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ORIGINAL RESEARCH ARTICLE

Safety, Tolerability, and Pharmacokinetics of Suvorexant: A Randomized Rising-Dose Trial in Healthy Men

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Abstract

Background and Objectives Suvorexant (MK-4305) is an orexin receptor antagonist approved for the treatment of insomnia in the USA and other regions. This randomized, double-blind, placebo-controlled, sequential-panel, Phase 1 trial assessed the safety, tolerability, and pharmacokinetic data following single and multiple dosing of suvorexant in healthy men (aged 18–45 years).

Methods Within allocated panels, subjects (n = 8) were randomized to receive nightly doses of suvorexant (10, 20, 40, 80, and 100 mg) administered orally for 14 days, or placebo. Safety assessments included daily adverse event (AE) monitoring; pharmacokinetic data were obtained through periodic sampling.

Results Of 40 subjects randomized, 39 completed the trial. The incidence of any AEs in the 10 and 20 mg groups was 67 and 83%, respectively, while 100% of subjects reported AEs in the dose groups of 40, 80, and 100 mg and the placebo group. The most frequently reported AEs were somnolence (n = 19 subjects), fatigue (n = 17), and headache (n = 15). Following single and multiple dosing, median time to reach maximum observed concentration ranged from 1.5 to 4.0 h and the apparent terminal half-life ranged from 7.7 to 14.5 h. Across the investigated doses, accumulation ratios for the area under the concentration–time curve and the maximum observed concentration were independent of dose and ranged from 1.21 to 1.60 and 1.00 to 1.46, respectively.

Conclusions Suvorexant was generally well tolerated after single and multiple dosing for 14 days. The findings support the once-nightly dosing regimen.

Key Points

This Phase 1 trial assessed the safety and tolerability of the orexin receptor antagonist, suvorexant, in healthy men during single and multiple dosing regimens (10, 20, 40, 80, and 100 mg).

Adverse events were reported for all suvorexant doses; somnolence, fatigue, and headache were the most frequently reported.

Pharmacokinetic evaluations showed that for suvorexant, the median time to reach maximum observed concentration ranged from 1.5 to 4.0 h and the apparent terminal half-life ranged from 7.7 to 14.5 h; pharmacokinetic data were supportive of the once-nightly dosing regimen.

1 Introduction

The orexinergic signaling pathway plays a central role in the regulation of the transition between wake and sleep [1–4]. The key signaling neuropeptides in this pathway are orexin A (OX-A) and orexin B (OX-B), which exert wake-

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promoting effects by activating their cognate orexin receptors (OX_1R and OX_2R) localized in the arousal and vigilance centers in the lateral hypothalamus and the lower brain stem nuclei [5, 6]. OXR antagonism has been extensively studied in the past decade as an alternative mechanism for the treatment of insomnia.

Historically, insomnia treatments have relied on the use of gamma-aminobutyric acid $(GABA)_A$ receptor agonists, which induce sleep by consolidating the inhibitory sleep-promoting influence of the neurotransmitter $GABA_A$. However, given the global distribution of $GABA_A$ receptors throughout the brain, and their pleiotropic roles in mediating myriad neurological processes, $GABA_A$ agonists are liable to side effects, including next-day sedation, memory deficits, rebound insomnia, hallucinations, and psychological dependence [7–9].

High-throughput screens for ligands that can block OXR activity resulted in the identification of suvorexant (MK-4305), an orexin receptor antagonist (ORA) with specificity for OX_1R and OX_2R that demonstrated sleep-promoting effects in preclinical and subsequent clinical trials [10–14]. In randomized clinical trials in patients with insomnia, suvorexant improved objective sleep measurements as assessed by polysomnography, and patient-reported subjective measures of sleep, including time to sleep onset, total sleep time and quality of sleep, and was associated with an acceptable safety profile [11, 12, 15, 16]. Suvorexant has been subsequently approved in the USA and other regions as a first-in-class ORA for the treatment of insomnia at doses of 10–20 mg.

In vitro and in vivo characterization of suvorexant metabolism and disposition following single oral dose administration in humans has been reported elsewhere [17]. In this trial, we report data from the first-in-human administration of suvorexant in a multiple-dose regimen, which served to guide dosing decisions in subsequent clinical trials and aided in the design of the wider clinical development program.

2 Methods

2.1 Trial Design and Objectives

This trial was conducted in accordance with the principles of Good Clinical Practice and the protocol and applicable amendments were approved by all Independent Ethics Committees (Commissie voor Medische Ethiek). All subjects provided informed consent.

This randomized, double-blind, placebo-controlled, sequential-panel, single and multiple oral rising-dose trial was performed between April 2008 and November 2008 (protocol number: MK-4305-003) at SGS Life Sciences Services, Antwerp, Belgium. The primary trial objective was to evaluate the safety and tolerability of suvorexant administered according to a rising, multiple-dose regimen in healthy men. Secondary endpoints assessed the pharmacokinetic profile of suvorexant following multiple dosing in the fasted state (reported herein). Plasma concentrations of circulating metabolite M9 were also determined.

The earliest time to achieve the sleep-promoting plasma concentration target of 0.4 μM after multiple-dose administration, plus the duration of time this concentration was maintained, was also assessed. However, these data are not reported herein as selection of the 0.4 μM target was based on preclinical data [18], and the relevance of this target concentration has subsequently been superseded by clinical efficacy data.

Pharmacodynamic parameters (cognitive, psychomotor, and arousal assessments) were included as exploratory endpoints; however, the trial was not designed to definitively evaluate residual effects. In fact, it was anticipated that morning pharmacodynamic assessments would potentially be influenced by the frequent sleep disruptions required for safety and pharmacokinetic assessments, namely the safety evaluations performed within the 2 h immediately following nightly dosing and the repeated waking of the subjects throughout the night for pharmacokinetic sampling purposes. These awakenings could also be expected to contribute to increased frequency of somnolence and drowsiness. Consequently, the pharmacodynamic endpoints were not considered applicable to the clinical setting and are therefore not reported.

2.2 Trial Population

Subjects were non-smoking, healthy men aged 18–45 years with a body mass index < 31 kg/m^2 at the screening visit. Subjects were generally healthy based on medical history, physical examination, vital signs, laboratory tests, and electrocardiogram (ECG) evaluations performed at screening and/or prior to administration of the initial dose of trial drug.

Subjects with a history of persistent difficulties in initiating and/or maintaining sleep for more than 3 months, and those with a history of sleep apnea, restless legs syndrome, or narcolepsy were excluded from the trial. Individuals who were frequent users of sedative hypnotics, including benzodiazepines, non-benzodiazepines, barbiturates, and/or other pharmaceutical sleep agents, were also excluded.

2.3 Treatments

Subjects were initially allocated to 1 of 5 panels: A, B, C, D, or E (Fig. 1). Within each panel, 8 subjects were

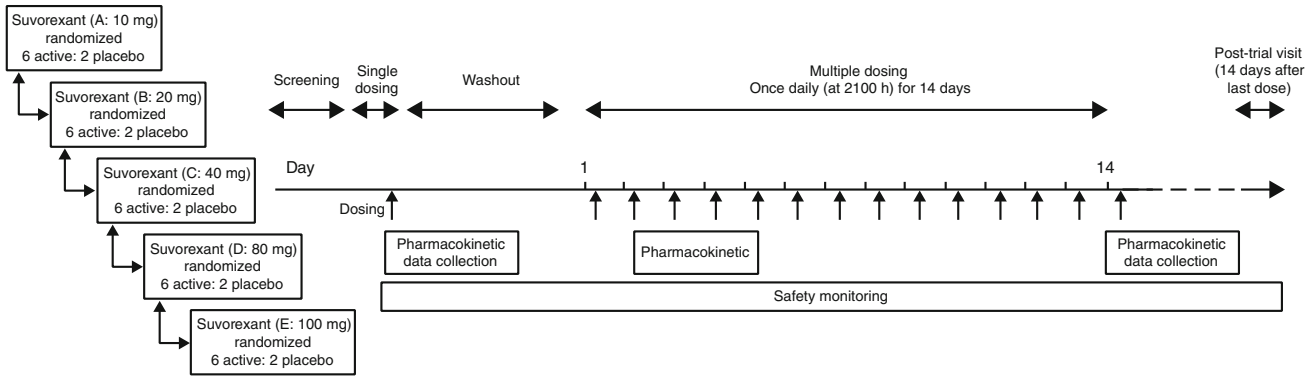

Fig. 1 Trial design

randomized according to a computer-generated allocation schedule to receive either oral suvorexant (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA) [10 mg (panel A), 20 mg (B), 40 mg (C), 80 mg (D), or 100 mg (E); $n = 6$] or matching placebo ($n = 2$) under fasted conditions at 2100 h, consistent with the intended use of suvorexant in subsequent clinical development. Both subjects and clinician were blinded to treatment. The dosing period (19 days in total) consisted of the following 3 parts: administration of a single suvorexant or matching placebo dose, a 120 h (5 day) washout period, and administration of a once-nightly suvorexant dose for 14 consecutive days (referred to as days 1–14, herein). Dose escalation and progression from one panel to the next panel was contingent upon acceptable results from interim analyses of safety, tolerability, and pharmacokinetic data (where available) from the preceding treatment panels.

2.4 Safety Assessments

Subjects were queried daily throughout the trial for the occurrence of adverse events (AEs). All reported AEs were evaluated with respect to seriousness, severity, relationship to trial drug, and action taken in response to their emergence. AEs of special interest included: cataplexy, sleep paralysis (including sleep-onset paralysis), hypnagogic or hypnopompic hallucinations, suicidal ideation and/or behaviors, complex sleep-related behaviors, falls, and events associated with potential for abuse. All subjects were monitored by the clinical staff for all activities of daily living, and clinical staff practiced fall precautions. Physical examinations including vital signs were performed at screening, pre-dose, and at various time points post-dose (single dosing: 1.5, 12, and 24 h post-dose; multiple dosing: 1.5 and 12 h post-dose on multiple-dosing days 1, 2, 4, 13, where appropriate), and at the post-trial visit (14 days after the last dose of suvorexant). A complete vital signs measurement (heart rate, respiratory rate, blood pressure, and oral temperature), in addition to a 12-lead ECG examination, and laboratory safety analyses (hematology, serum chemistry, and urinalysis) were conducted at screening and before dosing, at time points for 24 h after each dose, and at the post-trial visit.

2.5 Pharmacokinetic Evaluations

Venous blood samples were collected pre-dose and at selected time points through 72 h following single-dose administration, and up to 96 h post-dose on day 14 (the last day) of multiple dosing. In addition, blood samples were collected up to 16 h after dose administration on day 3 of multiple dosing. Trough concentration samples were collected on trial days 1–13 of multiple dosing.

Evaluated plasma pharmacokinetic parameters for suvorexant included area under the concentration–time curve (AUC) from time of administration to 24 h (AUC_{0-24h}), AUC from time of administration to infinity ($AUC_{0-\infty}$; for single-dose administration only), maximum observed concentration (C_{max}), concentration at 24 h post-dose (C_{24h}), time to reach the maximum observed concentration (t_{max}), and apparent terminal elimination half-life ($t_{½}$). These parameters were evaluated following single-dose administration and on days 3 and 14 of multiple dosing. The same pharmacokinetic parameters were also evaluated for M9, a circulating metabolite of suvorexant.

2.6 Sample Analysis, Data Analysis, and Statistics

AEs were tabulated for each dose of suvorexant and placebo by frequency of occurrence. For laboratory safety tests, ECG, and vital signs, summary statistics and plots were generated for the change from baseline values.

For the pharmacokinetic analysis, suvorexant concentration was determined by liquid–liquid extraction followed by analyte quantification using reverse-phase high-performance liquid chromatography–mass spectrometry (HPLC-MS; AB Sciex API 4000) operated in the Multiple

Reaction Monitoring (MRM), positive ion mode. The MRM transitions monitored were *m/z* (mass-to-charge ratio) 451–186 for suvorexant and 455–190 for the internal standard ([^{2}H,^{13}C]-suvorexant). The lower limit of quantification of the assay and its linear calibration range were 1 ng/mL and 1–1000 ng/mL, respectively. Metabolite M9 concentration was determined quantitatively using HPLC–MS/MS with a heated nebulizer interface (DM-928). The linear calibration range for the analysis of M9 in human plasma was 1–1000 ng/mL. Presence of suvorexant metabolites in plasma at 40–100 mg doses was also assessed semi-quantitatively using HPLC–high-resolution mass spectrometry following single and multiple dosing (days 3 and 14). Analysis of circulating suvorexant metabolites has been described previously [17].

Suvorexant and M9 plasma concentrations, and their corresponding sampling times relative to the dosing time, were used to derive the pharmacokinetic parameters for each analyte in each subject using the WinNonlin software (version 5.2.1; Pharsight Corporation, Mountain View, CA, USA). The apparent terminal rate constant (λ) was estimated by regression of the terminal log-linear portion of the plasma concentration–time profile. AUC from time of administration to the last time point of detectable plasma concentration (AUC_{0-last}) and AUC_{0-24h} were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations up to the last detectable plasma concentration and the 24 h post-dose sampling time, respectively. $AUC_{0-\infty}$ was estimated as the sum of AUC_{0-last} and the extrapolated area given by the quotient of the last detectable concentration and λ. C_{max} was obtained by inspection of the plasma concentration data, and C_{24h} was assessed from the plasma concentration determined for the nominal sampling time at 24 h post-dose; t_{max} was obtained by inspection of the plasma concentration data, and, finally, $t_{½}$ was calculated as the quotient of ln(2) and λ.

Least squares geometric means and 95% confidence intervals (CI) were obtained for AUC_{0-24h}, $AUC_{0-\infty}$, C_{max}, and C_{24h} by dose and day based on (separate) linear mixed-effects models having fixed effects for dose and day, interaction of dose and day, and a random effect for subject. Geometric means and 90% CI for the AUC_{0-24h} and C_{max} accumulation ratios (day 14 of multiple dose/single dose day) were also obtained using this model. Descriptive statistics were provided for t_{max} and $t_{½}$.

3 Results

3.1 Baseline Characteristics and Subject Disposition

Subject recruitment occurred over an 8-month period in 2008 (first subject enrolled, April 2008; last subject last visit, November 2008). A total of 40 healthy men were enrolled in the trial (Table 1, Online Resource 1), the majority of whom (n = 39, 98%) were Caucasian. Across the treatment cohorts, the mean age was 34.3 years (range 19–45 years), the mean height was 178.0 cm (166.0–193.0 cm), and the mean weight was 78.5 kg (61.6–108.0 kg). Of 40 subjects who were randomized, 1 subject in the 20 mg cohort discontinued after completion of day 6 of multiple dosing due to an AE. The single-dosing pharmacokinetic data for 1 other subject (40 mg cohort) were excluded from the analysis due to vomiting 100 minutes post-dose, which is within 2-times the median t_{max} of suvorexant and likely influenced the extent of absorption and, therefore, resultant concentrations. However, pharmacokinetic data from all other doses for this subject were included in the analysis.

Table 1 Baseline demographics (N = 40)

Demographic characteristic	Value
Gender	
Male, *n* (%)	40 (100.0)
Race	
White, *n* (%)	39 (97.5)
Black, *n* (%)	1 (2.5)
Age, mean (range), years	34.3 (19–45)
Height, mean (range), cm	178.0 (166.0–193.0)
Weight, mean (range), kg	78.5 (61.6–108.0)

3.2 Safety

The incidence of any AEs in the 10 and 20 mg groups was 67 and 83%, respectively, while 100% of the subjects reported AEs in the higher-dose groups and the placebo group (Table 2). No serious AEs, deaths, or AEs of clinical interest were reported. All clinical AEs were transient in duration and were mild-to-moderate in severity, except for 1 subject in the suvorexant 80 mg treatment cohort, who reported a severe AE consisting of somnolence occurring on 5 separate occasions starting on the first day of multiple dosing.

The most frequently reported AEs were somnolence (n = 19 subjects), fatigue (n = 17), and headache (n = 15) (Table 2). Nineteen subjects (suvorexant groups, n = 17; placebo, n = 2) reported somnolence on 1 or more occasions (51 total occurrences) while on treatment, and all events of somnolence were considered related to trial drug. Fifteen subjects across the suvorexant dose groups (20 mg, n = 3; 40 mg, n = 5; 80 mg, n = 4; 100 mg, n = 3) experienced somnolence within 1–2 h of dose administration, and of those subjects, 11 experienced somnolence that persisted for $\geq$ 10 h. Following evening dosing, subjects

Table 2 AE summary[a]

	Suvorexant dose										Placebo ($N = 10$)	
	10 mg[b] ($N = 6$)		20 mg[b] ($N = 6$)		40 mg[b] ($N = 6$)		80 mg[b] ($N = 6$)		100 mg[b] ($N = 6$)			
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Any AE	4	67	5	83	6	100	6	100	6	100	10	100
AEs in ≥ 2 subjects												
Somnolence	1	17	3	50	5	83	4	67	4	67	2	20
Fatigue	0	0	1	17	5	83	2	33	5	83	4	40
Headache	0	0	3	50	4	67	1	17	2	33	5	50
Insomnia	0	0	0	0	1	17	4	67	1	17	1	10
Diarrhea	0	0	1	17	1	17	1	17	1	17	2	20
Dizziness	0	0	0	0	0	0	1	17	2	33	1	10
Nasopharyngitis	0	0	0	0	0	0	1	17	0	0	3	30
Back pain	0	0	0	0	0	0	0	0	1	17	2	20
Erectile dysfunction	0	0	2	33	0	0	0	0	0	0	0	0
Phlebitis	0	0	0	0	0	0	0	0	2	33	0	0

AE adverse event

[a]Although a subject may have had 2 or more AEs, the subject was counted only once within a category. The same subject may appear in different categories

[b]For all panels, subjects received a single nightly dose followed by a 5-day washout period. After washout, subjects received 14 days of once-nightly multiple doses of suvorexant (day 1 to day 14)

had multiple procedures performed during the night, which were thought to influence the reporting of AEs such as somnolence and fatigue.

One subject discontinued due to a non-serious AE following administration of suvorexant 20 mg on day 6 of multiple dosing. This subject developed a maculo-papular rash approximately 15 h post-dosing, which was considered probably related to treatment. No AEs occurred in the post-trial follow-up period (14 days after last dose of suvorexant).

No clinically significant abnormalities were noted in routine blood chemistry panels, hematology, ECG, or physical examinations including vital signs.

3.3 Pharmacokinetics

Table 3 shows the pharmacokinetic parameters of suvorexant. Following single and multiple once-nightly dosing, suvorexant had a median t_{max} ranging from 1.5 to 4.0 h and $t_{½}$ ranging from 7.7 to 14.5 h (Fig. 2). Over the dose range studied, accumulation ratios for $AUC_{0–24h}$ and C_{max} were independent of dose and ranged from 1.21 to 1.60 and 1.00 to 1.46, respectively. Suvorexant exhibited less-than-dose-proportional increases in steady state $AUC_{0–24h}$ and C_{max}.

Suvorexant median time to 90% of steady state ranged from 2 to 3 days following multiple dosing at all doses studied, consistent with the observed mean $t_{½}$ for suvorexant. Individual time to steady state ranged from 1 to 6 days.

Metabolite profiling to identify circulating metabolites was conducted using plasma samples following the single dose and on days 3 and 14 of multiple dosing. After single dosing, suvorexant and metabolite M9 were the predominant components in human plasma. Several minor metabolites, M4, M7a, M8, M10a, M12, and M17, were also detected in plasma samples. Metabolite M17 became more prevalent after multiple dosing and accounted for ~ 6% and 9–10% of total drug-related material on days 3 and 14, respectively. In addition, M12 accounted for 12–17% of suvorexant-derived material on day 14. Although M10a was detected in human feces in a human Absorption, Distribution, Metabolism and Excretion (ADME) trial [17] it was not detected in human plasma.

The pharmacokinetic parameters of metabolite M9 are listed in Online Resource 2. M9 exposure was similar to that observed for suvorexant after a single dose, with metabolite/parent $AUC_{0–24h}$ ratios ranging from 1.03 (10 mg) to 1.17 (100 mg); these ratios declined to a range of 0.76 (80 mg) to 0.92 (20 mg) by day 14 of multiple dosing.

Following single and then multiple nightly dosing with suvorexant, M9 had a delayed median t_{max} (range 2.0–6.0 h across doses) compared with suvorexant (range 1.5–4.0 h across doses), and a mean $t_{½}$ comparable with the parent compound (range 8.7–17.5 h vs 7.7–14.5 h, respectively).

Table 3 Summary of plasma pharmacokinetic parameters of suvorexant following single-dose and once-nightly multiple-dose administration

Pharmacokinetic parameter	Suvorexant dose				
	10 mg	20 mg	40 mg	80 mg	100 mg
Single dose					
N	6	6	5	6	6
AUC_{0-24h}[a] (μM·h)	3.43 (2.62, 4.49)	5.03 (3.84, 6.58)	8.53 (6.45, 11.28)	11.48 (8.77, 15.01)	18.10 (13.83, 23.68)
$AUC_{0-\infty}$[a] (μM·h)	3.94 (2.85, 5.43)	5.97 (4.33, 8.24)	10.84 (7.62, 15.42)	15.57 (11.28, 21.48)	27.95 (20.25, 38.56)
C_{max}[a] (μM)	0.356 (0.288, 0.440)	0.572 (0.463, 0.708)	0.802 (0.640, 1.005)	1.329 (1.075, 1.644)	1.425 (1.152, 1.763)
C_{24h}[a] (μM)	0.038 (0.024, 0.062)	0.068 (0.042, 0.110)	0.121 (0.073, 0.201)	0.163 (0.101, 0.264)	0.403 (0.249, 0.650)
t_{max}[b] (h)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	2.0 (0.5, 4.0)	2.0 (2.0, 6.0)	4.0 (2.0, 6.0)
$t_{½}$[c] (h)	7.7 (1.7)	8.4 (1.7)	8.6 (1.1)	10.0 (5.2)	12.6 (7.0)
Day 3 of multiple dosing					
N	6	6	6	6	6
AUC_{0-24h}[a] (μM·h)	3.79 (2.90, 4.96)	6.11 (4.67, 7.99)	9.00 (6.88, 11.78)	14.97 (11.44, 19.58)	24.64 (18.83, 32.23)
C_{max}[a] (μM)	0.428 (0.346, 0.530)	0.557 (0.450, 0.688)	1.091 (0.882, 1.350)	1.288 (1.041, 1.593)	2.109 (1.705, 2.609)
t_{max}[b] (h)	2.0 (1.0, 4.0)	3.0 (2.0, 4.0)	1.5 (1.0, 2.0)	2.0 (1.0, 8.0)	3.0 (1.0, 6.0)
Day 14 of multiple dosing (last dose)					
N	6	5	6	6	6
AUC_{0-24h}[a] (μM·h)	4.36 (3.33, 5.70)	6.08 (4.60, 8.04)	10.64 (8.13, 13.92)	18.32 (14.00, 23.97)	27.62 (21.11, 36.14)
C_{max}[a] (μM)	0.414 (0.335, 0.512)	0.574 (0.458, 0.719)	1.080 (0.873, 1.336)	1.488 (1.203, 1.841)	2.085 (1.686, 2.579)
C_{24h}[a] (μM)	0.063 (0.039, 0.102)	0.107 (0.064, 0.178)	0.192 (0.119, 0.310)	0.395 (0.245, 0.638)	0.644 (0.399, 1.040)
t_{max}[b] (h)	2.0 (1.0, 4.0)	4.0 (2.0, 4.0)	2.0 (1.0, 2.0)	2.0 (2.0, 4.0)	4.0 (2.0, 8.0)
Apparent $t_{½}$[c] (h)	8.1 (2.3)	9.2 (0.9)	9.4 (1.5)	11.2 (5.3)	14.5 (7.0)
Accumulation ratio: multiple-dose day 14/single dose[d]					
N	6	5	5	6	6
AUC_{0-24h}[d]	1.27 (1.06, 1.52)	1.21 (1.00, 1.46)	1.25 (1.03, 1.51)	1.60 (1.33, 1.91)	1.53 (1.28, 1.83)
C_{max}[d]	1.16 (0.98, 1.39)	1.00 (0.83, 1.21)	1.35 (1.12, 1.62)	1.12 (0.94, 1.34)	1.46 (1.23, 1.75)

Square root of conditional mean squared error (residual error) from linear mixed-effects model = 0.185 for AUC_{0-24h}, 0.182 for C_{max}. When multiplied by 100, provides estimate of the pooled within-subject coefficient of variation

AUC_{0-24h} area under the concentration–time curve from time of administration to 24 h, *$AUC_{0-\infty}$* area under the concentration–time curve from time of administration to infinity, *C_{24h}* concentration at 24 h post-dose, *CI* confidence interval, *C_{max}* maximal observed concentration, *GM* geometric mean, *GMR* geometric mean ratio, *ln* natural log, *LSM* least squares mean, *max* maximum, *min* minimum, *SD* standard deviation, *t_{max}* time to reach the maximum observed concentration, *$t_{½}$* apparent terminal elimination half-life

[a]Back-transformed LSM (i.e. GM) and 95% CI from linear mixed-effects model performed on ln-transformed values

[b]Median (min, max)

[c]Harmonic mean (pseudo-SD)

[d]Back-transformed LSM difference (i.e. GMR) and 90% CI from linear mixed-effects model performed on ln-transformed values

M9 accumulation ratios for AUC_{0-24h} over the 10–100 mg dose range were independent of dose, and ranged from 0.97–1.04. M9 median time to 90% of steady state was 1 day following multiple dosing at all doses studied, and 1–3 days were required to attain steady state.

4 Discussion

The primary objective of this first-in-human administration trial of suvorexant in a multiple-dose regimen was to investigate the safety and tolerability of suvorexant in healthy young men. Following single and multiple nightly dosing of active compound (14 days in total), no significant safety signals were observed that would preclude further clinical development. Overall, the safety and pharmacokinetic data supported the appropriateness of once-nightly administration and aided the design of subsequent clinical trials.

The most frequently reported AEs in this trial were somnolence, fatigue, and headache. Notably, somnolence was reported at a higher rate (17–83% for suvorexant 10–100 mg) than in other trials of suvorexant in healthy young adults. For instance, in a trial evaluating next-morning driving performance after single and multiple dosing (8 consecutive nights) of suvorexant in healthy

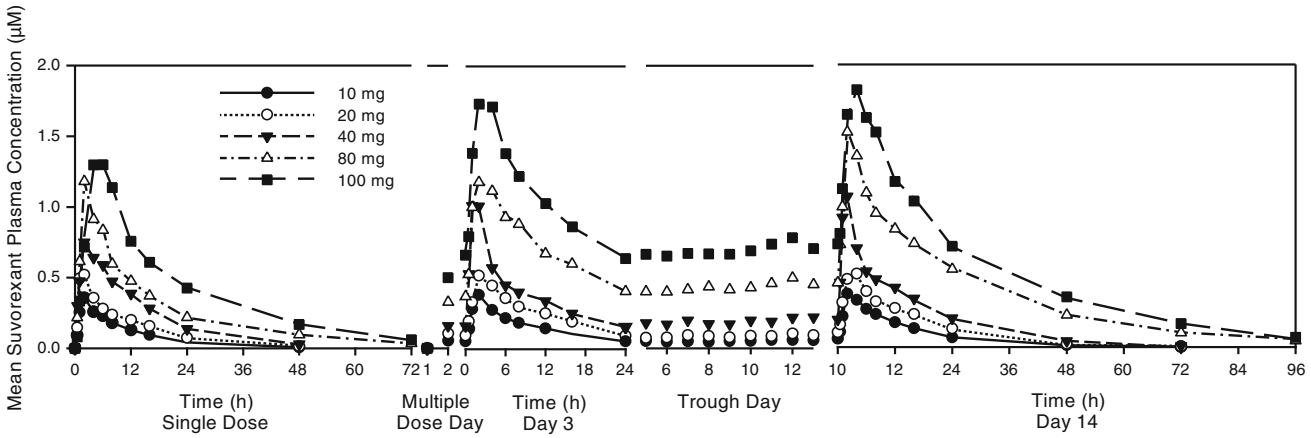

Fig. 2 Mean pharmacokinetic plasma concentrations vs time following single and once-daily multiple doses of 10–100 mg of suvorexant for 14 days (n = 5–6 per dose) (linear scale)

adults aged 23–64 years, somnolence was reported in 14% of subjects who received suvorexant 20 mg, and 25% of those who received suvorexant 40 mg [19]. However, the incidence of somnolence and its duration in the current trial should be interpreted with caution in light of the multiple pharmacokinetic sampling and pharmacodynamic endpoint measurements performed 1.5 h after nighttime dosing and throughout the night. The apparent higher incidence of somnolence may be a consequence of the nighttime procedures, which may have exacerbated the frequency and severity of somnolence.

Erectile dysfunction and phlebitis were reported by 2 subjects each in the suvorexant 20 and 100 mg groups, respectively. The events of erectile dysfunction were mild, deemed possibly related to study drug, and lasted in duration for 10–12 days. For those reporting phlebitis, the events were mild, deemed unrelated to study drug, and lasted in duration for 2–4 days. Subjects recovered in all instances.

In addition to an acceptable safety profile, the pharmacokinetic profile (secondary endpoint) of suvorexant supported once-nightly dosing and was used subsequently to inform dose-range selection in a Phase 2 trial [11], where once-nightly doses of 10, 20, 40, and 80 mg were investigated. The totality of the clinical experience with suvorexant, where efficacy observed in the Phase 2 and 3 trials was balanced against safety and residual effects, resulted in clinically approved doses marketed in the USA of 5, 10, 15, and 20 mg [20]. There was no evidence of time-dependent changes in pharmacokinetics following multiple dosing; accumulation ratios and time to steady state were consistent with that expected based on single-dose $t_{½}$.

Suvorexant and M9, an oxidative metabolite resulting from hydroxylation at the benzylic position of the parent compound, were the predominant circulating species in human plasma, and M9 exposure was similar to suvorexant. Based on the plasma pharmacokinetics of M9, the $t_{½}$ for M9 was similar to that observed for suvorexant, suggesting that metabolite elimination may be formation-rate-limited. Steady state for M9 was achieved after 1 day for all doses following 14 days of suvorexant administration. Aromatic hydroxylation and dechlorination of the M9 benzoxazole substituent affords metabolite M17. Plasma levels of M17 after a single dose ($\sim$ 2%) relative to day 3 (6%) and day 14 (9–10%) of multiple dosing suggested that M17 reached steady state by day 14. M9 and M17 have also been detected in plasma in preclinical safety studies. In addition, M12, a glucuronide of an oxidative metabolite (M10a), which has also been detected in preclinical species, accounted for 12–17% of suvorexant-derived material on day 14. M10a was present in human feces in the human ADME trial, with a minimal quantity observed in human plasma [17].

In vitro assessments and in vivo canine studies have suggested that M9 and M17 do not contribute to the pharmacological activity of suvorexant [17]. M17 shows reduced binding affinity for OX_1R and OX_2R compared with suvorexant [21]. Although M9 showed similar affinity to suvorexant for both OXRs in vitro, both M9 and M17 are P-glycoprotein substrates in humans and brain penetration is likely to be limited in vivo. As M12 is a glucuronide conjugate of an oxidative metabolite, it is unlikely to be pharmacologically active or to cross the blood–brain barrier.

As discussed above, the requirement for nighttime awakenings for data collection is one limitation of this trial, as this may have influenced the safety findings, particularly regarding reports of somnolence and fatigue. Another factor that may limit the interpretation of the results is that the subjects enrolled in this trial were healthy subjects aged 18–45 years, potentially limiting generalizability of the safety findings to elderly individuals and patients with insomnia. The overall clinical program in patients with insomnia included elderly patients treated with doses of 15

and 30 mg and suvorexant was generally well tolerated in this population [22].

5 Conclusion

The current first-in-human trial demonstrated that suvorexant was generally well tolerated in healthy young men over the range of single and multiple doses investigated. The pharmacokinetic data are supportive of once-nightly dosing and helped inform dosing regimens in subsequent trials.

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Compliance with Ethical Standards

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Conflict of interest KLY, JM, DP, WL, NL, TC, and REW are current or former employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and may own stock and/or stock options. At the time of the trial, SR was an employee of SGS Life Sciences Services, a Contract Research Organization contracted by Merck & Co., Inc., Kenilworth, NJ, USA, to conduct the trial.

Ethical approval All procedures performed in trials involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual subjects included in the trial.

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