Evaluation of next-morning residual effects by bedtime administration of vornorexant in healthy older participants: postural stability, neuropsychological functions and subjective sleepiness in a randomized clinical study

Psychopharmacology

Yusuke Miyazaki[1], Daiji Kambe*[1], Yumiko Imadera[1], Hironori Yamasaki[1], Naohisa Uchimura[2], Makoto Uchiyama[3,4]

Author affiliation

1 Development Headquarters, Taisho Pharmaceutical Co., Ltd., 3-24-1 Takada, Toshima, Tokyo 170-8633, Japan

2 Department of Neuropsychiatry, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan

3 Tokyoadachi Hospital, 5-23-20 Hokima, Adachi, Tokyo 121-0064, Japan

4 Department of Psychiatry, Nihon University School of Medicine, Oyaguchi-Kamicho, Itabashi, 173-8610 Tokyo, Japan

*Corresponding author

Daiji Kambe

d-kanbe@taisho.co.jp

Development Headquarters, Taisho Pharmaceutical Co., Ltd., 3-24-1 Takada, Toshima, Tokyo 170-8633, Japan

Supplementary information

Inclusion Criteria:

1. Japanese men and women aged 65 years or older at the time of consent.
2. Those with a body mass index (BMI: weight [kg] / height [m]^2) ≥18.5 and < 25.0, weighing at least 40.0 kg at the time of screening.
3. Those who meet all the following criteria during the postural stability test at screening (three times with eyes open and three trials with eyes closed) and Visit 1 (one trial with eyes open and one with eyes closed):
    - No failed measurements due to falling or stepping off the platform.
    - Maximum body-sway area with eyes open is <12.00 cm^2.
4. Those who meet all the following criteria for at least 10 d during the 14-d sleep survey before Visit 1:
    - Wake-up time: 05:00 to 09:00
    - Bedtime: 21:00 to 01:00
    - Time in bed: 7–9 h
5. Those who can stay in bed for 8 h the night before the postural stability test at each administration visit.
6. Those deemed eligible for trial participation by the principal investigator or sub-investigator based on the results of assessments conducted at screening, Visit 1, and prior to dosing.
    - Even if abnormal findings or values outside the reference range are present, participants may be included if the principal investigator or sub-investigator determines them to be clinically insignificant based on a comprehensive evaluation of other relevant findings and data.
7. Those who are able to comply with appropriate contraceptive methods, using approved or certified pharmaceuticals or medical devices in Japan, from the time of informed consent until the end of the examination/observation at Visit 6 or upon early discontinuation.
    - Contraception for both the participant and their partner: use of male condoms, female oral contraceptives (if the participant is male), or intrauterine devices.
8. Those who can comply with the management items specified in the protocol.
9. Those who can understand the explanation of this trial given in advance, comprehend the content, and provide written consent.

Exclusion Criteria:

1. Those who are not considered healthy because of any disease as judged by the principal investigator or sub-investigator.

2. Those with a history of respiratory, cardiovascular, gastrointestinal, hepatic, renal, urinary, endocrine, metabolic, hematologic, immunological, dermatological, neurological, or psychiatric diseases that are deemed to be inappropriate for participation in this trial.
3. Those with a history of drug or food allergies.
4. Those with significant allergic predisposition (e.g., asthma requiring treatment).
5. Those with a history of hypersensitivity to zopiclone or eszopiclone.
6. Those with a history of parasomnias (e.g., sleepwalking, abnormal dreams, nightmares), narcolepsy-like symptoms (e.g., cataplexy, hypnagogic hallucinations, sleep paralysis), suicidal ideation, or suicide attempts.
7. Those with diseases affecting body balance function, such as sudden deafness, Ménière's disease, vestibular neuritis, benign paroxysmal positional vertigo, orthostatic dysregulation, stroke, epilepsy, sleep apnea, restless legs syndrome, myasthenia gravis, or a history of these diseases within the past 5 years (participation is possible if more than 5 years have passed since recovery without treatment and no recurrence has been observed).
8. Those with urinary storage or voiding dysfunction due to diseases, such as overactive bladder, cystitis, or benign prostatic hyperplasia.
9. Those who regularly experience symptoms such as dizziness due to fatigue, hot flashes, muscle cramps, tremors, numbness, or paralysis of the limbs upon waking.
10. Those with a history of recurrent falls, fractures, or head injuries due to falls within the past two years.
11. Those with a visual acuity <0.3 (decimal scale) in either eye during ophthalmologic examination at screening. Contact lens correction is not allowed during ophthalmologic examinations; however, those who regularly use glasses and can adequately correct their vision with glasses can be included.
12. Those with a Berg Balance Scale (BBS) score ≤40 at screening.
13. Those who have used any medication (including over-the-counter drugs) within 1 week before Visit 1 (except for contact lens solution).
14. Those who have used hypnotic sedatives (including benzodiazepine receptor agonists [benzodiazepine and non-benzodiazepine], barbiturates, and other sleep medications [ramelteon, suvorexant, and lemborexant]) within 4 weeks before Visit 1.
15. Those who have experienced a time difference of ≥6 h due to travel within 4 weeks before Visit 1 or plan to do so during the study period.
16. Those who have engaged in irregular shift work or night shifts within 4 weeks before Visit 1 or need to do so during the study period.

17. Those who participated in a previous TS-142 (vornorexant) study and took the investigational drug.
18. Those participating in other clinical studies or who received other investigational drugs within 16 weeks before Visit 1.
19. Pregnant women, breastfeeding women, women who may be pregnant, women who wish to become pregnant during the study, or women who test positive for pregnancy at screening or before the first dose of the investigational drug.
20. Those who have undergone any of the following blood draws:
    - Component donation within 2 weeks before screening.
    - Blood donation of 200 mL or more within 4 weeks before screening.
    - Blood donation of 400 mL or more within 12 weeks before screening for men and 16 weeks for women.
21. Those with alcohol or drug dependence or a history of such dependence.
22. Those who test positive for drugs (benzodiazepines, cocaine, stimulants, cannabis, barbiturates, morphine, phencyclidine, tricyclic antidepressants) in the urine drug test during screening.
23. Those who test positive for the HBs antigen, HCV antibody, HIV antigen/antibody, or syphilis at screening.
24. Those with suicidal ideation or attempts, as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening.
25. Those deemed unsuitable for participation by the principal investigator or sub-investigator.

Table S1. Time schedule during hospitalization in the administration period

	Time from waking up	
Days 1/8/15/22		Admission
		Clinical routine test[a)], C-SSRS
		Postural stability test and PVT for habituation
	-8 h 5 min	Drug administration
	-8 h	Going to bed[b)]
Days 2/9/16/23	0	Waking up
	5 min	Postural stability test
	10 min	PVT
	25 min	KSS
	9 h[c)]	Pharmacokinetics
	1 h 5 min	DSST
	1 h 15 min	WRT (immediate recall)
		DSST (interference task in WRT)
	2 h 15 min	WRT (delayed recall)
		Vital sign check, C-SSRS, medical examination
		Discharge

a) Including laboratory test, vital sign check, 12-lead ECG, and medical examination. b) Bedtime during hospitalization was determined based on the participants' regular daily bedtime. c) Time since drug administration.

C-SSRS, Columbia-Suicide Severity Rating Scale; DSST, digital symbol substitution test; KSS, Karolinska sleepiness scale; PVT, psychomotor vigilance task; WRT, word recall test.

Table S2. *Post hoc* analysis results of postural stability

Group	Observed value Mean ± SD	Change from ZOP LSM 95% CI[a)]		p-value
Eyes open				
Total count of anterior-posterior and medial-lateral oscillations				
PBO	165.6 ± 44.7	35.3	20.3, 50.3	< 0.001*
VOR5	159.9 ± 48.9	29.6	14.5, 44.6	< 0.001*
VOR10	159.8 ± 39.3	29.5	14.5, 44.5	< 0.001*
ZOP	130.3 ± 27.7	-	-	-
Radius distance power spectrum				
Low frequency band: 0.02-0.2 Hz (%)				
PBO	21.20 ± 6.05	-5.89	-8.70, -3.08	< 0.001*
VOR5	21.57 ± 5.07	-5.52	-8.33, -2.71	< 0.001*
VOR10	20.70 ± 4.91	-6.39	-9.20, -3.58	< 0.001*
ZOP	27.09 ± 5.11	-	-	-
Medium frequency band: 0.2-2 Hz (%)				
PBO	58.45 ± 4.33	1.22	-1.19, 3.63	0.314
VOR5	58.60 ± 4.27	1.37	-1.04, 3.78	0.258
VOR10	59.58 ± 4.20	2.34	-0.07, 4.75	0.057
ZOP	57.23 ± 4.28	-	-	-
High frequency band: 2-10 Hz (%)				
PBO	20.35 ± 6.68	4.67	2.95, 6.40	< 0.001*
VOR5	19.82 ± 5.19	4.15	2.42, 5.87	< 0.001*
VOR10	19.72 ± 5.19	4.05	2.32, 5.77	< 0.001*
ZOP	15.68 ± 4.56	-	-	-
Eyes closed				
Total count of anterior-posterior and medial-lateral oscillations				
PBO	192.5 ± 63.5	32.9	18.6, 47.2	< 0.001*
VOR5	186.5 ± 58.9	26.9	12.6, 41.2	< 0.001*
VOR10	190.1 ± 49.8	30.4	16.1, 44.8	< 0.001*
ZOP	159.6 ± 40.0	-	-	-
Radius distance power spectrum				
Low frequency band: 0.02-0.2 Hz (%)				
PBO	19.26 ± 5.36	-4.02	-6.69, -1.36	0.004*
VOR5	20.09 ± 5.46	-3.20	-5.87, -0.53	0.020*
VOR10	18.97 ± 3.70	-4.31	-6.98, -1.65	0.002*
ZOP	23.29 ± 6.79	-	-	-
Medium frequency band: 0.2-2 Hz (%)				
PBO	57.42 ± 4.98	-1.95	-4.53, 0.64	0.137
VOR5	57.41 ± 5.41	-1.95	-4.54, 0.63	0.135
VOR10	59.15 ± 4.77	-0.21	-2.80, 2.38	0.871
ZOP	59.36 ± 3.68	-	-	-
High frequency band: 2-10 Hz (%)				
PBO	23.32 ± 7.33	5.97	4.39, 7.55	< 0.001*
VOR5	22.51 ± 7.97	5.15	3.58, 6.73	< 0.001*
VOR10	21.88 ± 7.19	4.52	2.95, 6.10	< 0.001*
ZOP	17.35 ± 5.76	-	-	-

N=16 in each group.

LSM, least-squares mean; PBO, placebo; SD, standard deviation; VOR5, vornorexant 5 mg; VOR10, vornorexant 10 mg; ZOP, zopiclone. *p <0.05.

a) Lower, upper limit

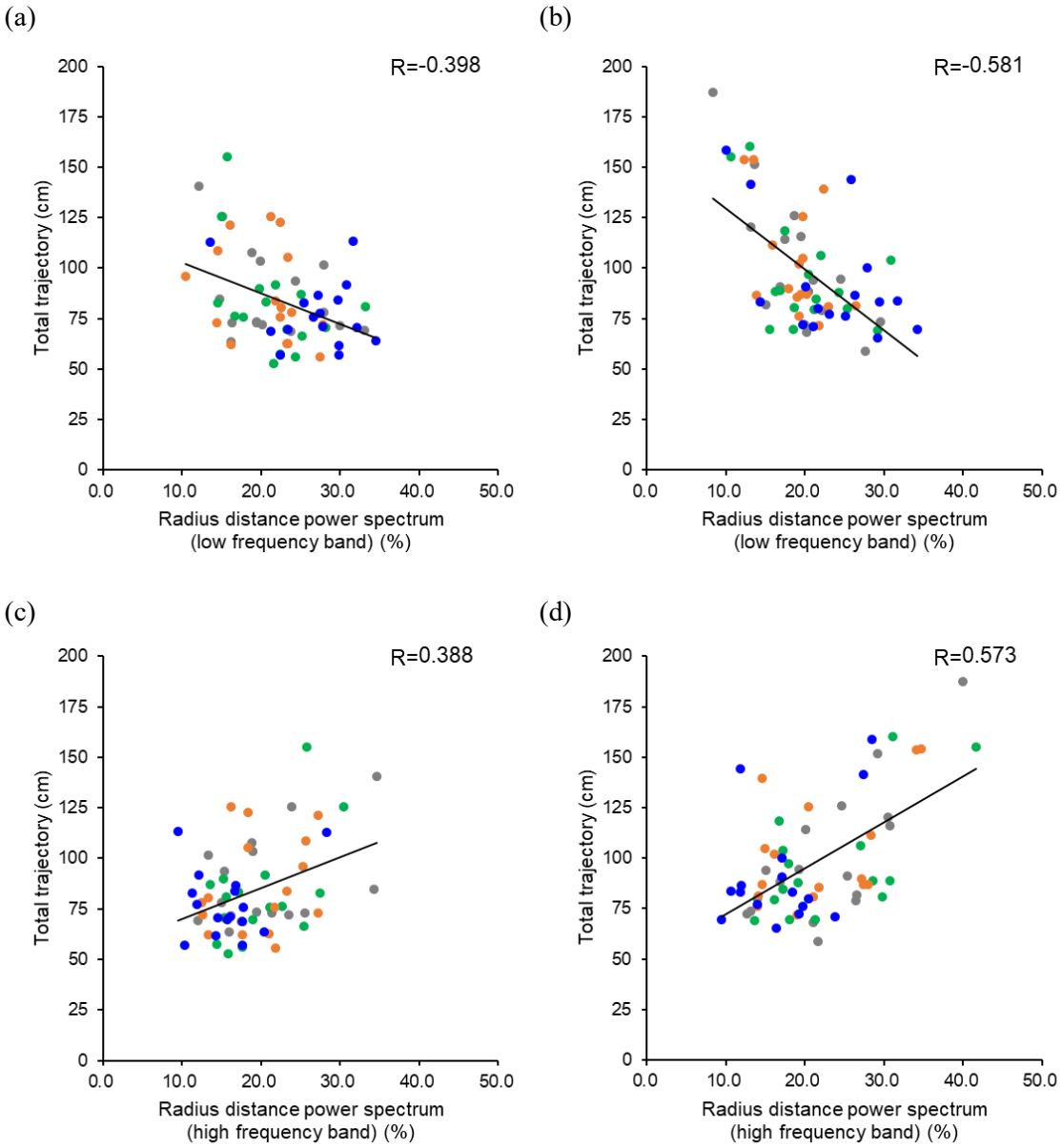

Figure S1. *Post hoc* analysis of scatter plots and regression lines for radius distance power spectrum and trajectory with (a) (c) eyes open and (b) (d) eyes closed conditions.

Gray dot, placebo; green dot, vornorexant 5 mg; dark yellow dot, vornorexant 10 mg; blue dot, zopiclone; black line, regression line; R, correlation coefficient.