁻¹)	0.3844 ± 0.1071 (20)	0.4094 ± 0.1025 (20)
t _{1/2} (h)	1.97 ± 0.66 (20)	1.80 ± 0.47 (20)

Metabolite M12

Summary of pharmacokinetic parameters for Metabolite M12 on Days 18 and 20 after oral administration of 20 mg QD (Day 5 through Day 20).

Parameter*	Day 18	Day 20
C _{max} (ng/mL)	93.7 ± 22.0 (23)	96.7 ± 21.8 (23)
T _{max} (h)	1.50 (23)	1.00 (23)
AUC(0-t) (h×ng/mL)	639 ± 281 (23)	619 ± 268 (23)
AUC(24) (h×ng/mL)	639 ± 280 (23)	619 ± 268 (23)
λ _z (h ⁻¹)	0.2398 ± 0.0852 (23)	0.2416 ± 0.0928 (23)
t _{1/2} (h)	3.20 ± 0.99 (23)	3.19 ± 0.94 (23)

Metabolite M13

Summary of pharmacokinetic parameters for Metabolite M13 on Days 18 and 20 after oral administration of 20 mg QD (Day 5 through Day 20).

Parameter*	Day 18	Day 20
C _{max} (ng/mL)	261 ± 100 (23)	296 ± 80.0 (23)
T _{max} (h)	0.50 (23)	0.50 (23)
AUC(0-t) (h×ng/mL)	372 ± 123 (23)	353 ± 123 (23)
AUC(24) (h×ng/mL)	372 ± 123 (23)	353 ± 123 (23)
λ _z (h ⁻¹)	0.6681 ± 0.2487 (23)	0.6016 ± 0.2454 (23)
t _{1/2} (h)	1.18 ± 0.42 (23)	1.31 ± 0.44 (23)

CONCLUSIONS:

- Oral administration of tasimelteon 20 mg daily for 14 days does not significantly change the overall exposure (AUC) of midazolam and 1-OH midazolam. Similarly there was no change in 1-OH midazolam C_{max}. There was a relatively small increase (13%) in midazolam C_{max}.
- Tasimelteon 20 mg daily administration for 16 days did not significantly change the plasma concentrations and mean pharmacokinetic parameters of rosiglitazone.
- There were no apparent changes in the pharmacokinetics of tasimelteon and metabolites M12 and M14 with dosing of 20 mg QD for 16 days. There were relatively small changes in concentration of Metabolites M9, M11, and M13.
- There is no significant induction of CYP3A4/5 or CYP2C8, when 20 mg tasimelteon was administered daily for 14 or 20 days respectively.

1.13 VP-VEC-162-1102: An Open-label, Two-period, Two-sequence, Randomized, Single Oral Dose, Crossover Study to Evaluate the Effect of Food on the Absorption of 100 mg VEC-162 in Healthy Subjects

Objectives:

Primary Objective: The primary objective of this study was to investigate the influence of food (highfat/ high-calorie meal) on the pharmacokinetics of 100 mg VEC-162 capsule in healthy subjects.

Secondary Objective: The secondary objective of this study was to assess the implications of CYP2D6, CYP2C9, and CYP1A2 genotypes for VEC-162 metabolism and overall pharmacokinetics.

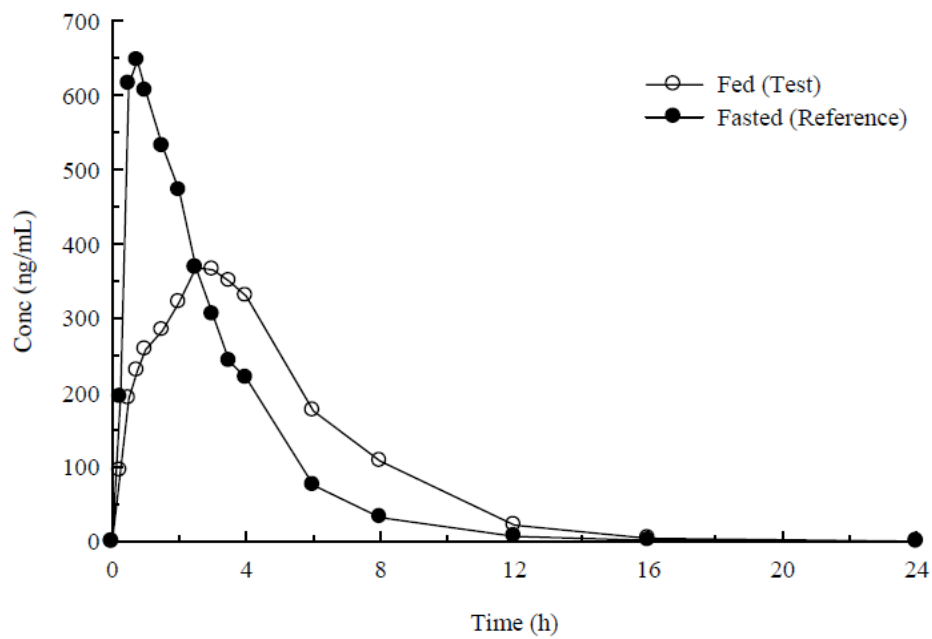
Study Design	This was a 2-period, randomized, 2-sequence crossover design where each subject received 100 mg of VEC-162 either with or without food.		
Study Population	Healthy male and female subjects Age: 18-50 years BMI: 18 to 35 kg/m ² . Twenty six subjects were enrolled and 26 completed the study		
Sampling:	Blood samples for the determination of VEC-162 in plasma were taken for each subject before dosing and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16 and 24hours after dosing		
Analysis	The plasma samples were analyzed for the concentration of tasimelteon by using LC-MS/MS method. The lower limit of quantification (LLOQ) was 0.1 ng/mL for tasimelteon.		
	Parameter	Quality Control Samples	Standard Curve Samples
	Quality Control or Standard Curve Concentration (ng/mL)	0.3, 45, and 90 ng/mL	0.1, 0.3, 1, 3, 10, 30, 60 and 100 ng/mL
	Between Batch Precision (%CV)	4.1 to 5.5	3.4 to 6.3
	Between Batch Accuracy (%RE)	-1.5 to 3.5	-4.1 to 7.0
	Linearity	Weighted linear equation (1/X ²), mean r= 0.994	
	Linear Range (ng/mL)	0.1 to 100 ng/mL	
	Sensitivity (LLOQ, ng/mL)	0.1 ng/mL	
PK Assessments	The pharmacokinetic parameters C _{max} , T _{max} , AUC _{0-t} , AUC _(0-inf) , apparent volume of distribution, CL, t _{lag} and t _{1/2} were calculated from the plasma concentration-time data using noncompartmental analysis.		
Safety Assessments	Safety assessments included physical examinations, vital signs (systolic/diastolic blood pressure, pulse rate, respiration rate, and oral body temperature), clinical laboratory tests (hematology, chemistry, and urinalysis), 12-lead electrocardiograms, and reported or observed adverse events.		
Statistical	Comparison of Cmax, AUC(0-t), and AUC(inf) with respect to the fed (test)		

Methods	and fasted (reference) treatments was done using an analysis of variance model with sequence, subject within sequence, treatment, and period as the classification variables. Confidence intervals (90%) were constructed for the treatment ratios (fed to fasted) of all 3 parameters using the log-transformed data and the 2 one-sided t-tests procedure. The point estimates and confidence limits were exponentiated back to the original scale. The 90% confidence intervals for the geometric mean ratios for Cmax, AUC(0-t), and AUC(inf) were calculated.
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RESULTS:

Following figure illustrates PK profile of tasimelteon following single oral 100 mg doses under fasted and fed conditions.

Mean Plasma Concentrations of VEC-162 after Single Oral 100 mg Doses Under Fasted and Fed Conditions



Following table summarizes PK parameters of tasimelteon under fasted and fed conditions.!

Summary of Pharmacokinetic Parameters for VEC-162 after Single Oral 100 mg Doses Under Fasted and Fed Conditions

Parameter ^a	Fed	Fasted
C _{max} (ng/mL)	445 ±255 (25)	786 ±432 (25)
T _{max} (h)	2.50 (25) [0.75 – 6.00]	0.75 (25) [0.50 – 4.00]
AUC(0-t) (h·ng/mL)	2276 ±1444 (25)	2120 ±1401 (25)
AUC(inf) (h·ng/mL)	2304 ±1471 (24)	2269 ±1468 (21)
λ _z (h ⁻¹)	0.3749 ±0.1279 (24)	0.2871 ±0.1010 (21)
t _{1/2} (h)	2.06 ±0.70 (24)	2.75 ±1.09 (21)

Following table summarizes statistical analysis conducted on PK parameters of tasimelteon.!

Statistical Analysis of Pharmacokinetic Parameters for VEC-162 after Single Oral 100 mg Doses Under Fasted and Fed Conditions

Parameter	Geometric Mean Ratio (%)	
	Estimate	90% Confidence Interval
C _{max}	55.82	49.71 – 62.67
AUC(0-t)	108.57	101.82 – 115.76
AUC(inf)	106.54	99.39 – 114.21

CONCLUSIONS:

High fat, high calorie meal did not influence on the overall exposure (did not affect AUC) of tasimelteon but C_{max} was reduced by 44%. The median T_{max} was delayed from 0.75 hours to 2.5 hours by high-fat meal.

In Vitro Study Reviews

1.14 *In vitro determination of protein binding of [¹⁴C]BMS-214778 in human, monkey, rat, and mouse sera.*

Study Title	In vitro determination of protein binding of [¹⁴ C]BMS-214778 in human, monkey, rat, and mouse sera.
Study number	910073823
Study Period	April 1999
Study Director	(b) (4)
Objective	This study was conducted to determine in vitro plasma protein binding of tasimelteon in human, monkey, rat, and mouse sera.

METHODS

Serum protein binding was determined by equilibrium dialysis for 4 hat 37°C at five concentrations. [¹⁴C]BMS-214778 was used to determine the time to reach equilibrium and the extent of protein binding in serum.

Stability in Serum and Plasma

The stability was determined by incubating BMS-214778 in human serum at 10 and 2,000 ng/mL in monkey, rat, and mouse plasma at 200 and 20,000 ng/mL at 37 °C. Samples were removed preincubation and at 3, 4, 6, and 24 h. All samples were stored at -20 °C until analyzed for BMS-214778 by an LC/MS method. Peak area response ratios of BMS-214778 to the internal standard were determined. Stability was assessed based on the peak area response ratios at various times relative to the response ratio at preincubation.

Equilibrium Dialysis

Serum protein binding was determined by equilibrium dialysis using sodium phosphate buffer (0.134M, pH 7.4) and Spectra/POR molecular porous dialysis membranes with a 12:000-14,000 Dalton molecular weight cutoff. Dialysis cells were rotated at 20 rpms in a water bath at 37 °C. The time to reach equilibrium study was carried out at two nominal concentrations in human serum. After establishing the time to reach equilibrium, samples for all subsequent experiments were collected at that time. The serum protein binding experiments were carried out at five nominal concentrations ranging from 10 to 2,000 ng/mL in human serum and 200 to 20,000 ng/mL in monkey, rat, and mouse sera.

RESULTS

The results of plasma protein binding are summarized in the table below.

Total Conc (ng/L)	Mean (SD) %Bound in Human	Total Cone (ng/mL)	Mean (SD) % Percent Bound in		
			Monkey	Rat	Mouse
10	90.3 (0.50)	200	79.7 (0.22)	84.8 (0.12)	77.6 (0.19)
50	89.9 (0.26)	1,000	78.2 (0.23)	83.5 (0.14)	77.5 (0.64)
200	89.1 (0.46)	5,000	74.0 (0.49)	80.6 (0.25)	76.3 (0.08)
1,000	87.7 (0.19)	10,000	71.9 (0.51)	78.0 (0.97)	75.3 (0.31)
2,000	85.8 (0.27)	20,000	69.0 (0.75)	76.8 (0.58)	73.5 (0.31)

CONCLUSIONS

- Tasimelteon is moderately bound in human, monkey, rat, and mouse sera. The plasma protein binding ranged from 89.1% in human serum to 77.6% in mouse serum
- The extent of serum protein binding was concentration dependent with relatively small change over 200 fold increases in concentration in human serum and a 100-fold range in monkey, rat, and mouse sera.

1.15 VEC-162/Tasimelteon: Cytochrome P450 Reaction Phenotyping

Study Title	VEC-162/Tasimelteon: Cytochrome P450 Reaction Phenotyping
Study number	(b) (4) 08639
Study Period	May 2009
Study Director	(b) (4)
Objective	This study was conducted to investigate the prominent Phase I metabolite profiles of VEC-162/tasimelteon in human liver microsomes and to characterize the cytochrome P450 enzymes responsible for the formation of the prominent metabolites.

METHODS

Metabolite Profiling

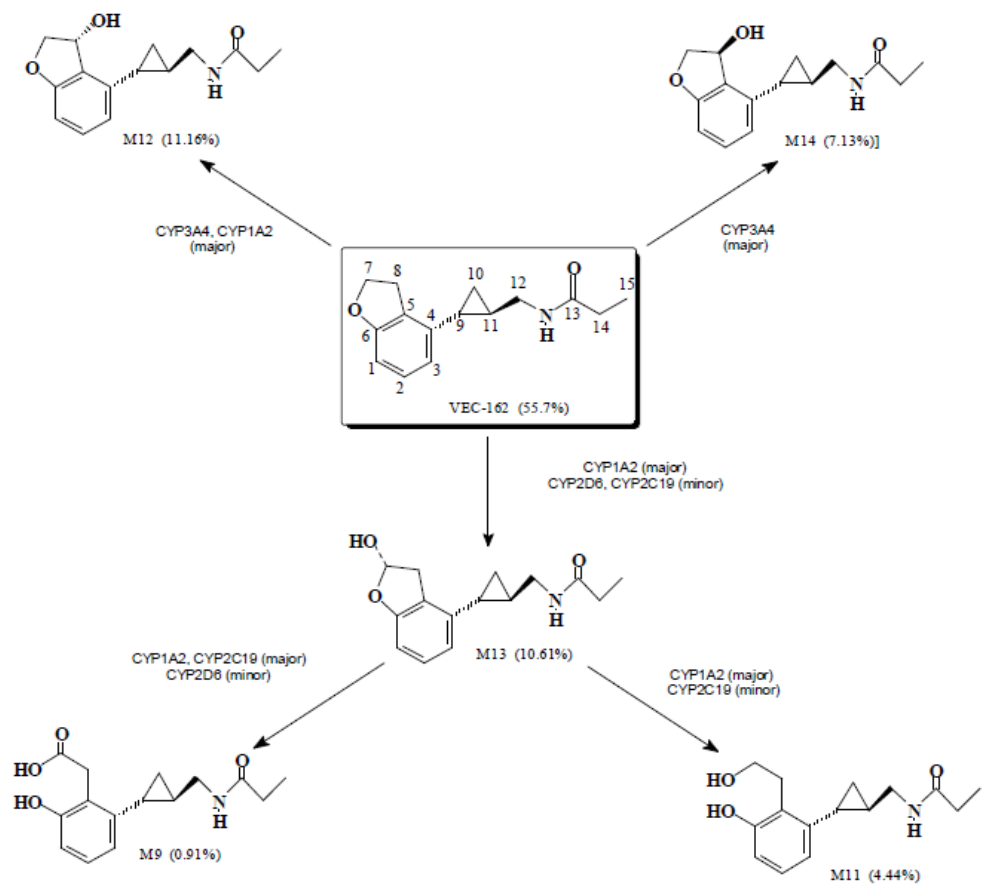
[¹⁴C]VEC-162, at concentrations of 5 µM and 10 µM in 0.1-M potassium phosphate buffer (pH 7.4), was incubated with human liver microsomes (HLM) at 37 °C for 1-hr. The incubations were carried out in the presence of 4 mM MgCl₂ and 1 mM NADPH. After 1-hr, the metabolic reactions were terminated by mixing with 2 volumes of ice-cold methanol, followed by centrifugation. Metabolite profiling was accomplished by HPLC with radiochemical detection. Characterization and/or identification of the prominent metabolites were conducted by LC/MS/MS in conjunction with radioactivity detection. 7-Ethoxycoumarin (100 µM), as a positive control, was incubated concurrently to assess the metabolic capacity of the human liver microsomes used in the incubation.

CYP Phenotyping

The incubation mixture, prepared in 0.1 M potassium phosphate buffer (pH 7.4), contained human liver microsomes (HLM) (0.25 mg/mL) or a recombinant human CYP isozyme (rCYP, 50 pmol/mL) and tasimelteon (100µM) or a marker substrate. After a pre-incubation at 37 °C for 5 min in a shaking water bath, the reaction was initiated by the addition of NADPH (1 mM) solution. Samples were incubated aerobically in a shaking water bath at 37 °C. The incubation was terminated by the addition of the appropriate quench solution. After centrifugation, the supernatant was analyzed by LC/MS/MS. Positive control incubations containing marker substrates were incubated concurrently to assess the metabolic capacity of HLM and rCYP used in each assay.

RESULTS

P450 Mediated Metabolism of Tasimelteon in HLM



Percentage Inhibition and Formation of M9, M11, M12, M13, and M14 in Human Liver Microsomes and rCYP Isoforms

CYP Isoform	Metabolite M9		Metabolite M11		Metabolite M12		Metabolite M13		Metabolite M14	
	% CI ^a	rCYP ^b	% CI ^a	rCYP ^b	% CI ^a	rCYP ^b	% CI ^a	rCYP ^b	% CI ^a	rCYP ^b
1A2	42.9	487 (High)	40.9	540 (High)	47.3	171(High)	69.3	434 (High)	67.6	ND
2B6	30.0	23 (Very Low) ^d	1.44	NA	49.3	NA	NA	42 (Low) ^e	58.8	ND
2C8	83.1	5 (Very Low) ^d	45.5	NA	NA	NA	37.6	6 (Very Low) ^d	NA	ND
2C9	80.8	15 (Very Low) ^d	4.38	NA	29.4	NA	NA	46 (Low) ^e	46.0	ND
2C19	41.9	117 (High)	21.2	130 (High)	4.50	NA	17.6	283 (High)	32.1	ND
2D6	13.5	98 (High)	NA	149 (High)	2.39	NA	11.9	571 (High)	43.4	ND
2E1	48.9	NA	35.2	NA	52.3	NA	12.9	NA	87.0	ND
3A4 ^c	44.2	7 (Very Low)	NA	0	74.3	287 (High)	7.28	NA	99.0	226 (High)

^a Percent inhibition of formation of tasimelteon metabolites by isoform-selective chemical inhibitor compared to no-inhibitor control in human liver microsomes.

^b Formation of tasimelteon metabolites by recombinant human cytochrome P450 isoform.

^c Inhibition of formation of tasimelteon metabolites using 6 β -hydroxy-testosterone as CYP3A4 substrate

ND: Not detected.

^d Formation of metabolite \leq 5% of the highest value

^e Formation of metabolite \leq 10% but $>$ 5% of the highest value

CYP1A1 is expressed in human liver only in very low levels, metabolism of tasimelteon was tested only in the recombinant CYP1A1 system. Metabolite M12 was formed in the recombinant system, and significant chemical inhibition was observed with the CYP1A1 selective chemical inhibitor, alpha naphoflavone.

CONCLUSIONS

- CYP1A2 plays a major role in the Phase I metabolism of tasimelteon.
- CYP2C19 plays a significant role, specifically in the formation of metabolite M9 and M11 and a minor role in the formation of M13.
- CYP3A4 plays a significant role, specifically in the formation of M12 and M14, respectively. CYP2D6 may be involved to a lesser extent in the formation of M9 and M13. CYP1A1 may play a role in the formation of M12.

1.16 *In Vitro Evaluation of VEC-162 as an Inhibitor of Human Cytochrome P450 Enzymes*

Study Title	In Vitro Evaluation of VEC-162 as an Inhibitor of Human Cytochrome P450 Enzymes
Study number	(b) (4) 065016
Study Period	August 2006
Study Director	(b) (4)
Objective	This study was conducted to evaluate the ability of VEC-162 to inhibit in vitro the major CYP enzymes in human liver microsomes (namely CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 [using two different substrates]).

METHODS

To evaluate VEC-162 as a direct inhibitor of CYP activity, human liver microsomes from a pool of 16 individuals were incubated with marker substrates, at concentrations approximately equal to each marker substrate's K_m , in the presence or absence of VEC-162. The target concentrations of VEC-162 ranged from 0.1 μ M to 100 μ M. In addition, VEC-162 was evaluated for its ability to function as a time-dependent inhibitor at the same concentrations mentioned above, in which case VEC-162 was pre-incubated with human liver microsomes and a NADPH-generating system for 30 minutes to allow for the generation of metabolites that might inhibit CYP activity.

Known direct and metabolism-dependent inhibitors of CYP enzymes were included as positive controls.

VEC-162 was evaluated for its ability to directly inhibit the following human CYP enzymes. VEC-162 was also evaluated for its ability to inhibit the following CYP enzymes in a time-dependent manner.

CYP1A2	Phenacetin O-deethylation
CYP2C8	Amodiaquine N-dealkylation
CYP2C9	Diclofenac 4'-hydroxylation
CYP2C19	S-Mephenytoin 4'-hydroxylation
CYP2D6	Dextromethorphan O-demethylation
CYP3A4/5	Testosterone 6 β -hydroxylation
CYP3A4/5	Midazolam 1' -hydroxylation

RESULTS

VEC-162 caused direct inhibition of CYP2C19 with an IC₅₀ value of 80 μ M.

There was evidence of direct inhibition of CYP1A2, CYP2C8, CYP2D6, and CYP3A4/5 the IC₅₀ values for these enzymes were greater than 100 μ M.

VEC-162 caused little or no direct inhibition of CYP2C9, and the IC₅₀ value determined for this enzyme was > 100 μ M).

There was little or no evidence that VEC-162 has the potential to cause time-dependent inhibition of any of the CYP enzymes evaluated (table below).

In Vitro Evaluation of VEC-162 as an Inhibitor of Human CYP Enzymes

Enzyme	CYP Reaction	Direct inhibition		Metabolism-dependent inhibition		tin
		Zero-minute pre-incubation		30-minute pre-incubation		
		IC ₅₀ (μM)	Maximum inhibition at 100 μM (%) ^a	IC ₅₀ (μM)	Maximum inhibition at 100 μM (%) ^a	
CYP1A2	Phenacetin <i>O</i> -deethylation	> 100 μM	30	> 100 μM	29	
CYP2C8	Amodiaquine <i>N</i> -dealkylation	> 100 μM	28	> 100 μM	13	
CYP2C9	Diclofenac 4'-hydroxylation	> 100 μM	12	> 100 μM	26	
CYP2C19	<i>S</i> -Mephenytoin 4'-hydroxylation	80 ± 24	55	68 ± 25	61	
CYP2D6	Dextromethorphan <i>O</i> -demethylation	> 100 μM	17	> 100 μM	1.2	
CYP3A4/5	Testosterone 6β-hydroxylation	> 100 μM	34	> 100 μM	35	
CYP3A4/5	Testosterone 6β-hydroxylation repeat ^c	> 100 μM	32	> 100 μM	38	
CYP3A4/5	Midazolam 1'-hydroxylation	> 100 μM	28	> 100 μM	34	

Note: The C_{max} of tasimelteon at the 20 mg therapeutic dose is approximately 0.2 μM.

CONCLUSIONS

Tasimelteon is less likely to cause direct inhibition or time-dependent inhibition of any of the CYP enzymes evaluated (i.e., CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5) at therapeutic levels.

1.17 *In Vitro* Evaluation of M9, M12 and M13 as Potential Inhibitors of Cytochrome P450 (CYP) Enzymes in Human Liver Microsomes

Study Title	In Vitro Evaluation of M9, M12 and M13 as Potential Inhibitors of Cytochrome P450 (CYP) Enzymes in Human Liver Microsomes
Study number	(b) (4) 12A024
Study Period	November 2010
Study Director	(b) (4)
Objective	This study was conducted to investigate inhibition potential of metabolites M9, M12 and M13

METHODS

The ability of M9, M12 and M13 to each directly inhibit human CYP enzymes was investigated with a pool of sixteen individual human liver microsomal samples. Each test article concentration was incubated with marker substrate and human liver microsomes in triplicate.

To examine its ability to act as a time-dependent inhibitor of CYP enzymes, M9, M12 or M13 (at the same concentrations used to evaluate direct inhibition) was preincubated with human liver microsomes and an NADPH-generating system for 30 minutes to allow for the generation of intermediates that could inhibit human CYP enzymes.

To evaluate its ability to inhibit the CYP2C9 and CYP2C19 in a time-dependent manner, experiments were designed to determine if any increase in inhibition in M12 observed after

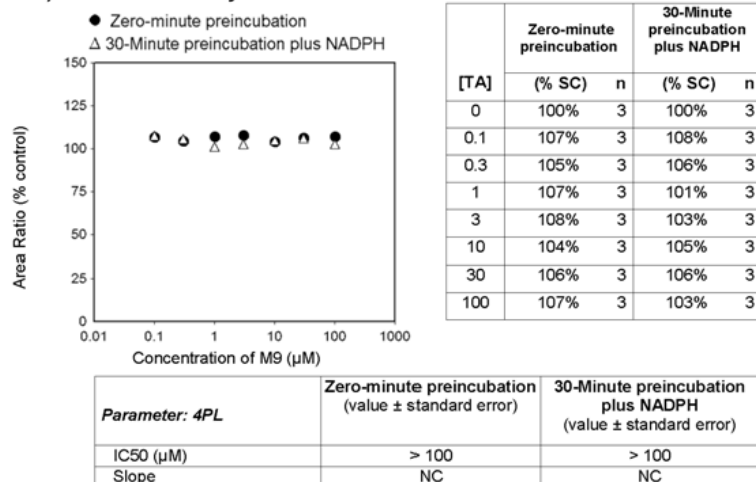
preincubation was NADPH-dependent (i.e., metabolism-dependent) and reversible by either microsomal re-isolation or by incubation with potassium ferricyanide prior to re-isolation.

RESULTS

M9 was not direct or time dependent inhibition of any CYP enzyme activity as shown in the figure below.

Inhibition of CYP1A2 (phenacetin O-dealkylation) by M9: IC₅₀ determination

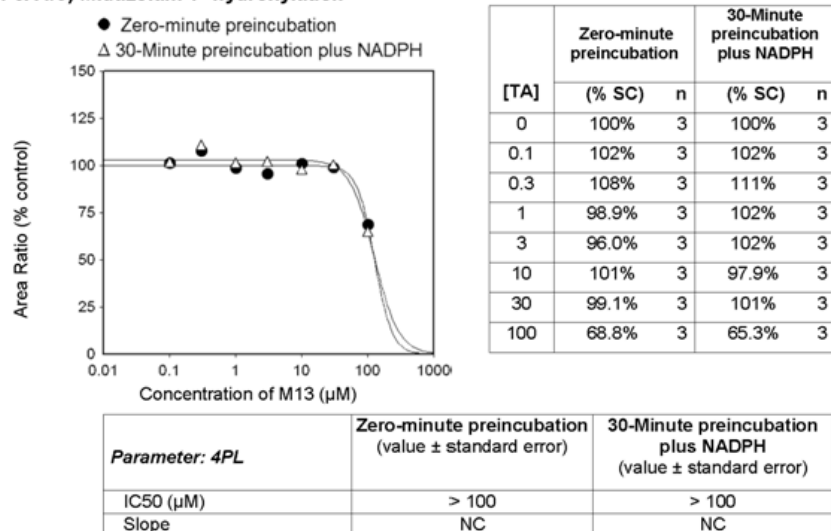
(CYP1A2) Phenacetin O-dealkylation



Metabolite M13 was a direct inhibitor of CYP3A4/5. The percent of control activity in the presence of 100 μM M13 was 69%. The IC₅₀ value is reported as > 100 μM since less than 50% inhibition of enzyme activity was observed at the highest concentration of M13 examined as shown in the figure below.

Inhibition of CYP3A4/5 (midazolam 1'-hydroxylation) by M13: IC₅₀ determination

(CYP3A4/5) Midazolam 1'-hydroxylation

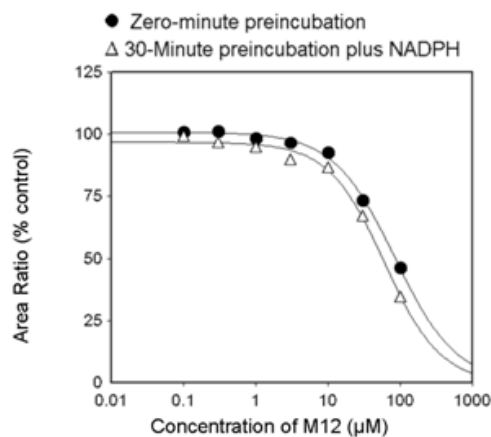


There was no evidence of direct inhibition of any other CYP enzyme activity by M13.

The IC50 values for M12 for CYP3A4/5 were 84 μ M.

Inhibition of CYP3A4/5 (midazolam 1'-hydroxylation) by M12: IC50 determination

(CYP3A4/5) Midazolam 1'-hydroxylation



[TA]	Zero-minute preincubation		30-Minute preincubation plus NADPH	
	(% SC)	n	(% SC)	n
0	100%	3	100%	3
0.1	101%	3	99.6%	3
0.3	101%	3	96.9%	3
1	98.4%	3	94.9%	3
3	96.7%	3	90.0%	3
10	92.8%	3	86.7%	3
30	73.5%	3	67.2%	3
100	46.4%	3	34.6%	3

Parameter: 4PL	Zero-minute preincubation (value \pm standard error)	30-Minute preincubation plus NADPH (value \pm standard error)
IC50 (μ M)	84 \pm 5	61 \pm 5
Slope	1.0 \pm 0.1	1.1 \pm 0.1

M12 was found to directly inhibit CYP2C8 and CYP2C19 with an IC50 value of >100 μ M since less than 50% inhibition of enzyme activity was observed at the highest concentration of M12 examined.

Summary of results: In vitro evaluation of M9, M12 and M13 as inhibitors of human CYP enzymes

Enzyme	Enzyme reaction	M9			M12			M13		
		^a IC ₅₀ (μM)	^a IC ₅₀ (μM)	^b Potential for TDI	^a IC ₅₀ (μM)	^a IC ₅₀ (μM)	^b Potential for TDI	^a IC ₅₀ (μM)	^a IC ₅₀ (μM)	^b Potential for TDI
		Zero-minute pre-incubation	30-min pre-incubation		Zero-minute pre-incubation	30-min pre-incubation		Zero-minute pre-incubation	30-min pre-incubation	
CYP1A2	Phenacetin O-dealkylation	>100	>100	No	>100	>100	Yes	>100	>100	No
CYP2B6	Efavirenz 8-hydroxylation	>100	>100	No	>100	>100	No	>100	>100	No
CYP2C8	Amodiaquine N-dealkylation	>100	>100	No	>100	>100	No	>100	>100	No
CYP2C9	Diclofenac 4'-hydroxylation	>100	>100	No	>100	^c 85, ^d >100	^c Yes/ ^d No	>100	>100	No
CYP2C19	S-Mephenytoin 4'-hydroxylation	>100	>100	No	>100	^c 24, ^d 92	^c Yes/ ^d Yes	>100	>100	No
CYP2D6	Dextromethorphan O-demethylation	>100	>100	No	>100	>100	No	>100	>100	No
CYP3A4/5	Midazolam 1'-hydroxylation	>100	>100	No	84	61	No	>100	>100	No

^a Mean data (i.e., percent of control activity) obtained from triplicate samples for each test article concentration were used to calculate IC₅₀ values.

^b Time-dependent inhibition (TDI) was determined by comparison of IC₅₀ values obtained with and without preincubation, by comparison of the observed inhibition (%) for all preincubation conditions and by visual inspection of the IC₅₀ plots.

^c Result as determined using the initial lot of M12 received.

^d Result as determined using a second, purer batch of M12.

Discussion

A drug is less likely to cause *in vivo* drug interactions if the R₁ value is greater than 1, as calculated using the formula $R_1 = 1 + [I]/K_i$.

Based on human plasma C_{max} for M12 of approximately 0.4 μM, R₁ is calculated to be approximately 1.01 for CYP3A4/5 direct inhibition. The calculated R₁ values for direct inhibition by M12 of other CYP enzymes as well as inhibition of all CYP enzymes by either M9 or M13 are less than 1.1.

CONCLUSION

The major metabolites of tasimelteon M9, M12 or M13 are less likely to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5 at therapeutic concentrations.

1.18 In Vitro Evaluation of Tasimelteon as an Inhibitor of CYP2B6 in Human Liver Microsomes

Study Title	In Vitro Evaluation of Tasimelteon as an Inhibitor of CYP2B6 in Human Liver Microsomes
Study number	(b) (4) 065016
Study Period	February 2013 to March 2013
Study Director	(b) (4)
Objective	This study was conducted to evaluate the ability of tasimelteon to inhibit, in vitro, CYP2B6 in human liver microsomes.

METHODS

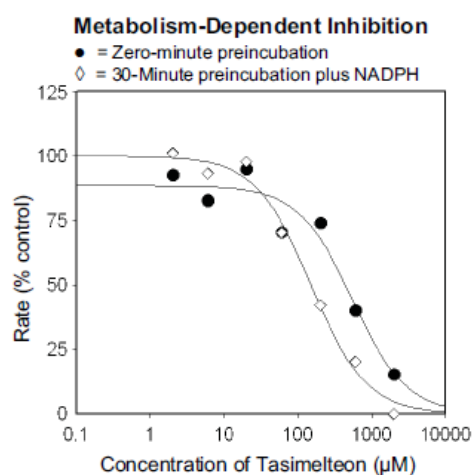
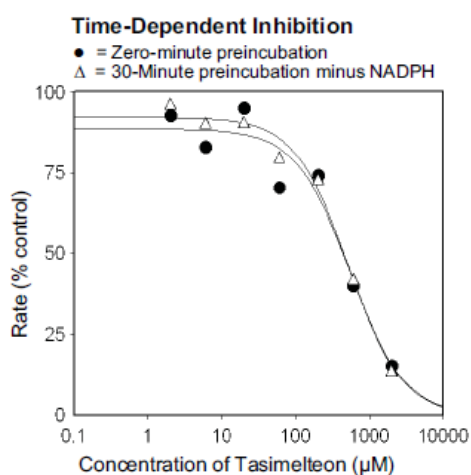
The ability of tasimelteon to directly inhibit human CYP2B6 was investigated with a pool of sixteen individual human liver microsomal samples. Each test article concentration was incubated with marker substrate and human liver microsomes in duplicate.

To examine its ability to act as a metabolism-dependent (i.e., time-dependent and NADPH-dependent) inhibitor of CYP2B6, tasimelteon (at the same concentrations used to evaluate direct inhibition) was preincubated with human liver microsomes and an NADPH-generating system for up to 30 minutes to allow for the generation of intermediates that could inhibit human CYP2B6. To distinguish between time-dependent (i.e., NADPH-independent) and metabolism-dependent inhibition, tasimelteon was also preincubated with human liver microsomes for 30 minutes without an NADPH-generating system, prior to incubation with the marker substrate. To further evaluate the ability of tasimelteon to inhibit CYP2B6 in a metabolism-dependent manner, experiments were designed to determine if the metabolism-dependent inhibition of CYP2B6 by tasimelteon was reversible by either microsomal re-isolation or by incubation with potassium ferricyanide prior to re-isolation. Another experiment was performed to determine the KI and kinact values associated with inactivation of CYP2B6 by tasimelteon.

RESULTS

Under the experimental conditions examined, tasimelteon was a direct inhibitor of CYP2B6 with an IC₅₀ value of 550 µM. Furthermore, tasimelteon was a metabolism-dependent (i.e., time-dependent and NADPH-dependent) inhibitor of CYP2B6 since the IC₅₀ value shifted approximately 3.7-fold lower (i.e., from 550 µM to 150 µM) after tasimelteon was preincubated with NADPH-fortified human liver microsomes for 30 minutes.

Inhibition of CYP2B6 (efavirenz 8-hydroxylation) by tasimelteon: IC₅₀ Determination



Parameter: 4PL	Zero-minute preincubation (value ± standard error)	30-Minute preincubation minus NADPH (value ± standard error)	30-Minute preincubation plus NADPH (value ± standard error)
IC ₅₀ (µM)	550 ± 150	520 ± 70	150 ± 20
Slope	1.2 ± 0.4	1.2 ± 0.2	1.2 ± 0.1

CONCLUSIONS

Tasimelteon is less likely to cause direct inhibition or time-dependent inhibition of, CYP2B6 at therapeutic levels.

1.19 *In vitro* Evaluation of VEC-162 as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes

Study Title	In vitro Evaluation of VEC-162 as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes
Study number	(b) (4) 063014
Study Period	March 2007
Study Director	(b) (4)
Objective	This study was conducted to to investigate the effect of treating primary cultures of human hepatocytes with VEC-162 on the expression of several microsomal cytochrome P450 (CYP) enzymes, namely CYP1A2, 2C8, 2C9, 2C19, and 3A4/5.

METHODS

Three preparations of cultured human hepatocytes from three separate human livers were treated once daily for three consecutive days with dimethyl sulfoxide (DMSO, vehicle, 0.1% v/v), one of three concentrations of VEC-162 (1, 10 or 100 µM), or one of two known human CYP inducers namely omeprazole (100 µM) and rifampin (10 µM). After treatment, cells were harvested to prepare microsomes for the analysis of phenacetin O-dealkylation (marker for CYP1A2), paclitaxel 6α-hydroxylation (marker for CYP2C8), diclofenac 4'-hydroxylation (marker for CYP2C9), S-mephenytoin 4'-hydroxylation (marker for CYP2C19), and testosterone 6β-

hydroxylation (marker for CYP3A4/5). Microsomes were also analyzed by Western immunoblotting to assess changes in the levels of CYP2C8, CYP2C9, CYP2C19 and CYP3A4.

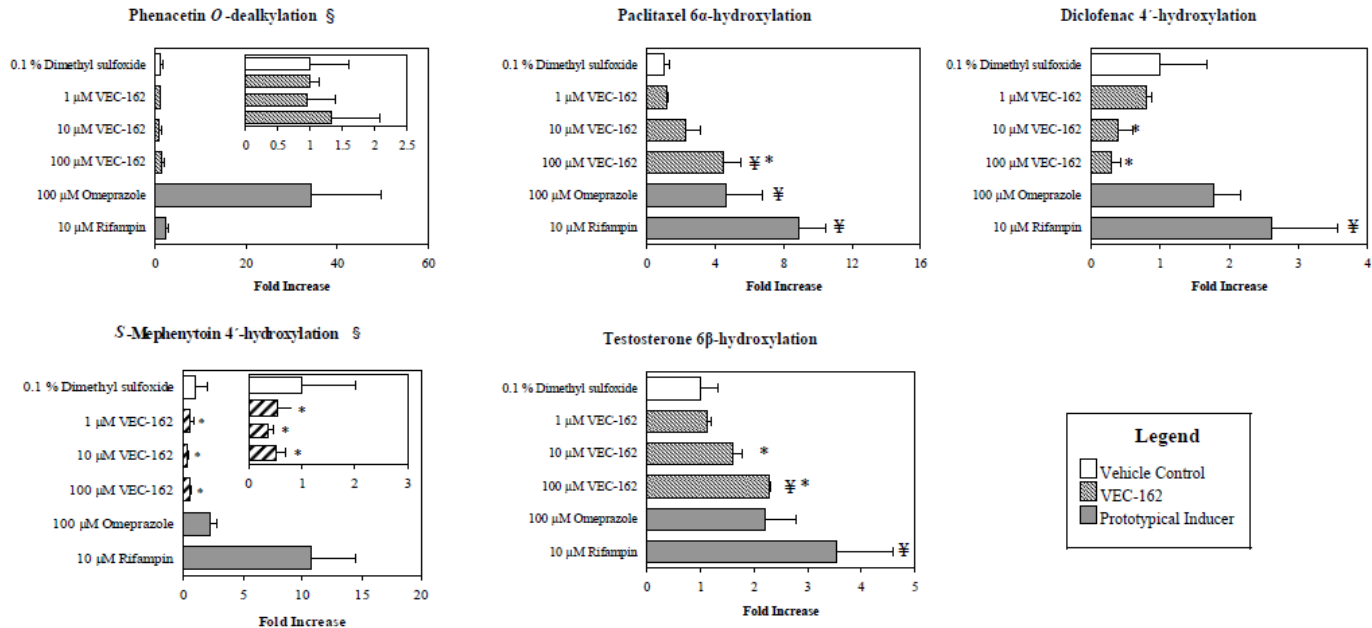
RESULTS

Treatment with omeprazole caused a 34.3-fold increase in CYP1A2 activity whereas treatment with rifampin caused an 8.85-, 2.60-, 10.8- and 3.55-fold increase in CYP2C8, 2C9, 2C19 and 3A4/5 activity, respectively. Treatment of cultured human hepatocytes with VEC-162 had no effect on CYP1A2 activity.

In all three hepatocyte preparations tested, treatment of hepatocytes with VEC-162 caused a statistically-significant and concentration-dependent increase in CYP2C8 activity (up to 4.43-fold). VEC-162 was up to 60.3% as effective as rifampin at inducing CYP2C8 activity. The increase in activity was accompanied by a similar increase in immunoreactive CYP2C8 protein levels.

In all three hepatocyte preparations, treatment with VEC-162 caused a statistically-significant and concentration-dependent increase in CYP3A4/5 activity (up to 2.27-fold). VEC-162 was up to 83.2% as effective as rifampin at inducing CYP3A4/5 activity. The increase in CYP3A4/5 activity was accompanied by a similar increase in CYP3A4 immunoreactive protein levels.

The effect of treating cultured human hepatocytes with VEC-162 on markers of cytochrome P450: expressed as average fold-increase



§ Significance found among treatment groups (where 0.1% Dimethyl sulfoxide is the vehicle control) according to Kruskal-Wallis One Way Analysis on Ranks ($p < 0.05$) but unable to specify the groups that statistically differ from the other groups according to Dunnett's Test with positive controls.

* Significantly different from 0.1% Dimethyl sulfoxide according to Dunnett's Test ($p < 0.05$) without positive controls.

¥ Significantly different from 0.1% Dimethyl sulfoxide according to Dunnett's Test ($p < 0.05$) with positive controls.

Note: VEC-162 did not increase CYP2C9 and CYP2C19 activity but actually decreased these activities without resulting in decrease in immunoreactive protein indicating metabolism dependent inhibition. However, there was no such inhibition when VEC-162 was evaluated a direct-acting and metabolism-dependent inhibitor of these enzymes, in Study (b) (4) 065016.

CONCLUSION

VEC-162 (1-100 μ M) induces CYP2C8 and 3A4 in cultured human hepatocytes (up to 83% of that induced by rifampin)

1.20 In Vitro Evaluation of Tasimelteon and Metabolites M9, M12 and M13 as Inducers of Cytochrome P450 Expression in Cultured Human Hepatocytes

Study Title	In Vitro Evaluation of Tasimelteon and Metabolites M9, M12 and M13 as Inducers of Cytochrome P450 Expression in Cultured Human Hepatocytes
Study number	(b) (4) 123078
Study Period	Sept 2012 to Oct 2012
Study Director	(b) (4)
Objective	This study was conducted to investigate the effects of treating cultured human hepatocytes with tasimelteon and its most abundant metabolites (namely M9, M12 and M13) on the expression of cytochrome P450 (CYP) 1A2 and 2B6 enzymes. Tasimelteon's potential for inducing CYP1A2 has been previously evaluated (Study (b) (4) 063014). It is not included in this study.

METHODS

Three preparations of cultured human hepatocytes from three separate livers were treated once daily for three consecutive days with one of the following: dimethyl sulfoxide (DMSO, 0.1% v/v, vehicle control), flumazenil (50 μ M, negative control), one of three concentrations of tasimelteon (CYP2B6 analysis only), M9, M12 or M13 (1, 10 or 100 μ M), omeprazole (50 μ M, strong CYP1A2 inducer) or phenobarbital (750 μ M, strong CYP2B6 inducer). After treatment, the cells were incubated in situ with the appropriate marker substrate and analyzed by LC/MS/MS. Following the in situ incubation, the same hepatocytes from the same treatment groups were harvested with Trizol to isolate RNA, which was analyzed by qRT-PCR to assess the effect of M9, M12 and M13 on CYP1A2 mRNA as well as the effect of tasimelteon, M9, M12 and M13 on CYP2B6 mRNA levels.

RESULTS

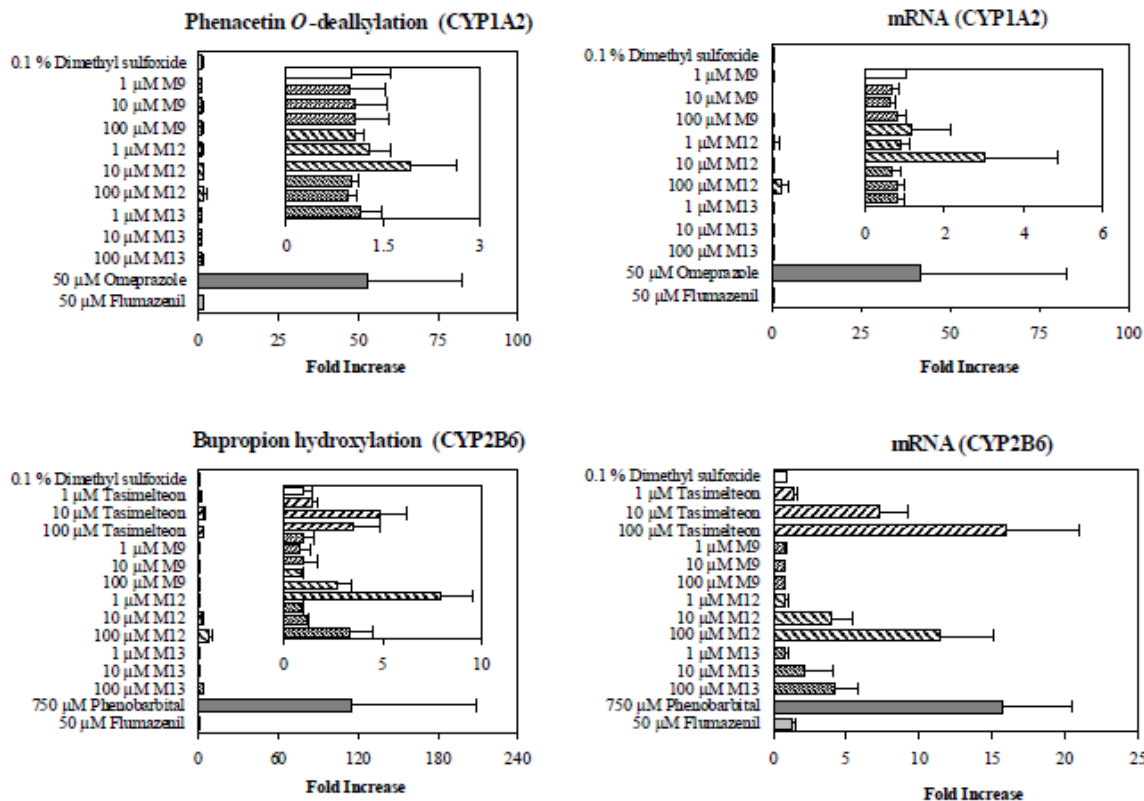
Omeprazole caused increases ranging from 19.1- to 73.6-fold and 9.35- to 88.1-fold in CYP1A2 activity and mRNA levels, respectively

Phenobarbital caused increases ranging from 10.7- to 191-fold and 11.5- to 20.9-fold in CYP2B6 activity and mRNA levels, respectively.

Treatment of human hepatocyte culture H835, H1123 and HC1-18 with up to 100 μ M M9 or M13 caused little to no change in CYP1A2 activity and mRNA levels (less than 2-fold increase). Treatment with up to 10 μ M M12 had little to no effect on CYP1A2 activity and mRNA levels (less than 2-fold increase), except for a 2.29-fold increase in CYP1A2 mRNA levels observed in one culture (H835).

Treatment with 100 μ M M12 caused a 2.71-fold increase in CYP activity in one hepatocyte culture (H835) and an increase in CYP1A2 mRNA levels in two of the hepatocyte preparations (3.40- and 4.64-fold increase).

Mean fold increase: The effects of treating cultured human hepatocytes with tasimelteon, M9, M12, M13 or prototypical inducers on cytochrome P450 (CYP) enzyme activity and mRNA levels



It should be noted that, at concentrations at or near the Sponsor reported average human maximum plasma concentrations at the 20 mg therapeutic dose) Cmax (1 to 2.5 μ M)

CONCLUSION

Tasimelteon and its most abundant metabolites (namely M9, M12 and M13) do not induce CYP1A2 or CYP2B6 enzymes at therapeutic concentration.

1.21 *In vitro Interaction Studies of Tasimelteon and Metabolites M9, M12, and M13 with the Human BCRP ABC (Efflux) Transporter, and with Human OATP1B1, OATP1B3, OCT2, OAT1 and OAT3 Uptake Transporters*

Study Title	In vitro Interaction Studies of Tasimelteon and Metabolites M9, M12, and M13 with the Human BCRP ABC (Efflux) Transporter, and with Human OATP1B1, OATP1B3, OCT2, OAT1 and OAT3 Uptake Transporters
Study number	12700
Study Period	November 2012
Study Director	(b) (4)
Objective	This study was conducted to determine the inhibitory potential of tasimelteon and metabolites M9, M12 and M13 on the human OATP1B1, OATP1B3, OCT2, OAT1 and OAT3 uptake transporters and the human BCRP efflux transporter.

METHODS

Uptake transporter inhibition and substrate assays

The inhibiting potential of a test article on the transporter is assessed by incubating the test article and a probe substrate with transporter overexpressing cells in parallel with control cells. A test article is considered to have inhibition potential on the transporter if the accumulation of probe substrate in the cells is reduced in the presence of test article. By testing the inhibition potential of the test article at several concentrations, an IC₅₀ was calculated if inhibition is observed.

Uptake inhibition assay

In the present study the in vitro interaction potential of tasimelteon, M9, M12 and M13 with the human OATP1B1, OATP1B3, OCT2, OAT1 and OAT3 uptake transporters were investigated at 7 concentrations (0.14, 0.41, 1.2, 3.7, 11, 33 and 100 µM) in uptake transporter inhibition assays.

Vesicular transport inhibition assays

The inhibiting potential of a test article on the transporter is assessed by incubating the test article and a probe substrate with transporter expressing vesicles in the presence and absence of ATP. A test article is considered to have inhibition potential on the transporter if the accumulation of probe substrate in the vesicles is reduced in the presence of test article. By testing the inhibition potential of the test article at several concentrations, an IC₅₀ was calculated if inhibition is observed.

MDCKII monolayer efflux assays

Madin-Darby Canine Kidney (MDCK) cell lines overexpressing efflux transporters are used to study interactions of compounds with the expressed transporter. A contribution of selected transporters to the drug permeability can be investigated in these MDCKII models by choosing the cell line expressing the transporter of interest. Interacting molecules display a difference in transport rates between apical to basolateral and reverse directions in cell monolayers expressing the transporter, whereas no, or significantly less, difference is observed in parental (control) cell monolayers. MDCKII-BCRP inhibition measurements were carried out at one concentration of the test articles in triplicate.

RESULTS

Inhibition of uptake transporters by tasimelteon and metabolites M9, M12, and M13.

	IC ₅₀ (μM)			
Transporter	Tasimelteon	M9	M12	M13
OATP1B1	> 100	> 100	> 100	> 100
OATP1B3	> 100	> 100	> 100	> 100
OCT2	60.1	> 100	41.3	75.2
OAT1	> 100	> 100	> 100	72.3
OAT3	34.5	6.80	> 100	37.2

Discussion

Tasimelteon and its metabolites M9, M12, and M13 were not actively transported by OATP1B1 and OATP1B3.

Tasimelteon did not inhibit OATP1B1, OATP1B3, OAT1 and BCRP. However, OCT2 and OAT3 were inhibited with an estimated IC₅₀ values of 60.1 and 34.5 M, respectively. The unbound C_{max} at the 20 mg therapeutic dose is at least 350 times lower than the 34.5 μM IC₅₀.

The metabolite M9 did not inhibit OATP1B1, OATP1B3, OCT2 and OAT1. However, OAT3 and BCRP were inhibited with IC₅₀ values of 6.8 M and 18.1 μM, respectively. The unbound C_{max} of M9 is reported to be 25-fold lower than the determined IC₅₀ for OAT3.

M12 did not inhibit OATP1B1, OATP1B3, OAT1 and OAT. However, OCT2 was inhibited with an IC₅₀ of 41.3 M, which is 585 times higher than the unbound C_{max}.

M13 did not inhibit OATP1B1, OATP1B3 and BCRP. However, OCT2, OAT1, and OAT3 were inhibited with an estimated IC₅₀ value of 75.2, 72.3 and 37.2 M, respectively, a minimum of 380 times higher than the unbound C_{max}.

CONCLUSIONS

- Tasimelteon and its metabolites M9, M12, and M13 were not actively transported by OATP1B1 and OATP1B3.
- Tasimelteon and its metabolites have low likelihood of in vivo inhibition of transporters, OATP1B1, OATP1B3, OAT1, BCRP, OCT2 and OAT3.

1.22 *P-gp Interaction Assessment of the Customer's Test Compound (VEC-162) and Metabolites*

Study Title	P-gp Interaction Assessment of the Customer's Test Compound (VEC-162) and Metabolites
Study number	10VNDAP1R1
Study Period	September 2011
Study Director	(b) (4)
Objective	This study was conducted to to assess if the test compound is a P-glycoprotein (P-gp) substrate in Caco-2 cell monolayers; and 3) to assess the P-gp inhibitor potential towards digoxin transport of the test compound in Caco-2 cells.

METHODS

P-gp Inhibitor Assessment

The bi-directional transport of digoxin was measured in the absence and presence of VEC-162, M9, M11, M12, M13, M14 or cyclosporine A (CsA). The purpose of this assay was to determine the effect of the test compound on digoxin efflux transport. CsA and ketoconazole are used as P-gp inhibitors.

A 30-minute pre-incubation with test compound and 5 μ M CsA solution was performed to preload the cells with test or control compounds. After this pre-incubation, the following procedure was performed: for AP to BL transport, 0.5 mL fresh dosing solutions of digoxin in the absence and presence of test compound or CsA were added to the AP side, and 1.5 mL of HBSSg alone, or containing test compound or CsA, was added to the BL side. For BL to AP transport, 1.5 mL dosing solutions of digoxin, in the absence and presence of test compound or CsA, were added to the BL side, and 0.5 mL of HBSSg alone, or containing test compound or CsA, was added to the AP side. Then, the Caco-2 plates were incubated in a humidified incubator ($37 \pm 1^\circ\text{C}$, $5 \pm 1\%$ CO₂) for 120 minutes. Each determination was performed in triplicate. For receiver samples, aliquots (200 μ L) were taken at 120 minutes. Aliquots (50 μ L) were taken from the donor compartment at 5 and 120 minutes.

P-gp Substrate Assessment

The P-gp substrate assessment was performed with the bidirectional permeability. The experiment was conducted in three replicates (n=3) in each AP-to-BL and BL-to-AP direction. Each compound was tested with three concentrations.

RESULTS

P-gp Inhibitor Assessment

Permeability and Recovery of Digoxin (VEC-162, M9, M11)

Treatment	Directions	Parameters	R 1	R2	R3	Average ± SD	Efflux Ratio
10 µM Digoxin + 326 µM VEC-162	AP-to-BL	P_{app} ($\times 10^{-8}$ cm/s)	1.56	0.908	1.31	1.26 ± 0.33	11.4
		Recovery (%)	70.9	66.8	75.3	71.0 ± 4.2	
	BL-to-AP	P_{app} ($\times 10^{-8}$ cm/s)	13.5	14.2	15.4	14.4 ± 1.0	
		Recovery (%)	87.7	95.6	113	98.8 ± 13	
10 µM Digoxin + 5 µM M9	AP-to-BL	P_{app} ($\times 10^{-8}$ cm/s)	0.418	0.403	0.457	0.426 ± 0.03	36.6
		Recovery (%)	67.7	64.6	72.9	68.4 ± 4.2	
	BL-to-AP	P_{app} ($\times 10^{-8}$ cm/s)	14.4	13.4	19.0	15.6 ± 3.0	
		Recovery (%)	82.0	78.8	103	88.0 ± 13	
10 µM Digoxin + 5 µM M11	AP-to-BL	P_{app} ($\times 10^{-8}$ cm/s)	1.05 ^a	0.396	0.412	0.404	62.5
		Recovery (%)	69.5 ^a	66.7	75.4	71.1	
	BL-to-AP	P_{app} ($\times 10^{-8}$ cm/s)	20.3	25.3	30.2	25.2 ± 5.0	
		Recovery (%)	79.8	86.7	107	91.2 ± 14	
10 µM Digoxin	AP-to-BL	P_{app} ($\times 10^{-8}$ cm/s)	0.737	0.862	0.833	0.811 ± 0.07	18.3
		Recovery (%)	77.4	91.8	91.5	86.9 ± 8.3	
	BL-to-AP	P_{app} ($\times 10^{-8}$ cm/s)	15.9	13.7	14.9	14.8 ± 1.1	
		Recovery (%)	94.9	90.5	105	96.8 ± 7.4	
10 µM Digoxin + 5 µM CsA	AP-to-BL	P_{app} ($\times 10^{-8}$ cm/s)	3.14	2.97	3.22	3.11 ± 0.12	1.11
		Recovery (%)	71.7	78.5	82.5	77.5 ± 5.5	
	BL-to-AP	P_{app} ($\times 10^{-8}$ cm/s)	3.45	3.54	3.35	3.45 ± 0.09	
		Recovery (%)	77.8	91.2	126.6	98.5 ± 25	

^aThe cell monolayer failed PELY test and its value was excluded from the calculation of the average.

Permeability and Recovery of Digoxin (M13)

Treatment	Directions	Parameters	R 1	R2	R3	Average ± SD	Efflux Ratio
10 µM Digoxin + 5 µM M13	AP-to-BL	P_{app} ($\times 10^{-6}$ cm/s)	0.713	0.638	0.740	0.697 ± 0.05	24.1
		Recovery (%)	76.6	65.0	68.2	69.9 ± 6.0	
	BL-to-AP	P_{app} ($\times 10^{-6}$ cm/s)	13.7	16.0	20.6	16.8 ± 3.5	
		Recovery (%)	82.0	85.5	74.2	80.6 ± 5.8	
10 µM Digoxin	AP-to-BL	P_{app} ($\times 10^{-6}$ cm/s)	0.790	0.395	0.453	0.546 ± 0.21	32.0
		Recovery (%)	56.8	56.1	59.9	57.6 ± 2.0	
	BL-to-AP	P_{app} ($\times 10^{-6}$ cm/s)	17.0	18.2	17.2	17.5 ± 0.62	
		Recovery (%)	67.4	78.0	83.3	76.2 ± 8.1	
10 µM Digoxin + 5 µM CsA	AP-to-BL	P_{app} ($\times 10^{-6}$ cm/s)	4.49	4.22	4.63	4.44 ± 0.21	1.16
		Recovery (%)	65.3	66.7	67.7	66.6 ± 1.2	
	BL-to-AP	P_{app} ($\times 10^{-6}$ cm/s)	5.91	5.08	4.49	5.16 ± 0.71	
		Recovery (%)	71.7	78.1	77.2	75.7 ± 3.5	

P-gp Substrate Assessment

Permeability and Recovery of VEC-162

Treatment	Directions	Parameters	R 1	R2	R3	Average ± SD	Efflux Ratio
0.6 µM VEC-162	AP-to-BL	P_{app} ($\times 10^{-6}$ cm/s)	26.2	56.1	15.6	32.6 ± 21	0.897
		Recovery (%)	83.2	94.1	86.2	87.8 ± 5.7	
	BL-to-AP	P_{app} ($\times 10^{-6}$ cm/s)	32.5	23.5	31.8	29.3 ± 5.0	
		Recovery (%)	89.9	99.8	100	96.6 ± 5.8	
6 µM VEC-162	AP-to-BL	P_{app} ($\times 10^{-6}$ cm/s)	20.8	16.3	21.1	19.4 ± 2.7	1.48
		Recovery (%)	80.0	87.8	102	90.1 ± 11	
	BL-to-AP	P_{app} ($\times 10^{-6}$ cm/s)	31.0	23.7	31.6	28.8 ± 4.4	
		Recovery (%)	84.0	92.7	90.1	88.9 ± 4.5	

60 μ M VEC-162	AP-to-BL	P_{app} ($\times 10^{-6}$ cm/s)	17.2 ^a	63.4	64.4	63.9	0.452
		Recovery (%)	84.9	89.1	96.9	90.3 \pm 6.1	
	BL-to-AP	P_{app} ($\times 10^{-6}$ cm/s)	27.6	29.6	29.4	28.9 \pm 1.1	
		Recovery (%)	95.5	88.8	88.8	91.1 \pm 3.9	
6 μ M VEC-162 + 5 μ M CsA	AP-to-BL	P_{app} ($\times 10^{-6}$ cm/s)	20.4	17.2	23.7	20.4 \pm 3.3	1.22
		Recovery (%)	92.3	90.4	91.5	91.4 \pm 1.0	
	BL-to-AP	P_{app} ($\times 10^{-6}$ cm/s)	27.8 ^b	22.0	27.9	24.9	
		Recovery (%)	102 ^b	85.6	94.0	93.8	

^a The value was a statistical outlier and it was excluded from the calculation of the P_{app} average.

^b The cell monolayer failed PELY test and its value was excluded from the calculation of the average.

- The efflux ratios of M9 were 0.868 and 0.698 at 1 and 5 μ M of M9. At 0.5 μ M and 1 μ M with CsA groups, since the receiver concentrations of M9 in the AP-to- BL direction were below the lower limit of quantification, an accurate efflux ratio was not obtained at these two treatments.
- In the absence of CsA, the efflux ratios of M11 were 1.52, 1.47, and 1.31 at M11 dosing concentrations of 0.5, 1, and 5 μ M. In the presence of 5 μ M CsA, the efflux ratio of M11 was 1.05.
- In the absence of CsA, the efflux ratios of M12 were 1.39, 1.34, and 1.46 at M12 dosing concentrations of 0.5, 1, and 5 μ M. In the presence of 5 μ M CsA, the efflux ratio of M12 was 1.15.
- In the absence of CsA, the efflux ratios of M13 were 1.09, 1.23, and 1.35 at M13 dosing concentrations of 0.5, 1, and 5 μ M (Table 26). In the presence of 5 μ M CsA, the efflux ratio of M13 was 1.07.
- In the absence of CsA, the efflux ratios of M14 were 1.01, 1.28, and 1.22 at M14 dosing concentrations of 0.5, 1, and 5 μ M (Table 27). In the presence of 5 μ M CsA, the efflux ratio of M14 was 1.26.
- None of the test compounds showed efflux ratios of greater than 2 at the tested concentrations where the accurate efflux ratio was available.

CONCLUSION

Tasimelteon and its major metabolites M9, M11, M12, M13 or M14 are not P-gp substrates or inhibitors.

4.3 OCP Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	205677	Brand Name	Hetlioz
OCPB Division (I, II, III)	DCP-1	Generic Name	Tasimelteon, VEC-162
Medical Division	HFD-120	Drug Class	Circadian Regulator
OCPB Reviewer	Jagan Mohan Parepally	Indication(s)	Treatment of Non-24 Hour Disorder in Totally Blind
OCPB Team Leader	Angela Men	Dosage Form	Capsules
Date of Submission	5/31/2013	Dosing Regimen	20 mg QD
Estimated Due Date of OCP Review	10/30/2013	Route of Administration	Oral
PDUFA Due Date	1/31/2014	Sponsor	Vanda
Division Due Date	11/8/2013	Priority Classification	P

Clin. Pharm. and Biopharm. Information

Summary: This NDA is to support the marketing approval of tasimelteon, a circadian regulator, proposed to reset the master body clock in the suprachiasmatic nucleus (SCN) of the hypothalamus. The activity is believed to be mediated by the affinity of tasimelteon at the MT1 and MT2 receptors in the SCN. Plasma protein binding of tasimelteon is approximately 90%. Tasimelteon is extensively metabolized primarily by oxidation at multiple sites and oxidative dealkylation. Glucuronidation is the major phase II metabolic route. 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 has many metabolites, 8 of which have been characterized - M1, M3, M8, M9, M11, M12, M13, and M14. All of these metabolites are present in plasma and M1, M3, M8, and M9 are also present in urine. M12 and M9 are present at higher plasma levels (180% and 130%, respectively) than the parent drug and M13 is present at about the same level. The pharmacokinetic profiles of the most abundant metabolites as well as other main metabolites (M3, M11, and M12) were studied in the clinical pharmacology program.

Exposure to tasimelteon and its main metabolites are affected by drugs that inhibit CYP1A2 (fluvoxamine). The exposures to tasimelteon and its main metabolites are also affected by the induction of CYP1A2 (e.g. cigarette smoking) and/ or CYP3A4 (e.g. rifampin) and in subjects with mild and moderate renal impairment - approximately 2-fold for the parent, less for the metabolites. Mild and moderate hepatic impairment resulted in a corresponding increase in exposure, as measured by AUC(inf), of 144% and 189% respectively, less for the metabolites. The geometric mean ratios (GMR) of tasimelteon C_{max} for subjects with mild or moderate hepatic impairment were 122.15% and 118.51%, respectively, as compared to healthy matched control subjects.

Food effect was evaluated using 100 mg strength capsule. At one of the EOP2 meetings we pointed out that the study should be conducted using highest strength of to-be-marketed formulation or a justification should be provided based on proportionality in composition of the formulation. The sponsor provided argument based on compositions and in vitro dissolution.

The clinical pharmacology evaluation included assessment of PK, tolerability, relative bioavailability, food effect, ADME, QTc prolongation, drug interaction and specific population studies, as summarized

below:

CN116-001 is a **single ascending dose** study evaluating safety, tolerability, PK and PD in Healthy Subjects.

CN116-002 is a **multiple ascending dose** study evaluating safety, tolerability, PK and PD in Healthy Subjects.

CN116-003 is a study comparing of the PK of single doses of tasimelteon in **young and elderly** subjects.

VP-VEC-162-1101 is a human **mass-balance** study evaluating absorption, metabolism and excretion of tasimelteon in healthy males.

VP-VEC-162-1102 is a study evaluating the **effect of food** on the absorption of 100 mg tasimelteon in healthy subjects.

VP-VEC-162-1103 is a **TQT study** defining the ECG Effects of tasimelteon using a clinical and a supratherapeutic dose compared to placebo and moxifloxacin in healthy men and women.

VP-VEC-162-1104 is a study conducted to evaluate potential PK interaction of co-administered tasimelteon at 100 mg with **midazolam** 10 mg in healthy subjects

VP-VEC-162-1105 is a study conducted to compare the PK of tasimelteon in subjects with mild or moderate **hepatic impairment** with that in matched healthy control subjects.

VP-VEC-162-1106 is a study conducted to compare the PK of tasimelteon in subjects with **renal impairment** and matched healthy control subjects.

VP-VEC-162-1107 is a study conducted to evaluate effects of **smoking status**, age and body size on the pharmacokinetics, safety, and tolerability of tasimelteon in healthy volunteers

VP-VEC-162-1108 is a study conducted to evaluate the pharmacodynamic and pharmacokinetic interactions of tasimelteon and **ethanol**

VP-VEC-162-1110 is a study conducted to evaluate the effect of multiple doses of tasimelteon on the **CYP 3A4 and 2C8** enzymes using midazolam and rosiglitazone as substrates in healthy subjects.

VP-VEC-162-1111 is a study conducted to evaluate the drug-drug interaction between tasimelteon and a **CYP1A2 inhibitor, fluvoxamine**.

VP-VEC-162-1112 is a study conducted to evaluate the drug-drug interaction between tasimelteon and a **CYP3A4 inhibitor, Ketoconazole, or a CYP3A4 inducer, rifampin**.

Phase II

VP-VEC-162-2101 is a study conducted to evaluate the effects of tasimelteon on circadian rhythm in healthy subjects. Characteristics of dose effectiveness relationship were evaluated in this **dose finding** study (10, 20, 50, and 100 mg).

Phase III

Clinical endpoints for the pivotal phase III studies, VP-VEC-162-3201 and VP-VEC-162-3203 included assessments of circadian period as measured by urinary 6-sulfatoxymelatonin (aMT6s) and urinary cortisol, nighttime sleep parameters, daytime sleep parameters, timing of sleep relative to desired bedtime and global functioning, Clinical Global Impression of Change (CGI-C).

The to-be marketed formulation is the same as the one used in clinical studies.

Dose Justification

The selection of 20 mg as the dose used in the phase III clinical studies for the Non-24 indication is based on dose-finding clinical study and a non-clinical study of chronic phase shifting/ entrainment activity.

!				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	6		
I. Clinical Pharmacology				
Mass balance:	X	1	-	VP-VEC-162-1101
Isozyme characterization:				
Blood/plasma ratio:	X	-	-	
Plasma protein binding:	X	1	-	Study 910073823
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	-	Study CN116-001
multiple dose:	X	1		Study CN116-002
Patients-				
single dose:	-	-		
multiple dose:	-	-		
Dose proportionality -				
fasting / non-fasting single dose:	X	-	-	Assessed in SD and MD studies
fasting / non-fasting multiple dose:	-	-	-	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	6	-	VP-VEC-162-1111 (Fluoxetine) , VP-VEC-162-1107 (Smoking), VP-VEC-162-1112 (Ketoconazole, Rifampin), VP-VEC-162-1108 (Ethanol), Study 1104 and Study 1110 (3A4 and 2C8)
In-vivo effects of primary drug:	-	-	-	
In-vitro:	X	9	-	Study 1101, Study BMS-10Nov97, Study (b) (4) 08639, Study (b) (4) 12A024, Study (b) (4) 065016, Study (b) (4) 063014, Study (b) (4) 135015, Study 10VNDAP1R1, and (b) (4) 12700
Subpopulation studies -				
ethnicity:	-	-	-	
gender:	X	1	-	Study CN116-003
pediatrics:	-	-	-	
geriatrics:				
renal impairment:	X	1	-	VP-VEC-162-1106
hepatic impairment:	X	1	-	VP-VEC-162-1105
PD:				
Phase 1:	-	-	-	
Phase 2:	X	1	-	VP-VEC-162-2101
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	-	-	Phase 2 dose-ranging study (VP-VEC-162-2101)
Phase 3 clinical trial:	X	-	-	Studies VP-VEC-162-3201 and VP-VEC-162-3203
Population Analyses -				
Data rich:	X	-	-	Study 1105, Study 1106, Study 1107, and Study 1110
Data sparse:	-	-	-	
II. Biopharmaceutics				
Absolute bioavailability:	-	-	-	

Relative bioavailability -	-	-		
solution as reference:				
alternate formulation as reference:	-	-		Study VP-VEC-162-1101
Bioequivalence studies -				
traditional design; single / multi dose:	-	-		
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		VP-VEC-162-1102
Dissolution:	-	-	-	
(IVIVC):				
In vivo alcohol dose dumping	-	-	-	
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
TQT	X	1	-	VP-VEC-162-1103
Literature References	X	-	-	
Total Number of Studies		16 + 10 in vitro + Bioanalytical		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm?		None		
QBR questions (key issues to be considered)	Is there a need for tasimelteon dose adjustment for subjects with hepatic or renal impairment? Is the Clinical Pharmacology of tasimelteon adequately characterized? Is dose selection for Non-24 indication in totally blind adequately supported?			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR	X			

	requirements?				
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

CC: NDA 205677 HFD-850 (Electronic Entry), HFD-120, HFD-860 (Jagan Parepally, Angela Men, Ramana

Uppoor, Mehul Mehta)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAGAN MOHAN R PAREPALLY
11/07/2013

YUXIN MEN
11/07/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment															
Application No.:	NDA 205-677	Reviewer: Kareen Riviere, Ph.D.													
Submission Dates:	5/31/13; 8/20/13; 10/10/13; 10/25/13														
Division:	DNP	Acting Biopharmaceutics Team Leader: Sandra Suarez, Ph.D.													
Applicant:	Vanda Pharmaceuticals	Biopharmaceutics Supervisor: Richard Lostritto, Ph.D.													
Trade Name:	Hetlio	Date Assigned:	6/4/13												
Generic Name:	tasimelteon	Date of Review:	10/30/13												
Indication:	Treatment of Non-24-Hour Disorder in the totally blind	Type of Submission: 505(b)(1) Original NDA													
Formulation/strengths:	IR Capsule/ 20 mg														
Route of Administration:	Oral														
<p>SUMMARY:</p> <p>Submission: This submission is a 505(b)(1) New Drug Application for 20 mg tasimelteon immediate release capsules. The proposed indication is for the treatment of Non-24-Hour Disorder in the totally blind.</p> <p>Review: The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of 1) the proposed dissolution methodology, 2) the proposed dissolution acceptance criterion.</p> <p>A. Dissolution Method</p> <p>The proposed dissolution method is shown below.</p> <table border="1"> <thead> <tr> <th>USP Apparatus</th> <th>Rotation Speed</th> <th>Media Volume</th> <th>Temp</th> <th>Medium</th> </tr> </thead> <tbody> <tr> <td>II</td> <td>50 rpm</td> <td>500 mL</td> <td>37 °C</td> <td>0.1 N HCl</td> </tr> </tbody> </table> <p>The proposed dissolution method is deemed acceptable.</p> <p>B. Dissolution Acceptance Criterion</p> <p>The proposed acceptance criterion is shown below.</p> <table border="1"> <thead> <tr> <th>Acceptance Criterion</th> </tr> </thead> <tbody> <tr> <td>Q = (b) (4)</td> </tr> </tbody> </table> <p>The proposed dissolution acceptance criterion is not supported by the data and is not acceptable. Therefore, in an IR letter to the Applicant dated September 20, 2013, the ONDQA Biopharmaceutics Team recommended a dissolution acceptance criterion of Q = (b) (4) at 15 minutes based on the mean in-vitro dissolution profiles of the pivotal clinical and primary stability batches at release and 12 month stability. In a submission dated October 25, 2013, the Applicant</p>				USP Apparatus	Rotation Speed	Media Volume	Temp	Medium	II	50 rpm	500 mL	37 °C	0.1 N HCl	Acceptance Criterion	Q = (b) (4)
USP Apparatus	Rotation Speed	Media Volume	Temp	Medium											
II	50 rpm	500 mL	37 °C	0.1 N HCl											
Acceptance Criterion															
Q = (b) (4)															

submitted a revised specifications sheet reflecting the recommended dissolution acceptance criterion.

C. Evaluation of Data to Support BCS Class (b) (4) Designation

The solubility and dissolution data demonstrate that the drug substance is (b) (4) soluble and the proposed product is (b) (4). However, the Clinical Pharmacology reviewer, Dr. Jagan Parepally, has not yet determined as of October 30, 2013 whether the drug substance can be classified as (b) (4) permeable. Thus, the determination of BCS Class (b) (4) Designation for this proposed product is still pending.

RECOMMENDATION:

1. Hetlioz (tasimelteon) capsules, 20 mg is recommended for approval from a Biopharmaceutics standpoint.
 - The following dissolution method and acceptance criterion are recommended and have been agreed upon with the Applicant (submission dated October 25, 2013):
 - i. Dissolution method: Apparatus II, 50 rpm agitation rate, 500 mL media volume, 37 °C, 0.1 N HCl.
 - ii. Acceptance criterion: $Q = (b) (4)$ at 15 minutes.

Kareen Riviere, Ph.D.

Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Sandra Suarez, Ph.D.

Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Dr. Richard Lostritto

ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

1. Background

Drug Substance

The structure of tasimelteon is shown in Figure 1. The applicant reports that tasimelteon is BCS Class **b** compound.

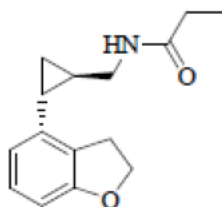


Figure 1. Chemical structure of tasimelteon

The solubility of tasimelteon at pH 1, 4.6, and 7.6 is shown in Table 1.

Table 1. Solubility of Tasimelteon at 37°C

pH	Media	Average Solubility at 37 °C (mg/ml)
1.0	0.1 N HCl	1.5
4.6	0.1N Sodium Acetate Buffer	1.5
7.6	0.1N Sodium Phosphate Buffer	1.2

Reviewer's Assessment:

From these data, it can be concluded that the solubility of tasimelteon is not pH dependent in the physiological pH range. For sink conditions to be achieved, the solubility of tasimelteon needs to be at least (b) (4) in the proposed medium. Hence, sink conditions are achieved in the physiological pH range. Less than (b) (4) of aqueous buffer with pH 1-7.6 is required to dissolve 20 mg of tasimelteon.

Drug Product

The composition of the proposed drug product is shown below.

Table 2. Composition of 20 mg Tasimelteon IR Capsule

Component	Function	Quantitative composition weight per capsule (mg)
Tasimelteon drug substance	Active ingredient	20.00 ¹
Lactose anhydrous		(b) (4)
Microcrystalline cellulose (b) (4)		
Colloidal silicon dioxide		
Croscarmellose sodium		
Magnesium stearate (b) (4)		
(b) (4)		
Size 1, dark blue opaque, hard gelatin capsules printed with "VANDA 20 mg" in white ²		
Total capsule weight for size 1	NA	376.00

2. Dissolution Method

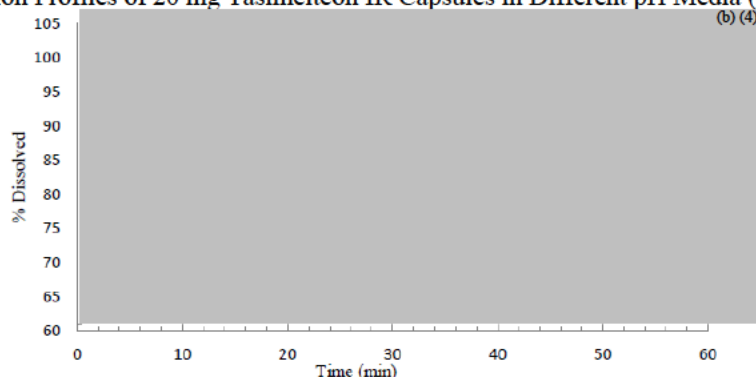
The proposed dissolution method is shown below.

USP Apparatus	Rotation Speed	Media Volume	Temperature	Medium
2	50 rpm	500 mL	37 °C	0.1 N HCl

Effect of Dissolution Medium

The Applicant evaluated the dissolution profiles of tasimelteon 20 mg capsules in four different dissolution media: (b) (4)

Figure 2. Dissolution Profiles of 20 mg Tasimelteon IR Capsules in Different pH Media (500 mL volume)



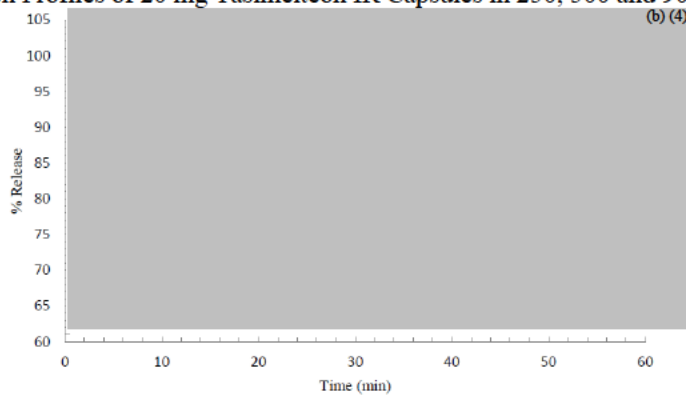
Reviewer's Assessment:

The data in Table 1 confirm that the solubility of tasimelteon is (b) (4). The 20 mg tasimelteon IR capsules (b) (4) in all the media tested. Thus, the Applicant's selection for the proposed dissolution medium (0.1 N HCl) is acceptable.

Effect of Dissolution Medium Volume

The Applicant generated dissolution profiles using (b) (4) 500 and (b) (4) mL of 0.1N HCl. These data are presented in Figure 3.

Figure 3. Dissolution Profiles of 20 mg Tasimelteon IR Capsules in 250, 500 and 900 mL of 0.1N HCl



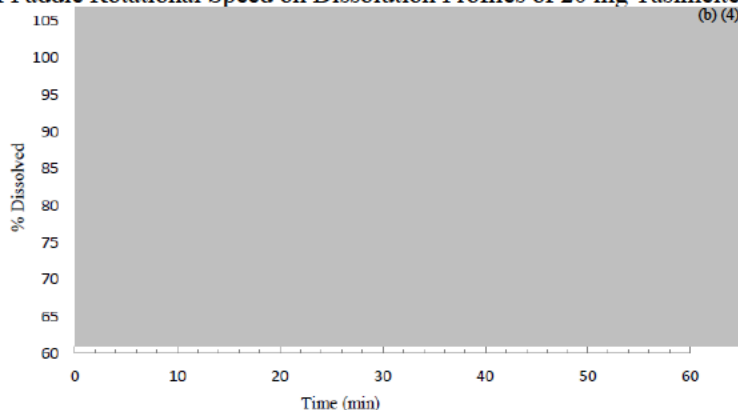
Reviewer's Assessment:

Figure 3 shows that 20 mg tasimelteon capsules (b) (4) in all the volumes tested. Therefore, the Applicant's selection of 500 mL for the dissolution medium volume is acceptable.

Effect of Rotation Speed and Apparatus

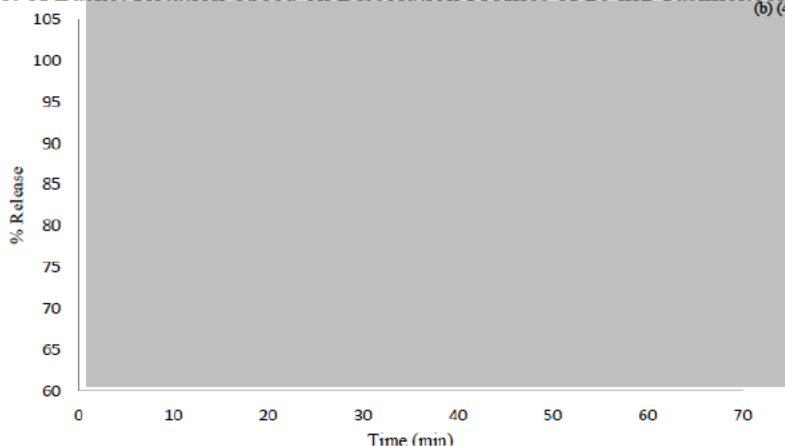
The effect of the paddle rotation speed on the dissolution profile was evaluated. The Applicant tested rotational speeds of 50 (b) (4) rpm in 500 mL of 0.1N HCl (refer to Figure 4).

Figure 4. Effect of Paddle Rotational Speed on Dissolution Profiles of 20 mg Tasimelteon IR Capsules



The Applicant also evaluated the basket apparatus at (b) (4) agitation speeds. Testing was performed using 500 mL of 0.1N HCl using basket rotation speeds of (b) (4).

Figure 5. Effect of Basket Rotation Speed on Dissolution Profiles of 20 mg Tasimelteon IR Capsules



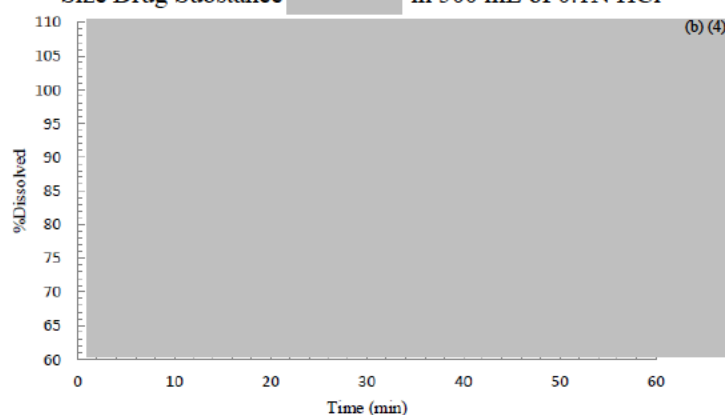
Reviewer's Assessment:

Figure 4 and 5 show that the dissolution profile of 20 mg tasimelteon capsules is similar using either the basket or paddle at the speeds tested. Hence, the Applicant's selection of 50 rpm paddle speed is acceptable.

Discriminating Ability

The Applicant evaluated the effect of drug substance particle size on dissolution. Note that the proposed particle size acceptance criterion is $D_{10} = \text{NMT } (b) (4)$, $D_{50} = \text{NMT } (b) (4)$ and $D_{90} = \text{NMT } (b) (4)$. A comparison of the dissolution profiles in 500mL of 0.1N HCl for the capsules containing different particle size (b) (4) is presented in Figure 6.

Figure 6. Dissolution Profiles for 20 mg Tasimelteon IR Capsules Containing Different Particle Size Drug Substance (b) (4) in 500 mL of 0.1N HCl



Reviewer's Assessment:

Figure 6 demonstrates that the proposed dissolution method can discriminate changes in drug substance particle size. Overall, the proposed dissolution method is deemed acceptable.

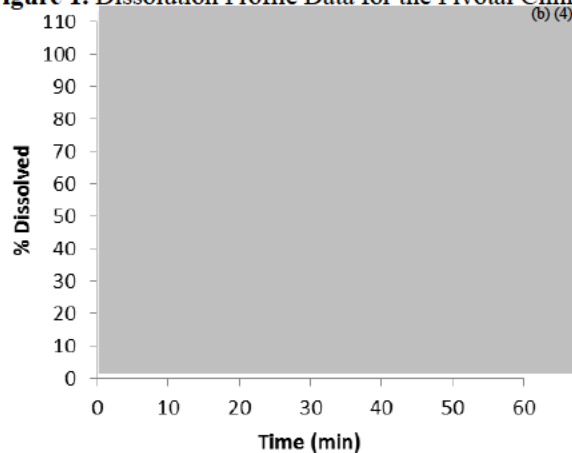
3. Dissolution Acceptance Criterion

The proposed dissolution acceptance criterion is shown below.

Acceptance Criterion	
Q =	(b) (4)

Dissolution profile data for the pivotal phase 3 clinical batches are shown in Reviewer's Figure 1.

Reviewer's Figure 1. Dissolution Profile Data for the Pivotal Clinical Batches



Reviewer's Assessment:

The proposed dissolution acceptance criterion is not supported by the data and therefore is not acceptable. The following IR comment was conveyed to the Applicant in a letter dated September 20, 2013.

FDA Comment

Your proposed dissolution criterion of Q = (b) (4) is not supported by the provided data and is not acceptable. Your dissolution data from the clinical and primary stability batches at

release and under long term stability (12 months) support an acceptance criterion of $Q = (b) (4)$ at 15 minutes. Implement this change and provide a revised drug product specification table incorporating the updated dissolution acceptance criterion.

The following IR comment was conveyed to the Applicant in a letter dated October 17, 2013 in response to their proposal of $Q = (b) (4)$

FDA Comment

We do not agree with your proposal of $Q = (b) (4)$. Your product is $(b) (4)$ and the dissolution data from the clinical and primary stability batches at release and under long term stability (12 months) support an acceptance criterion of $Q = (b) (4)$ at 15 minutes. Nevertheless, it must be recognized that some batches may require Stage 2 and, occasionally, Stage 3 testing.

Accordingly, please implement the dissolution acceptance criterion of $Q = (b) (4)$ at 15 minutes and provide the revised specification table for your drug product.

In a submission dated October 25, 2013, the Applicant accepted the recommendation to revise the dissolution acceptance criterion.

4. Dissolution Data to Bridge 20 mg and 100 mg Formulation used in Study 1102

The Applicant conducted Study 1102, a food effect study, with a 100 mg capsule, not the 20 mg strength commercial formulation. Table 3 compares the composition of tasimelteon capsules used in clinical studies.

Table 3. Composition of Tasimelteon Capsules used in Clinical Studies

Component	Reference to quality	Quantitative formula weight per capsule (mg)	
		(b) (4)	20 (b) (4)
Tasimelteon drug substance	Vanda (Section 3.2.S.4.1)	(b) (4)	(b) (4)
Lactose anhydrous	NF		
Microcrystalline cellulose (b) (4)	USP/EP/JP		
Colloidal silicon dioxide	NF/EP/JP		
Croscarmellose sodium	NF/EP/JP		
Magnesium stearate (b) (4)	NF/EP/JP		
Total fill weight			300.00

The Applicant performed a dissolution profile comparison study in four different dissolution media. The comparative dissolution profile data at 15 minutes are presented in Table 4.

Table 4. Comparative Dissolution Data for 20 mg and 100 mg Tasimelteon Capsules

Dissolution Medium	Percent of Label Claim Dissolved at 15 Minutes*	
	(b) (4)	(b) (4)

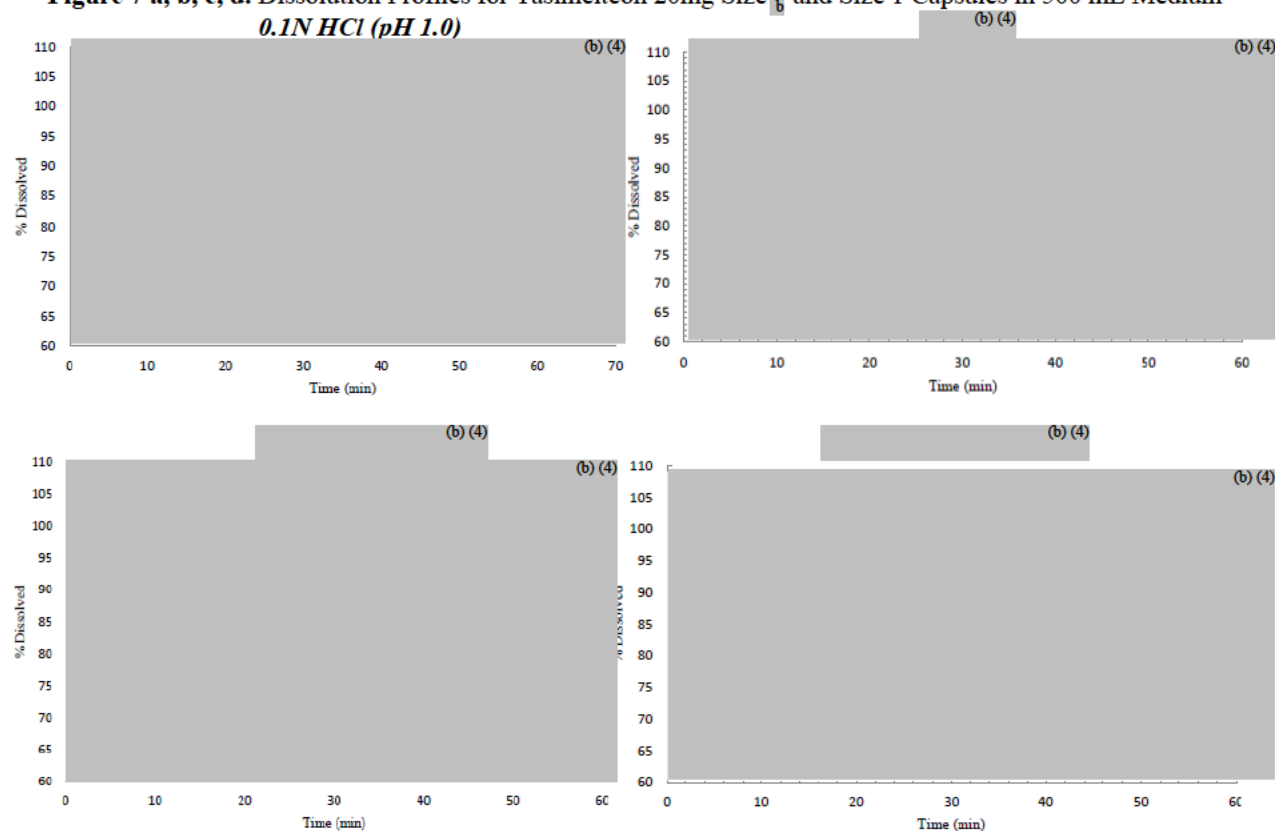
Reviewer's Assessment:

The dissolution data show that the 20 mg and 100 mg formulation (b) (4) in the physiological pH range. Therefore, the 20 mg and 100 mg formulation have similar dissolution rates. However, the 20 mg and 100 mg strengths are (b) (4). Thus, from the Biopharmaceutics perspective, in vitro dissolution data can not be used to bridge the 20 mg and 100 mg formulation. The Clinical Pharmacology reviewer, Dr. Jagan Parepally, will determine whether the food effect data generated with the 100 mg capsule formulation will be extrapolated to the 20 mg strength commercial product.

5. Dissolution Profile Comparison of Size (b) (4) and Size 1 Capsules

The Applicant changed the capsule size from size (b) (4) to size 1 and performed a dissolution profile comparison study in four different dissolution media: 0.1 N HCl, (b) (4). The comparative dissolution profile data are shown in Figure 7 a, b, c, d.

Figure 7 a, b, c, d. Dissolution Profiles for Tasimelteon 20mg Size (b) (4) and Size 1 Capsules in 500 mL Medium 0.1N HCl (pH 1.0)



Reviewer's Assessment:

Figure 7 shows that for both capsule sizes, the dissolution rate was (b) (4) dissolved prior to the 15-minute sample regardless of the dissolution medium. Thus, the dissolution of the proposed drug product is considered similar in Size (b) (4) and Size 1 capsules.

6. Evaluation of Data to Support BCS Class (b) (4) Designation

The solubility and dissolution data demonstrate that the proposed drug substance is (b) (4) and the drug product is (b) (4). However, the Clinical Pharmacology reviewer, Dr. Jagan Parepally, has not yet determined whether the drug substance has (b) (4) at the time of this review. Thus, the determination of BCS Class (b) (4) Designation for this proposed product is still pending.

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/s/

KAREEN RIVIERE
10/30/2013

SANDRA SUAREZ
10/30/2013

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	205677	Brand Name	Hetlioz
OCPB Division (I, II, III)	DCP-1	Generic Name	Tasimelteon
Medical Division	HFD-120	Drug Class	Circadian Regulator
OCPB Reviewer	Jagan Mohan Parepally	Indication(s)	Treatment of Non-24 Hour Disorder in Totally Blind
OCPB Team Leader	Angela Men	Dosage Form	Capsules
Date of Submission	5/31/2013	Dosing Regimen	20 mg QD
Estimated Due Date of OCP Review	10/30/2013	Route of Administration	Oral
PDUFA Due Date	1/31/2014	Sponsor	Vanda
Division Due Date	11/8/2013	Priority Classification	P

Clin. Pharm. and Biopharm. Information

Summary: This NDA is to support the marketing approval of tasimelteon, a circadian regulator, proposed to reset the master body clock in the suprachiasmatic nucleus (SCN) of the hypothalamus. The activity is believed to be mediated by the affinity of tasimelteon at the MT1 and MT2 receptors in the SCN. Plasma protein binding of tasimelteon is approximately 90%. Tasimelteon is rapidly and extensively metabolized primarily by oxidation at multiple sites and oxidative dealkylation. Glucuronidation is the major phase II metabolic route. 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 has many metabolites, 8 of which have been characterized - M1, M3, M8, M9, M11, M12, M13, and M14. All of these metabolites are present in plasma and M1, M3, M8, and M9 are also present in urine. M12 and M9 are present at higher plasma levels (160% and 95%, respectively) than the parent drug and M13 is present at about 92%. The pharmacokinetic profiles of the most abundant metabolites as well as other main metabolites (M3, M11, and M12) were studied in the clinical pharmacology program.

Exposure to tasimelteon and its main metabolites are affected by drugs that inhibit CYP1A2 (fluvoxamine). The exposures to tasimelteon and its main metabolites are also affected by the induction of CYP1A2 (e.g. cigarette smoking) and/ or CYP3A4 (e.g. rifampin) and in subjects with mild and moderate renal impairment - approximately 2-fold for the parent, less for the metabolites. Mild and moderate hepatic impairment resulted in a corresponding increase in exposure, as measured by AUC(inf), of 144% and 189% respectively, less for the metabolites. The geometric mean ratios (GMR) of tasimelteon Cmax for subjects with mild or moderate hepatic impairment were 122.15% and 118.51%, respectively, as compared to healthy matched control subjects.

Food effect was evaluated using 100 mg strength capsule. At one of the EOP2 meetings we pointed out that the study should be conducted using highest strength of to-be-marketed formulation or a justification should be provided based on proportionality in composition of the formulation. The sponsor provided argument based on compositions and in vitro dissolution.

The clinical pharmacology evaluation included assessment of PK, tolerability, relative bioavailability, food effect, ADME, QTc prolongation, drug interaction and specific population studies, as summarized below:

CN116-001 is a **single ascending dose** study evaluating safety, tolerability, PK and PD in Healthy

Subjects.

CN116-002 is a **multiple ascending dose** study evaluating safety, tolerability, PK and PD in Healthy Subjects.

CN116-003 is a study comparing of the PK of single doses of tasimelteon in **young and elderly** subjects.

VP-VEC-162-1101 is a human **mass-balance** study evaluating absorption, metabolism and excretion of tasimelteon in healthy males.

VP-VEC-162-1102 is a study evaluating the **effect of food** on the absorption of 100 mg tasimelteon in healthy subjects.

VP-VEC-162-1103 is a **TQT study** defining the ECG Effects of tasimelteon using a clinical and a supratherapeutic dose compared to placebo and moxifloxacin in healthy men and women.

VP-VEC-162-1104 is a study conducted to evaluate potential PK interaction of co-administered tasimelteon at 100 mg with **midazolam** 10 mg in healthy subjects

VP-VEC-162-1105 is a study conducted to compare the PK of tasimelteon in subjects with mild or moderate **hepatic impairment** with that in matched healthy control subjects.

VP-VEC-162-1106 is a study conducted to compare the PK of tasimelteon in subjects with **renal impairment** and matched healthy control subjects.

VP-VEC-162-1107 is a study conducted to evaluate effects of **smoking status**, age and body size on the pharmacokinetics, safety, and tolerability of tasimelteon in healthy volunteers

VP-VEC-162-1108 is a study conducted to evaluate the pharmacodynamic and pharmacokinetic interactions of tasimelteon and **ethanol**

VP-VEC-162-1110 is a study conducted to evaluate the effect of multiple doses of tasimelteon on the **CYP 3A4 and 2C8** enzymes using midazolam and rosiglitazone as substrates in healthy subjects.

VP-VEC-162-1111 is a study conducted to evaluate the drug-drug interaction between tasimelteon and a **CYP1A2 inhibitor, fluvoxamine**.

VP-VEC-162-1112 is a study conducted to evaluate the drug-drug interaction between tasimelteon and a **CYP3A4 inhibitor, Ketoconazole, or a CYP3A4 inducer, rifampin**.

Phase II

VP-VEC-162-2101 is a study conducted to evaluate the effects of tasimelteon on circadian rhythm in healthy subjects. Characteristics of dose effectiveness relationship were evaluated in this **dose finding** study (10, 20, 50, and 100 mg).

Phase III

Clinical endpoints for the pivotal phase III studies, VP-VEC-162-3201 and VP-VEC-162-3203 included assessments of circadian period as measured by urinary 6-sulfatoxymelatonin (aMT6s) and urinary cortisol, nighttime sleep parameters, daytime sleep parameters, timing of sleep relative to desired bedtime and global functioning, Clinical Global Impression of Change (CGI-C).

The to-be marketed formulation is the same as the one used in clinical studies.

Dose Justification

The selection of 20 mg as the dose used in the phase III clinical studies for the Non-24 indication is based on dose-finding clinical study and a non-clinical study of chronic phase shifting/ entrainment activity.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				

Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	6		
I. Clinical Pharmacology				
Mass balance:	X	1	-	VP-VEC-162-1101
Isozyme characterization:				
Blood/plasma ratio:	X	-	-	
Plasma protein binding:	X	1	-	Study 910073823
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	-	Study CN116-001
multiple dose:	X	1		Study CN116-002
Patients-				
single dose:	-	-		
multiple dose:	-	-		
Dose proportionality -				
fasting / non-fasting single dose:	X	-	-	Assessed in SD and MD studies
fasting / non-fasting multiple dose:	-	-	-	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	6	-	VP-VEC-162-1111 (Fluoxetine) , VP-VEC-162-1107 (Smoking), VP-VEC-162-1112 (Ketoconazole, Rifampin), VP-VEC-162-1108 (Ethanol), Study 1104 and Study 1110 (3A4 and 2C8)
In-vivo effects of primary drug:	-	-	-	
In-vitro:	X	9	-	Study 1101, Study BMS-10Nov97, Study (b) (4) 08639, Study (b) (4) 12A024, Study (b) (4) 065016, Study (b) (4) 063014, Study (b) (4) 135015, Study 10VNDAP1R1, and (b) (4) 12700
Subpopulation studies -				
ethnicity:	-	-	-	
gender:	X	1	-	Study CN116-003
pediatrics:	-	-	-	
geriatrics:				
renal impairment:	X	1	-	VP-VEC-162-1106
hepatic impairment:	X	1	-	VP-VEC-162-1105
PD:				
Phase 1:	-	-	-	
Phase 2:	X	1	-	VP-VEC-162-2101
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	-	-	Phase 2 dose-ranging study (VP-VEC-162-2101)
Phase 3 clinical trial:	X	-	-	Studies VP-VEC-162-3201 and VP-VEC-162-3203
Population Analyses -				
Data rich:	X	-	-	Study 1105, Study 1106, Study 1107, and Study 1110
Data sparse:	-	-	-	
II. Biopharmaceutics				
Absolute bioavailability:	-	-	-	
Relative bioavailability -	-	-		

solution as reference:							
alternate formulation as reference:	-	-		Study VP-VEC-162-1101			
Bioequivalence studies -							
traditional design; single / multi dose:	-	-					
replicate design; single / multi dose:							
Food-drug interaction studies:	X	1		VP-VEC-162-1102			
Dissolution:	-	-	-				
(IVIVC):							
In vivo alcohol dose dumping	-	-	-				
BCS class							
III. Other CPB Studies							
Genotype/phenotype studies:	-	-	-				
Chronopharmacokinetics	-	-	-				
TQT	X	1	-	VP-VEC-162-1103			
Literature References	X	-	-				
Total Number of Studies		16 + 10 in vitro + Bioanalytical					
Filability and QBR comments							
	"X" if yes	Comments					
Application filable?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?					
Comments sent to firm?		None					
QBR questions (key issues to be considered)	Is there a need for tasimelteon dose adjustment for subjects with hepatic or renal impairment? Is the Clinical Pharmacology of tasimelteon adequately characterized? Is dose selection for Non-24 indication in totally blind adequately supported?						
Other comments or information not included above							
Primary reviewer Signature and Date							
Secondary reviewer Signature and Date							

On initial review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			

6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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/s/

JAGAN MOHAN R PAREPALLY
10/01/2013

YUXIN MEN
10/01/2013

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	205-667
Submission Date	5/31/2013
Product name, generic name of the active	Hetlioz (tasimelteon)
Dosage form and strength	IR Capsule/ 20 mg
Applicant	Vanda Pharmaceuticals
Clinical Division	DNP
Indication	Treatment of Non-24-Hour Disorder in the totally blind
Type of Submission	505(b)(1) Original NDA
Biopharmaceutics Reviewer	Kareen Riviere, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.
Acting Biopharmaceutics Supervisor	Richard Lostritto, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS <u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?	x		
2.	Is the dissolution test part of the DP specifications?	x		Refer to the Initial Assessment.
3.	Does the application contain the dissolution method development report?	x		
4.	Is there a validation package for the analytical method and dissolution methodology?	x		
5.	Does the application include a biowaiver request?		x	Not Applicable.
6.	Is there information provided to support the biowaiver request?		x	Not Applicable.
7.	Does the application include an IVIVC model?		x	Not Applicable.
8.	Is information such as BCS classification mentioned, and supportive data provided?	x		The Applicant reports that tasimelteon is a BCS Class ^(b) compound. A comment will be conveyed to the Applicant to clarify whether they are requesting BCS Class ^(b) designation.
9.	Is information on mixing the product with foods or liquids included?		x	Not Applicable.
10.	Is there any <i>in vivo</i> BA or BE information in the submission?	x		There are several PK studies that will be reviewed by the Clinical Pharmacology reviewer.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
11.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	x		
12.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.	-	-	
13.	Are there any potential review issues to be forwarded to the Applicant?	x		IR comments will be sent to the Applicant prior to the 74 day letter. The comments are outlined in the Initial Assessment.

{See appended electronic signature page}

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

7/11/13
Date

{See appended electronic signature page}

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

7/11/13
Date

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

INITIAL ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

This submission includes a drug product development section with the proposed dissolution method, the proposed dissolution acceptance criterion, and dissolution data bridging the 20 mg commercial product with the 100 mg formulation used in Study 1102 (a food effect study). Note that the 20 mg and 100 mg strengths are (b) (4). There are PK, efficacy, and safety data/information on the to-be marketed 20 mg strength commercial product.

The proposed dissolution method is:

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	50 rpm	500 mL	37 °C	0.1 N HCl

The proposed acceptance criterion is:

Acceptance Criterion
Q = (b) (4)

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of 1) the proposed dissolution methodology, 2) the proposed dissolution acceptance criterion, and 3) dissolution data to bridge the 20 mg commercial product with the 100 mg formulation used in Study 1102 (a food effect study).

Although the Applicant claims that tasimelteon is a BCS Class II compound, it is unclear whether the Applicant is requesting BCS Class II designation for the drug product. If the Applicant is requesting BCS Class II designation for the drug product, the Biopharmaceutics review will also focus on the evaluation and acceptability of the data/information to support this designation.

RECOMMENDATION:

The ONDQA Biopharmaceutics team has reviewed NDA 205677 for filing purposes. We found this NDA **fileable** from a Biopharmaceutics perspective. The Applicant has submitted a reviewable submission.

To aid the review of the NDA submission, the following comments will be conveyed to the Applicant:

1. Provide complete dissolution profile data (raw data and mean values) from the pivotal clinical and primary stability batches supporting the selection of the proposed dissolution acceptance criteria (i.e., specification-sampling time points and values) for your proposed product.
2. Clarify whether you are requesting FDA to designate your proposed product as a BCS Class II drug product. Note that solubility, permeability, gastric stability, and dissolution data will be needed to support the BCS-Class II designation for your product. For the specific information/data that are needed to classify your proposed product, please refer to the attached BCS document and the BCS guidance (link is below).

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070246.pdf>

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/s/

KAREEN RIVIERE
07/11/2013

ANGELICA DORANTES
07/11/2013