Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Pharmacokinetics, Pharmacodynamic, Safety and Tolerability of Fazamorexant, a Novel Dual Orexin Receptor Antagonist: Report of the First-in-Human Study

Jun Ni[1], Lu Jin[2], Dong Zhao[1], Wen Zhang[1], Baoshun Li[1], Xingxing Huang[2], Xiaohua Hao[3]

[1]Beijing Ditan Hospital, Capital Medical University, Beijing, People's Republic of China; [2]Yangtze River Pharmaceutical Group Co, Ltd., Taizhou, People's Republic of China; [3]Beijing Shijitan Hospital, Capital Medical University, Beijing, People's Republic of China

Correspondence: Xiaohua Hao, Beijing Shijitan Hospital, Capital Medical University, Beijing, People's Republic of China, Email xiaohualuck@sina.com; Xingxing Huang, Yangtze River Pharmaceutical Group Co, Ltd, Taizhou, People's Republic of China, Email xingxingh@haiyanpharma.com

Purpose: This is the first-in-human study to investigate the pharmacokinetic and pharmacodynamic profiles, safety, and tolerability of Fazamorexant (a novel dual orexin receptor antagonist) in healthy subjects.

Methods: Here, we summarize pharmacokinetic, pharmacodynamic, and safety data from the randomized, double-blind placebo-controlled studies in healthy adults: single ascending doses (2–80 mg; N = 64), multiple ascending doses (10–60 mg; N = 40).

Results: Following single and multiple dosing, the pharmacokinetic profile was characterized by quick absorption and elimination, with median t_{max} of 0.625–1.25 h and arithmetic mean $t_{1/2}$ of 1.91–3.68 h. C_{max} and $AUC_{0\text{-}t}$ were positively correlated with doses and no apparent Fazamorexant plasma accumulation was detected on Day 7. The hypnotic effects were observed after administration and the effects of high dose groups were slightly higher than that of low dose groups, the results of pharmacodynamics showed a dose-dependent effect and the change in SSS from baseline was greatest in the 80 mg group (2.5). There were no clinically relevant effects of gender on Fazamorexant pharmacokinetics. No serious dose-dependent adverse events (AEs) or deaths were observed during the study.

Conclusion: Fazamorexant at a single dose of 2–80 mg or 10–60 mg at multiple doses presented satisfactory safety and tolerability in healthy subjects. The findings in this comprehensive first-in-humans study support the continued investigation of Fazamorexant as a therapeutic option for insomnia therapy.

Keywords: first-in-humans, Fazamorexant, orexin receptor antagonist, pharmacokinetics, pharmacodynamics, safety

Introduction

Insomnia, a common sleep disorder, is characterized by difficulty falling asleep and difficulty maintaining sleep.[1] In recent years, the incidence of insomnia has been on the rise, with prevalence rates ranging from 35% to 50% of the adult population for insomnia symptoms, and 10–20% for insomnia disorder.[2–4] To date, most hypnotic drugs mainly act on gamma-aminobutyric acid (GABA) receptor channel coupling, including barbiturates, benzodiazepines, non-benzodiazepines (such as Zolpidem, Zopiclone, Zalyplon, etc).[5] Nevertheless, such drugs bear abuse potential as well as serious adverse reactions such as psychiatric disorders and insomnia rebound.[6,7] Due to the low likelihood of withdrawal reactions, medications based on new mechanisms, for instance, melatonin receptor agonists (Ramelteon)[8,9] and histamine-1 (H1) receptor antagonists (low-dose Doxepin)[10,11] are gradually being used for insomnia treatment. However, the potential side effects they may cause consist of gastrointestinal reactions, abnormal thinking, allergic reactions, and central nervous system suppression, which cannot be ignored.[5,12]

Fazamorexant (YZJ-1139), a novel oral medication for insomnia treatment, is a member of the dual orexin receptor antagonists that blocks both orexin type 1 receptors (OX1Rs) and OX2Rs selectively, resulting in a rapid transition to

Received: 19 November 2024
Accepted: 28 April 2025
Published: 19 June 2025

sleep via inhibiting the activity of wake-promoting neurons.[13,14] Different from GABA receptor modulators that primarily increase non rapid eye movement (NREM) sleep, orexin receptor antagonists increase the maintenance time of REM sleep as well as non-rapid eye movement (NREM) sleep, which are closer to physiological sleep.[15–17] The dual orexin receptor represents a sound strategy for treating insomnia, as pre-clinical and clinical data support the efficacy and safety of orexin receptor antagonists, several of them have been translated from basic research to clinical interventions.[18] Currently, three orexin receptor antagonists have been approved for the treatment of primary insomnia, Suvorexant (MK-4305) was the first, approved in 2014,[19] followed by Lemborexant in 2019 and Daridorexant in 2022[20,21] The results of in-vitro experiments show that the IC_{50} of Fazamorexant on OX1R and OX2R is 32 nM and 41 nM, and that of Suvorexant were 147 nM and 126 nM, respectively. Moreover, compared to Suvorexant, Fazamorexant showed better receptor selectivity and safety in its excitatory or antagonistic effects against 21 G Protein-Coupled Receptor (GPCR) targets (Table S1), making it a new strategy for insomnia therapy. Up to now, Fazamorexant has applied for 39 patents worldwide and has completed a number of clinical trials including the single- and multiple -dose escalation, drug-drug interaction, special population and insomnia patients (https://clinicaltrials.gov/search?cond=YZJ-1139). The chemical structure of Fazamorexant is shown in Figure S1.

Here, we describe the first-in-human single- and multiple-dose escalation studies investigating the pharmacokinetic and pharmacodynamic profiles, safety, and tolerability of Fazamorexant in healthy subjects.

Materials and Methods

Study Subjects

Eligible subjects were men or women aged 18–45 years with a body mass index of 19–24 kg/m^2 and were evaluated to be healthy based on comprehensive physical examination (vital signs, height, weight, chest and abdomen examination, etc), laboratory tests (blood routine, blood biochemistry, urine routine, electrocardiogram, infectious disease screening, etc), 12-lead electrocardiogram, abdominal B-ultrasound (Liver, gallbladder, pancreas, spleen and kidney), frontal and lateral chest X-ray. Subjects were excluded if they had a history of alcohol abuse, or had a positive alcohol test, or smoked more than 5 cigarettes per day for the 3 months prior to the trial, or consumed excessive amounts of tea and coffee (more than 8 cups) per day, or frequently used sedation, sleeping pills or other addictive drugs, or with drug screening positive. Subjects who took any prescription drugs and Chinese herbs within 1 month, and CYP3A enzyme inhibitors (itraconazole, erythromycin, boceprevir, etc), CYP3A enzyme inducers (rifampicin, carbamazepine, etc) and/or CNS inhibitors (benzodiazepines, opioids, tricyclic antidepressants, etc) within 14 days were also excluded. Subjects were prohibited from using any drug during the trial, except due to adverse events. Pregnant or lactating subjects were excluded.

Study Design and Treatment

Both studies had a randomized, double-blind, single-center, placebo-controlled, dose-escalation design to evaluate the tolerance, safety, pharmacokinetics and pharmacodynamics of Fazamorexant tablets in healthy subjects. The clinical study protocol and informed consent forms were approved by the Ethics Committee of the Capital Medical University Beijing Ditan Hospital-Clinical Research Institute. Our study followed the World Medical Congress Declaration of Helsinki and Good Clinical Practice guidelines. All subjects have provided written informed consent forms prior to their participation in the study.

In this trail, block randomization was used to randomized the single-ascending-dose (SAD) and multiple-ascending-dose (MAD) study, respectively. Randomization schemes were generated by independent statisticians not associated with this trial. After signing the consent form, each subject was assigned a subject number and screened, and those who met the criteria were assigned a unique randomization number, which was used to determine which treatment group to receive. Random numbers were assigned in ascending order.

There were seven dose cohorts of Fazamorexant to evaluate the PK profiles of SAD study (2 mg: n = 4, experimental drug-to-placebo ratio was 2:2; 5, 10, 20, 40, 60 and 80 mg: n = 10, experimental drug-to-placebo ratio was 8:2 per dose cohort). First, 4 subjects were enrolled in the 2 mg cohort of the SAD study before the subsequent study, and 10 subjects were then enrolled in the 5 mg cohort of the SAD study after safety evaluation. The administration of Fazamorexant was

 https://doi.org/10.2147/DDDT.S501111

initiated with the lowest dose (2 mg) and the same subject received only one dose. According to the safety and tolerability of SAD, four dose cohorts (10, 20, 40 and 60 mg: n = 10, study drug-to-placebo ratio was 8:2 per dose cohort) were selected for MAD study, and each dose was administrated orally for 7 consecutive days. To ensure double-blinding in this trail, the investigational drugs had the identical appearance and packaging.

In both SAD and MAD study, subjects were required to fast for at least 10 h starting on the day before study drug administration and took oral administration with 240 mL of water from the next morning. 4 h and 10 h after administration, subjects ate the standard meal, respectively. During the study period, strenuous exercise and smoking were avoided. No tea, coffee and other beverages containing coffee and alcoholic beverages were permitted.

Analysis of Pharmacokinetic Profiles

In the SAD study, the blood samples (3 mL each) were collected with an indwelling intravenous catheter at different time points: 0 h (predose) and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 h after dosing. Samples in the MAD study were collected before drug administration on day 1, 5, 6 and were collected before drug administration, at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 h after drug administration on day 7. All of the biological samples were stored at −80°C before further analysis. After the samples were pretreated by protein precipitation, the quantification of the plasma concentrations of Fazamorexant was performed using high performance liquid chromatography and tandem mass spectrometry (HPLC-MS/MS) method. The chromatography was performed on Waters, Acquity BEH C18 column, 1.7 μm 50×2.1 mm. The mass spectrometer detected in positive ion mode and scanning mode was multiple reaction detection (MRM). The ionic reactions used for quantitative analysis were m/z 433.1→197.0 (Fazamorexant) and m/z 436.1→200.0 (internal standard). The validated accuracy, linearity, sensitivity, specificity, matrix effect, relative recovery, stability of the analytical method were determined according to the FDA Guidelines on bioanalytical validation.

Pharmacokinetic parameters were calculated using a non-compartmental model by WinNonlin Software version 6.4 (Pharsight, Cary, NC, USA). Main PK parameters included area under the concentration–time curve (AUC), AUC from time zero (pre-dose) to the time of the last measurable concentration ($AUC_{0\text{-}t}$), AUC from time zero (pre-dose) to infinity ($AUC_{0\text{-}inf}$), maximum observed plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal elimination half-life ($t_{1/2}$), apparent distribution volume (V_z/F), clearance rate (CL/F), and mean retention time (MRT). $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ were calculated using the linear up/log down method. T_{max} and C_{max} were based on the actual measured values. MRT was mean residence time from the time of dosing to the time of the last measurable concentration, which is $AUMC_{last}/AUC_{last.}$

Pharmacodynamic Assessment

The pharmacodynamic of Fazamorexant were assessed using Stanford sleepiness scale (SSS): screening period, 1 h (± 15 min) after administration on Day 1, 9:00 am (± 15 min) on Day 2 and Day 3 (SAD); screening period, 1 h (± 15 min) after administration on Day 1–7, 9:00 am (± 15 min) on Day 8, and Day 14 ± 1 (MAD). In addition, subjects receiving multiple dosing were required to fill out the sleep diary forms within 30 minutes of each wake up in the morning of baseline, Day 1–7, and Day 8. Bedtime = time of getting up - time of going to bed. Wake time after falling asleep was the time period between the point of falling asleep and the point of active/inactive wake time. Since the drug was administered during the day, in order to initially explore the efficacy of the treatment for insomnia, the total sleep time was agreed to be the sum of the time after falling asleep and waking up within 24 hours, and Sleep efficiency (%) = total sleep time/bedtime × 100%.

Safety Assessment

Adverse events (AE) and serious adverse events (SAE) were evaluated with reference to NCI-CTCAE 4.03 through physical examination, vital signs, electrocardiogram (ECG), laboratory tests of hematuria routine, blood biochemistry, coagulation function, blood pregnancy (only for female subjects), evaluation of cognitive scale (including scores in various dimensions: orientation, memory, attention, numeracy, recall or language ability and total score): screening period and Day 3 (SAD); screening period and Day 14 ± 1 (MAD). The incidence and severity of any AEs were recorded throughout the trial from direct observation of events and subjects' spontaneous reports. The clinical study would be terminated if: more than half of the subjects had grade II drug-related AEs; or more than a quarter of subjects had grade III–IV drug-related AEs; or 1 case of drug-related SAE; it indicated that the subjects could not tolerate it; major errors in the clinical trial protocol were found in the trial, making it difficult to evaluate the drug.

Statistical Analysis

The recommended population size for a PK study, according to the "Technical Guidelines for Clinical Pharmacokinetic Studies of Chemical Drugs" issued by the China National Medical Products Administration (NMPA), is 8–12 subjects per dose group. Therefore, both SAD and MAD in this study were planned to randomly assign 8 subjects to receive the experimental drug and 2 subjects to receive placebo in each group, except for the 2 mg group (2 subjects to receive the experimental drug and 2 subjects to receive placebo). No formal statistical sample size calculation was performed in this study. The final sample size of the trial depended on the number of dose levels evaluated in the dose escalation phase and the occurrence of adverse effects of Fazamorexant tablets. 104 participants were expected to be enrolled to evaluate the tolerability and safety of single and multiple doses of Fazamorexant tablets.

The analysis of pharmacokinetic data was performed using Phoenix WinNonlin software (version 6.4). The pharmacokinetic parameters of each subject were calculated by non-compartmental analysis (NCA). Arithmetic mean, standard deviation, coefficient of variation, quartile, maximum, minimum and arithmetic mean of each parameter were calculated.

The dose ratio correlation of Fazamorexant was evaluated by Power Model. If the 90% confidence interval of the C_{max}, AUC_{0-t} slope is between $(1+\ln(\theta_L)/\ln(r)$~$1+\ln(\theta_H)/\ln(r))]$, PK parameters are considered to be linearly dependent on dose. The convention for θ_L and θ_H is $\theta_L = 0.80$ and $\theta_H=1.25$, and r = highest dose/lowest dose.

Descriptive statistical analysis was carried out on each visit observation value and the relative changes of baseline of pharmacodynamic indexes.

Results

Baseline Characteristics

A total of 313 healthy adult male and female subjects were screened in Capital Medical University Beijing Ditan Hospital, of whom 104 were selected and enrolled including 64 in the SAD and 40 in the MAD study. Some subjects failed screening due to weight or BMI inadequacy or failed physical examination. Among them, all subjects completed the trial, and no subjects withdrew from the trial in the SAD study and 1 subject in the placebo group dropped out due to the serious protocol violations/deviations in the MAD study. Table S2 presented the baseline demographic of the subjects.

Pharmacokinetic Properties

The Fazamorexant plasma concentration–time profiles and pharmacokinetic parameters after a single dose of Fazamorexant treatment are shown in Figure 1A and B and Table 1. After a single-dose administration of Fazamorexant within the range from 2 mg to 80 mg, the median T_{max} value was calculated to be 0.625–1.25 h. In all dose cohorts of Fazamorexant, the arithmetic mean $t_{1/2}$ of Fazamorexant was 1.91–3.68 h. In the different dose cohorts (2–80 mg) of Fazamorexant, the C_{max} of Fazamorexant increased from 155 ng/mL to 1970 ng/mL as the dose increased. The values of AUC also increased in a dose-dependent manner.

The Fazamorexant concentration–time profiles after treatment with multiple doses are presented in Figure 1C and D. In addition, the plasma pharmacokinetic parameters of Fazamorexant are shown in Table 2. The median T_{max} values after multiple dosing were 0.63–1.00 h on days 7. Moreover, the arithmetic mean $t_{1/2}$ of Fazamorexant was 2.41 h–3.07 h. The arithmetic mean of C_{max} (CV%) were 688 ng/mL (31.6%), 1030 ng/mL (24.6%), 1550 ng/mL (29.5%) and 2200 ng/mL (26.5%), for 10 mg, 20 mg, 40 mg, and 60 mg dose groups, respectively. Arithmetic mean AUC_{0-t} values also increased with increasing dose over the range of 10 mg to 60 mg.

After 7 days of continuous administration, the accumulation ratio (AR) of AUC_{0-24} in Fazamorexant dose groups 10 mg, 20 mg, 40 mg and 60 mg were 1.80, 1.27, 1.08 and 1.03, respectively; the AR of C_{max} were 1.42, 1.12, 0.985 and 1.21, respectively (Table 3). As presented in Table 4, the 90% confidence intervals for the slopes of ln C_{max} to ln Dose were not

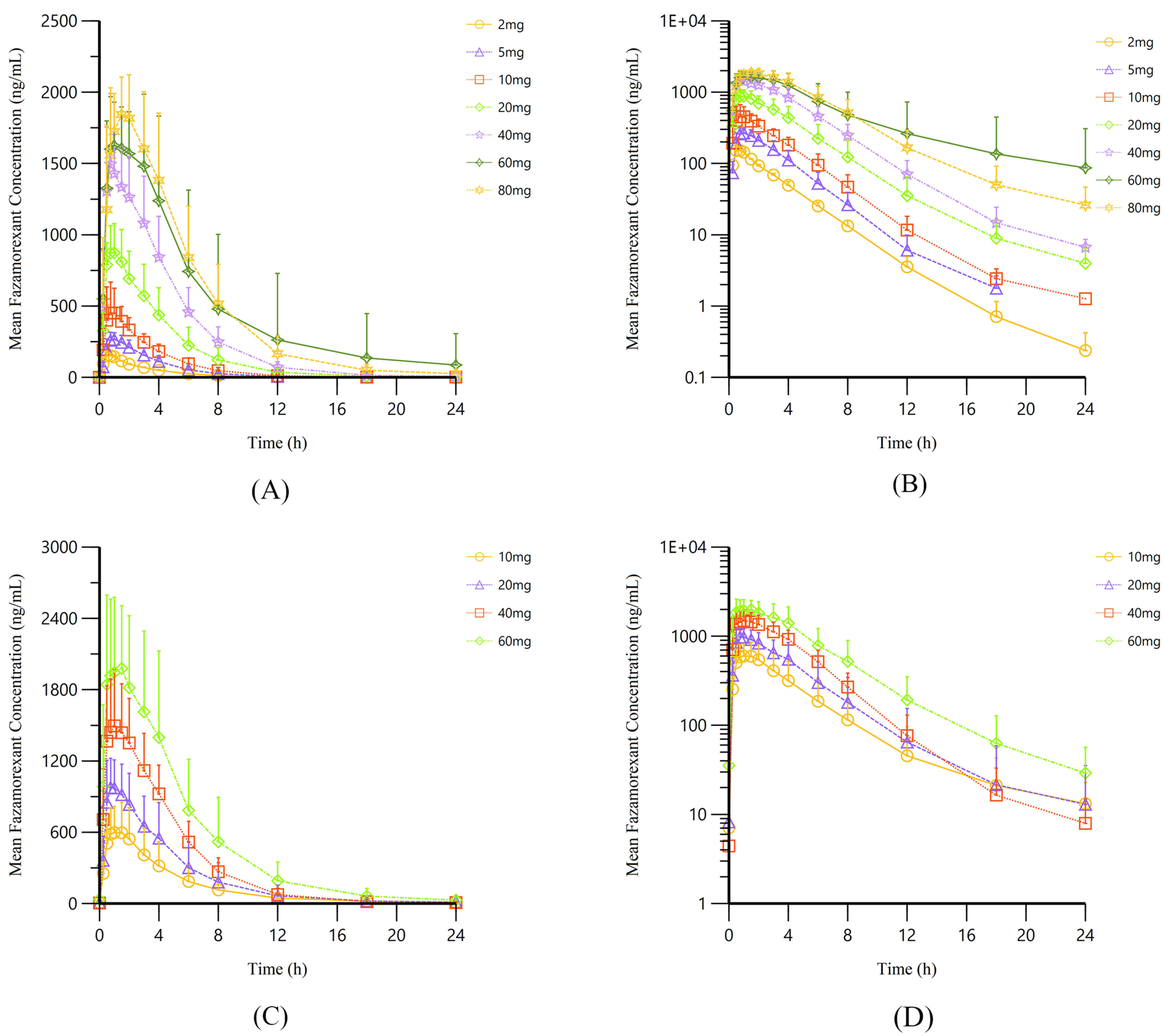


Figure 1 The plasma concentration–time profiles of Fazamorexant in single-ascending-dose study (**A**) linear scale; (**B**) semi-log scale.The plasma concentration–time profiles at Day 7 of Fazamorexant in multiple-ascending-dose study (**C**) linear scale; (**D**) semi-log scale.

included in the linear determination interval, suggesting that C_{max} is positively correlated with dose, but exhibits a less than dose-proportional increase over the range of 5–80 mg for single administration and 10–60 mg for multiple administration. The 90% confidence intervals for the slopes of ln $AUC_{0\text{-}t}$ to ln Dose of Fazamorexant were not completely included in the linear determination interval, which indicates that the linear relationship between $AUC_{0\text{-}t}$ and dose in the above dose ranges could not be definitively concluded.

Furthermore, the comparison of exposure levels of Fazamorexant in subjects of different genders is shown in Table 5. In the single dose range of 2–80 mg, the ratios of $AUC_{0\text{-}t}$ (male/female) and C_{max} (male/female) were 0.697–2.11 and 0.822–1.21, respectively. The ratio of $AUC_{0\text{-}t}$ (male/female) in the dosage range of 10–60 mg for continuous administration of Fazamorexant was 0.507–1.36, and the ratio of C_{max} (male/female) was 0.741–0.96, thus indicating that the pharmacokinetics parameters of Fazamorexant are similar in both the male and female subjects.

Table 1 Plasma Pharmacokinetic Parameters of Fazamorexant in Single-Ascending-Dose Study

	2 mg	5 mg	10 mg	20 mg	40 mg	60 mg	80 mg
	(N=2)	(N=8)	(N=8)	(N=8)	(N=8)	(N=8)	(N=8)
*T_{max} (h)	0.625 (0.501, 0.749)	0.878 (0.751, 1.50)	0.753 (0.502, 1.50)	0.877 (0.501, 1.50)	0.876 (0.500, 1.00)	0.880 (0.500,4.00)	1.25 (0.754, 2.00)
$t_{1/2}$ (h)	2.40	1.91±0.252 (13.2%)	2.00±0.374 (18.7%)	2.21±0.541 (24.5%)	2.46±0.462 (18.8%)	3.68±2.86 (77.9%)	3.35±1.40 (41.9%)
C_{max} (ng/mL)	155	285±43.7 (15.4%)	485±187 (38.6%)	919±206 (22.4%)	1570±451 (28.7%)	1820±386 (21.2%)	1970±245 (12.5%)
AUC_{0-t}(ng·h/mL)	525	1020±288 (28.3%)	1740±555 (31.9%)	3910±1550 (39.8%)	7240±2190 (30.2%)	11900±9190 (77.3%)	11500±3290 (28.5%)
AUC_{0-inf}(ng·h/mL)	526	1030±288 (28.0%)	1750±555 (31.8%)	3920±1560 (39.8%)	7270±2200 (30.2%)	13100±12500 (95.3%)	11700±3390 (29.1%)
CL/F (L·h-1)	3.83	5.25±1.61 (30.7%)	6.31±2.15 (34.0%)	6.03±2.94 (48.7%)	6.15±2.54 (41.2%)	6.57±2.86 (43.5%)	7.38±2.12 (28.8%)
V_z/F (L)	13.1	14.2±3.48 (24.6%)	17.3±3.00 (17.4%)	17.6±4.67 (26.6%)	20.6±4.43 (21.5%)	26.2±3.96 (15.1%)	33.5±11.1 (33.0%)
MRT (h)	3.30	3.18±0.491 (15.4%)	3.34±0.637 (19.0%)	3.56±0.720 (20.3%)	3.93±0.517 (13.1%)	4.83±2.10 (43.6%)	4.72±1.08 (22.8%)

Notes: Data are expressed as the arithmetic mean±standard deviation (% coefficient of variation). *Presented as median (minimum, maximum).
Abbreviations: T_{max}, time to reach maximum concentration; $t_{1/2}$, terminal elimination half-life; C_{max}, maximum observable concentration; AUC_{0-inf}, area under the concentration–time curve from time 0 to infinity; CL/F, apparent clearance; V_z/F, apparent volume of distribution; MRT, mean residence time, was mean residence time from the time of dosing to the time of the last measurable concentration, which is $AUMC_{last}/AUC_{last}$.

Table 2 Plasma Pharmacokinetic Parameters at Day 7 of Fazamorexant in Multiple-Ascending-Dose Study

	10 mg	20 mg	40 mg	60 mg
	(N=8)	(N=8)	(N=8)	(N=8)
*T_{max} (h)	0.755 (0.501, 2.00)	0.630 (0.502, 1.00)	1.00 (0.503, 1.50)	0.751 (0.498, 3.00)
$t_{1/2}$ (h)	3.01±1.39 (46.2%)	2.56±0.850 (33.3%)	2.41±0.631 (26.1%)	3.07±0.978 (31.9%)
C_{max} (ng/mL)	688±217 (31.6%)	1030±253 (24.6%)	1550±456 (29.5%)	2200±583 (26.5%)
AUC_{0-tau} (ng·h/mL)	3150±1930 (61.2%)	4960±2580 (52.1%)	7800±2350 (30.1%)	12,200±5740 (46.9%)
Cl_{ss}/F (L/h)	4.32±2.27 (28.0%)	4.86±1.98 (40.8%)	5.76±2.58 (44.7%)	6.05±3.10 (51.2%)
V_{ss}/F (L)	15.2±4.27 (28.0%)	16.2±3.74 (23.1%)	18.7±4.80 (25.7%)	23.4±5.40 (23.0%)

Notes: Data are expressed as the arithmetic mean±standard deviation (% coefficient of variation). *Presented as median (minimum, maximum).
Abbreviations: T_{max}, time to reach maximum concentration; $t_{1/2}$, terminal elimination half-life; C_{max}, maximum observable concentration; AUC_{0-tau}, area under the concentration–time curve from time 0 until end of the dosage interval; Cl_{ss}/F, apparent clearance at steady state; V_{ss}/F, apparent volume of distribution at steady state.

Table 3 Accumulation Ratios in Fazamorexant Dose Groups After 7 days of Continuous Administration

Dose (mg)	Pharmacokinetic parameters	Day 7	Day 1	Accumulation ratio
10	AUC_{0-24} (ng·h/mL)	3150	1740	1.80
20		4960	3910	1.27
40		7800	7250	1.08
60		12200	11900	1.03
10	C_{max} (ng/mL)	688	485	1.42
20		1030	919	1.12
40		1550	1570	0.985
60		2200	1820	1.21

Notes: Day 1 and Day 7 data are expressed as the arithmetic mean.

Table 4 Slope and 90% CI of Ln(AUC) or Ln(C_{max}) From Power Model

Day	Dependent	Slope	Standard Error	Denom_DF	Conf_Level	T_critical	90% CI (lower)	90% CI (upper)
1[a]	LnC_{max}	0.732	0.0394	46	90	1.68	0.666	0.799
1[a]	Ln$AUC_{0\text{-}t}$	0.920	0.0556	46	90	1.68	0.827	1.01
7[b]	LnC_{max}	0.640	0.0703	30	90	1.70	0.521	0.759
7[b]	Ln$AUC_{0\text{-}t}$	0.780	0.123	30	90	1.70	0.571	0.988

Notes: a: If the slope and 90% CI range of Ln(AUC) or Ln(C_{max}) from 0.920 to 1.08, ie (1+ln (0.8)/ln (80/5) ~1 +ln (1.25)/ln (80/5)), the effect is considered to be linearly dose-dependent in single-ascending-dose study. b: If the slope and 90% CI range of Ln(AUC) or Ln(C_{max}) from 0.875 to 1.12, ie (1+ln (0.8)/ln (60/10) ~1 +ln (1.25)/ln (60/10)), the effect is considered to be linearly dose-dependent in multiple-ascending-dose study.

Table 5 Gender-Specific Analysis of $AUC_{0\text{-}t}$ and C_{max} of Fazamorexant

		SAD							MAD			
		2 mg	5 mg	10 mg	20 mg	40 mg	60 mg	80 mg	10 mg	20 mg	40 mg	60 mg
		Male 1, Female 1	Male 5, Female 3	Male 4, Female 4	Male 4, Female 4	Male 5, Female 3	Male 4, Female 4	Male 5, Female 3	Male 4, Female 4	Male 4, Female 4	Male 4, Female 4	Male 5, Female 3
C_{max}(ng/mL)	Male	169	272	437	877	1490	1960	1950	586	1010	1370	2170
	Female	140	305	532	961	1700	1680	1990	790	1050	1730	2250
	Ratio	1.21	0.891	0.822	0.913	0.881	1.17	0.977	0.741	0.956	0.791	0.968
$AUC_{0\text{-}t}$(ng·h/mL)	Male	566	891	1430	3570	7430	16100	10300	2110	5430	7640	13,600
	Female	483	1240	2050	4250	6940	7640	13500	4170	4480	7960	9970
	Ratio	1.17	0.72	0.697	0.84	1.07	2.11	0.763	0.507	1.21	0.96	1.36

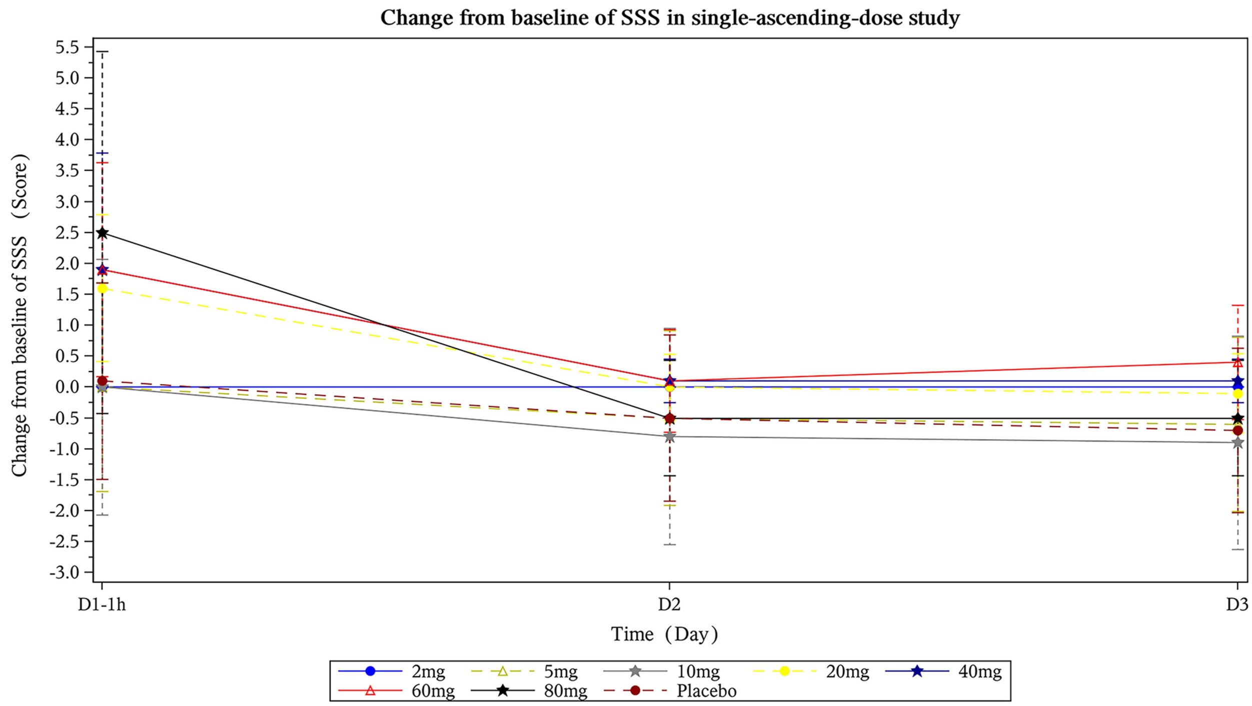
Notes: Data of male and female are expressed as the arithmetic mean; ratios are expressed as male/female.

Pharmacodynamic Assessment

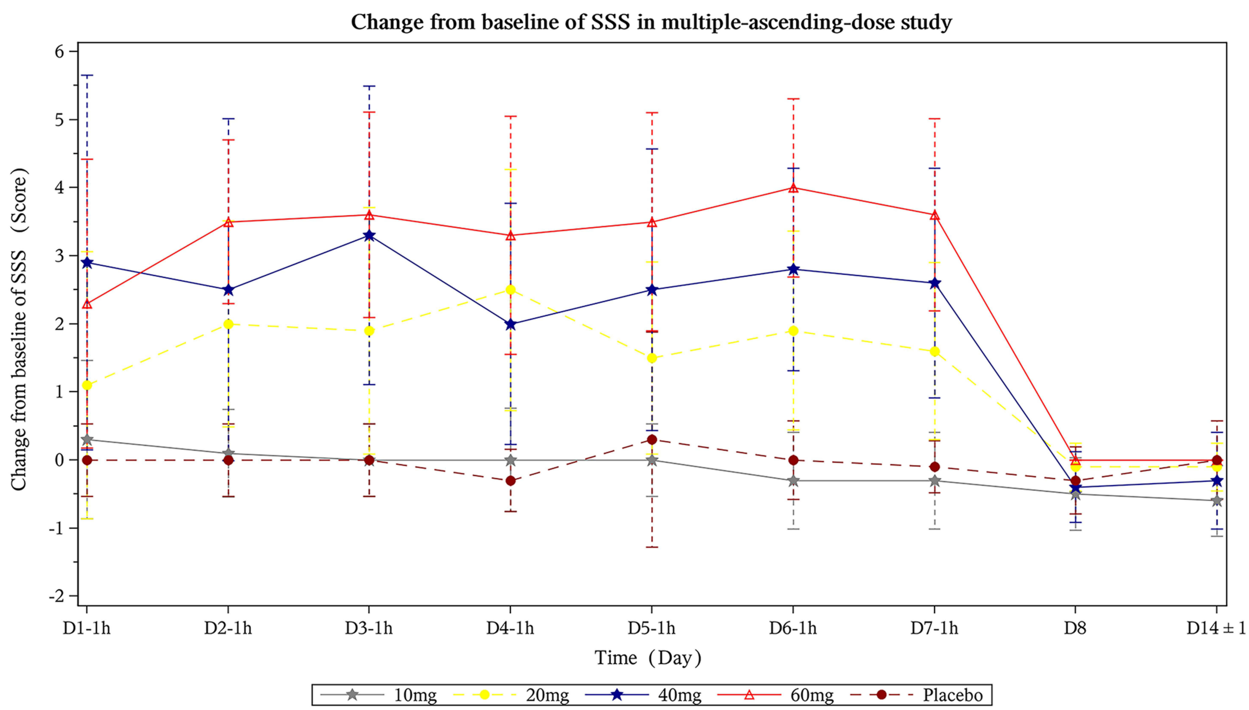
Subjects were asked to evaluate their sleepiness on the Stanford sleepiness scale (SSS), a standard way of self-assessing sleepiness on a seven-point scale, with higher scores indicating more severe sleepiness. In the SAD study, the evaluations at 1 h after Day 1 administration showed that Fazamorexant had the hypnotic effects on healthy subjects in the dose range of 2–80 mg and the maximum effect occurred at 80 mg, with the mean and standard deviation of 2.5 (2.93). Overall, the effects returned to baseline on Day 2 and Day 3 after drug intake, respectively (Figure 2A and Table S3A). In the MAD study, the hypnotic effects were also observed by the increased scale points of the evaluations at 1 h after administration on Day 1–7, which were positively correlated with the doses and returned to the baseline on Day 8 and Day 14±1 (Figure 2B and Table S3B). In addition, subjects receiving multiple dosing were required to fill out the sleep diary forms within 30 minutes of each wake up in the morning of baseline, Day 1–7, and Day 8, recording bedtime, wake up time, fall asleep time, and active/inactive wake time. The baseline total sleep time of all groups was approximately 2 h, which was due to the fact that the subjects checked in the day before drug administration, and the total sleep time of all groups was approximately 2 h as of 0 o 'clock that night. The administration's findings indicated that the high-dose group had slightly higher total sleep time and sleep efficiency than the low-dose group at each visit. Additionally, the placebo group exhibited the lowest total sleep time, ranging from 6 to 8 h, and a sleep efficiency of approximately 80% (Figure S2).

Safety and Tolerability

The drug-related treatment-emergent AEs (TEAEs) of all the enrolled subjects that observed were in the range of 50.0–87.5% (Fazamorexant) and 64.3% (placebo) in the SAD study, 87.5–100% (Fazamorexant) and 75.0% (placebo) in the MAD study, respectively. Overall, the most frequently occurring TEAEs were neurological symptoms including drowsiness, lethargy, and dizziness. All of the TEAEs in the SAD and MAD studies belong to CTCAE 4.03 grade I in severity. No serious TEAEs or TEAE-related deaths were reported during the study and no subjects discontinued Fazamorexant due to a TEAE. The number and percentage of healthy subjects experiencing TEAEs are summarized in Tables 6 and 7.



(A)



(B)

Figure 2 Change from baseline in Stanford sleepiness scale (**A**) single-ascending-dose study; (**B**) multiple-ascending-dose study.

Table 6 Drug-Related Adverse Events in Single-Ascending-Dose Study

Preferred Term	2 mg (N=2) n (%)	5 mg (N=8) n (%)	10 mg (N=8) n (%)	20 mg (N=8) n (%)	40 mg (N=8) n (%)	60 mg (N=8) n (%)	80 mg (N=8) n (%)	Placebo (N=14) n (%)
TEAEs	0	4 (50.0)	5 (62.5)	7 (87.5)	5 (62.5)	7 (87.5)	7 (87.5)	9 (64.3)
Drowsiness	0	3 (37.5)	5 (62.5)	7 (87.5)	1 (12.5)	1 (12.5)	1 (12.5)	8 (57.1)
Somnolence	0	1 (12.5)	0	0	4 (50.0)	5 (62.5)	6 (75.0)	0
Dizziness	0	0	0	0	0	1 (12.5)	0	0
White blood cell count decreased	0	0	0	0	0	0	1 (12.5)	1 (7.1)
The percentage of neutrophils decreased	0	1 (12.5)	0	0	0	0	0	0
Neutrophil count decreased	0	1 (12.5)	0	0	0	0	0	0
Fatigue	0	0	0	0	0	0	1 (12.5)	0
Irregular menstruation	0	0	0	0	0	0	0	1 (7.1)

Abbreviation: TEAEs, treatment-emergent adverse events.

Table 7 Drug-Related Adverse Events in Multiple-Ascending-Dose Study

Preferred Term	10 mg (N=8) n (%)	20 mg (N=8) n(%)	40 mg (N=8) n(%)	60 mg (N=8) n(%)	Placebo (N=8) n(%)
TEAEs	7 (87.5)	8 (100)	8 (100)	8 (100)	6 (75.0)
Drowsiness	6 (75.0)	8 (100)	8 (100)	8 (100)	5 (62.5)
Somnolence	0	0	2 (25.0)	1 (12.5)	0
Dizziness	0	2 (25.0)	0	0	0
Neutrophil count decreased	1 (12.5)	1 (12.5)	1 (12.5)	0	0
Creatinine increased	3 (37.5)	0	0	0	0
The percentage of neutrophils decreased	1 (12.5)	0	1 (12.5)	0	0
Alanine aminotransferase increased	0	0	0	0	1 (12.5)
Aspartate aminotransferase increased	0	0	0	0	1 (12.5)
White blood cell count decreased	1 (12.5)	0	0	0	0
Hyperuricemia	1 (12.5)	0	0	0	0
Colporrhagia	1 (12.5)	0	1 (12.5)	1 (12.5)	0
Ventricular extrasystole	1 (12.5)	0	0	0	0
Atrioventricular block	0	1 (12.5)	0	0	0
Upper respiratory infection	0	1 (12.5)	0	0	1 (12.5)
Naupathia	0	0	0	1 (12.5)	0
Stomachache	0	0	0	0	1 (12.5)

Abbreviation: TEAEs, treatment-emergent adverse events.

Discussion

Fazamorexant, a member of the dual orexin receptor antagonists family, is a new oral therapeutic candidate for insomnia treatment. During the recent decade, the development of orexin receptor antagonists has progressed. Our study was designed to assess the pharmacokinetic profiles, safety, and tolerability of Fazamorexant in healthy volunteers through a randomized, double-blind, single-center, placebo-controlled, dose-escalation Phase I trial.

According to the data of animal studies, the no observed-adverse-effect levels in dogs and rats are 120mg/kg and 70mg/kg, respectively, which correspond to 69.9mg/kg and 12.5 mg/kg of the recommended maximum starting doses in humans (safety factor: 10). Additionally, the initial effective dose of Fazamorexant in rats and machines are reported to be 3 mg/kg and 10 mg/kg, which is calculated to 1.8–6 mg in humans. Referring to the similar dual orexin receptor antagonists Suvorexant, its oral administration was conducted with the doses: 10 mg, 50 mg, 100 mg in a phase I study, and 10 mg, 20 mg, 40 mg, 80 mg in a Phase II study (for 4 weeks and crossover studies were performed).[22,23] As considering the above information, our trial was designed to randomly allocate healthy Chinese subjects to the different

 https://doi.org/10.2147/DDDT.S501111

oral dose cohorts of Fazamorexant to receive a single dose of 2 mg, 5 mg, 10 mg, 20 mg, 40 mg, 60 mg, 80 mg; a multiple dose of 10 mg, 20 mg, 40 mg, 60 mg; or placebo.

As compared with the results of the similar dual orexin receptor antagonists,[24–26] Fazamorexant showed quicker absorption and elimination, with median t_{max} of 0.625–1.25 h and arithmetic mean $t_{1/2}$ of 1.91–3.68 h, indicating faster onset time and weaker residual effect on the next day. The pharmacokinetic parameters of dual orexin receptor antagonists is shown in Table S4. When ascending doses of Fazamorexant over the range of 2–80 mg for single administration and 10–60 mg for multiple administration, there was a less than dose-proportional elevation in C_{max} and $AUC_{0\text{-}t}$. Indeed, in the SAD study, these parameters did not exhibit significant changes as the oral dose increased from 60 to 80 mg ($AUC_{0\text{-}t}$: 11900 vs 11500 ng·h/mL; C_{max}: 1820 vs 1970 ng/mL), implicating the possibility of drug absorption saturation. As an important factor affecting drug absorption, drug solubility reaches saturation at the absorption site, contributing to the maximum drug absorption.[27,28] Our findings may be due to the incomplete solubility of Fazamorexant formulation in the gastrointestinal tract, resulting in reducing bioavailability with increasing dosage. Moreover, the C_{max} accumulation ratio (AR) of the 10 mg, 20 mg, 40 mg, 60 mg dose groups were 1.42, 1.12, 0.99 and 1.21, respectively, and the AR of the AUC was 1.80, 1.27, 1.08 and 1.03, respectively, showing no apparent plasma accumulation of Fazamorexant doses after 7 days of continuous administration. Given the similar pharmacokinetic characteristics of Fazamorexant in male and female subjects, it is suggested that dose adjustment does not need to be based on gender.

Overall, the safety evaluation illustrated that a single dose (2–80 mg) or multiple doses (10–60 mg) of Fazamorexant presented satisfactory safety and tolerability in healthy Chinese subjects, with all the TEAEs belonging to CTCAE 4.03 grade I in severity and no serious TEAEs or deaths were observed during the trial. Notably, Fazamorexant also had no significant impact on cognitive functions following dose administration of up to 80 mg.

In fact, there was no obvious dose-related trend, with the higher proportion of subjects reporting TEAEs following administration of Fazamorexant than following administration of placebo (50.0–87.5% vs 64.3% in the SAD study, 87.5–100% vs 75.0% in the MAD study). Similar to previously published that neurological symptoms are the most frequent adverse drug reaction in insomnia patients who received orexin receptor antagonists agents,[18,23] in the current trial, the TEAEs with the highest incidence rate consist of drowsiness, drowsiness, and dizziness, with a total of 43 subjects (including 8 in the placebo group) for single administration and 35 subjects (including 5 in the placebo group) for multiple administration, surprisingly, there was no reports of adverse reactions involving headache in our SAD and MAD studies, which is inconsistent with the fact that it is the most common TEAE of Suvorexant in healthy men.[22] Over all, Fazamorexant has been identified in the acceptable degree of systemic exposure variability, suggesting that Fazamorexant might be applied as a potential medication for treating patients with insomnia.

Conclusion

The current trial revealed that Fazamorexant had an acceptable pharmacokinetic profile and was safe and well tolerated in healthy subjects who were administrated with a single dose of 2–80 mg or multiple doses of 10–60 mg. These findings support the continued investigation of Fazamorexant as a therapeutic option for insomnia therapy.

Study Highlights

What question did this study address?

Are the pharmacokinetic, pharmacodynamic, safety, and tolerability profiles of Fazamorexant in healthy subjects compatible with the requirements for a new oral therapeutic candidate for insomnia treatment?

What does this study add to our knowledge?

The current trial revealed that Fazamorexant had an acceptable pharmacokinetic profile and was safe and well tolerated in healthy subjects who were administrated with a single dose of 2–80 mg or multiple doses of 10–60 mg.

How might this change clinical pharmacology or translational science?

The current findings help inform dosing regimens in subsequent trials and support the continued investigation of Fazamorexant as a therapeutic option for insomnia therapy.

Registration Statement

According to the ICMJE recommendations, the authors declare that the study has been registered on http://www.chinadrugtrials.org.cn/ (registration number: CTR20170806, date: 2017-08-01) and retrospectively register on the WHO-recognized registry: https://clinicaltrials.gov/ (registration number: NCT06673927, date: 2024-11-05).

Data Sharing Statement

The authors intend to share individual deidentified participant data, such as the individual PK and the safety data, in form of supplementary data. The data will be available from the corresponding authors Xiaohua Hao and Xingxing Huang.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Sutton EL. Insomnia. *Ann Internal Med*. 2021;174:Itc33–itc48. doi:10.7326/AITC202103160
2. Mirchandaney R, Barete R, Asarnow LD. Moderators of cognitive behavioral treatment for insomnia on depression and anxiety outcomes. *Curr Psychiatry Rep*. 2022;24:121–128. doi:10.1007/s11920-022-01326-3
3. Dean YE, Shebl MA, Rouzan SS, et al. Association between insomnia and the incidence of myocardial infarction: a systematic review and meta-analysis. *Clin Cardiology*. 2023;46:376–385. doi:10.1002/clc.23984
4. Buysse DJ. Insomnia. *JAMA*. 2013;309:706–716. doi:10.1001/jama.2013.193
5. Zammit G. Comparative tolerability of newer agents for insomnia. *Drug Safety*. 2009;32:735–748. doi:10.2165/11312920-000000000-00000
6. Winrow CJ, Gotter AL, Cox CD, et al. Promotion of sleep by suvorexant-a novel dual orexin receptor antagonist. *J Neurogen*. 2011;25:52–61. doi:10.3109/01677063.2011.566953
7. Zheng JW, Meng SQ, Liu WY, Chang XW, Shi J. [Appropriate use and abuse of sedative-hypnotic drugs]. *Sichuan Da Xue Xue Bao Yi Xue Ban*. 2023;54:231–239. Danish. doi:10.12182/20230260302
8. Hardeland R. Investigational melatonin receptor agonists. *Expert Opin Invest Drugs*. 2010;19:747–764. doi:10.1517/13543784.2010.482926
9. Uchiyama M. [Melatonin receptor agonist]. *Nihon Rinsho Japan J Clin Med*. 2015;73:1017–1022. Danish
10. Dupuis G, Vaugeois JM. [The interesting anti-H1 effects in maintenance insomnia: a reflection on the comparative advantages of doxylamine and doxepin]. *L'Encephale*. 2020;46:80–82. doi:10.1016/j.encep.2019.01.006
11. Owen RT. Selective histamine H(1) antagonism: a novel approach to insomnia using low-dose doxepin. *Drugs Today*. 2009;45:261–267. doi:10.1358/dot.2009.45.4.1358835
12. Norman JL, Anderson SL. Novel class of medications, orexin receptor antagonists, in the treatment of insomnia - critical appraisal of suvorexant. *Nat Sci Sleep*. 2016;8:239–247. doi:10.2147/NSS.S76910
13. Han Y, Yuan K. Orexin receptor antagonists as emerging treatments for psychiatric disorders. *Neurosci Bulletin*. 2020;36:432–448. doi:10.1007/s12264-019-00447-9
14. Boss C, Roch C. Recent trends in orexin research--2010 to 2015. *Bioorg Med Chem Lett*. 2015;25:2875–2887. doi:10.1016/j.bmcl.2015.05.012
15. Dugovic C, Shelton JE, Yun S, Bonaventure P, Shireman BT, Lovenberg TW. Orexin-1 receptor blockade dysregulates REM sleep in the presence of orexin-2 receptor antagonism. *Front Neurosci*. 2014;8:28. doi:10.3389/fnins.2014.00028
16. Mieda M, Hasegawa E, Kisanuki YY, Sinton CM, Yanagisawa M, Sakurai T. Differential roles of orexin receptor-1 and −2 in the regulation of non-REM and REM sleep. *J Neurosci*. 2011;31:6518–6526. doi:10.1523/JNEUROSCI.6506-10.2011
17. Adamantidis AR, Zhang F, Aravanis AM, Deisseroth K, de Lecea L. Neural substrates of awakening probed with optogenetic control of hypocretin neurons. *Nature*. 2007;450:420–424. doi:10.1038/nature06310
18. Wu X, Xue T, Chen Z, Wang Z, Chen G. Orexin receptor antagonists and insomnia. *Curr Psychiatry Rep*. 2022;24:509–521. doi:10.1007/s11920-022-01357-w
19. Coleman PJ, Gotter AL, Herring WJ, Winrow CJ, Renger JJ. The discovery of suvorexant, the first orexin receptor drug for insomnia. *Ann Rev Pharmacol Toxicol*. 2017;57:509–533. doi:10.1146/annurev-pharmtox-010716-104837
20. Scott LJ. Lemborexant: first Approval. *Drugs*. 2020;80:425–432. doi:10.1007/s40265-020-01276-1
21. Markham A. Daridorexant: first approval. *Drugs*. 2022;82:601–607. doi:10.1007/s40265-022-01699-y
22. Sun H, Kennedy WP, Wilbraham D, et al. Effects of suvorexant, an orexin receptor antagonist, on sleep parameters as measured by polysomnography in healthy men. *Sleep*. 2013;36:259–267. doi:10.5665/sleep.2386
23. Xue T, Wu X, Chen S, et al. The efficacy and safety of dual orexin receptor antagonists in primary insomnia: a systematic review and network meta-analysis. *Sleep Med Rev*. 2022;61(101573):101573. doi:10.1016/j.smrv.2021.101573
24. BELSOMRA® (suvorexant) tablets [prescribing information]. U.S.; August, 2014.
25. DAYVIGOTM® (lemborexant) tablets [prescribing information]. U.S.; December, 2019.
26. QUVIVIQ® (daridorexant) tablets [prescribing information]. U.S.; January, 2022.
27. Rajbhar K, Karodadeo GR, Kumar V, et al. Comparative assessment of solubility enhancement of itroconazole by solid dispersion and co-crystallization technique: investigation of simultaneous effect of media composition on drug dissolution. *Ann Pharm Fr*. 2023;81:843–855. doi:10.1016/j.pharma.2023.05.004
28. Siepmann J, Siepmann F. Sink conditions do not guarantee the absence of saturation effects. *Int J Pharm*. 2020;577:119009. doi:10.1016/j.ijpharm.2019.119009