2 STUDY SYNOPSIS

Name of Company: Eisai Inc.	INDIVIDUAL STUDY TABLE		(For National Authority Use Only)
Name of Finished Product: E2006 Oral Tablets	Referring to Module 5 of the Dossier		
Name of Active Ingredient: (1*R*,2*S*)-2-{[(2,4-Dimethylpyrimidin-5-yl)oxy]methyl}-2-(3-fluorophenyl)-*N*-(5-fluoropyridin-2-yl)cyclopropanecarboxamide	Volume:	Page:	

Study Title

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Bayesian Adaptive Randomization Design, Dose-Response Study of the Efficacy of E2006 in Adults and Elderly Subjects with Chronic Insomnia

Investigators/Sites

The Principal Investigator was David W. Mayleben, PhD, Community Research, Cincinnati, Ohio. Subjects were randomized into the study at 22 sites in the United States (US).

Study Period

13 Nov 2013 to 29 Apr 2014 (first subject in to last subject out)

Phase of Development

Phase 2

Objective(s)

Primary Objectives

The primary objectives of the study were to:

1. Identify a dose or doses of E2006 that maximize efficacy and minimize next-day residual sleepiness in subjects with chronic insomnia at the beginning of treatment by comparing the effect of 6 doses of E2006 with placebo using a composite utility function that incorporated changes from baseline on sleep efficiency (SE) and change from baseline on the Karolinska Sleepiness Scale (KSS) at 1 hour after morning waketime after dosing on Day 1 and Day 2
2. Compare the effect of 6 doses of E2006 with placebo on the KSS at 1 hour after morning waketime on Day 15 and Day 16 in subjects with chronic insomnia, in order to confirm that the dose or doses that maximize efficacy and minimize next-day residual sleepiness at the beginning of treatment were not associated with unacceptable levels of next-day residual sleepiness at the end of treatment

Secondary Objectives

The secondary objectives of the study were to evaluate:

1. Efficacy at beginning of treatment:
   - Overall: Compare each dose level of E2006 with placebo on change from mean SE at Baseline to mean SE after dosing on Day 1 and Day 2

- Sleep induction: Compare each dose level of E2006 with placebo on change from mean latency to persistent sleep (LPS) at Baseline to mean LPS after dosing on Day 1 and Day 2
- Sleep maintenance: Compare each dose level of E2006 with placebo on change from mean wakefulness after sleep onset (WASO) at Baseline to mean WASO after dosing on Day 1 and Day 2

2. Efficacy at end of treatment:
   - Overall: Compare each dose level of E2006 with placebo on change from mean SE at Baseline to mean SE after dosing on Day 14 and Day 15
   - Sleep induction: Compare each dose level of E2006 with placebo on change from mean LPS at Baseline to mean LPS after dosing on Day 14 and Day 15
   - Sleep maintenance: Compare each dose level of E2006 with placebo on change from mean WASO at Baseline to mean WASO after dosing on Day 14 and Day 15
3. Potential habituation of efficacy from beginning to end of treatment:
   - Overall: Compare each dose level of E2006 with placebo on change from mean SE at Baseline to mean SE after dosing on Day 1 and Day 2 versus change from mean SE at Baseline to mean SE after dosing on Day 14 and Day 15
   - Sleep induction: Compare each dose level of E2006 with placebo on change from mean LPS at Baseline to mean LPS after dosing on Day 1 and Day 2 versus change from mean LPS at Baseline to mean LPS after dosing on Day 14 and Day 15
   - Sleep maintenance: Compare each dose level of E2006 with placebo on change from mean WASO at Baseline to mean WASO after dosing on Day 1 and Day 2 versus change from mean WASO at Baseline to mean WASO after dosing on Day 14 and Day 15
4. Potential for rebound insomnia: Compare each dose level of E2006 with placebo on change from mean SE at Baseline to mean SE after dosing (with placebo) on Day 16 and Day 17
5. Safety and tolerability of E2006: Assess the safety and tolerability of multiple doses of E2006 across the therapeutic dose range

Exploratory Objectives

The exploratory objectives of the study were to evaluate:

1. Potential emergence of signal of next-day residual sleepiness
2. Subjective, subject-reported outcomes on the Sleep Diary and Insomnia Severity Index (ISI)
3. Whether improvements in sleep enhanced waking function and daytime mood
4. Pharmacokinetic (PK) and PK/pharmacodynamic (PD) relationships
5. Preliminary abuse potential of E2006
6. Withdrawal symptoms using the Tyrer Benzodiazepine Withdrawal Symptom Questionnaire
7. Absolute melatonin levels as a potential biomarker for responsiveness to E2006
8. Potential circadian phase-shifting effect of E2006 using Dim Light Melatonin Onset (DLMO) as a phase marker

Methodology

E2006-G000-201 was a multicenter, multiple dose, randomized, double-blind, placebo-controlled, parallel-group, Bayesian adaptive, dose-response study in subjects with chronic insomnia. Subjects were randomized to 1 of 6 doses of E2006 (1 mg, 2.5 mg, 5 mg, 10 mg, 15 mg, or 25 mg) or placebo according to the randomization scheme.

The study had 2 phases: Prerandomization and Randomization. The Prerandomization Phase lasted up to 21 days and consisted of a Screening Period (Days –21 to –2) and a Baseline Period (Day –1). After the Baseline Period, all eligible subjects were randomized in a double-blind manner to receive E2006 or placebo for 15 nights during the Treatment Period (Days 1 to 15). All subjects then received placebo in a single-blind manner, for 2 nights (Days 16 to 17) during the Rebound Insomnia Assessment Period (Days 16 to 18). Subjects did not receive study drug during the Follow-up Period (Days 19 to 30).

All subjects came to the clinic for screening procedures. During the Screening Period, subjects completed the Sleep Diary each day. Polysomnographic sleep was measured during the Screening Period on 2 consecutive nights between Day –9 and Day –3. The 8-hour polysomnograms (PSGs) were started at the median habitual bedtime calculated from responses on the Sleep Diary, which were completed for 7 days before the first PSG night. These recordings served as both eligibility screening PSGs and as Baseline PSGs. Subjects could leave the clinic between the screening/Baseline PSG nights.

All subjects returned to the clinic on Day –1 for Baseline Period procedures. They remained in the clinic until Day 3. On the evening of Day –1, timed collection of saliva samples took place to estimate melatonin levels and the Baseline circadian phase of the DLMO. Morning assessments on Day 1 provided the Baseline values for the KSS, the Digit Symbol Substitution Test (DSST), and the Reaction Time Index (RTI). Assessments at 6 hours after waketime provided the Baseline values for the Waking Function Battery (WFB), and the Profile of Mood States-Brief (POMS-B). Subjects were then randomized to receive 1 of 6 doses of E2006 or placebo for the next 15 days. Study drug was to be ingested 30 minutes before the median habitual bedtime calculated from their Sleep Diary responses during the Screening Period. An 8-hour PSG, starting at the same bedtime as used for the screening and Baseline PSG nights, was recorded on the first 2 treatment nights (Days 1 and 2). The Sleep Diary continued to be completed each day in the clinic, and assessments of insomnia severity (ISI), next-day residual effects (KSS, DSST, and RTI), WFB, and POMS-B were conducted while subjects were in the clinic. On specified study days, plasma concentrations of E2006 were assessed while subjects were in the clinic in the morning after awakening and at trough just before dosing.

Subjects continued to take E2006 or placebo 30 minutes before their anticipated, self-selected bedtime and continued to complete the Sleep Diary each day while at home during the Treatment Period. On Day 14 of the Treatment Period, subjects returned to the clinic. They remained in the clinic for 4 nights and the intervening days until Day 18. Eight-hour PSGs were recorded each night in the clinic, to start at the median habitual bedtime calculated from responses on the Sleep Diary completed on Days 3 to 13. The Sleep Diary continued to be completed each day in the clinic, and the ISI, KSS, DSST, RTI, WFB, and POMS-B were administered at prespecified time points during the daytime hours. On the evening of Day 15, timed collection of saliva samples took place to estimate melatonin levels and the circadian phase of DLMO.

After the Treatment Period ended, all subjects received placebo in a single-blind manner on the final 2 nights spent in the clinic (Days 16 and 17). On these 2 nights, 8-hour PSGs starting on the same bedtime as Days 14 and 15 were recorded to assess for rebound insomnia (Rebound Insomnia Assessment Period). Thereafter, subjects received no study treatment for the remainder of the study. While at home during the Follow-up Period, subjects continued to complete the Sleep Diary each day. Responses on the Sleep Diary during this time were reviewed for adverse events (AEs) during the Follow-up Period. On Day 30, at the end of the Follow-up Period, subjects returned to the clinic for end-of-study procedures.

Routine safety monitoring took place throughout the study, including all treatment-emergent and non-treatment-emergent AEs, 12-lead electrocardiogram (ECGs), vital signs, clinical hematology and blood chemistry laboratory tests. In addition to standard AEs of special interest (eg, pregnancy), prespecified compound-specific AEs of special interest (eg, cataplexy, sleep paralysis) were documented in detail on a Serious Adverse Event (SAE) form. Suicidality was assessed at Baseline, during the Treatment Period, during the Rebound Insomnia Assessment Period, and at the End-of-Study visit, using the Columbia-Suicide Severity Rating Scale (C-SSRS). Assessments of abuse potential were performed at prespecified timepoints.

Response-adaptive Randomization: Initially, 105 subjects were each randomized to 1 of 6 dose levels of E2006 or E2006-matched placebo (15 subjects at each dose level). After these 105 subjects were enrolled, the first interim analysis (IA) took place. The utility function for SE/KSS after the first 2 treatment nights was applied, and response adaptive randomization (RAR) was initiated. If specified criteria for early success or futility were achieved, enrollment in the trial could stop. If not achieved, enrollment could continue, and

IAs could occur every 2 weeks until stopping criteria were achieved or until 300 subjects were enrolled in the study.

The maximum estimated period for each subject on study was anticipated to be approximately 51 days (maximum 21-day Prerandomization Phase + 30-day Randomization Phase).

Number of Subjects (Planned and Enrolled)

616 subjects were screened, and 291 subjects were randomized.

Diagnosis and Main Criteria for Inclusion

Inclusion criteria are briefly summarized as follows:

- Male and female 18 to 80 years of age, at the time of informed consent
- Met all specified criteria for Insomnia Disorder as specified in the 5th Edition of the Diagnostic and Statistical Manual of Mental Disorders
- Sleep diary data for the 7 nights before the first screening/Baseline PSG must confirm current insomnia symptoms
- Met objective criteria for insomnia (ie, LPS and/or WASO, and SE) at screening/Baseline PSG visits
- Females of childbearing potential were required to use 2 forms of highly effective contraception throughout the study period and for 30 days after study drug discontinuation.
- Males were required to have had a successful vasectomy or they and their female partners were required to use 2 forms of highly effective contraception throughout the study period and for 30 days after study drug discontinuation

Exclusion criteria are briefly summarized as follows:

- Sleep apnea or sleep disorders other than insomnia
- Use of sleep medication or other concomitant medications for the purpose of treating insomnia symptoms within 2 weeks of first screening/Baseline PSG
- Unwilling to limit caffeine consumption, alcohol consumption, or use of recreational drugs as specified in protocol
- Specified criteria related to QT interval
- Current diagnosis or being treated for depressive, psychotic, or addiction disorders

Test Treatment, Dose, Mode of Administration, and Batch Number(s)

E2006 in tablet form was taken orally, 30 minutes before bedtime, each night for 15 consecutive nights. E2006 dose levels were 1 mg, 2.5 mg, 5 mg, 10 mg, 15 mg, and 25 mg.

Investigational drug: E2006 1 mg, 2.5 mg, 5 mg, and 10 mg administered as tablets; Lot numbers: P31004ZZA (1 mg), P31005ZZA (2.5 mg), P31006ZZA (5 mg), and P31007ZZA (10 mg).

Reference Therapy, Dose, Mode of Administration, and Batch Number(s)

E2006-matched placebo, in tablet form, taken orally, 30 minutes before bedtime, each night for 15 consecutive nights. Lot number: P31003ZZB

Duration of Treatment

The duration of the study phases and treatment for each subject were as follows:

Prerandomization: Screening = Days –21 to –2

Baseline = Day – 1

Randomization: Treatment Period = Days 1 to 15

Rebound Insomnia Period = Days 16 to18 (Subjects received placebo, in a single-blind manner, for 2 nights [Days 16 to 17] during the Rebound Insomnia Assessment Period [Days 16 to 18])

Follow-up Period = Days 19 to 30

Assessments

Efficacy

Polysomnograms

PSG recordings were obtained on 2 consecutive nights between Day –9 and Day –3 during the Screening Period, on the first 2 treatment days and the last 2 treatment days of the Treatment Period, and on 2 nights during the Rebound Insomnia Assessment Period. Each PSG included electrode montage with electroencephalography (EEG), electromyography, electrooculography, and ECG channels, which permitted scoring of sleep stages via standard sleep scoring criteria. In addition, on the first screening/Baseline PSG, as well as the Day 1 and Day 15 PSG recordings, channels were required that permitted assessment of diagnostic criteria for sleep apnea and periodic limb movements (PLM) in sleep.

A PSG manual was provided by the central PSG laboratory.

All PSG parameters were obtained separately for each PSG and averaged across the 2 consecutive PSG nights at each Period. For the PSG parameters obtained during the Treatment Period, values obtained during the first 2 treatment days were averaged separately from the last 2 treatment days.

The 2 PSGs obtained during the Screening period were used: a) to determine eligibility and b) as Baseline PSG measures.

The following efficacy parameters were derived from all PSGs:

- SE: total sleep time divided by time spent in bed multiplied by 100. An increase in SE indicates improvement in sleeping, in that the subject spends more of the time in bed asleep.
- LPS: minutes from lights off to the first 30-second epoch of 20 consecutive epochs of non-wakefulness. A decrease in LPS indicates improvement in time needed to fall asleep.
- WASO: minutes of wakefulness from the onset of persistent sleep until lights on. A decrease in WASO indicates improvement in sleep maintenance.

Additional parameters were calculated from each PSG, including:

- Total sleep time
- Number of awakenings after persistent sleep, with an awakening defined as at least 2 consecutive epochs of wakefulness; an awakening cannot be interrupted by stage N1, but must be interrupted by stage N2, N3, or rapid eye movement (REM)
- Number of awakenings after persistent sleep greater than 5 minutes in duration
- Mean and median duration of awakenings after persistent sleep
- Percentage of sleep stages per time in bed: wakefulness, non-rapid eye movement (NREM) sleep (stages N1, N2, N3), REM sleep
- Percentage of sleep stages per total sleep time: wakefulness, NREM sleep (stages N1, N2, N3), REM sleep
- Minutes of sleep stages per time in bed: wakefulness, NREM sleep (stages N1, N2, N3), REM sleep
- REM episode frequency and duration
- Mean REM/NREM cycle duration
- REM latency

These parameters provided data for the effect of E2006 on sleep stages.

Sleep Diary

The Sleep Diary was completed on each day of the study. This Sleep Diary provided assessments of responses for several self-reported measures of sleep that were used to further assess efficacy:

- Subjective Sleep Onset Latency (sSOL): estimated minutes from lights off to sleep onset
- Subjective Wakefulness After Sleep Onset (sWASO): estimated minutes of wakefulness during the night after initial sleep onset
- Subjective Time in Bed (sTIB): time from lights out to time out of bed
- Subjective Total Sleep Time (sTST): estimated amount of time spent asleep
- Subjective Sleep Efficiency (sSE): proportion of time spent asleep per time spent in bed derived from sTST divided by sTIB

Pharmacokinetics

During the Treatment period, blood samples for plasma concentrations of E2006 were obtained within 30 minutes predose each night (except on Day 1) in the clinic and within 1 hour of morning waketime following each night spent in the clinic.

Pharmacodynamics

Karolinska Sleepiness Scale

The KSS was used to measure next-day residual effects at prespecified timepoints. In this test, subjects rate their sleepiness using the KSS, a 9-point verbally anchored scale. Categories and scores range from "extremely alert" (score = l), "alert" (3), "neither alert nor sleepy" (5), "sleepy-but no difficulty remaining awake" (7), to "extremely sleepy-fighting sleep" (9). The key outcome parameter for the KSS was the score from 1 to 9.

Digital Symbol Substitution Test

The DSST was used to measure next-day residual effects at prespecified timepoints. The key outcome parameter for the DSST was the number correctly matched in 90 seconds.

Reaction Time Index

The RTI task was used to measure next-day residual effects at prespecified timepoints. A computerized RTI task was required for subjects to respond as quickly and accurately as possible to a stimulus. The outcome variables analyzed included the reaction time and movement time for both simple and 5-choice parts of the RTI task, and the 5-choice error score.

Insomnia Severity Index

The ISI was used to assess the severity of recent problems with sleep at Baseline, and at prespecified timepoints postdose. The ISI total score was the outcome parameter.

Waking Function Battery

The WFB was used to assess relationships between treatment-induced changes in sleep and daytime functioning. The WFB is a computerized battery which comprises 3 tasks measuring specific cognitive processes, including reaction time, visual sustained attention, and working memory capacity.

Profile of Mood States-Brief Scale

The 30-item POMS-Brief (POMS-B) Scale was completed at prespecified time points on days spent in the clinic, to assess relationships between treatment-induced changes in sleep and daytime mood. The POMS-B is a computerized task that automatically calculates POMS-B total mood disturbance (TMD) and subscale scores. Key outcome parameters from the POMS-B included the POMS-B TMD score and selected subscale scores.

Dim Light Melatonin Onset

The change from baseline in the DLMO estimate for each subject was evaluated to assess the circadian phase-shifting potential of E2006. During the Day 1 evening of the Baseline period and the evening of the last treatment day, subjects provided samples of saliva every 30 minutes starting 3 hours before bedtime, for subsequent assay of melatonin levels and estimation of the circadian phase of the DLMO.

Other Biomarker Assessments

Melatonin levels

Absolute melatonin levels were explored as a potential predictor of response to E2006. Absolute melatonin levels at Baseline, as measured by the sample taken closest to bedtime on Day -1, were to be correlated with change from baseline in PSG variables.

Pharmacogenomics

Consent for blood sampling for pharmacogenomic assessments was not mandatory for participation in the study. For subjects who provided consent for the blood sample, obtained for purposes of pharmacogenetic or pharmacogenomic analyses, samples were planned to be collected on Day 1, but could also be taken either on Day 2 or Day 3.

Safety

Safety assessments consisted of monitoring and recording all AEs and SAEs; regular laboratory evaluation for hematology, blood chemistry, and urine values; periodic measurement of vital signs, weight, and ECGs; and the performance of physical examinations.

An assessment of suicidality using the C-SSRS was performed at Baseline, during the Treatment Period, during the Rebound Insomnia Assessment Period, and at the End-of-Study/Early Termination Visit.

In addition to typical AEs of special interest (eg. pregnancy), designated compound-specific AEs of special interest were documented in-depth. These included sleep paralysis, cataplexy, sleep attacks, narcolepsy, and reported motor vehicle accidents related to sleepiness or drowsiness.

Other

The Abuse Potential Questionnaire was used to assess drug-liking and abuse potential of E2006.

Potential effects of withdrawal from E2006 were assessed using the Tyrer Benzodiazepine Withdrawal Symptom Questionnaire.

Bioanalytical Methods

Plasma concentrations of E2006 were measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. Salivary melatonin levels were measured using a direct saliva melatonin enzyme-linked immunosorbent assay (ELISA) with a detection limit of 0.500 pg/mL.

Statistical Methods

All statistical tests were based on the 5% level of significance, except for the Bayesian methods used for the primary endpoint. Details of statistical methods and analyses were specified in the Statistical Analysis Plan (SAP) and body of the clinical study report.

Study Endpoints

Primary Endpoints

- SE/KSS at beginning of treatment: A utility function combining a) change from mean SE at Baseline to mean SE after dosing on Day 1 and Day 2 and b) change from KSS at 1 hour after morning waketime at Baseline to mean KSS at 1 hour after morning waketime on Day 2 and Day 3. The components of the utility function were also analyzed separately as sensitivity analyses.
- KSS at end of treatment: Change from KSS at 1 hour after morning waketime at Baseline to mean KSS at 1 hour after morning waketime on Day 15 and Day 16.

Secondary Endpoints

Efficacy at beginning of treatment (Secondary Objective 1):

- SE: change from mean SE at Baseline to mean SE after dosing on Day 1 and Day 2

- LPS: change from mean LPS at Baseline to mean LPS after dosing on Day 1 and Day 2
- WASO: change from mean WASO at Baseline to mean WASO after dosing on Day 1 and Day 2

Efficacy at end of treatment (Secondary Objective 2):

- SE: change from mean SE at Baseline to mean SE after dosing on Day 14 and Day 15
- LPS: change from mean LPS at Baseline to mean LPS after dosing on Day 14 and Day 15
- WASO: change from mean WASO at Baseline to mean WASO after dosing on Day 14 and Day 15

Potential habituation effect (Secondary Objective 3):

- SE: change from mean SE at Baseline to mean SE after dosing on Day 1 and Day 2 versus change from mean SE at Baseline to mean SE after dosing on Day 14 and Day 15
- LPS: change from mean LPS at Baseline to mean LPS after dosing on Day 1 and Day 2 versus change from mean LPS at Baseline to mean LPS after dosing on Day 14 and Day 15
- WASO: change from mean WASO at Baseline to mean WASO after dosing on Day 1 and Day 2 versus mean WASO after dosing on Day 14 and Day 15

Rebound insomnia (Secondary Objective 4): Change from mean SE at Baseline to mean SE after administration of placebo on Day 16 and Day 17

Safety and tolerability (Secondary Objective 5): Treatment-emergent adverse events (TEAEs) and SAEs, clinical laboratories, vital signs, and ECGs

Exploratory Endpoints

Potential emergence of a signal of next day residual sleepiness (Exploratory Objective 1):

- KSS: change from time-matched points of KSS at Baseline to the mean of time-matched points of KSS on Day 2 and Day 3, and to the mean of time-matched points of KSS on Day 15 and Day 16
- DSST: change from time-matched points of DSST at Baseline to the mean of time-matched points of DSST on Day 2 and Day 3, and to the mean of time-matched points of DSST on Day 15 and Day 16
- RTI: change from time-matched points of RTI at Baseline to the mean of time-matched points of RTI on Day 2 and Day 3, and to the mean of time-matched points of RTI on Day 15 and Day 16

Subjective, subject-reported outcomes from Sleep Diary (Exploratory Objective 2):

- sSE: change from sSE at Baseline to mean sSE on Days 1 to 7, and to mean sSE on Days 8 to 15
- sSOL: change from sSOL at Baseline to mean sSOL on Days 1 to 7, and to mean sSOL on Days 8 to 15
- sWASO: change from sWASO at Baseline to mean sWASO on Days 1 to 7, and to mean sWASO on Days 8 to 15

Subjective, subject-reported outcomes from the Insomnia Severity Scale (Exploratory Objective 2):

- Change from ISI score at Baseline to ISI score on Day 2 and to ISI score on Day 15

Correlation between effects of E2006 on sleep quality and waking function (Exploratory Objective 3):

- Change from mean SE at Baseline to SE on each PSG recording night and change from baseline on summary variables from each of 3 tasks on the WFB on Day 2, Day 15, and Day 16

Correlation between effects of E2006 on sleep quality and mood (Exploratory Objective 3):

- Change from mean SE at Baseline to SE on each PSG recording night and change from baseline on total POMS-B score and selected subscale scores on Day 2, Day 15, and Day 16

PK parameters and PK/PD relationships (Exploratory Objective 4):

- Relationships between plasma concentrations of E2006 from samples obtained at predose (trough), and within 1 hour after morning waketime, and selected PD parameters as listed in the separate PK/PD analysis plan

Abuse potential of E2006 (Exploratory Objective 5):

- Abuse Potential Questionnaire responses on Day 2, Day 3, Day 15, Day 16, Day 17, and Day 18

Withdrawal symptoms (Exploratory Objective 6):

- Responses on the Tyrer Benzodiazepine Withdrawal Symptom Questionnaire on Day 18 and Day 30

Melatonin levels at Baseline as predictor of responsiveness to E2006 (Exploratory Objective 7):

- Correlation between absolute level of melatonin at the last sample before bedtime on Day -1 and change from mean SE, mean LPS, and mean WASO at Baseline to mean SE, mean LPS, and mean WASO on Day 1 and Day 2 and on mean SE, mean LPS, and mean WASO on Day 14 and Day 15

DLMO (Exploratory Objective 8):

- Change from DLMO clock time at Baseline to DLMO clock time at Day 15, as estimated from assay of timed saliva samples

Analysis Sets

The Safety Analysis Set was the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.

The Full Analysis Set (FAS) was the group of randomized subjects who received at least 1 dose of study drug and had at least 1 postdose primary efficacy measurement.

The PK Analysis Set was the group of randomized subjects who received at least 1 dose of E2006 and had at least 1 quantifiable E2006 concentration.

The PD Analysis Set was the group of subjects who had sufficient PD data to derive at least 1 PD parameter.

The PK/PD Analysis Set was the group of randomized subjects who received at least 1 dose of E2006 or placebo, and had at least 1 quantifiable concentration of E2006 concentration (active subjects), and at least 1 postdose PD assessment.

Efficacy Analyses

Response-adaptive randomization was used to allocate subjects to placebo or 1 of the 6 active doses on the basis of emerging data that were used to calculate the utility function at frequent IAs, with the goal of characterizing the dose response and determining if treatment results improved SE compared to placebo, with adequate lack of residual sleepiness as measured by the KSS on subsequent mornings. The study was monitored for early success and early futility through frequent IAs.

Key definitions relevant to the Bayesian aspects of the adaptive design are given below.

Study Definitions

Clinically Significant Difference: A difference from placebo of at least 6% in the change from baseline of mean SE at Day 1 and Day 2 was considered the minimum clinically significant difference (CSD).

Acceptable KSS: Each dose was assessed for next-day residual sleepiness using the KSS. A mean difference of change from baseline in KSS at 1 hour after waketime on Day 2 and Day 3 of less than 4 units was incorporated into the utility function. A dose of E2006 was considered to have an acceptable KSS at Day 15 and Day 16 if the mean difference of change from baseline in KSS at 1 hour after waketime on Day 15 and Day 16 at this dose relative to placebo was less than 4 units. Operationally, acceptable KSS for Day 15 and Day 16 was defined as the lower boundary of a 90% confidence interval (CI) being less than 4 units (of the mean difference of change from baseline in KSS at 1 hour after waketime at this dose relative to placebo).

Utility Function: The utility at a dose was a function of both SE and KSS, constructed by specifying the 1-dimensional component for each endpoint and then combining them multiplicatively. Sufficient utility was defined as a Pr(Utility >1).

Maximum Utility Dose (dUmax**):** The dose that produced the maximum utility score, ie, the best combination of efficacy and residual sleepiness as judged by the utility above.

Early Futility: The study could stop for early futility at each IA if there was less than 20% posterior probability that dUmax had sufficient utility (ie, Pr [Utility >1] <0.20).

Early Success: The study could stop randomization for early success at an IA if (1) there was at least 85% posterior probability that dUmax or another dose achieved sufficient utility (ie, Pr(Utility>1) >0.85) and (2) the dose in (1) achieved the operational definition of acceptable KSS at Days 15 and 16.

Trial Completion: The final analysis could occur when both accrual and follow-up were complete for all subjects. If, at the completion of the trial, (1) there was at least 80% posterior probability that the dUmax or another dose achieves sufficient utility (ie, Pr(Utility >1) >0.80) and (2) the dose in (1) achieved the operational definition of acceptable KSS at Days 15 and 16, this trial was considered a success.

Study Success: The study was considered a success if either of the following criteria was met:

1. The study met early success criteria at IA (as outlined above).

2. The study met success criteria in the final analysis at trial completion.

Analysis for the Primary Endpoints: The primary analysis was based on subjects from the FAS. The dose-response of the primary endpoint, the utility score combining SE (change from mean SE at Baseline to mean SE after dosing on Day 1 and Day 2) and the KSS (change from KSS at Baseline to mean KSS at 1 hour after morning waketime on Day 2 and 3), was modeled with a normal dynamic linear model, where Normal and Inverse-Gamma priors were used. The primary analysis calculated the posterior probability that the dose(s) identified was the most likely to be the maximum utility dose(s) (MUD). At each IA and the final analysis, 2 Bayesian probabilities were summarized for each active dose: the probability of being the dUmax dose and the probability of having sufficient utility (ie, Pr Utility >1). The endpoint of KSS at Days 15 and 16 was analyzed using a 90% CI as described in the definition of acceptable KSS.

After unblinding, the primary endpoint was analyzed using the Bayesian methods described above and the components of the primary endpoint were analyzed as sensitivity analyses using the following conventional statistical methods

The SE change from baseline to the mean of Day 1 and Day 2 was analyzed using analysis of covariance (ANCOVA), with treatment and Baseline as fixed effects on the FAS. The KSS change from baseline to the mean of Days 2 and 3 and to the mean of Days 15 and 16 were analyzed with ANCOVA, with treatment and Baseline as fixed effects on the PD Analysis Set. If SE or KSS was found to have a non-normal distribution, the appropriate data were to be log-transformed before analysis to normalize the data.

Null Hypothesis for Conventional Analyses: no difference exists in the mean change from baseline to mean of Day 1 and 2 of SE, between any E2006 dose compared to placebo.

Alternative Hypothesis for Conventional Analyses: a difference exists in the mean change from baseline to mean of Day 1 and 2 of SE, between any E2006 dose compared to placebo.

Additional analyses included other covariates including age, sex, race, body mass index (BMI), and DLMO, Baseline levels of depression symptoms (Beck Depression Inventory-II score) or anxiety symptoms (Beck Anxiety Inventory score), as well as subgroup analyses of subtypes of insomnia (eg, sleep onset insomnia, sleep maintenance insomnia, mixed insomnia), and site.

Secondary Efficacy Analyses: The secondary efficacy endpoints (SE, LPS, and WASO) from the beginning of treatment, end of treatment, and rebound insomnia period were analyzed using the same conventional statistical method as the SE component of the primary endpoint.

Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Analyses

Pharmacokinetic Analyses

The Safety Analysis Set was used for individual E2006 plasma concentration listings. The PK Analysis Set was used for summaries of E2006 plasma concentrations.

A population PK approach was used to characterize the PK of E2006. For this approach, PK analysis data from this study were pooled with relevant data from Phase 1 studies. The effect of covariates (eg, demographics) on E2006 PK was evaluated. The PK model was parameterized for apparent oral clearance (CL/F) and apparent volumes of distribution. Derived exposure parameters such as area under the concentration-time curve (AUC) were calculated from the model using the individual posterior estimate of CL/F and dosing history.

Pharmacodynamic Analyses

The PD Analysis Set was used for the summaries and analyses of PD parameters.

Analysis for Exploratory Endpoints:

The endpoints for next-day residual effects (KSS, DSST, and RTI) were analyzed using the same conventional statistical method as for the KSS component of the primary endpoint.

The endpoints for subjective subject-reported outcomes (sSE, sSOL, sWASO, ISI) were analyzed using the same statistical methods as the secondary efficacy endpoints.

The relationship between effects of E2006 on nighttime sleep quality and waking function (ie, correlation of change from baseline of SE with neurobehavioral tasks from WFB on Days 2, 15, and 16) was analyzed using Pearson's correlation coefficient.

The relationship between effects of E2006 on nighttime sleep quality and mood (ie, correlation of changes from baseline of SE with POMS-B TMD scores on Days 2, 15, and 16) was analyzed using Pearson's correlation coefficient.

The relationship between absolute level of melatonin at the last sample before bedtime on Day –1 and change from baseline to the mean of Day 1 and Day 2 and mean of Day 14 and Day 15 on SE, LPS, and WASO was analyzed using Pearson's correlation coefficient.

The change from baseline in clock time of the DLMO estimated from assay of timed saliva samples was analyzed using ANCOVA, with treatment and Baseline as fixed effects for Day 15.

Plots of all PD parameters were produced by time. Scatter plots with lines of best fit were plotted for variables explored with correlations.

Pharmacokinetic/Pharmacodynamic Analyses

The PK/PD Analysis Set was used to evaluate relationships between E2006 concentrations and selected PD parameters. The relationships between exposure to E2006 and selected PD endpoints (eg. KSS, DSST, RTI) were explored graphically and could be followed by population PK/PD modeling.

The relationship between plasma concentrations of E2006 at predose (trough), and within 1 hour after morning waketime, and selected PD parameters, was analyzed using Nonmem version 7.2 or later.

Pharmacogenomic Analyses

Variations in E2006 exposure or AEs could be explored by correlation of single-nucleotide polymorphisms with PK, safety, or PD data. The pharmacogenomic analysis plan would be defined and reported separately from this study report.

Safety Analyses

Evaluations of safety were performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical examination), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, and suicidality (C-SSRS), along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements, were summarized by treatment group using descriptive statistics.

Other Analyses

Summaries of responses on the Abuse Potential Questionnaire and Tyrer Benzodiazepine Withdrawal Symptom Questionnaire were presented.

Interim Analyses and Response Adaptive Randomization

An unblinded Independent Monitoring Committee (IMC) provided oversight to ensure that the RAR process and IAs performed as expected. An independent data analysis group performed all of the IAs and provided the results to the IMC.

There was an initial burn-in period in which 105 subjects were allocated in a ratio of 1:1:1:1:1:1:1 to placebo and the active dose arms. After this initial burn-in, adaptive randomization began. The goal of the adaptive randomization was to preferentially allocate subjects to the doses most likely to be the dUmax. Adaptive randomization probabilities were updated on a bi-weekly basis. The subjects were randomized using block randomization on the basis of updated randomization probabilities and the prespecified randomization block.

The randomization probability for each of the 6 active doses was initially weighted according to the probability that the dose was the dUmax. These allocation probabilities were adjusted to 0 for any dose that had a Pr(dUMax) <0.05 or any dose that did not meet the operational definition of acceptable KSS on Days 15 and 16. After adjustment of any allocation probabilities to 0, the remaining probabilities were renormalized to sum to 1. Data at the first IA included KSS data through Day 3 for the 105th subject; it was not expected that data from Days 15 and 16 was obtained from all 105 subjects at the time the dataset for the initial IA was compiled. Thereafter, each IA included relevant data (ie, SE and KSS) obtained and available for all randomized subjects at scheduled bi-weekly intervals.

The study was monitored for early success and early futility as previously described. If the study stopped for early success, subjects who had completed the first screening/Baseline PSG continued in the study.

Sample Size Rationale

A maximum sample size of 300 subjects was considered appropriate. Simulations showed that this sample size was sufficient to achieve a desirable chance of success for a wide range of different efficacy and next day residual effect scenarios. While the overall type I error was 2%, the final number of subjects per group could differ depending on the observed interim treatment responses. The simulation plan is described in the Appendix section of the SAP.

Results

Interim Analyses and Study Stopping for Early Success

There were 5 IAs in this dose-response Bayesian adaptive design study. The last of these analyses, Interim Analysis 5 (IA-5), analyzed the data of 262 subjects and resulted in stopping of the study for early success. At the time that IA-5 occurred, 262 subjects had undergone the assessments required for evaluation of the utility function, and 29 subjects were either already enrolled or randomized before the decision to stop was communicated to Eisai. The study ended when all 29 subjects completed the study.

Subject Disposition/Analysis Sets

A total of 616 subjects were screened, and 291 of these subjects were randomized into the study. All 291 randomized subjects received study drug. The Bayesian design and the RAR approach was to randomize the first 105 subjects evenly to the 6 E2006 doses and placebo (n=15 per dose group). Subsequent randomization allocations varied according to the results of each IA (see Study Definitions section, above). Thus, a variable number of subjects were randomized to each dose of E2006 and placebo. The final number of subjects randomized to each treatment group respectively was: placebo (n=56), 1 mg (n=32), 2.5 mg (n=27), 5 mg (n=38), 10 mg (n=32), 15 mg (n=56), 25 mg (n=50).

The planned treatment regimen was completed by 222 subjects (more than 94%) in the E2006 dose group and by 51 subjects (more than 90%) in the placebo group. The FAS was the primary analysis set used for efficacy analyses. In this study, the FAS and the Safety Analysis Set were identical.

In this study, 62.1% of the subjects across E2006 dose groups and 64.3% in the placebo group were female. The majority of subjects were white. The median age was 49.0 years for subjects who received E2006 (range: 19 to 80 years) and 46.5 years for subjects who received placebo (range: 20 to 79 years).

The most common insomnia subtype was mixed insomnia (59.8%), followed by sleep maintenance insomnia (29.2%). For all subjects, mean SE (60.5%), median LPS (67.4 minutes), and the mean WASO

(109.2 minutes) at Baseline were consistent with the presence of insomnia. The mean sSE (64.6%), median sSOL (52.1 minutes), and mean sWASO (109.8 min) at Baseline were in agreement with the corresponding PSG data. The mean ISI score at Baseline (19.7) was consistent with moderate-to-severe insomnia. On average, subjects reported low levels of symptoms of depression or anxiety.

Efficacy

Analysis and Results of Primary Objectives

Utility Function

The utility function was defined such that at the beginning of treatment, a given dose of E2006 would have a utility >1 if it (a) was superior to placebo on change from baseline of SE at Days 1 and 2 by at least 6%, and (b) did not have a change from baseline of KSS at 1 hour after morning waketime on Days 2 and 3 of more than 4 units. In addition, the study would not stop for early success until it was determined that any dose which achieved the 85% criterion had an acceptable KSS at the end of treatment (ie, the lower boundary of a 90% CI was less than 4 units).

The study was stopped for early success after IA-5 determined that there was an 85% probability that at least one dose of E2006 achieved utility >1 (see above, Interim Analyses and Response Adaptive Randomization). At the final Bayesian analysis, it was determined that all doses achieved the 80% utility function threshold for overall study success. The final Bayesian analysis showed that the E2006 15 mg dose had the highest probability (93.5%) to be the dUmax (ie, probability of utility >1) and did not have unacceptable KSS at Days 15 and 16. The lower doses of 5 and 10 mg of E2006 and the higher dose of 25 mg also reached the 85% threshold set a priori, that the probability of utility was >1.

The components of the primary endpoints were further analyzed with ANCOVA, using Baseline values as a covariate. Results of each component of the utility function (SE and KSS) are described below in the respective sections for analyses of results of secondary and exploratory objectives.

Acceptable KSS at End of Treatment

At IA-5, all doses that achieved the 85% threshold for the first primary objective also met the second primary objective of having acceptable KSS at Days 15 and 16. At the final analysis with all subjects, all E2006 doses had acceptable KSS at Days 15 and 16.

Results of the second primary endpoint of KSS at 1 hour after morning waketime on Days 15 and 16 are described below in the section for analyses of results of exploratory objectives.

Analysis and Results of Secondary Objectives

Efficacy at Beginning of Treatment

Sleep Efficiency

Sleep Efficiency at beginning of treatment (Days 1 and 2): For each dose of E2006, at the beginning of treatment (Days 1 and 2), the change from baseline of SE was significantly greater than the change from baseline of SE for placebo, with generally greater SE as E2006 dose increased from 1 mg to 25 mg. Treatment differences (ie, increases as compared with placebo) ranged from 4.57 at the 1-mg dose to 10.1 at the 15-mg dose.

Latency to Persistent Sleep

On Days 1 and 2, the decrease in mean LPS from baseline was larger in each E2006 dose group than in the placebo group. This effect was dose-related, with generally shorter LPS as the E2006 dose increased. The difference from placebo was statistically significant in all dose groups except 1 mg. Treatment differences (ie, decreases in mean latency relative to placebo) ranged from 20.0 minutes at 1 mg to 28.9 mg at 15 mg.

Wake After Sleep Onset

On Days 1 and 2, the decrease in mean WASO from baseline was larger in each E2006 dose group than in the placebo group, indicating that WASO was decreased relative to placebo by all doses of E2006. This effect was dose-related with generally decreased WASO as the E2006 dose increased. For E2006 dose groups 10 mg and higher, the change from baseline of WASO was significantly different from that for placebo. Treatment differences (ie, decreases in mean WASO relative to placebo) ranged from 2.3 minutes at 2.5 mg to 29.3 minutes at 15 mg.

Efficacy at End of Treatment

For each dose group of E2006 except 1 mg, the increase in SE from baseline at Days 14 and 15 was statistically significant compared to placebo.

At Days 14 and 15, the decrease in LPS from baseline was significantly greater than that for placebo at E2006 doses of 2.5 mg and higher.

There were decreases in WASO from baseline on Days 14 and 15, as compared with placebo, at E2006 doses of 15 mg and 25 mg. At lower doses of E2006, these comparisons did not reach statistical significance.

Potential Habituation of Efficacy from Beginning to End of Treatment

On the basis of placebo-corrected comparisons, the increases in mean SE from baseline after administration of E2006 on Days 14 and 15 did not differ significantly from those after E2006 on Days 1 and 2. Changes in mean values of WASO also did not differ over this treatment interval. Mean LPS was numerically shorter on Days 14 and 15 as compared with Days 1 and 2, and at the E2006 dose of 10 mg, this comparison reached statistical significance. Rather than habituation, this result suggests an increase in efficacy (as indicated by objective sleep onset) from beginning to end of treatment. Taken together, these findings provide no evidence for habituation of PSG-derived sleep variables during the 15-day treatment period.

Potential for Rebound Insomnia Using PSG

On Days 16 and 17, during which all subjects received placebo, although there were no longer any statistically significant changes from baseline in SE, LPS, or WASO, values for SE remained numerically greater and values for LPS and WASO remained numerically lower than at Baseline in all E2006 dose groups. Thus, PSG-derived variables provided no evidence for rebound insomnia at these time points.

Analysis and Results of Exploratory Objectives

Next-Day Residual Sleepiness

On Days 2 and 3 (ie, at the beginning of treatment), within 15 minutes, at 1 hour, and at 2 hours after waketime, the mean change from baseline on the KSS did not differ from placebo at doses through 10 mg. The 15 mg dose resulted in significant increases from baseline on the KSS versus placebo at 2 hours after waketime. At 25 mg E2006, the KSS was significantly increased from baseline versus placebo at 1 hour and 2 hours after waketime. These group mean increases were of small magnitude. However, despite the lack of statistically significant increases at lower doses, there was a dose-related trend for increased next-day residual sleepiness as measured by the KSS.

Similarly, on Days 15 and 16 (ie, at the end of treatment with E2006), there were no statistically significant differences in change in KSS from baseline between placebo and E2006 doses from 1 mg to 10 mg. At the dose of 15 mg, the increase in KSS from baseline was significantly different from placebo within 15 minutes after waketime, but not at 1 hour and 2 hours after waketime. The corresponding change at the 25 mg dose reached statistical significance at the 1-hour and 2-hour time points. The dose-related trend for increased next-day residual sleepiness was also apparent on Days 15 and 16, although the magnitude of change was small.

Statistical comparisons between Days 2 and 3 versus Days 15 and 16 did not show any significant differences between beginning and end of E2006 treatment with respect to changes from baseline on the KSS. Thus, despite PK accumulation of E2006 there was not an increase in next-day residual sleepiness between acute dosing and steady state.

Subjective, Subject-Reported Outcomes on the Sleep Diary and ISI

Subjective Sleep Efficiency

Similar to PSG results, subjective efficacy as measured by the Sleep Diary showed that there was a dose-related increase in sSE, with substantially larger increases from baseline in E2006 dose groups 2.5 mg and higher. As compared with placebo, statistically significant increases in subjective sSE were observed at E2006 doses of 5 mg and higher on Days 1 to 7 and at doses of 2.5 mg and higher on Days 8 to 15. There were no statistically significant differences between results for Days 1 to 7 and those for Days 8 to 15, suggesting that the effect of E2006 on sSE was maintained across the 2-week treatment interval. Ad hoc analyses of the at-home intervals of Days 3 to 7 and Days 8 to 13 also showed increases in sSE from baseline that significantly exceeded those for placebo at 5 mg and higher doses.

Subjective Sleep Onset Latency

There were decreases in sSOL compared to placebo in all E2006 dose groups except 1 mg. Analyses of log-transformed data for sSOL (geometric mean ratios) indicated that mean sSOL was significantly lower than Baseline compared to placebo at doses of 2.5 mg to 25 mg during both of the intervals from Days 1 to 7 and from Days 8 to 15. Results for Days 1 to 7 did not differ from those for Days 8 to 15 for doses of 2.5 mg to 25 mg, indicating that the effect of E2006 on sleep onset during the first week of treatment was maintained during the second week of treatment. Results were similar during the at-home intervals of Days 3 to 7 and Days 8 to 13, although comparisons with placebo were generally not statistically significant.

Subjective Wake After Sleep Onset

Although there was a relatively large decrease in sWASO in the placebo group, the effect of E2006 on sWASO was greater than that of placebo for all dose groups of E2006 except 1 mg. At E2006 doses of 2.5 mg to 25 mg, mean sWASO was lower than Baseline from Days 1 to 7 and from Days 8 to 15. The decrease in sWASO from baseline was significantly greater than that for placebo at the 10mg dose during both weeks of treatment, but the observed trends did not reach statistical significance at the other doses of E2006.

Insomnia Severity Index

There were dose-related decreases from baseline in ISI scores on both Day 2 and Day 15. At the end of the 2-week treatment interval, ISI scores decreased from baseline and by more than with placebo in all E2006 dose groups, and these decreases reached statistical significance on Day 15 at doses of 15 and 25 mg. Results were similar when ISI items querying insomnia subtype (Questions 1 through 3) were excluded from analysis. On Day 15, at doses of 15 and 25 mg, a significantly greater proportion of subjects had scores equal to or less than 15 (considered the threshold for clinically meaningful insomnia severity) as compared with placebo.

Correspondence Between Objective (Polysomnogram) and Subjective (Sleep Diary) Measures

Results from the objective, PSG–derived sleep parameters (sSE, sSOL, and sWASO) were compared with those from the corresponding subjective, sleep-diary-derived outcomes to evaluate agreement between the objective and subjective sleep assessments. Changes from baseline tended to be smaller for the subjective measures, but were in the same direction as for the objective measures.

Relationships Between Changes in Sleep and Changes in Daytime Mood or Waking Function

While there were decreases from baseline in POMS-B TMD scores for all E2006 dose groups, and increases in POMS-B TMD for the placebo group, there were no statistically significant correlations between change from baseline of SE and change from baseline in mood as measured by the POMS-B TMD. There were no consistent patterns to indicate that a change in sleep was associated with a change in mood as measured by the POMS-B TMD or subscale scores. There were also no consistent patterns to indicate that a change in sleep was associated with a change in waking function as measured by reaction time, spatial span, or rapid visual processing tasks.

PK and PK/PD Relationships

The PK of E2006 was best described by a 2-compartment model with elimination from the central compartment. Apparent clearance of E2006 was independent of dose and time, indicating linearity in PK. No statistically significant effect of sex, race (Caucasian vs Other), body weight, liver function, or renal function was found on CL/F. There was approximately a 2-fold accumulation of E2006 over the treatment period.

The CL/F decreased and exposure increased with age and BMI, but these effects were small relative to variability in the data and not considered clinically important.

Measures of the PD effects of E2006 included KSS, RTI, DSST, the WFB (RTI, Rapid Visual Processing [RVP], and Spatial Span [SSP]), POMS, melatonin levels, and the DLMO.

Due to high variability and non-normal distribution in change from baseline of LPS, it was not possible to reliably model the concentration-response relationship between E2006 PK parameters and LPS. Nonetheless, higher plasma concentrations of E2006 were associated with larger decreases in LPS, up to approximately 10 ng/mL. This finding was consistent with the efficacy results, where LPS was decreased at doses of 2.5 mg and higher. Above this concentration, the relationship appeared to reach an asymptote, suggesting that there was no apparent additional benefit of higher E2006 concentrations with regard to sleep onset . From 1 to 15 mg, E2006, decreases in sSOL also appeared to be linearly related to increases in E2006 plasma concentrations.

When modeled, WASO data were best described by log-linear relationships with the maximum observed concentration (C_{max}). The exposure-response relationship for WASO showed a log-linear relationship with C_{max}, such that higher concentrations of E2006 at C_{max} were associated with larger decreases in WASO.

PK/PD analyses for next-day residual sleepiness assessments (KSS, DSST, and RTI) did not show any apparent relationship with time-matched E2006 plasma concentrations. However, subjects whose E2006 plasma concentrations were greater than 20 ng/mL at 1 hour after waking had slightly greater increases on the KSS and a higher incidence of AEs of somnolence. This concentration is predicted to be achieved by most subjects receiving doses greater than 10 mg.

Preliminary Abuse Potential of E2006

Adverse events potentially related to signals of abuse were as follows. Elevated mood was reported in 1 subject in the 1-mg dose group and in 1 subject in the 25-mg E2006 groups, and euphoric mood was reported in 1 subject treated with 15 mg E2006. Three subjects administered 25 mg E2006 reported feeling drunk. Overall, individual AEs potentially associated with abuse occurred at very low frequencies.

Withdrawal Symptoms

Mean scores on the Tyrer Benzodiazepine Withdrawal Symptom Questionnaire showed no consistent evidence of withdrawal symptoms for E2006 when compared to placebo.

Absolute Melatonin Levels as a Potential Biomarker for Responsiveness to E2006

There were no significant correlations between baseline melatonin levels and change from baseline of SE, LPS, or WASO on Day 2 or Day 15. These results indicate that endogenous melatonin levels in subjects with insomnia did not predict the effects of E2006 on PSG sleep variables.

Potential Circadian Phase Shifting Effect of E2006 using DLMO as a Phase Marker

Although there was an apparent dose-related trend towards an advance in the phase marker of DLMO between Baseline and Day 15, the phase changes were variable and of small magnitude. These results suggest that E2006 does not have a clinically meaningful effect on circadian phase as measured by DLMO.

Safety Evaluation

Exposure

A total of 235 subjects were exposed to E2006, and 56 subjects were exposed to placebo. Across the treatment groups, there was no difference in exposure duration. In all treatment groups, the median duration of exposure was 17 days.

Treatment-emergent Adverse Events

There was a higher incidence of treatment-related TEAEs with E2006 (all doses) (50.2%) compared to placebo treatment (37.5%). At the 25 mg E2006 dose, 3 subjects had TEAEs that led to interruption of study drug dosing, and 1 subject had a TEAE that led to study drug discontinuation. There were no study drug dose interruptions or discontinuations due to TEAEs in any other dose groups.

The most common TEAE was somnolence, which was dose-related and consistent with the known pharmacology of E2006. Somnolence TEAE rates were dose-related. The only other TEAE occurring at ≥5% in the overall E2006 group was headache. Most TEAEs were mild in severity.

No deaths occurred during the study. There were 2 treatment-emergent SAEs. One subject randomized to placebo was found to have hyperkalemia. The subject recovered and completed the study as planned. One subject who received 25 mg E2006 (63-year-old white female with no known seizure history) had 2 focal onset seizures postdose during Stage Non-REM 2 sleep on the night after the second dose of 25 mg. These and all EEG records from the subject's PSGs were reviewed by an epileptologist. It was determined that both episodes of seizure activity were of focal onset in the left frontal region, and then became generalized. The subject was discontinued from the study due to this SAE; there were no sequelae.

Ten (4.3%) subjects experienced sleep paralysis, an AE known to be associated with orexin receptor antagonists. These occurrences were transient, without sequelae, and did not result in any discontinuations from the study. One possible occurrence of cataplexy (<1%) was reported during the study in a subject taking 15 mg E2006.

Blood Chemistry, Vital Signs and ECG

Occurrences of markedly abnormal laboratory results were sporadic and asymptomatic, with no consistent pattern. There were no notable changes from baseline for any vital sign parameters in any treatment group, and no changes of clinical importance in mean ECG parameters over time. No suicidality, suicidal behavior, or suicidal ideation was reported during the study.

Conclusions

- The first primary objective of the study was met when the study was stopped for early success, at which time 4 doses of E2006 (5 mg, 10 mg, 15 mg, and 25 mg) achieved the prespecified threshold of having an 85% probability of being the MUD according to the results of the utility function.
- The second primary objective of the study was also met, as each E2006 dose studied had acceptable KSS values at the end of treatment.
- At the final analysis, the probability that utility was >1 was >80% for each dose of E2006 studied.
- E2006 increased sleep efficiency and decreased the time to sleep onset after the first 2 doses as measured by both objective PSG and subjective Sleep Diary measures. These changes were larger than for placebo at all doses of E2006. The improvements relative to Baseline were maintained at the end of the 2-week treatment interval for dose groups at 2.5 mg or higher.
- E2006 also decreased the time spent awake after sleep onset after the first 2 doses, as measured by time spent awake after sleep onset on both PSG and Sleep Diary measures at doses of 10 mg and higher. The decreases in WASO observed at the beginning of treatment were maintained at the end of the 2-week treatment interval.
- At E2006 doses of 1 mg to 10 mg, there were no statistically significant increases in next-day residual sleepiness as measured by the KSS. Doses of 15 mg and 25 mg E2006 at some time points were associated with small increases in subjective sleepiness that were statistically significant compared to placebo. There were no consistent effects of any dose of E2006 on objective measures of next-day residual sleepiness.

- There was no evidence of rebound insomnia 1 and 2 days after cessation of treatment with any dose of E2006 as measured by PSG, nor was there any evidence of rebound insomnia as measured by the Sleep Diary for the first and second weeks posttreatment.

- Apparent clearance of E2006 was independent of dose and time, indicating linearity in PK. There were no clinically important effects of sex, race, body weight, or age on apparent clearance. PK/PD modeling showed that blood concentrations of 10 ng/mL (achieved at doses of 2.5 mg and higher) at the time of sleep onset were associated with maximal decreases in LPS. PK/PD modeling also showed that at approximately 9 hours postdose, morning blood concentrations greater than 20 ng/mL (most frequently achieved at doses of 15 mg and 25 mg) were associated with slightly greater increases on the KSS and a higher probability of experiencing an adverse event of somnolence.

- Rates of AEs showed some evidence of dose response in the E2006 groups compared to placebo subjects, particularly for somnolence. There were no deaths. There were 2 SAEs, 1 each in the placebo and E2006 25 mg group. TEAEs of sleep paralysis occurred at E2006 doses of 10 mg and above, but did not lead to study drug discontinuation or study discontinuation in any subjects. The TEAEs of somnolence and sleep paralysis typically occurred after the first 1 or 2 doses. These two AEs are consistent with the known pharmacology of E2006.

- There were no clinically important differences between E2006 treatment and placebo on blood chemistry, vital signs, weight, or ECG.

- There was no evidence of withdrawal following cessation of treatment. Individual AEs potentially associated with abuse occurred at very low frequencies.

- On the basis of the reported safety data, doses of 1 mg to 25 mg E2006 were considered to be well tolerated.

Date of Report

FINAL 17 Mar 2015