

FK199B (Zolpidem MR Tablet) Phase III Clinical Study

*— A Double-Blind, Parallel-group Comparative Study Using Zolpidem (Myslee®) Tablet as a Comparative Drug in Adult Japanese Patients with Insomnia without Schizophrenia or Manic-depressive Psychosis—
(6199-CL-0007)*

Study Drug Name:	Zolpidem MR Tablet (FK199B)
Indication:	Insomnia without schizophrenia or manic-depressive psychosis
Study Initiation Date:	6 February 2006
Study Completion Date:	27 June 2007
Country:	Japan
Sponsor:	Astellas Pharma Inc. 17-1, Hasune 3-chome, Itabashi-ku, Tokyo 174-8612, Japan Tel: 03-5916-5111

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

1 SUMMARY OF STUDY METHODS

Item	Content								
Study title	FK199B (Zolpidem MR Tablet) Phase III Study — A Double-Blind, Parallel-group Comparative Study using Zolpidem (Myslee [®]) Tablet as a Comparative Drug in Adult Japanese Patients with Insomnia without Schizophrenia or Manic-depressive Psychosis — (6199-CL-0007)								
Phase of development	Phase III study (confirmatory study)								
Study objective	To investigate the efficacy and safety of FK199B (zolpidem MR 12.5 mg Tablet) in adult Japanese patients with insomnia without schizophrenia or manic-depressive psychosis by a randomized double-blind parallel-group comparative study using zolpidem 10 mg (Myslee [®]) tablet as a comparative drug								
Study design	Zolpidem (Myslee[®]) tablet-controlled, multicenter, randomized, double-dummy, double-blind, parallel-group comparative study In a run-in period, the patients received the drugs for the period (FK199B tablet placebo and zolpidem tablet placebo) in a single-blind manner, taking two tablets once daily immediately before bedtime for one week. In a double-blind period, the FK199B 12.5 mg group was given the FK199B tablet 12.5 mg and the Zolpidem tablet placebo, and the zolpidem 10 mg group was given the zolpidem tablet 10 mg and FK199B tablet placebo, taking two tablets once daily immediately before bedtime for two week. In a post-treatment period, the patients received the drugs for the period (FK199B tablet placebo and Zolpidem tablet placebo), taking two tablets once daily immediately before bedtime for one week.								
Number of subjects	Planned number of subjects: 960 (400 eligible subjects/group, 800 in total, for efficacy analysis) Rationale for setting the planned number of subjects The number of subjects was determined based on the results of subjective wake time after sleep onset from a multinational study (Australia, Canada and United States of America; EFC5202) comparing zolpidem MR 12.5 mg and zolpidem 10 mg to placebo (see the table below) in order to verify the superiority of the FK199B tablet to the Zolpidem tablet as follows: The value of subjective wake time after sleep onset following drug administration in the zolpidem MR 12.5 mg group and the zolpidem 10 mg group was set to 43.40 minutes and 52.41 minutes, respectively; the standard deviation for both groups was set to 45 minutes. Calculation with a statistical power of 80% at 2.5% significance (one-sided test) gave 392 subjects/group, determining the efficacy analysis set to 400 subjects/group. <table border="1" style="margin-left: auto; margin-right: auto;"><thead><tr><th>N=106</th><th>Screening</th><th>After administration</th></tr></thead><tbody><tr><td>Zolpidem 10 mg group</td><td rowspan="2" style="text-align: center;">77:39 ± 44:06</td><td style="text-align: center;">52:25 ± 47:10</td></tr><tr><td>FK199B 12.5 mg group</td><td style="text-align: center;">43:24 ± 41:21</td></tr></tbody></table> <p style="text-align: center;">mean ± SD (min:sec)</p> Considering dropouts during the observation periods (run-in and post-treatment periods), the planned number of subjects was set to 960, which was 1.2 times that of the efficacy analysis set.	N=106	Screening	After administration	Zolpidem 10 mg group	77:39 ± 44:06	52:25 ± 47:10	FK199B 12.5 mg group	43:24 ± 41:21
N=106	Screening	After administration							
Zolpidem 10 mg group	77:39 ± 44:06	52:25 ± 47:10							
FK199B 12.5 mg group		43:24 ± 41:21							
Number of subjects	Planned number of subjects: 960 (400 eligible subjects/group, 800 in total, for efficacy analysis)								
Subjects	Japanese patients who were diagnosed as having nonorganic insomnia (except for insomnia with schizophrenia or manic-depressive psychosis) in the nonorganic sleep disorders classified in the International Classification of Diseases, 10th edition (ICD-10)								
Criteria for inclusion	(1) At primary registration 1. Patients who were diagnosed as having nonorganic insomnia (except for insomnia with schizophrenia or manic-depressive psychosis) in the nonorganic sleep disorders classified in the International Classification of Diseases, 10th edition (ICD-10) 2. Patients who complained of insomnia for more than four consecutive weeks 3. Patients whose time for bed was usually between 9 p.m. and 1 a.m., and who slept for between six and nine hours within four weeks before the start of the run-in period according to the health check sheet 4. Patients who usually slept for a total of between three and six hours within four weeks before the start of the run-in period according to the health check sheet 5. Patients whose wake time after sleep onset was usually ≥45 minutes per night within four weeks before the start of the run-in period according to the health check sheet 6. Patients who had a washout period before the start of the run-in period, when given antihistamine (H ₁ blocker only, including combination cold remedy, except for eye-drops, nose drops or external medicine), hypnotics, or anxiolytic or antidepressant drugs for sleep								

Item	Content
	<p>7. Patients aged between 20 and 65 when their informed consent was obtained</p> <p>8. Patients who had an ability to fill in the sleep diary</p> <p>9. It does not matter whether the patients are inpatients or outpatients (they were not allowed to change this status for one week before the start of the run-in period)</p> <p>10. Patients who provided written informed consent</p> <p>(2) At secondary registration</p> <p>11. Patients whose time for bed was between 9 p.m. and 1 a.m., and who slept for between six and nine hours during the run-in period according to the sleep diary</p> <p>12. Patients who on average slept for a total of between three and six hours during the run-in period according to the sleep diary on the day of administration of the study drug</p> <p>13. Patients whose wake time after sleep onset during the run-in period was ≥ 45 minutes per night ≥ 3 nights and mean wake time after sleep onset during the run-in period is ≥ 30 minutes per night, according to the sleep diary on the day of administration of the study drug</p>
Criteria for exclusion	<p>(1) At primary registration</p> <ol style="list-style-type: none"> 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. Patients with alcoholic sleep disorder 5. Patients with history or suffering from alcohol or drug dependence 6. Patients with insomnia related with drugs including antiparkinson, antihypertensive, or steroid drugs 7. Patients with sleep apnea syndrome, restless legs syndrome, and periodic limb movement disorder 8. Patients with epileptic insomnia 9. Patients who had received psychotropic drugs other than hypnotics (including anxiolytic or antidepressant drugs for sleep) within four weeks before the start of the run-in period 10. Patients who had gone on an overseas trip to a place with a time difference of five or more hours within twelve weeks before the start of the run-in period 11. Patients who had received zolpidem within two weeks before the start of the run-in period 12. Patients with a history of allergy to zolpidem 13. Patients with myasthenia gravis 14. Patients with acute narrow-angle glaucoma 15. Patients whose respiratory function is severely decreased during acute stages of cor pulmonale, emphysema, bronchial asthma, or cerebrovascular disorders 16. Patients with organic brain disorders 17. Patients with serious cardiac diseases, hepatic diseases, renal diseases, or blood diseases* *In reference to Grade 3 in "Criteria for classification of grade of adverse drug reactions to pharmaceutical products" (PAB/SD Notification No. 80, issued on 29 June 1992). 18. Patients who drive or operate machinery with high risks 19. Pregnant women, female patients with an intention of pregnancy during the study period, or female patients under lactation 20. Patients who were judged to be in a clinical condition not appropriate for the safe conduct of this study by the principal investigator or subinvestigator <p>Patients who had participated in other clinical study or post-marketing study within 12 weeks before the informed consent was obtained</p> <p>(2) At secondary registration At secondary registration, patients were confirmed not to have violated the exclusion criteria 1 to 8, and 13 to 19 at primary registration, and the following exclusion criteria.</p> <ol style="list-style-type: none"> 21. Patients who received prohibited concomitant drugs or therapies during the run-in period 22. Patients with a compliance of $< 50\%$ during the run-in period 23. Patients who changed their status from inpatient to outpatient or vice versa during the run-in period 24. Patients who were judged to be inappropriate as subjects because of clinical laboratory test values or others by the principal investigator or subinvestigator
Dose and administration method	<p>(1) Dose FK199B 12.5 mg group: zolpidem (MR tablet), 12.5 mg/day Zolpidem 10 mg group: zolpidem (immediate release tablet), 10 mg/day</p> <p>(2) Administration method Patients received a combination of the following study drugs, taking two tablets once daily immediately</p>

Item	Content			
	before bedtime.			
	Run-in period (placebo single-blind)	Double-blind period	Post-treatment period (placebo single-blind)	
FK199B 12.5 mg group	FK199B tablet placebo, 1 tablet	FK199B tablet 12.5 mg, 1 tablet	FK199B tablet placebo, 1 tablet	
	Zolpidem tablet placebo, 1 tablet	Zolpidem tablet placebo, 1 tablet	Zolpidem tablet placebo, 1 tablet	
Zolpidem 10 mg group	FK199B tablet placebo, 1 tablet	FK199B tablet placebo, 1 tablet	FK199B tablet placebo, 1 tablet	
	Zolpidem tablet placebo, 1 tablet	Zolpidem tablet 10 mg, 1 tablet	Zolpidem tablet placebo, 1 tablet	
	<p>Rationale for dose setting</p> <p>For the zolpidem tablet, which is used as a prescription drug, the standard treatment is considered to be administration at 10 mg to adults in both Japan and foreign countries. According to the results of a previous clinical study conducted outside Japan, as compared to placebo, the administration of zolpidem MR 12.5 mg showed a similar sleep initiation effect in adults to that of zolpidem 10 mg but reduced the duration of nocturnal awakenings more effectively than that of zolpidem tablet 10 mg. Based on the results, a cross-over single oral administration study in healthy, male fasting subjects using the FK199B tablet 12.5 mg and the Zolpidem tablet 10 mg was conducted in Japan to compare the pharmacokinetic profiles of both drugs. The plasma exposure (AUC) observed after a single administration of the FK199B tablet 12.5 mg increased by 24%, compared with that observed with zolpidem 10 mg. This increase in AUC reflects the increase in amount of active ingredient contained in the FK199B tablet 12.5 mg as compared to zolpidem 10 mg tablet. C_{max} of the FK199B tablet 12.5 mg was similar to that of the Zolpidem tablet 10 mg, suggesting that the sustained-release formulation in the FK199B tablet 12.5 mg did not lead to an increase in C_{max} related to the increase in the amount. Also, there was no statistically significant difference in oral clearance or half life in blood, showing no difference in oral availability or pharmacokinetics after absorption between both drugs. MRT and HVD values, which are indicators for sustainability in concentrations in plasma, were statistically significantly prolonged in the FK199B tablet 12.5 mg compared with those in the Zolpidem tablet 10 mg. Based on these results, the FK199B tablet 12.5 mg and the zolpidem tablet 10 mg were compared in the CL-0007 clinical study.</p>			
Administration period	<ol style="list-style-type: none"> 1. Run-in period (placebo single-blind): 1 week 2. Double-blind period: 2 weeks 3. Post-treatment period (placebo single-blind): 1 week 			
Prior treatment	<p>A washout period was scheduled when the following drugs had been used before the start of the run-in period.</p> <ol style="list-style-type: none"> 1. Antihistamine (H_1 blocker only, including cold medicine, except for eye-drops, nose drops or external medicine): ≥ 7 days (the day of the final treatment was defined as Day 1) 2. Sleeping drug, and anxiolytic or antidepressant drug for sleep: i) seven days or ii) three times the elimination half-life, whichever was longer, or more (the day of the final treatment was defined as Day 1) 			

Item	Content																																																																																																																																																																			
Concomitant treatment	<p>(1) Prohibited concomitant drugs and therapies Use of the following drugs and therapies were prohibited during the study period after the day of the start of the run-in period.</p> <ol style="list-style-type: none"> 1. Antipsychotics, antidepressants, antimanics, antiepileptic drugs, hypnotics, ameliorants of cerebral circulation/metabolism, anti-dementia drugs, antiparkinson drugs, and Chinese herbal medicines to act on the central nervous system 2. Antihistamine (H₁ blocker only, including cold medicine but not including eye-drops, nose drops or external medicine) 3. Sedatives including bromovalerylurea 4. Cognitive behavior therapy and bright light therapy 5. Prescription drugs, supplements, and dietary supplements containing melatonin or Saint John's wort 6. Vitamin B12-based prescription drugs (except for eye-drops, nose drops, or external medicine) 7. Supplements and dietary supplements containing glycine for sleeping 8. Rifampicin 9. Central nervous system depressants such as phenothiazine derivatives and barbiturates 10. Anesthetics 11. Other study drugs and post-marketing study drugs <p>(2) Permitted concomitant drugs Caffeine-containing drugs (cold medicine, analgesic antipyretic drugs, and quasi-drugs) might be used concomitantly, if the administration was performed 10 hours or more before bedtime.</p>																																																																																																																																																																			
	Observation/ Evaluation schedule	<table border="1"> <thead> <tr> <th rowspan="2"></th> <th rowspan="2">Before study start</th> <th colspan="2">Run-in period¹</th> <th colspan="3">Double-blind period</th> <th>Post-treatment</th> <th rowspan="2">At discontinuation</th> </tr> <tr> <th>Week -1</th> <th>Week 0</th> <th>Week 1²</th> <th>Week 2</th> <th>Week 3</th> </tr> </thead> <tbody> <tr> <td>Visit</td> <td>●</td> <td>●</td> <td>●</td> <td>●</td> <td>●</td> <td>●</td> <td>●</td> <td>●</td> </tr> <tr> <td>Written informed consent</td> <td>●</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Subject's background</td> <td>●</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Health check sheet</td> <td></td> <td>●</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Primary case registration</td> <td></td> <td>●</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Secondary case registration</td> <td></td> <td></td> <td>●</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td rowspan="2">Study drug</td> <td>Prescription</td> <td></td> <td>●</td> <td>●</td> <td>●</td> <td>●</td> <td></td> <td></td> </tr> <tr> <td>Collection</td> <td></td> <td></td> <td>●</td> <td>●</td> <td>●</td> <td>●</td> <td>●</td> </tr> <tr> <td rowspan="2">Sleep diary</td> <td>Delivery</td> <td></td> <td>●</td> <td>●</td> <td>●</td> <td>●</td> <td></td> <td></td> </tr> <tr> <td>Collection</td> <td></td> <td></td> <td>●</td> <td>●</td> <td>●</td> <td>●</td> <td>●</td> </tr> <tr> <td>Dependence</td> <td></td> <td></td> <td>●</td> <td></td> <td>●</td> <td>●</td> <td>●</td> <td>●^{*3}</td> </tr> <tr> <td>Body weight</td> <td></td> <td>●</td> <td></td> <td></td> <td>●</td> <td></td> <td></td> <td>●^{*4}</td> </tr> <tr> <td>Blood pressure and pulse rate</td> <td></td> <td>●</td> <td></td> <td></td> <td>●</td> <td></td> <td></td> <td>●^{*4}</td> </tr> <tr> <td>Clinical laboratory tests</td> <td></td> <td>●</td> <td></td> <td></td> <td>●</td> <td></td> <td></td> <td>●^{*4}</td> </tr> <tr> <td>Pregnancy test^{*5}</td> <td></td> <td>●</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Adverse event^{*6}</td> <td colspan="8" style="text-align: center;"> </td> </tr> </tbody> </table>									Before study start	Run-in period ¹		Double-blind period			Post-treatment	At discontinuation	Week -1	Week 0	Week 1 ²	Week 2	Week 3	Visit	●	●	●	●	●	●	●	●	Written informed consent	●								Subject's background	●								Health check sheet		●							Primary case registration		●							Secondary case registration			●						Study drug	Prescription		●	●	●	●			Collection			●	●	●	●	●	Sleep diary	Delivery		●	●	●	●			Collection			●	●	●	●	●	Dependence			●		●	●	●	● ^{*3}	Body weight		●			●			● ^{*4}	Blood pressure and pulse rate		●			●			● ^{*4}	Clinical laboratory tests		●			●			● ^{*4}	Pregnancy test ^{*5}		●							Adverse event ^{*6}							
		Before study start	Run-in period ¹		Double-blind period			Post-treatment	At discontinuation																																																																																																																																																											
			Week -1	Week 0	Week 1 ²	Week 2	Week 3																																																																																																																																																													
Visit		●	●	●	●	●	●	●	●																																																																																																																																																											
Written informed consent		●																																																																																																																																																																		
Subject's background		●																																																																																																																																																																		
Health check sheet			●																																																																																																																																																																	
Primary case registration			●																																																																																																																																																																	
Secondary case registration				●																																																																																																																																																																
Study drug		Prescription		●	●	●	●																																																																																																																																																													
		Collection			●	●	●	●	●																																																																																																																																																											
Sleep diary		Delivery		●	●	●	●																																																																																																																																																													
		Collection			●	●	●	●	●																																																																																																																																																											
Dependence				●		●	●	●	● ^{*3}																																																																																																																																																											
Body weight			●			●			● ^{*4}																																																																																																																																																											
Blood pressure and pulse rate		●			●			● ^{*4}																																																																																																																																																												
Clinical laboratory tests		●			●			● ^{*4}																																																																																																																																																												
Pregnancy test ^{*5}		●																																																																																																																																																																		
Adverse event ^{*6}																																																																																																																																																																				
<p>*1: A washout period was scheduled when the following drugs had been used before the start of the run-in period.</p> <ol style="list-style-type: none"> 1. Antihistamine (H₁ blocker only, including cold medicine but not including eye-drops, nose drops or external medicine): ≥7 days (the day of the final treatment was defined as Day 1) 2. Hypnotics, and anxiolytic or antidepressant drugs for sleep: i) seven days or ii) three times the elimination half-life, whichever was longer, or more (the day of the final treatment was defined as Day 1) <p>*2: The subjects were requested to visit the study institute at Week 1 in the double-blind period, unless it was impossible for them to do so for personal reasons. When it was impossible for the subjects to come to the study institute, the study drug and sleep diary up to Week 2 of the double-blind period were handed to them on the first day of the double-blind period.</p> <p>*3: Cases which had been discontinued during the run-in period were not evaluated in terms of dependence.</p> <p>*4: Cases which had been discontinued during the run-in period or the post-treatment period were not evaluated in terms of measurements of body weight, blood pressure, or pulse rate, or clinical laboratory tests.</p> <p>*5: Conducted only in female subjects. However, the test could be 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)</p> <p>*6: Observations looking for undesirable clinical events were made during the period between the informed consent obtained and the time before the start of the treatment with the drug for the double-blind period. Monitoring of these adverse events began after the start of the treatment with the drug for the double-blind period.</p>																																																																																																																																																																				

Item	Content
<p>Endpoints and evaluation criteria</p>	<p>(1) Efficacy Primary endpoints: Mean subjective wake time after sleep onset during the double-blind period</p> <p>Secondary endpoints:</p> <ol style="list-style-type: none"> 1. Mean subjective total sleep time during the double-blind period 2. Mean subjective number of awakenings during the double-blind period 3. Mean subjective sleep onset latency during the double-blind period 4. Patient impression during the double-blind period 5. Mean subjective wake time after sleep onset without bed out latency during the double-blind period (added in the statistical analysis plan) 6. Mean subjective number of awakenings without bed out latency during the double-blind period (added in the statistical analysis plan) <p>(2) Safety</p> <ol style="list-style-type: none"> 1. Adverse events 2. Dependence 3. Clinical laboratory tests 4. Vital signs (body weight, blood pressure, pulse rate) 5. Withdrawal signs (added in the statistical analysis plan)
<p>Statistical methods</p>	<p>(1) Analysis sets Efficacy analysis sets FAS (Full Analysis Set) and PPS (Per Protocol Set) were defined as efficacy analysis sets as follows. The FAS was used as the primary efficacy analysis set, and the PPS was used as the secondary efficacy analysis set.</p> <ol style="list-style-type: none"> 1. Full Analysis Set (FAS) FAS consisted of all subjects who received the study drug for the double-blind period at least once and had at least one efficacy measurement (whether primary endpoint or secondary endpoint) after receiving the study drug for the double-blind period. 2. Per Protocol Set (PPS) PPS consisted of the FAS's subjects satisfying the following criteria. <ul style="list-style-type: none"> • Subjects who correspond to the inclusion criteria and do not correspond to the exclusion criteria • Subjects whose wake time after sleep onset during the double-blind period can be evaluated for ≥ 7 days in the sleep diary, and of these days, three or more days are included in the period at and after Day 8* of administration of the study drug for the double-blind period. <p>*The day of the start of the administration for the double-blind period was defined as Day 1. Even when subjects do not correspond to the second criteria, cases of discontinuation owing to insufficient efficacy were included in the PPS.</p> <p>Safety analysis set Safety analysis set consisted of the subjects who received the study drug for the double-blind period.</p> <p>(2) Demographic and other baseline characteristics Analysis sets: FAS, PPS, safety analysis sets The distribution of patient's background variables and measurement values in the run-in period was tabulated. To assess the homogeneity of variances between the treatment groups, categorization variables were analyzed by the χ^2 test or Fisher test; ordinal variables by the Wilcoxon rank sum test; continuous variables by the t test etc.(target two-sided significance level: 5%). If any imbalance was observed between treatment groups in individual analyses and was considered to clinically affect a primary endpoint, analysis adjusted in terms of the endpoint was performed to examine its effect on primary analysis of the primary endpoint.</p> <p>(3) Efficacy Unless otherwise noted, the FAS was used as the analysis set. The significance level was set as 5% (two-sided). Efficacy data for days without administration of the study drug were not included in the analysis. Analysis of primary endpoints Primary analysis: To verify the superiority of the FK199B tablet compared with the Zolpidem tablet, analysis of covariance</p>

Item	Content
	<p>was performed for the mean wake time after sleep onset during the double-blind period using the mean wake time after sleep onset during the run-in period as a covariate in the following model. For the difference between treatment groups (FK199B 12.5 mg group – Zolpidem 10 mg group), the adjusted mean, its standard deviation and its two-sided 95% confidence interval were calculated.</p> <p>Model Mean wake time after sleep onset during the double-blind period = Treatment group + Mean wake time after sleep onset during the run-in period</p> <p>Secondary analysis:</p> <ul style="list-style-type: none"> • The same analysis described “Primary analysis” in PPS was performed to confirm the robustness of the result of Primary analysis.. • Summary statistics of mean values during each period and their changes from the run-in period (mean value during each period – mean value during the run-in period) were shown by treatment group. • Interaction between treatment group and mean wake time after sleep onset during the run-in period was examined. <p>(4) Safety The safety analysis set was used as the analysis set. The level of significance was set as 5% (two-sided). Any adverse events and any discontinuation caused by adverse events were summarized with respect to the number of subjects and the incidence by treatment group to compare groups using the Fisher test. For associated symptoms and abnormal changes in clinical laboratory test values, the number of subjects and the incidence of were classified by organ (MedDRA: SOC code) and by symptom (MedDRA: PT code). For clinical laboratory test values, summary statistics for observed values at each period and changes from the run-in period were calculated by treatment group. For measured values, a cross table was prepared to list values at the start of the run-in period and at each period. For blood pressure, pulse rate and body weight, summary statistics for observed values at each period and changes from the run-in period were calculated by treatment group. For dependence, a cross table was prepared to list values at the start of the double-blind period and at each period. For withdrawal signs, summary statistics were calculated for changes in each of the wake time after sleep onset, total sleep time, number of awakenings, sleep onset latency, and patient impression.</p> <p>(5) Changes in statistical analysis plan The statistical analysis plan had not been changed since the data hard lock. After breaking the key code, the following additional analyses were performed to mainly obtain more detailed data.</p> <ol style="list-style-type: none"> 1. Disposition of subjects <ul style="list-style-type: none"> • Discontinuation and its reasons in all subjects during the double-blind period and the post-treatment period 2. Efficacy analysis <ul style="list-style-type: none"> • Mean bed out latency (time from the final awakening to rising) during the double-blind period • Analysis of covariance was performed for of the mean wake time after sleep onset during the double-blind period using the mean wake time after sleep onset during the run-in period and the interaction between treatment group and mean wake time after sleep onset during the run-in period as a covariate.
Study institution	99 sites in Japan
Study period	February 2006 to June 2007

2 RESULTS

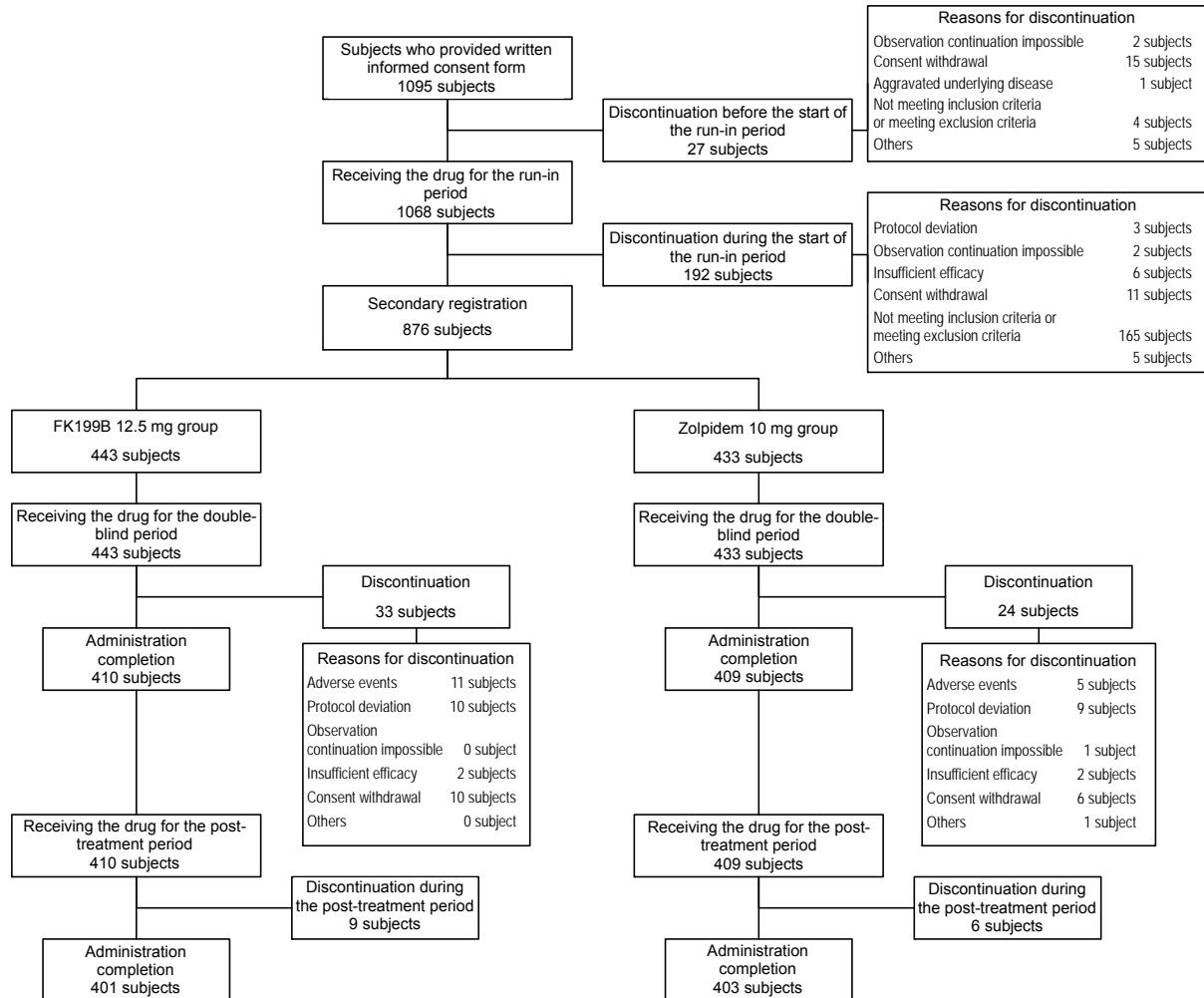
2.1 Disposition of Patients and Analysis Sets

(1) Disposition of Subjects

Written informed consent to participate in the study was obtained from 1095 Japanese adult patients. Of them, 219 patients dropped out of the study before the end of the run-in period, and the remaining 876 were enrolled as qualified patients for secondary registration. The drugs for the double-blind period were randomly allocated to the 876 patients (443 in the FK199B 12.5 mg group, 433 in the zolpidem 10 mg group), all of whom received the drug.

Of them, 819 patients (410 and 409, respectively) completed the two-week administration, and 57 patients (33 and 24, respectively) discontinued administration. Most of the patients who completed the administration course also completed administration with the drug for the post-treatment period; 15 patients (9 in the FK199B 12.5 mg group, 6 in the zolpidem 10 mg group) discontinued administration during the post-treatment period.

Figure 1: Disposition of Patients



The major reasons for discontinuation during the double-blind period included protocol deviation (10 in the FK199B 12.5 mg group and 9 in the Zolpidem 10 mg group), adverse events (11 and 5, respectively), and consent withdrawal (10 and 6, respectively). The major reasons for discontinuation before the secondary registration included disqualification by not meeting inclusion criteria or meeting exclusion criteria (169), and consent withdrawal (26).

(2) Analysis Sets

The FAS included 856 subjects (437 in the FK199B 12.5 mg group, and 419 in the zolpidem 10 mg group), and the PPS included 795 subjects (402 and 393, respectively). The safety analysis set was identical to the FAS. Twenty subjects who were found to have participated in this study or other studies in multiple medical institutes (duplicate registration) were excluded from all the analysis sets. The most common reason for exclusion from the PPS was shortage of days for evaluation.

Table 1: Analysis Sets

Item	FK199B 12.5 mg group	Zolpidem 10 mg group	Total
Subjects in secondary registration	443	433	876
Efficacy Analysis Set (FAS)			
Included	437 (98.6%)	419 (96.8%)	856 (97.7%)
Excluded	6 (1.4%)	14 (3.2%)	20 (2.3%)
Efficacy Analysis Set (PPS)			
Included	402 (90.7%)	393 (90.8%)	795 (90.8%)
Excluded	41 (9.3%)	40 (9.2%)	81 (9.2%)
Safety Analysis Set			
Included	437 (98.6%)	419 (96.8%)	856 (97.7%)
Excluded	6 (1.4%)	14 (3.2%)	20 (2.3%)

No. of subjects (%)

2.2 Demographic and Other Baseline Characteristics

In terms of the patients' background in the FAS, the FK199B 12.5 mg group was similar to the zolpidem 10 mg group in general. In each group, about 60% was female, the mean age was about 43 years, and the median of the duration of the disease was about 16 months. Patients who had not received any drug for the treatment of insomnia within four weeks before the start of the run-in period amounted to about 80% in each group. The mean body weight was about 59 kg in the FK199B 12.5 mg group, and 61 kg in the zolpidem 10 mg group. It was almost the same, but a statistically imbalance was observed between the groups ($p=0.028$, target two-sided significance level: 0.05).

Table 2: Demographic Characteristics: FAS, Safety Analysis Set

Item		FK199B 12.5 mg group (n=437)	Zolpidem 10 mg group (n=419)	Total (n=856)	Test
Sex	Male	163 (37.3%)	183 (43.7%)	346 (40.4%)	P=0.060 †
	Female	274 (62.7%)	236 (56.3%)	510 (59.6%)	
Age (years)	Mean ± SD	43.1 ± 12.31	42.9 ± 12.44	–	P=0.745 ‡
	(Minimum - Maximum)	(20 - 64)	(20 - 76)		
Ethnic origins	-	Japanese	Japanese	-	-
Body weight (kg)	Mean ± SD	58.85 ± 13.068	60.75 ± 12.171	–	P=0.028 ‡
	(Minimum - Maximum)	(30.4 - 116.8)	(40.0 - 108.4)		
Duration of the disease [¶] (months)	Mean ± SD	36.4 ± 57.87	43.3 ± 67.04	–	P=0.150 §
	Median	15.0	16.5		
	(Minimum - Maximum)	(2 - 445)	(2 - 585)		
Drinking habit	Absent	161 (36.8%)	153 (36.5%)	314 (36.7%)	P=0.944 †
	Present	276 (63.2%)	266 (63.5%)	542 (63.3%)	
Previous treatment for insomnia	Absent	349 (79.9%)	337 (80.4%)	686 (80.1%)	P=0.864 †
	Present	88 (20.1%)	82 (19.6%)	170 (19.9%)	

Compiled data on frequency is No. of subjects (%).

† Fisher test

‡ t test

§ Wilcoxon rank sum test

¶ Analysis set for the duration of the disease: 337 subjects in the FK199B 12.5 mg group, and 324 in the Zolpidem 10 mg group

2.3 Compliance with the Treatment and Exposure to the Study Drug

Drug compliance was good for the drug used in the double-blind period. In each group, the administration period and the number of administration days were about 13 days, and the mean compliance rate was about 99%. Drug compliance was also good for the drugs used in the run-in period and the post-treatment period.

Table 3: Drug Compliance for the Double-blind Period: FAS, Safety Analysis Set

Item	FK199B 12.5 mg group (n=437)	zolpidem 10 mg group (n=419)
Administration period (Day)	13.1 ± 2.26 (1 - 15)	13.4 ± 1.76 (1 - 15)
No. of administration days (Day)	13.0 ± 2.30 (1 - 14)	13.3 ± 1.79 (1 - 14)
Compliance rate (%)	98.92 ± 3.674 (64.3 - 100.0)	99.27 ± 2.799 (78.6 - 100.0)

Mean ± SD (Minimum - Maximum)

2.4 Efficacy

(1) Primary Endpoint: Mean subjective Wake Time after Sleep Onset (WASO)

In the FAS, which is the main analysis set, the mean subjective wake time after sleep onset during the double-blind period decreased (improved), compared with that during the run-in period; the amount of change was –33.20 minutes in the FK199B 12.5 mg group, and –30.40

minutes in the Zolpidem 10 mg group. Analysis of covariance (two-sided significance level: 0.05) with the mean value during the run-in period as a covariate showed that the difference in mean-adjusted measured values between the treatment groups (FK199B 12.5 mg group – Zolpidem 10 mg group) was –3.25 minutes. The 95% confidence interval was –6.824 minutes to 0.333 minutes, with no statistically significant difference (p=0.075).

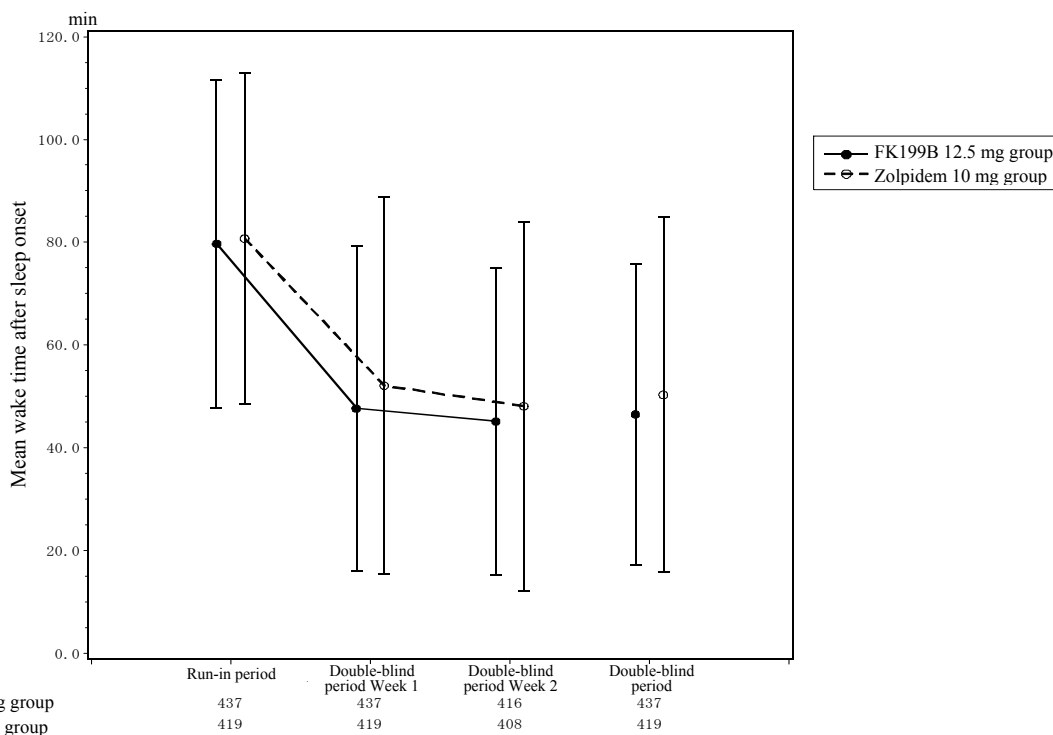
Table 4: Mean subjective Wake Time after Sleep Onset: FAS

Item	Mean wake time after sleep onset (min) [†]		FK199B 12.5 mg group – Zolpidem 10 mg group [‡]	
	Run-in period	Double-blind period	Adjusted mean [95% confidence interval]	P value
FK199B 12.5 mg group (n=437)	79.72 ± 31.888	46.52 ± 29.324 (-33.20 ± 30.737)	-3.25 [-6.824 to 0.333]	0.075
Zolpidem 10 mg group (n=419)	80.73 ± 32.198	50.32 ± 34.589 (-30.40 ± 29.721)		

[†] Mean ± SD (change from the run-in period)

[‡] Analysis of covariance for the mean wake time after sleep onset during the double-blind period using the mean value during the run-in period as a covariate

Figure 2: Change in Mean Wake Time after Sleep Onset: FAS



Data show mean ± SD, and numbers under the horizontal axis indicate the number of subjects in each group.

(2) Secondary Endpoint

“Mean wake time after sleep onset without bed out latency” was calculated by subtracting bed out latency (time from the final awakening to rising) from the wake time after sleep, decreasing (improving) from the run-in period in both the groups. The amount of change was -28.38 minutes in the FK199B 12.5 mg group, and -25.45 minutes in the zolpidem 10 mg group; there was no major difference from the mean wake time after sleep onset. The difference between the adjusted means (FK199B 12.5 mg group – zolpidem 10 mg group) was -3.10 minutes. “Mean wake time after sleep onset without bed out latency” during the double-blind period in the FK199B 12.5 mg group was statistically significantly shorter than that in the zolpidem 10 mg group ($p=0.026$).

In both the FK199B 12.5 mg group and the zolpidem 10 mg group, the mean subjective sleep onset latency, mean subjective number of awakenings, and mean subjective number of awakenings without bed out latency were decreased in the double-blind period from those in the run-in period; mean total sleep time was increased. These parameters were similarly improved in both groups; no statistically significant difference was observed in the adjusted means between the groups ($p=0.864$, $p=0.184$, $p=0.137$, and $p=0.558$, respectively). Ratio of the mean bed out latency in the mean wake time after sleep onset was relatively high in both groups (about 35%). The amount of change in the mean bed out latency was -4.81 minutes in the FK199B 12.5 mg group, and -4.96 minutes in the zolpidem 10 mg group; its ratio in the mean wake time after sleep onset (-33.20 minutes and -30.40 minutes, respectively) was small.

In both groups, mean subjective sleep onset latency was decreased (improved) in the double-blind period from that in the run-in period; the amount of change was -17.77 minutes in the FK199B 12.5 mg group, and -21.13 minutes in the zolpidem 10 mg group. The difference between the adjusted means (FK199B 12.5 mg group – Zolpidem 10 mg group) was 5.16 minutes; mean sleep onset latency in the double-blind period in the FK199B 12.5 mg group was statistically significantly longer than that in the Zolpidem 10 mg group ($p<0.001$).

Table 5: Mean Sleep Parameters (Secondary Endpoint): FAS

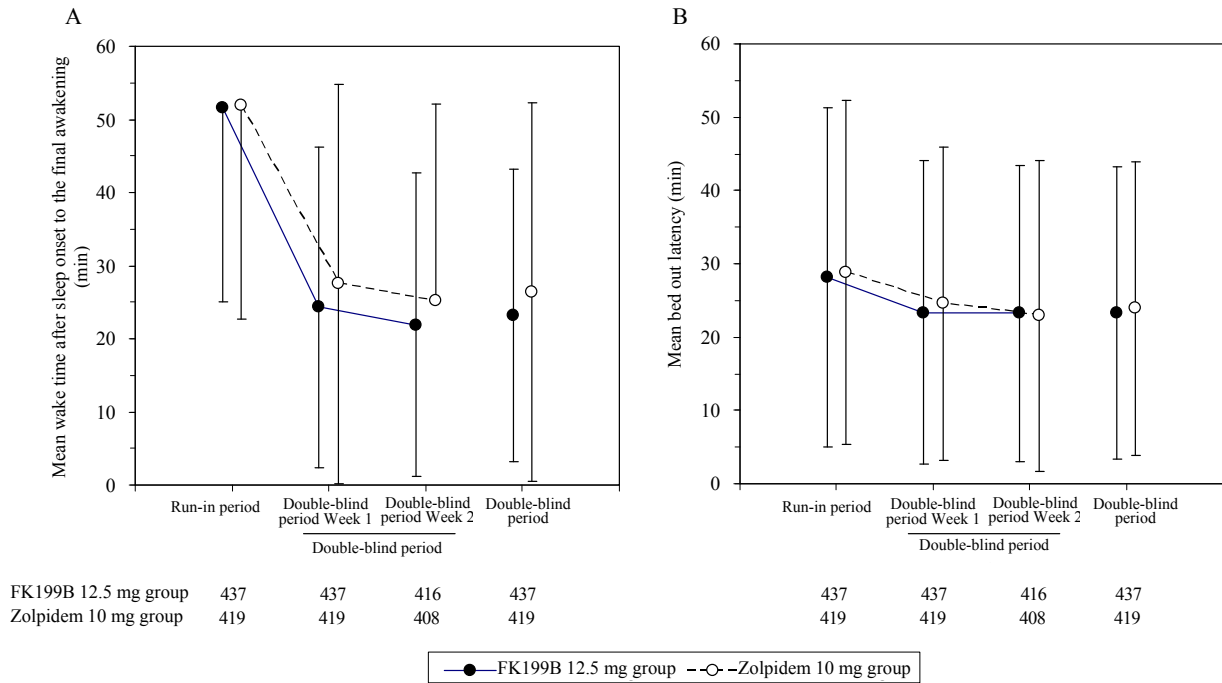
Item	Mean sleep parameter [†]		FK199B 12.5 mg group – Zolpidem 10 mg group [‡]	
	Run-in period	Double-blind period	Adjusted mean [95% confidence interval]	P-value
Mean wake time after sleep onset to the final awakening (min)				
FK199B 12.5 mg group	51.59 ± 26.626	23.21 ± 19.955 (-28.38 ± 27.161)	-3.10 [-5.829 - -0.379]	0.026
Zolpidem 10 mg group	51.86 ± 29.246	26.42 ± 25.887 (-25.45 ± 25.745)		
Mean bed out latency (min)				
FK199B 12.5 mg group	28.12 ± 23.159	23.31 ± 19.921 (-4.81 ± 17.773)	-0.18 [-2.189 - 1.838]	0.864
Zolpidem 10 mg group	28.86 ± 23.462	23.90 ± 20.036 (-4.96 ± 18.397)		
Mean number of awakenings (times)				
FK199B 12.5 mg group	2.13 ± 0.758	1.44 ± 0.692 (-0.69 ± 0.706)	-0.05 [-0.135 - 0.026]	0.184
Zolpidem 10 mg group	2.14 ± 0.750	1.50 ± 0.761 (-0.64 ± 0.674)		
Mean number of awakenings after sleep onset to the final awakening (times)				
FK199B 12.5 mg group	1.48 ± 0.714	0.81 ± 0.574 (-0.67 ± 0.652)	-0.05 [-0.122 - 0.017]	0.137
Zolpidem 10 mg group	1.48 ± 0.705	0.86 ± 0.642 (-0.62 ± 0.645)		
Mean total sleep time (min)				
FK199B 12.5 mg group	302.95 ± 39.513	354.37 ± 45.968 (51.41 ± 45.836)	-1.65 [-7.160 - 3.866]	0.558
Zolpidem 10 mg group	302.26 ± 41.040	355.58 ± 50.199 (53.32 ± 41.553)		
Mean sleep onset latency (min)				
FK199B 12.5 mg group	56.86 ± 35.885	39.09 ± 22.882 (-17.77 ± 28.394)	5.16 [2.802 - 7.524]	<0.001
Zolpidem 10 mg group	53.82 ± 32.292	32.68 ± 21.954 (-21.13 ± 25.000)		

Each parameter was evaluated for 437 subjects in the FK199B 12.5 mg group and 419 in the Zolpidem 10 mg group.

[†] Mean ± SD (change from the run-in period)

[‡] Analysis of covariance for the mean wake time after sleep onset during the double-blind period using the mean value during the run-in period as a covariate

Figure 3: Changes in Mean Wake Time after Sleep Onset to the Final Awakening and Mean Bed Out Latency: FAS



Data show mean \pm SD, and numbers under the horizontal axis indicate the number of subjects in each group.

No statistically significant difference was showed in adjusted means of most of the question items in patient impression between the groups. In the double-blind period, the average score in the question, “How was your health in the daytime?” (1 to 5: a higher number means a better sleep condition) was statistically significantly low in the FK199B 12.5 mg group, compared with that in the Zolpidem 10 mg group ($p=0.041$), but the amount of the change from the run-in period was low (<0.2) in both the groups.

(3) Analysis Results in the PPS, Secondary Analysis Set

The same analysis as primary analysis was performed in PPS, which is the secondary analysis set. The result showed almost the same result as that in the FAS.

(4) Subgroup Analysis

The between-group difference in the adjusted mean of the mean wake time after sleep onset during the double-blind period, which is the primary endpoint, was -8.34 minutes in patients aged ≥ 50 years, and -8.57 minutes in patients with the duration of the disease of <12 months. These were markedly low compared with -0.67 minutes in subjects aged <50 years, and -0.28 minutes in subjects with the duration of the disease of ≥ 12 months. The mean wake time after sleep onset during the run-in period was higher in subjects aged ≥ 50 years than

<50 years. A subgroup analysis by mean wake time after sleep onset during the run-in period showed that the between-group difference in the adjusted mean of mean wake time after sleep onset was greater in ≥ 60 minutes (-4.08 minutes) than < 60 minutes (-0.59 minutes).

2.5 Safety

(1) Adverse Events

The incidence of adverse events (AEs) (including abnormal changes in clinical laboratory test values) was 40.0% (175/437) in the FK199B 12.5 mg group, and 33.7% (141/419) in the zolpidem 10 mg group. The FK199B 12.5 mg group was higher than the Zolpidem 10 mg group; however no statistically significant difference was observed between the groups ($p=0.056$). Most of the AEs were mild or moderate. Severe AEs occurred only in three subjects in the Zolpidem 10 mg group.

Common AEs (incidence $\geq 1\%$) in the FK199B 12.5 mg group were as follows in descending order: somnolence 6.9% (30), nasopharyngitis 6.6% (29), dizziness 4.3% (19), headache 3.9% (17), diarrhoea 2.3% (10), nausea 1.8% (8), vomiting 1.8% (8), protein urine present 1.1% (5), and feeling abnormal 1.1% (5). Of these, AEs with an incidence that was $\geq 1\%$ higher than that in the Zolpidem 10 mg group were nasopharyngitis and vomiting. All common AEs in the FK199B 12.5 mg group were mild or moderate; the majority of them resolved within seven days.

Table 6: Adverse Events by SOC and PT: Safety Analysis Set

System Organ Class (SOC) Preferred Terms (PT) MedDRA/J Version 9.0	FK199B 12.5 mg group (n=437)	Zolpidem 10 mg group (n=419)	Total (n=856)
All AEs	175 (40.0%)	141 (33.7%)	–
Blood and lymphatic system disorders	3 (0.7%)	0	3 (0.4%)
Anaemia	1 (0.2%)	0	1 (0.1%)
Eosinophilia	1 (0.2%)	0	1 (0.1%)
Iron deficiency anaemia	1 (0.2%)	0	1 (0.1%)
Cardiac disorders	4 (0.9%)	1 (0.2%)	5 (0.6%)
Arrhythmia supraventricular	1 (0.2%)	0	1 (0.1%)
Palpitations	3 (0.7%)	1 (0.2%)	4 (0.5%)
Ear and labyrinth disorders	3 (0.7%)	3 (0.7%)	6 (0.7%)
Ear pain	1 (0.2%)	1 (0.2%)	2 (0.2%)
Motion sickness	0	1 (0.2%)	1 (0.1%)
Tinnitus	1 (0.2%)	0	1 (0.1%)
Vertigo	1 (0.2%)	1 (0.2%)	2 (0.2%)
Eye disorders	2 (0.5%)	2 (0.5%)	4 (0.5%)
Asthenopia	0	1 (0.2%)	1 (0.1%)
Conjunctivitis	1 (0.2%)	0	1 (0.1%)
Eye pain	0	1 (0.2%)	1 (0.1%)
Visual acuity reduced	1 (0.2%)	0	1 (0.1%)
Gastrointestinal disorders	32 (7.3%)	23 (5.5%)	55 (6.4%)
Abdominal distension	1 (0.2%)	0	1 (0.1%)
Abdominal pain	0	3 (0.7%)	3 (0.4%)
Abdominal pain upper	1 (0.2%)	3 (0.7%)	4 (0.5%)
Aphthous stomatitis	1 (0.2%)	0	1 (0.1%)
Constipation	1 (0.2%)	1 (0.2%)	2 (0.2%)
Diarrhoea	10 (2.3%)	6 (1.4%)	16 (1.9%)
Enterocolitis	2 (0.5%)	1 (0.2%)	3 (0.4%)
Gastritis	2 (0.5%)	2 (0.5%)	4 (0.5%)
Gingival swelling	1 (0.2%)	0	1 (0.1%)
Irritable bowel syndrome	0	2 (0.5%)	2 (0.2%)
Nausea	8 (1.8%)	5 (1.2%)	13 (1.5%)
Periodontitis	1 (0.2%)	0	1 (0.1%)
Reflux oesophagitis	1 (0.2%)	0	1 (0.1%)
Stomach discomfort	1 (0.2%)	0	1 (0.1%)
Vomiting	8 (1.8%)	1 (0.2%)	9 (1.1%)
Epigastric discomfort	0	1 (0.2%)	1 (0.1%)
Hypoesthesia oral	0	1 (0.2%)	1 (0.1%)
General disorders and administration site conditions	17 (3.9%)	7 (1.7%)	24 (2.8%)
Asthenia	0	1 (0.2%)	1 (0.1%)
Chills	1 (0.2%)	0	1 (0.1%)
Drug withdrawal syndrome	1 (0.2%)	0	1 (0.1%)
Feeling abnormal	5 (1.1%)	1 (0.2%)	6 (0.7%)
Feeling hot	2 (0.5%)	1 (0.2%)	3 (0.4%)
Malaise	4 (0.9%)	4 (1.0%)	8 (0.9%)
Pyrexia	1 (0.2%)	0	1 (0.1%)
Thirst	2 (0.5%)	0	2 (0.2%)
Puncture site pain	1 (0.2%)	0	1 (0.1%)
Hepatobiliary disorders	1 (0.2%)	2 (0.5%)	3 (0.4%)
Hepatic function abnormal	1 (0.2%)	2 (0.5%)	3 (0.4%)
Immune system disorders	1 (0.2%)	1 (0.2%)	2 (0.2%)
Seasonal allergy	1 (0.2%)	1 (0.2%)	2 (0.2%)
Infections and infestations	43 (9.8%)	30 (7.2%)	73 (8.5%)
Acute tonsillitis	0	1 (0.2%)	1 (0.1%)
Bronchitis	1 (0.2%)	1 (0.2%)	2 (0.2%)
Cystitis	2 (0.5%)	1 (0.2%)	3 (0.4%)
Dental caries	1 (0.2%)	0	1 (0.1%)
Gastroenteritis	1 (0.2%)	0	1 (0.1%)
Genital candidiasis	1 (0.2%)	0	1 (0.1%)
Hordeolum	1 (0.2%)	0	1 (0.1%)

System Organ Class (SOC)	FK199B 12.5 mg group	Zolpidem 10 mg	Total
Preferred Terms (PT) MedDRA/J Version 9.0	(n=437)	group (n=419)	(n=856)
Influenza	0	1 (0.2%)	1 (0.1%)
Nasopharyngitis	29 (6.6%)	23 (5.5%)	52 (6.1%)
Otitis externa	1 (0.2%)	0	1 (0.1%)
Pharyngitis	4 (0.9%)	1 (0.2%)	5 (0.6%)
Rhinitis	2 (0.5%)	0	2 (0.2%)
Tonsillitis	0	1 (0.2%)	1 (0.1%)
Vaginal candidiasis	1 (0.2%)	0	1 (0.1%)
Infective spondylitis	0	1 (0.2%)	1 (0.1%)
Injury, poisoning and procedural complications	5 (1.1%)	5 (1.2%)	10 (1.2%)
Arthropod sting	1 (0.2%)	0	1 (0.1%)
Fall	0	1 (0.2%)	1 (0.1%)
Joint sprain	1 (0.2%)	0	1 (0.1%)
Contusion	2 (0.5%)	2 (0.5%)	4 (0.5%)
Wound	1 (0.2%)	0	1 (0.1%)
Thermal burn	0	1 (0.2%)	1 (0.1%)
Lower limb fracture	0	1 (0.2%)	1 (0.1%)
Investigations	25 (5.7%)	21 (5.0%)	46 (5.4%)
Alanine aminotransferase increased	1 (0.2%)	2 (0.5%)	3 (0.4%)
Aspartate aminotransferase increased	1 (0.2%)	1 (0.2%)	2 (0.2%)
Basophil count increased	1 (0.2%)	0	1 (0.1%)
Bilirubin conjugated increased	0	1 (0.2%)	1 (0.1%)
Blood bilirubin increased	3 (0.7%)	3 (0.7%)	6 (0.7%)
Blood potassium increased	1 (0.2%)	1 (0.2%)	2 (0.2%)
Blood pressure increased	2 (0.5%)	1 (0.2%)	3 (0.4%)
Blood urea increased	0	1 (0.2%)	1 (0.1%)
Eosinophil count increased	1 (0.2%)	0	1 (0.1%)
Gamma-glutamyltransferase increased	3 (0.7%)	3 (0.7%)	6 (0.7%)
Glucose urine present	1 (0.2%)	3 (0.7%)	4 (0.5%)
Blood urine present	1 (0.2%)	0	1 (0.1%)
Liver function test abnormal	0	1 (0.2%)	1 (0.1%)
Lymphocyte count decreased	1 (0.2%)	0	1 (0.1%)
Neutrophil count decreased	1 (0.2%)	0	1 (0.1%)
White blood cell count decreased	3 (0.7%)	0	3 (0.4%)
White blood cell count increased	4 (0.9%)	1 (0.2%)	5 (0.6%)
Platelet count increased	0	1 (0.2%)	1 (0.1%)
Protein urine present	5 (1.1%)	6 (1.4%)	11 (1.3%)
Blood alkaline phosphatase increased	0	2 (0.5%)	2 (0.2%)
Metabolism and nutrition disorders	1 (0.2%)	1 (0.2%)	2 (0.2%)
Anorexia	1 (0.2%)	0	1 (0.1%)
Dehydration	0	1 (0.2%)	1 (0.1%)
Musculoskeletal and connective tissue disorders	12 (2.7%)	4 (1.0%)	16 (1.9%)
Arthralgia	2 (0.5%)	0	2 (0.2%)
Back pain	4 (0.9%)	3 (0.7%)	7 (0.8%)
Muscle spasms	1 (0.2%)	0	1 (0.1%)
Myalgia	2 (0.5%)	0	2 (0.2%)
Osteoarthritis	0	1 (0.2%)	1 (0.1%)
Pain in extremity	1 (0.2%)	0	1 (0.1%)
Musculoskeletal stiffness	2 (0.5%)	0	2 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.2%)	1 (0.1%)
Uterine cancer	0	1 (0.2%)	1 (0.1%)
Nervous system disorders	66 (15.1%)	57 (13.6%)	123 (14.4%)
Amnesia	1 (0.2%)	0	1 (0.1%)
Cervicobrachial syndrome	0	1 (0.2%)	1 (0.1%)
Depressed level of consciousness	0	1 (0.2%)	1 (0.1%)
Dizziness	19 (4.3%)	16 (3.8%)	35 (4.1%)
Headache	17 (3.9%)	17 (4.1%)	34 (4.0%)
Hypoesthesia	1 (0.2%)	0	1 (0.1%)
Memory impairment	1 (0.2%)	0	1 (0.1%)
Migraine	1 (0.2%)	0	1 (0.1%)

System Organ Class (SOC)	FK199B 12.5 mg group	Zolpidem 10 mg	Total
Preferred Terms (PT) MedDRA/J Version 9.0	(n=437)	group (n=419)	(n=856)
Neuropathy peripheral	1 (0.2%)	0	1 (0.1%)
Somnolence	30 (6.9%)	26 (6.2%)	56 (6.5%)
Intracranial hypotension	0	1 (0.2%)	1 (0.1%)
Psychiatric disorders	3 (0.7%)	3 (0.7%)	6 (0.7%)
Abnormal dreams	0	1 (0.2%)	1 (0.1%)
Anxiety	1 (0.2%)	0	1 (0.1%)
Disorientation	0	1 (0.2%)	1 (0.1%)
Euphoric mood	1 (0.2%)	0	1 (0.1%)
Hallucination	1 (0.2%)	0	1 (0.1%)
Nightmare	0	1 (0.2%)	1 (0.1%)
Renal and urinary disorders	1 (0.2%)	0	1 (0.1%)
Urinary incontinence	1 (0.2%)	0	1 (0.1%)
Reproductive system and breast disorders	1 (0.2%)	1 (0.2%)	2 (0.2%)
Dysmenorrhoea	1 (0.2%)	1 (0.2%)	2 (0.2%)
Respiratory, thoracic and mediastinal disorders	9 (2.1%)	7 (1.7%)	16 (1.9%)
Cough	1 (0.2%)	0	1 (0.1%)
Dysphonia	1 (0.2%)	0	1 (0.1%)
Hyperventilation	1 (0.2%)	1 (0.2%)	2 (0.2%)
Nasal congestion	1 (0.2%)	0	1 (0.1%)
Pharyngolaryngeal pain	0	3 (0.7%)	3 (0.4%)
Rhinitis allergic	0	1 (0.2%)	1 (0.1%)
Rhinorrhoea	1 (0.2%)	0	1 (0.1%)
Snoring	1 (0.2%)	0	1 (0.1%)
Upper respiratory tract inflammation	4 (0.9%)	2 (0.5%)	6 (0.7%)
Skin and subcutaneous tissue disorders	5 (1.1%)	6 (1.4%)	11 (1.3%)
Dermatitis contact	1 (0.2%)	0	1 (0.1%)
Drug eruption	0	1 (0.2%)	1 (0.1%)
Eczema	3 (0.7%)	2 (0.5%)	5 (0.6%)
Night sweats	1 (0.2%)	1 (0.2%)	2 (0.2%)
Pruritus	0	1 (0.2%)	1 (0.1%)
Swelling face	0	1 (0.2%)	1 (0.1%)
Surgical and medical procedures	0	1 (0.2%)	1 (0.1%)
Orthopedic procedure	0	1 (0.2%)	1 (0.1%)
Vascular disorders	0	1 (0.2%)	1 (0.1%)
Hypertension	0	1 (0.2%)	1 (0.1%)

No. of subjects (incidence)

The incidence of AEs for which a causal relationship to the study drug cannot be ruled out (adverse drug reactions) was 22.0% (96/437) in the FK199B 12.5 mg group, and 17.9% (75/419) in the zolpidem 10 mg group; no statistically significant difference in the groups was found (p=0.146). Common adverse drug reactions (incidence $\geq 1\%$) in the FK199B 12.5 mg group were as follows in descending order: somnolence 6.9% (30), dizziness 4.1% (18), headache 2.3% (10), nausea 1.4% (6), and vomiting 1.4% (6). Of these, AEs with an incidence that was $\geq 1\%$ higher than that in the zolpidem 10 mg group was vomiting. The incidence was 1.4% (6) in the FK199B 12.5 mg group, and 0.2% (1) in the zolpidem 10 mg group.

Table 7: Adverse Events for Which a Causal Relationship to the Study Drug Cannot be Ruled out (Adverse Drug Reactions): Safety Analysis Set

System Organ Class (SOC) Preferred Terms (PT) MedDRA/J Version 9.0	FK199B 12.5 mg group (n=437)	Zolpidem 10 mg group (n=419)	Total (n=856)
All AEs for which a causal relationship to the study drug cannot be ruled out	96 (22.0%)	75 (17.9%)	–
Blood and lymphatic system disorders	2 (0.5%)	0	2 (0.2%)
Anaemia	1 (0.2%)	0	1 (0.1%)
Eosinophilia	1 (0.2%)	0	1 (0.1%)
Cardiac disorders	3 (0.7%)	0	3 (0.4%)
Arrhythmia supraventricular	1 (0.2%)	0	1 (0.1%)
Palpitations	2 (0.5%)	0	2 (0.2%)
Ear and labyrinth disorders	2 (0.5%)	1 (0.2%)	3 (0.4%)
Ear pain	1 (0.2%)	0	1 (0.1%)
Tinnitus	1 (0.2%)	0	1 (0.1%)
Vertigo	0	1 (0.2%)	1 (0.1%)
Gastrointestinal disorders	16 (3.7%)	10 (2.4%)	26 (3.0%)
Abdominal distension	1 (0.2%)	0	1 (0.1%)
Abdominal pain upper	1 (0.2%)	1 (0.2%)	2 (0.2%)
Aphthous stomatitis	1 (0.2%)	0	1 (0.1%)
Constipation	1 (0.2%)	1 (0.2%)	2 (0.2%)
Diarrhoea	4 (0.9%)	0	4 (0.5%)
Gastritis	0	1 (0.2%)	1 (0.1%)
Gingival swelling	1 (0.2%)	0	1 (0.1%)
Irritable bowel syndrome	0	1 (0.2%)	1 (0.1%)
Nausea	6 (1.4%)	4 (1.0%)	10 (1.2%)
Vomiting	6 (1.4%)	1 (0.2%)	7 (0.8%)
Hypoesthesia oral	0	1 (0.2%)	1 (0.1%)
General disorders and administration site conditions	12 (2.7%)	6 (1.4%)	18 (2.1%)
Asthenia	0	1 (0.2%)	1 (0.1%)
Chills	1 (0.2%)	0	1 (0.1%)
Drug withdrawal syndrome	1 (0.2%)	0	1 (0.1%)
Feeling abnormal	4 (0.9%)	1 (0.2%)	5 (0.6%)
Feeling hot	1 (0.2%)	1 (0.2%)	2 (0.2%)
Malaise	3 (0.7%)	3 (0.7%)	6 (0.7%)
Pyrexia	1 (0.2%)	0	1 (0.1%)
Thirst	1 (0.2%)	0	1 (0.1%)
Hepatobiliary disorders	1 (0.2%)	1 (0.2%)	2 (0.2%)
Hepatic function abnormal	1 (0.2%)	1 (0.2%)	2 (0.2%)
Infections and infestations	3 (0.7%)	1 (0.2%)	4 (0.5%)
Nasopharyngitis	2 (0.5%)	1 (0.2%)	3 (0.4%)
Rhinitis	1 (0.2%)	0	1 (0.1%)
Injury, poisoning and procedural complications	0	2 (0.5%)	2 (0.2%)
Fall	0	1 (0.2%)	1 (0.1%)
Contusion	0	1 (0.2%)	1 (0.1%)
Investigations	21 (4.8%)	16 (3.8%)	37 (4.3%)
Alanine aminotransferase increased	1 (0.2%)	1 (0.2%)	2 (0.2%)
Aspartate aminotransferase increased	1 (0.2%)	1 (0.2%)	2 (0.2%)
Basophil count increased	1 (0.2%)	0	1 (0.1%)
Bilirubin conjugated increased	0	1 (0.2%)	1 (0.1%)
Blood bilirubin increased	2 (0.5%)	3 (0.7%)	5 (0.6%)
Blood potassium increased	1 (0.2%)	1 (0.2%)	2 (0.2%)
Blood pressure increased	2 (0.5%)	1 (0.2%)	3 (0.4%)
Blood urea increased	0	1 (0.2%)	1 (0.1%)
Eosinophil count increased	1 (0.2%)	0	1 (0.1%)
Gamma-glutamyltransferase increased	3 (0.7%)	1 (0.2%)	4 (0.5%)
Glucose urine present	0	2 (0.5%)	2 (0.2%)
Blood urine present	1 (0.2%)	0	1 (0.1%)
Liver function test abnormal	0	1 (0.2%)	1 (0.1%)
Neutrophil count decreased	1 (0.2%)	0	1 (0.1%)
White blood cell count decreased	2 (0.5%)	0	2 (0.2%)

System Organ Class (SOC) Preferred Terms (PT) MedDRA/J Version 9.0	FK199B 12.5 mg group (n=437)	Zolpidem 10 mg group (n=419)	Total (n=856)
White blood cell count increased	3 (0.7%)	0	3 (0.4%)
Platelet count increased	0	1 (0.2%)	1 (0.1%)
Protein urine present	3 (0.7%)	5 (1.2%)	8 (0.9%)
Musculoskeletal and connective tissue disorders	3 (0.7%)	0	3 (0.4%)
Muscle spasms	1 (0.2%)	0	1 (0.1%)
Myalgia	2 (0.5%)	0	2 (0.2%)
Nervous system disorders	56 (12.8%)	47 (11.2%)	103 (12.0%)
Amnesia	1 (0.2%)	0	1 (0.1%)
Cervicobrachial syndrome	0	1 (0.2%)	1 (0.1%)
Dizziness	18 (4.1%)	14 (3.3%)	32 (3.7%)
Headache	10 (2.3%)	10 (2.4%)	20 (2.3%)
Memory impairment	1 (0.2%)	0	1 (0.1%)
Neuropathy peripheral	1 (0.2%)	0	1 (0.1%)
Somnolence	30 (6.9%)	25 (6.0%)	55 (6.4%)
Intracranial hypotension	0	1 (0.2%)	1 (0.1%)
Psychiatric disorders	2 (0.5%)	2 (0.5%)	4 (0.5%)
Abnormal dreams	0	1 (0.2%)	1 (0.1%)
Disorientation	0	1 (0.2%)	1 (0.1%)
Euphoric mood	1 (0.2%)	0	1 (0.1%)
Hallucination	1 (0.2%)	0	1 (0.1%)
Renal and urinary disorders	1 (0.2%)	0	1 (0.1%)
Urinary incontinence	1 (0.2%)	0	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	1 (0.2%)	1 (0.2%)	2 (0.2%)
Hyperventilation	0	1 (0.2%)	1 (0.1%)
Snoring	1 (0.2%)	0	1 (0.1%)
Skin and subcutaneous tissue disorders	1 (0.2%)	3 (0.7%)	4 (0.5%)
Drug eruption	0	1 (0.2%)	1 (0.1%)
Night sweats	1 (0.2%)	1 (0.2%)	2 (0.2%)
Swelling face	0	1 (0.2%)	1 (0.1%)

No. of subjects (incidence)

The incidence of AEs in the FK199B 12.5 mg group was higher in subjects aged ≥ 50 (49.3% [73/148]) than that < 50 (35.3% [102/289]); a similar tendency was found in the zolpidem 10 mg group.

(2) Deaths, Other Serious Adverse Events, and Adverse Events Causing Discontinued Administration

There were no deaths during this clinical study. Serious AEs occurred in the Zolpidem 10 mg group at an incidence of 1.2% (5/419), but not in the FK199B 12.5 mg group.

Table 8: Listing of Serious Adverse Events: Subjects at Second Registration

Subject No. [†]	Sex/Age	AEs		Duration of AE [§]	Severity	Administration period [§]	Treatments		Outcome	Causal relationship to the study drug
		Terms on case report form	MedDRA preferred term [‡]				Study drug	Others		
Zolpidem 10 mg group										
P00713	Male/32 years	Fracture of tibia and fibula (left)	Lower limb fracture	Day 14 -	Severe	11 days	Not applicable	Drug therapy, non-drug therapy	Remitted	Can be ruled out
P01409	Male/44 years	Cold	Nasopharyngitis	Day 21 to Day 26	Moderate	14 days	Not applicable	Drug therapy	Resolved	Can be ruled out
P04702	Female/33 years	Uterine cancer (suspected)	Uterine cancer	Day 4 -	Mild	14 days	Not changed	-	Unknown	Can be ruled out
P05109	Male/54 years	Compression fracture of 12th thoracic vertebra	Thoracic vertebral fracture	Day -3 -	Severe	3 days	-	Drug therapy, non-drug therapy	Remitted	-
		Purulent spondylitis	Infective spondylitis				Day 4 -	Severe	Discontinued	-
P06103	Female/53 years	Orthopedic procedure	Orthopedic procedure	Day 12 to Day 14	Severe	6 days	Not applicable	-	Resolved	Can be ruled out

[†] Each event was included in the safety analysis set.

[‡] MedDRA/J Version 9.0

[§] The number of days after the start day of the double-blind period (start day = Day 1, the day before = Day -1)

The incidence of AEs causing discounted administration was 3.4% (15/437) in the FK199B 12.5 mg group, and 1.7% (7/419) in the zolpidem 10 mg group. Common AEs in the FK199B 12.5 mg group included dizziness (7), somnolence (4), vomiting (3), nausea (3), and headache (2). The majority of the AEs causing discontinued administration in the FK199B 12.5 mg group, for which a causal relationship to the study drug could not be ruled out, resolved within two days after administration was discontinued. Each of the events was mild or moderate.

(3) Clinical Laboratory Test Values

In both the FK199B 12.5 mg group and the zolpidem 10 mg group, clinical laboratory test values after administration of the drug for the double-blind period were almost the same as those before administration. Changes from the values before administration were analyzed in each subject, showing no specific pattern of changes for any test parameter in the FK199B 12.5 mg group or zolpidem 10 mg group. Grade 3 abnormal changes in clinical laboratory test values occurred in two subjects in the zolpidem 10 mg group, but not in the FK199B 12.5 mg group.

(4) Vital Signs, Physical Findings, and Other Observations Related to Safety

In both the FK199B 12.5 mg group and the zolpidem 10 mg group, vital signs (systolic blood pressure, diastolic pressure, pulse rate, and body weight) after administration of the drug for the double-blind period were almost the same as those before administration.

Based on the responses to the questions about dependence, response to each question item was similar in both the FK199B 12.5 mg group and the Zolpidem 10 mg group, from the start of the double-blind period to the end of the post-treatment period; there was no sign of dependence.

Except for time points in which the number of evaluated subjects was extremely small, the wake time after sleep onset increased in the post-treatment period from the double-blind period in both the FK199B 12.5 mg group and the zolpidem 10 mg group; there was no sign of an increase from the run-in period (withdrawal sign).