Pharmacokinetics of the Dual Melatonin Receptor Agonist Tasimelteon in Subjects With Hepatic or Renal Impairment

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Abstract

Tasimelteon is a circadian regulator that resets the master clock in the suprachiasmatic nuclei of the hypothalamus by binding to both melatonin MT_1 and MT_2 receptors making it a dual melatonin receptor agonist. Tasimelteon has been approved by the United States Food and Drug Administration for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24). Two prospective, single-center, open-label studies evaluated the pharmacokinetics of tasimelteon and its main metabolites after a single 20 mg dose administered to subjects with mild or moderate hepatic impairment or severe renal impairment, including subjects on dialysis compared to healthy controls. In subjects with mild or moderate hepatic impairment, exposure to tasimelteon after a single 20 mg dose, as measured by area under the plasma concentration-time curve to infinity, was increased by approximately 2-fold. There was no apparent relationship between tasimelteon clearance and renal function. No safety concerns were apparent in either study. Based on these results, the changes in the pharmacokinetics of tasimelteon due to mild or moderate hepatic or severe renal impairment are not considered clinically relevant, and no dose adjustment is necessary in these patients.

Keywords

The endogenous circadian pacemaker resides in the suprachiasmatic nucleus (SCN) of the hypothalamus, and its function is to regulate biological functions in an approximate, but not exact, 24-hour cycle. Circadian rhythms must be synchronized or entrained to the 24-hour day by exposure to environmental synchronizers, of which light is the most important.[1–7] Light entrains the circadian pacemaker through a set of specialized intrinsically photosensitive retinal ganglion cells. These specialized cells detect the light and send signals to the SCN via the retinohypothalamic tract which, in turn, synchronizes the circadian pacemaker to the 24-hour light-dark cycle.[8,9] Non-24-Hour Sleep-Wake Disorder (Non-24) is a serious, rare, circadian rhythm disorder caused by the inability of ocular photoreception to reset the circadian pacemaker to the 24-hour light-dark cycle. As a result of light information failing to reach the SCN to synchronize the circadian pacemaker and its outputs, the circadian pacemaker reverts to its endogenous non-24-hour period.[5,6,7,10] Consequently, the timing of physiology and behavior that is controlled by the circadian system—for example, the timing of melatonin and cortisol production, the core body temperature rhythm, metabolic processes, the sleep-wake cycle, and alertness and performance patterns—become desynchronized from the 24-hour day, leading to the pacemaker and the 24-hour day oscillating in and out of phase. This desynchrony has a significant impact on patients, including episodes of excessive daytime sleepi-

ness and/or nighttime sleep disruption.[5,6,11,12] Non-24 occurs in both sighted and nonsighted individuals, but it is most prevalent in totally blind individuals, with a prevalence of up to 70.0%.[13,14] Tasimelteon was approved by the United States Food and Drug Administration (FDA) in January 2014 for the treatment of Non-24. Tasimelteon is the first approved therapy for Non-24.

Daily dosing with tasimelteon resets the circadian pacemaker in the SCN. This activity is believed to be mediated by specific and high affinity of tasimelteon to the MT_1 and MT_2 receptors. Tasimelteon exhibits a greater affinity for the MT_2 receptor than it does for the MT_1 receptor.[15] The major metabolites of tasimelteon are M9, M11, M12, M13, and M14. M9 is a phenol-

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carboxylic acid derivative of tasimelteon. M11 is a hydroxy-phenol tasimelteon. M12 and M14 are α- and β-isomers of 8-hydroxy tasimelteon. M13 is a mixture of α- and β-isomers of 7-hydroxy tasimelteon. These metabolites also bind to the melatonin receptors but have 13-fold or less activity compared with that of tasimelteon.[16] Therefore, the metabolites of tasimelteon do not contribute to its efficacy. Tasimelteon and its major metabolites have no appreciable affinity for more than 160 other pharmacologically relevant receptors.[15] This includes the gamma-aminobutyric acid receptor complex, the binding site for sedative hypnotics, and receptors that bind neuropeptides, cytokines, serotonin, noradrenaline, acetylcholine, and opiates. Tasimelteon is rapidly and extensively metabolized, primarily by the isozymes CYP1A2 and CYP3A. CYP1A1, CYP2C9/19, and CYP2D6 also minimally contribute to the metabolism of tasimelteon[17] (Ogilvie BW, Torres R, Dressman MA, Kramer WG, Baroldi P, unpublished data, 2014).

Tasimelteon is highly metabolized and mainly excreted in urine as metabolites. In a mass balance study, less than 1.0% of the administered dose was recovered as unchanged tasimelteon. In contrast, mean recovery of total radioactivity in urine was 80.4%, with 3.7% of the radioactive dose recovered in feces. Total recovery in urine and feces combined was 84.1%. The observed mean elimination half-life ($t_{1/2}$) was 1.3 hours.[16] Tasimelteon has a mean absolute bioavailability of approximately 38.3%.

Clinical studies demonstrated that the pharmacokinetics of tasimelteon is dose proportional and linear over single doses ranging from 3 to 300 mg. The efficacy and safety of 20 mg tasimelteon has been demonstrated in 2 phase III clinical studies: Safety and Efficacy of Tasimelteon and Randomized Withdrawal Study of the Efficacy and Safety of Tasimelteon, in totally blind patients with Non-24[18] (Lockley SW, Dressman MA, Licamele L, et al, unpublished data, 2014) (CinicalTrials.gov identifiers: NCT01163032 and NCT01430754). In general, tasimelteon was found to be well-tolerated in the indicated population as well as in the broader safety database, with no specific safety signals or trends. As part of the clinical development of tasimelteon, 2 clinical studies were conducted to assess the effect that varying degrees of hepatic and renal impairment have on its pharmacokinetics, safety, and tolerability.

Methods

The hepatic and renal impairment studies were open-label, single-dose, parallel-group studies conducted according to United States and international Good Clinical Practice standards, as well as all appropriate regulatory guidances. The protocols and all modifications and appropriate consent procedures were reviewed and approved by a properly constituted institutional review board (Independent Investi-gational Review Board, Inc., Plantation, Florida) before study commencement. All study participants provided written informed consent prior to enrollment into the study. The hepatic and renal studies were conducted at the Orlando Clinical Research Center in Orlando, Florida. The renal study was also conducted at 2 additional sites—DaVita Clinical Research in Minneapolis and Clinical Pharmacology of Miami, Inc., in Miami, Florida.

Study 1: Hepatic Study (ClinicalTrials.gov Identifier: NCT01271387)

Subjects. Male and female subjects were aged between 18 and 75 years, with a body mass index (BMI) of >18 and <35 kg/m^2 and appropriate renal function confirmed by having an estimated creatinine clearance (eCLcr) greater than 50 mL/min (based on the Cockcroft-Gault formula).

Twenty-nine subjects were enrolled and divided into 3 groups according to their liver function. Subjects in Groups 1 and 2 had stable hepatic impairment, satisfying the criteria for Class A or B of the modified Child-Pugh classification. Eight subjects with mild hepatic impairment, defined as having a Child-Pugh Score of ≥5 and ≤6 points, were enrolled in Group 1, and 8 subjects with moderate hepatic impairment, defined as having a Child-Pugh Score of ≥7 and ≤9 points, were enrolled in Group 2. Additionally, subjects in Group 2 had to have either liver cirrhosis (hepatic fibrosis with evidence of either micro- or macronodular regeneration) confirmed by imaging techniques, ultrasound, biopsy, magnetic resonance imaging or computerized tomography within 6 months of the screening visit, or physical signs consistent with a clinical diagnosis of liver cirrhosis (eg, liver firmness to palpation, splenic enlargement, spider angiomata, palmar erythema, parotid hypertrophy, testicular atrophy, gynecomastia). Thirteen control subjects matched in sex, age (±10 years), smoking status, and BMI category (normal [18–24 kg/m^2], overweight [25–30 kg/m^2] or obese [31–35 kg/m^2]) to Group 1 and/or Group 2 were enrolled in Group 3. Control subjects were in good health, as determined during the screening visit based on past medical history, physical examination, 12-lead electrocardiography (ECG), laboratory tests, and urinalysis.

Hepatically impaired subjects were excluded if they had >Grade 1 encephalopathy or clinical evidence of severe ascites. Subjects also were excluded if they had a previous surgical portosystemic shunt or evidence of progressive liver disease within 4 weeks prior to the screening visit. Healthy subjects were excluded if they had a positive hepatitis B or C serology test, or had a history or presence of liver disease or liver injury, as indicated by an abnormal liver function profile.

Blood sample collection. Blood samples for determining the concentration of tasimelteon (HETLIOZ®; Vanda Pharmaceuticals, Inc., Washington, DC) and its metabolites were obtained for each subject over the course of 36 hours.

Study 2: Renal Study (ClinicalTrials.gov Identifier: NCT01526746)

Subjects. Male and female subjects were aged 18–79 years, inclusive; their BMIs ranged from 18 to 40 kg/m^2.

Thirty-two subjects were enrolled and divided into 3 groups according to their renal function. Group 1 consisted of 8 subjects with stage 5 end-stage renal disease (ESRD; estimated glomerular filtration rate [eGFR] <15 mL/min/1.73 m^2) requiring dialysis; Group 2 consisted of 8 subjects with stage 4 severe renal impairment (eGFR ≤29 mL/min/1.73 m^2) for whom dialysis was not required, as calculated using the Modification of Diet in Renal Disease (MDRD) equation;[19] Group 3 consisted of 16 healthy subjects with normal renal function, defined as eGFR ≥80 mL/min/1.73 m^2, as calculated using the MDRD equation and matched by sex, smoking status, age (±10 years), and BMI category (normal [≥18–<25], overweight [≥25–<31], and obese [≥31–40]) to Group 1 and/or Group 2. Control subjects were in good health, as determined during the screening visit based on past medical history, physical examination, 12-lead ECG, laboratory tests, and urinalysis. The eGFR values for these subjects were calculated using the MDRD equation: eGFR (mL/min/1.73 m^2 = 175 × 7S$_{cr,std}$)$^{-1.154}$ × 1Age$_{-0.203}$ × (0.742 if female) 260 (1.212 if African American), where S$_{cr,std}$ = serum creatinine measured with a standardized assay

Renally impaired subjects were excluded if there was any evidence of them having progressive renal disease within 4 weeks prior to the screening visit. Subjects also were excluded if they had acute renal failure or nephrotic syndrome, or a current hematuria of urologic origin. Healthy subjects were excluded if they had a positive hepatitis C serology test, or a history or presence of impaired renal function, as indicated by abnormal (greater than the upper limit of normal) creatinine or blood urea nitrogen values or abnormal urinary constituents.

Blood sample collection. Blood samples for determining the concentration of tasimelteon and its metabolites were obtained for each subject over the course of 36 hours. An additional 3-mL blood sample was collected at 0.5 and 3 hours postdose for the determination of protein binding of tasimelteon and its metabolites. For Group 1, paired arterial and venous blood samples were obtained at approximately 4, 6, and 8 hours (based on a typical 4-hour session) after dosing during the hemodialysis session. Each subject's hemodialysis session may have varied in regard to run time, and the sampling schedule was adjusted such that paired samples were collected at the beginning, middle, and end of the session. A new dialyzer was used during this session.

Study Design

Both studies were open-label, parallel-group, phase I studies. For each study group, there was a 21-day screening period, a baseline period, a single-dose treatment period with an on-site observation period of 36 hours, and a study completion evaluation conducted after the last pharmacokinetic blood sample was drawn.

Subjects who met the inclusion/exclusion criteria at screening entered the study center at least 12 hours prior to dosing for baseline safety evaluations (baseline safety evaluation results were available prior to dosing). Subjects were administered a single oral dose of 20 mg tasimelteon with 200 mL of water between 7:00 am and 9:00 am. Subjects fasted 6 hours before dosing and for 4 hours after dosing. Following a single 20 mg dose of tasimelteon, safety assessments were made for up to 36 hours, and blood samples for pharmacokinetic analysis were collected throughout the 36-hour period. The end-of-study evaluations were performed after the last pharmacokinetic sample was collected. Safety assessments included physical examinations, ECGs, vital signs, laboratory evaluations (biochemistry, urinalysis, and hematology), suicidal ideation and behavior, and adverse event (AE) monitoring. Subjects were discharged from the site after the end-of-study evaluation was completed.

Bioanalysis

A liquid chromatography-mass spectrometry (LC-MS/MS) assay for the simultaneous determination of tasimelteon and metabolites M9, M11, M12, M13, and M14 in plasma was developed and validated according to the FDA Good Laboratory Practice Regulations, as set forth in Title 21 of the US Code of Federal Regulations, Part 58 and FDA guidance for bioanalytical method validation.[20,21] The analytes and internal standards were extracted from human plasma by liquid-liquid extraction and analyzed using reversed-phase high-performance liquid chromatography with Turbo Ion Spray® MS/MS detection (Applied Biosystems, Carlsbad, California). Positive (M + H)+ ions for tasimelteon, M9, M11, M12, M13, and M14 and the internal standards were monitored in multiple-reaction monitoring mode. Drug-to-IS peak area ratios for the standards were used to create a linear calibration curve using $1/x^2$ weighted least-squares regression analysis. The validated linear range for the assays for tasimelteon, M11, and M12 was from 0.3 to 300 ng/mL, for M9 and M13 was from 1 to 1,000 ng/mL, and for M14 was from 0.3 to 326.3 ng/mL. The QC concentrations and the between- and within-day coefficients of variation for the assay are summarized in Supplemental Table S1.

A validated LC-MS/MS assay for metabolite M3 alone in plasma also was developed using similar methodology. The validated linear range for the assay was from 0.3 to 300 ng/mL. The QC concentrations and between- and within-day coefficients of variation for the assay are summarized in Supplemental Table S1.

Pharmacokinetic Analysis

Only those plasma concentrations greater than the lower limit of quantitation (LOQ) were used in the pharmacokinetic analyses. Actual blood sampling times were used in all pharmacokinetic analyses. Per-protocol times were used to calculate mean plasma concentrations for graphical displays. All pharmacokinetic calculations and generation of individual subject concentration vs. time graphs were done using SAS® for Windows® Version 9.1.3 (SAS Institute Inc., Cary, North Carolina) under Windows XP Professional (Microsoft, Redmond, Washington). Graphs of mean plasma concentration vs. time were prepared using SigmaPlot™ for Windows Version 12.2 (Systat Software, Inc., San Jose, California).

Pharmacokinetic parameters for tasimelteon and metabolites were calculated using noncompartmental analysis. The maximum plasma concentration (C_{max}) and time to C_{max} were taken directly from the data. The elimination rate constant (λz) was calculated as the negative of the slope of the terminal log-linear segment of the plasma concentration-time curve. Values for $t_{1/2}$ were calculated using the equation $t_{1/2} = 0.693/\lambda z$. Area under the curve from time zero to the last time with a concentration $\geq$ LOQ ($AUC_{[0-t]}$) was calculated using the linear trapezoidal method and was extrapolated to infinity ($AUC_{[inf]}$). Only $AUC_{(inf)}$ will be reported in this paper, as the studies were single-dose and we characterized over 80.0% of the $AUC_{(inf)}$ with the sampling scheme that was used in the studies. For tasimelteon, clearance (CL/F) and volume of distribution (Vz/F), uncorrected for bioavailability, were calculated according to CL/F = dose/$AUC_{(inf)}$ and Vz/F = dose/$AUC_{(inf)} \times \lambda z$, respectively.

Statistical Analysis

Comparison of the pharmacokinetic parameters C_{max}, $AUC_{(0-t)}$, $AUC_{(inf)}$, and $t_{1/2}$, and, for tasimelteon, CL/F and Vz/F, between each special population group and the corresponding matched controls, was done using an analysis of variance model with renal or hepatic impairment function group as the classification variable, using the natural logarithms of the data. Ninety percent confidence intervals (CIs) were constructed for the treatment ratios (hepatic or renal impairment-to-control) of all parameters using the log-transformed data and the 2 one-sided *t*-test procedure. The point estimates and confidence limits were exponentiated back to the original scale.

Results

Study 1: Hepatic Study

Demographics. Enrolled subjects were predominantly white males, ranging in age from 46 to 62 years. The 3 groups were comparable in terms of age, height, weight, and BMI. The moderate hepatic impairment group included more smokers than either of the other groups. Demographic and baseline characteristics are summarized in Supplemental Table S2. One subject in the mild hepatic impairment group was excluded from the pharmacokinetic analyses because the subject's concentrations of tasimelteon and metabolites M11, M12, and M14 at the 36-hour time point were inconsistent with this subject's concentration-time profiles, as well as those of the other subjects in the cohort. Therefore, the concentrations at 36 hours for this subject were excluded from the descriptive statistics for plasma concentrations and from the pharmacokinetic analyses.

Pharmacokinetics. As hepatic function diminished, mean tasimelteon plasma concentrations increased, and these concentrations declined at a slower rate compared with the rates observed for the controls (Figure 1). For subjects with mild hepatic impairment, tasimelteon CL/F was reduced to 850 mL/min compared with 1,128 mL/min for matched controls (Table 1A). For subjects with moderate hepatic impairment, CL/F was 721 mL/min compared with 1,318 mL/min for matched controls (Table 1A). Although the associated 90%CIs included 100% for the comparison of subjects with mild hepatic impairment to controls but did not include 100% for subjects with moderate hepatic impairment vs. controls (Table 1B), their interpretation must be viewed in light of the small numbers of subjects and the necessary parallel group design. Overall, this reduction in CL/F indicates that hepatic impairment reduces the rate of metabolism of tasimelteon. The decrease in CL/F resulted in a corresponding increase in exposure, as measured by $AUC_{(inf)}$, of 143.7% and 189.3% in subjects with mild and moderate hepatic impairment, respectively (Table 1B). Similarly, the C_{max} was higher in subjects with mild hepatic impairment compared to controls (Table 1A). Exposure to key metabolites was modestly increased in subjects with mild and moderate hepatic impairment and to a lesser extent than observed for the parent compound (Figure 2A).

There were smaller changes in Vz/F, with geometric mean ratios (GMRs) of 89.5% and 79.6% for mild impairment vs. controls and moderate impairment vs. controls and associated 90%CIs that contained 100% (Table 1B). Compared to controls, the mean $t_{1/2}$ increased 28.6% and 50.7% in subjects with mild and moderate hepatic impairment, respectively (Table 1B).

Safety and tolerability. There were no deaths or other serious AEs or early terminations due to AEs reported. There were no clinically significant findings from clinical laboratory, vital sign, or ECG evaluations. All subjects, regardless of treatment, reported "no" to all baseline and post-baseline Columbia Suicide Severity Rating Scale (C-SSRS) questions. Five subjects reported a total of 6 AEs. The most frequently reported AEs were somnolence (reported by 2 subjects in the mild hepatic impairment group) and headache (reported by 1 subject each in the
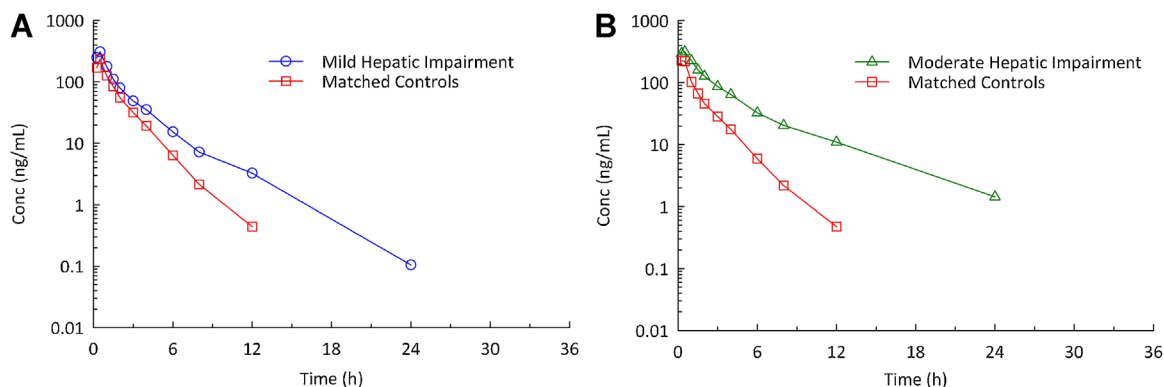
Figure 1. Mean plasma concentrations of tasimelteon (plotted on a semilogarithmic scale) after oral administration of 20 mg of tasimelteon to subjects with (A) mild (N = 8) or (B) moderate (N = 8) hepatic impairment and healthy matched controls (N = 8 for both groups).

mild hepatic impairment and healthy groups). No other AE was reported by more than 1 subject in any group. All AEs were of mild intensity and resolved by the end of the study.

Study 2: Renal Study

Demographics. The demographic and renal function information for the subjects entered in each of the renal

function groups in this study is provided in Supplemental Table S3.

In total, 32 subjects were enrolled and completed the study. The subjects were matched for age, sex, smoking status, and BMI whenever possible across the renal function groups. There were 16 healthy (matched control) subjects and 8 subjects in each of 2 renally impaired
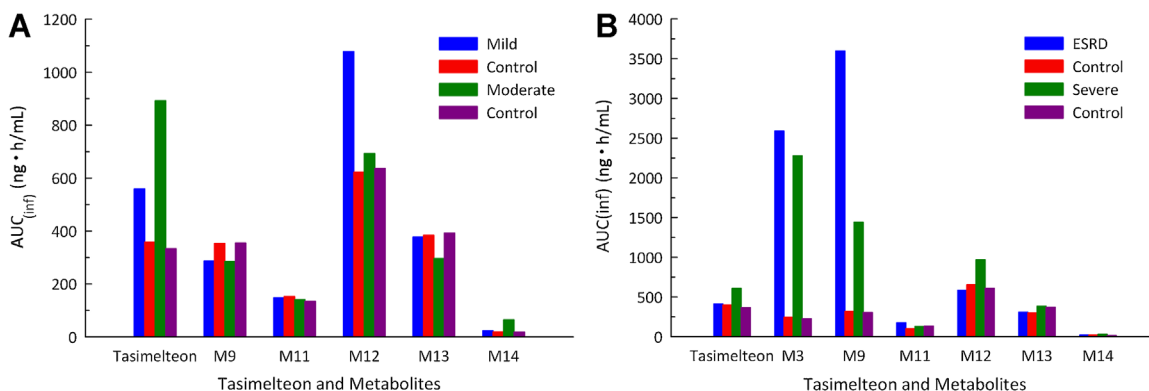
Table 1. Pharmacokinetic Parameters for Tasimelteon After Oral Administration of 20 mg of Tasimelteon to Subjects With Mild or Moderate Hepatic Impairment and Healthy Matched Controls

Parameter[a]	Mild Hepatic Impairment		Moderate Hepatic Impairment	
	Patients (N = 8)	Controls (N = 8)	Patients (N = 8)	Controls (N = 8)
A. Arithmetic Mean				
C_{max} (ng/mL)	366.2 ± 182.4	272.5 ± 58.8	381.5 ± 289.2	283.8 ± 109.8
$AUC_{(inf)}$ (ng·h/mL)	559.5 ± 401.2	358.3 ± 123.8	892.9 ± 990.2	334.1 ± 195.4
CL/F (mL/min)	849.7 ± 521.3	1,128.3 ± 709.3	721.0 ± 505.1	1,318.3 ± 743.5
Vz/F (L)	117.9 ± 58.5	117.2 ± 44.1	106.7 ± 58.3	137.2 ± 51.6
$t_{1/2}$ (h)	1.8 ± 0.7	1.3 ± 0.3	2.2 ± 1.1	1.3 ± 0.3

Parameter	Geometric Mean Ratio (%)[b]	
	Estimate	90% Confidence Interval
B. Geometric Mean Ratio		
Mild hepatic impairment vs. matched controls		
C_{max}	122.2	89.4 → 166.9
$AUC_{(inf)}$	143.7	94.2 → 219.5
CL/F	69.6	45.6 → 106.2
Vz/F	89.5	64.2 → 124.7
$t_{1/2}$	128.6	98.7 → 167.6
Moderate hepatic impairment vs. matched controls		
C_{max}	118.5	83.9 → 167.5
$AUC_{(inf)}$	189.3	113.8 → 314.9
CL/F	52.8	31.8 → 87.9
Vz/F	79.6	56.4 → 112.4
$t_{1/2}$	150.7	116.8 → 194.4

AUCinf, area under the plasma concentration-time curve to infinity; CL/F, clearance; C_{max}, maximum concentration; $t_{1/2}$, elimination half-life; Vz/F, volume of distribution.
[a]Arithmetic mean ± standard deviation.
[b]Based on analysis of natural log-transformed parameters.

Figure 2. Summary of AUC for tasimelteon and its metabolites after oral administration of 20 mg of tasimelteon to (A) subjects with mild or moderate hepatic impairment and healthy matched controls and (B) subjects with severe renal impairment or ESRD and healthy matched controls. AUC, area under the plasma concentration-time curve; $AUC_{(inf)}$, area under the plasma concentration-time curve to infinity; ESRD, end-stage renal disease.

groups (ESRD and severe). There were 22 males and 10 females in the study between the ages of 18 and 79, inclusive, with approximately the same ratio of males and females in each of the renal function groups. The mean age, weight, and BMI were similar across the renal function groups.

Protein binding. There were no apparent differences in the protein binding of tasimelteon, M9, M11, and M12 between subjects with severe impairment or ESRD and matching controls. These relationships are illustrated in Supplemental Figure S1 for tasimelteon. The percent unbound at 0.5 and 3 hours after drug administration was comparable in all groups. Similar relationships were observed with metabolites M9, M11, and M12. Although the data were sparser, the same trend was apparent for M13. However, due to the low concentrations of metabolite M14, the data were too sparse to allow for any meaningful assessment.

Effect of dialysis. Supplemental Figure S2 shows the effect of dialysis on tasimelteon and metabolites in

subjects with ESRD. Metabolites M3 and M9, which are excreted in the urine, had the largest percent changes between the arterial and venous sides of the dialyzer 2 and 4 hours after the start of dialysis (6 and 8 hours after dosing). Tasimelteon and metabolites M11, M12, and M14 had smaller differences between the arterial and venous concentrations at 6 and 8 hours, ranging from approximately 5.8% to 9.8%, and M13 had essentially no differences between the arterial and venous concentrations. This indicates that M3 and M9 are dialyzable; tasimelteon, M11, M12, and M14 are dialyzable, but to a lesser extent; and M13 is not removed by hemodialysis.

Pharmacokinetics. The arithmetic 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 are provided in Figure 3A and B. Subjects with severe renal impairment had, on average, a lower CL/F (Table 2A), with a GMR of 70.5% (Table 2B), indicating a nontrivial decrease. This decrease in CL/F resulted in
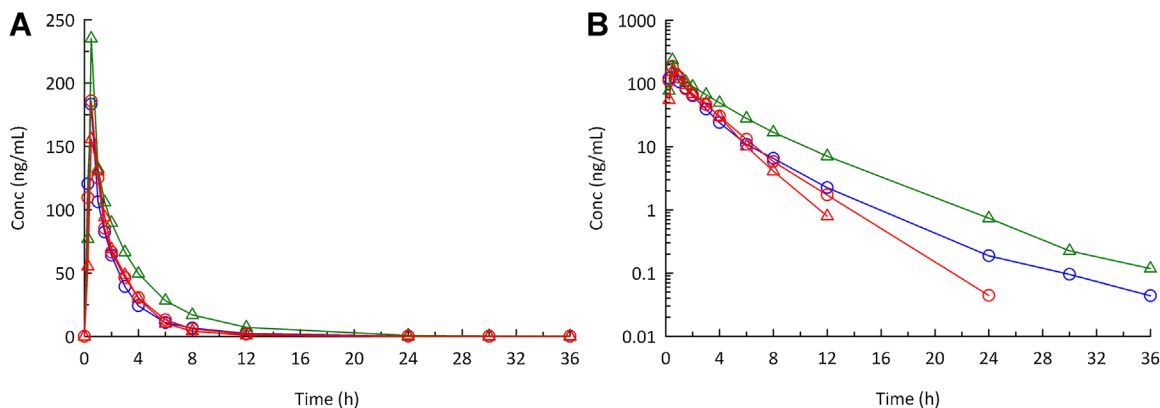
Figure 3. Mean plasma concentrations of tasimelteon after oral administration of single 20 mg doses of tasimelteon to subjects with ESRD (N = 8), subjects with severe impairment (N = 8), and matched controls (N = 8 for both groups)—linear (A) and semilogarithmic axes (B). ESRD, end-stage renal disease. Lines with blue circles indicate ESRD, lines with red circles indicate controls for ESRD, lines with green triangles indicate severe impairment, and lines with red triangles indicate controls for severe impairment.

Table 2. 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[a]	ESRD		Severe Renal Impairment	
	Patients (N = 8)	Controls (N = 8)	Patients (N = 8)	Controls (N = 8)
A. Arithmetic Mean				
C_{max} (ng/mL)	196.7 ± 120.8	197.1 ± 75.8	255.4 ± 142.2	176.2 ± 93.3
$AUC_{(inf)}$ (ng · h/mL)	409.4 ± 326.5	401.0 ± 343.5	607.2 ± 641.1	366.1 ± 209.5
$t_{1/2}$ (h)	3.4 ± 1.8	1.4 ± 0.5	2.3 ± 1.0	1.4 ± 0.5
CL/F (mL/min)	1,416.8 ± 1,023.8	1,555.8 ± 1,633.4	1,075.6 ± 814.4	1,561.4 ± 1,545.3
Vz/F (L)	399.1 ± 430.1	148.8 ± 100.5	187.5 ± 148.6	160.5 ± 112.9

Parameter	ESRD vs. Matched Controls Geometric Mean Ratio (%)[b]		Severe Impairment vs. Matched Controls Geometric Mean Ratio (%)[b]	
	Estimate	90% Confidence Interval	Estimate	90% Confidence Interval
B. Geometric Mean Ratio				
C_{max}	95.7	59.9 → 152.7	143.2	84.5 → 242.8
$AUC_{(inf)}$	102.2	47.5 → 220.3	141.8	67.4 → 298.5
$t_{1/2}$	221.5	137.1 → 358.0	157.2	112.8 → 219.0
CL/F	97.8	45.4 → 210.8	70.5	33.5 → 148.5
Vz/F	216.7	107.6 → 436.6	110.9	60.9 → 201.9

AUC_{inf}, area under the plasma concentration-time curve to infinity; CL/F, clearance; C_{max}, maximum concentration; ESRD, end-stage renal disease; $t_{1/2}$, elimination half-life; Vz/F, volume of distribution.
[a]Arithmetic mean ± standard deviation.
[b]Based on analysis of natural log-transformed parameters.

increased mean plasma tasimelteon concentrations (Figure 3A) and arithmetic mean values for C_{max} and $AUC_{(inf)}$, with GMRs of 143.2% and 141.8%, respectively (Table 2B). In contrast, subjects with ESRD, ie, more severe renal impairment, had a comparable arithmetic mean CL/F (Table 2A), with a GMR of 97.8% (Table 2B), and comparable mean plasma concentrations (Figure 3A) and arithmetic mean values for C_{max} and $AUC_{(inf)}$ (Table 2A), with GMRs of 95.7% and 102.2%, respectively (Table 2B). Although members of this group

received dialysis during the period from 4 to approximately 8 hours after dosing, the mean plasma concentrations were essentially superimposable with those from the matched controls prior to 4 hours (Figure 3B), suggesting that dialysis did not contribute to the clearance of tasimelteon, consistent with the relatively low arterial-to-venous difference.

Consistent with the lack of renal excretion of tasimelteon, there was no apparent relationship between tasimelteon CL/F and renal function, as measured by
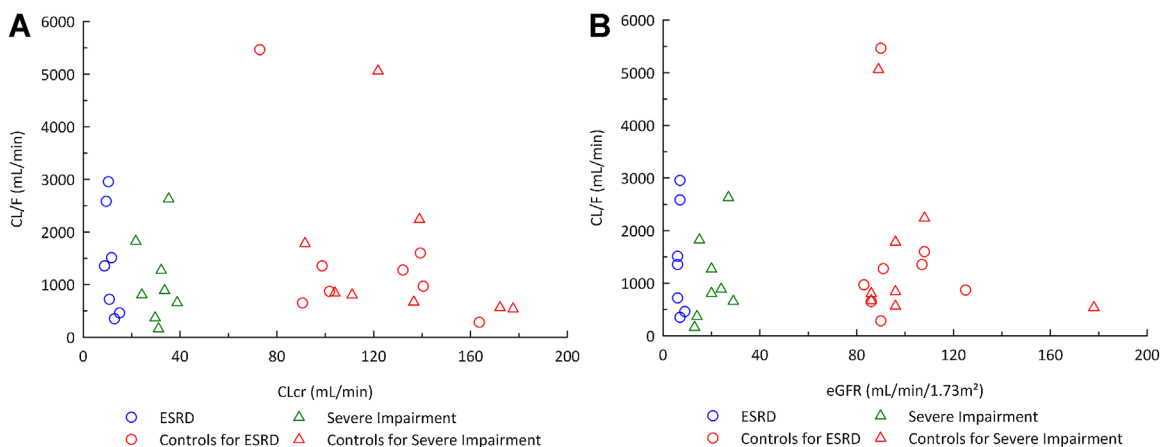
Figure 4. Relationship between the individual subject tasimelteon CL/F and (A) CLcr or (B) eGFR after oral administration of single 20 mg doses of tasimelteon to subjects with ESRD, subjects with severe impairment, and matched controls. CL/F, clearance; CLcr, creatinine clearance; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.

either eCLcr (Figure 4A) or eGFR (Figure 4B). This suggests that the apparent differences in CL/F in subjects with severe impairment but the lack of differences in subjects with ESRD may be a consequence of the variability intrinsic with small numbers of subjects per group rather than a true difference.

There were minor differences in the mean Vz/F in subjects with severe impairment, and an approximate 2-fold increase in subjects with ESRD compared with matched controls (Table 2A).

There was an increase in the mean $t_{1/2}$ in both renal impairment groups compared with matched controls (Table 2A), with a GMR of 157.2% in subjects with severe impairment and GMR of 221.5% in ESRD subjects (Table 2B).

There were no significant changes in the M11, M12, M13, and M14 pharmacokinetic parameters between subjects with severe renal impairment or ESRD and their respective matched healthy controls (Figure 2B). Metabolites M3 and M9 may potentially accumulate in patients with severe renal impairment and/or ESRD patients (Figure 2B). The clinical significance of the projected accumulation rates in ESRD patients (20.0% for M9 and at least 1.4-fold for M3) and severely impaired patients (1.2-fold for M3) is unknown but not expected to be a safety concern.

Safety and tolerability. There were no serious AEs, severe AEs, or discontinuations during the study. There were no clinically significant changes in chemistry, hematology, urinalysis, ECG readings, and physical examinations following dosing with tasimelteon for subjects in any of the renal function groups. All subjects, regardless of treatment, reported "no" to all baseline and post-baseline C-SSRS questions. Treatment-emergent AEs that were considered to be related to the administration of the study drug and reported by at least 1 subject were somnolence, headache, nausea, vomiting, and retching. All AEs were of mild intensity and resolved by the end of the study.

Discussion

Studies were conducted to investigate the effect of renal and hepatic impairment on the pharmacokinetics of tasimelteon after a single oral dose. Hepatic impairment was expected to potentially have an impact on the clearance of tasimelteon, as the major route of elimination of tasimelteon is via hepatic metabolism, primarily oxidation at multiple sites and oxidative dealkylation. As such, patients with impaired liver function might have reduced capacity to metabolize tasimelteon. Conversely, renal impairment was not expected to have a great impact on the clearance of tasimelteon and most of its metabolites, because renal elimination contributed minimally to the clearance of unchanged tasimelteon. The results of these studies were consistent with these expectations.

In the hepatic impairment study, there was a decrease in the CL/F of tasimelteon in subjects with mild or moderate impairment, the extent of which was related to the severity of hepatic impairment. This resulted in a corresponding increase in exposure to tasimelteon. Taking into account the therapeutic margin of tasimelteon (ie, doses up to 300 mg were well tolerated in our clinical studies), this increase in exposure to tasimelteon—approximately 2-fold for the parent, less for the metabolites—is not likely to impact clinical safety. The effect of hepatic impairment on clearance was not co-founded by the subject's renal clearance, as the creatine clearance of mildly impair, moderately impair, and healthy control were similar (117.9 mL/min, 117.3 mL/min, and 111.6 mL/min, respectively).

The lack of correlation between tasimelteon's CL/F and renal function, as measured by either CLcr or eGFR, was consistent with tasimelteon not being renally eliminated, as less than 1.0% of the unchanged parent was detectable in the urine. Metabolites M3 and M9 were the 2 major urinary metabolites, accounting for $12.5 \pm 1.9\%$ and $29.7 \pm 4.2\%$, respectively, of the administered dose (mean $\pm$ SD) in urine collected from all 6 subjects during the 72-hour period. All other urinary metabolites were minor, accounting for less than 5.0% of the dose. M3 and M9 showed higher exposure and lower clearance in renal patients. This was evident by the sustained higher plasma concentrations of these metabolites. These results showed that M3 and M9 could accumulate upon chronic dosing of tasimelteon. However, these metabolites are not known to contribute to clinical efficacy or be implicated in any adverse effects.

There was an observed increase in $t_{1/2}$ in both renal impairment groups compared with rates in matched controls. This increase in subjects with severe impairment could be a consequence of the decreased CL/F, but the lack of an overall relationship between CL/F and renal function suggests that this is unlikely, and that the increase is related to random variability. However, the increase in $t_{1/2}$ in subjects with ESRD could be a consequence of the comparable increase in Vz/F.

In the current studies, a single oral dose of tasimelteon 20 mg was well tolerated in all subject groups, and no safety concerns were raised. In addition, tasimelteon has been shown to be well tolerated at single doses of up to 300 mg, much higher than the 20 mg used in these 2 studies. In the clinical development program of tasimelteon, there were no clinically relevant events, trends, or changes in clinical or laboratory parameters and no evidence of risk due to suicidal ideations or behavior. The increase in exposure to tasimelteon observed in subjects with mild or moderate hepatic impairment at a dose of 20 mg—approximately 2-fold for the parent, less for the metabolites—is not likely to impact clinical safety, as there does not seem to be any correlation between

higher doses and increased frequency of adverse event. These results suggest that tasimelteon can be given to Non-24 patients with mild or moderate hepatic impairment, as well as those with renal disease, regardless of severity.

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