

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212028Orig1s000

OTHER REVIEW(S)

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24**

Date: December 16, 2019

Reviewer: Jacqueline Puigbo, PhD, MS
Division of Epidemiology I

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Division of Epidemiology I

Deputy Division Director: CAPT Sukhminder K. Sandhu, PhD, MS, MPH
Division of Epidemiology I

Subject: ARIA Sufficiency Memo for Pregnancy Safety Concerns

Drug Name: Dayvigo (Lemborexant)

Application Type/Number: NDA 0212028

Applicant/sponsor: Eisai Inc.

OSE RCM #: 2019-2282

1. BACKGROUND INFORMATION

1.1. Medical Product

Lemborexant is a new molecular entity that is a dual orexin receptor antagonist with the proposed indication to treat insomnia characterized by difficulties with sleep onset and/or sleep maintenance. The recommended dose is 5 mg taken no more than once per night before going to bed, with at least 7 hours remaining before the planned time of awakening. Dosage may be increased to 10 mg based on clinical response and tolerability. The maximum recommended dose is 10 mg once daily. The terminal half-life is 17 and 19 hours for 5 and 10 mg, respectively. The mechanisms of action involve blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R, which are thought to suppress wakefulness. Currently approved treatments for insomnia include benzodiazepines, nonbenzodiazepine hypnotics, melatonin agonists, doxepin, and suvorexant. Suvorexant is currently the only FDA-approved dual orexin receptor antagonist available on the market.

As of November 20, 2019, the proposed label's Warnings and Precautions section has warnings for central nervous system (CNS) depressant effects and daytime impairment, sleep paralysis/hallucinations/cataplexy-like symptoms, complex sleep behaviors, and worsening of depression/suicidal ideation. The most common treatment emergent adverse events (TEAEs) occurring in > 5% of patients and at a frequency greater than placebo in clinical lemborexant studies was somnolence (6.7%) and headache (8.4%).¹

1.2. Describe the Safety Concern

The Division of Psychiatry Products (DPP) requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for broad-based signal detection studies of lemborexant during pregnancy.

Risks of drug exposure during pregnancy are a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background rate of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Reproductive and developmental toxicity of lemborexant were assessed in embryo-fetal development studies in pregnant rats and rabbits, and a pre- and post-natal development study in rats.² In pregnant rats treated orally with lemborexant, maternal toxicity consisting of decreased body weight and food consumption was observed at the highest dose of 600 mg/kg/day. Toxicities to fetuses were observed at this maternally toxic dose and included an increase in post-implantation loss and decrease in mean fetal weights, increased incidence of the external malformations, cleft palate and omphalocele, increased incidence of visceral malformation of membranous ventricular septum defect, increase in skeletal variations including 14th cervical rib, and an increase in incomplete ossification. One fetus each at the low and mid dose also had membranous ventricular septum defect. However, based on an additional study investigating the background incidence of membranous septum defect in the conducting laboratory and data from published literature, the incidence in the low and mid dose groups was determined to be within the historical/lab control background and therefore is not considered drug-related. The no-observed adverse-effect-level (NOAEL) is 200 mg/kg/day for maternal toxicity and embryofetal development findings, which is greater than 100 times the maximum recommended human dose (MRHD) based on the area under the curve (AUC). In pregnant rabbits, maternal toxicity was observed at the



highest dose of 100 mg/kg/day which consisted of decreased body weight that correlated with decreased food consumption. Toxicities to fetuses were observed at this maternally toxic dose and included the skeletal variation of the presence of cervical ribs and the visceral variation of supernumerary lung lobes. The NOAEL is 30 mg/kg/day for maternal toxicity and embryofetal development in rabbits, which is approximately 23 times the MRHD, based on AUC. In a pre- and post-natal development study in rats treated with lemborexant during pregnancy and lactation, maternal toxicity consisting of a decrease in body weight gain and food consumption was observed at the highest dose of 300 mg/kg/day. At this dose, offspring body weights and femur lengths were significantly decreased indicating an adverse effect on pup growth and development. There was also a significant decrease in the acoustic startle response in pups from the high dose group. There were slight decreases in the bone biomarkers, total iron binding capacity and unsaturated iron binding capacity for pups from the high dose along with an increase in bone fluoride levels. The maternal and offspring NOAEL is 100 mg/kg/day, which is approximately 93 times the MRHD based on AUC.

Women who were pregnant were excluded from lemborexant clinical studies and birth control during participation was required for women of reproductive potential. Per the Division of Pediatric and Maternal Health (DPMH) review entitled, "Pregnancy and lactation labeling formatting recommendations", no available published data exist on the use of lemborexant during pregnancy. However, there was one pregnancy reported in a 22-year-old African-American female, with a past medical history significant for elective abortion, who received lemborexant during clinical study 012. The subject had a negative pregnancy test the day before receiving single doses of famotidine 40 mg and lemborexant. During the next visit 10 days later, the subject had a positive urine pregnancy test which was confirmed by serum pregnancy testing. The subject followed up with her primary physician and elected to terminate the pregnancy. The investigator classified the termination of pregnancy as not related to the study medication. The pregnancy was electively terminated. No further information was provided.³

As of December 13, 2019, the risk summary in Section 8.1 of the proposed labeling states:

There are no available data on DAYVIGO (lemborexant) use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.

In animal reproduction studies, oral administration of lemborexant to pregnant rats and rabbits during the period of organogenesis caused toxicities only at high multiples of the human exposure at the maximum recommended human dose (MRHD) based on AUC. The no observed adverse effect levels (NOAEL) are approximately >100 and 23 times the MRHD based on AUC in rats and rabbits, respectively. Similarly, oral administration of lemborexant to pregnant and lactating rats caused toxicities only at high multiples of the human exposure at the MRHD based on AUC. The NOAEL is 93 times the MRHD based on AUC (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively.

¹ Eisai Inc. Dayvigo (lemborexant), Module 2.7.4 Summary of Clinical Safety.

² Ceresa C. Pregnancy and Lactation Labeling Formatting Recommendations. August 5, 2019.

³ NDA Multi-disciplinary review and evaluation (NDA 212028) lemborexant. October 12, 2018.



Data

Animal data:

Lemborexant was administered orally to pregnant rats during the period of organogenesis in 2 studies at doses of 60, 200, and 600 mg/kg/day or 20, 60, and 200 mg/kg/day, which are approximately 6 to >300 times the MRHD based on AUC. Lemborexant caused maternal toxicity, manifested by decreased body weight and food consumption, decreased mean fetal body weight, an increased number of dead fetuses, and skeletal, external and visceral malformations (omphalocele, cleft palate, and membranous ventricular septal defect) at >300 times the MRHD based on AUC. The NOAEL of 200 mg/kg/day is approximately 143 times the MRHD based on AUC.

Lemborexant was administered orally to pregnant rabbits during the period of organogenesis at doses of 10, 30, And 100 mg/kg/day, which are approximately 7 to 139 times the MRHD based on AUC. Lemborexant caused Maternal toxicity that consisted of decreased body weight and food consumption and a higher incidence of Skeletal variations (presence of cervical ribs and supernumerary lung lobes) at approximately 139 times the MRHD based on AUC. The NOAEL of 30 mg/kg/day is approximately 23 times the MRHD based on AUC.

Lemborexant was administered orally to pregnant rats during pregnancy and lactation at doses of 30, 100, and 300 mg/kg/day, which are approximately 15 to 206 times the MRHD based on AUC. Lemborexant caused maternal toxicity that consisted of decreased body weight and food consumption and toxicity to offspring consisting of decreased pup body weights, decreased femur length, and decreased acoustic startle responses at 206 times the MRHD based on AUC. The NOAEL of 100 mg/kg/day is approximately 93 times the MRHD based on AUC.

1.1. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- ☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
- ☐ No approved indication, but practitioners may use product off-label in pregnant women
- ☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
- ☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

- ☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
- ☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. [†]
- ☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). [†]

[†] If checked, please complete [General ARIA Sufficiency Template](#).

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

- ☒ Pregnancy registry with internal comparison group
- ☐ Pregnancy registry with external comparison group
- ☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- ☒ Electronic database study with chart review
- ☒ Electronic database study without chart review
- ☒ Other, please specify: Alternative study designs for the electronic database study without chart review would be considered: e.g., retrospective cohort study using claims or electronic medical record data or a case control study.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

- ☐ Study Population

- ☐ Exposures
- ☐ Outcomes
- ☐ Covariates
- ☒ Analytical Tools

For any checked boxes above, please describe briefly:

Analytical Tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

Because broad-based signal detection is not currently available, other parameters were not assessed.

2.5. Please include the proposed PMR language in the approval letter.

The Division of Psychiatric Products requests two PMRs (PMR 3753-4 and 3753-5): one related to a registry-based and the other for a non-registry study to examine pregnancy outcomes. The PMR templates were finalized on November 22, 2019 and provide the following PMR language:

Conduct a prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to lemborexant during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

Conduct an additional pregnancy study that uses a different design from the Pregnancy Registry (for example a case control study or a retrospective cohort study using claims or electronic medical record data with outcome validation) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to lemborexant during pregnancy compared to an unexposed control population.

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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: November 25, 2019

To: Tiffany Farchione, MD
Director
Division of Psychiatry Products (DPP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Susan Redwood, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Domenic D'Alessandro, PharmD, MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): DAYVIGO (lemborexant)

Dosage Form and Route: tablets for oral use

Application Type/Number: NDA 212028

Applicant: Eisai Inc.

1 INTRODUCTION

On December 27, 2018, Eisai Inc., submitted for the Agency's review an original New Drug Application (NDA) 212028 for DAYVIGO (lemborexant) tablets for oral use indicated for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry Products (DPP) on January 17, 2019 for DMPP and on January 16, 2019 for OPDP to review the Applicant's proposed Medication Guide (MG) for DAYVIGO (lemborexant) tablets for oral use.

2 MATERIAL REVIEWED

- Draft DAYVIGO (lemborexant) tablets, for oral use MG received on December 27, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 13, 2019.
- Draft DAYVIGO (lemborexant) tablets for oral use Prescribing Information (PI) received on December 27, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 13, 2019.
- Approved BELSOMRA (suvorexant) tablets, for oral use, labeling dated July 12, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

*****Pre-decisional Agency Information*****

Memorandum

Date: November 19, 2019

To: Michele S. Horner, M.D., Clinical Reviewer
Division of Psychiatry Products (DPP)

Keith J. Kiedrow, PharmD, Regulatory Project Manager, (DPP)

Kimberly Updegraff, PharmD, MS, Associate Director for Labeling, (DPP)

From: Domenic D'Alessandro, PharmD, MBA, BCPS, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for DAYVIGO™ (lemborexant) tablets, for oral use, [controlled substance schedule pending]

NDA: 212028

In response to DPP consult request dated January 16, 2019, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for DAYVIGO™ (lemborexant) tablets, for oral use, [controlled substance schedule pending].

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPP (Keith J. Kiedrow) on November 13, 2019, and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on September 13, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Domenic D'Alessandro at (301) 796-3316 or domenic.dalessandro@fda.hhs.gov.

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MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: October 28, 2019

To: Tiffany Farchione, M.D., Acting Director
Division of Psychiatry Products (DPP)

Through: Dominic Chiapperino, Ph.D., Director
Chad Reissig, Ph.D., Supervisory Pharmacologist
Controlled Substance Staff (CSS)

From: Katherine Bonson, Ph.D., Senior Pharmacologist
Controlled Substance Staff (CSS)

Subject: Lemborexant (proposed tradename, Dayvigo)
NDA 212028 (IND 111871)
Indication: Treatment of insomnia
Dosage Form: film-coated tablets, 5 mg and 10 mg, of
anhydrous lemborexant base, for oral administration
Sponsor: Eisai

Materials reviewed: NDA 212028 (December 27, 2018) and subsequent
amendments
Statistical review of human abuse potential study (Ling Chen,
Ph.D., Office of Biostatistics, May 29, 2019)

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I. SUMMARY

1. Background

The Division of Psychiatry Products (DPP) requested that CSS review the abuse-related preclinical and clinical studies conducted with lemborexant (to be marketed as Dayvigo film-coated tablets), a new molecular entity proposed for the treatment of insomnia under NDA 212028.

Lemborexant (code name E2006) is a competitive dual orexin receptor antagonist (DORA) that has activity at both orexin-1 receptors (OX1R) and orexin-2 receptors (OX2R). Blockade of orexin suppresses the wake drive and promotes sleepiness and sleep.

The proposed dose of lemborexant is 5 mg administered orally, (b) (4) going to bed. If a sufficient clinical response is not achieved, the dose may be increased to 10 mg once daily. There should be at least 7 hours remaining before the planned time of awakening prior to each drug dose administration.

During drug development, lemborexant was tested in 3371 subjects with sleep disorders in Phase 2/3 clinical studies at doses ranging from 1-25 mg. Lemborexant was also tested in 512 healthy volunteers, 16 subjects with hepatic impairment, and 8 subjects with renal impairment in Phase 1 studies at doses ranging from 1-200 mg.

In the NDA submission, the Sponsor concludes that lemborexant has a relative potential for abuse lower than drugs or other substances in Schedule IV and should be placed into Schedule V of the Controlled Substances Act (CSA).

In 2014, the first DORA medication, suvorexant (Belsomra, NDA 204569) was approved by FDA for the treatment of insomnia and placed in Schedule IV of the CSA.

2. Conclusions

CSS has reviewed the nonclinical and clinical abuse-related data submitted in NDA 212028 for lemborexant and concludes that the drug has abuse potential and should be recommended for placement in Schedule IV under the Controlled Substances Act. This conclusion is based on the data described below:

- In receptor binding and functional studies, lemborexant is a highly selective orexin antagonist at both orexin 1 and orexin 2 receptors (OX1R and OX2R).

- In animal general behavior tests, lemborexant did not produce any changes in overt behaviors or in the ability to maintain balance on a rotorod.
- In a drug discrimination study in rats, lemborexant did not generalize to the cue produced by zolpidem (a GABA agonist). This would be expected since the pharmacological mechanisms of action of the two drugs are different.
- In a self-administration study, lemborexant did not produce self-administration. This suggests that lemborexant does not produce rewarding effects sufficient to maintain reinforcement.
- In an animal physical dependence study, chronic administration of lemborexant did not produce signs of withdrawal during drug discontinuation. This suggests that lemborexant does not produce physical dependence.
- In a human abuse potential (HAP) study, oral administration of lemborexant at therapeutic (10 mg) and supratherapeutic (20-30 mg, 2-3X) doses produced statistically significant increases on positive subjective measures such as Drug Liking, Overall Drug Liking, and Good Drug Effects that were greater than those produced by placebo. These subjective responses were similar to those produced by the positive control drugs, zolpidem (30 mg) and suvorexant (40 mg), both of which are Schedule IV sedatives under the CSA. This demonstrates that lemborexant produces rewarding effects that are similar to Schedule IV drugs.
- The adverse event of “euphoria” was not reported at a rate greater than placebo in Phase 1 or Phase 2/3 clinical studies following acute or chronic administration of lemborexant. There was a high incidence (up to 59%) of somnolence in clinical studies, as would be expected from a drug indicated for the treatment of insomnia. However, in the absence of a euphoria signal, this is not considered to be an abuse-related AE.
- Following discontinuation of lemborexant in Phase 2/3 clinical studies, patient scores on the Tyrer Benzodiazepine Withdrawal Symptom Questionnaire were not significantly different from the scores from patients treated with placebo. This suggests that lemborexant does not induce physical dependence.

3. Recommendations

Based on the CSS determinations that lemborexant has abuse potential, will have a currently accepted medical use upon NDA approval, but does not appear to produce physical dependence, CSS concludes that:

- a) Lemborexant should be recommended for control under the Controlled Substances Act in Schedule IV.

b) Section 9 (Drug Abuse and Dependence) should reflect the abuse-related data submitted in the NDA, as shown below:

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

[This section cannot be completed until the Drug Enforcement Administration completes a scheduling action under the Controlled Substances Act.]

9.2 Abuse

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. In a human abuse potential study conducted in recreational sedative abusers (n=29), lemborexant (10, 20, and 30 mg) produced responses on positive subjective measures such as “Drug Liking,” “Overall Drug Liking,” “Take Drug Again,” and “Good Drug Effects” that were statistically similar to those produced by the sedatives zolpidem (30 mg) and suvorexant (40 mg), and statistically greater than the responses on these measures that were produced by placebo.

9.3 Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. In animal and human evaluations of physical dependence, chronic administration of lemborexant did not produce withdrawal signs or symptoms upon drug discontinuation. This suggests that lemborexant does not produce physical dependence.

II. DISCUSSION

1. Chemistry

1.1 Drug Substance

Lemborexant is a new molecular entity identified by CAS registry number: 1369764-02-2. It is chemically known as (1*R*,2*S*)-2-([(2,4-Dimethylpyrimidin-5-yl)oxy]methyl)-2-(3-fluorophenyl)-*N*-(5-fluoropyridin-2-yl)cyclopropanecarboxamide. It has a molecular formula of C₂₂H₂₀F₂N₄O₂ and a molecular weight of 410.42 g/mol. It is a white to off-white powder that is soluble in dimethyl sulfoxide, methanol, acetone, benzyl alcohol, ethyl acetate, acetonitrile and ethanol, sparingly soluble in 1-octanol, and practically insoluble in water and heptane.

1.2 Drug Product

The drug product is formulated in two strengths: 5 and 10 mg, in film-coated tablets. The formulation contains the following inactive ingredients: lactose monohydrate, low-substituted hydroxypropyl cellulose, hydroxypropyl cellulose, and magnesium stearate.

1.3 Drug Product Manipulation (Study #1802061)

The Sponsor conducted a series of drug product manipulation tests with lemborexant film-coated tablets at a variety of doses that were under consideration at the time of the testing (b) (4). These tests included physical manipulation of the tablets, extractability of the active drug substance from the tablet, and assessments of abuse by insufflation (nasal route), smoking (inhalation route), and injection (parenteral route).

However, given that the Sponsor is not seeking an abuse deterrent claim for their lemborexant drug product, CSS defers review of these studies to the FDA Office of Pharmaceutical Quality.

2. Nonclinical Abuse-Related Studies with Lemborexant

2.1 Receptor Binding and Functional Studies

a. Receptor Binding Studies with Lemborexant (Study #100026610, M14007, M13009, 929062, 100023762)

In Chinese hamster ovary (CHO) cell membranes, lemborexant has high affinity for the OX1R (IC₅₀ = 6.1 nmol/L) and OX2R (IC₅₀ = 2.6 nmol/L). In comparison, the OX1R and OX2R antagonist, suvorexant, has a similar IC₅₀ at these receptors: 8.8 nmol/L and 12.0 nmol/L, respectively.

When lemborexant was tested at 88 other receptors, it was found to be inactive (defined as <50% inhibition at concentrations up to 10 µmol/L) including the following sites: GABA, central and peripheral benzodiazepine, cannabinoid (CB1), dopamine (D1, D2, D3, D4, and D5), opioid (mu, kappa, and delta), phencyclidine (PCP), serotonin (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT₃, 5-HT_{5a}, 5-HT₆, 5-HT₇), and monoamine transporters (norepinephrine, dopamine, and serotonin).

Lemborexant has three metabolites (M4, M9, and M10) that also have high affinity for OX1R (IC₅₀ = 12, 19, and 4.2 nmol/L, respectively) and OX2R (IC₅₀ = 3.8, 4.7, and 2.9 nmol/L, respectively). When these metabolites were tested at concentrations up to 10 µmol/L, they were found to be inactive at the other abuse-related sites tested for lemborexant. Of the three metabolites, only M10 was found to be present in humans at concentrations >10%, making it a major metabolite.

Thus, lemborexant and its major metabolite, M10, are highly-selective ligands at both OX1R and OX2R, without affinity for other CNS sites.

b. Functional Study with Lemborexant (Study # M16023)

A functional study was conducted to evaluate lemborexant in a fluorescence-based calcium mobilization assay either alone (agonistic function) or against the synthetic peptide agonist orexin (antagonistic function) on cells recombinantly expressing either OX1R or OX2R.

Lemborexant did not cause agonist-like responses when tested at concentrations up to 13.28 $\mu\text{mol/L}$ in the calcium mobilization test. In contrast, orexin produced a concentration-dependent increase in calcium mobilization.

When the antagonist test was conducted, lemborexant produced a concentration-dependent reduction in orexin-induced calcium mobilization, at concentrations up to 9.96 $\mu\text{mol/L}$. The K_i values of lemborexant activity against orexin were:

- 8.1 nmol/L on human OX1R and 0.48 nmol/L on human OX2R
- 23 nmol/L on rat OX1R and 0.68 nmol/L on rat OX2R
- 23 nmol/L on murine OX1R and 0.44 nmol/L on murine OX2R

These data show that lemborexant has activity as a dual orexin receptor antagonist, without any agonist activity at these receptor sites.

2.2 Animal Behavioral Studies

a. General Behavioral Observations

i. Irwin Test (Study #S10120)

An Irwin test (functional observational battery) was conducted during toxicology testing with male and female rats (10 – 15 animals/group/sex) that had received an acute dose of lemborexant (100, 300, and 1000 mg/kg) or vehicle (1 mol/L hydrochloric acid: 0.5% methylcellulose solution [1: 4]) by oral gavage. These toxicological doses in rats are 10-100X greater than the 10 mg/kg oral dose in rats that produces plasma levels that are similar to those produced by in humans at the 10 mg therapeutic dose. Animals were evaluated in cage-side, hand-held, and open-field observations, as well as for hindlimb foot splay, forelimb and hindlimb grip strength, and rectal temperature, using functional observational battery methods.

The results of these evaluations showed that none of the three doses of lemborexant tested produced overt changes in behavior.

ii. Rotorod Test (Study #W-20110154)

The effects of lemborexant on motor coordination and balance were evaluated in male mice (n = 11/group). Animals were first trained to balance on a slowly rotating rod (the rotorod test). After animals could maintain themselves on the rod, they received an acute dose of lemborexant (30, 100, and 300 mg/kg), zolpidem (100 mg/kg), or vehicle (0.5% methylcellulose) by oral gavage. These lemborexant doses in rats are 3-30X greater than the 10 mg/kg oral dose in rats that produces plasma levels that are similar to those produced in humans at the 10 mg therapeutic dose. The study report states that the highest dose of lemborexant (300 mg/kg) was chosen because it is "300 times higher than the minimum significant dose increasing total sleep time." Mice were observed for their performance on the rotorod 2.0 hours before and 0.5, 2.0, 3.5, and 5.0 hours after drug administration.

Over the 5-hour observation period, mice that received vehicle stayed on the rod for 154-170 seconds during each of the 180-second test periods. There were no statistically significant differences between the responses to lemborexant (30, 100, and 300 mg/kg) and the response to vehicle at any of the observation time points: the duration on the rotating rod for each lemborexant dose was (respectively) 145-164 seconds, 124-156 seconds, and 125-170 seconds). In contrast, zolpidem produced a statistically significant impairment in the ability of mice to stay on the rotating rod (44-170 seconds) compared to vehicle.

These data show that lemborexant does not produce motor impairment in mice, even at doses that produce plasma levels that are equivalent to supratherapeutic doses in humans.

b. Abuse-Related Behavioral Studies*i. Drug Discrimination Study in Rats with Lemborexant (Study #463-058)*

Drug discrimination is an experimental method of determining whether a test drug produces physical and behavioral responses that are similar to a training drug with specific pharmacological effects. Any centrally-acting drug can serve as the training drug. When the training drug is a known drug of abuse, drug discrimination in animals serves as an important method for predicting whether the effects of a new drug will similarly have abuse potential. Drugs that produce a response similar to known drugs of abuse in animals are also likely to be abused by humans.

In drug discrimination, an animal learns to press one bar when it receives the training drug and another bar when it receives a placebo. Once responding to the training drug and placebo is stable, an animal is given a challenge session with the test drug. A test drug is said to have "full generalization" to the training drug when the test drug produces bar pressing $\geq 80\%$ on the bar associated with the training drug.

Method

Female rats (n = 6) were trained to discriminate the GABA agonist, zolpidem (3.0 mg/kg, p.o.), from vehicle (10% w/v polysorbate 80 in deionized water), with a 30 minute pretreatment time. During training, the schedule of reinforcement was gradually raised from fixed ratio (FR) 1 to FR10. Full generalization was defined as 80% accuracy on the drug-associated lever.

When zolpidem discrimination was stable, animals were challenged with a range of zolpidem doses (0.32, 0.56, 1, 1.8, 3, and 5.6 mg/kg, p.o., 30 minute pretreatment time), suvorexant doses (30, 100, 300, 1000 mg/kg, 4 hour pretreatment time), lemborexant doses (10, 30, 100, and 1000 mg/kg, 1 hour pretreatment time), or vehicle (30 minute pretreatment time). The lemborexant doses produce 1X, 3X, 10X and 100X of the plasma levels produced in humans following administration of the proposed therapeutic dose (10 mg/day).

Results

Full generalization ($\geq 80\%$) to the zolpidem cue was seen following administration of 1.8 to 5.6 mg/kg zolpidem, but not at lower doses of zolpidem (0.32 to 1.0 mg/kg). Neither suvorexant or lemborexant produced full generalization to the zolpidem cue. The greatest degree of generalization from these two drugs was seen following administration of the highest dose of suvorexant (1000 mg/kg), which produced a 50% generalization to the zolpidem cue.

Conclusions

This study shows that at therapeutic or supratherapeutic doses, the orexin antagonists, lemborexant and suvorexant, do not produce full generalization to the cue for the GABA agonist, zolpidem. This would be expected since these two drugs have non-overlapping mechanisms of action.

ii. Self-Administration Study in Rats with Lemborexant (Study #ES13262)

Methods

A self-administration study was conducted in Rhesus monkeys (n = 4; 3 males and 1 female) to evaluate whether lemborexant produces sufficiently rewarding effects to produce reinforcement. Animals were trained to press a lever to receive the sedative, sodium pentobarbital (1.0 mg/kg/infusion, i.v.), using an FR5 schedule of reinforcement. After sodium pentobarbital self-administration was stable for three sessions (≥ 11 infusions/session, with infusions limited to 20 infusions/day), animals were provided access to the “negative control formulation” (1 v/v% dimethyl sulfoxide (DMSO)/10% 2-hydroxypropyl- β -cyclodextrin [HP- β -CD]/glucose solution, i.v.) to induce extinction. Challenge sessions with lemborexant were then started.

Lemborexant was tested at five doses (0.3, 0.1, 0.03, 0.01, and 0.003 mg/kg/infusion, i.v., in descending order) for 2 hours/day and at 4-7 days/dose, using an FR5 schedule of reinforcement. Based on a previously-conducted pharmacokinetic study with monkeys, acute administration of lemborexant at 0.04, 0.2, and 1 mg/kg (i.v.) produced plasma concentrations of 27-32 ng/ml, 146-173 ng/ml, and 543-661 ng/ml, respectively. Since the C_{max} in humans at the proposed therapeutic dose of lemborexant (10 mg/day) is ~62 ng/ml, the lemborexant doses tested produce plasma levels that range from subtherapeutic (0.01X) to supratherapeutic (~3X) in humans.

On the first day of each drug testing period, two consecutive, non-contingent infusions of study treatment (sodium pentobarbital, lemborexant, or vehicle) were administered. Forced administration did not occur if self-administration was observed at least twice prior to the first forced administration. The number of self-administrations was calculated by subtracting the number of forced administrations.

Results

The results show that all 4 monkeys self-administered sodium pentobarbital (n = 14.3 to 19.0 of the 20 allowed infusions/session), while there was a low degree of self-administration of the “negative control formulation” (n = 1.3 to 8.7 infusions). Self-administration of lemborexant at each of the 5 doses (0.0 to 3.7 infusions) was within the range produced by the “negative control formulation”.

Conclusions

Lemborexant did not produce rewarding effects sufficient to produce reinforcement.

2.3 Physical Dependence Studies in Animals

Rat Physical Dependence Study with Lemborexant (Study #ES13070)

Methods

A rat physical dependence study was conducted in which rats (n = 10/group) received twice daily oral gavage doses of lemborexant (100 or 300 mg/kg BID = 200 or 600 mg/kg/day), diazepam (100 or 200 mg/kg BID = 200 or 400 mg/kg/day) or vehicle (0.5 w/v% methylcellulose solution/1 mol/L hydrochloric acid (4:1, v/v)) over an 28-day period.

The Sponsor states that, “The dose level of 600 mg/kg/day was selected as the high dose level for this study, at which plasma concentrations was considered to sufficiently maintain higher than an expected efficacious plasma concentration in humans (i.e., 100 ng/mL) throughout the dosing period. The 200 mg/kg/day dose was selected as the low dose level to evaluate a dose-response relationship.” A pharmacokinetic analysis conducted in parallel with the behavioral analysis showed that the lemborexant plasma levels on the 8th day of dosing were 79 ng/ml in the 200 mg/kg/day dose group and 336

ng/ml in the 600 mg/kg/day dose group. In comparison, the plasma level produced in humans at the proposed therapeutic dose of 10 mg/day is 62 ng/ml. Thus, in the present study, the 200 mg/kg/day repeated dose was approximately equivalent to the human therapeutic dose while the 600 mg/kg/day repeated dose was approximately 6X greater than the human therapeutic dose. Notably, the results of this repeat-dose pharmacokinetic analysis are incongruent with results from other analyses in which acute dosing was utilized. In the acute dosing studies, much lower doses of lemborexant produce similar plasma levels.

Rats were evaluated for withdrawal signs for 7 days after final drug administration. This duration is appropriate, since the half-life of lemborexant in rats is 2-6 hours. Evaluation during the drug discontinuation period occurred by monitoring food intake, body weight and changes in behavior, including piloerection, salivation, hyperreactivity to handling, tremors, and convulsions. Other behavioral signs were recorded when they were observed, but a comprehensive checklist was not used. Animals were observed for loose stools and diarrhea (muddy and watery stools).

Results

In the diazepam group, behaviors during the drug discontinuation period included hyperreactivity, scant feces, salivation and paleness. The study report does not provide quantitation or severity for any of these behaviors. However, the report does state that there were statistically significant decreases in body weights and food consumption. These responses during the discontinuation period are characterized by the Sponsor as demonstrating a withdrawal syndrome, which would validate the study. However, this conclusion appears weak, based on how few behaviors emerged in the drug discontinuation period following diazepam administration.

In contrast, lemborexant did not produce any pattern of changes in behavioral signs or changes in food consumption at any point during the drug discontinuation period. There were statistically significant changes in body weight in the 600 mg/kg/day group, but not in the 200 mg/kg/day group.

Conclusions

Lemborexant did not produce signs of withdrawal during drug discontinuation following chronic administration. This suggests that lemborexant does not produce physical dependence.

3. Pharmacokinetics of Lemborexant in Animal and Humans

Table 1 (below) shows the pharmacokinetic profile following oral administration of lemborexant to rats and humans with regard to maximum plasma levels (T_{max}), maximum plasma levels (C_{max}) and half-life (t_{1/2}).

Table 1: Pharmacokinetic Parameters in Rats and Humans Following Acute Oral Administration of Lemborexant

Species	T _{max} (hr)	C _{max} (ng/ml)	t _{1/2} (hr)
Rat (10 mg/kg)	0.25-1.0	50	1.5
Human (10 mg)	1-2	62	17-19

In humans, acute administration of 10 mg oral lemborexant (the proposed therapeutic dose) produces a C_{max} of 60 ng/ml, with a time to maximal plasma concentration (T_{max}) of 1-2 hours and a half-life of 17-19 hours.

Lemborexant is metabolized primarily by cytochrome P450 CYP3A4 into three metabolites: M4, M9, and M10. Of these, only M10 was identified as the major circulating metabolite in humans (>10% of total drug-related exposure).

4. Clinical Abuse-Related Studies with Lemborexant

4.1 Human Abuse Potential Study

A Randomized, Double-Blind, 6-Way Crossover Study to Determine the Abuse Potential of Single Oral Doses of Lemborexant Compared to Zolpidem, Suvorexant and Placebo in Healthy, Non-Dependent, Recreational Sedative Users (Study # E2006-A001-103)

This was a randomized, double-blind, placebo-controlled 6-way crossover study that evaluated the oral abuse potential, safety, and tolerability of lemborexant compared to zolpidem, suvorexant, and placebo in healthy nondependent recreational sedative users. The study consisted of a Screening Phase, the Main Study (Qualification Phase and Treatment Phase), and a Follow-Up Visit.

Subjects

Subjects

Subjects were healthy male and female adults, between 18 and 55 years of age, who were non-dependent, non-treatment seeking recreational sedative users. Of the 107 subjects who participated in the Qualification Phase, 39 entered the Treatment Phase, with a total of 32 study completers.

Inclusion Criteria for participation are standard but included the following criteria that are relevant for a human abuse potential study:

- The subject had a history of at least 5 lifetime non-therapeutic experiences (i.e., for psychoactive effects) with sedatives (“e.g., zolpidem, benzodiazepines”).

- The subject had at least 1 non-therapeutic experience with sedatives in the prior year.

Exclusion Criteria are standard but included the following criteria that are relevant for a human abuse potential study:

- Alcohol or substance dependence within the 12 months prior to Screening (except nicotine) including cannabis, as defined by the DSM-IV-TR, or any self-reported dependence or “addiction” within the subject’s lifetime (with the exception of nicotine).
- Subjects who had ever been in treatment for substance use disorder.
- Subjects who tested positive on urine drug screen or breath alcohol test.
- Self-reported sleep disorder.

Main Study:

The Main Study consisted of a Qualification Phase and a Treatment Phase. Subjects passed the following criteria in the Qualification Phase to be eligible to enter the Treatment Phase:

- Ability to distinguish orally administered zolpidem 30 mg and suvorexant 40 mg from placebo on the bipolar Drug Liking VAS, defined as ≥ 15 -point peak increase for Drug Liking in response to zolpidem and suvorexant relative to placebo. Subjects must have had a peak score of ≥ 65 on the bipolar measure of Drug Liking in response to zolpidem and suvorexant.
- Displayed an acceptable placebo response, defined as a VAS response between 40 to 60 inclusive, for peak (E_{max}) Drug Liking.
- Demonstrated responses to zolpidem and suvorexant that are consistent with discrimination relative to placebo on other subjective measures, as judged by the study center staff.
- Tolerated study treatment (e.g., no episodes of vomiting within the first 3 hours postdose) and demonstrated ability to complete the subjective assessments (e.g., no unarousable sedation within 4 hours postdose).
- Demonstrated general behavior suggestive that the subject could successfully complete the study, as judged by the study center staff.

Oral Drug Doses

Main Study

Qualification Phase (single blinded)

The following treatments were administered orally:

- zolpidem 30 mg
- suvorexant 40 mg
- placebo

The zolpidem and suvorexant doses are the same ones used in the Treatment Phase.

There was a washout period of at least 72 hours in between treatments. At the conclusion of the Qualification Phase, there was a 7-day washout period before initiation of the Treatment Phase.

Proposed 3-day washout period in between treatments administered in the Qualification phase is adequate based on the half-life of positive controls (zolpidem and suvorexant). Zolpidem has a T_{max} of ~1.6 hours, and a half-life of ~2.5 hours for the 10 mg dose, whereas suvorexant has a T_{max} of ~2 hours, and a half-life of ~12 hours. Thus, a 72-hour washout period between single dose treatments is equivalent to 6 times the half-life of suvorexant, which has the longest half-life of the two positive control drugs.

Subjects were fasted for 8 hours before and for at least 2 hours after drug administration.

Treatment Phase (double-blind)

The following treatments were administered orally:

- lemborexant 10 mg
- lemborexant 20 mg
- lemborexant 30 mg
- zolpidem 30 mg
- suvorexant 40 mg
- placebo

The 10, 20, and 30 mg doses of lemborexant are equivalent to 1 to 3 times the maximum recommended 10 mg dose. The 30 mg dose of zolpidem is equivalent to 3 times the recommended 10 mg dose. The 40 mg dose of suvorexant is equivalent to 4 times the recommended 10 mg dose. The Sponsor claims that the maximum dose of lemborexant to be tested in the study (30 mg) was chosen based on safety data from clinical studies and that the 30 mg dose was selected to reduce daytime sleepiness.

Subjects were fasted for 8 hours before and for at least 2 hours after drug administration.

There was a washout period of at least 14 days between treatments, based on the half-lives of the study drugs: zolpidem = ~2.5 hours, suvorexant = ~12 hours, and lemborexant = 17-19 hours.

Pharmacodynamic Variables

All VAS subjective endpoints were assessed at baseline, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48 and 72 hours after drug administration, except for VAS for Overall Drug Liking, Take Drug Again, and Subjective Drug Value, which were assessed at 12, 24, and 48 hours. The Addiction Research Center Inventory- Pentobarbital-Chlorpromazine-Alcohol Group (ARCI-PCAG) scale was assessed at 1, 2, 4, and 8 hours after drug administration. The Observer's Assessment of Alertness/Sedation was assessed at baseline, 0.5, 1, 1.5, 2, 3, 4, 6, 12, and 24 hours. The Choice Reaction Time and Divided Attention measures were assessed at baseline, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours after drug administration

Primary Measure:

Drug Liking VAS (bipolar)

Secondary Measures:

Balance of effects:

- ☐ Overall Drug Liking VAS (bipolar)
- ☐ Take Drug Again VAS (bipolar)

Positive and negative effects:

- ☐ Good Effects VAS (unipolar)
- ☐ Stoned VAS (unipolar)
- ☐ High VAS (unipolar)
- ☐ Bad Effects VAS (unipolar)

Sedative effects:

- ☐ Alertness/Drowsiness VAS (bipolar)
- ☐ ARCI PCAG (sedative) scale (unipolar)

Other drug effects:

- ☐ Any Effects VAS (unipolar)
- ☐ Subjective Drug Value VAS

Observer-rated measures of sedation and cognitive impairment:

- ☐ Observer's Assessment of Alertness/Sedation
- ☐ Choice Reaction Time
- ☐ Divided Attention

Safety Variables

- Adverse events
- Clinical laboratory parameters (hematology, chemistry, and urinalysis)
- Vital signs measurements (heart rate, sitting blood pressure, respiratory rate, oxygen saturation, and oral temperature)
- Physical examination findings

Pharmacokinetic Evaluation

During the Treatment Phase, a pharmacokinetic evaluation was conducted to determine plasma concentration of lemborexant and its metabolites (M4, M9 and M10), as well as zolpidem and suvorexant. Timing for pharmacokinetic sampling was at 1.5 hours, 24 and 72 hours post-dose

Results

The following analysis of the HAP study subjective measures presented below in quotations are **verbatim** statements selected from the Statistical Review and Evaluation of the present HAP study, as conducted by Dr. Ling Chen (“the reviewer”), FDA Office of Biostatistics (DARRTS, May 29, 2019):

“According to FDA 2017 Guidance for the primary endpoint, Drug Liking Emax, the following hypotheses were tested:

1. $H_a: \mu_C - \mu_P \leq 15$ vs. $H_a: \mu_C - \mu_P > 15$ (Study validation);
2. $H_0: \mu_C \leq \mu_P$ vs. $H_a: \mu_C > \mu_P$ (Assess relative abuse potential);
3. $H_0: \mu_T - \mu_P \geq 11$ vs. $H_a: \mu_T - \mu_P < 11$ (Assess abuse potential compared to placebo).

“Reviewer’s comments: The sponsor changed margin for the validation test from 15 to 11, after treatment unblinding.” (see further discussion below)

“For all key secondary endpoints, the hypotheses for the comparisons between each positive control and placebo as well as between each dose of lemborexant and each positive control were prespecified as the same as those in the primary analysis. For non-key secondary endpoints, 2- sided tests with a test value zero were used. A p-value less than 0.05 was considered statistically significant for all individual 1-sided and 2-sided hypothesis tests.

“The validation tests for both 40 mg suvorexant and 30 mg zolpidem compared to placebo failed. However, the sponsor changed the test value to 11 after treatment unblinding. The sponsor’s arguments were:

1. Although the original SAP was changed to comply with the FDA’s request, the validation margin initially planned for the study was 11. The planned margin was

identified on the basis of published data defining clinically important differences in Drug Liking Emax in abuse potential studies (Schoedel et al., 2012).

2. In addition, the margin of 11 was purposefully selected to be less than the 15-point difference in maximum drug liking between the positive controls and placebo used for qualification purposes. A comparison of the maximum drug liking in response to an active comparator in the qualification versus treatment phases of a human abuse liability study has shown that during treatment subjects do not endorse drug liking at the same high levels as they do during the qualification period (Milovan et al., 2017).

“In the Qualifications Phase, for Drug Liking Emax the means were 89.8, 89, and 50.4, and the standard deviations were 11.1, 11.1 and 0.6 produced by 40 mg suvorexant, 30 mg zolpidem and placebo, respectively. However, in the Treatment Phase, the means were 76.1, 78.3 and 57.8 and the standard deviations were 17.8, 16.0 and 16.2, produced by 40 mg suvorexant, 30 mg zolpidem and placebo, respectively. The smaller means and larger standard deviations from the Treatment Phase compared to those from Qualification Phase were due to 6 and 3 subjects who had a maximum liking score less than 55 for 40 mg suvorexant and 30 mg zolpidem, respectively; and 3 and 1 subjects who had maximum liking scores 100 and 89 for placebo, respectively.

“The FDA 2017 Guidance states that the actual values of δ_1 , δ_2 , and δ_3 vary according to such factors as subjective measures, drug class, and route of drug administration.

“In this reviewer’s opinion, whether the δ_1 for the validation test must be greater than or equal to 15 for all Schedule IV positive controls should be further investigated and should not be determined only by statisticians. However, the qualification procedure for selecting qualified subjects should be improved. It is important to put effort on preventing disqualified subjects from being selected to the Treatment Phase.

“By using the test value 11 proposed by the sponsor, the p-values for the validation tests were 0.0251 (for S40 vs. P) and 0.0065 (for Z30 vs. P). Assuming that the test value 11 for the validation test is acceptable, the reviewer’s primary analysis showed that for Drug Liking Emax:

□ Both 40 mg suvorexant and 30 mg zolpidem produced LSMeans (76.5 and 78.5, respectively) [that were statistically] significantly larger than placebo (58.3) by 11 points ($p \leq 0.0251$);

□ None of the 3 lemborexant doses (10 mg, 20 mg and 30 mg) had a [statistically] significantly smaller LSMean (78.9, 80.9 and 83.9, respectively) compared to either 40 mg suvorexant or 30 mg zolpidem ($p \geq 0.5376$). Note that the p-value of the comparison between 30 mg lemborexant and 40 mg suvorexant was 0.9767, which indicates that 30 mg lemborexant had a [statistically] significantly larger LSMean compared to 40 mg suvorexant ($p = 1 - 0.9767 = 0.0233$).

“The peak mean response for Good Effects VAS and High VAS produced by each dose of lemborexant was larger than both 40 mg suvorexant and 30 mg zolpidem. For Good Effects VAS the peak mean response produced by 30 mg lemborexant were 35.3 and 25.4 points larger compared to 40 mg suvorexant and 30 mg zolpidem, respectively. Similarly, for High VAS the peak mean response produced by 30 mg lemborexant were 40.8 and 33.3 points larger compared to 40 mg suvorexant and 30 mg zolpidem, respectively. For Good Effects VAS, all three doses of lemborexant reached the peak mean responses at hour 1.5, and both peak mean responses produced by 40 mg suvorexant and 30 mg zolpidem reached at hour 2.0. For High VAS the peak mean responses reached at hours 1.0, 1.0, and 1.5 for 10 mg, 20 mg, and 30 mg lemborexant, and reached at hours 1.5 and 2.0 for 40 mg suvorexant and 30 mg zolpidem, respectively.

“For both Overall Drug Liking VAS and Take Drug Again VAS, [there was] not much difference among mean responses cross time and within each treatment or among active treatments would cause the reviewer’s concern.”

Sensitivity Analysis

“The reviewer did sensitivity analysis by eliminating subjects who had a negative difference between both positive controls and placebo (Subject ID (b) (6)). The same statistical methodologies as those used in the primary analysis were used for the sensitivity analyses for the primary and key secondary endpoints.

“The sensitivity analysis on Drug Liking Emax showed that:

- ☐ Both 40 mg suvorexant and 30 mg zolpidem produced LSMeans (78.2 and 78.8, respectively) [that were statistically] significantly larger than placebo (55.0) by 15 points ($p \leq 0.0128$).
- ☐ Both 40 mg suvorexant and 30 mg zolpidem did not have [statistically] significantly larger LSMeans compared to the 3 lemborexant doses (78.2, 80.4, and 83.7 for 10 mg, 20 mg and 30 mg, respectively, $p \geq 0.4336$).

“The sensitivity analysis on the key secondary endpoints showed that:

- ☐ For High Emax, 40 mg suvorexant produced [statistically] significantly smaller LSMeans compared to each dose of lemborexant ($p \leq 0.0115$). The LSMeans produced by 30 mg zolpidem was not [statistically] significantly larger than those produced by 10 mg and 20 mg of lemborexant ($p \geq 0.1207$), and the LSMeans produced by 30 mg zolpidem was [statistically] significantly smaller compared to that produced by 30 mg lemborexant ($p = 0.0203$).
- ☐ For Good Effects Emax, 20 mg and 30 mg lemborexant produced mean [values that] were [statistically] significantly larger than 40 mg suvorexant ($p \leq 0.0140$). The median difference between 40 mg suvorexant and 10 mg lemborexant was

not [statistically] significantly greater than zero ($p=0.9461$). Zolpidem 30 mg did not produce larger mean [values] than each dose of lemborexant ($p \geq 0.2305$).

□ None of the mean or median differences between each positive control and each dose of lemborexant were [statistically] significantly greater than zero for Overall Drug Liking Emax and Take Drug Again Emax.

Statistical Conclusion

“Because the primary analysis did not pass the validation test based on 32 completers, by using the test value 11 proposed by the sponsor, the reviewer performed analyses on primary endpoint Drug Liking Emax, as well as the four key secondary endpoints: Good Effects Emax, High Emax, and Take Drug Again Emax. The reviewer also performed the sensitivity analysis by eliminating 3 subjects who had a negative difference in maximum liking between both positive controls and placebo.

“Based on the data from 29 subjects, both positive controls passed the validation test with the prespecified test value 15. The test results from the comparisons between positive controls and each dose of lemborexant based on 32 subjects and 29 subjects were the same for the primary and key secondary endpoints with an exception that LSMean produced by 40 mg suvorexant was [statistically] significantly smaller than that produced by 30 mg lemborexant in the completers analysis for Drug Liking Emax but the difference was not [statistically] significant in the sensitivity analysis.”

Table 2 (below) depicts the effects of study treatments on subjective measures used in this study. The mean and standard deviation numbers provided below were drawn from the statistical review performed by Dr. Ling Chen, as was the statistical evaluation of comparisons between treatments. The table only depicts data from 29 subjects who passed the sensitivity analysis (see above), rather than the 32 subjects who completed the study.

The subjective measures of Drug Liking, Take Drug Again, and Overall Drug Liking are bipolar scales ranging from 0-100 with 50 as neutral, and an acceptable placebo range of 40-60. The measures Good Drug Effects, High, and Bad Drug Effects are unipolar scales ranging from 0-100 with 0 as neutral and an acceptable placebo range of 0-20.

Study Validation

As shown in Table 2 (below), the positive control drugs, zolpidem and suvorexant, produced expected increases in positive subjective responses on the primary measure of Drug Liking (79 and 78 out of 100, respectively), that were outside the acceptable placebo range (40-60 out of 100 on a bipolar scale) and were statistically significantly greater than those produced by placebo. This validates the study.

For the subjective measures described below, the data are described in terms of statistical significance when the analysis was conducted by Dr. Chen. When the analysis was only

conducted by the Sponsor, the data are described in terms of their relation to each other, but not in terms of statistical significance.

Drug Liking and Overall Drug Liking

- On the Drug Liking primary measure (bipolar scale), lemborexant at 10, 20, and 30 mg produced an increase in response that was statistically significantly greater than placebo (78=84 vs. 55 out of 100, respectively). These data are statistically similar to those produced by the positive control drugs, zolpidem (79) and suvorexant (78).
- On Overall Drug Liking (bipolar scale), all three lemborexant doses produced statistically significant increases on this measure compared to placebo (75-79 vs. 53 out of 100, respectively). These data are statistically similar to those produced by the positive control drugs, zolpidem (78) and suvorexant (81).

Table 2: Effects of Oral Placebo, Zolpidem (30 mg), Suvorexant (40 mg) and Lemborexant (10, 20, and 30 mg) on Key Subjective Measures (VAS) – E_{max} Scores (scale 0-100, mean and standard error) (n = 29)

	Placebo	ZOLP 30 mg	SUVO 40 mg	LEMB 10 mg	LEMB 20 mg	LEMB 30 mg
Drug Liking (bipolar)	55 ± 2	79 ± 3 *	78 ± 3 *	78 ± 4 *	80 ± 3 *	84 ± 3 *
Overall Drug Liking (bipolar)	53 ± 2	78 ± 4 *	81 ± 4 *	75 ± 4 *	78 ± 4 *	79 ± 4 *
Good Drug Effects (unipolar)	9 ± 4	70 ± 5 *	54 ± 7 *	64 ± 6 * ~	70 ± 6 * ~	77 ± 5 * ~
High (unipolar)	11 ± 4	67 ± 5 *	43 ± 6 *	58 ± 7 * ~	65 ± 6 * ~	81 ± 5 * ~
Take Drug Again (bipolar)	54 ± 2	81 ± 4 *	81 ± 4 *	78 ± 4 *	80 ± 5 *	81 ± 4 *
Stoned (unipolar)	8 ± 3	58 ± 7	33 ± 7	45 ± 7	52 ± 7	62 ± 7
Bad Drug Effects (unipolar)	6 ± 3	41 ± 6	12 ± 4	24 ± 6	34 ± 7	41 ± 6
Alert/Drowsy (bipolar)	11 ± 4	67 ± 5	43 ± 6	58 ± 7	65 ± 6	81 ± 5
ARCI-PCAG (unipolar)	5.2 ± 0.7	10.9 ± 0.6	9.6 ± 0.5	10.5 ± 0.5	11.5 ± 0.5	11.3 ± 0.5

OAA-S (unipolar)	19 ± 0.3	12 ± 0.4	16 ± 0.4	15 ± 0.3	15 ± 0.4	14 ± 0.3
Any Drug Effects (unipolar)	8 ± 3	58 ± 7	33 ± 7	45 ± 7	52 ± 7	62 ± 7

ZOLP = zolpidem, SUVO = suvorexant, LEMB = lemborexant

* = p < 0.01 compared to placebo, ^ = p < 0.01 compared to zolpidem

~ = p < 0.01 compared to suvorexant

Notations of statistical significance are only for those measures that were evaluated by Dr. Chen.

Good Drug Effects, High, Stoned, Take Drug Again, and Bad Drug Effects

- For Good Drug Effects (unipolar scale), lemborexant produced a dose-dependent increase in scores (64-77 out of 100) that were statistically significantly greater than placebo (9 out of 100) at the two higher doses (20 and 30 mg). This is statistically similar to the response from zolpidem (70 out of 100) but is statistically greater than the response from suvorexant (54 out of 100).
- For High (unipolar scale), lemborexant produced a dose-dependent increase in scores (58-81 out of 100) that were statistically significantly greater than placebo (11 out of 100). This is statistically similar to the response from zolpidem (67 out of 100) but is statistically greater than the response from suvorexant (43 out of 100).
- For Take Drug Again (bipolar scale), lemborexant at each of the three doses produced a similar increase in scores (78-81 out of 100) that were statistically significantly greater than placebo (54 out of 100). This is statistically similar to the response from zolpidem (81 out of 100) and suvorexant (81 out of 100).
- For Stoned (unipolar scale), lemborexant produced a dose-dependent increase in scores (45-62 out of 100) that were greater than placebo (8 out of 100). This is similar to the response from zolpidem (58 out of 100) but is greater than the response from suvorexant (33 out of 100).
- For Bad Drug Effects (unipolar scale), lemborexant produced a dose-dependent increase in scores (24-41 out of 100) that were greater than placebo (6 out of 100). This is similar to the response from zolpidem (41 out of 100) but is greater than the response from suvorexant (12 out of 100).
- For Alert/Drowsy (bipolar scale), lemborexant produced a dose-dependent increase in scores for drowsiness (58-81 out of 100) that were greater than placebo (11 out of 100). This is similar to the response from zolpidem (67 out of 100) but is greater than the response from suvorexant (43 out of 100).

- For ARCI-PCAG (unipolar, sedation scale), lemborexant produced a similar increase in scores across all three doses (10.5-11.3 out of 15) that were greater than placebo (5.2 out of 15). This is similar to the response from zolpidem (10.9 out of 15). The 20 and 30 mg lemborexant doses produced scores that were higher than suvorexant (9.6 out of 15).
- For Any Drug Effect (unipolar scale), lemborexant produced a dose-dependent increase in scores (45-62 out of 100) that were greater than placebo (8 out of 100). This is similar to the response from zolpidem (58 out of 100) but is greater than the response from suvorexant (33 out of 100).

Subjective Drug Value

On the Subjective Drug Value question, the mean monetary values of the study treatments were as follows:

- Zolpidem (30 mg) = \$16.55
- Suvorexant (40 mg) = \$13.74
- Lemborexant (10 mg) = \$14.44
- Lemborexant (20 mg) = \$16.92
- Lemborexant (30 mg) = \$14.88
- Placebo = \$2.65

Each of the doses of lemborexant were reported as having a monetary value (~\$15-17) that was similar to that of zolpidem (~\$17) and suvorexant (~\$14). The monetary value provided for the active drug treatments (~\$13 to \$17) were greater than those provided for placebo (~\$3).

Observer's Assessment of Alertness/Sedation (OAA/S)

The OAA/S is an observer rating of the level of alertness in subjects who are sedated and is composed of the following 4 assessment categories: responsiveness, speech, facial expression, and eyes. The OAA/S endpoints included a composite score, defined as the lowest score in any of the assessment categories, and a sum score (range 9–20), defined as the total of the scores in the assessment categories. Lower scores are indicative of increased sedation.

On the OAA/S, lemborexant produced a similar decrease in scores (14-15 out of 20) that were greater than placebo (19 out of 20). The response from lemborexant is similar to the response from suvorexant (16 out of 20). Zolpidem produced the greatest reduction in scores (12 out of 20).

Choice Reaction Time (CRT) and Divided Attention (DA)

Cognitive and psychomotor results for CRT showed that lemborexant was associated with less delay in reaction times and better ability to respond correctly compared to

zolpidem indicative of faster speed of processing of information and faster simple motor reaction abilities. Compared to suvorexant, all lemborexant doses showed similar simple motor reaction capabilities based on MRT data. Similarly, for the DAT, lemborexant showed better motor precision and improved divided attention as reflected in the greater percentage of target hits compared to zolpidem.

Adverse Events

The adverse event profile was evaluated in the safety population (n = 34-37) who received lemborexant during the Treatment Phase.

As shown in Table 3, the most frequently reported AE following lemborexant was somnolence (92-97%) at therapeutic (10 mg) and supratherapeutic (20-30 mg) doses. This response is consistent with its therapeutic use as a treatment for insomnia. Fatigue in response to lemborexant was also reported in the 10 mg group (3 of 37 subjects, 8%), and 20 mg group (2 of 34 subjects, 6%), but not in the group that received the highest dose of 30 mg (0%).

There were no other abuse-related AEs in response to lemborexant that were reported in more than 3 subjects. “Euphoric mood” was reported in 3 of 37 subjects (8%) who received 10 mg therapeutic dose of lemborexant and in 2 of 35 subjects (6%) who received the 30 mg supratherapeutic dose. However, there were no reports of “euphoric mood” in the 20 mg supratherapeutic dose group.

In the 10 mg therapeutic dose group, “disturbance in attention” and “anxiety” were reported by one of 37 subjects (2.7%) each. In the 20 mg supratherapeutic dose, “feeling abnormal,” “disturbance in attention,” “dissociation,” and “hallucination” were reported by one of 34 subjects (2.9%) each. In the 30 mg supratherapeutic dose, “feeling abnormal” was reported by 2 of 35 subjects (6%) while “agitation” was reported by one of 35 subjects (2.9%).

Table 3: Abuse-Related Adverse Events Reported Following Oral Placebo, Zolpidem (30 mg), Suvorexant (40 mg) and Lemborexant (10, 20, and 30 mg) (n = 34-37)

MedDRA Preferred Term	Placebo (N=36) n (%)	Zolpidem 30 mg (N=35) n (%)	Suvorexant 40 mg (N=34) n (%)	Lemborexant		
				10 mg (N=37) n (%)	20 mg (N=34) n (%)	30 mg (N=35) n (%)
Somnolence	6 (16.7)	30 (85.7)	29 (85.3)	34 (91.9)	30 (88.2)	34 (97.1)
Fatigue	2 (5.6)	2 (5.7)	0	3 (8.1)	2 (5.9)	0
Euphoric mood	0	2 (5.7)	0	3 (8.1)	0	2 (5.7)
Feeling abnormal	0	1 (2.9)	0	0	1 (2.9)	2 (5.7)
Agitation	0	0	0	0	0	1 (2.9)

Disturbance in attention	0	2 (5.7)	1 (2.9)	1 (2.7)	1 (2.9)	0
Dissociation	0	0	0	0	1 (2.9)	0
Hallucination	0	0	0	0	1 (2.9)	0
Abnormal dreams	1 (2.8)	0	2 (5.9)	1 (2.7)	0	0
Anxiety	1 (2.8)	0	0	1 (2.7)	0	0

Overall Conclusions

Zolpidem (30 mg) and suvorexant (40 mg) produced expected positive subjective responses (Drug Liking, Overall Drug Liking, Good Effects, High, and Take Drug Again) that were statistically significantly greater than placebo This validates the study.

Lemborexant at the doses tested (10, 20, and 30 mg) produced statistically significant increases on the positive subjective measures (Drug Liking, Overall Drug Liking, Good Effects, High, and Take Drug Again) compared to placebo.

A very small number of subjects (1-3 subjects out of 34-37 subjects who were part of the safety pool) reported abuse-related AEs in response to lemborexant.

These data support the conclusion that lemborexant has abuse potential.

4.2 Abuse-Related Adverse Events in Clinical Studies

a. Phase 1 Studies

Abuse-related AEs in response to a range of lemborexant doses (<5 mg up to > 30 mg) were reported from Phase 1 single and multiple dose studies.

As shown in Table 4 (below), in the single-dose Phase 1 studies (n = 18-299/group) at doses ranging from < 5 mg up to >30 mg, “somnolence” was the most frequently reported AE.

Table 4: Phase 1 Single Dose Studies: Abuse-Related Adverse Events Reported at ~2% in Response to Oral Lemborexant (<5 mg to > 30 mg) (n = 18-299/group) [ISS, Table 4.5.5.3]

	Placebo (n = 149)	LEMB <5 mg (n = 36)	LEMB 5 mg (n = 65)	LEMB 10 mg (n = 299)	LEMB >10 to <30 mg (n = 120)	LEMB >30 mg (n = 18)
Somnolence	9 (6%)	2 (5.6%)	0	75 (25%)	71 (59%)	1 (5.6%)
Fatigue	5 (3.4%)	3 (8%)	0	8 (2.7%)	9 (8%)	0
Euphoric mood	0	0	0	4 (1.3%)	2 (1.7%)	0

Abnormal Dreams	1 (0.7%)	0	0	3 (1.0%)	0	1 (6%)
Hallucination	0	0	0	0	1 (0.8%)	1 (6%)

This somnolence response is consistent with the proposed therapeutic use of lemborexant as a treatment for insomnia. However, the somnolence response was not dose-dependent. The greatest incidence occurred after administration of the 10-30 mg doses (25-59%), with only 1-2 subjects reporting the AE at <5 mg and > 30 mg and no subjects reporting the AE at 5 mg. “Fatigue” was reported without dose dependency at an incidence of 3-8%, with the highest response at the >10 to <30 mg range.

“Euphoria” was reported at low incidence (<2%) for all doses of lemborexant. “Abnormal dreams” and “hallucinations” were reported by 1 of 18 subjects (6%) in the >30 mg dose group.

As shown in Table 5 (below), in the multiple-dose Phase 1 studies (n = 12-70/group) at doses ranging from < 5 mg up to >30 mg, “abnormal dreams” was the most frequently reported AE. This response was dose-dependent, ranging from 4.5% at doses < 5 mg to 25% at doses >30 mg. Other than “abnormal dreams,” there were few incidents of other abuse-related AEs (e.g., “euphoric mood,” “disturbance in attention,” and “memory impairment”). Of particular interest for an abuse assessment, “euphoric mood” was only seen in the group that received a dose greater than 30 mg/day in one of 12 subjects (8%).

Table 5: Phase 1 Multiple Dose Studies: Abuse-Related Adverse Events Reported at ~2% in Response to Oral Lemborexant (<5 mg to > 30 mg) (n = 12-44/group) [ISS, Table 4.6.2.1]

	Placebo (n = 70)	LEMB <5 mg (n = 44)	LEMB 5 mg (n = 38)	LEMB 10 mg (n = 70)	LEMB >10 to <30 mg (n = 17)	LEMB >30 mg (n = 12)
Euphoric mood	0	0	0	0	0	1 (8%)
Abnormal dreams	2 (2.9%)	2 (4.5%)	3 (8%)	6 (9%)	3 (18%)	3 (25%)
Disturbance in attention	0	1 (2.3%)	0	0	0	0
Memory impairment	0	0	0	1 (1.4%)	1 (6%)	0

b. Phase 2/3 Studies

To identify potential safety signals in the Phase 2/3 database, studies were evaluated in which lemborexant was administered to patients experiencing insomnia. These studies were double-blind, placebo-controlled investigations that tested lemborexant at 1-25 mg/day. The Sponsor defined a treatment-emergent adverse event (TEAE) as an AE with

onset date on or after the first dose of study drug up to 14 days after the last dose of study drug. Subjects with two or more adverse events with the same preferred term were counted only once for that preferred term.

As shown in Table 6 (below), lemborexant produced dose-dependent somnolence (3-18%) as the most frequently reported TEAE. This response is consistent with the proposed therapeutic use of lemborexant as a treatment for insomnia.

There were only three other TEAEs that were reported in response to lemborexant at an incidence at approximately 2%. Fatigue was reported in 17 of 835 patients (2.1%) who received the 5 mg subtherapeutic dose of lemborexant and in 18 of 881 patients (2.2%) who received the 10 mg therapeutic dose.

Of particular interest for an abuse assessment are “euphoric mood” and “feeling drunk,” but each of these were only reported in 3 of 131 patients (2.5%) who received lemborexant at supratherapeutic doses (15-25 mg/day). “Euphoric mood” was not reported at the therapeutic dose (10 mg/day) or at 5 mg/day. There was one patient of 84 (1.2%) who reported “euphoric mood” at a dose ≤ 2.5 mg. “Feeling drunk” was reported in one patient of 835 (0.1%) who received the 5 mg subtherapeutic dose of lemborexant.

There were no other abuse-related TEAEs that were reported at an incidence greater than 1.0%, including “confusional state,” “feeling abnormal,” “disorientation,” and “memory impairment.”

Table 6: Abuse-Related Adverse Events Reported Following Discontinuation of Oral Lemborexant Reported in >1 Subject in Any Treatment Group (n = 84-881/group) [ISS All Insomnia Pool (Table 4.2.5.1.2)]

MedDRA Preferred Term	Placebo (N=714) n (%)	Lemborexant			
		1-2.5 mg (N=84) n (%)	5 mg (N=835) n (%)	10 mg (N=881) n (%)	15-25 mg (N=131) n (%)
Somnolence	9 (1.4)	2 (2.8)	51 (6.2)	84 (10.3)	21 (17.8)
Euphoric mood	0	1 (1.4)	0	0	3 (2.5)
Feeling drunk	0	0	1 (0.1)	0	3 (2.5)
Fatigue	1 (0.2)	0	17 (2.1)	18 (2.2)	0
Confusional state	0	0	0	5 (0.6)	0
Feeling abnormal	1 (0.2)	0	3 (0.4)	0	0
Disorientation	0	0	0	0	0
Memory impairment	2 (0.3)	0	0	0	0

These data show that in patients who participated in Phase 2/3 studies, lemborexant does not produce a clinically meaningful degree of euphoria or other AEs indicative of abuse potential

4.3 Assessment of Human Physical Dependence (Study #201, 303, and 304)

The Sponsor did not conduct a clinical study to evaluate the ability of lemborexant to produce physical dependence in humans.

However, patients who participated in the Phase 2/3 studies to evaluate lemborexant for insomnia did have a physical dependence assessment at the conclusion of the studies. Patients received lemborexant over a range of time that included less than 30 days up to greater than 180 days. The physical dependence assessment occurred through the administration of the Tyrer Benzodiazepine Withdrawal Symptom Questionnaire (T-BWSQ), in which were asked about 20 withdrawal symptoms, with response options of “No” (Score=0), “Yes, moderate” (Score=1) or “Yes, severe” (Score=2). The total possible score on the questionnaire is 40.

As shown in Table 7, there was no difference in the mean TBWS-Q scores between any of the doses of lemborexant and placebo: all of the responses were ≤ 1.2 out of 40.

Table 7: Tyrer Benzodiazepine Withdrawal Symptom Questionnaire Scores Reported Following Discontinuation of Oral Lemborexant and Placebo (n = 59-881/group) [ISS All Insomnia Pool (Table 7.2.13.1)]

	Placebo (N=584) n (%)	Lemborexant			
		1-2.5 mg (N=59) n (%)	5 mg (N=750) n (%)	10 mg (N=881) n (%)	15-25 mg (N=131) n (%)
TBWS score	1.0 \pm 2.2	1.2 \pm 2.7	0.3 \pm 0.9	1.1 \pm 1.9	0.7 \pm 2.1

These data show that lemborexant does not produce withdrawal symptoms indicative of physical dependence. These results are consistent with the rat physical dependence study in which chronic administration of lemborexant did not produce withdrawal signs.

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MEMORANDUM
REVIEW OF REVISED LABELS
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 10, 2019
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 212028
Product Name and Strength:	Dayvigo (lemborexant) tablets, 5 mg and 10 mg
Applicant/Sponsor Name:	Eisai Inc.
OSE RCM #:	2018-2813-1
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on September 13, 2019 for Dayvigo. The Division of Psychiatry Products (DPP) requested that we review the revised container labels for Dayvigo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous labels and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Holmes L. Labels and Labeling Review for Dayvigo (NDA 212028). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Aug 27. RCM No.: 2018-2813.

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/s/

LORETTA HOLMES
10/10/2019 03:56:11 PM

SEVAN H KOLEJIAN
10/11/2019 03:26:29 PM

Clinical Inspection Summary

Date	October 7, 2019
From	Roy Blay, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Michael Davis, M.D., Ph.D., Team Leader Michell Horner, M.D., Medical Officer Keith Kiedrow, Pharm.D., Regulatory Project Manager Division of Psychiatry Products (DPP)
BLA#	212028
Applicant	Eisai, Inc.
Drug	Dayvigo (lemborexant)
NME	Yes
Review Priority	Standard
Proposed Indication	Treatment of insomnia
Consultation Request Date	February 6, 2019
Summary Goal Date	October 18, 2019
Action Goal Date	December 20, 2019
PDUFA Date	December 27, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Garcia-Borreguerro, Harper, and Safirstein were inspected in support of this NDA. Based on the results of these inspection, the studies (Protocols E20006-G000-303 and E2006-G000-304) appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

The Applicant submitted this NDA to support the use of Dayvigo (lemborexant) for the treatment of insomnia.

Clinical inspections were requested for the following protocols in support of this application:

Protocol E20006-G000-303

Title: “A Long-Term Multicenter, Randomized, Double-Blind, Controlled, Parallel-Group Study of the Safety and Efficacy of Lemborexant in Subjects With Insomnia Disorder”

The primary objective was to determine the efficacy of lemborexant 5 mg (LEM5) and 10 mg (LEM10) compared to placebo (PBO) on *subjective sleep onset latency* (sSOL) after 6 months of treatment in subjects with insomnia disorder.

This was a 12-month, multicenter, randomized, double-blind, controlled, parallel-group study of two dose levels of lemborexant in subjects with insomnia disorder. The study had two phases: Pre-randomization and Randomization. The Pre-randomization Phase consisted of 3 periods that lasted up to a maximum of 35 days: a Screening Period, a Run-In Period, and a Baseline Period. The Randomization Phase comprised a 6-month, placebo-controlled treatment period (Period 1). During the next 6 months (Period 2), subjects received only active treatment. Subjects were informed that they would all receive placebo at some point during the study and that all would receive active treatment for at least 6 months. They were not informed of either the timing of these periods or the timing of the second randomization. A 2-week Follow-Up Period then took place, followed by an End of Study (EOS) Visit.

The primary efficacy endpoint for the study was the mean change from Study Baseline in *subjective sleep onset latency* (sSOL) at Month 6. Efficacy assessments were based on information recorded by the subject in an electronic Sleep Diary.

Protocol E2006-G000-304

Title: “A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Parallel-Group Study of the Efficacy and Safety of Lemborexant in Subjects 55 Years and Older with Insomnia Disorder”

The primary objective of the study was to demonstrate using polysomnography (PSG) that lemborexant (lemborexant 10 mg [LEM10] and lemborexant 5 mg [LEM5]) was superior to placebo (PBO) on objective sleep onset as assessed by *latency to persistent sleep* (LPS) after the last 2 nights of 1 month of treatment in subjects 55 years and older with insomnia disorder.

This was a global, multicenter, randomized, double-blind, placebo-controlled, active comparator (zolpidem; ZOL), parallel-group study of two dose levels of lemborexant for 30 nights in subjects with insomnia disorder. The study had 2 phases, the Pre-randomization Phase and the Randomization Phase. The Pre-randomization Phase comprised three periods that lasted up to a maximum of 35 days: a Screening Period that included two visits, a Run-in Period that began when eligible subjects were dispensed PBO tablets and included 2 consecutive nights on which PSG was recorded, and a Baseline Period that included the Day 1 assessments.

The Randomization Phase was comprised of a Treatment Period during which subjects were treated for 30 nights, followed by a minimum 14-day interval before an End of Study (EOS) Visit. The Treatment Period began on Day 1, when subjects were randomized in a double-blinded manner to receive LEM5, LEM10, ZOL, or placebo. Study drug was administered and overnight PSGs were initiated on the evenings of Days 1 and 2. On Days 29 and 30, subjects returned to the clinic for overnight PSGs.

The primary efficacy endpoint was the change from baseline for mean *latency to persistent sleep* (LPS), as measured by polysomnography (PSG), on Days 29 and 30 of LEM10 and LEM5 compared to placebo.

The key secondary efficacy endpoints were the following:

- Change from baseline for mean *sleep efficiency* (SE) on Days 29 and 30 of LEM10 and LEM5 compared to PBO
- Change from baseline for mean *wake after sleep onset* (WASO, i.e. minutes of wake from the onset of persistent sleep until lights on) on Days 29 and 30 of LEM10 and LEM5 compared to PBO
- Change from baseline for mean *WASO second half* (WASO2H, i.e. minutes of wake during the interval from 240 minutes after lights off until lights on) on Days 29 and 30 of LEM10 and LEM5 compared to ZOL

Reviewer's comment: The primary and key secondary efficacy parameters for both studies as presented in the sponsor line listings were in the form of derived data. To assist the FDA field investigators in the verification of the efficacy endpoints, OSI requested that the sponsor provide the respective sites with the raw data used to derive the efficacy parameters of interest. Of note, for Study -303, the sites received raw electronic Sleep Diary data from the vendor (through the sponsor), and for Study -304, sites received the relevant raw polysomnography parameters from the vendor (again, through the sponsor). In addition, OSI requested that the raw data be submitted by the sponsor to the NDA.

Rationale for Site Selection

Dr. Garcia-Borreguerro's site was selected for inspection because of its relatively large enrollment and particularly strong efficacy results in favor of the drug.

Dr. Harper's site was selected for inspection because of its relatively large enrollment and unusually high dropout rate (60%).

Dr. Safirstein's site was selected for inspection because of its relatively large enrollment and a higher rate of dropouts as compared to other sites with similar enrollment numbers.

III. RESULTS (by site):

1. Site #4102

Diego Garcia-Borreguero, M.D.
Institute of Research in Sleep of Madrid
Paseo de la Habana 151
Madrid, Spain 28040

At this study site for Protocol E2006-G000-304, 60 subjects were screened, 48 subjects were randomized into the study, and 12 subjects were screen failures.

No deficiencies were observed in the review of the informed consent forms for all screened subjects. Other records audited for 12 of the 48 randomized subjects included, but were not limited to, financial disclosure, sponsor and monitor correspondence, laboratory accreditation, ethics committee approvals, delegation log, inclusion/exclusion criteria, randomization, primary and secondary efficacy data (i.e., polysomnography parameters), monitoring reports, protocol deviations, audit trails, and test article accountability.

Source documents and electronic medical records were compared with the electronic Case Report Forms (eCRFs) and the data listings. The primary and secondary efficacy endpoints were verifiable. There appeared to be no under-reporting of adverse events.

2. Site #5002

Linda Harper, M.D.
618 East South Street
Orlando, FL 32801

At this site for Protocol E2006-G000-303, 83 subjects were screened, 32 subjects were enrolled, 16 subjects discontinued the study, and 16 subjects completed the study. No deficiencies were observed in the review of the informed consent forms for all 83 screened subjects. Other records audited for the 32 enrolled subjects included, but were not limited to, financial disclosure forms, training documents and logs, delegation logs, inclusion/exclusion criteria, sponsor/IRB/monitor correspondence, physician notes, laboratory reports, electronic sleep diary data (primary efficacy endpoint), concomitant medications, protocol deviations, and test article accountability.

Source documents and electronic Case Report Forms (eCRFs) were compared with the data listings. The primary efficacy endpoints were verifiable. There appeared to be no under-reporting of adverse events.

3. Site #4006

Beth Safirstein, M.D.
911 East Hallandale Beach
Boulevard
Hallandale Beach, FL 33009

At this site for Protocol E2006-G000-304, 159 subjects were screened, 58 subjects were randomized into the study, and 53 subjects completed the study.

No deficiencies were observed in the review of the informed consent forms for all randomized subjects. Efficacy data and adverse event reporting were reviewed for all 58 randomized subjects. Other records audited for 30 of the 58 randomized subjects included, but were not limited to, financial disclosure, delegation logs, source documentation, sponsor and monitor correspondence, electronic case report forms (eCRFs), electronic diary data, training documentation, monitoring visit logs, subject questionnaires, protocol deviations, concomitant medications, and test article accountability.

Source data was verified against the eCRFs and the data listings. Primary and key secondary polysomnogram (PSG) parameters were verified for all subjects, including the latency to persistent sleep, sleep efficiency, wake after sleep onset and wake after sleep onset during the second half of the night.

A Form FDA 483 was issued at the conclusion of the inspection with the following observations:

- Subject (b) (6) was enrolled into the study, received the investigational product, and completed the study despite being a female of childbearing potential, thus meeting one of the exclusion criteria. The observation was acknowledged by Dr. Safirstein in her August 20, 2019, written response. She noted that the issue was reported to the sponsor and the IRB and that corrective actions had been implemented, including retraining on the inclusion/exclusion criteria of the study and a preliminary check on the childbearing potential of prospective subjects that would be confirmed by the clinical investigator or sub-investigator during the prescreening interview. Subjects (b) (6) and (b) (6) were enrolled into the study, received the investigational product, and completed the study despite a lack of complete documentation of eligibility criteria. Exclusion criteria of current enrollment in another clinical trial, use of any investigational drug or device, or the subject's previous participation in any clinical trial of lemborexant were not addressed for Subject (b) (6). A positive HIV status was exclusionary. Subject (b) (6) HIV status was not documented in either the inclusion /exclusion criteria checklist or in source documentation. Dr. Safirstein concurred that the subject's HIV status was not explicitly documented. These deficiencies for Subjects (b) (6) and (b) (6) were not reported as protocol deviations.

As a corrective action, Dr. Safirstein stated that she will appoint an individual responsible for data quality control for each future study to prevent similar omissions of source data. These data will be further checked by periodic reviews conducted by Dr. Safirstein.

Reviewer's comment: These deficiencies appear isolated in nature and would not appear to have affected the efficacy or safety considerations of the study. Dr. Safirstein's written responses to the observations presented on the Form FDA 483 appear adequate.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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DPP\CDTL\Michael Davis
DPP\Reviewer\Michelle Horner
DCRP\Project Manager\Keith Kiedrow
OSI\DCCE\Division Director\Ni Khin
OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew
OSI\DCCE\GCPAB\Team Leader\Phillip Kronstein
OSI\DCCE\GCPAB\Reviewer\Roy Blay
OSI\DCCE\Program Analysts\Yolanda Patague

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/s/

ROY A BLAY
10/07/2019 04:28:02 PM

PHILLIP D KRONSTEIN
10/08/2019 09:48:35 AM

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10/08/2019 09:56:32 AM

LABELS AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 27, 2019
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 212028
Product Name and Strength:	Dayvigo (lemborexant) tablets, 5 mg and 10 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eisai Inc.
FDA Received Date:	December 27, 2018 and July 31, 2019
OSE RCM #:	2018-2813
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF REVIEW

As part of the NDA approval process for Dayvigo^a (lemborexant) tablets, 5 mg and 10 mg, the Division of Psychiatry Products (DPP) requested that we review the proposed labels and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Labels and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
ISMP Newsletters	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Table 3, below, includes the identified medication error issues with the submitted labels and labeling, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 3: Identified Issues and Recommendations for Eisai (entire table to be conveyed to Eisai)

Container Labels			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The 5 mg statement of strength is difficult to read because the (b) (4) font against (b) (4) background lacks sufficient contrast.	The lack of readability may lead to difficulty in identifying the product strength.	Consider the use of font outlining, a different font color, or some other means to provide adequate contrast to improve the readability of the strength statement.

^a The proposed proprietary name "Dayvigo" was found conditionally acceptable in the following review: Holmes, L. Proprietary Name Review for Dayvigo (lemborexant) NDA 212028. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Mar 20. RCM No.: 2018-28313392.

2.	The proposed expiration date format is not indicated on the labels.	We are unable to evaluate the expiration date format because it is not indicated on the labels. It is important that the expiration date formatting is clearly presented in order to minimize confusion and reduce the risk of deteriorated drug medication errors.	We recommend the human-readable expiration date on the drug package label include a year, month, and non-zero day. We recommend the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or a space be used to separate the portions of the expiration date.
3.	The container labels do not have a 2D matrix barcode.	A 2D data matrix barcode is used for tracking and tracing purposes.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. ¹ The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the

			<p>product identifier requirements apply to your product's labeling.</p> <p>¹The draft guidance is available at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.</p>
4.	The controlled substance symbol lacks prominence.	The "symbol on labels should be clear and large enough to afford easy identification of the schedule of the controlled substance upon inspection without removal from the dispenser's shelf" (per 21 CFR 1302.04).	Increase the prominence of the controlled substance symbol. Consider using a larger font size and bolder font to increase its prominence.
5.	The net quantity statement is too prominent.	The prominence of the net quantity statement may divert attention away from important information on the principal display panel such as the proprietary name, established name, and strength.	Consider decreasing the font size and unbolding the font of the net quantity statement in order to decrease its prominence.
6.	The labels do not appear to have a linear barcode.	The linear barcode is used as a means of product identification to help reduce medication errors.	Add a linear barcode to the labels as required per 21 CFR 201.25(c)(2).
7.	It is not clear what information you plan to place in the "FPO" area of the labels.	We are unable to assess the FPO area of the labels.	Explain or indicate on the labels the information that will be placed in the FPO area.

4 CONCLUSION

Our evaluation of the proposed container labels identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to the Applicant so that our recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Dayvigo that Eisai submitted on December 27, 2018.

Table 4. Relevant Product Information for Dayvigo	
Initial Approval Date	N/A
Active Ingredient	lemborexant
Indication	Treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance, (b) (4)
Route of Administration	Oral
Dosage Form	Tablets
Strengths	5 mg and 10 mg
Dose and Frequency	The recommended dose of is 5 mg, taken no more than once per night and (b) (4) before going to bed, with at least 7 hours remaining before the planned time of awakening. If the 5 mg dose is well-tolerated but greater effect is needed, the dose can be increased to 10 mg once daily. The maximum recommended dose is 10 mg once daily.
How Supplied	30-count and 90-count bottles
Storage	Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature].
Container Closure	Child-resistant cap

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Dayvigo labels and labeling submitted by Eisai on July 31, 2019.

- Container labels received on July 31, 2019
- Medication Guide received on December 27, 2018
- Prescribing Information (image not shown) received on December 27, 2018

F.2 Label and Labeling Images

Container Labels



^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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08/27/2019 05:28:07 PM

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08/27/2019 05:48:56 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

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Tel 301-796-2200
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Division of Pediatric and Maternal Health Review

Date: August 5, 2019 **Date consulted:** January 16, 2019

From: Carrie Ceresa Pharm D., MPH, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: The Division of Psychiatry Products (DPP)

Drug: DAYVIGO (lemborexant) tablets for oral use

NDA: 212028

Applicant: Eisai Inc.

Subject: Pregnancy and Lactation Labeling Formatting Recommendations

Proposed
Indication: for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance, (b) (4)

Materials
Reviewed:

- December 28, 2018, Original New Drug Application (NDA 212028) for lemborexant tablets
- January 16, 2019, consult to DPMH, NDA 212028, DARRTS Reference ID 4376984

Consult Question: “Review the FPI for PLLR Compliance”

INTRODUCTION AND BACKGROUND

On December 28, 2018, Eisai Inc. submitted an Original New Drug Application for NDA 212028, for lemborexant, an orexin receptor antagonist for the treatment of insomnia. The Division of Psychiatry Products (DPP) consulted the Division of Pediatric and Maternal Health (DPMH) on January 16, 2019, to assist with the Pregnancy and Lactation subsections of labeling.

Table 1: Lemborexant Drug Characteristics¹

Drug Class	Orexin receptor antagonist
Mechanism of Action	Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R is thought to suppress (b) (4)
Dose and Administration	5 mg taken no more than once per night (b) (4) of going to bed with at least 7 hours remaining before awakening; maximum dose 10 mg daily
Molecular Weight	410.42 Daltons
Protein Binding	(b) (4)
Terminal Half-Life	17 and 19 hours for 5 and 10 mg, respectively
Bioavailability	(b) (4)
Adverse Reactions	(b) (4)

REVIEW

PREGNANCY

Insomnia and Pregnancy

- Insomnia is one of the most commonly complained about medical conditions and is defined as difficulty initiating and maintaining sleep and waking up early. Sleep difficulty occurs notwithstanding adequate opportunities and sleep circumstances; lack of sleep affects daytime function.²
- There are three types of insomnia according to The International Classification of Sleep Disorders (ICSD-3) and those include short-term insomnia (expected to resolve when the individual adapts to the stressor), chronic insomnia and other insomnia (patient does not meet the criteria for short-term or chronic insomnia).³
- Behavioral modification and pharmacological medications are both used to treat insomnia.

¹ Applicant's Proposed Product Insert for lemborexant

² Bonnet M and D Arand. (2017). Overview of insomnia in adults. R Benca (Ed.), *UpToDate*.

https://www.uptodate.com/contents/overview-of-insomnia-in-adults?search=insomnia&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2

³ American Academy of Sleep Medicine. International Classification of Sleep Disorders, 3rd ed., American Academy of Sleep Medicine, Darien, IL 2014.

- Sleep disturbances, including insomnia, affect approximately 66 to 94% of pregnant women. The rate of sleep disturbances varies across trimesters. The rate of insomnia in the first trimester is the lowest at 12.6%. The rate of insomnia increases to 73.5% (50.5% mild, 15.7% moderate and 3.8% severe) in the last trimester with 69.9% of women complaining of difficulty maintaining sleep, 34.8% of women waking early and 23.7% of women having difficulty falling asleep.^{4,5,6,7}
- The most common causes of sleep disturbances in the first trimester include frequent urination and nausea/vomiting; in the second and third trimester, fetal movements, heartburn, cramps and restless legs are the common reasons for insomnia.⁴ Due to increases in oxytocin levels, insomnia can worsen just before labor begins.⁴
- The nonpharmacological treatment of insomnia during pregnancy includes avoiding naps and caffeine and establishing a regular sleep-wake cycle and minimizing fluid intake close to bedtime. Approximately 4% of pregnant women admit to using some type of pharmacologic sleep aid during pregnancy. Gamma-aminobutyric acid (GABA) receptor agonists, such as zaleplon, zolpidem and eszopiclone, are the most commonly prescribed medications for insomnia during pregnancy.^{4,8}

Nonclinical Experience

In animal reproduction studies, oral administration of lemborexant to pregnant rats and rabbits during the period of organogenesis caused toxicities only at high multiples of the human exposure at the maximum recommended human dose (MRHD) based on AUC. The no observed adverse effect level (NOAEL) is approximately >100- and 23- times the MRHD based on AUC in rats and rabbits, respectively. Similarly, oral administration of lemborexant to pregnant rats during pregnancy and lactation caused toxicities only at high multiples of the human exposure at the MRHD based on AUC. The NOAEL is 93 times the MRHD based on AUC. The reader is referred to the full Pharmacology/Toxicology review by Amy Avila, Ph.D., DARRTS.

Review of Literature

There are no available published data on the use of lemborexant during pregnancy. However, there was one pregnancy reported in a female subject who received lemborexant during clinical study 012. The pregnancy was electively terminated. No further information was provided.

Reviewer comment: The applicant addressed the Pregnancy and Lactation Labeling Rule (PLLR) requirements. There are no clinical data for review. The reader is referred to the Discussion/Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

⁴ Reichner C, 2015, Insomnia and sleep deficiency in pregnancy, *Obstetric Medicine*, 8(4):168-171.

⁵ Okun ML et al., 2015, Identifying insomnia in early pregnancy: validation of the insomnia symptoms questionnaire (ISQ) in pregnant women, *J Clin Sleep Med*, 11:645-654.

⁶ Fernandez-Alfonson AM et al., 2012, Factors related to insomnia and sleepiness in the late third trimester of pregnancy, *Arch Glycol Obstet*, 286:55-61.

⁷ Marques M et al., 2011, Is insomnia in late pregnancy a risk factor for postpartum depression/depressive symptomatology? *Psychiatry Res*, 186:272-280.

⁸ Okun M et al., 2015, A review of sleep-promoting medications used in pregnancy, *American Journal of Obstetrics and Gynecology*;428-439.

LACTATION

Nonclinical Experience

In animal reproduction studies lemborexant and its metabolites are present in rat milk at concentrations approximately 3 times higher (based on AUC) in milk compared to plasma. The reader is referred to the full Pharmacology/Toxicology review by Amy Avila, Ph.D., DARRTS.

Review of Literature

There are no available published data on the use of lemborexant during breastfeeding as the product is not yet marketed for use.

Reviewer comment:

The applicant addressed the PLLR requirements. There are no clinical data for review. The reader is referred to the Discussion/Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

The effect of lemborexant on human fertility has not been established. The effect of lemborexant on human fertility has not been established. Effects on female fertility were observed in rats at oral doses of 100 and 1000 mg/kg/day which are >60 times the MRHD based on AUC. The NOAEL is 30 mg/kg/day which is approximately 12 times the MRHD based on AUC. The reader is referred to the full Pharmacology/Toxicology review by Amy Avila, Ph.D., DARRTS.

Review of Literature

There are no available published data on the use of lemborexant and effects on fertility as the product is not yet marketed for use.

Reviewer comment:

The applicant addressed the PLLR requirements. There are no clinical data for review. The reader is referred to the Discussion/Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

There are no available clinical data for review. There was one pregnancy during the clinical trial that ended in elective abortion with no further details provided. In animal reproduction studies, oral administration of lemborexant to pregnant rats and rabbits during the period of organogenesis caused toxicities only at high multiples of the human exposure at the MRHD based on AUC. The NOAEL is approximately >100- and 23- times the MRHD based on AUC in rats and rabbits, respectively. Similarly, oral administration of lemborexant to pregnant rats during pregnancy and lactation caused toxicities only at high multiples of the human exposure at the MRHD based on AUC. The NOAEL is 93 times the MRHD based on AUC. The applicant has proposed the following statement with regard to pregnancy exposure for Highlights, (b) (4) The findings from the animal reproduction studies do not appear to be clinically relevant; therefore, DPMH recommends deletion of this statement.

In addition, since lemborexant is indicated for a condition that would be expected to be seen in females of reproductive potential and during pregnancy, DPMH recommends a post-marketing requirement (PMR) for the applicant to conduct a pregnancy exposure registry and a complementary study of a different design. DPMH also recommends that language regarding the pregnancy exposure registry is included in subsection 8.1 of labeling.

Lactation

There are no available clinical data for review as the product is not yet on the market. Lemborexant and its active metabolite are present in the milk of lactating rats at concentrations approximately 3 times higher (based on AUC) in milk compared to plasma. When a drug is present in animal milk, it is likely that the drug will also be present in human milk. In addition, lemborexant has characteristics that suggest that the drug may accumulate in human milk (molecular weight <800, long half-life, low bioavailability).

Lemborexant is indicated for a condition that would be expected to be seen in females of reproductive potential and during lactation. The drug is present in animal milk and given the drug's characteristics, it is possible that the drug will be present and may accumulate in human milk. Therefore, DPMH recommends a PMR for the applicant to conduct a lactation study.

Females and Males of Reproductive Potential

There are no available clinical data for review with regard to fertility as the product is not yet on the market. The effect of lemborexant on human fertility has not been established. Effects on female fertility were observed in rats at oral doses 60 times the MRHD based on AUC. The NOAEL is 12 times the MRHD based on AUC. (b) (4)

PMR RECOMMENDATIONS

DPMH recommends the following:

- 1) The applicant should be required to conduct a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to lemborexant during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.
- 2) The applicant should be required to conduct an additional pregnancy study that uses a different design from the Pregnancy Registry (for example a case control study or a retrospective cohort study using claims or electronic medical record data with outcome validation) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to lemborexant during pregnancy compared to an unexposed control population.

- 3) The applicant should be required to conduct a lactation study in lactating women who have received therapeutic doses of lemborexant using a validated assay to assess concentrations of lemborexant in breast milk.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1 and 8.2 of labeling for compliance with the PLLR (see below).

DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women who are inadvertently exposed to DAYVIGO during pregnancy. (b) (4)

Risk Summary

There are no available data on DAYVIGO use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.

In animal reproduction studies, oral administration of lemborexant to pregnant rats and rabbits during the period of organogenesis caused toxicities only at high multiples of the human exposure at the maximum recommended human dose (MRHD) based on AUC. The no observed adverse effect level (NOAEL), is approximately >100- and 23- times the MRHD based on AUC in rats and rabbits, respectively. Similarly, oral administration of lemborexant to pregnant rats (b) (4)

(b) (4) caused toxicities only at high multiples of the human exposure at the MRHD based on AUC. The NOAEL is 93 times the MRHD based on AUC (*See Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Lemborexant was administered orally to pregnant rats during the period of organogenesis in 2 separate studies at doses of 60, 200, and 600 mg/kg/day or 20, 60, and 200 mg/kg/day, which are approximately 6 to >300 times the MRHD based on AUC. Lemborexant caused maternal toxicity (b) (4) decreased body weight and food consumption, decreased mean fetal body weight, an increased number of dead fetuses and skeletal, external and visceral malformations (omphalocele, cleft palate, and membranous ventricular septal defect) at >300 times the MRHD based on AUC. The NOAEL of 200 mg/kg/day is approximately 143 times the MRHD based on AUC.

Lemborexant was administered orally to pregnant rabbits during the period of organogenesis at doses of 10, 30, and 100 mg/kg/day, which are approximately 7 to 139 times the MRHD based on AUC. Lemborexant caused maternal toxicity that consisted of decreased body weight and food consumption and a higher incidence of skeletal variations (presence of cervical ribs and supernumerary lung lobes) at approximately 139 times the MRHD based on AUC. The NOAEL of 30 mg/kg/day is approximately 23 times the MRHD based on AUC.

Lemborexant was administered orally to pregnant rats during pregnancy and lactation at doses of 30, 100, and 300 mg/kg/day, which are approximately 15 to 206 times the MRHD based on AUC. Lemborexant caused maternal toxicity that consisted of decreased body weight and food consumption and toxicity to offspring consisting of decreased pup body weights, femur length, and decreased acoustic startle responses at 206 times the MRHD based on AUC. The NOAEL of 100 mg/kg/day is approximately 93 times the MRHD based on AUC.

8.2 Lactation

Risk Summary

There are no data on the presence of lemborexant in human milk, the effects on the breastfed infant, or the effects on milk production. Lemborexant and its metabolites are present in the milk of lactating rats ^{(b) (4)}. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Infants exposed to DAYVIGO through breastmilk should be monitored for excess sedation. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DAYVIGO and any potential adverse effects on the breastfed infant from DAYVIGO or from the underlying maternal condition.

(b) (4)

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/s/

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08/05/2019 12:18:22 PM

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08/12/2019 04:09:59 PM



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 3, 2019

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Keith Kiedrow, RPM;
Michelle Horner, M.D., Medical Officer;
and Tiffany Farchione, M.D., Acting Division Director
DPP

Subject: QT-IRT Consult to NDA # 212028 (SDN # 001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 2/1/2019 regarding the Division's QT related question. The QT-IRT reviewed the following materials:

- Previous QT-IRT review for IND # 111871 dated 06/29/2015 in DARRTS ([link](#));
- Sponsor's clinical study report # E2006-A001-002 (SN0000 / SDN001; [link](#));
- Sponsor's clinical study report # E2006-A001-003 (SN0000 / SDN001; [link](#));
- Sponsor's summary of clinical safety (SN0000 / SDN001; [link](#)); and
- Sponsor's proposed product label (SN0012 / SDN015; [link](#)).

1 QT-IRT RESPONSES

Background: Eisai submitted NDA 212028 for lemborexant, a dual orexin receptor antagonist, for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance, (b) (4). Lemborexant was developed under INDs 111871 (treatment of insomnia; sleep onset and or maintenance) (b) (4). This NDA is considered an NME and is on a 12-month review clock.

Question: For DPP the QT-IRT team previously reviewed 2 submitted QT studies under IND 111871, which are being referenced in support of this NDA. The sponsor has proposed language in section 12.2 of labeling describing the QT effect of lemborexant. DPP would appreciate it if the QT team would review this proposed language and comment as appropriate.

QT-IRT's response:

Previously, the QT-IRT reviewed the sponsor's concentration-QTc relationship and confirmed that the upper bounds of the 2-sided 90% CI for the predicted mean $\Delta\Delta QTcF$ at the supratherapeutic exposures (50-mg dose) were below 10 ms. However, the data on exposures of lemborexant associated with the worst-case scenario was not available due to pending clinical pharmacology studies. Drug interaction studies with CYP3A4 inhibitors (itraconazole and fluconazole) indicate increased exposure of lemborexant (Cmax by ~1.6-fold). Thus, the supratherapeutic exposures (50-mg dose) in previous analysis offers adequate margin for the characterization of the exposure-response relationship.

2 PROPOSED LABEL

Below are proposed edits to the product label submitted by the Sponsor (link) from the QT-IRT. Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

In a concentration-QT analysis using the data from 2 randomized, double-blind, placebo-controlled, multiple ascending dose studies in healthy subjects, TRADENAME does not prolong the QT interval to any clinically relevant extent at a dose 5 times the maximum (b) (4) recommended dose.

We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SUMMARY

3.1 Product Information

Eisai Inc. is developing lemborexant (E2006; MW: 410) for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance, (b) (4)

Lemborexant is a competitive orexin receptor antagonist (OX1R and OX2R, with a higher affinity for OX2R). The orexin neuropeptide signaling system is a central promoter of wakefulness. Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R is believed to suppress wake drive. The product is formulated as immediate-release film coated tablet containing 5 mg or 10 mg of lemborexant. The proposed initial dose is 5 mg and the maximum recommended dose is 10 mg once daily.

Previously, the QT-IRT reviewed to the Sponsor's substitution request for conducting a thorough QT study for the characterization of QT prolongation risk of lemborexant under IND 111871 (10/15/2014). The QT-IRT review responded that the sponsor may potentially have sufficient data to characterize the proarrhythmic risk of lemborexant and the sponsor was requested to submit required data in order to confirm the results independently. Subsequently, the sponsor submitted exposure-response analysis using time-matched PK/ECG data from 2 phase-1, randomized, double-blind, placebo-controlled, multiple ascending dose (once daily for 14 days) studies conducted in healthy adult subjects (E2006-A001-002 and E2006-A001-003). In study # E2006-A001-002, a total of 48 healthy adult subjects were randomized to 6 cohorts (2.5, 5, 10, 25, 50, 75 mg, and placebo) in part-A of the study with adequate ECGs. In study # E2006-A001-003, a total of 24 healthy adult Japanese subjects were randomized to 3 cohorts (2.5, 10, 25 mg, and placebo) in part A and a total of 8 healthy adult Caucasian subjects were randomized to 2 cohorts (10 mg and placebo) with adequate ECGs. The relationship between plasma concentrations of lemborexant and the primary endpoint $\Delta\Delta\text{QTcI}$ (placebo-corrected change-from-baseline QTcI) was quantified using a linear mixed-effects model. The sponsor claimed no concentration-dependent effect of lemborexant on QTcI with the estimated population intercept and slope of 1.34 ms and -0.0090 ms per ng/mL (90% CI: -0.0348 to 0.0168), respectively.

The QT-IRT review independently confirmed that there is no significant concentration-QTc relationship for lemborexant, with a possibly small positive trend, in an independent analysis (06/29/2015). Although the study was not adequately powered to central tendency analysis with small sample size ($n=6/\text{cohort}$), the results were generally inconclusive. The review highlighted that there appears no clear dose-related QT effect with the largest upper bounds of the 2-sided 90% CIs for the mean differences between pooled lemborexant 10 mg and placebo below 20 ms (with point estimates all below 10 ms) using the by-timepoint analysis. Based on the concentration-QTc relationship, the review concluded that the upper bounds of the 2-sided 90% CI for the predicted mean $\Delta\Delta\text{QTcF}$ at the supratherapeutic exposures (50-mg dose) which are at least 5-fold the therapeutic mean peak concentrations were well below 10 ms. However, there was no adequate estimate of the worst-case scenario with pending clinical pharmacology studies. It was suggested to re-evaluate the safety margin of 5-fold the therapeutic exposure as more information is available.

The peak concentrations of 47 ± 15 ng/mL ($n=6$) and 420 ± 140 ng/mL ($n=6$) were observed at 10 mg and 75 mg dose levels in healthy subjects on Day 14 with once daily administration (Study # E2006-A001-002). The accumulation factor ranging between 1.75 and 2.39 for C_{max} and between 1.83 and 3.26 for AUC. Lemborexant exhibits almost linear pharmacokinetics with 2- to 3-fold accumulation at steady-state (2.39 for C_{max} ; 3.26 for AUC). The effective half-life ranges

between 17 and 28 h for lemborexant (terminal half-life ~55 h) and 26 to 28 h for metabolites (M4, M9 and major M10). Lemborexant is substrate of CYP3A4 and concomitant administration with 3A4 inhibitors (itraconazole and fluconazole) resulted in increased exposures (C_{max} by ~1.6-fold and AUC by ~4-fold) (Study # E2006-A001-004 P-1; # E2006-A001-012 P-3). Similarly, the exposure of lemborexant (C_{max} and AUC by ~1.5-fold; C_{max} 63 ng/mL in mild) was found to be increased in subjects with mild and moderate hepatic impairment (Study # E2006-A001-104).

3.2 Sponsor's position related to the question

Not Applicable

3.3 Nonclinical Cardiac Safety

In vitro electrophysiology studies were conducted to assess the effect of lemborexant and its metabolites on the human ether-à-go-go-related gene (hERG) tail current. Additional in vitro studies conducted included an evaluation of the effects of lemborexant on the inhibition of the slow component of delayed rectifier potassium currents (IKs) in Chinese hamster ovary (CHO) cells and a field potential duration (FPD) assay in human embryonic stem (hES) cell-derived cardiomyocytes. In vivo studies in dogs and monkeys were conducted to evaluate the effects of lemborexant on heart rate, blood pressure, and electrocardiogram (ECG) parameters.

Lemborexant inhibited the hERG potassium current with an IC₅₀ value of 6.1 µmol/L. M4, M9, and M10, 3 metabolites of lemborexant, also inhibited hERG potassium current in a concentration-dependent manner with IC₅₀ values of 5.2, 11.2, and 9.0 µmol/L, respectively. Lemborexant also significantly inhibited IKs by 24% at 10 µmol/L. Lemborexant prolonged FPD in a concentration-dependent manner, and the prolongation was approximately 10% at 10 µmol/L.

In 3 in vitro studies, lemborexant showed inhibition of hERG at 1 µmol/L and higher, inhibition of IKs channels at 10 µmol/L, and FPD prolongation in hES cell-derived cardiomyocytes at concentrations of 10 µmol/L and above. The degrees of inhibition of both ion channels were not large, but dual channel inhibition might have synergistically contributed to the prolongation of FPD and QTc interval.

Four in vivo studies were conducted to assess the effects of lemborexant on the CV system.

In an exploratory ECG study, lemborexant did not prolong the QTc interval at oral doses up to 30 mg/kg in conscious telemetered beagle dogs. In a second exploratory ECG study, intravenously administered lemborexant shortened PQ interval and increased heart rate in anesthetized beagle dogs at 1.08 and 3.6 mg/kg. No changes in QTc interval were observed in exploratory studies in anesthetized dogs receiving intravenous infusions or conscious dogs after oral administration that generated plasma concentrations of 6958.0 and 973.8 ng/mL, respectively.

In the definitive study, effects of oral doses of lemborexant administered during the daytime on blood pressure, heart rate, and ECG parameters were examined in 4 conscious telemetered male cynomolgus monkeys at 10, 30, and 100 mg/kg. Lemborexant did not affect blood pressure, heart rate, PR interval, or QRS duration at doses up to 100 mg/kg. Lemborexant did not affect QT interval or corrected QT (QTc) interval at 10 mg/kg, but a statistically significant prolongation of QTc interval (up to 6.3% at 30 mg/kg and 4.2% at 100 mg/kg versus predose) was observed at higher doses. To further investigate the effects of lemborexant on QT prolongation, the effects of oral doses of lemborexant administered before habitual sleeping time on blood pressure, heart rate, and ECG parameters were examined in 4 conscious telemetered male cynomolgus monkeys at 30

and 100 mg/kg. However, lemborexant administered during the daytime statistically significantly prolonged QTc interval at 30 and 100 mg/kg in conscious cynomolgus monkeys. Prolongation of QTc up to 6.3% (versus predose) at 30 mg/kg and up to 4.2% at 100 mg/kg was observed. Plasma concentrations at 2 and 4 hours after 30 mg/kg were 1335 ng/mL (unbound plasma concentration = 235.0 ng/mL) and 1316 ng/mL (unbound plasma concentration = 231.6 ng/mL), respectively. Lemborexant administered before habitual sleeping time also significantly prolonged QTc interval at 100 mg/kg in cynomolgus monkeys. Prolongation of QTc interval (9.5% to 11.0% versus predose) at 100 mg/kg was observed at 4 to 12 hours after dosing, with a statistically significant prolongation of QTc noted 4 hours after dosing.

Plasma concentrations at 4 and 14 hours after 100 mg/kg were 2167 ng/mL (unbound plasma concentration = 381.4 ng/mL) and 3193 ng/mL (unbound plasma concentration = 561.9 ng/mL), respectively. Plasma concentrations in the monkey CV studies were markedly higher than the steady state C_{max} at the proposed MRHD (61.6 ng/mL; Study CPMS-E2006-004R-v1).

The doses prolonging QTc in conscious monkeys were different when lemborexant was administered during the daytime (30 and 100 mg/kg) and at habitual sleeping time (100 mg/kg), and there was no clear dose dependency for QTc interval prolongation in conscious monkeys after administration during the daytime. It should be noted that QTc interval prolongation was not detected in clinical multiple ascending-dose studies at concentrations up to 400 ng/mL (Murphy, et al., 2017) suggesting that the clinical risk is negligible.

3.4 Clinical Cardiac Safety

Healthy Subjects:

In the Single-Dose Pool, twelve-lead ECGs were recorded predose and at various times postdose (30 min, 1, 2, 4, 6, 8, 9, 12, 24 hours, 2 to 7 days, and 8 to 27 days), and from Baseline to EOS (ISS Table 6.5.6.2). In addition to the ECG parameters analyzed in the Single-Dose Pool, QRS Axis was assessed. Mean Baseline values were within normal ranges for all ECG parameters, and there were no clinically meaningful changes over time for mean values in the PBO, LEM5, LEM10, and other groups. There were no shifts from Baseline of clinical concern, and the pattern of shifts was similar across the groups. There were no notable differences in the incidence of abnormal QTcF results between the PBO and LEM5, LEM10, and other groups.

In the Multiple-Dose Pool, ECG recordings obtained predose and at various time points postdose on each dosing night were evaluated for whether they were normal or abnormal based on investigator judgment. As a result, only shifts between normal and abnormal were analyzed. There were no shifts from Baseline of clinical concern.

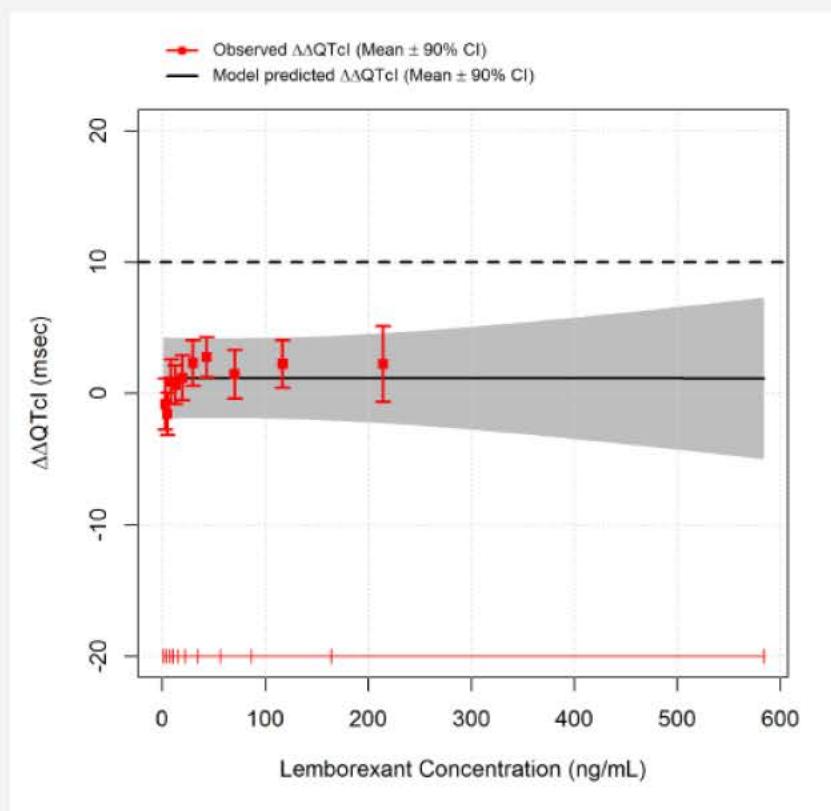
Subjects with Insomnia:

In the Phase 3 Pool, ECG parameters (heart rate, QRS duration, PR, QT, QTcF, and RR intervals) were analyzed at Baseline and at Month 1. Mean Baseline values were within normal ranges for these ECG parameters. There were no clinically meaningful changes over time for mean values in the PBO, LEM5 and LEM10 groups. There were no dose-related trends. There were no shifts from Baseline of clinical concern, and the pattern of shifts was similar across the groups. There were no notable differences in the incidence of abnormal QTcF, PR, and QRS results between the PBO and LEM5 or LEM10 groups. When comparing the Month 1 data to longer exposures of up to Month 12 there were no clinically important mean values or mean changes from Baseline by duration of exposure for any ECG parameter.

3.5 Summary results of prior QTc assessments

Refer to the sponsor's previous submission and QT-IRT review under IND # 111871 dated 06/29/2015 in DARRTS.

Figure 01: Model-Predicted $\Delta\Delta\text{QTcI}$ (Mean and 90% CI) and Observed $\Delta\Delta\text{QTcI}$ (Mean and 90% CI) across Deciles of Plasma Concentrations for Lemborexant (Study E2006 A001-002 and Study E2006 A001-003).



In the pooled analysis, the slope of the CR relationship was -0.00002 msec per ng/mL (90% CI: -0.01019 to 0.01014). The highest observed C_{\max} was 400 ng/mL, representing a margin 7.5-fold above exposures expected for the highest planned clinical dose. The model-predicted QTc effect at 400 ng/mL was 1.1 msec (90% CI: -3.49 to 5.78).

The FDA analysis indicated a statistically non-significant slope (estimate: 0.0161 ms·mL/ng with a 95% confidence interval of -0.0065 to 0.0387 ms·mL/ng) was observed with a linear mixed effect model assessing the relationship between ΔQTcF and drug exposure. Thus, upper bounds of the 2-sided 90% CI for the predicted mean $\Delta\Delta\text{QTcF}$ at the supratherapeutic exposures (at 50-mg dose level) were below 10 ms.

Table 01: Least-square Mean Estimates from Lemborexant- QTcF Exposure Response Analysis (FDA Analysis; QT-IRT review under IND # 111871 dated 06/29/2015 in DARRTS).

Dose (mg)	C _{max} (ng/mL)	ΔΔQTcF		
		Mean	90% CI	
10	46.90	2.00	-0.26	4.27
25	128.00	3.31	0.16	6.46
50	220.00	4.79	0.05	9.53
75	420.00	8.01	-0.68	16.70

3.6 Relevant details of planned Phase 3 study

Not Applicable

The sponsor conducted 2 multicenter, randomized, double-blind, placebo-controlled, active comparator, parallel-group studies in subjects with insomnia disorder (Study # E2006-G000-303 and E2006-G000-304). Refer to Section 3.4.

Reviewer's comments:

- Previously, the QT-IRT analyzed the concentration-QTc relationship and suggested that the upper bounds of the 2-sided 90% CI for the predicted mean ΔΔQTcF at the supratherapeutic exposures (50-mg dose) were below 10 ms. However, the data on exposures of lemborexant associated with the worst-case scenario was not available due to pending clinical pharmacology studies. It was suggested to re-evaluate the safety margin of 5-fold the therapeutic exposure as more information is available.
- Lemborexant is substrate of CYP3A4 and concomitant administration with 3A4 inhibitors (itraconazole and fluconazole) resulted in increased exposures (C_{max} by ~1.6-fold and AUC). The highest dose evaluated in the concentration-QTc relationship was 75 mg (once daily for 14 days) and offers >2-fold exposures margin over the highest clinically relevant exposures satisfying the requirement to waive a positive control for assay sensitivity (ICH E14Q&A (R3), 5.1). Thus, the supratherapeutic exposures (50-mg dose) in previous analysis offers adequate margin for the characterization of the concentration-QTc relationship.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrprpqt@fda.hhs.gov.

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/s/

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