

FK199B (Zolpidem MR Tablet) Phase III Clinical Study

—A Double-Blind, Crossover, Comparative Polysomnographic Study Using Zolpidem (Myslee®) as a Positive Control in Patients with Insomnia, Excluding Patients with Schizophrenia or Manic-Depressive Psychosis—

(6199-CL-0006)

Clinical Study Report

Synopsis

Study Drug Name:	FK199B
Indication:	Insomnia without schizophrenia or manic-depressive psychosis
Study Initiation Date:	27 March 2006
Study Completion Date:	05 July 2007
Responsible Officer or Designee:	Tomokazu Saito Vice president, Clinical Development Administration Department, Astellas Pharma Inc. 17-1, Hasune 3-chome, Itabashi-ku, Tokyo, Japan Tel: 03-5916-5340 Fax: 03-5916-5570
Country	Japan
Sponsor:	Astellas Pharma Inc. 2-3-11, Nihonbashi-Honcho, Chuo-ku, Tokyo, Japan Tel: 03-3244-3000 (representative)

This study was performed in compliance with Good Clinical Practice (GCP).

1 SUMMARY OF STUDY METHODS

Title of Study: FK199B (Zolpidem MR Tablet) Phase III Clinical Study —A Double-Blind, Crossover, Comparative Polysomnographic Study Using Zolpidem (Myslee®) as a Positive Control in Patients with Insomnia, Excluding Patients with Schizophrenia or Manic-Depressive Psychosis—	
Study Site: 18 sites	
Initiation Date: 27 March 2006	Phase of Development: III
Completion Date: 05 July 2007	
Study Objective(s) To investigate the efficacy and safety of FK199B (Zolpidem MR Tablet) by polysomnography (PSG) in patients with insomnia, excluding patients with schizophrenia or manic-depressive psychosis, by a randomized double-blind crossover comparative study using Zolpidem (Myslee®) as the positive control	
Design and Methodology: Zolpidem (Myslee®)-controlled, multicenter, randomized, double-dummy, double-blind, crossover comparative study [Rationale for study design] To scientifically and objectively assess the efficacy and safety of FK199B in patients with insomnia, polysomnography (PSG), a primary efficacy endpoint widely used in clinical studies of hypnotics, was employed for a randomized double-blind crossover comparative trial	
Planned Number of Subjects: Efficacy analysis set: 50 (25 each in FK199B-first group and Zolpidem tablet-first group) [Rationale] The number was set in order to ascertain trends in drug efficacy, and according to the available number of subjects in Japan.	
Diagnosis and Criteria for Inclusion/Exclusion: 1. Inclusion Criteria The subjects of this study met all the following criteria. [At primary registration] <ol style="list-style-type: none">1. Patient is diagnosed as a primary insomnia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)2. Patients complaining of insomnia continuously for 4 weeks or longer3. Patient's usual bedtime is between 9 p.m. and 12 a.m. for the 4 week period prior to initial screening4. Patient on most occasions sleeps for a total of ≥ 3 and < 6.5 hours over the 4 week period prior to initial screening5. Patient's usual wake time after sleep onset in a single night is ≥ 45 minutes per night for the 4 week period prior to initial screening6. Patients have a body weight of ≥ 45 kg and ≤ 85 kg, a BMI of ≥ 18.5 and < 307. Patients aged between 20 and 65 when their informed consent was obtained8. Patient considered able to undertake a washout period before start of the screening examination, Period 1 administration, and Period 2 administration, where medication in question is an antihistamine (H₁ blocker only, including combination cold remedies, not including eye-drops, nasal or topical preparations), an hypnotic, or an anxiolytic or	

- antidepressant drug used for hypnotic effect
9. Patients who had an ability to fill in the sleep check sheet
 10. It does not matter whether the patients are inpatients or outpatients (However, patient is able to undergo PSG monitoring over screening examination, Period 1, and Period 2)
 11. Patients who provided written informed consent

[At secondary registration]

12. Patient on average slept for a total of ≥ 3 and < 6.5 hours during PSG at the screening examination
13. Patient has a mean wake time after sleep onset during a single night measured on PSG at the screening examination of ≥ 45 minutes, and an actual wake time of ≥ 30 minutes in total on every night

2. Exclusion Criteria

Patients who met any of the following criteria were excluded from the study.

[At primary registration]

1. Patients with schizophrenia or manic-depressive psychosis
2. Patients with insomnia caused by physical diseases including chronic obstructive pulmonary disease, bronchial asthma, fibrositis syndrome, chronic fatigue syndrome, rheumatic disease, climacteric disturbance, and dermatitis atopic
3. Patients with circadian rhythm sleep disorder
4. Patient works night shifts
5. Patients with alcoholic sleep disorder
6. Patients with alcohol or drug dependence or a history of these
7. Patients with insomnia related with drugs including antiparkinson, antihypertensive, or steroid drugs
8. Patients with sleep apnea syndrome
9. Patients with restless legs syndrome or periodic limb movement disorder
10. Patients with epileptic insomnia
11. Patients smoke on average 40 or more cigarettes a day
12. Patients who had received psychotropic drugs other than hypnotics (including anxiolytic or antidepressant drugs for hypnotic effect) within a 4 week period prior to the initial screening
13. Patients who had gone on an overseas trip to a place with a time difference of five or more hours within the twelve weeks before the start of the initial screening
14. Patients who used Zolpidem within two weeks before the start of the initial screening
15. Patients with a history of allergy to Zolpidem
16. Patients with myasthenia gravis
17. Patients with acute closed-angle glaucoma
18. Patient has highly impaired respiratory function, e.g., in the acute phase of cor pulmonale, emphysema, bronchial asthma, or cerebrovascular disease
19. Patients with organic brain disorder
20. Patient with serious heart disease, liver disease, renal disease, or hematological disorder. Grade 3 according to "Criteria for classification of seriousness of adverse drug reactions to pharmaceutical products, etc." (PAB/SD Notification No. 80, issued on 29 June 1992)
21. Pregnant women, women with an intention of pregnancy during the study period, and

- nursing mothers
22. Patient with clinical conditions that are judged to be inappropriate for a safe conduct of the clinical study by the investigator or subinvestigator
 23. Patients who participated in other clinical studies or post-marketing clinical studies within 12 weeks before providing the informed consent (not including patients in which administration of a study drug had not begun, according to Protocol No. 6199-CL-0007)

[At secondary registration]

At secondary registration patients were tested against the following exclusion criteria, and excluding criteria of primary registration of 1 to 7, 10, 11, and 16 to 21.

24. Patient diagnosed with sleep apnoea syndrome with an AHI of ≥ 10 on PSG at the screening examination
25. Patient diagnosed with restless legs syndrome or periodic limb movement disorder with PLMI ≥ 10 on PSG at the screening examination
26. Patient judged to be inappropriate as a subject for this study by the investigator or subinvestigator on the basis of laboratory test results or such like at the screening examination

Test Product, Dose and Mode of Administration, Lot Number

1. Study Drug and Lot Number

[Test drug]

Code: FK199B

Drug product:

FK199B 12.5 mg : Yellow, round, film-coated tablet containing 12.5 mg of Zolpidem

FK199B placebo : Yellow, round, film-coated tablet, indistinguishable from the

FK199B 12.5 mg tablet

Lot No.: 708350K

Expiration date: October 2007

[Control drug]

Control drug: Zolpidem (Myslee®) tablet

Drug product:

Zolpidem 10 mg : Round, light-orange, film-coated tablet containing Zolpidem 10 mg

Zolpidem placebo : Round, light-orange, film-coated tablet, indistinguishable from the 10 mg Zolpidem tablet

Lot No.: 708350K

Expiration date: October 2007

2. Dose and Mode of Administration

One tablet of FK199B 12.5 mg or Zolpidem 10 mg was administered orally in a double-blind manner once daily before bedtime on 2 consecutive nights for each period: Period 1 and Period 2.

Drug administration was performed in the following combinations.

	FK199B-first group	Zolpidem-first group
Period 1	FK199B 12.5 mg 1 tablet + Zolpidem placebo 1 tablet	FK199B placebo 1 tablet + Zolpidem 10 mg 1 tablet

Period 2	FK199B placebo 1 tablet + Zolpidem 10 mg 1 tablet	FK199B 12.5 mg 1 tablet + Zolpidem placebo 1 tablet
<p>[Rationale] Rationale for dose establishment: The control drug Zolpidem was administered at 10 mg according to standard treatment for adults both inside and outside Japan. According to the results of an international clinical study conducted outside Japan (EFC4529), administration with FK199B 12.5 mg shows a similar sleep initiation effect in adults to that of Zolpidem 10 mg, while inhibiting nightly awakenings more effectively than the Zolpidem dose. A crossover single oral administration pharmacokinetics study in healthy, fasted male subjects with FK199B 12.5 mg and Zolpidem 10 mg was conducted in Japan. On pharmacokinetic comparison, AUC of FK199B increased by 24% compared to Zolpidem, while C_{max} was similar. The elevated AUC for FK199B was comparable to a difference in active drug content, while similar C_{max} suggested the sustained-release Zolpidem formulation prevented an increase in C_{max}. Also, the oral clearance and half-life in the blood were almost equivalent between the drugs, with no suggestion of difference in oral availability or pharmacokinetics. Mean residence time and time period of plasma concentrations above 50% of C_{max}, both indicators for sustainability of plasma concentrations, were significantly prolonged for FK199B compared to Zolpidem. Based on these results, with similar C_{max} the dose of FK199B 12.5mg was expected to show better efficacy in decreasing night awakenings compared to zolpidem 10 mg. Administration method was by oral administration before bedtime for evaluation of efficacy and safety in conditions similar to those of the patients' everyday life.</p>		
<p>Investigational Period A total of 4 days for both Period 1 and Period 2 (2 consecutive nights of each) [Rationale for investigational period] From PSG examination of patients with primary insomnia, alternating nights of severe and less severe insomnia symptoms are known to occur; therefore, analysis was made on an averaged two nights of sleep, with 2 consecutive nights set for each period of drug administration.</p>		
<p>Concomitant Medication (Drugs and Therapies) [Prior treatment] The following drugs, including antipsychotics, were considered prohibited concomitant drugs, and their use was prohibited on and after obtaining informed consent.</p> <ul style="list-style-type: none"> • Antipsychotics, anxiolytics, antidepressants, antimaniacs, antiepileptics, hypnotics, cerebral circulation and metabolism improvers, antimentia agents, antiparkinson agents, Chinese herbal medicine that acts on the central nervous system, antihistamine agents (H_1 blockers only, including combination cold remedies but not including eye-drops, nasal and topical preparations) <p>Where the following drugs were being taken for treatment, a washout period was scheduled for prior to and during the screening examination.</p> <ul style="list-style-type: none"> • Hypnotics, and anxiolytic or antidepressant drugs for hypnotic effect: i) a 7 day period or ii) a period corresponding to 3 times the elimination half-life, whichever longer (the day of final treatment was defined as Day 1.) • Antihistamine agents (H_1 blockers only, including combination cold remedies but not 		

including eye-drops, nasal and topical preparations): ≥ 7 days (day of final treatment was defined as Day 1.)

[Concomitant treatment]

The following drugs and therapies were defined as prohibited concomitant drugs and therapies, and restricted concomitant drugs and therapies, for the purpose of this study.

[Prohibited concomitant drugs and therapies]

1. Antipsychotics, anxiolytics (except for hypnotic effect), antidepressants (except for hypnotic effect), antimanics, antiepileptics, cerebral circulation and metabolism improvers, antimentia agents, antiparkinson agents, and Chinese herbal medicines acting on the central nervous system.
2. Sedatives containing bromovalerylurea
3. Cognitive behavior therapy, bright light therapy
4. Prescription drugs, supplements, and dietary supplements containing melatonin or Saint John's wort
5. Vitamin B₁₂-based prescription drugs (except for eye-drops, nasal and topical preparations)
6. Supplements and dietary supplements containing glycine with hypnotic effect
7. CNS depressants, such as phenothiazine derivatives, barbiturates
8. Other study drugs and post-marketing study drugs

[Restricted concomitant drugs]

Use of the following drugs was prohibited during Period 1 and Period 2.

1. Hypnotics, and anxiolytic or antidepressant drugs used for hypnotic effect
2. Antihistamine agents (H₁ blockers only, including combination cold remedies but not including eye-drops, nasal and topical preparations)
3. Combination cold remedies, antipyretic analgesics, and quasi-drugs containing caffeine preparations
4. Rifampicin
5. Anesthetics

A period of drug abstinence was scheduled for before the start of Period 1 and Period 2 when one or more of the following restricted concomitant drugs was in use.

- Hypnotics, and anxiolytic or antidepressant drugs used for hypnotic effect: i) a 7 day period or ii) a period corresponding to 3 times the drug elimination half-life, whichever longer (day of final treatment defined as Day 1.)
- Antihistamine agents (H₁ blockers only, including combination cold remedies but not including eye-drops, nasal and topical preparations): ≥ 7 days (day of final treatment defined as Day 1.)

Variables, Schedule of Assessments, and Criteria for Assessments

1. Study schedule

	Initial screening	Screening examination* ¹				Period 1* ^{1,2}				Period 2* ^{1,2}				Follow-up examination	Discontinuation
		Day 1		Day 2		Day 1		Day 2		Day 1		Day 2			
		Night	Morning	Night	Morning	Night	Morning	Night	Morning	Night	Morning	Night	Morning		
Visit	●	●—●		●—●		●—●		●—●		●—●		●—●		●	●
Written informed consent	● ^{※7}														
Investigation of patients' background	●	●													
Health questionnaire	●														
Primary registration	●														
Secondary registration						● ^{※8}									
Study drug administration ³						●		●		●		●			
PSG recording ⁴		●—●		●—●		●—●		●—●		●—●		●—●			
Sleep questionnaire		●	●	●	●	●	●	●	●	●	●	●	●		
Life questionnaire		●				●				●					
Medical examination	●	●				●			●	●			●	●	●
Height/Weight	●														
General laboratory tests		● ^{※9}				●			●	●			●		● ^{※10}
Pregnancy test ⁵		● ^{※9}													
Adverse events ⁶		←————→				←————→				←————→					

^{*1}: A washout period was scheduled where the following drugs were in use.

- Hypnotics, and anxiolytic or antidepressant drugs used for hypnotic effect: i) a 7 day period or ii) a period 3 times the drug elimination half-life, whichever was longer (day of final treatment defined as Day 1.)
- Antihistamine agents (H₁ blockers only, including combination cold remedies but not including eye-drops, nasal and topical preparations): ≥7 days (day of final treatment defined as Day 1.)

^{*2}: The start days of Period 1 and Period 2 were on the same day of the week.

^{*3}: PSG monitoring and recording were started at the same time as study drug administration

^{*4}: PSG recording was performed for 8 hours after starting measurements.

^{*5}: Conducted only in female subjects. However, the test was skipped for female patients for which the possibility of pregnancy could be clearly ruled out (e.g. ≥3 years after the last menses, hysterectomy, oophorectomy)

^{*6}: Observations looking for “undesirable clinical events” were made during the period between obtaining informed consent and before the start of Period 1. Monitoring of adverse events was conducted from the start of Period 1 to the end of the study.

^{*7}: Written informed consent was obtained by the time of the initial screening.

^{*8}: Case secondary registration was conducted prior to Period 1 and after results of the screening examination were obtained.

^{*9}: For the second or subsequent screening examination, general laboratory tests and pregnancy tests were not always performed.

^{*10}: For patients who received the study drug but discontinued during Period 1 or Period 2, general laboratory tests were carried out. For patients who discontinued outside of Period 1 or Period 2, no general laboratory tests were carried out at discontinuation.

2. Variables (Efficacy)

Primary endpoint

- Sleep parameters estimated from 8 hours of PSG records (wake time after sleep onset and number of awakenings)

Secondary endpoints

- Mean sleep parameters estimated from 8 hours of PSG records (sleep time, total sleep time, sleep efficiency, sleep onset latency, latency to persistent sleep, time of each sleep stage, proportion of each sleep stage, wake time after sleep onset per hour, number of awakenings per hour, proportion of wake after sleep onset, number of stage shifts, early morning wake, number of awakenings without bed out latency, bed out latency, wake time after sleep onset from hour 1 to hour 6, number of awakenings from hour 1 to hour 6)
- Sleep parameters estimated from the sleep questionnaire (wake time after sleep onset, number of awakenings, total sleep time, sleep onset latency, wake time after sleep onset without bed out latency, number of awakenings without bed out latency, bed out latency)
- Patient impression observed from the sleep questionnaire

3. Variables (Safety)

- Adverse events
- Clinical laboratory tests

Statistical Methods:

1. Analysis Set:

Full Analysis Set (FAS) and Per Protocol Set (PPS) were defined for the efficacy analysis sets as follows. The PPS was used as the primary analysis set, and FAS as the secondary analysis set.

[Efficacy analysis sets]

1. Full Analysis Set (FAS)

FAS consisted of all subjects who received the study drug and underwent at least one efficacy measurement after receiving the study drug.

2. Per Protocol Set (PPS)

PPS consisted of the FAS's subjects satisfying the following criteria.

- Subject fulfills the inclusion criteria and does not correspond to any exclusion criteria
- Subject received the study drug both in Period 1 and Period 2
- Subject exhibited at least one of the sleep parameters (wake time after sleep onset and number of awakenings) gained from observation of 8 hours of PSG records for at least one night in both Period 1 and Period 2

[Safety analysis set]

Safety analysis set consisted of all subjects administered with the study drug

2. Analysis of Efficacy:

[Primary endpoint]

1. Primary analysis

Wake time after sleep onset and number of awakenings were analyzed using a mixed effect model with period, sequence, and drug as fixed effects and inter-individual variability as a random effect to calculate the adjusted means of difference in drug efficacy (FK199B–Zolpidem), their standard errors, and two-sided 95% confidence intervals.

2. Secondary analysis

- For FAS, the same analysis was performed as described in “Primary analysis.”
- Mean wake time after sleep onset and mean number of awakenings by administration drug for each period were shown.

[Secondary endpoints]

- Mean sleep parameters estimated from 8 hours of PSG records (sleep time, total sleep time, sleep efficiency, sleep onset latency, latency to persistent sleep, time of each sleep stage, proportion of each sleep stage, wake time after sleep onset per hour, number of awakenings per hour, proportion of wake after sleep onset, number of stage shifts, early morning wake, number of awakenings without bed out latency, bed out latency, wake time after sleep onset from hour 1 to hour 6, and number of awakenings from hour 1 to hour 6)
- Mean sleep parameters estimated from the sleep questionnaire (wake time after sleep onset, number of awakenings, total sleep time, sleep onset latency, wake time after sleep onset without bed out latency, number of awakenings without bed out latency, and bed out latency)
- Patient impression estimated from the sleep questionnaire

For secondary endpoints, the following analyses were performed. For patient impression, scores were assigned to the categories by parameter and score-based analyses were performed.

- Each secondary endpoint was analyzed using a mixed effect model with period, sequence, and drug as fixed effects and inter-individual variability as a random effect to calculate the adjusted means of difference in drug efficacy (FK199B-Zolpidem), their standard errors, and two-sided 95% confidence intervals.
- Mean values by administration drug were shown for each period.

3. Analysis of Safety:

The safety analysis set was used as the analysis set. The level of significance was set as 5% (two-sided). Analysis was performed per administration drug unless otherwise noted.

Adverse events were analyzed according to classification made by the Medical Dictionary for Regulatory Activities Terminology 9.0 (MedDRA 9.0). Analyses by organ used System Organ Class (SOC) and those by symptom used the Preferred Terms (PT) of MedDRA 9.0.

Date of Report: 5 June 2008

2 STUDY POPULATION

2.1 Disposition of Subjects and Analysis Set

While the planned number of subjects for the study was 50 patients, written informed consent was obtained from 113 subjects. Of these subjects, 55 dropped out as a result of inclusion/exclusion criteria violation or for other reasons, and 58 were registered as eligible subjects by secondary registration. These subjects were randomly allocated to either the FK199B-first group or the Zolpidem-first group. Before administration of the study drug in Period 1, 2 subjects in the FK199B-first group were discontinued. After administration of the study drug, 2 subjects in the Zolpidem-first group were discontinued due to deviation from protocol and continuation of observation not possible. A total of 54 subjects, 26 in the FK199B-first group and 28 in Zolpidem-first group, completed the follow-up examination.

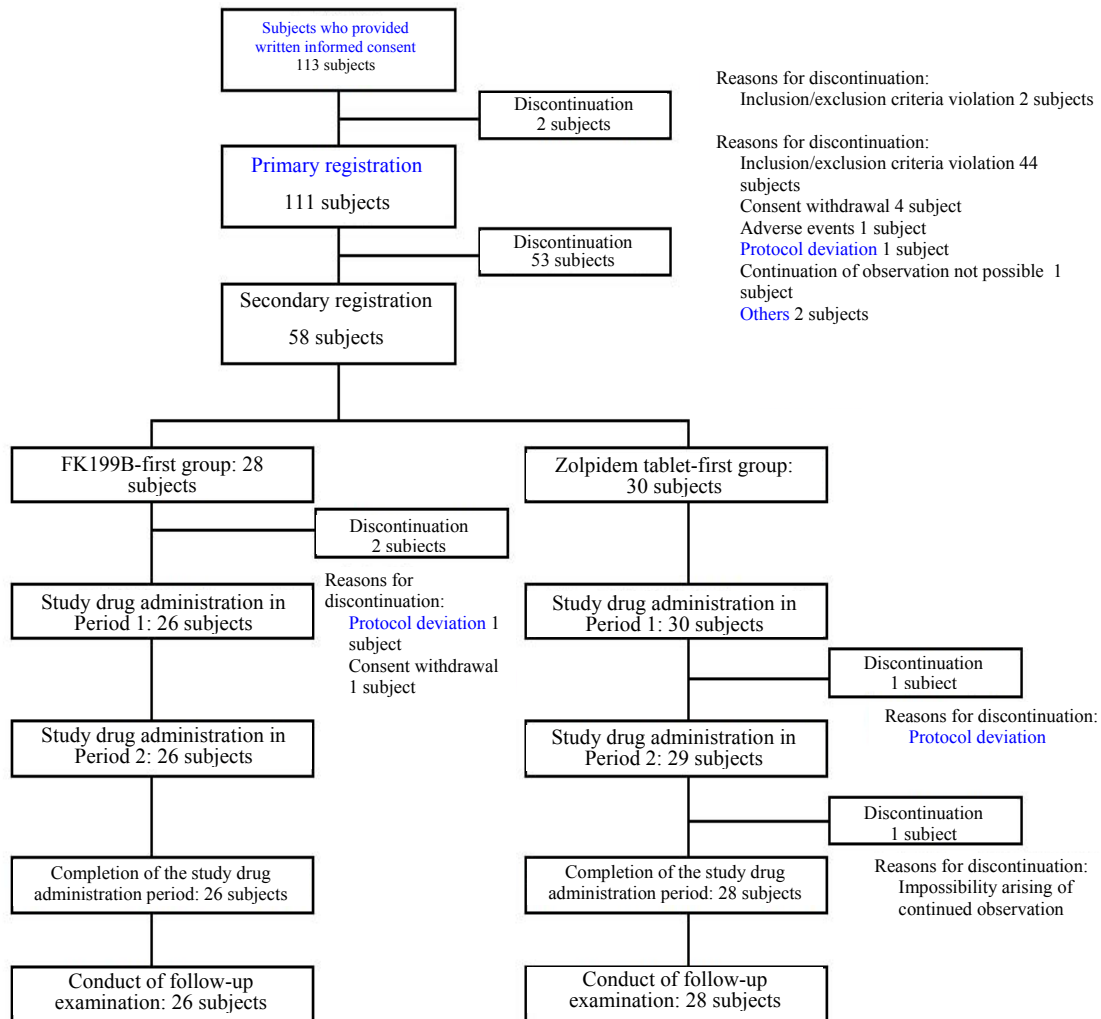


Figure 1 Disposition of Subjects

Of 58 subjects at secondary registration, 4 subjects were excluded from the PPS, and 3 subjects were excluded each from the FAS and Safety analysis set.

Table 1 Composition of Analysis Sets

Analysis set	Inclusion/Exclusion	FK199B-first group	Zolpidem-first group	Total
PPS	Included	26	28	54
	Excluded	2	2	4
FAS	Included	26	29	55
	Excluded	2	1	3
Safety analysis set	Included	26	29	55
	Excluded	2	1	3

2.2 Demographics and Other Baseline Characteristics

Investigation of demographic characteristics in terms of imbalance between groups showed no difference between the FK199B-first group and the Zolpidem-first group according to patients' backgrounds.

In terms of sleep parameters obtained from PSG monitoring during the screening period, wake time after sleep onset was estimated to be approximately 100 minutes and the number of awakenings to be approximately 40; from the sleep questionnaire wake time after sleep onset was estimated to be approximately 120 minutes and the number of awakenings to be approximately 3. No marked difference was observed between the groups in either PSG results or the sleep questionnaire.

Table 2 Demographic Characteristics (PPS)

Item		FK199B-first group (n=26)	Zolpidem-first group (n=28)	Total (n=54)	P-value
Sex [†]	Male	12 (46.2%)	17 (60.7%)	29 (53.7%)	0.413 ^{††}
	Female	14 (53.8%)	11 (39.3%)	25 (46.3%)	
Age (year)	Mean ± SD (Min.-Max.)	44.0 ± 12.71 (23-62)	45.1 ± 13.04 (20-64)	44.5 ± 12.77 (20-64)	0.753 ^{‡‡}
Body weight (kg)	Mean ± SD (Min.-Max.)	60.53 ± 9.491 (47.7-82.0)	60.99 ± 9.530 (45.0-79.0)	60.77 ± 9.424 (45.0-82.0)	0.858 ^{‡‡}
Duration of the disease [‡] (month)	Mean ± SD (Min.-Max.)	45.4 ± 47.32 (4-149)	72.9 ± 99.15 (1-314)	57.6 ± 74.73 (1-314)	0.890 [§]
Drinking habit [†]	Absent	13 (50.0%)	11 (39.3%)	24 (44.4%)	0.584 ^{††}
	Present	13 (50.0%)	17 (60.7%)	30 (55.6)	

[†]: No. of subjects (%), [‡]: FK199B-first group (n=19), Zolpidem-first group (n=15),

^{††}: Fisher test, ^{‡‡}: t test, [§]: Wilcoxon rank sum test

Table 3 Sleep Parameters Estimated From PSG Records during the Screening Period (PPS)

Item	No.	Mean	SD	Minimum	Maximum	Median
Sleep time (min)	54	435.940	29.7987	329.75	477.50	443.125
Total sleep time (min)	54	347.190	36.7584	221.75	388.25	357.875
Sleep onset latency (min)	54	28.133	20.1923	2.50	80.25	21.225
Sleep efficiency (%)	54	72.331	7.6580	46.20	80.89	74.557
Wake time after sleep onset (min)	54	104.677	33.9454	48.00	216.00	101.250
Number of awakenings (episodes)	54	40.33	20.969	6.5	138.0	38.00
Proportion of wake after sleep onset (%)	54	23.229	7.5281	11.68	49.41	22.195
Time of sleep stage 1 (min)	54	45.801	29.4484	6.75	179.50	41.125
Time of sleep stage 2 (min)	54	194.921	42.2431	64.50	285.75	200.250
Time of sleep stage 3 (min)	54	21.250	15.0589	0.00	53.75	21.000
Time of sleep stage 4 (min)	54	12.787	20.2729	0.00	69.25	1.125
Stage wake duration [†] (min)	54	88.750	35.6778	28.25	216.00	80.000
Slow-wave sleep time (min)	54	34.037	30.0630	0.00	112.75	24.375
Non-REM sleep time (min)	54	274.759	31.2954	194.75	330.75	281.125
REM sleep time (min)	54	72.431	20.4538	23.00	123.25	73.750
Proportion of sleep stage 1 (%)	54	10.516	6.6832	1.51	41.37	9.145
Proportion of sleep stage 2 (%)	54	44.945	10.2595	14.82	66.69	45.576
Proportion of sleep stage 3 (%)	54	4.875	3.4483	0.00	12.41	4.563
Proportion of sleep stage 4 (%)	54	2.872	4.4750	0.00	14.50	0.267
Proportion of wake in sleep stages (%)	54	20.187	7.8976	8.48	49.41	18.069
Percentage of slow-wave sleep (%)	54	7.747	6.7151	0.00	23.61	5.765
Percentage of non-REM sleep (%)	54	63.208	6.9921	45.38	83.28	64.060
Percentage of REM sleep (%)	54	16.604	4.8021	5.21	28.23	16.780
Number of awakenings without bed out latency (episodes)	54	39.73	20.986	6.0	138.0	37.00
Bed out latency (min)	54	15.927	19.7262	0.00	92.50	9.500

[†]: Comparable to “wake time after sleep onset without bed out latency,” a sleep parameter in the sleep questionnaire.

Table 4 Sleep Parameters Estimated From the Sleep Questionnaire during the Screening Period (PPS)

Item	No.	Mean	SD	Minimum	Maximum	Median
Wake time after sleep onset (min)	54	126.13	53.240	25.0	285.0	120.00
Number of awakenings (episodes)	54	3.19	1.361	1.0	7.0	3.00
Total sleep time (min)	54	293.06	62.094	115.0	422.5	292.50
Sleep onset latency (min)	54	58.68	45.009	0.0	235.0	48.75
Wake time after sleep onset without bed out latency (min)	54	80.76	49.332	7.5	205.0	70.00
Number of awakenings without bed out latency (episodes)	54	2.55	1.364	0.5	6.0	2.50
Bed out latency (min)	54	45.37	45.337	0.0	202.5	30.00
How well did you sleep last night?	54	2.54	0.621	1.5	4.0	2.50
How clear was your head when you got up this morning?	54	2.67	0.566	1.5	4.0	2.50
How satisfied are you with the last night's sleep?	54	2.39	0.612	1.0	3.5	2.50

2.3 Treatment Compliance and Study Drug Exposure

The following tables show the number of patients given the study drug in the PPS, the primary efficacy analysis set, and safety analysis set per administration period and per administered drug. Each study drug was administered on 2 consecutive nights of each period.

Table 5 Number of Patients Given Study Drug (PPS)

Item	Zolpidem tablet	FK199B	Total
Administration drug in Period 1	28	26	54
Administration drug in Period 2	26	28	54

Table 6 Number of Patients Given Study Drug (Safety Analysis Set)

Item	Zolpidem tablet	FK199B	Total
Administration drug in Period 1	29	26	55
Administration drug in Period 2	26	28	54

3 EFFICACY

3.1 Efficacy Results

Primary Endpoints

The wake time after sleep onset in the PPS, which is the primary analysis set for efficacy evaluation, was significantly shorter in FK199B administration than in Zolpidem administration; the difference in the adjusted means was -7.607 minutes. The number of awakenings was fewer for FK199B administration than for Zolpidem administration; the difference in adjusted means was -1.37 , with no statistically significant difference. No period or sequence effect was observed for wake time after sleep onset or number of awakenings.

Table 7 Sleep Parameters Estimated from PSG Records (PPS): Primary Endpoints

Item	Mean ± SD (No. of subjects) in each drug administration	FK199B administration – Zolpidem administration [†]	
		Difference between adjusted means [95% confidence interval]	P-value
Wake time after sleep onset (min)			
FK199B administration	30.884 ± 21.8011 (54)	-7.607 [-12.0821 to -3.1322]	0.001
Zolpidem administration	38.417 ± 25.5502 (54)		
Number of awakenings (episodes)			
FK199B administration	23.80 ± 10.570 (54)	-1.37 [-3.518 to 0.776]	0.206
Zolpidem administration	25.16 ± 11.024 (54)		

[†] Analysis using a mixed effect model with period, sequence, and drug as fixed effects and inter-individual variability as a random effect

The wake time after sleep onset in the FAS, which is the secondary analysis set for efficacy evaluation, was significantly shorter for FK199B administration as compared to Zolpidem administration. The number of awakenings was fewer for FK199B administration than for Zolpidem administration, with no significant difference. Results in the FAS were similar to those in the PPS; there was no difference between the analysis sets.

Table 8 Sleep Parameters Estimated from PSG Records (FAS): Primary Endpoints

Item	FK199B administration – Zolpidem administration [†]	
	Difference between adjusted means [95% confidence interval]	P-value
Wake time after sleep onset (min)	-7.550 [-12.0010 to -3.0980]	0.001
Number of awakenings (episodes)	-1.42 [-3.556 to 0.719]	0.189

The number of patients given FK199B was 54; the number of patients given Zolpidem was 55.

[†]: Analysis using a mixed effect model with period, sequence, and drug as fixed effects and inter-individual variability as a random effect

Secondary Endpoints

1. Sleep Parameters Estimated from PSG Records

Drug effects were observed in 16 of 44 parameters measured. Compared to Zolpidem administration, FK199B administration showed increases in time of sleep stage 2, non-REM sleep time, percentage of sleep stage 2, and percentage of non-REM sleep, and decreases in stage wake duration, proportion of stage wake duration, proportion of wake after sleep onset, early morning wake, wake time after sleep onset from hour 1 to hour 6, number of awakenings from hour 1 to hour 6, wake time after sleep onset per hour (3 to 4 hours), wake time after sleep onset per hour (4 to 5 hours), wake time after sleep onset per hour (5 to 6

hours), number of awakenings per hour (3 to 4 hours), number of awakenings per hour (4 to 5 hours), and number of awakenings per hour (5 to 6 hours). Both wake time after sleep onset and number of awakenings per hour following bedtime significantly decreased during the time zone of 3 to 6 hours after bedtime for FK199B administration, when compared to Zolpidem administration, confirming extended efficacy due to the sustained-release formulation.

No period or sequence effect was observed for any of the parameters.

2. Sleep Parameters Estimated From the Sleep Questionnaire

In terms of sleep parameters estimated from the sleep questionnaire, drug effect was observed in two parameters, wake time after sleep onset and wake time after sleep onset without bed out latency, both of which were significantly shorter in FK199B administration than in Zolpidem tablet administration. No sleep parameter was significantly aggravated with FK199B administration when compared to Zolpidem administration.

4 SAFETY

4.1 Adverse Events

Thirteen (13) adverse events occurred in 9 subjects (16.7%) for FK199B administration, and 12 adverse events occurred in 9 subjects (16.4%) of Zolpidem administration. No serious adverse events, adverse events causing discontinued administration, or severe adverse events were observed. Eight (8) adverse drug reactions (adverse events for which a causal relationship to the study drug cannot be ruled out) occurred in 7 subjects (13.0%) in FK199B administration, and 10 adverse drug reactions occurred in 7 subjects (12.7%) in Zolpidem administration.

Comparative analysis using a McNemar test showed $P=1.000$ in terms of adverse events and adverse drug reactions with no difference between the 2 drugs administered.

Table 9 Overall Incidence of Adverse Events and Adverse Drug Reactions (Safety Analysis Set)

Item	FK199B administration (n=54)	Zolpidem administration (n=55)
Adverse events		
All adverse events	9 (16.7%)	9 (16.4%)
No. of adverse events [†]	13	12
Serious adverse events	0	0
Adverse events causing discontinued administration	0	0
Severe adverse events	0	0
Adverse drug reactions (adverse events for which a causal relationship to the study drug cannot be ruled out)		
All adverse drug reactions	7 (13.0%)	7 (12.7%)
No. of adverse drug reactions [†]	8	10
Serious adverse drug reactions	0	0
Adverse drug reactions causing discontinued administration	0	0
Severe adverse drug reactions	0	0

No. of subjects (incidence); [†]: No. of events

Adverse events by organ and by symptom are shown in Table 10. In adverse events by organ, nervous system disorders most commonly occurred both in FK199B administration and Zolpidem administration, but no symptoms were observed with markedly high incidence.

The causal relationship for most of the adverse events was judged as “Possibly related” or “Probably related,” but most of them were judged as mild. Moderate adverse events were anterograde amnesia in FK199B administration and atrial fibrillation in Zolpidem administration; there were no severe adverse events.

Table 10 Adverse Events (Safety Analysis Set)

MedDRA/J Version 9.0 System organ class (SOC) Preferred term (PT)	FK199B administration (n=54)	Zolpidem administration (n=55)
All adverse events	9 (16.7%)	9 (16.4%)
Cardiac disorders	0	1 (1.8%)
Atrial fibrillation	0	1 (1.8%)
Gastrointestinal disorders	0	1 (1.8%)
Nausea	0	1 (1.8%)
Vomiting	0	1 (1.8%)
General disorders and administration site conditions	1 (1.9%)	0
Feeling drunk	1 (1.9%)	0
Infections and infestations	2 (3.7%)	0
Nasopharyngitis	2 (3.7%)	0
Investigations	2 (3.7%)	1 (1.8%)
Eosinophil count increased	1 (1.9%)	0
Neutrophil count decreased	1 (1.9%)	1 (1.8%)
Musculoskeletal and connective tissue disorders	1 (1.9%)	1 (1.8%)
Pain in extremity	1 (1.9%)	0
Shoulder pain	1 (1.9%)	0
Musculoskeletal stiffness	0	1 (1.8%)
Nervous system disorders	4 (7.4%)	3 (5.5%)
Anterograde amnesia	1 (1.9%)	1 (1.8%)
Dizziness	1 (1.9%)	0
Headache	1 (1.9%)	1 (1.8%)
Sleep paralysis	1 (1.9%)	0
Somnolence	1 (1.9%)	1 (1.8%)
Skin and subcutaneous tissue disorders	1 (1.9%)	2 (3.6%)
Erythema	1 (1.9%)	2 (3.6%)

No. of subjects (incidence)

4.2 Clinical Laboratory Evaluations

Assessment of changes in clinical laboratory test values by administered drug showed no clinically significant changes in any parameter.