

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214985Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	214985
Priority or standard	Standard
Submit date(s)	1/8/2021
Received date(s)	1/8/2021
PDUFA goal date	1/8/2022
Division/office	Division of Psychiatry (DP)
Review completion date	1/7/2022
Established/proper name	Daridorexant
cc(Proposed) proprietary name	Quviviq
Pharmacologic class	Dual orexin receptor antagonist (DORA)
Code name	DRX
Applicant	Idorsia
Dosage form(s)/formulation(s)	25 mg & 50 mg (b) (4)
Dosing regimen	50 mg once per night, taken orally within 30 minutes before going to bed
Applicant proposed indication(s)/ population(s)	treatment of adult patients with insomnia, (b) (4)
Proposed SNOMED indication	193462001 Insomnia (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	25 mg to 50 mg of QUVIVIQ taken orally no more than once per night within 30 minutes of going to bed (with at least 7 hours remaining prior to planned awakening).
Approved indication(s)/ population(s) (if applicable)	treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance
Approved SNOMED term for indication (if applicable)	193462001 Insomnia (disorder)

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Glossary

ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AHI	apnea-hypopnea index
ALT	alanine aminotransferase
AUC	area under the concentration-time curve
BA	bioavailability
BID	twice daily
CI	confidence interval
C _{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
COA	Clinical Outcome Assessment
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CPN	chronic progressive nephropathy
CSR	clinical study report
DDI	drug-drug interaction
DORA	dual orexin receptor antagonist
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5 th edition)
EC ₅₀	half maximal effective concentration
ECAC	Executive Carcinogenicity Assessment Committee
eCDF	empirical cumulative distribution function
ECG	electrocardiogram
E-R	exposure-response
FeSSIF	fed state simulated intestinal fluid
FaSSIF	fasted state simulated intestinal fluid
FDA	Food and Drug Administration
FMQ	FDA MedDRA query
GGT	gamma-glutamyl transferase
GMR	geometric mean ratio
GLP	good laboratory practice
HAP	human abuse potential
HD	high dose
HDF	high dose females
HDM	high dose males
IC ₅₀	half maximal inhibitory concentration
ICE	intercurrent event
ICH	International Conference on Harmonisation
IDSIQ	Insomnia Daytime Symptoms and Impacts Questionnaire
IND	investigational new drug
IV	intravenous
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LD	low dose
LPS	latency to persistent sleep

MAD	multiple-ascending dose
MAR	missing at random
MCID	minimal clinically important difference
MCP	modified completer population
MD	mid dose
MDF	mid dose female
MDM	mid dose male
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MRHD	maximum recommended human dosage
MTD	maximum tolerated dose
NDA	new drug application
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OSA	obstructive sleep apnea
PBPK	physiological-based pharmacokinetics
PD	pharmacodynamic
PGI-S	patient global impression-severity
PGI-C	patient global impression-change
PK	pharmacokinetic
PMR	postmarketing requirement
PND	postnatal day
PREA	Pediatric Research Equity Act
PSG	polysomnography
PSUR	periodic safety update report
PT	preferred term
PTSD	post-traumatic stress disorder
PXR	pregnane X receptor
QD	once daily
REM	rapid eye movement
SAD	single-ascending dose
SAE	serious adverse event
SDLP	standard deviation of the lateral position
SI	suicidal ideation
sLSO	subjective latency to sleep onset
SMQ	Standard Medical Dictionary for Regulatory Activities queries
SOC	system organ class
SPV	systolic pressure variation
sTST	subjective total sleep time
SUD	substance use disorder
sWASO	subjective wake after sleep onset
TEAE	treatment-emergent adverse event
TK	toxicokinetic
T _{max}	time to maximum concentration
TSH	thyroid stimulating hormone
TST	total sleep time

505(b)1 NME NDA 214985
Daridorexant (Quviviq) for Insomnia

VAS visual analog scale
WASO wake after sleep onset

I. Executive Summary

1. Summary of Regulatory Action

Idorsia submitted a new drug application (NDA) 214985 for daridorexant, an orexin receptor antagonist, for the treatment of insomnia.

NDA 214985 was reviewed by a multidisciplinary review team that did not identify any issues that preclude approval. Each discipline has recommended approval. I, the signatory authority for this application, concur with those recommendations and agree that the benefit-risk assessment supports approval.

The Applicant submitted results from two positive adequate and well-controlled trials that provide substantial evidence of effectiveness based on statistically significant and clinically meaningful treatment effects on the two primary efficacy endpoints, wake after sleep onset and latency to persistent sleep.

The available safety data show that risks of daridorexant are acceptable for its intended use. I concur that identified risks can be mitigated through labeling and further evaluated during routine pharmacovigilance. There will also be a post-marketing requirement to assess the effects of daridorexant on balance and cognition after arousal. The overall benefit-risk is favorable as described in the Benefit-Risk Framework below. For detailed information supporting the basis for this approval, please refer to the detailed reviews included in this Interdisciplinary Assessment document and the Product Quality Review.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Insomnia disorder (ID), as defined by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) is characterized by – Dissatisfaction with sleep accompanied by disturbance in sleep onset and/or maintenance – Distress or impairment in daytime function due to the sleep disturbance, including impairment in at least one of: energy, alertness, mood, or elements of role function – Sleep is impaired ≥ 3 nights/week for ≥ 3 months despite adequate opportunity for sleep • The prevalence of one or more symptoms of insomnia is high at around 30%. ID is also common but less prevalent, at less than 10%. • The prevalence of ID is higher in women, older adults, and individuals with low socioeconomic status, including the homeless population. • Other vulnerable patient groups include military personnel and veterans, people with a traumatic brain injury, patients with depressive and anxiety disorders, and peri- and postmenopausal women. • Prescription sleep aid use is common; about 4% of U.S. adults aged 20 and over used prescription sleep aids in the past month (Chong et al. 2013).	• Insomnia is a common condition and presents with functional impairment in a substantial portion of the population. It disproportionately affects several US subpopulations, including women and older adults. It is important that these demographic subgroups are represented in the study populations. • Use of medication to treat insomnia is common.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Psychotherapeutic and behavioral interventions are considered first line, with Cognitive Behavioral Therapy for Insomnia recommended by most practice guidelines. • Two other dual orexin receptor antagonists are approved for the treatment of insomnia disorder: suvorexant and lemborexant • Nonbenzodiazepine GABA receptor agonists are indicated for the short-term treatment of insomnia (zolpidem) and treatment of insomnia (eszopiclone). • Doxepin, ramelteon, and certain benzodiazepines (e.g., quazepam) are also approved for the treatment of insomnia. • Several barbiturates (e.g., secobarbital) are labelled for the short-term treatment of insomnia. • Efficacy of some pharmacological treatments are limited by duration, development of tolerance, or are efficacious in only sleep onset or sleep maintenance but not both. • Safety concerns with available pharmacological treatments include next-morning residual effects, fall risk, complex sleep behaviors, physical dependence and withdrawal, and risk of nonmedical use, abuse, and addiction.	• There are limitations to the efficacy and safety of available treatments, and efficacy described in approved products is largely based on measures of sleep onset and sleep maintenance without evidence of effects on distress or impairment.
Benefit	<u>Primary efficacy endpoints</u> • Wake after sleep onset (WASO) Month 1 showed statistically significant treatment effects for the 25 mg dose in Trial ID-078A302 and the 25 mg and 50 mg doses in Trial ID-078A301. • Latency to persistent sleep (LPS) Month 1 demonstrated statistically significant treatment effects for the 50-mg dose and the 25-mg dose in Trial ID-078A301. A dose response relationship between the 25 mg and 50 mg doses was observed for effects on sleep parameters in Trial ID-078A301. Sensitivity analysis using log-transformed data (viewed as preferred handling of the observed data by the statistical review team) in Trial ID-078A302 yielded a statistically significant treatment effect for the 25-mg dose.	<u>Primary efficacy endpoints</u> • The application provides substantial evidence of effectiveness for the treatment of insomnia based on statistically significant treatment effects on the two primary efficacy endpoints, WASO and LPS, in two adequate and well-controlled studies. <u>Secondary efficacy endpoints</u> • The subjective total sleep time (sTST) supports the primary efficacy endpoints and merits inclusion in the description of the study results in the prescribing information (PI). • The Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) sleepiness domain findings for 50 mg in Trial ID-078A301 are promising but were not independently substantiated (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<u>Secondary efficacy endpoints with control for type I error in statistical analysis</u> • sTST showed statistically significant treatment effects for the 25 mg dose in Trial ID-078A302 and the 25 mg and 50 mg doses in Trial ID-078A301 • IDSIQ sleepiness domain showed a statistically significant treatment effect for 50 mg in Trial ID-078A301 but not for 25 mg in Trials ID-078A301 and ID-078A302. <u>Study population</u> • <u>Women:</u> Women were represented in the sample in proportion with their representation in the target treatment population. Numerical trends suggest greater efficacy in women than in men. No prespecified efficacy comparison was made and differences are trend-level only. • <u>Older adults:</u> Older adults (≥65 years of age) were represented in the sample in proportion with their representation in the target treatment population. Numerical trends suggest greater efficacy in older than in younger adults. No prespecified efficacy comparison was made and differences are trend-level only. • <u>Racial and ethnic subgroups:</u> Some subgroups were underrepresented in the study sample. There was no evidence of differences in treatment effects. Analysis was limited by unreliable point estimates due to the small sample sizes for these populations.	<u>Study population</u> • Women and older adults were adequately represented in the study populations. • Some racial and ethnic subgroups were underrepresented the study populations compared to the US target population. Examination of subgroups did not suggest differences in treatment response from the overall study population.
Risk and Risk Management	<u>CNS depressant effects and daytime impairment</u> • Somnolence and sedation adverse reactions (AR) were observed in the registration trials. There was a relationship to dose between 10 mg and 25 mg but no meaningful differences between 25 mg and 50 mg. • On the simulated driving performance study there was impairment and a relationship to dose between 50 mg and 100 mg. The findings for daridorexant are consistent with a known class effect.	<u>CNS depressant effects and daytime impairment</u> • The adverse reactions indicative of CNS depressant effects observed in the development program and the daytime impairment observed in the simulated driving performance study warrant description in the prescribing information and support inclusion of a CNS depressant effects warning in the PI that is similar to the warning for other drugs in the class. <u>Sleep paralysis, hallucinations, and narcolepsy/cataplexy-like symptoms</u> • The adverse reactions observed in the development program warrant description in the prescribing information and support

<u>Sleep paralysis, hallucinations, and narcolepsy/cataplexy-like symptoms</u> • Sleep paralysis consistent with a drug effect was observed in less than 1% of subjects treated with 50 mg in controlled studies. • No cases of hypnagogic or hypnopompic hallucinations were observed in subjects treated with 50 mg in controlled studies; these ARs were observed in less than 1% of subjects treated with 25 mg. • Cataplexy-like ARs were observed with supratherapeutic 200-mg dose. <u>Worsening of depression/suicidal ideation</u> • Depressive symptoms were observed in 1 to 2% of patients taking daridorexant (no dose relationship) compared to less than 1% of patients taking placebo in controlled studies. • Prospective assessment of suicidal ideation and behavior in the registration studies elicited no treatment-emergent findings. <u>Abuse and dependence</u> • Controlled Substance Staff concluded that the human abuse potential study results and overall evaluation of the clinical data support a recommendation for Schedule IV. • Withdrawal effects were not observed during the run-out period. <u>Rebound insomnia</u> • WASO data during the runout period suggest the potential for rebound insomnia, with smaller effects on LPS. The data suggest that effects may be larger in patients over age 65. <u>Pregnancy and lactation</u> • Daridorexant is indicated for a condition that would be expected to be seen in females of reproductive potential and during pregnancy and lactation. • Pregnant and lactating women were excluded from clinical trials with daridorexant, and no pregnancy or lactation exposure cases have been reported.	inclusion of a warning in the PI that is similar to the warning for other drugs in the class. <u>Worsening of depression/suicidal ideation</u> • Depressive symptoms observed in the clinical data appear to be treatment-related and warrant description in the labeling; the class warning is suitable to describe the risk for daridorexant based on the observed data. <u>Abuse and dependence</u> • Recommendation is for Schedule IV, which is consistent across the drug class. <u>Rebound insomnia</u> • There are findings that suggest rebound insomnia on WASO. As there is not currently a standard approach to assessing and defining rebound insomnia in clinical trials, (b) (4) the Division will give further consideration to the appropriate approach for assessing and defining rebound insomnia in clinical trials for insomnia therapies. <u>Pregnancy and lactation</u> • Pregnancy labeling will include a statement that there are no available data on daridorexant use in pregnant women. A postmarketing requirement (PMR) will be issued for the Applicant to conduct a pregnancy exposure registry and a complimentary study of a different design. • Lactation labeling will include a statement consistent with labeling for other drugs in class that infants exposed to daridorexant through breast milk should be monitored for excess sedation, and a PMR will be issued for the Applicant to conduct a clinical lactation study. <u>Comorbid respiratory disorders</u> • These studies warrant description in product labeling with limitations of the studies noted. They do not negate the class warning for patients with compromised respiratory function. <u>Middle-of-night safety</u> • A PMR is recommended to assess the effects on balance and cognition after arousal from sleep. Such information will enhance safety-informed decision-making regarding its use.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Animal studies do not suggest an increased risk for embryo-fetal toxicity. • The drug is present in animal milk and given the drug's characteristics (such as molecular weight less than 800 Daltons), it is possible that the drug will also be present in human milk. <u>Comorbid respiratory disorders</u> • Respiratory safety findings from dedicated studies in patients with mild to moderate COPD and mild to moderate OSA were unremarkable, but due to study limitations, clinically important respiratory effects in these populations cannot be excluded. • Patients with severe COPD, severe OSA, and moderate OSA requiring CPAP were not studied. <u>Middle-of-night safety</u> • Adverse reactions of dizziness and impairments in balance and coordination, and, to a lesser extent, cognition were common. • Information about what levels of impairment in arousability and post-middle-of-night arousal psychomotor function should be expected from use of this drug is not available.	This additional information is not needed prior to approval because there was adequate information provided to assess CNS depressant effects and associated adverse reactions to describe them in the product labeling, including as a warning.

Abbreviations: CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; ID, insomnia disorder; LPS, latency to persistent sleep; OSA, obstructive sleep apnea; PMR, postmarketing requirement; WASO, wake after sleep onset

2.2. Conclusions Regarding Benefit-Risk

Insomnia disorder is a common condition and presents with functional impairment in a substantial portion of the population. It disproportionately affects several US subpopulations, including women and older adults. Use of medication to treat insomnia is common. Although there are a number of medications approved for the treatment of insomnia, there are limitations to the efficacy and safety of available treatments. Daridorexant will be the third orexin receptor antagonist approved for the treatment of insomnia disorder.

The Applicant has provided substantial evidence of effectiveness for daridorexant with two positive adequate and well-controlled trials. Although both trials included a 25-mg treatment group, only one trial (ID-078A301) included a 50-mg arm. The Applicant utilized a complex statistical testing procedure for evaluation of primary and secondary endpoints, but had appropriate controls for

Type I error. The primary endpoints consisted of WASO and LPS at both the high dose (50 mg in Trial ID-078A301 and 25 mg in Trial ID-078A302) and the low dose (25 mg in Trial ID-078A301 and 10 mg in Trial ID-078A302) at Month 1 and Month 3. WASO Months 1 and 3 showed statistically significant treatment effects for the 25-mg and 50-mg doses in Trials ID-078A301 and for the 25-mg dose in ID-078A302, with a clear dose-response relationship for effects on sleep parameters. There were also statistically significant treatment effects on LPS Months 1 and 3 for both doses in Trial ID-078A301. The treatment effect on LPS for the 25-mg dose was supported by a post hoc analysis in ID-078A302 using a model more suitable to the observed data.

The safety profile for daridorexant is consistent with that of other orexin receptor antagonists. Among the most common AEs, headache and dizziness exhibited a shallow dose-response relationship; somnolence (including hypersomnia, sedation, lethargy, and fatigue) did not. There was no indication of serious or potentially serious adverse reactions that are unmonitorable. Patient and provider awareness of the most important observed or pharmacologically plausible potential risks associated with treatment (along with risk-appropriate caution) should be sufficient to mitigate those risks. Overall daridorexant appears well-tolerated and broadly safe in the proposed dose range of 25 to 50 mg such that benefits clearly outweigh the risks.

In sum, the evidence thus suggests potential relative advantages and disadvantages for each dose that would depend on individual patient preferences and characteristics. Therefore, both doses should be recommended in the dosage and administration section and information to differentiate the benefits and risks of the doses should be included in the prescribing information, including in the special populations section, to support dose selection decisions in clinical practice. The product label will include a recommendation to initiate treatment with 25 or 50 mg.

II. Interdisciplinary Assessment

3. Introduction

Daridorexant is a dual orexin receptor antagonist (DORA) developed for the treatment of insomnia, with a proposed dose of 50 mg by mouth within 30 minutes of bedtime (and 25 mg for patients with moderate hepatic impairment or when used with moderate CYP3A4 inhibitors). Insomnia disorder is characterized by a predominating complaint of dissatisfaction with sleep quality or quantity with associated impairment in sleep onset or maintenance that is frequent, persistent, and associated with distress or impairment in daytime function. Two other drugs in this class (suvorexant and lemborexant) are approved and indicated for the treatment of insomnia. Most other drugs indicated for the treatment of insomnia are GABA-receptor agonists.

Substantial evidence of effectiveness for daridorexant is provided by two multisite, international, double-blind, 1:1:1 randomized, placebo-controlled trials of identical design with the exception of dose, evaluating the safety and efficacy of fixed monotherapy 50-mg and 25-mg doses (Trial ID-078A301) and 25-mg and 10-mg doses (Trial ID-078A302) compared to placebo for adults aged 18 to 65 (~60%) and older adults aged greater than 65 (~40%) with insomnia disorder.

3.1. Review Issue List

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

3.1.1.1. Efficacious Dose and Labeling of Dosing and Administration

Three doses were evaluated in the two registration trials: 10 mg, 25 mg, and 50 mg. Only the 25-mg dose was studied in both trials. Efficacy findings across endpoints were less consistent for 25 mg than 50 mg. Thus, labeling of the recommended dose requires discussion (see Section [6.3.1](#)).

3.1.1.2. Next Day Functioning

(b) (4) improvement of next-day functioning using a novel measure, Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ). Impairment of daytime function is an important (though not strictly required) element of insomnia disorder, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) diagnostic criteria, (b) (4). Thus, review of the new measure and the associated patient-reported outcome data are needed (see Section [6.3.2](#)).

3.1.2. Key Review Issues Relevant to Evaluation of Risk

The key review issues involved in the evaluation of risk are those inherent to the broad class of sedative-hypnotic medications. Within that grouping, the specific potential risk associated with the pharmacology of DORAs are narcolepsy/cataplexy-like symptoms (Section [3.1.2.2](#)). Other potential safety issues derived from the pharmacology of DORAs in particular involve subtle metabolic changes that do not present major safety concerns and are thus discussed primarily in Section [7.6.6](#), rather than in Section [7.7](#).

3.1.2.1. CNS Depressant Effects (Symptoms of Hypo-Arousal)

Potential for undesirable symptoms of hypo-arousal is intrinsic to the broad class of sedative hypnotics, and these effects are not fully monitorable by either patients or prescribers. Therefore, they require special attention in the safety evaluation for daridorexant as well (see Section [7.7.1](#)).

3.1.2.2. Parasomnias

Potential for parasomnias including those that are commonly distressing but not intrinsically dangerous, namely sleep paralysis and hypnogogic/hypnopompic hallucinations, and those that are potentially dangerous to patients and/or others, namely complex sleep behaviors and narcolepsy/cataplexy like symptoms, is broadly recognized for sedative hypnotics. These effects are not fully monitorable by either patients or prescribers. Therefore, they require special attention in the safety evaluation for daridorexant as well (see Section [7.7.2](#)).

3.1.2.3. Worsening of Depression/Suicidal Ideation

Potential for worsening of depression/suicidal ideation is broadly recognized for sedative hypnotics. Primary insomnia may overlap with and predispose towards mood and anxiety disorders that increase risk for suicide. Thus, patients with a history of depression and anxiety disorders or who may go on to develop depression or anxiety disorders are likely to be prescribed sedative hypnotics such as daridorexant. Therefore, potential for worsening of depression/suicidal ideation requires special attention in the safety evaluation for daridorexant as well (see Section [7.7.3](#)).

3.1.2.4. Abuse and Dependence

Potential for abuse or dependence is intrinsic to the broad class of sedative hypnotics, and these effects are not fully monitorable by either patients or prescribers. Therefore, they require special attention in the safety evaluation for daridorexant (see Section [7.7.4](#)).

3.2. Approach to the Review

Primary evidence for safety and efficacy is provided by the two submitted phase 3 trials, Trials ID-078A301 and ID-078A302, to support a balanced evaluation of benefits and risks. Supportive evidence regarding efficacy is provided by the two submitted dose-finding studies, 201 and 202, which provide support for the overall dose-response relationship observed across the phase 3 trials and the timing of treatment effect emergence. Supportive evidence of efficacy is also

provided by the long-term extension Study ID-078A303, which demonstrates durability of treatment response on subjective outcomes among primary study completers.

Supportive general evidence of safety is provided by:

- the long-term extension Trial ID-078A303, which also addresses the question of safety of extended use of daridorexant
- the aforementioned dose-finding studies, which inform dose-responsiveness of adverse effects

Supportive evidence of safety focused on specific safety issues is provided by:

- the single-ascending dose (SAD) and SAD/multiple-ascending dose (MAD) studies (Study 101 and 102, respectively), which address the limits of tolerability and expected acute effects of doses greater than the maximum proposed recommended dose of 50 mg
- clinical safety studies addressing clinically relevant drug-drug interactions (DDIs) with drugs likely to be used or abused at higher rates in the population with insomnia disorder:
 - alcohol (Study 111)
- clinical safety studies addressing other specific safety topics
 - human abuse potential (Study 107)
 - next-day psychomotor impairment (driving Study 108)
 - respiratory suppression in vulnerable populations: chronic obstructive pulmonary disease (Study 109) and obstructive sleep apnea (Study 110)
 - thorough QT (Study 117)

See [Table 3](#) for a more detailed listing of the studies supporting evaluation of efficacy and safety.

Clinical studies addressing pharmacologically motivated drug-drug interactions (diltiazem, Study 103; midazolam, Study 104; rosuvastatin, Study 106; citalopram, Study 114; famotidine and efavirenz, Study 120) and the effects of hepatic (Study 112) or renal (Study 115) impairments on daridorexant pharmacokinetics (PK) were not designed for characterization of daridorexant safety in the populations participating in those studies. Thus, safety findings from these studies are addressed primarily in Section [5](#) Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology.

The data from the 120-day safety update were reviewed for any new safety signals and assessed qualitatively for consistency with the safety findings observed in Trials ID-078A301, ID-078A302 and ID-078A303.

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations¹ for Daridorexant

Trial Identifier [NCT#]	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects, Randomized	Number of Centers and Countries
Clinical studies providing primary evidence for efficacy						
ID-078A301 (Registration trial) [NCT03545191]	Adult and elderly subjects with insomnia disorder according to DSM-5 criteria	Control type: Placebo-controlled Randomization: Randomized, 1:1:1 ratio to daridorexant 25 mg, 50 mg or placebo Blinding: Double-blind. Sleep Biomarkers: WASO, LPS Safety biomarkers: Vital signs, ECG, hematology, blood chemistry Innovative design features: N/A	Drug: Daridorexant/Placebo Dosage: 25 mg, 50 mg Number treated: 310 (daridorexant 25 mg) 308 (daridorexant 50 mg) 309 (placebo) Duration (quantity and units): 3 months	Primary: 2-night mean WASO and LPS change from baseline to Month 1 and Month 3 Key Secondary: sTST and IDSIQ sleepiness subscale score: Change from baseline to Month 1 and Month 3	Planned: 900 Actual: 930	75 centers in 10 countries, of which 51 centers in 7 countries (CAN, CHE, DEU, DNK, ESP, POL, US) randomized subjects.
ID-078A302 (Registration trial) [NCT03575104]	Adult and elderly subjects with insomnia disorder according to DSM-5 criteria	Control type: Placebo-controlled Randomization: Randomized, 1:1:1 ratio to daridorexant 10 mg, 25 mg or placebo Blinding: Double-blind. Sleep Biomarkers: WASO, LPS Safety biomarkers: Vital signs, ECG, hematology, blood chemistry Innovative design features: N/A	Drug: Daridorexant/Placebo Dosage: 10 mg, 25 mg Number treated: 306 (daridorexant 10 mg), 308 (daridorexant 25 mg) 306 (placebo) Duration (quantity and units): 3 months	Primary: 2-night mean WASO and LPS change from baseline to Month 1 and Month 3 Key Secondary: sTST and IDSIQ sleepiness subscale score: Change from baseline to Month 1 and Month 3	Planned: 900 Actual: 924	81 centers in 11 countries (BEL, BGR, CAN, CZE, DEU, FIN, FRA, HUN, KOR, SWE, US) of which 61 centers randomized subjects.

Trial Identifier [NCT#]	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects, Randomized	Number of Centers and Countries
Clinical studies providing supportive evidence for efficacy and safety						
ID-078A303 (long-term extension study) [NCT03679884]	Adult and elderly subjects with insomnia disorder according to DSM-5 criteria who completed Trial ID-078A301 or 302	Control type: Placebo-controlled Randomization: Subjects on daridorexant in Trial ID-078A301 and 302 continued on assigned daridorexant dose of either 10 mg, 25 mg, or 50 mg. Subjects assigned placebo in Trial ID-078A301 and 302 were rerandomized to daridorexant 25 mg or placebo. Blinding: Double-blind Sleep biomarkers: N/A Safety biomarkers: Vital signs, ECG, hematology, blood chemistry Innovative design features: Inclusion of randomized placebo control arm	Drug: Daridorexant/Placebo Dosage: 10 mg, 25 mg, 50 mg Number treated: 142 (daridorexant 10 mg) 394 (daridorexant 25 mg) 137 (daridorexant 50 mg) 128 (placebo) Duration (quantity and units): 9 months	There were no primary or key secondary endpoints. Objectives: To assess the long-term safety and tolerability of 10 mg, 25 mg and 50 mg daridorexant.	Planned: Approximately 1260 Actual: 804	94 sites in 14 countries (BEL, BGR, CAN, CHE, DEU, DNK, ESP, FIN, FRA, HUN, KOR, POL, SWE, US)

Trial Identifier [NCT#]	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects, Randomized	Number of Centers and Countries
AC-078A201 (Adult dose-finding study) [NCT02839200]	Adults (18-64 years of age) with insomnia disorder according to DSM-5 criteria	Control type: Placebo-controlled and active-reference. Randomization: Randomized, 1:1:1:1:1 ratio (stratified by sex) to placebo, daridorexant 5, 10, 25, or 50 mg, or 10 mg zolpidem. Blinding: Double-blind. Sleep Biomarkers: WASO, LPS Safety biomarkers: Vital signs, ECG, hematology, blood chemistry Innovative design features: N/A	Drug: Daridorexant, Zolpidem, Placebo Dosage: 5, 10, 25 and 50 mg of daridorexant 10 mg zolpidem Number treated: 60 (daridorexant 5 mg) 58 (daridorexant 10 mg) 60 (daridorexant 25 mg) 61 (daridorexant 50 mg) 60 (zolpidem 10 mg) 60 (placebo). Duration (quantity and units): 30 days.	Primary: 2-night mean WASO change from Baseline to Days 1&2. Key Secondary: 2-night mean LPS change from Baseline to Days 1&2. Change from baseline to Week 4 in mean sWASO and sLSO.	Planned: 300 Actual: 360	38 centers in 6 countries (DEU, HUN, ISR, ESP, SWE, US).

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 Daridorexant (Quviviq) for Insomnia

Trial Identifier [NCT#]	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects, Randomized	Number of Centers and Countries
AC-078A202 (Geriatric dose-finding study) [NCT02841709]	Elderly subjects (≥65 years of age) with insomnia disorder according to DSM-5 criteria	Control type: Placebo-controlled Randomization: Randomized, 5-way crossover: 1:1:1:1:1 to five different sequences of five study treatments: (daridorexant 5 mg, 10 mg, 25 mg and 50 mg, and placebo) Blinding: Double-blind. Sleep Biomarkers: WASO, LPS Safety biomarkers: Vital signs, ECG, hematology, blood chemistry Innovative design features: N/A	Drug: Daridorexant, Placebo Dosage: Daridorexant 5, 10, 25 and 50 mg. Number treated: 58 total (56, 54, 55, 56, and 54 subjects took 5 mg, 10 mg, 25 mg, 50 mg daridorexant, and placebo, respectively) Duration (quantity and units): 10 days in total (2 on each double-blind treatment)	Primary: 2-night mean WASO change from Baseline to Days 1&2. Key Secondary: 2-night mean LPS change from Baseline to Days 1&2.	Planned: 50 Actual: 58	10 centers in 2 countries (DEU, US).

Trial Identifier [NCT#]	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects, Randomized	Number of Centers and Countries
Studies addressing specific safety issues						
ID-078-109 (Respiratory suppression study—COPD) [NCT03646864]	Adults with mild to moderate COPD	Control type: Placebo-controlled Randomization: Two-way crossover Blinding: Double-blind Respiratory biomarkers: AHI and SaO2 during TST, nonREM, REM; Percentage of TST during which SaO2 was <90%, <85%, and <80%. Sleep Biomarkers: TST, nonREM/REM duration, WASO, LPS, SEI PK assessment: C8h Innovative design features: N/A	Drug: Daridorexant, Placebo Dosage: 50 mg. Number treated: 28 subjects received at least 1 dose of daridorexant 26 received at least one dose of placebo Duration (quantity and units): o.d. for 5 days	Primary: Treatment difference (daridorexant – placebo) for SaO2 during TST after multiple dosing Secondary: Treatment difference (daridorexant – placebo) for respiratory- and sleep-related variables after single and multiple dosing	Planned: 28 Actual: 28	5 centers in 1 country (DEU)
ID-078-110 (Respiratory suppression study—OSA) [NCT03765294]	Adults with mild to moderate OSA	Control type: Placebo-controlled Randomization: Two-way crossover Blinding: Double-blind Respiratory biomarkers: AHI and SaO2 during TST, nonREM, REM; Percentage of TST during which SaO2 was <90%, <85%, and <80%. Sleep biomarkers: TST, nonREM/REM duration, WASO, LPS, SEI PK assessment: C8h Innovative design features: N/A	Drug: Daridorexant, Placebo Dosage: 50 mg Number treated: 26 subjects received at least 1 dose of daridorexant 27 received at least one dose of placebo Duration (quantity and units): Once daily for 5 days	Primary: Treatment difference (daridorexant – placebo) for AHI during TST after multiple dosing Secondary: Treatment difference (daridorexant – placebo) for respiratory- and sleep-related variables after single and multiple dosing	Planned: 28 Actual: 28	5 centers in 1 country (DEU)

Trial Identifier [NCT#]	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects, Randomized	Number of Centers and Countries
ID-078-107 (HAP Study) [NCT03657355]	Healthy recreational drug users	Control type: Placebo and active controlled Randomization: Randomized, 6-way crossover Blinding: Double-blind Biomarkers: Reaction time, Rapid visual information processing, Paired Associates Learning PK assessment: C _{max} , t _{max} , AUC, t _{1/2} Innovative design features: N/A	Drug: Daridorexant, Suvorexant, Zolpidem, Placebo Dosage: Daridorexant 50 mg, 100 mg, 150 mg Suvorexant 150 mg Zolpidem 30 mg Number treated: 71 Duration (quantity and units): Single dose, 6-way, crossover	Primary: The Emax of the Drug Liking VAS assessed repeatedly over 24 h postdose. Secondary: Balance of effects, positive effects, negative effects, sedative effects, other effects (drug similarity, any effects), and objective PD effects (reaction time, five choice error score, paired associates learning, and rapid visual information processing)	Planned: 80 Actual: 72	1 (US)
ID-078-108 (Driving study) [NCT03892902]	Healthy middle-aged and elderly subjects	Control type: Placebo and active-controlled Randomization: Randomized, 4-way crossover Blinding: Double-blind Biomarkers: SDLP (derived from the MLP), MLP, mean speed, SD of mean speed, lapses, PK assessment: C8h Innovative design features: N/A	Drug: Daridorexant, Zopiclone, Placebo. Dosage: Daridorexant 50 and 100 mg. Zopiclone 7.5 mg. Number treated: 60 Duration (quantity and units): Daridorexant 50 and 100 mg once daily for 4 days, Zopiclone 7.5 mg on Days 1 and 4 only. Placebo for 4 days.	Primary: Driving performance as measured by the SDLP (difference from placebo, cm) on Days 2 and 5 at 9 h post dose. Other endpoints: Mean lateral position, mean speed, SD of mean speed, number of lapses, subjective driving quality and effort.	Planned: 60 Actual: 60	1 (NED)

Trial Identifier [NCT#]	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects, Randomized	Number of Centers and Countries
ID-078-117 (TQT study) [NCT04250506]	Healthy male and female subjects	Control type: Placebo and active-controlled Randomization: Randomized, 4-way cross-over Blinding: Double-blind (placebo/daridorexant) and open-label (moxifloxacin) Biomarkers: Baseline QTcF, HR, PR, and QRS intervals, Δ QTcF, Δ HR, Δ PR, Δ QRS, $\Delta\Delta$ QTcF, $\Delta\Delta$ HR, $\Delta\Delta$ PR, $\Delta\Delta$ QRS, U-waves, and T-waves PK assessment: C_{max} , t_{max} , AUC, $t_{1/2}$ Innovative design features: N/A	Drug: Daridorexant, Moxifloxacin, Placebo Dosage: Daridorexant 50 and 200 mg Moxifloxacin 400 mg Number treated: 36 Duration (quantity and units): Single dose, 4-way crossover.	Primary: Placebo-corrected change from baseline in the HR-corrected QTcF ($\Delta\Delta$ QTcF). Secondary: - Central tendency analysis of $\Delta\Delta$ QTcF - Change-from-baseline QTcF, HR, PR, and QRS intervals (Δ QTcF, Δ HR, Δ PR, and Δ QRS) - Placebo-corrected Δ HR, Δ PR, and Δ QRS intervals ($\Delta\Delta$ HR, $\Delta\Delta$ PR, and $\Delta\Delta$ QRS) - Categorical analyses for HR, QTcF, PR, and QRS intervals - Treatment-emergent changes in T-wave morphology and U-wave presence.	Planned: 36 Actual: 36	1 (CZE)

Trial Identifier [NCT#]	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects, Randomized	Number of Centers and Countries
ID-078-111 (Alcohol DDI study) [NCT03609775]	Healthy male and female subjects.	Control type: Placebo (both for daridorexant and for alcohol) Randomization: Randomized, 4-way crossover. Blinding: Double-blind. Biomarkers: Saccadic peak velocity, smooth pursuit, adaptive tracking, body sway. PK assessment: C _{max} , t _{max} , AUC, t _{1/2} Innovative design features: alcohol (administered per IVIV) concentration was clamped at a constant blood level of 0.6 g/L for a duration of 5 h.	Drug: Daridorexant, Daridorexant placebo, Alcohol, Alcohol placebo. Dosage: Daridorexant 50 mg, alcohol IV perfusion to a blood concentration of 0.6 g/L Number treated: 22 Duration (quantity and units): Daridorexant 50 mg for 2 days, daridorexant placebo for 2 days, alcohol IV for 2 days, alcohol placebo (IV) for 2 days, i.e., Treatment A: Alcohol IV + daridorexant 50 mg. Treatment B: Alcohol placebo IV + daridorexant 50 mg. Treatment C: Alcohol IV + daridorexant placebo. Treatment D: Alcohol placebo IV + daridorexant placebo.	There were no primary or key secondary endpoints. Objectives: Investigating tolerability, safety, PK, and PD of the coadministration of daridorexant and alcohol.	Planned: 22 Actual: 22	1 (DEU)

Trial Identifier [NCT#]	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects, Randomized	Number of Centers and Countries
AC-078-101 (SAD study) [NCT02919319]	Healthy male subjects	Control type: Placebo controlled Randomization: Randomized SAD trial Blinding: Double-blind Biomarkers: Saccadic peak velocity, body sway, adaptive tracking PK assessment: C _{max} , t _{max} , AUC, t _{1/2} , absolute bioavailability, total body clearance, and V _{ss} , % dose of ¹⁴ C-labeled daridorexant excreted in feces and urine, C _{max} , t _{max} , AUC, t _{1/2} , of radioactivity in whole blood and plasma, protein binding. Innovative design features: Inclusion of a microtracer in the first-in-humans trial to investigate ADME properties of daridorexant	Drug: Daridorexant as the hydrochloride salt, as hard gelatin capsules for oral administration. Daridorexant (b) (4) soft gelatin capsules for oral administration (only at 25 mg) Dosage: 5, 25, 50, 100, 200 mg Number treated: 40 subjects Duration (quantity and units): Single dose (Subjects in the 25-mg dose group were treated twice in two separate treatment periods) Subjects at 50 and 100 mg were dosed with the orally and IV administered microtracer.	There were no primary or key secondary endpoints. Objectives: Investigating tolerability, safety, PK, PD, absolute bioavailability, mass balance, and metabolism following single-dose administration of daridorexant	Planned: 40 Actual: 40	1 (NED)

Trial Identifier [NCT#]	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects, Randomized	Number of Centers and Countries
AC-078-102 (MAD study) [NCT02571855]	Healthy male and female adult and elderly subjects	Control type: Placebo controlled Randomization: Part A: Randomized MAD trial Part B: Randomized SAD trial Part C: Randomized, repeated dose trial Blinding: Double-blind Biomarkers: Saccadic peak velocity, body sway, adaptive tracking. PK assessment: C _{max} , t _{max} , AUC, t _{1/2} Innovative design features: N/A	Drug: Daridorexant Dosage: Part A: 10, 25, and 75 mg Part B: 5, 15, and 25 mg Part C: 25 mg Number treated: 85 Duration (quantity and units): Part A: 10, 25, or 75 mg once daily for 5 days Part B: 1 Day (single dose) Part C: 25 mg once daily for 7 days (4 subjects had an additional 8th day of study drug administration)	There were no primary or key secondary endpoints. Objectives: Investigating tolerability, safety, PK, and PD of daridorexant: Part A: Multiple-ascending doses in healthy young adults after morning administration Part B: Single-ascending doses in healthy elderly subjects after morning administration Part C: Repeated doses in both healthy young adults and elderly subjects after evening administration	Planned: 85 Actual: 85	1 (NED)

Source: 9/1/2021 Applicant response to IR, edited by clinical reviewer

¹ Includes all submitted clinical trials, even if not reviewed in-depth, except for primarily pharmacokinetic studies. Phase 1 studies are included as they are the primary source of information regarding the potential effects of doses exceeding the proposed recommended dose

² If no randomization, then replace with "Actual Enrolled"

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; AHI, apnea-hypopnea index; AUC, area under the concentration-time curve; BEL, Belgium; BGR, Bulgaria; BID, twice daily; CAN, Canada; CHE, Switzerland; C_{max}, maximum plasma concentration; COPD, chronic obstructive pulmonary disease; CZE, Czech Republic; DB, double-blind; DEU, Germany; DNK, Denmark; ECG, electrocardiogram; ESP, Spain; FIN, Finland; FRA, France; HUN, Hungary; IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; ISR, Israel; IV, intravenous; KOR, South Korea; LPS, latency to persistent sleep; LTE, long-term extension study; MC, multicenter; MLP, mean lateral position; N, number of subjects; Netherlands, NED; OL, open-label; OSA, obstructive sleep apnea; PC, placebo-controlled; PD, pharmacodynamic; PG, parallel group; PK, pharmacokinetic; POL, Poland; R, randomized; REM, rapid eye movement; SAD, single-ascending dose; SD, standard deviation; SDLP, standard deviation of the lateral position; SEI, sleep efficiency index; sLSO, subjective latency to sleep onset; sTST, subjective total sleep time; sWASO, subjective wake after sleep onset; SWE, Sweden; t_{max}, time to maximum concentration; TST, total sleep time; US, United States; VAS, visual analog scale; WASO, wake after sleep onset

4. Patient Experience Data

This application is supported by several forms of patient experience data, including self-reported daytime function, Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ), self-reported perceived total sleep time (sTST), and clinician assessment of global illness severity and improvement.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical outcome assessment data submitted in the application		
☒	Patient-reported outcome	IDSIQ: 6.3.2 ; sTST 6.3.1 ; PGI: 6.3.1 , 6.3.2
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☒	Performance outcome	
Driving Study: III.17.2		
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	6.3.2.1
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☒	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	7.2
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☒	Other: Findings from labelled drugs in same class	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Orexin receptor antagonist
Mechanism of action	The mechanism of action of daridorexant in the treatment of insomnia is unknown but thought to be through antagonism of orexin 1 (OX1R) and 2 (OX2R) receptors. The orexin neuropeptide signaling system plays a role in wakefulness. Blocking the binding of wake-promoting neuropeptides, orexin A and orexin B, to receptors OX1R and OX2R is thought to suppress wake drive.
Active moieties	There are no pharmacologically active metabolites. There are three major circulating metabolites: M1, M3, and M10. At steady state, the C_{max} for all circulating metabolites were significantly lower than daridorexant levels.
QT prolongation	Daridorexant does not have any clinically relevant QT prolongation up to a 200-mg dose, which is 4-times the recommended maximum dose of 50 mg. The thorough QT study was a single-center, randomized, double-blind, placebo- and open-label moxifloxacin-controlled 4-way crossover study to evaluate the effect of single therapeutic and supratherapeutic doses of daridorexant (tablet) on the QT/QTc interval duration in healthy male and female subjects. Daridorexant was assessed at two dose levels: 50 mg and 200 mg. The primary endpoint analysis showed that the mean model-predicted $\Delta\Delta QTcF$ and its 90% CI were <10 ms across the entire daridorexant concentration range (up to 3030 ng/mL). At the 50-mg and 200-mg doses, a mean (90% CI) prolongation of $\Delta\Delta QTcF$ of 1.40 ms (0.48-2.32) and 1.84 ms (-0.12 to 3.79), respectively, was determined.
	General Information
Bioanalysis	Daridorexant was quantified in human plasma with a concentration range from 0.5 to 2000 ng/mL using a validated LC-MS/MS method. It was successfully validated with respect to specificity, selectivity, precision, accuracy, stability, storage etc. and was fit-for-purpose.
Healthy subjects versus patients	PK of daridorexant is similar in healthy subjects versus patients with insomnia.
Drug exposure at steady state following the therapeutic dosing regimen (or single dosage, if more relevant for the drug)	Based on population PK, the key PK parameters for daridorexant in patients at steady state were: 50 mg/day (QD) PK parameters represent a typical subject. Dosing interval, $Tau = 24$ hours. $AUC_{tau} = 9981.47$ ng/mL*h $C_{max} = 954.68$ ng/mL $T_{max} = 2.09$ h
Range of effective dosage(s) or exposure	Single ascending dose (SAD, AC-078-101) study up to 200 mg/day in healthy subjects. Multiple ascending dose (MAD, AC-078-102) study up to 75 mg/day for 5 days in healthy subjects.
Maximally tolerated dosage or exposure	Maximum tolerated dose was not determined.
Dosage proportionality	Daridorexant PK was dose-proportional up to 50-mg dose.
Accumulation	There was no accumulation at steady-state.
Time to achieve steady-state	n/a

Characteristic	Drug Information
Bridge between to-be-marketed and clinical trial formulations	The final to-be-marketed formulation was used in the both the pivotal phase 3 studies as well as all the key clinical pharmacology studies.
Absorption	
Bioavailability	Daridorexant has an absolute bioavailability of 62%.
T _{max}	Daridorexant is rapidly absorbed following oral administration and reaches peak plasma concentrations within 1 to 2 hours.
Food effect (fed/fasted) Geometric least square mean and 90% CI	In healthy subjects, a high-fat and high-calorie meal had minor effects on the PK of daridorexant. In fed state, there was ~10% decrease in AUC, ~16% decrease in C _{max} , and the t _{max} of daridorexant was delayed by 1.3 hours. Thus, food had a minimal effect on the absorption and overall exposure of daridorexant. Daridorexant can be administered with or without food, but its sleep-promoting effect could be delayed when administered with or soon after a meal, specifically when a high-fat high-calorie meal is consumed.
Distribution	
Volume of distribution	Daridorexant has a volume of distribution of 31 L.
Plasma protein binding	Daridorexant is extensively bound (99.7%) to plasma proteins.
Drug as substrate of transporters	Daridorexant is not a substrate of any major influx or efflux transporters. Similarly, the three major circulating metabolites (M1, M3 and M10) were also nonsubstrates.
Elimination	
Mass balance results (% excreted via different routes)	The primary route of excretion is via feces (approximately 57%) and urine (approximately 28%). Only traces of daridorexant were found in urine and feces.
Clearance	3.7 to 4.1 L/h
Half-life	The terminal half-life of daridorexant is approximately 8 hours.
Metabolic pathway(s)	Daridorexant undergoes extensive metabolism and is primarily metabolized by CYP3A4 (89%). Other CYP enzymes are not of clinical relevance. All three major human circulating metabolites (M1, M3 and M10) are unlikely to have any pharmacological effect.
Intrinsic Factors and Specific Populations	
Body weight	No clinically significant differences in the PK of daridorexant were detected based on body weight
Age	No clinically significant differences in the PK of daridorexant were detected based on age
Renal impairment	PK parameters of daridorexant were not impacted by renal impairment. Exposure (C _{max} and AUC) was similar in subjects with severe renal impairment compared to healthy subjects.
Hepatic impairment	PK parameters of daridorexant were impacted by hepatic impairment. Though mild hepatic impairment had minimal effect, moderate hepatic impairment led to significant increases in exposure (1.6-fold for AUC and 2.1-fold for T _{1/2}) compared to healthy subjects. The effect of severe hepatic impairment was not assessed.

Characteristic	Drug Information
	Drug Interaction Liability (drug as perpetrator)
Inhibition/induction of metabolism	Daridorexant was a noninhibitor for most cytochrome P450 enzymes. However, it was a weak inhibitor of CYP3A4 with an IC ₅₀ of ~7μM. The circulating metabolites were noninhibitors. Daridorexant and its metabolites elicited a concentration-dependent activation of human Pregnane X receptor (PXR) with EC ₅₀ values ~3μM.
Inhibition/induction of transporter systems	Daridorexant and its metabolites were noninhibitors for most relevant transporters. However, daridorexant was a weak inhibitor of BCRP with IC ₅₀ of ~3μM. Daridorexant and its metabolites were noninducers of all transporters.

Abbreviations: AUC, area under the concentration-time curve; BCRP, breast cancer resistance protein; CI, confidence interval; C_{max}, maximum plasma concentration; PK, pharmacokinetic; PXR, pregnane X receptor; T_{1/2}, terminal half-life; t_{max}, time to maximum concentration

5.1. Nonclinical Assessment of Potential Effectiveness

Daridorexant binds to and inhibits orexin receptors, OX1R and OX2R (K_i =0.47 and 0.93nM, respectively).

In rats and dogs, oral administration of daridorexant at doses up to 300 and 100 mg/kg, respectively, caused dose-dependent decreases in time awake and activities and increases in rapid eye movement (REM) and nonREM sleep time.

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

Dose selection for the phase 3 studies was based on the findings from the phase 2 dose-finding studies, Study 201 and Study 202. Both phase 2 studies were primarily designed to evaluate the dose response of daridorexant in adult and elderly subjects with insomnia, in order to select the doses to be further studied in phase 3. Each of these studies investigated daridorexant doses of 5 mg, 10 mg, 25 mg, and 50 mg, and assessed the acute effects of drug averaged over the first two nights of treatment. Study 201 also assessed subjective effects on perceived latency to sleep onset (sLSO) after four weeks of treatment.

Study 201 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-response phase 2 study conducted in adult subjects (aged 18 to 64 years at screening) with insomnia disorder. The study also included a zolpidem (10 mg) arm as an active reference. The study had a screening phase of 14 to 28 days, including a 7 to 14-day run-in period, during which subjects received single-blind placebo treatment on 2 consecutive polysomnography (PSG) nights, followed by 5 to 12 days at home with no treatment. The double-blind treatment phase had a duration of 29 days and included 3 visits with 2 PSG nights each (Days 1/2, Days 15/16, and Days 28/29). Double-blind study treatment was taken every night during this phase. Subjects were randomized evenly to treatment with daridorexant 5 mg, 10 mg, 25 mg, 50 mg, placebo, or 10 mg zolpidem. The primary efficacy endpoint was the absolute change from baseline to Days 1/2 in wake after sleep onset (WASO). Secondary efficacy endpoints were the change from baseline to Days 1/2 in latency to persistent sleep (LPS), and the change from baseline to Week 4

in subjective wake after sleep onset (sWASO) and sLSO. The dose response on objective (WASO and LPS) and subjective (sWASO and sLSO) sleep parameters were explored at Days 1/2 for WASO and LPS and at Days 28/29 (Week 4) for sWASO and sLSO. The study showed a clear dose-response relationship of daridorexant on WASO as well as LPS. Visual inspection of the predicted dose-response curve did not suggest that the plateau of the effect was reached for WASO and increasing effect size was observed going from 5-mg to 50-mg doses. However, the predicted dose-response curve suggested that a near maximum effect on LPS was reached at the 10-mg dose, with limited additional efficacy obtained on this endpoint when increasing daridorexant doses up to 50 mg.

Study 202 was a multicenter, randomized, double-blind, placebo-controlled, 5-period, 5-treatment crossover dose-response phase 2 study in elderly subjects (aged ≥ 65 years at screening) with insomnia disorder. The study had a screening phase of 14 to 28 days, including a 7- to 14-day run-in period during which subjects received single-blind placebo treatment on two consecutive PSG nights, followed by 5 to 12 days at home with no treatment. The double-blind treatment phase comprised 5 treatment periods, each consisting of 2 consecutive PSG nights on the assigned study treatment. Treatment periods were separated by a 5- to 12-day washout period at home. The last treatment period was followed by a 30-day safety follow-up. Subjects were randomized evenly to 5 different sequences of 5 study treatments (daridorexant 5 mg, 10 mg, 25 mg, 50 mg, or placebo), according to a Latin square design. The primary efficacy endpoint was the absolute change from baseline to Days 1/2 in WASO. The secondary efficacy endpoint was the absolute change from baseline to Days 1/2 in LPS. The dose response on the objective sleep parameters, WASO and LPS, was explored at Days 1/2. Similar to Study 201, Study 202 showed a clear dose-response relationship of daridorexant on WASO as well as LPS, with the same general attributes as in Study 201. Namely, visual inspection of the predicted dose-response curve did not suggest that the plateau of the effect was reached for WASO and increasing effect size was observed going from 5-mg to 50-mg doses. However, the predicted dose-response curve suggested that a near maximum effect on LPS was reached at the 10-mg dose, with limited additional efficacy obtained on this endpoint when increasing daridorexant doses up to 50 mg.

In conclusion, both phase 2 studies in adults and in elderly patients demonstrated a clear dose-response relationship of daridorexant on objective endpoints (WASO and LPS). In both studies, the near maximal effect on sleep induction was observed at 10 mg, but the plateau of the effect on sleep maintenance did not appear to be achieved within the range of doses studied. These data supported the selection of the dose range of 10 to 50 mg for the subsequent phase 3 studies.

6.2. Clinical Trials Intended to Demonstrate Efficacy

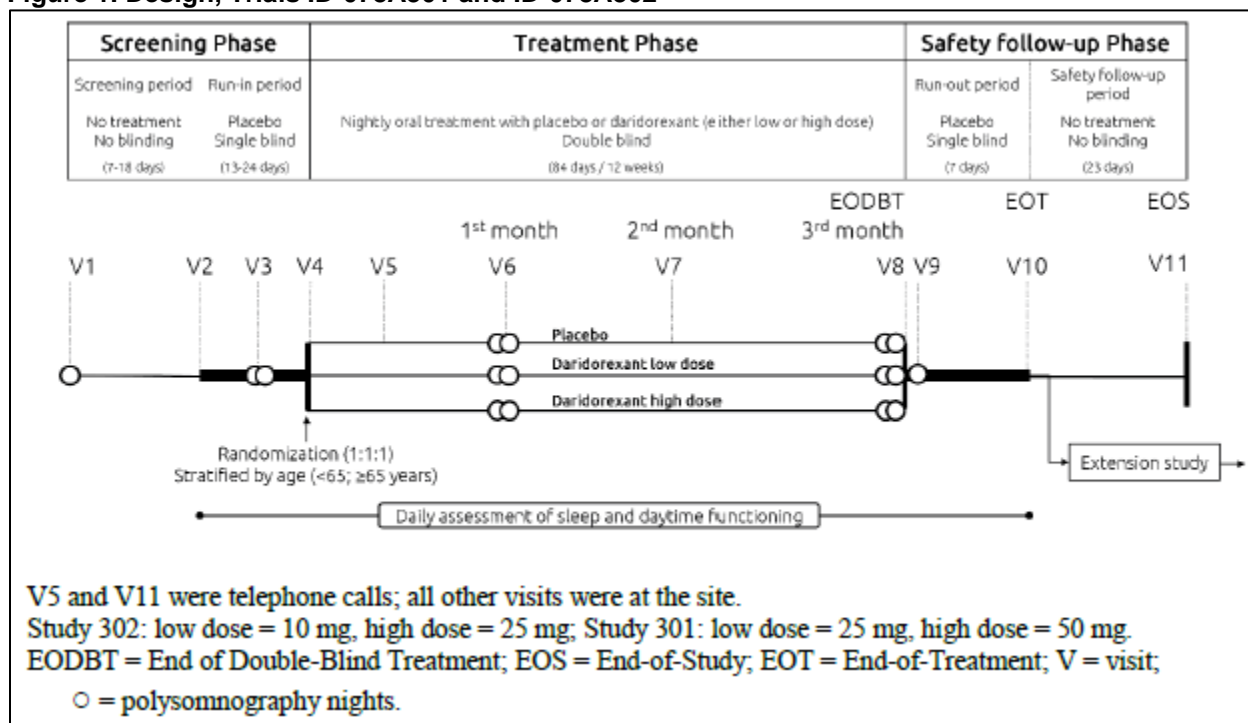
Because the two registration trials were essentially identical in design and conduct, with the exception of the doses studied, the trial design and population characteristics will be discussed jointly for both trials. The efficacy findings will then be discussed for each trial separately.

6.2.1. Description of Trial ID-078A301 and ID-078A302

6.2.1.1. Design

Trials ID-078A301 and ID-078A302 were identically designed multicenter, international, fixed dose, 1:1:1 randomized studies conducted in parallel at nonoverlapping investigational sites. In Trial ID-078A301 25-mg and 50-mg doses were compared to placebo, whereas in Trial ID-078A302, 10-mg and 25-mg doses were compared to placebo. The key features of the common study design are summarized in the Applicant's study design schematic below (Figure 1).

Figure 1. Design, Trials ID-078A301 and ID-078A302



Source: Applicant generated figure. 2.5 Clinical Overview. Doc No D-20.243 p.36

The primary endpoints were defined using change in the PSG variables of interest (LPS and WASO) from baseline (defined as the V3 2-night PSG mean value) to Month 1 (defined as the V6 2-night PSG mean value) and from baseline to Month 3 (defined as the V8 2-night PSG mean value).

6.2.1.2. Eligibility Criteria

Study participants were adults aged 18 to <65 and older adults aged ≥65 years meeting DSM-5 criteria for insomnia disorder.

- Meeting the sleep disturbance criteria for the diagnosis was assessed by self-reported history of ≥30 min to fall asleep, wake time during sleep-period ≥30 min, and of subjective total sleep time (sTST) ≤6.5 h during the night. Those three self-reported parameters were required to be present on at least three nights per week for at least three months prior to the screening visit and on the sleep diary sleep data collected during the

period between Visit 2 and Visit 3. Subjectively reported sleep disturbance at screening Visit 1 was corroborated by PSG over two nights at screening Visit 3 for which all of the following three thresholds had to be met:

- Mean LPS ≥ 20 min (with none of the two nights < 15 min)
- Mean WASO ≥ 30 min (with none of the two nights < 20 min)
- Mean TST < 420 min (i.e., < 7 hours)
- Meeting the distress or impairment criterion was corroborated by requiring that the self-reported insomnia severity index score be ≥ 15 at screening Visit 1.
- Meeting the insomnia disorder diagnostic criterion excluding sleep disturbance attributable to another disorder or condition was supported by the following study exclusion criteria:
 - Periodic limb movement disorder with arousal index ≥ 15 /h (assessed on the 1st screening PSG night between Visit 1 and 2), restless legs syndrome, circadian rhythm disorder, REM behavior disorder, or narcolepsy.
 - Self-reported usual daytime napping ≥ 1 hour per day, and ≥ 3 days per week.
 - Acute or unstable psychiatric conditions (including but not restricted to anxiety disorder, major depression, bipolar disorder, schizophrenia, obsessive compulsive disorder, or depression) that are diagnosed by the Mini International Neuropsychiatric Interview[®] or that require pharmacological treatment for these disorders.
 - Mini Mental State Examination[®] score < 25 in subjects ≥ 50 years.
 - Shift work within 2 weeks prior to the screening visit, or planned shift work during the study.
 - Travel across ≥ 3 time zones within 2 weeks prior to the screening visit, or planned travel across ≥ 3 time zones during study.
 - Unstable medical condition, significant medical disorder or acute illness, electrocardiogram (ECG), hematology or biochemistry test results within 1 month prior to the screening visit, which, in the opinion of the investigator, could affect the subject's safety or interfere with the study assessments.
 - Diagnosis of alcohol or substance use disorder within 2 years prior to the screening visit or inability to refrain from drinking alcohol for at least 3 consecutive days
 - Heavy tobacco use (at least one pack of cigarettes a day or inability to refrain from smoking during the night).
 - Caffeine consumption ≥ 600 mg per day or any caffeine consumption after 4 pm.

Other inclusion and exclusion criteria pertained to ensuring feasibility of subject participation, safety (e.g., exclusion of subjects with moderate to severe sleep apnea), and exclusion of confounding factors (e.g., treatment with moderate or strong CYP3A4 inhibitors or inducers, or stimulant or sedating medications).

***Clinical Reviewer Comment:** Sleep disturbance characterized by high sleep latency and/or wake after sleep onset represents the core feature of insomnia disorder and is, in and of itself, distressing to patients. Thus, the rigorous ascertainment of sleep impairment in the study design is a laudable feature of the study, and the selection of LPS and WASO as primary endpoints for the determination of efficacy is appropriate. The assessment of the primary endpoints following 1 and 3 months of treatment is also appropriate because insomnia disorder and its pharmacological treatment in clinical settings are typically*

chronic. It is therefore important that the efficacy of a drug for this indication not be found to wane with continued use.

Notably the same level of rigor was not applied to the assessment on severity of daytime impairment as was applied to the assessment of sleep impairment. Thus, these study design features may produce a study population that may be considered relatively enriched for symptoms of sleep impairment compared to symptoms of impairment in daytime function.

6.2.1.3. Statistical Analysis Plan

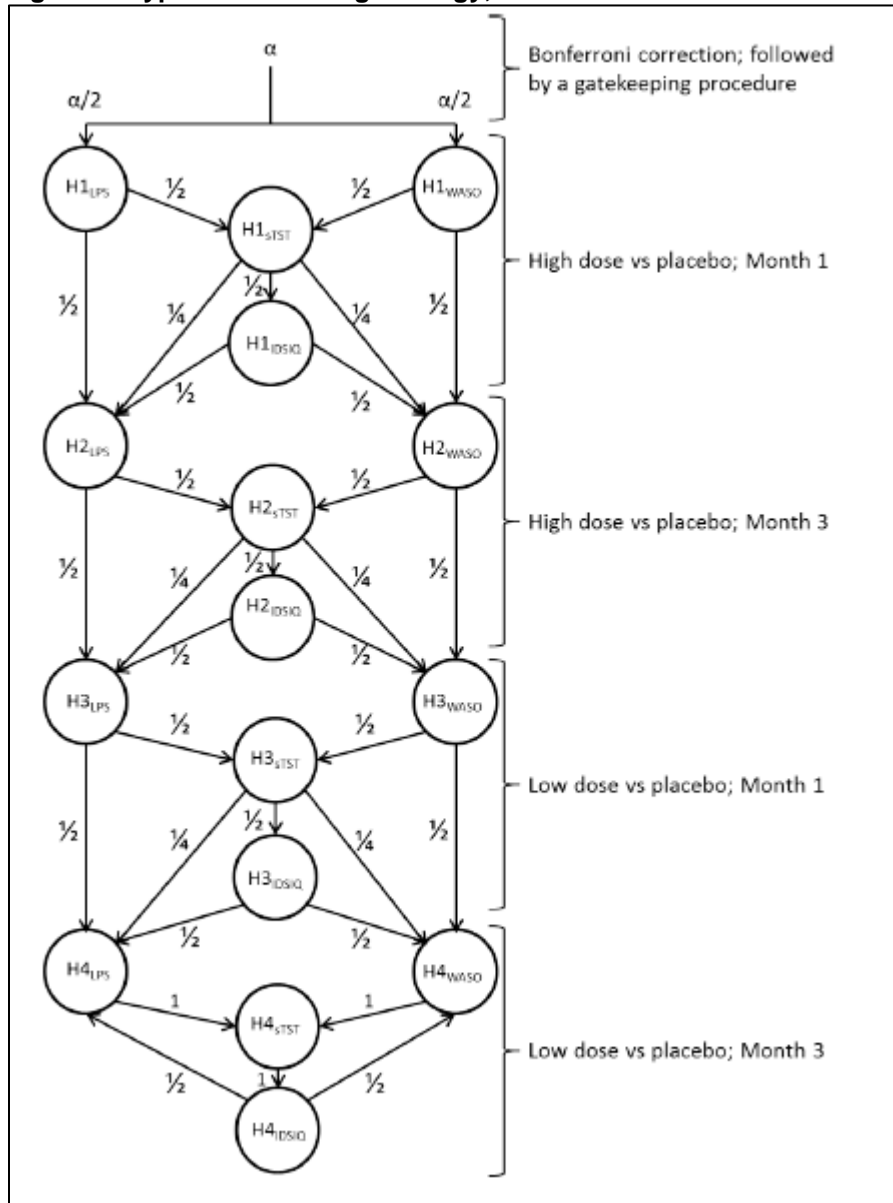
The Applicant proposed to test eight primary and eight secondary endpoints in both Trial ID-078A301 and ID-078A302. The primary endpoints consisted of WASO and LPS at both the high dose (50 mg in Trial ID-078A301 and 25 mg in Trial ID-078A302) and the low dose (25 mg in Trial ID-078A301 and 10 mg in Trial ID-078A302) at Month 1 and Month 3. The secondary endpoints are the subjective endpoints of sTST and IDSIQ sleep score at the same doses and time points as the primary endpoints. The Applicant controlled Type I error rate over these 16 endpoints using a combination of Bonferroni and a graphical method, see [Figure 2](#). The eight statistical null hypotheses associated with the primary efficacy endpoints are:

- Sleep maintenance:
 - H1 WASO: Higher Dose – Placebo =0 for WASO at Month 1
 - H2 WASO: Higher Dose – Placebo =0 for WASO at Month 3
 - H3 WASO: Lower Dose – Placebo =0 for WASO at Month 1
 - H4 WASO: Lower Dose – Placebo =0 for WASO at Month 3
- Sleep onset:
 - H1 LPS: Higher Dose – Placebo =0 for LPS at Month 1
 - H2 LPS: Higher Dose – Placebo =0 for LPS at Month 3
 - H3 LPS: Lower Dose – Placebo =0 for LPS at Month 1
 - H4 LPS: Lower Dose – Placebo =0 for LPS at Month 3

The eight statistical null hypotheses associated with the secondary efficacy endpoints are:

- Sleep quantity:
 - H1 sTST: Higher Dose – Placebo =0 for sTST at Month 1
 - H2 sTST: Higher Dose – Placebo =0 for sTST at Month 3
 - H3 sTST: Lower Dose – Placebo =0 for sTST at Month 1
 - H4 sTST: Lower Dose – Placebo =0 for sTST at Month 3
- Next day performance:
 - H1 IDSIQ: Higher Dose – Placebo =0 for IDSIQ sleepiness domain score at Month 1
 - H2 IDSIQ: Higher Dose – Placebo =0 for IDSIQ sleepiness domain score at Month 3
 - H3 IDSIQ: Lower Dose – Placebo =0 for IDSIQ sleepiness domain score at Month 1
 - H4 IDSIQ: Lower Dose – Placebo =0 for IDSIQ sleepiness domain score at Month 3

Figure 2. Hypothesis Testing Strategy, Trials ID-078A301 and ID-078A302



Source: Applicant's Protocol

Statistical Reviewer Comment: The Applicant's proposed multiple comparison procedure is acceptable to control type I error.

The main analysis was performed using the full analysis set. A longitudinal data analysis method (i.e., linear mixed effects model) was used for the analysis of change from baseline in WASO, LPS, sTST, and IDSIQ scores, separately. All available data, regardless of occurrence of intercurrent events (e.g., study treatment discontinuation, the use of prohibited medication), was included in the model. The analysis model adjusted for the baseline value of the relevant response variable (either WASO, LPS, sTST or IDSIQ sleepiness domain score), age group (<65; ≥65 years), treatment (higher dose; lower dose; placebo), time point (Month 1; Month 3), and the interaction of treatment by time point and baseline by time point. To evaluate the efficacy hypotheses, appropriate

contrasts were used to test the treatment differences of interest (i.e., the difference in least squares mean change from baseline between higher dose daridorexant versus placebo and lower dose daridorexant versus placebo at Month 1 and Month 3). An unstructured covariance matrix was used to model the correlation among repeated measurements. This approach relies on the missing at random (MAR) assumption. The Applicant conducted two sensitivity analyses to explore violations of the MAR assumptions:

Jump-to-reference: a multiple imputation sensitivity analysis in which patients who discontinue study treatment are assumed to have the same mean trajectory as patients who complete the study in the placebo arm.

Tipping point analysis: multiple imputation analyses are conducted in which patients who drop out are assumed to follow a trajectory similar to the completers but with a fixed shift in the mean trajectory ($\mu_{\text{completers}} + \Delta$). The Applicant explored shift parameters from 0 to 60 minutes.

Clinical Reviewer Comment: *From a clinical perspective the population-level summary comparing differences in mean score appears acceptable.*

From a clinical perspective, a treatment policy approach to discontinuation of study medication appropriately targets an estimate of the expected treatment effect for the general population of patients with insomnia disorder. Similarly, a treatment policy approach to sporadic use of potentially sedating prohibited medications is appropriate as this is likely to reflect behavior in the target population, and medications with sedating properties may also be used for purposes other than sleep improvement (e.g., pain relief). Likewise, a treatment policy approach to use of prohibited medications with stimulant properties is appropriate as this is likely to reflect behavior in the target population and there is no evidence that acute or chronic use of such medications would treat insomnia. Thus, the primary estimand is generally acceptable and should tend to provide an estimate of treatment effects that more closely resembles the expected effects of treatment for patients with insomnia disorder under real-world clinical conditions than estimands treating these intercurrent events with hypothetical strategies.

With respect to the impact of this approach on the estimate of treatment effect relative to an estimate of an idealized treatment effect (i.e., the effect of treatment expected were no intercurrent events [ICEs] to occur), we can also expect that impact to be small. From a clinical perspective it is reasonable to assume, based on the phase 2 data and the pharmacology of the drug, that daridorexant will not worsen insomnia symptoms compared to placebo. Thus, ICEs pertaining to the use of prohibited medications liable to have sedative or sleep promoting properties would be expected to occur with equal or greater frequency in the placebo arm. Disregarding the use of such medications would therefore lead to a potentially more conservative estimate of drug effects.

ICEs pertaining to the use of stimulant medications, which could worsen sleep, particularly LPS, but improve next day function symptoms, might be attributable to the following causes:

- a) *Daytime function impairments attributable to insomnia*

- b) *Daytime function impairments attributable to exaggerated pharmacology of the investigational product*
- c) *Reasons unrelated to insomnia or its treatment*

Thus, if the investigational product is effective compared to placebo cause (a) would tend to increase estimates of efficacy in favor of drug while cause (b) would tend to counter this impact, although likely to a lesser degree, and cause (c) would not be expected to produce a biasing effect.

Taken together, ICEs pertaining to use of sedative and stimulant prohibited medications, may therefore be expected to tend towards mutually negating impacts on the estimate of treatment effects.

In the case of an ICE of treatment discontinuation the treatment policy approach will tend to deflate the estimate of treatment effect compared to the idealized effect in proportion to the rate of discontinuation when rates are balanced between arms. This is because insomnia disorder tends to be chronic and not episodic, and discontinuation of chronic sedative hypnotic treatment may be associated with worsening or rebound insomnia (see related discussion in Section 7.7.4.1.3). If there were an imbalance in such events the deflation of the ideal effect would be increased or decreased in accordance with the direction of the imbalance. However, this will only hold if the estimator, in the case that treatment discontinuation is followed by study withdrawal, is in fact aligned with the treatment policy estimand.

Statistical Reviewer Comments: *Regarding the Applicant's treatment policy estimand and mixed model for repeated measures (MMRM) estimation model, estimates from the MMRM model will answer the clinical question under the treatment policy estimand if the intercurrent event does not lead to study discontinuation. In the case that an intercurrent event leads to study discontinuation and therefore missing data, MMRM estimates will estimate the treatment policy when it is reasonable to assume that treatment discontinuation does not change the expected symptoms. After discussion with the clinical team, this assumption is unlikely to be met (patients suffer mean worsening of PSG measures of insomnia that exceed in magnitude the mean treatment effects (see Section 7.7.4.1.3); therefore, MMRM estimates may not estimate the treatment policy estimand when many patients discontinue treatment.*

The proposed sensitivity analyses were reasonable to explore deviations from MAR because patients are expected to worsen after treatment discontinuation.

The Applicant's proposed MMRM analysis assumes that LPS, Δ LPS, WASO, and Δ WASO are normally distributed. There is a priori evidence that WASO, LPS, and Δ LPS distributions are not normally distributed (Ratti et al. 2013; Murphy et al. 2017). Because LPS and WASO can only take on positive values, they are unlikely to be normally distributed. In this situation, the treatment effect standard errors may be inflated, yielding a decrease in statistical power. In some situations, this could cause a type II error. In addition, most statistical tests using the estimates resulting from an MMRM model with a mis-specified error distribution may be conservative (i.e., the observed type I error may be smaller than its nominal level [e.g., 3% instead of 5%]).

6.2.2. Results of Analyses, Trials ID-078A301 and ID-078A302

Trials ID-078A301 and ID-078A302 were both adequate and well-controlled trials, each contributing to substantial evidence of effectiveness for daridorexant as a treatment for insomnia disorder. Further, each supported durability of efficacy over a 3-month treatment period.

Limitations of study adequacy are discussed in Section [6.2.2.1](#) and primary findings in Sections [6.2.2.2](#) and [6.2.2.3](#). Supportive analyses evaluating dose-response across these trials and patient factors potentially influencing efficacy are discussed in Sections [6.2.2.4](#) and [6.2.2.5](#), respectively. Interpretations, including evaluations of the clinical meaningfulness and implications, of the efficacy findings are discussed in Section [6.3](#).

6.2.2.1. Baseline Study Population Characteristics, Trials ID-078A301 and ID-078A302

Both registration trials were balanced between arms and mutually similar in terms of participants' baseline demographic and clinical characteristics and predominant study countries. Approximately 2/3 of the sample was female, approximately 3/5 were adults <65 years of age, 80 to 90% were white and non-Hispanic, 1/2 of subjects were in Germany and 1/3 in the US. The greater proportion of female than male participants reflects a similarly greater prevalence of insomnia among women (Zhang and Wing 2006). Nonwhite and Hispanic or Latino patients were underrepresented, however (Bureau 2019). Most subjects had at least one ongoing medical condition at baseline, and between 1 in 6 to 1 in 5 were obese. In sum, the study population adequately included male and female patients, elderly patients, patients with medical comorbidities, and patients residing in the US. Rates of concomitant psychiatric and historical psychiatric disorders were low, and very few subjects had a resolved history of substance use disorder other than nicotine (see [Table 6](#), [Table 7](#), and [Table 8](#), and Section [16.1](#)).

***Clinical Reviewer Comment:** Patients with characteristics underrepresented in the registration trials compared to the general US population also represent a disproportionate segment of the target treatment population. Increased risk for chronic insomnia among US racial/ethnic minority patients appears likely to be driven by associated psychosocial factors (Singareddy et al. 2012; Kaufmann et al. 2016),. Sequelae of such factors (e.g., chronic stress and its biological effects) have complex implications for the orexin system and interactions with mental health. For example, although orexin receptor antagonism produces an antidepressant-like effect in certain chronic stress paradigms in animals, it increases anxiety-like behaviors in others (Sargin 2019). Thus, safety (particularly rates of psychiatric AEs) or efficacy may differ to some extent from what was observed in the studied population. See Section [6.2.2.5](#).*

Table 6. Baseline Demographic Characteristics, Randomized Population, Trials ID-078A301 and ID-078A302

Demographic Characteristic	ID-078A301				ID-078A302			
	Daridorexant 25 mg N=310	Daridorexant 50 mg N=310	Placebo N=310	Total N=930	Daridorexant 10 mg N=307	Daridorexant 25 mg N=309	Placebo N=308	Total N=924
Sex, n (%)								
f	215 (69)	199 (64)	210 (68)	624 (67)	215 (70)	218 (71)	205 (67)	638 (69)
m	95 (31)	111 (36)	100 (32)	306 (33)	92 (30)	91 (29)	103 (33)	286 (31)
Age, years								
Mean (SD)	55.8 (15.3)	55.5 (15.3)	55.1 (15.4)	55.4 (15.3)	57.1 (14.0)	56.3 (14.4)	56.7 (14.1)	56.7 (14.2)
Median	59.0	58.0	58.0	59.0	59.0	59.0	58.5	59.0
Min, Max	18, 88	21, 86	19, 83	18, 88	19, 84	22, 84	20, 85	19, 85
25th percentile	46.0	44.0	44.2	45.0	48.0	46.0	47.0	47.0
75th percentile	67.8	67.8	68.0	68.0	68.0	68.0	68.0	68.0
Age Categories, n (%)								
18 - <65 Years	189 (61)	189 (61)	188 (61)	566 (61)	186 (61)	188 (61)	187 (61)	561 (61)
65 - <75 Years	103 (33)	102 (33)	105 (34)	310 (33)	99 (32)	110 (36)	98 (32)	307 (33)
75 - <85 Years	16 (5)	18 (6)	17 (5)	51 (5)	22 (7)	11 (4)	22 (7)	55 (6)
≥ 85 Years	2 (1)	1 (0)	0 (0)	3 (0)	0 (0)	0 (0)	1 (0)	1 (0)
Ethnicity, n(%)								
Hispanic or Latino	51 (16)	44 (14)	51 (16)	146 (16)	17 (6)	14 (5)	16 (5)	47 (5)
Not Hispanic or Latino	259 (84)	265 (85)	259 (84)	783 (84)	288 (94)	295 (95)	290 (94)	873 (94)
Not Reported	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	1 (0)	2 (0)
Unknown	0 (0)	1 (0)	0 (0)	1 (0)	1 (0)	0 (0)	1 (0)	2 (0)
Race, n (%)								
American Indian or Alaska Native	0 (0)	1 (0)	0 (0)	1 (0)	2 (1)	0 (0)	0 (0)	2 (0)
Asian	3 (1)	4 (1)	2 (1)	9 (1)	14 (5)	11 (4)	10 (3)	35 (4)
Black or African American	19 (6)	30 (10)	28 (9)	77 (8)	16 (5)	26 (8)	29 (9)	71 (8)
Native Hawaiian or Other Pacific Islander	1 (0)	1 (0)	0 (0)	2 (0)	0 (0)	1 (0)	1 (0)	2 (0)
Not Reported	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	1 (0)	2 (0)
Other	0 (0)	0 (0)	2 (1)	2 (0)	1 (0)	0 (0)	0 (0)	1 (0)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
White	287 (93)	274 (88)	278 (90)	839 (90)	273 (89)	271 (88)	267 (87)	811 (88)

505(b)1 NME NDA 214985
 Daridorexant (Quviviq) for Insomnia

Demographic Characteristic	ID-078A301				ID-078A302			
	Daridorexant 25 mg N=310	Daridorexant 50 mg N=310	Placebo N=310	Total N=930	Daridorexant 10 mg N=307	Daridorexant 25 mg N=309	Placebo N=308	Total N=924
Country, n (%)								
AUS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BEL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	1 (0)
BGR	0 (0)	0 (0)	0 (0)	0 (0)	16 (5)	21 (7)	26 (8)	63 (7)
CAN	6 (2)	6 (2)	1 (0)	13 (1)	11 (4)	12 (4)	11 (4)	34 (4)
CHE	2 (1)	3 (1)	0 (0)	5 (1)	0 (0)	0 (0)	0 (0)	0 (0)
CZE	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	2 (1)	3 (0)
DEU	150 (48)	147 (47)	147 (47)	444 (48)	159 (52)	145 (47)	132 (43)	436 (47)
DNK	21 (7)	20 (6)	22 (7)	63 (7)	0 (0)	0 (0)	0 (0)	0 (0)
ESP	27 (9)	34 (11)	30 (10)	91 (10)	0 (0)	0 (0)	0 (0)	0 (0)
FIN	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	5 (2)	2 (1)	10 (1)
FRA	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	1 (0)	2 (0)
HUN	0 (0)	0 (0)	0 (0)	0 (0)	10 (3)	9 (3)	15 (5)	34 (4)
ITA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
KOR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (1)	2 (1)	6 (1)
POL	5 (2)	3 (1)	6 (2)	14 (2)	0 (0)	0 (0)	0 (0)	0 (0)
SRB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SWE	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	4 (1)	3 (1)	10 (1)
US	99 (32)	97 (31)	104 (34)	300 (32)	103 (34)	108 (35)	114 (37)	325 (35)

Source: Statistical Reviewer Analysis; adsl.xpt.

Abbreviations: AUS, Australia; BEL, Belgium; BGR, Bulgaria; CAN, Canada; CHE, Switzerland; CZE, Czech Republic; DEU, Germany; DNK, Denmark; ESP, Spain; FIN, Finland; FRA, France; HUN, Hungary; ITA, Italy; KOR, South Korea; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation; POL, Poland; SRB, Serbia; SWE, Sweden; US, United States

Table 7. Baseline Ongoing Medical Conditions by System Organ Class (SOC) and BMI, Trials ID-078A301 and ID-078A302, Safety Population

System Organ Class	ID-078A301			ID-078A302			Pooled	
	Daridorexant 25 mg N=310	Daridorexant 50 mg N=308	PBO N=309	Daridorexant 10 mg N=306	Daridorexant 25 mg N=308	PBO N=306	Daridorexant 25 mg N=618	Pooled PBO N=615
Subjects with at least one event	229 (73.9)	208 (67.5)	207 (67.0)	222 (72.5)	231 (75.0)	221 (72.2)	460 (74.4)	428 (69.6)
Blood and lymphatic system disorders	5 (1.6)	5 (1.6)	4 (1.3)	6 (2.0)	6 (1.9)	2 (0.7)	11 (1.8)	6 (1.0)
Cardiac disorders	23 (7.4)	11 (3.6)	26 (8.4)	20 (6.5)	20 (6.5)	20 (6.5)	43 (7.0)	46 (7.5)
Congenital, familial, and genetic disorders	7 (2.3)	1 (0.3)	4 (1.3)	4 (1.3)	6 (1.9)	3 (1.0)	13 (2.1)	7 (1.1)
Ear and labyrinth disorders	12 (3.9)	10 (3.2)	4 (1.3)	17 (5.6)	13 (4.2)	16 (5.2)	25 (4.0)	20 (3.3)
Endocrine disorders	33 (10.6)	25 (8.1)	29 (9.4)	35 (11.4)	40 (13.0)	43 (14.1)	73 (11.8)	72 (11.7)
Eye disorders	31 (10.0)	25 (8.1)	25 (8.1)	23 (7.5)	18 (5.8)	22 (7.2)	49 (7.9)	47 (7.6)
Gastrointestinal disorders	39 (12.6)	30 (9.7)	25 (8.1)	44 (14.4)	42 (13.6)	34 (11.1)	81 (13.1)	59 (9.6)
General disorders and administration site conditions	6 (1.9)	6 (1.9)	4 (1.3)	5 (1.6)	3 (1.0)	6 (2.0)	9 (1.5)	10 (1.6)
Hepatobiliary disorders	3 (1.0)	1 (0.3)	1 (0.3)	2 (0.7)	7 (2.3)	2 (0.7)	10 (1.6)	3 (0.5)
Immune system disorders	46 (14.8)	40 (13.0)	38 (12.3)	54 (17.6)	54 (17.5)	58 (19.0)	100 (16.2)	96 (15.6)
Infections and infestations	10 (3.2)	5 (1.6)	10 (3.2)	9 (2.9)	9 (2.9)	11 (3.6)	19 (3.1)	21 (3.4)
Injury, poisoning and procedural complications	3 (1.0)	4 (1.3)	4 (1.3)	5 (1.6)	3 (1.0)	3 (1.0)	6 (1.0)	7 (1.1)
Investigations	13 (4.2)	4 (1.3)	10 (3.2)	13 (4.2)	12 (3.9)	11 (3.6)	25 (4.0)	21 (3.4)
Metabolism and nutrition disorders	81 (26.1)	76 (24.7)	76 (24.6)	71 (23.2)	70 (22.7)	70 (22.9)	151 (24.4)	146 (23.7)
Musculoskeletal and connective tissue disorders	71 (22.9)	55 (17.9)	71 (23.0)	79 (25.8)	86 (27.9)	73 (23.9)	157 (25.4)	144 (23.4)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	5 (1.6)	2 (0.6)	2 (0.6)	8 (2.6)	6 (1.9)	2 (0.7)	11 (1.8)	4 (0.7)
Nervous system disorders	36 (11.6)	41 (13.3)	44 (14.2)	56 (18.3)	63 (20.5)	58 (19.0)	99 (16.0)	102 (16.6)
Product issues	0	0	0	0	0	1 (0.3)	0	1 (0.2)
Psychiatric disorders	17 (5.5)	14 (4.5)	12 (3.9)	10 (3.3)	7 (2.3)	6 (2.0)	24 (3.9)	18 (2.9)
Renal and urinary disorders	11 (3.5)	8 (2.6)	2 (0.6)	13 (4.2)	10 (3.2)	14 (4.6)	21 (3.4)	16 (2.6)
Reproductive system and breast disorders	6 (1.9)	17 (5.5)	12 (3.9)	14 (4.6)	11 (3.6)	9 (2.9)	17 (2.8)	21 (3.4)
Respiratory, thoracic, and mediastinal disorders	13 (4.2)	25 (8.1)	16 (5.2)	16 (5.2)	16 (5.2)	24 (7.8)	29 (4.7)	40 (6.5)
Skin and subcutaneous tissue disorders	12 (3.9)	9 (2.9)	16 (5.2)	16 (5.2)	19 (6.2)	19 (6.2)	31 (5.0)	35 (5.7)

System Organ Class	ID-078A301			ID-078A302			Pooled	
	Daridorexant 25 mg N=310	Daridorexant 50 mg N=308	PBO N=309	Daridorexant 10 mg N=306	Daridorexant 25 mg N=308	PBO N=306	Daridorexant 25 mg N=618	Pooled PBO N=615
Social circumstances	2 (0.6)	4 (1.3)	4 (1.3)	5 (1.6)	5 (1.6)	8 (2.6)	7 (1.1)	12 (2.0)
Surgical and medical procedures	0	2 (0.6)	1 (0.3)	4 (1.3)	4 (1.3)	2 (0.7)	4 (0.6)	3 (0.5)
Vascular disorders	79 (25.5)	70 (22.7)	73 (23.6)	96 (31.4)	82 (26.6)	107 (35.0)	161 (26.1)	180 (29.3)
BMI (kg/m ²)								
N	310	308	309	306	308	306	618	615
Mean (SD)	26.6 (4.4)	26.3 (4.3)	26.4 (4.1)	26.0 (4.3)	26.1 (4.2)	26.2 (4.3)	26.4 (4.3)	26.3 (4.2)
BMI category (kg/m ²)								
<18.5	0	0	0	1 (0.3)	1 (0.3)	0	1 (0.2)	0
18.5 - <25	122 (39.4)	126 (40.9)	117 (37.9)	145 (47.4)	133 (43.2)	135 (44.1)	255 (41.3)	252 (41.0)
25 - <30	125 (40.3)	127 (41.2)	135 (43.7)	114 (37.3)	120 (39.0)	117 (38.2)	245 (39.6)	252 (41.0)
≥30	63 (20.3)	55 (17.9)	57 (18.4)	46 (15.0)	54 (17.5)	54 (17.6)	117 (18.9)	111 (18.0)

Source: CDS generated table. admh.xpt, adsl.xpt; Software: SAS

Abbreviations: BMI, body mass index; N, number of subjects in treatment arm; n, number of subjects with at least one event; PBO, placebo

Table 8. Baseline Patient Insomnia Characteristics, Trials ID-078A301 and ID-078A302, ITT Population

Insomnia Characteristic	ID-078A301				ID-078A302			
	Daridorexant 25 mg N=310	Daridorexant 50 mg N=309	Placebo N=309	Total N=928	Daridorexant 10 mg N=306	Daridorexant 25 mg N=309	Placebo N=308	Total N=923
LPS, min								
Mean (SD)	67.3 (38.6)	63.6 (37.4)	66.5 (39.8)	65.8 (38.6)	67.4 (41.7)	68.9 (40.5)	71.8 (46.1)	69.4 (42.8)
Median	57.0	54.2	58.2	56.5	55.5	56.0	58.5	56.0
Min, max	22, 258	14, 296	20, 242	14, 296	20, 268	20, 217	5, 256	5, 268
25th percentile	38.8	37.8	40.2	39.0	37.8	40.8	40.9	39.6
75th percentile	88.4	77.8	77.5	80.8	83.4	85.2	88.7	85.6
WASO, min								
Mean (SD)	97.9 (38.8)	95.5 (37.8)	102.5 (40.8)	98.6 (39.2)	104.6 (46.2)	106.0 (49.1)	108.1 (48.7)	106.2 (48.0)
Median	93.5	90.8	97.2	94.0	96.9	97.2	103.1	99.0
Min, max	30, 217	30, 255	33, 292	30, 292	30, 266	30, 338	24, 352	24, 352
25th percentile	68.1	67.8	74.0	69.2	72.8	71.0	72.2	72.0
75th percentile	122.0	117.8	125.5	121.3	130.6	131.2	131.8	131.4

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 Daridorexant (Quviviq) for Insomnia

Insomnia Characteristic	ID-078A301				ID-078A302			
	Daridorexant 25 mg N=310	Daridorexant 50 mg N=309	Placebo N=309	Total N=928	Daridorexant 10 mg N=306	Daridorexant 25 mg N=309	Placebo N=308	Total N=923
sTST, min								
N	310	309	309	928	306	309	308	923
Mean (SD)	309.8 (60.1)	313.2 (57.6)	315.9 (53.1)	313.0 (57.0)	308.4 (51.4)	308.5 (52.8)	307.6 (51.5)	308.2 (51.9)
Median	317.5	322.9	324.2	321.4	315.7	313.6	310.7	312.9
Min, max	111, 431	77, 424	146, 413	77, 431	106, 411	77, 436	107, 423	77, 436
Missing	0	0	1	1	0	0	0	0
25th percentile	275.1	280.0	285.0	280.0	275.2	278.6	277.1	278.2
75th percentile	358.2	355.0	355.0	355.7	347.1	347.4	344.3	347.1
IDSIQ sleep subscale total								
N	308	309	308	925	305	308	307	920
Mean (SD)	22.1 (6.9)	22.5 (7.2)	22.3 (6.9)	22.3 (7.0)	22.7 (6.3)	22.2 (6.2)	22.6 (5.8)	22.5 (6.1)
Median	22.1	21.9	21.5	21.9	22.3	22.1	22.1	22.3
Min, max	1, 40	1, 40	0, 40	0, 40	1, 38	2, 37	6, 39	1, 39
Missing	2	0	2	4	1	1	1	3
25th percentile	18.6	18.0	18.0	18.1	19.0	18.4	19.1	18.9
75th percentile	25.8	27.4	26.6	26.7	26.1	26.2	25.9	26.0
PGI-S								
N	236	238	241	715	239	241	245	725
Mean (SD)	3.3 (0.7)	3.3 (0.6)	3.3 (0.7)	3.3 (0.7)	3.3 (0.6)	3.3 (0.6)	3.3 (0.6)	3.3 (0.6)
Median	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Min, max	1, 4	1, 4	1, 4	1, 4	1, 4	1, 4	1, 4	1, 4
Missing	74	71	69	214	67	68	63	198
25th percentile	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
75th percentile	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
ISI Total Score								
N	300	298	299	897	298	302	297	897
Mean (SD)	19.0 (4.4)	19.2 (4.0)	19.1 (4.0)	19.1 (4.1)	19.9 (3.8)	19.5 (4.0)	19.5 (4.1)	19.6 (4.0)
Median	19.0	19.0	19.0	19.0	20.0	20.0	19.0	20.0
Min, max	2, 28	7, 28	6, 28	2, 28	5, 28	5, 28	9, 28	5, 28
Missing	0	1	1	2	0	1	2	3
25th percentile	16.0	17.0	16.0	16.0	17.0	17.0	17.0	17.0
75th percentile	22.0	22.0	22.0	22.0	23.0	22.0	22.0	22.0

Source: Statistical Reviewer Analysis; adsl.xpt

Abbreviations: IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; ISI, Insomnia Severity Index; LPS, latency to persistent sleep; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; PGI-S, Patient Global Impression of Severity Score (Night-time); SD, standard deviation; sTST, subjective total sleep time; WASO, wake after sleep onset

Table 9. Patient Screening and Randomization, Trials ID-078A301 and ID-078A302

Screening Disposition	Trial ID-078A301	Trial ID-078A302	Combined
Patients screened	3326	3683	7009
Not randomized	2396	2759	5155
Screen failure	2168	2535	4703
Patients randomized	930*	924	1854

Source: adds.xpt and Clinical Study Report; Software: R, clinical reviewer based on CSR 301, 302
 *3 subjects (Subject (b) (6) and Subject (b) (6) [daridorexant 50 mg] and Subject (b) (6) [placebo]) were discontinued from the study before receiving DB treatment as they did not meet eligibility criteria and had been randomized in error.

Clinical Reviewer Comment: Nearly 1 in 3 prospective participants screened were randomized in each study. This rate appears reasonable. The similarity of rates between the two trials suggests similarity of trial conduct.

Table 10. Patient Disposition, Trials ID-078A301 and ID-078A302

Disposition Outcome	078A301			078A302		
	Daridorexant 25 mg N=310	Daridorexant 50 mg N=310	PBO N=310	Daridorexant 10 mg N=307	Daridorexant 25 mg N=309	PBO N=308
Patients randomized	310	310	310	307	309	308
Safety population	310	308	309	306	308	306
Discontinued study	22 (7.1)	24 (7.7)	30 (9.7)	24 (7.8)	29 (9.3)	22 (7.1)
Adverse event	4 (1.3)	2 (0.6)	7 (2.3)	4 (1.3)	3 (1.0)	4 (1.3)
Lost to follow-up	1 (0.3)	2 (0.6)	3 (1.0)	1 (0.3)	2 (0.6)	1 (0.3)
Other	3 (1.0)	11 (2.9)	8 (2.3)	6 (1.6)	8 (2.3)	6 (1.9)
Withdrawal by subject	13 (4.2)	10 (3.2)	12 (3.9)	13 (4.2)	16 (5.2)	11 (3.3)
Death	1 (0.3)	0	0	0	0	0
Discontinued study drug	25 (8.1)	24 (7.8)	30 (9.7)	26 (8.5)	23 (7.4)	18 (5.9)
Adverse event	7 (2.3)	3 (1.0)	10 (3.2)	6 (2.0)	4 (1.3)	7 (2.3)
Lack of efficacy	5 (1.6)	6 (1.9)	4 (1.3)	4 (1.3)	4 (1.3)	5 (1.6)
Lost to follow-up	1 (0.3)	1 (0.3)	3 (1.0)	1 (0.3)	2 (0.6)	0 (0.0)
Other	2 (0.6)	4 (1.3)	2 (0.6)	2 (0.7)	0 (0.0)	2 (1.0)
Withdrawal by subject	8 (2.6)	8 (2.6)	9 (2.9)	10 (3.3)	13 (4.2)	4 (1.3)
Death	1 (0.3)	0	0	0	0	0

Source: adds.xpt, adsl.xpt; Software: R; Clinical data scientist generated
 Risk difference: 078A301 Daridorexant 50 mg group minus placebo group.
 Abbreviations: N, number of subjects in treatment arm; n, number of subjects in specified population or group; NA, not applicable; PBO, placebo

Clinical Reviewer Comment: Overall, discontinuation rates were moderately low and similar between arms. The low overall rate of discontinuation supports reliability of efficacy findings. ICEs not involving treatment discontinuation occurred at rates too low to have meaningful impact on the trial results for either study. Per the Applicant's clinical study reports (CSRs) for Trials ID-078A301 and ID-078A302, occurrence of protocol deviations for forbidden medications being taken within five half-lives before any assessment for the primary, secondary, or rebound endpoints was reported for four subjects (0.4%) (2 in the 25 mg and 1 each in the 50 mg and placebo arms, respectively) in Trial ID-078A301, and for 11 subjects (1.2%; 1.0%, 1.6%, and 1.0% in the daridorexant 10 mg, 25 mg, and placebo groups, respectively) in Trial ID-078A302.

Baseline medical histories and comorbidities were observed at appropriately high rates overall, supporting representativeness of study population for primary insomnia disorder and similar between arms.

Most comorbidities appear to have potential to contribute to insomnia but the balance between arms obviates concern for bias in estimation due to imbalances in comorbidities.

Psychiatric disorders and substance use disorders (SUDs) in remission were not excluded from but were rare (absent in case of SUDs) in the study population. This is significant as populations characterized by these comorbidities have high rates of insomnia, and insomnia presents as an important risk factor for relapse. Efficacy may not generalize to the remitted SUD population. Thus, further study is needed in this population.

Nonwhite participants are underrepresented in the study sample. This is of concern as psychosocial factors affecting sleep quality may be impacted by racial/ethnic identity or correlates thereof in the study countries. This concern is mitigated by the absence of consistent differences in treatment effect between racial/ethnic identity groups; see Section [6.2.2.5](#) for a discussion of those differences.

6.2.2.2. Results of Efficacy Analyses, Trial ID-078A301

For all eight primary endpoints the null hypothesis could be excluded, demonstrating for each an improvement over placebo at Month 1 and Month 3 compared to baseline. See Table 11.

For the LPS endpoint, the 50 mg daridorexant dose arm had an 11-minute improvement compared to placebo, and 25 mg had an 8-minute improvement compared to placebo. The treatment effect remained approximately constant from Month 1 to Month 3, while treatment response in all arms increased from Month 1 to Month 3 (see [Figure 15-A](#)). Thus, there was no indication of waning response to treatment nor of waning of drug effects. Given the 3-month duration of the study, it is reasonable to conclude that efficacy would be sustained for those patients needing chronic treatment. This interpretation is not undercut by the reported results of the extension Trial ID-078A303, which showed no decline over 40 weeks in sTST, consistent with longer term durability of treatment response.

This study thus contributes to a conclusion that there is substantial evidence of efficacy for daridorexant for the treatment of insomnia.

Table 11. Primary Endpoints, Trial ID-078A301, FAS

Endpoint	Treatment Arm	Visit	Treatment Effect	SE	Lower 95% CI	Upper 95% CI	Unadjusted p-value	P-value Threshold	Reject H ₀
LPS	(Daridorexant 50 mg) – Placebo	Month 1	-11.35	2.38	-16.02	-6.69	0.0000	0.025	Yes
		Month 3	-11.67	2.38	-16.34	-7.00	0.0000	0.025	Yes
	(Daridorexant 25 mg) – Placebo	Month 1	-8.32	2.39	-13.01	-3.63	0.0005	0.025	Yes
		Month 3	-7.59	2.38	-12.26	-2.93	0.0014	0.01875	Yes
WASO	(Daridorexant 50 mg) – Placebo	Month 1	-22.78	2.66	-27.99	-17.57	<0.0001	0.025	Yes
		Month 3	-18.30	2.87	-23.94	-12.66	<0.0001	0.025	Yes
	(Daridorexant 25 mg) – Placebo	Month 1	-12.20	2.67	-17.43	-6.96	<0.0001	0.025	Yes
		Month 3	-11.86	2.87	-17.49	-6.23	<0.0001	0.01875	Yes

Source: Statistical Reviewer, adpsg.xpt.

Abbreviations: CI, confidence interval; LPS, latency to persistent sleep; SE, standard error; WASO, wake after sleep onset

Table 12. Change From Baseline for Primary Endpoints, Trial ID-078A301, FAS

Endpoint	Treatment Arm	Visit	Change From Baseline	SE	Lower 95% CI	Upper 95% CI
LPS	Placebo	Month 1	-20.38	1.70	-23.71	-17.05
		Month 3	-23.67	1.70	-27.00	-20.34
	Daridorexant 25 mg	Month 1	-29.44	1.70	-32.78	-26.10
		Month 3	-32.00	1.69	-35.31	-28.69
	Daridorexant 50 mg	Month 1	-28.82	1.68	-32.12	-25.52
		Month 3	-32.42	1.69	-35.73	-29.11
WASO	Placebo	Month 1	-10.25	1.90	-13.97	-6.52
		Month 3	-15.16	2.05	-19.17	-11.14
	Daridorexant 25 mg	Month 1	-17.80	1.90	-21.53	-14.08
		Month 3	-22.38	2.03	-26.36	-18.40
	Daridorexant 50 mg	Month 1	-26.00	1.88	-29.68	-22.32
		Month 3	-26.43	2.03	-30.41	-22.45

Source: Statistical Reviewer, adpsg.xpt.

Abbreviations: CI, confidence interval; LPS, latency to persistent sleep; SE, standard error; WASO, wake after sleep onset

Table 13. Secondary Endpoints, Trial ID-078A301, FAS

Endpoint	Treatment Arm	Visit	Treatment Effect	SE	Lower 95% CI	Upper 95% CI	Unadjusted P-value	P-value Threshold	Reject H₀
sTST	(Daridorexant 50 mg) – Placebo	Month 1	22.05	3.90	14.41	29.70	0.0000	0.025	Yes
		Month 3	19.78	4.66	10.64	28.92	0.0000	0.025	Yes
	(Daridorexant 25 mg) – Placebo	Month 1	12.62	3.91	4.96	20.28	0.0013	0.025	Yes
		Month 3	9.94	4.66	0.81	19.08	0.0330	0.0375	Yes
IDSIQ - sleep	(Daridorexant 50 mg) – Placebo	Month 1	-1.74	0.39	-2.51	-0.98	0.0000	0.0125	Yes
		Month 3	-1.92	0.51	-2.92	-0.91	0.0002	0.0125	Yes
	(Daridorexant 25 mg) – Placebo	Month 1	-0.75	0.39	-1.52	0.01	0.0536	0.0125	No
		Month 3	-0.97	0.51	-1.97	0.04	0.0604	0.0375	No

Source: Statistical Reviewer, adpsg.xpt.

Abbreviations: CI, confidence interval; IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; SE, standard error; sTST, subjective total sleep time

This conclusion is supported by findings of efficacy for both the 25-mg and 50-mg dose on sTST—an assessment of total sleep time as *perceived* by the patient at Month 1, with minimal decrement in drug effect but further improvement in response at Month 3. It is also supported by findings of efficacy for 50-mg dose on the IDSIQ sleepiness subscale—a measure of patients’ subjective level of daytime sleepiness. On this measure both treatment effects and treatment response increased from Month 1 to Month 3, further supporting the durability of efficacy for daridorexant. See [Table 12](#).

For the WASO endpoint, the results of the sensitivity analyses (tipping point analysis and jump to reference) indicated that the primary analysis is unlikely to be impacted by violation of the MAR assumptions. For the LPS endpoint, conclusions about the 50-mg dose were unlikely to be impacted by violations of MAR. However, for the 25-mg dose, the p-value crossed the testing threshold for 30 minutes at Month 3 and 60 minutes at Month 1. These tipping points indicate that the LPS results are robust up to worsening greater than a return to baseline, see [Table 12](#).

6.2.2.3. Results of Efficacy Analyses, Trial ID-078A302

For 25 mg, the null hypothesis was excluded for two of four primary endpoints, demonstrating an improvement over placebo at Month 1 and Month 3 compared to baseline in WASO (see [Table 14](#)). The 10-mg daridorexant dose arm did not demonstrate superiority to placebo on any endpoint and will therefore not be discussed further. The 25-mg dose showed a 12-minute improvement compared to placebo at Month 1 and a 10-minute improvement at Month 3, while treatment response was unchanged from Month 1 to Month 3. Thus, there was no substantive indication of waning response to treatment nor of meaningful waning of drug effects. Given the 3-month duration of the study it is reasonable to conclude that efficacy would be sustained for those patients needing chronic treatment. This interpretation is not undercut by the reported results of the extension Trial ID-078A303, which showed no decline over 40 weeks in sTST.

For LPS, although the treatment effects for 25 mg were close to those observed in Trial ID-078A301, the null hypothesis was not rejected. The Applicant conducted several assessments of the model assumption of normally distributed LPS. The Applicant also conducted a post hoc MMRM analysis using the log transformed LPS and reported that LPS at Month 1 was statistically significant.

This study thus contributes to a conclusion that there is substantial evidence of efficacy for daridorexant for the treatment of insomnia, independently substantiating the Trial ID-078A301 findings of efficacy for 25 mg in improving WASO and providing nonconclusive supportive evidence for Trial ID-078A301 findings of efficacy for 25 mg in improving LPS.

Statistical Reviewer Comment: For the LPS endpoint, the Applicant prespecified an MMRM analysis using the untransformed data with planned sensitivity analysis to assess the impact of non-normality on the p-value for the primary analysis. This sensitivity analysis consisted of conducting an MMRM analysis to the primary MMRM analysis but with the log transformed LPS data. The change from assuming a normal LPS distribution to a log-normal distribution changes the population level summary compared from

differences in means to ratios of geometric means. Therefore, this sensitivity may be better considered as a supplementary analysis estimating a supplementary estimand with the new population level summary. The Applicant reported that the p-values of the 25-mg dose at Month 1 and Month 3 decreased to 0.0004 and 0.0021. This Statistical Reviewer recreated this sensitivity analysis, see Section [16.2](#). Although this sensitivity analysis suggested a lack of robustness to model assumptions, the prespecified analysis must be used for decision making because it is the only analysis with the type I error rate controlled. Because the sensitivity analysis is conducted after seeing the data, its type I error rate is not controlled.

Table 14. Primary Endpoints, Trial ID-078A302, FAS

Endpoint	Treatment Arm	Visit	Treatment Effect	SE	Lower 95% CI	Upper 95% CI	Unadjusted P-value	P-value Threshold	Reject H ₀
LPS	(Daridorexant 25 mg) – Placebo	Month 1	-6.45	2.97	-12.28	-0.62	0.0302	0.025	No
		Month 3	-9.01	3.22	-15.33	-2.69	0.0052	0.00313	No
	(Daridorexant 10 mg) – Placebo	Month 1	-2.61	2.96	-8.41	3.19	0.3781	0.00195	No
		Month 3	-3.19	3.23	-9.52	3.14	0.3231	0	No
WASO	(Daridorexant 25 mg) – Placebo	Month 1	-11.62	3.05	-17.60	-5.64	0.0001	0.025	Yes
		Month 3	-10.25	3.41	-16.94	-3.55	0.0027	0.01563	Yes
	(Daridorexant 10 mg) – Placebo	Month 1	-2.74	3.03	-8.69	3.21	0.3668	0.00977	No
		Month 3	-1.95	3.42	-8.66	4.76	0.5685	0	No

Source: Statistical Reviewer, adpsg.xpt.

Abbreviations: CI, confidence interval; LPS, latency to persistent sleep; SE, standard error; WASO, wake after sleep onset

Table 15. Change From Baseline for Primary Endpoints, Trial ID-078A302, FAS

Endpoint	Treatment Arm	Visit	Change From Baseline	SE	Lower 95% CI	Upper 95% CI
LPS	Placebo	Month 1	-20.01	2.11	-24.14	-15.88
		Month 3	-19.89	2.29	-24.38	-15.41
	Daridorexant 10 mg	Month 1	-22.62	2.10	-26.73	-18.51
		Month 3	-23.09	2.30	-27.60	-18.57
	Daridorexant 25 mg	Month 1	-26.46	2.12	-30.62	-22.30
		Month 3	-28.91	2.30	-33.41	-24.40
WASO	Placebo	Month 1	-14.68	2.16	-18.93	-10.44
		Month 3	-16.11	2.42	-20.87	-11.36
	Daridorexant 10 mg	Month 1	-13.94	2.15	-18.16	-9.72
		Month 3	-14.58	2.44	-19.36	-9.80
	Daridorexant 25 mg	Month 1	-24.26	2.18	-28.53	-19.98
		Month 3	-24.32	2.43	-29.09	-19.55

Source: Statistical Reviewer, adpsg.xpt.

Abbreviations: CI, confidence interval; LPS, latency to persistent sleep; SE, standard error; WASO, wake after sleep onset

This conclusion is supported by findings of efficacy for the 25-mg dose on sTST—an assessment of total sleep time as perceived by the patient. However, the null hypothesis could not be rejected for 25-mg dose effects on IDSIQ sleepiness. On that measure, even if the null hypothesis had been rejected, effects were numerically small and unlikely to be clinically significant.

Table 16. Secondary Endpoints, Trial ID-078A302, FAS

Endpoint	Treatment Arm	Visit	Treatment Effect	SE	Lower 95% CI	Upper 95% CI	Unadjusted P-value	P-value Threshold	Reject H₀
sTST	(Daridorexant 25 mg) – Placebo	Month 1	16.13	4.03	8.23	24.03	0.0001	0.0125	Yes
		Month 3	19.06	4.55	10.13	27.99	0.0000	0.00781	Yes
	(Daridorexant 10 mg) – Placebo	Month 1	13.37	4.00	5.51	21.22	0.0009	0	No
		Month 3	13.58	4.53	4.70	22.47	0.0028	0	No
IDSIQ - sleep	(Daridorexant 25 mg) – Placebo	Month 1	-0.75	0.42	-1.58	0.07	0.0730	0.00625	No
		Month 3	-1.25	0.50	-2.23	-0.28	0.0119	0.00391	No
	(Daridorexant 10 mg) – Placebo	Month 1	-0.43	0.42	-1.25	0.39	0.3045	0	No
		Month 3	-0.73	0.50	-1.70	0.24	0.1391	0	No

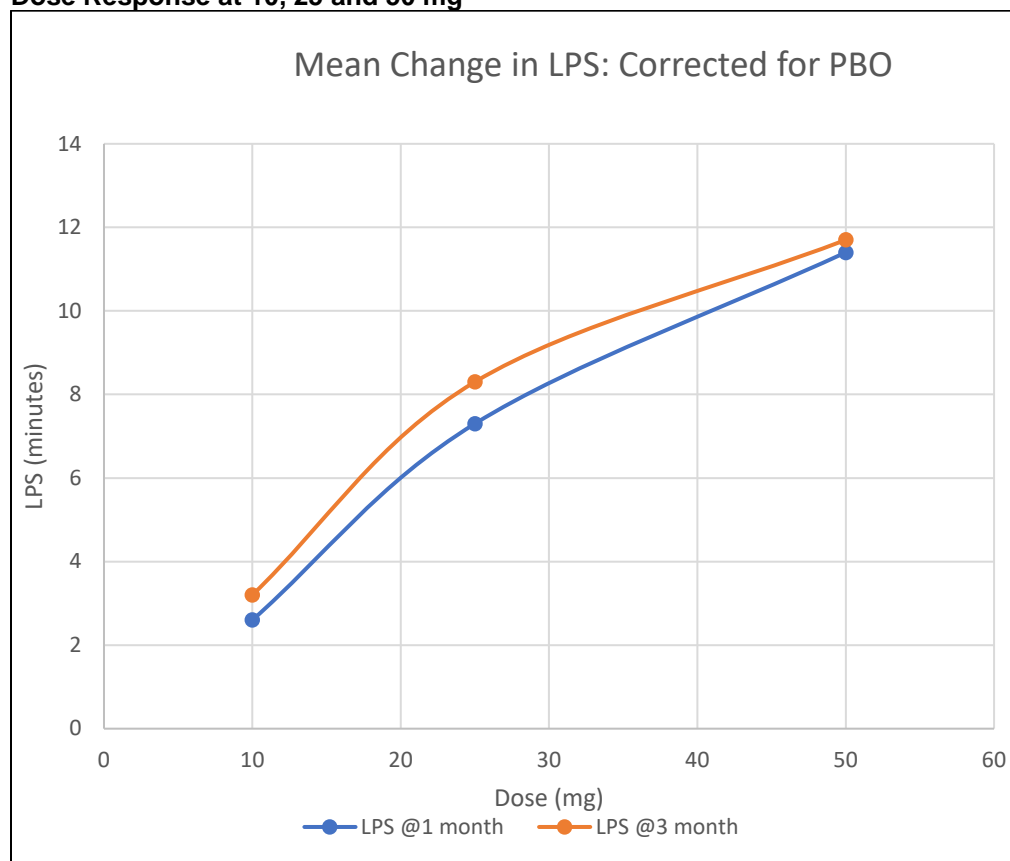
Source: Statistical Reviewer, adpsg.xpt.

Abbreviations: CI, confidence interval; IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; SE, standard error; sTST, subjective total sleep time

6.2.2.4. Dose- and Exposure-Response Relationships Across Trials ID-078A301 and ID-078A302

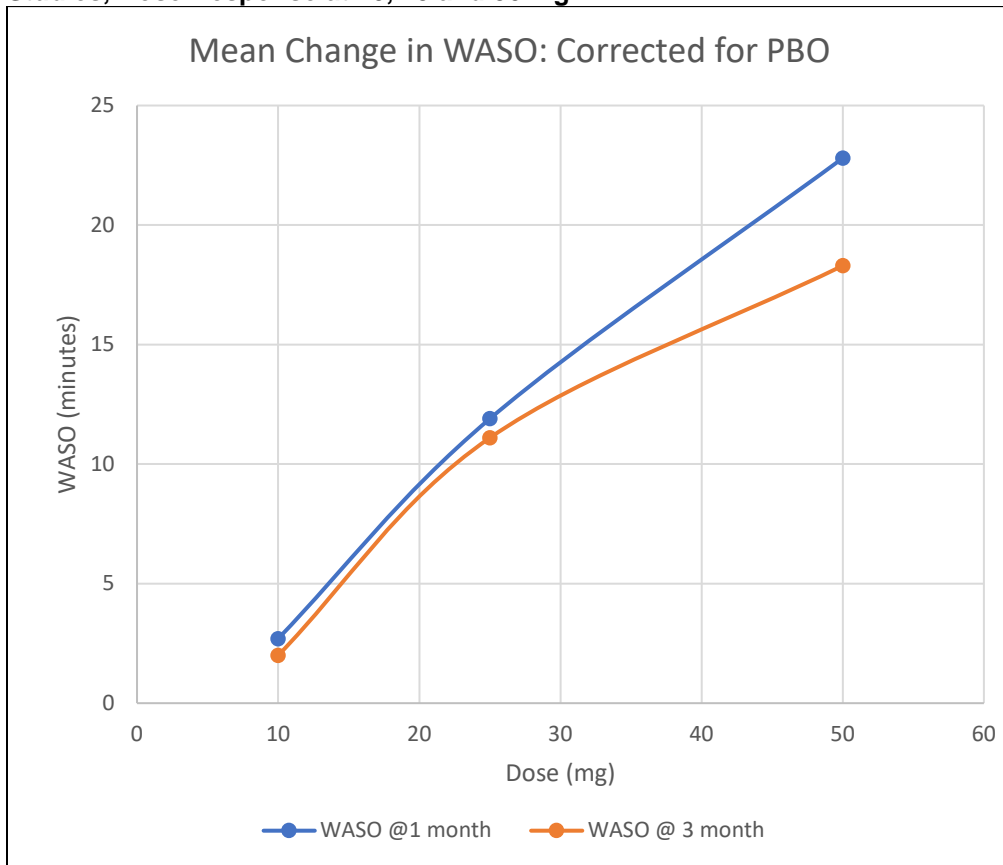
The results from the two phase 3 efficacy trials (ID-078A301 and ID-078A302) also demonstrated a dose-response for the primary efficacy endpoints, LPS (Figure 3) and WASO (Figure 4), and secondary efficacy endpoints, IDSIQ (sleepiness domain; Figure 5) and sTST (Figure 6). The results from the two trials are combined in a single plot by averaging the effect size observed at 25 mg, which was included in both trials. The plots represent the mean placebo-subtracted change from baseline for the endpoints. All the endpoints demonstrated clear dose-responses with effect size increasing with dose. The trend for increasing effect size with dose persisted for both the 1-month and 3-month assessments. These plots demonstrated that numerically the highest effect size for the primary as well as secondary efficacy endpoints was observed at the 50-mg dose, which is the Applicant's proposed recommended starting and target dose.

Figure 3. Mean Change From Baseline in LPS (min) Corrected for Placebo in the Phase 3 Studies, Dose Response at 10, 25 and 50 mg



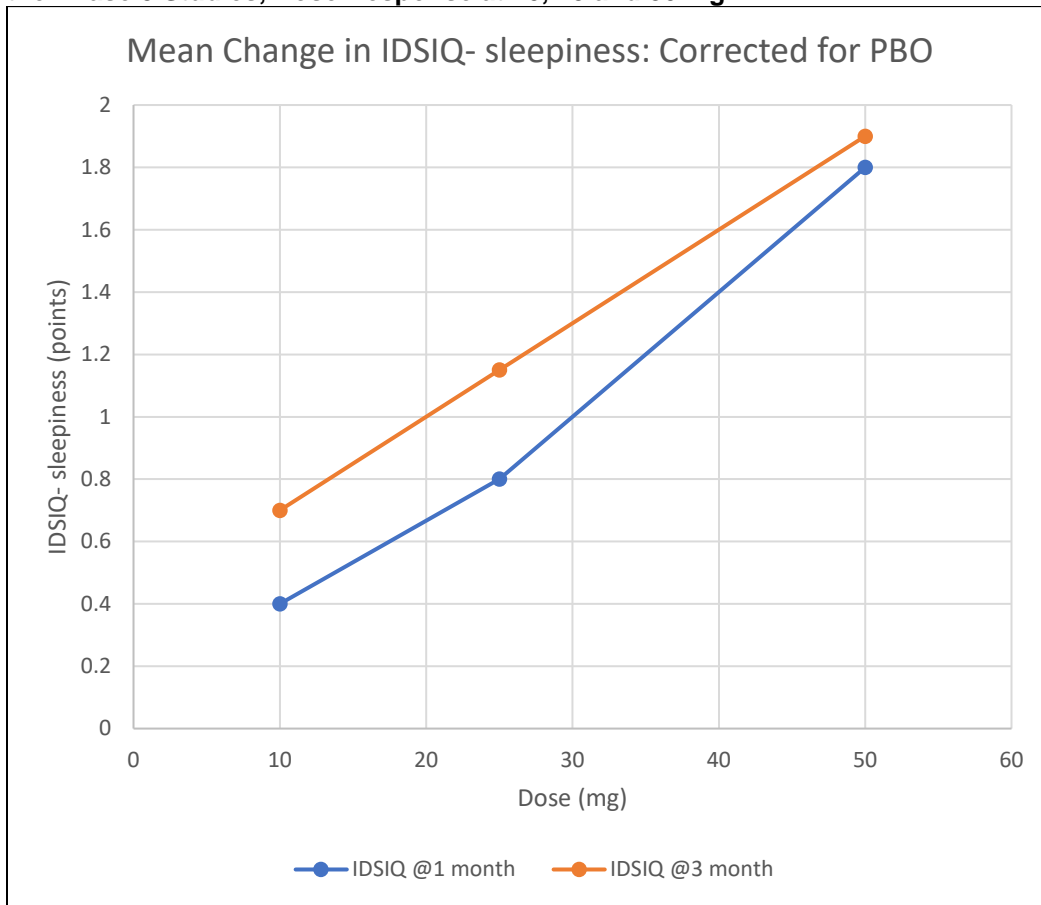
Source: Clinical Pharmacology Reviewer generated
The Y-axis in the plot shows unit improvement (from baseline) in LPS score.
Abbreviations: LPS, latency to persistent sleep; PBO, placebo

Figure 4. Mean Change From Baseline in WASO (min) Corrected for Placebo in the Phase 3 Studies, Dose Response at 10, 25 and 50 mg



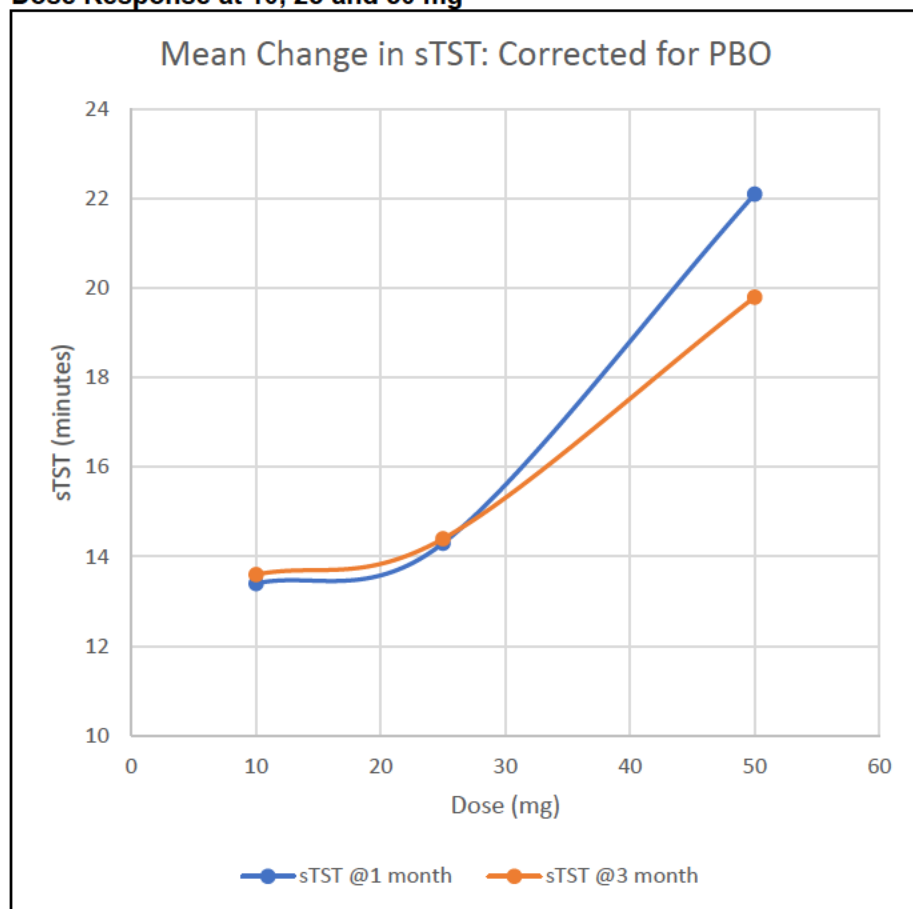
Source: Clinical Pharmacology Reviewer generated
The Y-axis in the plot shows unit improvement (from baseline) in WASO score.
Abbreviations: PBO, placebo; WASO, wake after sleep onset

Figure 5. Mean Change From Baseline in IDSIQ Sleepiness Score (min) Corrected for Placebo in the Phase 3 Studies, Dose Response at 10, 25 and 50 mg



Source: Clinical Pharmacology Reviewer generated
The Y-axis in the plot shows unit improvement (from baseline) in IDSIQ score.
Abbreviations: IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; PBO, placebo

Figure 6. Mean Change From Baseline in sTST (min) Corrected for Placebo in the Phase 3 Studies, Dose Response at 10, 25 and 50 mg



Source: Clinical Pharmacology Reviewer generated
Abbreviation: PBO, placebo; sTST, subjective total sleep time

Additionally, the Applicant assessed the relationship between efficacy in the phase 3 trials and daridorexant PK. Based on these exposure-response analyses, which include treatment and placebo groups, there was no apparent correlation between next-day daridorexant plasma concentration and the change from baseline in efficacy endpoints assessed during the previous night. If an exposure-response relationship exists for these endpoints, such a relationship is expected to be “flatter” when using the next-day daridorexant plasma concentration (collected 9 to 10 hours after dosing; over 1 half-life) compared to C_{max} (which is expected to occur during PSG recording; $T_{max} \sim 2.09$ h). However, considering the high PK variability (i.e., percent coefficient of variation ranged from 63 to 137% and from 32 to 61%, in Studies AC-078-101 and AC-078-102, respectively), and that subjects in the phase 3 trials provided a single PK sample occurring after PSG completion (obtained 9 to 10 hours postdose, over 1 half-life), the PK profile (i.e., C_{max}) cannot be reliably predicted for the time period during PSG recording for individual subjects. Please refer to Section 14.6 for details. Considering that a dose-response relationship is apparent for four efficacy endpoints in phase 3 trials (WASO, LPS, IDSIQ, and sTST), the lack of an apparent exposure-response relationship for efficacy may be a consequence of the PK sample being collected on the next day after efficacy assessments. In other words, these exposure-response analysis results using PK collected after efficacy assessment do not rule

out the possibility of an exposure-response relationship existing with PK if it were collected during efficacy assessment (i.e., $C_{\max}$).

6.2.2.5. Potential Moderators of Efficacy – Analyses of Baseline Patient Characteristic Impacts on Treatment Effects

The potential for patient baseline characteristics to moderate daridorexant treatment effects was explored to ensure that efficacy findings were not driven by a particular demographic subgroup, or that dosing and administration might need to be modified based on broad baseline patient characteristics. There was no evidence of substantial moderation of treatment effects by age group, race, sex, or study region. The 95% confidence intervals for point estimates of within subgroup treatment effects were almost all substantially overlapping, and where relatively larger differences were observed between subgroups, the patterns of difference were not consistent across timepoints or endpoints, reducing the likelihood that the differences observed were in fact attributable to the subgroup characteristics (e.g., male versus female sex). See Section [16.3](#) for illustrative forest plots.

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. Efficacious Dose and Labeling of Dosage and Administration

Issue

What dose or doses of daridorexant should be considered efficacious for the treatment of insomnia disorder?

Background

Insomnia disorder may be characterized by impairments in sleep onset that may be measured by PSG as latency to persistent sleep or as wake after sleep onset, and early termination of sleep, or any combination of the above.

LPS and WASO were each assessed as primary endpoint measures (with partial allocation of alpha to each). The 50-mg dose was significantly superior to placebo on both measures at all timepoints in the only registration study in which it was assessed (Trial ID-078A301). The 25-mg dose was superior to placebo on WASO at all timepoints in both registration studies, but superior to placebo on LPS only in Trial ID-078A301. In Trial ID-078A302, the efficacy of the 25-mg dose for LPS could be considered a “near-miss.” Further, the prespecified analysis method for this endpoint assumed normal distribution of LPS data. Previous studies indicate the typical distribution of LPS is skewed. Post hoc assessment of the model assumption indicated that the statistical inference from the primary analysis is sensitive to violation of the normality assumption. A post hoc sensitivity analysis that assumed an underlying log-normal distribution suggested that there is statistical evidence for the observed improvement in LPS. However,

changing the statistical analysis post hoc (e.g., from comparing means to comparing geometric means) increases the primary analysis type I error by an unknown amount.

Thus, the 25-mg dose has substantial evidence of efficacy for improving one criterion symptom (difficulties in sleep maintenance) but falls just shy of meeting the standard regulatory criteria for substantial evidence of efficacy for improving another of the criterion symptoms of insomnia (difficulty falling asleep).

- This raises the question of if and how the 25-mg dose should be labelled for patients who do not have hepatic impairment or take other medications that would increase exposures to daridorexant from the 25-mg dose.

The efficacy of the 50-mg dose was only evaluated in one adequate and well-controlled trial.

- This raises the question of whether substantial evidence of efficacy has been provided for the 50-mg dose.

6.3.1.1. Primary Endpoints: LPS and WASO

For each endpoint examined, the 50-mg dose produced numerically superior efficacy to the 25-mg dose and superiority to placebo, whereas the 25-mg dose demonstrated numerically superior efficacy to the 10-mg dose and statistically significant superiority to placebo on WASO in both Trial ID-078A301 and ID-078A302 and superiority to placebo on LPS in Trial ID-078A301, with a near miss in Trial ID-078A302. The consistency of the dose response observations across studies and endpoints supports 50 mg as a more effective dose than 25 mg, though both doses may be considered effective in treating independently important aspects of insomnia disorder.

Analysis of differences in treatment effects between patient groups characterized by age, sex, and study region (US/nonUS), showed treatment effects on WASO and LPS for 50 mg that were consistently numerically greater than or equal to those of 25 mg daridorexant.

Clinical Reviewer Comment: Analysis of efficacy results by race (Section [6.2.2.5](#)) demonstrated unreliable point estimates for Black subjects, with 95% confidence intervals generally wholly containing those for the much larger sample of white subjects. No consistent pattern of difference in treatment effects was observed; some point estimates were higher, and others lower for Black subjects compared to white subjects, nor was there consistency in ordering of point estimates of treatment effects by dose within the subgroup of Black subjects. Thus, there is no evidence for a difference in efficacy for Black compared to white subjects.

In light of very limited differences in safety and tolerability of 50- versus 25-mg doses (see Sections [7.6](#) and [7.7](#)), the 50-mg dose is an appropriate starting dose. This appears to be supported for all subgroups evaluated as well.

Clinical Meaningfulness

Evaluation of clinical meaningfulness of statistically significant results for WASO and LPS was approached in several ways:

- (1) Results were compared to the American Academy of Sleep Medicine expert consensus threshold for clinically meaningful mean difference from placebo for group-level results,

defining 20 and 10 minutes (lower) difference from placebo as clinically meaningful for WASO and sleep latency, respectively (Sateia et al. 2017). According to this guideline, for WASO, only daridorexant 50 mg effects at Month 1 were clinically meaningful, though they approached the threshold for Month 3 as well. For LPS, daridorexant 50-mg treatment effects were clinically meaningful at Month 1 and 3, and 25-mg treatment effects approached the threshold at Month 1 and 3 in Trial ID-078A301. In Trial ID-078A302, for 25 mg, only change in LPS at Month 3 approached the American Academy of Sleep Medicine threshold for clinical meaningfulness.

Thus, according to the expert-panel consensus criteria there is evidence of clinically meaningful efficacy only for the 50-mg dose.

***Clinical Reviewer Comment:** Clinically meaningful improvement occurs at an individual level; thus, group means may mask clinically meaningful benefits occurring in a subpopulation and are in this way limited. Further, given that these criteria were based on expert consensus the evidence for their validity is indirect.*

It is worth noting that the trials reported in the labeling for suvorexant achieved clinical meaningfulness only at Month 1 in one study according to the above definition for LPS, but at Month 1 in both and Month 3 in one study for WASO. Lemborexant labeling only reported PSG data for one trial that assessed primary outcomes only at Month 1. There, although statistically significant, changes in LPS did not meet the above definition of clinical significance; however, the treatment effect for WASO did.

The clinical reviewer evaluated rates of 50% and 75% reduction in WASO and LPS as proxies for levels of symptom reduction expected to be considered meaningful (50%) or substantial (75%) at an individual level. In Trial ID-078A301, based on results as shown in [Table 17](#) and [Table 18](#)

- *Placebo subtracted likelihood of a patient experiencing a clinically meaningful improvement with daridorexant 50 mg was approximately 20% for meaningful and 10% for substantial improvement in LPS at Month 1,*
- *For daridorexant 25 mg the likelihood was similar for meaningful but lower for substantial improvement in LPS at Month 1*
- *For WASO, with a 50 mg dose of daridorexant the likelihood was similar for meaningful but lower for substantial improvement at Month 1*
- *For daridorexant 25 mg the likelihood of meaningful or substantial improvement was notably lower.*

(It can be inferred from the group means, which showed similar to slightly larger treatment effects compared to Month 1, that the likelihoods at Month 3 are similar.)

Thus, as defined here, there is reasonable likelihood of meaningful to substantial benefit for LPS with both 50- and 25-mg doses. For WASO, there was reasonable likelihood for meaningful benefit only, and only for the 50-mg dose. Thus evaluated, there is reasonable evidence for clinically meaningful benefit from daridorexant 50 mg on LPS and WASO

and reasonable evidence for clinically meaningful benefit from daridorexant 25 mg on LPS only.

Table 17. Subjects Achieving Substantial Reduction in LPS at Month 1, Trial ID-078A301

Improvement From Baseline in LPS	Actual Treatment					
	Daridorexant 25 mg		Daridorexant 50 mg		Placebo	
	N	Column %	N	Column %	N	Column %
>75%						
No	246	82.55%	243	79.67%	268	89.63%
Yes	52	17.45%	62	20.33%	31	10.37%
>50%						
No	154	51.68%	149	48.85%	203	67.89%
Yes	144	48.32%	156	51.15%	96	32.11%

Source: Clinical reviewer generated table, adpsg.xls with custom variables calculated by clinical reviewer. Program JMP 7.1A
 Abbreviations: LPS, latency to persistent sleep; N, number of subjects in treatment arm

Table 18. Subjects Achieving Substantial Reduction in WASO at Month 1, Trial ID-078A301

Improvement From Baseline in WASO	Actual Treatment					
	Daridorexant 25 mg		Daridorexant 50 mg		Placebo	
	N	Column %	N	Column %	N	Column %
≥75%						
No	291	97.65%	289	94.75%	296	99.00%
Yes	7	2.35%	16	5.25%	3	1.00%
≥50%						
No	245	82.21%	219	71.80%	269	89.97%
Yes	53	17.79%	86	28.20%	30	10.03%

Source: Clinical reviewer generated table, adpsg.xls with custom variables calculated by clinical reviewer. Program JMP 7.1
 Abbreviations: N, number of subjects in treatment arm; WASO, wake after sleep onset

- (2) Finally, evaluation of the clinical meaningfulness of daridorexant treatment effects, given statistically significant group differences on objective sleep parameters, can be assessed indirectly by evaluating the rates at which subjects reported, or were observed by clinicians, to experience clinically meaningful global improvement in sleep quality as assessed by change in patient-assessed global impressions of severity (with improvement of two or more categories representing clinically meaningful improvement).

Analysis reliability is limited by imbalances in missing patient global impression (PGI) data for Trial ID-078A301 and ID-078A302 but is acceptable for the exploratory purpose here. Analysis indicated for 50 mg approximately 10% and 14% (placebo subtracted) of patients experienced meaningful improvement at Month 1 and 3, respectively. For 25 mg, >5% of patients (placebo subtracted) experienced a meaningful benefit only at Month 3, suggesting only marginal likelihood of clinically meaningful benefit beyond placebo response in Trial ID-078A301 (see [Table 19](#)). In Trial ID-078A302, however, rates for 25 mg were more supportive of a reasonable likelihood of a treated individual experiencing clinically meaningful effects (see [Table 20](#)).

Table 19. Clinically Meaningful Improvement From Baseline in Nighttime Symptoms of Insomnia as Assessed by Change From Baseline in Patient Global Impression of Severity, Trial ID-078A301

Analysis Visit	Actual Treatment	Clinically Meaningful Improvement From Baseline			
		No		Yes	
		N	%	N	%
Month 1	Daridorexant 25 mg	209	93.30%	15	6.70%
	Daridorexant 50 mg	203	87.50%	29	12.50%
	Placebo	225	96.98%	7	3.02%
Month 3	Daridorexant 25 mg	179	82.87%	37	17.13%
	Daridorexant 50 mg	165	74.66%	56	25.34%
	Placebo	194	88.99%	24	11.01%

Source: clinical reviewer generated table, Trial ID-078A301 addiary.xpt, JMP
 Clinically meaningful improvement defined as PGI-S decreased from baseline ≥ 2 points
 Abbreviations: N, number of subjects in treatment arm

Table 20. Clinically Meaningful Improvement From Baseline in Nighttime Symptoms of Insomnia as Assessed by Change From Baseline in Patient Global Impression of Severity, Trial ID-078A302

Analysis Visit	Actual Treatment	Clinically Meaningful Improvement From Baseline			
		No		Yes	
		N	%	N	%
Month 1	Daridorexant 10 mg	211	89.79%	24	10.21%
	Daridorexant 25 mg	198	87.61%	28	12.39%
	Placebo	225	94.94%	12	5.06%
Month 3	Daridorexant 10 mg	186	84.16%	35	15.84%
	Daridorexant 25 mg	171	79.53%	44	20.47%
	Placebo	202	91.82%	18	8.18%

Source: clinical reviewer generated table, Trial ID-078A302 addiary.xpt, JMP
 Clinically meaningful improvement defined as PGI-S decreased from baseline ≥ 2 points
 Abbreviations: N, number of subjects in treatment arm

6.3.1.2. Secondary Endpoints: sTST and IDSIQ Sleepiness Domain

Both sTST and IDSIQ sleepiness domain appear fit-for-purpose for this drug development program. See Section 6.3.2, and detailed evaluation in Section 19.1.

sTST

During drug development, the clinical significance of sTST was discussed, and the Applicant was instructed to submit an evidence dossier with anchor-based analyses to evaluate thresholds for clinically meaningful change in sTST. On face, the sTST evaluates subject perception of total time slept the previous night. Anchor-based analyses showed that there are clear separations between the 50 mg, 25 mg, and placebo arms in the empirical cumulative distribution function (eCDF) curves by treatment arm at the estimated thresholds of clinically meaningful within-patient change in sTST scores from baseline to Month 1 and from baseline to Month 3. Review of the dossier suggests that across studies and anchors, 80 minutes represented a reasonably conservative threshold value for sTST improvement to be considered ‘at least moderate’ or improved by two PGI categories in severity across all time-points (see Section 19.1.1). Exploratory analysis by the clinical reviewer is summarized for Trial ID-078A301 and ID-078A302 in Table 21, showing fair to modest likelihood of clinically meaningful improvement attributable to daridorexant 50 mg and 25 mg, respectively.

Table 21. Subjects Achieving >80 Minutes Increase From Baseline in Mean Weekly sTST at Month 1 and 3, Trials ID-078A301 and ID-078A302

Change From BL >80	N	Column %	N	Column %	N	Column %
Trial ID-078A301 – Month 1	Daridorexant 25 mg		Daridorexant 50 mg		Placebo	
No	249	82.18%	235	77.30%	271	89.74%
Yes	54	17.82%	69	22.70%	31	10.26%
Trial ID-078A302 – Month 1	Daridorexant 25 mg		Daridorexant 10 mg		Placebo	
No	228	76.77%	244	80.26%	250	84.18%
Yes	69	23.23%	60	19.74%	47	15.82%
Trial ID-078A301 – Month 3	Daridorexant 25 mg		Daridorexant 50 mg		Placebo	
No	211	72.26%	191	66.09%	229	79.24%
Yes	81	27.74%	98	33.91%	60	20.76%
Trial ID-078A302 – Month 3	Daridorexant 25 mg		Daridorexant 10 mg		Placebo	
No	202	70.88%	214	74.05%	232	80.84%
Yes	83	29.12%	75	25.95%	55	19.16%

Source: Clinical reviewer generated table from addiary.xpt data set
 Abbreviations: BL, baseline; N, number of subjects in treatment arm

IDSIQ Sleepiness Domain

During drug development, the clinical significance of IDSIQ (daytime) sleepiness subscale scores was discussed, and the Applicant was instructed to submit an evidence dossier with anchor-based analyses to evaluate thresholds for clinically meaningful change. Review of the Dossier suggests that across studies and anchors, 5 to 10 point decreases represented reasonable lower and upper bounds, respectively, for IDSIQ improvement to be considered meaningful (i.e., indicative of at least moderate improvement or improved by two clinician assessment of global illness categories in severity; see Section 6.3.2.1 for discussion of relevance of IDSIQ and Section 19.1.2 for detailed evaluation of its fitness for purpose). Exploratory analysis by the clinical reviewer of rates of clinically meaningful change in IDSIQ sleepiness domain scores is summarized for Trial ID-078A301 in Table 22 (equivalent analysis for Trial ID-078A302 was obviated by the lack of separation from placebo and very small point estimates of for treatment effects).

Table 22. Subjects Achieving ≥5 and ≥10 Points Decrease From Baseline in Mean Weekly IDSIQ Sleepiness Domain Scores at Month 1 and 3, Trial ID-078A301

Change From BL ≤ -5	N	Column %	N	Column %	N	Column %
Month 1	Daridorexant 25 mg		Daridorexant 50 mg		Placebo	
No	226	75%	194	64%	236	78%
Yes	75	25%	110	36%	65	22%
Month 3	Daridorexant 25 mg		Daridorexant 50 mg		Placebo	
No	166	57%	152	52%	177	61%
Yes	124	43%	139	48%	111	39%
Change From BL ≤ -10	N	Column %	N	Column %	N	Column %
Month 1	Daridorexant 25 mg		Daridorexant 50 mg		Placebo	
No	279	93%	257	85%	284	94%
Yes	22	7%	47	15%	17	6%
Month 3	Daridorexant 25 mg		Daridorexant 50 mg		Placebo	
No	240	83%	215	74%	243	84%
Yes	50	17%	76	26%	45	16%

Source: Clinical reviewer generated table from Trial ID-078A301 addiary.xpt
 Abbreviations: BL, baseline; N, number of subjects in treatment arm

- The placebo subtracted likelihood of an individual patient experiencing a clinically meaningful improvement based on sTST change from baseline at Months 1 and 3 with daridorexant 50 mg was >10%.
- Regardless of the selection of threshold for clinical meaningfulness of change from baseline on the IDSIQ, the placebo subtracted likelihood of an individual patient experiencing a clinically meaningful improvement with daridorexant 50 mg was approximately 10% at both Months 1 and 3.
- The placebo subtracted likelihood of achieving remission of insomnia disorder (defined by insomnia severity index total score ≤ 7) with daridorexant 50 mg nightly was approximately 10% at Month 3.

Table 23. Subjects Achieving ISI total score <8 at Month 1 and 3, Trial ID-078A301

	Actual Treatment					
	Daridorexant 25 mg Analysis Visit		Daridorexant 50 mg Analysis Visit		Placebo Analysis Visit	
	Month 1-2nd Night	Month 3-2nd Night	Month 1-2nd Night	Month 3-2nd Night	Month 1-2nd Night	Month 3-2nd Night
ISI Total ≤ 7						
No	89.73%	75.87%	88.63%	73.85%	94.95%	83.63%
Yes	10.27%	24.13%	11.37%	26.15%	5.05%	16.37%

Source: Clinical reviewer generated table from Trial ID-078A301 adqs.xpt
 Abbreviations: ISI, insomnia severity index

6.3.1.3. Exploration of Benefit Versus Risk Trade-Offs

Although the likelihood of a patient experiencing clinically meaningful benefit with 50 mg appeared greater than for 25 mg, the likelihood of clinically meaningful experiences of harm also may be greater. As discussed in detail in Section 7, the risks attributable or potentially attributable to daridorexant are for the most part similar in nature to the potential harms associated with ongoing insomnia and sleep deficits (e.g., psychomotor impairment and accidental injury, somnolence, mood disturbance). It is therefore reasonable to consider such risks and benefits in aggregate as well as individual phenomenon by individual phenomenon. Nonetheless individual experiences of benefit and of adverse effects are bound to be highly variable. Thus, comparison of rates of benefit with rates of harm remains limited by the qualitative differences between harms and benefits, the valuation of which occurs at the individual patient level. Accordingly, the evidence suggests advantages and disadvantages for each dose, that would depend on individual patient preferences and characteristics such as a history of sensitivity to or tolerance of potential adverse drug reactions:

- We can conservatively estimate the placebo subtracted likelihood of achieving a clinically meaningful improvement in insomnia as approximately 10% for daridorexant 50 mg overall and between 6% and 7% for daridorexant 25 mg .
- By comparison the placebo-subtracted likelihood of an individual patient experiencing a treatment-emergent adverse event (TEAE) of moderate or greater intensity with daridorexant 50 mg was approximately 2%. On the other hand, with 25 mg such AEs occurred at a lower rate than in the placebo arm. (Clinical reviewer calculation based on [Table 35](#)).
- Thus, the lesser likelihood of clinically meaningful benefit with the 25 mg dose compared to the 50 mg dose may be offset by a lesser likelihood of clinically meaningful harm.

- However, a comparison of efficacy outcomes with adverse events is arguably highly conservative because the benefits of treatment were sustained and tended to be numerically increased from Month 1 to Month 3 of assessment whereas the median clinically meaningful TEAE was transient, with a median duration of 11 days in the 50-mg treatment arm. Thus, in comparing 25 mg versus 50 mg doses, the value of the trade-off between efficacy and safety remains uncertain, and subject to individual patient values and susceptibilities.
- Therefore, the observation of such a trade-off supports an approach of individualized patient-prescriber selection of the most appropriate starting dose and argues against indicating in labelling that the 50 mg dose be the recommended starting dose (or converse, that the 25 mg dose be the recommended starting dose).

6.3.2 Conclusion

Daridorexant 50 mg: The findings of Trial ID-078A301 for the overall efficacy of 50 mg are persuasive with statistically robust “wins” on all primary and prespecified secondary endpoints. These results are supported by consistent dose-response patterns for efficacy endpoints across studies for both WASO and TST, with improvements from baseline numerically increasing by regular, roughly equal increments from 0 (i.e., placebo) to 10- to 20- to 50-mg doses. Dose-ranging Study 202 provides further support for efficacy of the 50-mg dose.

Evaluations of the clinical meaningfulness of treatment effects with daridorexant 50 mg indicated a fair likelihood of achieving a clinically meaningful benefit attributable to treatment across multiple endpoints and methods of evaluation of clinically meaningful effects.

Daridorexant 25 mg: The equivocal findings for the 25-mg dose for LPS, with lack of statistical significance for LPS in Trial ID-078A302, are partially offset by consistent treatment responses numerically superior to placebo with similar effect sizes across trials and supportive sensitivity analyses with good face validity, as well as consistent dose-response.

Evaluations of the clinical meaningfulness of treatment effects with daridorexant 25 mg indicated a fair but generally lower likelihood of achieving a clinically meaningful benefit attributable to treatment for many endpoints and methods of evaluation of clinically meaningful effects. However, the likelihood of clinically meaningful change was substantially lower for other endpoints. Thus, the likelihood of clinically meaningful effects with 25 mg was generally somewhat to substantially lower than for 50 mg. These effects could be considered as falling towards the lower range of acceptable utility.

Implications for dosing and administration: The generally numerically superior effects of the 50-mg compared to the 25-mg dose, supported by a consistent dose-response pattern across the range of doses studied supports labeling the 50-mg dose as the recommended dose. The 25-mg dose appears less effective, but also has substantial evidence of overall efficacy from:

- superiority to placebo on the WASO endpoint in two independent studies
- superiority on the independently supportive endpoint of sTST in two independent studies
- a “win” for the LPS endpoint in one of two studies with effects of similar magnitude in both studies
- acceptable evidence of clinically meaningful benefit associated with the observed treatment effects

Given lack of major meaningful group-level differences in safety or tolerability between the 50- and 25-mg doses, but consistently numerically greater benefit with the 50-mg dose, one approach is to label 50 mg as the recommended dose for the general insomnia disorder population. The 25-mg dose could be used as a stepdown dose in case of lack of tolerability for the 50-mg dose without changing the indication from “treatment of insomnia characterized by difficulties with sleep onset OR maintenance.” However, a stepdown approach in the dosage and administration section was not studied in the clinical development program and will not necessarily improve tolerability for an individual patient. Given the greater dose-response relationship for efficacy than for safety between 25 mg and 50 mg, a blanket recommendation to start with the 25-mg dose is also not justified because, depending on the clinical situation, there are patients for whom a prescriber may view the greater expected benefit of the 50-mg dose to be of sufficient clinical importance to bypass the 25-mg dose, particularly in light of the small differences in safety and tolerability between the 25-mg and 50-mg doses. In addition, an approach of starting at either 25 mg or 50 mg is supported by the designs of the registration studies, which did not employ a titration approach. Therefore, both doses should be recommended in the dosage and administration section and information to differentiate the benefits and risks of the doses should be included in the prescribing information, including in the special populations section, to support dose selection decisions in clinical practice.

6.3.2. Next Day Functioning

Issue

(b) (4)

Background

Although insomnia is distressing in and of itself, such that improvement in sleep only may be considered clinically meaningful, the B criterion for a diagnosis of Insomnia Disorder in DSM-5 requires that “The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.” Thus, impairment of daytime function (for a person with primarily diurnal activity) is an important element of insomnia disorder, such that its improvement would also be of potential clinical significance (provided adequate magnitude).

Clinical Reviewer Comment: This conclusion is consistent with the findings of the Applicant’s patient preference study EVM-22357, using a discrete choice experiment questionnaire administered at baseline and Month 3 to participants in Trials ID-078A301 and ID-078A302 with the objectives to “identify insomnia patients’ perspectives on which treatment attributes are most valuable to them” and to quantify “the trade-offs that subjects are willing to make between attributes of insomnia treatments.” This study, on face, supported the importance to patients of daytime functioning as a treatment outcome. Because it is clear that reduction of impairments in daytime function associated with insomnia would be of great significance for patients with insomnia disorder, and because the patient preference study did not specifically evaluate the importance of daytime sleepiness/fatigue, that study is not reviewed in detail.

The IDSIQ is a novel patient-reported outcome assessment developed by the Applicant to assess and evaluate change in impairments in daytime function in patients with insomnia.

The IDSIQ comprises three subscales, each assessing patient perceptions of their daytime function in one of three domains: sleepiness, alertness/cognition, and mood.

This issue thus comprises two questions. First, are the instrument and its sleepiness domain subscale fit for purpose, and contingently, second, is there substantial evidence for clinically meaningful drug effect on the endpoints defined by the instrument?

Assessment

(b) (4)

as next day impairment forms a part of the diagnostic criteria for insomnia disorder and is intrinsically meaningful. Sleepiness in the face of demand for alertness is typically distressing and is a marker of sleep drive that presents risk for serious harm to self and others (e.g., in the context of operating machinery in a setting that requires vigilance). Thus, the first question is “Is the instrument fit for purpose?”

6.3.2.1. IDSIQ Sleepiness Fitness for Purpose

The development of IDSIQ was initiated in 2008. Several modifications were made to reach the final version of IDSIQ. In the Advice Letter dated May 3, 2018, the final version of IDSIQ sleepiness domain was considered acceptable for inclusion as a secondary efficacy endpoint in phase 3 trials. Evidence from qualitative studies and other psychometric property evaluation supports that the IDSIQ sleepiness subscale is fit for purpose. Content validity of IDSIQ sleepiness domain was established and confirmed through literature review, qualitative input from subjects with insomnia, Rasch analysis, and exploratory and confirmatory factor analyses. Assessment results of interitem correlations, internal consistency, test-retest reliability, known groups validity, responsiveness, and meaningful change showed acceptable measurement properties of IDSIQ sleepiness domain.

The clinical construct it targets is meaningful, relevant, and nonredundant with other outcome measures used. It comprises four items, one of which assesses sleepiness, which can be thought of as representing sleep drive, and three of which assess fatigue, which can be thought of as describing deficit in wake drive. Subjective assessment of these symptoms is expected to have limited correlation with level of objective sleep deprivation because patients habituate to sleep deprivation such that subjective effects plateau while performance impairments continue to increase (Van Dongen et al. 2003). On the other hand, excess daytime sleepiness and fatigue are common symptoms of sleep deficit and disturbed sleep architecture, and cause distress and potentially objective impairment in function. Thus, while improvement in this domain may exhibit independence from improvement in nighttime sleep (assessed either subjectively or objectively), it is also a treatment outcome desired and valued by patients with insomnia disorder.

It is reasonably sensitive to change. Anchor-based analyses also showed that there are clear separations between the 50 mg treatment arm and placebo arm in the eCDF curves by treatment arm at the estimated thresholds of clinical meaningful within patient change in IDSIQ sleepiness domain scores from baseline to Month 1 and from baseline to Month 3. However, separation was minimal between the 25 mg treatment arm and placebo arm in the eCDF curves at the estimated thresholds of clinically meaningful within patient change in IDSIQ sleepiness domain scores

from baseline to Month 1 and from baseline to Month 3. As reported in Section 19.1.2, the threshold for clinically meaningful improvement ranged approximately from 5 to 10 points or 25 to 50% reduction from the mean subject baseline score of approximately 20 (out of a maximum of 40).

6.3.2.2. Adequacy of Evidence (b) (4)

Given the evidence provided for the IDSIQ's fitness for purpose, is there substantial evidence for efficacy in this domain?

The 50-mg dose demonstrated superiority to placebo in the prespecified analysis for Trial ID-078A301 on the IDSIQ sleepiness domain score. The treatment effect was approximately 2 points at both 1 and 3 months with approximately 10% of patients (placebo subtracted) experiencing a clinically meaningful improvement on this measure (see page 5361). However, no significant effect was found for the 25-mg dose in either Trial ID-078A301 or ID-078A302. See Sections 6.2.2.2 and 6.2.2.3. Thus, the efficacy at 50 mg is not independently supported by other evidence of efficacy for this endpoint. (b) (4)

(b) (4) the significant evidence of moderately clinically meaningful efficacy for daridorexant 50 mg in reducing daytime sleepiness provided by effects on the IDSIQ sleepiness subscale requires support from a second adequate and well-controlled trial.

6.3.2.3. Conclusion

We find the IDSIQ sleepiness domain subscale to be fit for purpose. However, in light of only a single study (Trial ID-078A301) and single dose (50 mg) supporting statistically significant improvement on the IDSIQ sleepiness domain, we conclude that there is not sufficient evidence (b) (4) of improvement in next day function (b) (4), because there is no independent substantiation of this finding. In addition, the 50 mg results are not supported by other contextual factors such as another statistically significant result in another active treatment arm at a different dose or in another closely related outcome measure. The small p-value on the 50 mg dose is not adequate to obviate the need for confirmatory evidence in this condition for this outcome, because confirming the result would not be impracticable or unethical and even a robust result can be a result of bias or chance. This shortcoming may be addressed by a second adequate and well-controlled study to substantiate the effects of the 50-mg dose on next day sleepiness in patients with insomnia disorder.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The nonclinical program for daridorexant included an adequate battery of genotoxicity studies: repeat dose general toxicology studies in the mouse for up to 28 days, rat for up to 26 weeks, and dog for up to 39 weeks; 2-year and 6-month carcinogenicity studies in the rat and Tg.rasH2 mouse, respectively; a complete battery of reproductive and developmental toxicology studies in the rat and/or rabbit; juvenile rat toxicology study; special toxicology studies; and studies to

qualify impurities. All pivotal toxicology studies were conducted under good laboratory practice (GLP). The major human metabolites of daridorexant (M1, M3, and M10) are adequately qualified in nonclinical studies as the exposure levels in the nonclinical species (general toxicology studies in the rat and dog, carcinogenicity study in the rat, and embryofetal development studies in the rat and rabbit) are equal to or higher than the clinical exposure at the maximum recommended human dose (MRHD) of 50 mg.

The target organs in the nonclinical studies and their clinical relevance are summarized and discussed below.

7.1.1. CNS

In animal studies (mouse, rat, and dog), daridorexant induced multiple CNS clinical signs, ranging from decreased activity in all animal species at lower doses to intermittent head tremors or head shaking and cataplexy-like clinical signs (sudden onset of muscle weakness in the presence of positive stimulation) in the dog at high doses. The mild hypnotic-sedative effects at lower doses are expected based on the pharmacology of orexin receptor antagonism and are not considered to be adverse. The cataplexy-like effects at higher doses in the dog are due to the exaggerated pharmacology of orexin receptor antagonists. Drug-related cataplexy was not associated with long term neurological effects or microscopic brain lesions. Nevertheless, given the nature of cataplexy, particularly the sudden onset, they are considered to be adverse.

The no observed adverse effect level (NOAEL)/no observed effect level for cataplexy is 20 mg/kg/day in the dog,¹ which provides a 3-fold margin relative to the MRHD of 50 mg based on both C_{max} and AUC.² Although the safety margin is relatively small, no cataplexy was observed at the MRHD in phase 3 and long-term extension clinical studies. Therefore, the potential risk of drug-related cataplexy at the proposed clinical doses appears to be relatively low.

7.1.2. Liver

In the mouse, rat, and dog studies, repeat oral administration of daridorexant caused dose-dependent increases in hepatocellular hypertrophy or hepatomegaly at ≥ 100 mg/kg/day in the mouse, ≥ 50 mg/kg/day in the rat, and ≥ 30 mg/kg/day in the dog. The histopathology changes correlated with increased liver weight and elevations in liver enzymes (e.g., alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase [GGT], and/or glutamate dehydrogenase). At lower doses, these changes were generally mild and reversible and

¹ This NOEAL is based on the 13-week dog study.

² Because cataplexy is primarily C_{max} driven, the safety margin for cataplexy was calculated by both C_{max} and AUC, which provided comparable safety margins.

are considered to be adaptive in response to the enzyme induction effects of daridorexant. This is further supported by the following in vitro and in vivo findings:

- Daridorexant and its major metabolites activate human pregnane X receptor (PXR) in vitro.
- Daridorexant and/or its metabolites M1 and M3 increased mRNA expression of multiple CYP enzymes in primary human hepatocytes.
- In the 4-week repeat dose studies, daridorexant increased mRNA levels of CYP3A1, 2B1, 2B2, UGT1a1, UGT1a6, and UGT2b1 in the rat and CYP3A12 in the dog.

At higher doses, daridorexant induced significant increases in liver enzyme levels and correlative histopathology changes in animals; therefore, these are considered to be adverse ([Table 24](#)).

Table 24. Summary of Daridorexant-Related Adverse Liver Findings in Nonclinical Studies

Species	Duration (weeks)	Dose (mg/kg/day)	Adverse Liver Findings	Exposure Multiples ^a
Rat	26	450	Clinical chemistry: ↑up to 4x in males and 2x in females in GGT; ↑up to 91% in females in triglyceride; ↑up to 86% in females in cholesterol. Liver weight: ↑120% in females and 59% in males. Pathology: centrilobular hepatocellular hypertrophy and liver enlargement in both sexes	13
Dog	39	100	Clinical chemistry: ↑up to 10x in ALT in females; ↑up to 19x in GLDH in females; ↑up to 3x in AST in females; ↑up to 2.5x in GGT in females; ↑up to 3x in ALP in both males and females. Liver weight: ↑~30% in males and 65% in females Pathology: Hepatomegaly in both sexes (homogenous increases in the size and volume of hepatocytes)	37
Mouse	4	1500	Clinical chemistry: ↑up to 3x in ALT in females. Liver weight: ↑60-65% in both sexes Pathology: Focal necrosis (cluster of necrotic cells) in both sexes	0.5 ^b

Source: Summarized from the Applicant's Study Reports

^a, human exposure levels are based on clinical Study AC-078-105, AUC of 6300 ng*hr/mL at the MRHD of 50 mg; b, the small exposure multiple in the mouse study was due to extensive metabolism of daridorexant despite the high doses administered
 Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; GLDH glutamate dehydrogenase

From a nonclinical perspective, the adverse liver findings occurred at relatively large exposure multiples and are clinically monitorable. Therefore, the findings in nonclinical studies do not pose an unacceptable risk at clinically relevant doses. No abnormal changes in liver enzyme levels were observed in the clinical studies.

7.1.3. Thyroid and Pituitary Gland (Primarily in the Rat)

Drug-related changes in thyroid and pituitary gland were observed with repeat administration of daridorexant, primarily in the rat. However, these changes are most likely secondary to the liver enzyme induction effects of the drug. Rats are known to be sensitive to liver enzyme inductions

and increased metabolism of thyroid hormones, which lead to the compensatory activation of the hypothalamus-pituitary-thyroid axis and follicular hyperplasia in the thyroid (Greaves 2011). Given the difference in thyroid hormone metabolism between the rat and human, the clinical relevance of the thyroid and pituitary gland findings in the rat appears to be limited.

In the 26-week rat study, doses tested were 0, 50, 150, and 450 mg/kg/day. At ≥ 150 mg/kg/day, daridorexant caused dose-dependent histopathology of follicular cell hypertrophy in the thyroid, with correlative increases in thyroid stimulating hormone (TSH) levels at ≥ 150 mg/kg/day and decreases in T4 levels at 450 mg/kg/day. In the 2-year rat carcinogenicity study, doses tested were 0, 15, 50, and 150 mg/kg/day. At 150 mg/kg/day, males had numerically increased incidence of follicular adenomas and carcinoma, and females had increased incidence of cystic follicles in the thyroid gland.

In the 4-week rat study, doses tested were 0, 100, 300, and 1000 mg/kg/day. Males treated at 1000 mg/kg/day showed hypertrophy in the pars distalis of the pituitary gland. In the 2-year rat carcinogenicity study, males dosed at 150 mg/kg/day had hyperplasia of the pars distalis in the pituitary gland.

In the 4-week dog study, doses tested were 0, 30, 100 and 300/200 (male/female) mg/kg/day. Similar findings of follicular hypertrophy in the thyroid were observed at ≥ 100 mg/kg/day. However, this effect appeared to be transient because no histopathology changes in the thyroid were observed at doses up to the high dose of 150 mg/kg/day in the 13-week study or at the high dose of 100 mg/kg/day in the 39-week study. Thyroid hormone levels were not affected after 26 and 39 weeks of daridorexant treatment in the dog, which explains the absence of histopathology findings in the thyroid and pituitary gland in the dog.

7.1.4. Gallbladder (Dog)

In the dog studies, drug-related findings in the gallbladder were observed with repeat administration of daridorexant. However, these findings have relatively large safety margins, and there were no similar findings in the clinical studies. Therefore, toxicological and clinical relevance of the gallbladder findings in the dog appears to be limited.

In the dog, dose- and duration-dependent increases in the secretory material in the gallbladder was observed at 600 mg/kg/day after 2 weeks of treatment, 200 mg/kg/day after 4 weeks of treatment, 150 mg/kg/day after 13 weeks of treatment, and 100 mg/kg/day after 39 weeks of treatment. In all cases, the gallbladder structure was normal with no evidence indicative of gallstone formation (such as presence of crystals), and no inflammation was observed after 4 to 39 weeks of treatment. At the most conservative NOAEL of 30 mg/kg/day for gallbladder findings,³ the safety margin relative to the MRHD of 50 mg is ~8-fold.

7.1.5. Cholesterol (Rat and Mouse)

In the mouse and rat, dose-dependent mild-to-moderate increases in plasma cholesterol levels were observed with repeat administration of daridorexant, primarily in females ([Table 25](#)). Dogs were not affected.

³ The lowest NOAEL of 30 mg/kg/day for gallbladder findings is determined from the longest 39-week dog study.

The increases in cholesterol levels are possibly related to the enzyme induction effect of daridorexant via PXR activation and decreased thyroid hormone levels (due to increased metabolism of thyroid hormones). The changes were generally mild and reversible and did not correlate with any other serious histopathology findings.

Given the mild magnitude and monitorable nature of the changes, the increases in cholesterol levels in the mouse and rat studies do not impose an unacceptable risk at therapeutically relevant levels.

Table 25. Daridorexant-Related Increases in Plasma Cholesterol Level

Animal	Duration (weeks)	Dose (mg/kg/day)	Exposure Multiples Relative to MRHD of 50 mg (Based on AUC) ^{a, b}	% Change in Cholesterol Levels	
				Male	Female
Mouse (CByB6F1)	2	1000	-- ^c	↑46%	↑47%
		2000	-- ^c	↑110%	↑98%
Rat (Wistar)	2	600	~7x	--	↑35%
		1000	~10x	--	↑42%
		100	~2x	--	↑42%
	4	300	~7x	--	↑63%
		1000	~16 x	--	↑100%
		150	~4x	--	↑23%
	13	450	~8x	--	↑77%
		150	~4x	↓20%	↑30%
26	450	~8x	↓40%	↑90%	

Source: Summarized from the Applicant's Study Reports

^a, human exposure levels are based on clinical Study AC-078-105, AUC of 6300 ng*hr/mL and C_{max} of 1006 ng/mL

^b, exposure multiples calculated based on female exposure levels in the animal studies because the effects were primarily in females

^c, exposure multiples could not be determined because only AUC_{0-7h} (rather than AUC_{0-24h}) values were available from this nonGLP study; --, not available

Abbreviations: AUC, area under the concentration-time curve; MRHD, maximum recommended human dosage

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Daridorexant's putative mechanism of action in promoting sleep and thus treating insomnia disorder is through inhibition of arousal via antagonism of orexin receptors in the hypothalamus. The orexin system affects a variety of homeostatic functions including arousal/sleep-wake regulation, reward, and feeding (Harris and Aston-Jones 2006). Further, orexin system deficits have been implicated in the pathoetiology of narcolepsy (Harris and Aston-Jones 2006), and orexin is involved in regulating respiratory drive (Nattie and Li 2012).

Therefore, the primary pharmacologically-based risks that may be expected for daridorexant relate to

- symptoms of hypo-arousal and destabilization of arousal states, including somnolence and sedation, narcolepsy/cataplexy (intrusion of sleep into wakeful state), and complex sleep behaviors (intrusion of wakeful state elements into sleep)
- respiratory suppression
- depressive symptoms related to reward-responsiveness such as anhedonia and suicidal ideation
- potentially, changes in appetite or metabolism

Warnings and precautions common to drugs labelled for the treatment of insomnia across pharmacological classes are:

- complex sleep behaviors
- CNS depressant effects and daytime impairment
- worsening of depression/suicidal ideation
- need to evaluate for comorbid diagnoses

Somnolence and related adverse reactions were the most common adverse reaction across drugs labelled for the treatment of insomnia.

DORAs labelled for the treatment of insomnia do not carry any boxed warnings but are contraindicated in patients with narcolepsy. In addition, sleep paralysis, hypnagogic/hypnopompic hallucinations, and cataplexy-like symptoms are listed among the warnings and precautions. Headache and nightmares/abnormal dreams were the common adverse events (AEs) associated with both DORAs currently labelled for the treatment of insomnia.

Benzodiazepines, as a class, carry a boxed warning for the potential to induce respiratory suppression when used concomitantly with opioids. Given the pharmacology of DORAs, it might be expected that they would also present such a risk. FDA research in animal models, however, found that suvorexant neither increased oxycodone exposure nor exhibited pharmacodynamic interaction, and that most nonbenzodiazepine sedative drugs that increased respiratory suppression in interaction with oxycodone substantially increased oxycodone exposure. If daridorexant were expected to increase oxycodone exposure, respiratory suppression would be a concern. However, given daridorexant is not expected to increase the exposure of oxycodone, the concern for potentiation of oxycodone-induced respiratory suppression is obviated by the published findings for suvorexant (Xu et al. 2021).

Finally, there is nonclinical literature implicating the orexin system in regulation of intraocular pressure (Samuels et al. 2017; DeCarlo and Samuels 2020). Based on this literature an orexin receptor agonist might be expected to result in increases in intraocular pressure. However, it is also possible that an antagonist with a short half-life could result in sensitization that would result in increased intraocular pressure during drug trough periods.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Daridorexant is not approved in the US market or in any foreign market; therefore, no postmarketing experience is available.

7.4. FDA Approach to the Safety Review

Safety analysis is focused on

- SAEs observed in all clinical trials for subjects exposed to daridorexant
- Comparative analysis of AE rates and laboratory value changes for Trials ID-078A301, ID-078A302 with supplementation from long-term Trial ID-078A303
- Interpretation of results from dedicated safety studies (e.g., findings from the Driving Study)

Comparative analysis of AEs examined

- Individual AE preferred terms (PTs)
- Standard Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQ)
- FDA MedDRA queries (FMQ)
- Custom group queries (CGQ) defined by the clinical reviewer based on inspection and a priori rational clustering of all listed AE verbatim and preferred AE terms reported for Trials ID-078A301 and ID-078A302 related to adverse events of special interest (representing exaggerated pharmacology of either sedative hypnotic drugs in general, or previously observed recognized DORA-associated AEs) not adequately represented by SMQ or FMQs.

Comparative analysis of AEs focused on detection and evaluation of imbalances in rates of occurrence that were unfavorable compared to placebo. Where no potentially meaningful imbalance was detected but AE categories (e.g., “accidental injury,” “fatigue, somnolence and sedation”) were considered clinically important and consistent with the pharmacology of daridorexant, time-to-event analyses were conducted (where event counts allowed) to evaluate the potential for AE association with daridorexant treatment initiation counterbalanced by subsequent reductions in AE rates attributable to longer term effects of improved sleep.

7.5. Adequacy of Clinical Safety Database

Overall, there were 712 subject years of exposure to drug at any dose, 157 at the proposed recommended dose (50 mg) and 389 at the lowest effective dose (25 mg). Eighty-five subjects were exposed to daridorexant 50 mg and 164 to daridorexant 25 mg for at least a year. The exposures to the drug in the entire development program meet the minimum specified in the International Conference on Harmonisation (ICH) E1A guideline recommendations (March 1995). As seen in [Table 26](#), the total exposed population is >1500; the population exposed for ≥ 1 year is >100.

Clinical Reviewer Comment: Although the population exposed to the maximum dose (50 mg) for ≥ 1 year is slightly below 100, differences in safety findings between 25 mg and 50 mg were minimal overall and tended to favor the 50-mg dose (see e.g., [Table 26](#)).

Table 26. Total Duration of Exposure Across Development Program

Duration of Exposure	Daridorexant				Placebo	
	5 mg	10 mg	25 mg	Ex-Placebo 25 mg	50 mg	Overall
Study 201						
N	60	58	60	-	61	60
Subject-years	4.7	4.6	4.7	-	4.8	4.7
Trial ID-078A301						
N			310	-	308	309
Subject-years			68.1	-	69.2	69.3
Trial ID-078A302						
N		306	308	-		306
Subject-years		68.8	68.3	-		68.6
Trial ID-078A303 ^a						
N		142 ^b	268 ^b	126 ^b	137 ^b	128
Subject-years		86.9	168.5	79.7	83.3	73.0
Overall						
N	60	364	804*		369	1597
At least 3 months	-	285	681*		289	1255
At least 6 months	-	126	341*		122	589
At least 9 months	-	110	301*		103	514
>48 weeks	-	98	189*		96	383
>50 weeks	-	93	186*		95	374
>52 weeks	-	82	164		85	331
Subject-years	4.7	160.3	389.3*		157.3	711.6
Study 202 ^c						
N	56	54	55		56	58

Source: Abridged from Clinical Study Report AC-078A201 table 12-1; Clinical Study Report AC-078A202 table 12-1; Clinical Study Report ID-078A301, table 12-1; Clinical Study Report ID-078A302 table 12-1; 120-Day update, appendix 1 table 15.3.1-1.3, table 15.3.1-1.1, listing 16.2.5-1.1 and listing 16.2.5-1.2.

Note: This table is an updated version of Module 2.7.4 table 1-4. Values that have been updated are in **bold/italic**.

* Includes exposure (N=126; subject-years =79.7) in Trial ID-078A303 from ex-placebo/daridorexant 25 mg subjects.

^a Exposure up to the cut-off date for the 120-Day Safety Update report (Nov 16, 2020).

^b Not included in the Overall N to avoid double-counting of subjects.

^c Study 202 (2-day crossover study) included 58 subjects who received at least one dose of double-blind study treatment. Study was too short to calculate subject-years of exposure and therefore not included in the Overall summary.

Abbreviations: N, number of subjects in treatment arm

Table 27. Duration of Exposure, Trials ID-078A301 and ID-078A302, Safety Population

Variable	078A301			078A302			Pooled	
	Daridorexant 25 mg N=310	Daridorexant 50 mg N=308	PBO N=309	Daridorexant 10 mg N=306	Daridorexant 25 mg N=308	PBO N=306	Daridorexant 25 mg N=618	PBO N=615
Duration of exposure, (days)								
Mean (SD)	80.3 (15.5)	82.1 (11.3)	81.9 (13.1)	82.1 (12.7)	81 (14.5)	81.8 (13.1)	80.6 (15)	81.9 (13.1)
Median (Q1, Q3)	84 (82, 85)	84 (83, 85)	84 (82, 85)	84 (83, 85)	84 (83, 85)	84 (83, 86)	84 (82, 85)	84 (83, 86)
Min, max	2, 122	15, 117	7, 145	5, 121	3, 117	2, 101	2, 122	2, 145
Total exposure (person years)	68	69	69	69	68	69	136	138
Patients treated, by duration, n (%)								
<12 days	5 (1.6)	0	3 (1.0)	2 (0.7)	4 (1.3)	4 (1.3)	9 (1.5)	7 (1.1)
≥12 to <26 days	5 (1.6)	5 (1.6)	2 (0.6)	0	3 (1.0)	1 (0.3)	8 (1.3)	3 (0.5)
≥26 to <50 days	8 (2.6)	5 (1.6)	6 (1.9)	11 (3.6)	9 (2.9)	7 (2.3)	17 (2.8)	13 (2.1)
≥50 to <100 days	291 (93.9)	295 (95.8)	295 (95.5)	288 (94.1)	291 (94.5)	292 (95.4)	582 (94.2)	587 (95.4)
≥100 days	1 (0.3)	3 (1.0)	3 (1.0)	5 (1.6)	1 (0.3)	2 (0.7)	2 (0.3)	5 (0.8)

Source: adex.xpt; Software: R; CDS generated table

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; PBO, placebo; Q1, first quartile; Q3, third quartile; SD, standard deviation

Clinical Reviewer Comment: [Table 27](#) indicates that extents and distributions of exposure differed minimally between treatment arms in both Trials ID-078A301 and ID-078A302, and retention in study was good for all treatment arms. This indicates that crude AE rates can generally be considered as representative, such that safety comparisons are not liable to be substantively changed by consideration of the extent of exposure. Safety Findings and Concerns Based on Review of Clinical Safety Database

7.6. Safety Findings and Concerns, Trials ID-078A301 and ID-078A302

Because the two registration trials were essentially identical in design and conduct, with the exception of the doses studied, and the trial population characteristics were also highly similar (see [Table 6](#), [Table 7](#), and [Table 8](#)), safety findings for the two trials will be presented and discussed jointly.

Rates of SAEs, AEs leading to discontinuation or change in study treatment, and AEs rated as severe in intensity all occurred with frequency <5% in any study arm, and rates in active treatment arms were generally lower than for placebo. AEs leading to dose interruption occurred at rates higher than placebo for active treatment arms in Trial ID-078A302 but not ID-078A301. In the context of low rates of such events overall this does not indicate a signal. Overall Treatment-Emergent Adverse Event Summary, Trials ID-078A301 and ID-078A302.

Table 28. Overview of Adverse Events, Trials ID-078A301 and ID-078A302, Safety Population

Event Category	078A301					078A302				Pooled		
	Daridorexant 25 mg N=310	Daridorexant 50 mg N=308	PBO N=309	RD Between 25 mg and PBO (%)	RD Between 50 mg and PBO (%)	Daridorexant 10 mg N=306	Daridorexant 25 mg N=308	PBO N=306	RD Between 25 mg and PBO (%)	T-541468 25 mg N=618	PBO N=615	RD Between Pooled 25 mg and PBO (%)
	n (%)	n (%)	n (%)	(95% CI)	(95% CI)	n (%)	n (%)	n (%)	(95% CI)	n (%)	n (%)	(95% CI)
SAE	2 (0.6)	2 (0.6)	6 (1.9)	-1.3 (-3.1, 0.5)	-1.3 (-3.1, 0.5)	2 (0.7)	3 (1.0)	4 (1.3)	-0.3 (-2.0, 1.3)	5 (0.8)	10 (1.6)	-0.8 (-2.0, 0.4)
SAEs with fatal outcome	1 (0.3)	0	0	0.3 (-0.3, 1.0)	0 (0, 0)	0	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)
Life- threatening SAEs	0	0	0	0 (0, 0)	0 (0, 0)	0	0	0	0 (0, 0)	0	0	0 (0, 0)
AE leading to permanent discontinuation of study drug	7 (2.3)	2 (0.6)	10 (3.2)	-1.0 (-3.6, 1.6)	-2.6 (-4.8, -0.4)	6 (2.0)	5 (1.6)	7 (2.3)	-0.7 (-2.9, 1.5)	12 (1.9)	17 (2.8)	-0.8 (-2.5, 0.9)
AE leading to dose modification of study drug	3 (1.0)	5 (1.6)	8 (2.6)	-1.6 (-3.7, 0.5)	-1 (-3.2, 1.3)	5 (1.6)	7 (2.3)	2 (0.7)	1.6 (-0.3, 3.5)	10 (1.6)	10 (1.6)	-0.0 (-1.4, 1.4)
AE leading to interruption of study drug	3 (1.0)	5 (1.6)	8 (2.6)	-1.6 (-3.7, 0.5)	-1 (-3.2, 1.3)	5 (1.6)	7 (2.3)	2 (0.7)	1.6 (-0.3, 3.5)	10 (1.6)	10 (1.6)	-0.0 (-1.4, 1.4)
AE leading to reduction of study drug	0	0	0	0 (0, 0)	0 (0, 0)	0	0	0	0 (0, 0)	0	0	0 (0, 0)
AE leading to dose delay of study drug	0	0	0	0 (0, 0)	0 (0, 0)	0	0	0	0 (0, 0)	0	0	0 (0, 0)
Other	0	0	0	0 (0, 0)	0 (0, 0)	0	0	0	0 (0, 0)	0	0	0 (0, 0)

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Event Category	078A301					078A302				Pooled		
	Daridorexant 25 mg N=310 n (%)	Daridorexant 50 mg N=308 n (%)	PBO N=309 n (%)	RD Between 25 mg and PBO (%) (95% CI)	RD Between 50 mg and PBO (%) (95% CI)	Daridorexant 10 mg N=306 n (%)	Daridorexant 25 mg N=308 n (%)	PBO N=306 n (%)	RD Between 25 mg and PBO (%) (95% CI)	T-541468 25 mg N=618 n (%)	PBO N=615 n (%)	RD Between Pooled 25 mg and PBO (%) (95% CI)
AE	128 (41.3)	120 (39.0)	114 (36.9)	4.4 (-3.3, 12.1)	2.1 (-5.6, 9.7)	131 (42.8)	126 (40.9)	110 (35.9)	5.0 (-2.7, 12.6)	254 (41.1)	224 (36.4)	4.7 (-0.8, 10.1)
Death	1 (0.3)	0	0	0.3 (-0.3, 1.0)	0 (0, 0)	0	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)
Life-threatening	0	0	0	0 (0, 0)	0 (0, 0)	0	0	0	0 (0, 0)	0	0	0 (0, 0)
Severe	4 (1.3)	4 (1.3)	7 (2.3)	-1.0 (-3.1, 1.1)	-1.0 (-3.1, 1.1)	3 (1.0)	4 (1.3)	4 (1.3)	-0.0 (-1.8, 1.8)	8 (1.3)	11 (1.8)	-0.5 (-1.9, 0.9)
Moderate	40 (12.9)	53 (17.2)	44 (14.2)	-1.3 (-6.7, 4.1)	3.0 (-2.8, 8.7)	48 (15.7)	44 (14.3)	48 (15.7)	-1.4 (-7.0, 4.2)	84 (13.6)	92 (15.0)	-1.4 (-5.3, 2.5)
Mild	83 (26.8)	63 (20.5)	63 (20.4)	6.4 (-0.3, 13.1)	0.1 (-6.3, 6.4)	80 (26.1)	78 (25.3)	58 (19.0)	6.4 (-0.2, 12.9)	161 (26.1)	121 (19.7)	6.4 (1.7, 11.1)

Source: adae.xpt; Software: R; CDS generated table

Treatment-emergent adverse events defined as the events occurred up to 30 days after double-blind study treatment, discontinuation, or until enrollment in the extension study

Duration includes the double-blind treatment period and the placebo run-out period

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; PBO, placebo; RD, risk difference; SAE, serious adverse event

Clinical Reviewer Comment: *The clinical reviewer performed a quality check on the classification of AE intensity and found likely misclassification in a small number of cases in each trial. Specifically, the definition of “mild” intensity in the study protocols (the event may be noticeable to the subject, it does not usually influence daily activities, and normally does not require intervention) is largely inconsistent with a change in treatment, particularly for an AE judged to be treatment-related.*

- *In Trial ID-078A301, six subjects experienced a TEAE rated as mild in intensity that resulted in treatment change (interruption or discontinuation of study drug) and was also assessed as treatment-related (three in the 25 mg arm and three in the placebo arm).*
- *In Trial ID-078A302, two subjects experienced a TEAE rated as mild in intensity that resulted in treatment change (interruption or discontinuation of study drug) and was also assessed as treatment-related (one in the 25 mg arm and one in the 10 mg arm).*

This does not raise concern regarding study validity or validity of exploratory analyses reliant upon AE intensity ratings because of the low overall number of misclassifications, which are balanced across treatment arms.

7.6.1. Deaths, Trials ID-078A301 and ID-078A302

There was one death in total in Trials ID-078A301 and ID-078A302, combined. This event occurred in the 25 mg treatment arm of Trial ID-078A301, in Subject (b) (6), a 78-year-old male with history of stroke, hypertension, and systolic murmur on cardiac examination (ECG normal) receiving appropriate concomitant medications for these conditions. In addition, he had high cholesterol, which was untreated. On Day 49 of treatment, he experienced cardiac arrest leading to hospitalization and death on the same day.

Clinical Reviewer Comment: *Although death was treatment-emergent, this subject was at relatively high risk for a cardiovascular death, based on age and medical history. There is no evident mechanistic association between orexin receptor antagonism and heart attack that would increase the index of suspicion and no substantial or dose dependent imbalance of events indicative of ischemic heart disease (two additional events in the 10 mg arm of Trial ID-078A302) that would be indicative of a potential signal independent of mechanistic plausibility. Those events occurred in Subject (b) (6), a 67-year-old female with a history of smoking and borderline high cholesterol at baseline with subsequent diagnosis of arteriosclerotic heart disease and coronary sclerosis in hospital following reported dizziness and chest pressure/pain. ECG showed borderline depressed ST segment in V5 and a single ventricular extrasystole. Further, it was noted that the subject began to experience decreased appetite from study Day 14 to Day 77. This symptom may in fact have been attributable to her microvascular coronary artery disease, which can manifest with gastrointestinal symptoms. Thus, her ischemic event appears better attributable to her prior medical condition than to treatment with study drug, despite investigator attribution of the event to study drug.*

7.6.2. Serious Adverse Events, Trials ID-078A301 and ID-078A302

There were fairly few SAEs, particularly considering that approximately 40% of each study population was ≥ 65 years of age. The small negative risk differences for most SAEs for drug versus placebo arms indicates no general signal for SAEs associated with treatment (see [Table 29](#)). Fall and injury SAEs were rare and not more common in drug than placebo arms, and thus falls and injuries are discussed irrespective of seriousness or severity (see Section [7.7.1.4](#)). The SAE of vertigo occurred in one subject and may be more usefully considered as being subsumed under the AE grouping of Dizziness discussed in Section [7.7.1.3](#). Most other SAEs lacked plausible potential relation to drug treatment.

SAEs of schizophrenia and syncope warrant discussion, however:

- The SAE of schizophrenia (exacerbation) occurred in Subject (b) (6) in the 25 mg treatment group of Trial ID-078A302. The subject was a 50-year-old female who had been included despite a prior diagnosis of schizophrenia and was unmedicated for this condition at the time. The SAE occurred on study Day 15 and involved persecutory delusions and hallucinations with associated suicidal ideation culminating in a possible suicide attempt (although the nature of the action was unclear): “The subject became conspicuous at the main railway station, after having deliberately driven her car against a pillar/lantern. She told the rescue services she hit the pillar because some voices told her they would chop her head off.” Based on clinical review of the subject case narrative, it appears that her insomnia was secondary to her psychotic disorder, as was her suicidal ideation (and possible attempt) and does not appear to be related to drug effect. Because psychotic exacerbations are typically an initially gradual process followed by an accelerating increase in severity, it may be expected that the subject was experiencing a gradual increase of psychotic symptoms beginning prior to active treatment initiation, given the fairly short interval from treatment initiation to emergence of overt psychotic symptoms. In psychotic patients with persecutory delusions, insomnia is often a presenting complaint in the experience of this clinical reviewer.

Suicidal ideation has been associated with other DORAs and was present in this case. However, in this case there was no evidence of depressed mood or motivation, which may constitute a pharmacologically plausible mechanism for such an association. In this case the most likely causal attribution is exacerbation of underlying psychotic disorder resulting in distressing persecutory delusions and hallucinations in the context of no effective antipsychotic treatment regimen being followed.

- All other psychiatric SAEs occurred in the placebo arms.

SAEs of syncope occurred in two placebo-arm subjects in each study (ID-078A301 and ID-078A302), and in one subject in the 50 mg arm of Trial ID-078A301. Thus, crude incidence does not support a potential causal role for daridorexant. With such a low event rate, examination of the 50-mg dose-exposed subject is warranted, however.

Subject [REDACTED]^{(b) (6)}, experienced apparently interrelated SAEs of syncope, postprocedural hemorrhage, and hemoglobin decreased with the hemorrhage as the proximal causal factor for her decreased hemoglobin and syncope. Thus, syncope was almost certainly unrelated to sedative-hypnotic effects of daridorexant in this case. The hemorrhage is best explained by her preexisting condition of hemorrhoids. There is no evidence that the drug caused a coagulopathy that could have contributed to her hemorrhage as she had no other symptoms of coagulopathy nor AE report of coagulopathy.

Table 29. Serious Adverse Events by System Organ Class and Preferred Term, Trials ID-078A301 and ID-078A302, Safety Population

System Organ Class Preferred Term	078A301					078A302				Pooled		
	Daridorexant 25 mg N=310 n (%)	Daridorexant 50 mg N=308 n (%)	PBO N=309 n (%)	RD Between 25 mg and PBO (%) (95% CI)	RD Between 50 mg and PBO (%) (95% CI)	Daridorexant 10 mg N=306 n (%)	Daridorexant 25 mg N=308 n (%)	PBO N=306 n (%)	RD Between 25 mg and PBO (%) (95% CI)	Daridorexant 25 mg N=618 n (%)	PBO N=615 n (%)	RD Between Pooled 25 mg and PBO (%) (95% CI)
Cardiac disorders (SOC)	1 (0.3)	0	0	0.3 (-0.3, 1.0)	0 (0, 0)	1 (0.3)	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)
Cardiac arrest	1 (0.3)	0	0	0.3 (-0.3, 1.0)	0 (0, 0)	0	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)
Microvascular coronary artery disease	0	0	0	0 (0, 0)	0 (0, 0)	1 (0.3)	0	0	0 (0, 0)	0	0	0 (0, 0)
Ear and labyrinth disorders (SOC)	0	0	0	0 (0, 0)	0 (0, 0)	1 (0.3)	0	0	0 (0, 0)	0	0	0 (0, 0)
Vertigo	0	0	0	0 (0, 0)	0 (0, 0)	1 (0.3)	0	0	0 (0, 0)	0	0	0 (0, 0)
General disorders and administration site conditions (SOC)	1 (0.3)	0	0	0.3 (-0.3, 1.0)	0 (0, 0)	0	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)
Influenza like illness	1 (0.3)	0	0	0.3 (-0.3, 1.0)	0 (0, 0)	0	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)
Infections and infestations (SOC)	0	2 (0.6)	1	-0.6 (-1.5, 0.2)	-0.6 (-1.5, 0.2)	0	0	0	0 (0, 0)	0	2 (0.3)	-0.3 (-0.8, 0.1)
Anal abscess	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	-0.3 (-1, 0.3)	0	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Herpes zoster	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	-0.3 (-1, 0.3)	0	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Injury, poisoning and procedural complications (SOC)	0	1 (0.3)	1 (0.3)	-0.3 (-1.0, 0.3)	0 (-0.9, 0.9)	0	2 (0.7)	0	-0.7 (-1.6, 0.2)	0	3 (0.5)	-0.5 (-1.0, 0.1)
Post procedural haemorrhage	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 1)	0	0	0	0 (0, 0)	0	0	0 (0, 0)
Joint dislocation	0	0	0	0 (0, 0)	0 (0, 0)	0	1 (0.3)	0	-0.3 (-1.0, 0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Meniscus injury	0	0	0	0 (0, 0)	0 (0, 0)	0	1 (0.3)	0	-0.3 (-1.0, 0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Ankle fracture	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	-0.3 (-1, 0.3)	0	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.5, 0.2)

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System Organ Class Preferred Term	078A301					078A302				Pooled		
	Daridorexant 25 mg N=310 n (%)	Daridorexant 50 mg N=308 n (%)	PBO N=309 n (%)	RD Between 25 mg and PBO (%) (95% CI)	RD Between 50 mg and PBO (%) (95% CI)	Daridorexant 10 mg N=306 n (%)	Daridorexant 25 mg N=308 n (%)	PBO N=306 n (%)	RD Between 25 mg and PBO (%) (95% CI)	Daridorexant 25 mg N=618 n (%)	PBO N=615 n (%)	RD Between Pooled 25 mg and PBO (%) (95% CI)
	Investigations (SOC)	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 1)	0	0	0	0 (0, 0)	0	0
Haemoglobin decreased	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 1)	0	0	0	0 (0, 0)	0	0	0 (0, 0)
Musculoskeletal and connective tissue disorders (SOC)	0	0	0	0 (0, 0)	0 (0, 0)	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Rotator cuff syndrome	0	0	0	0 (0, 0)	0 (0, 0)	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps) (SOC)	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 1)	0	0	0	0 (0, 0)	0	0	0 (0, 0)
Adenocarcinoma of colon	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 1)	0	0	0	0 (0, 0)	0	0	0 (0, 0)
Nervous system disorders (SOC)	0	1 (0.3)	2 (0.6)	-0.6 (-1.5, 0.2)	-0.3 (-1.4, 0.8)	0	1 (0.3)	0	0.3 (-0.3, 1.0)	1 (0.2)	2 (0.3)	-0.2 (-0.7, 0.4)
Lumbar radiculopathy	0	0	0	0 (0, 0)	0 (0, 0)	0	1 (0.3)	0	0.3 (-0.3, 1.0)	1 (0.2)	0	0.2 (-0.2, 0.5)
Syncope	0	1 (0.3)	2 (0.6)	-0.6 (-1.5, 0.2)	-0.3 (-1.4, 0.8)	0	0	0	0 (0, 0)	0	2 (0.3)	-0.3 (-0.8, 0.1)
Psychiatric disorders (SOC)	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	-0.3 (-1, 0.3)	0	1 (0.3)	0	0.3 (-0.3, 1.0)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.4)
Schizophrenia	0	0	0	0 (0, 0)	0 (0, 0)	0	1 (0.3)	0	0.3 (-0.3, 1.0)	1 (0.2)	0	0.2 (-0.2, 0.5)
Depression	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	-0.3 (-1, 0.3)	0	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Panic attack	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	-0.3 (-1, 0.3)	0	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Respiratory, thoracic, and mediastinal disorders (SOC)	0	0	0	0 (0, 0)	0 (0, 0)	0	1 (0.3)	0	0.3 (-0.3, 1.0)	1 (0.2)	0	0.2 (-0.2, 0.5)
Haemoptysis	0	0	0	0 (0, 0)	0 (0, 0)	0	1 (0.3)	0	0.3 (-0.3, 1.0)	1 (0.2)	0	0.2 (-0.2, 0.5)

System Organ Class Preferred Term	078A301					078A302				Pooled		
	Daridorexant 25 mg N=310 n (%)	Daridorexant 50 mg N=308 n (%)	PBO N=309 n (%)	RD Between 25 mg and PBO (%) (95% CI)	RD Between 50 mg and PBO (%) (95% CI)	Daridorexant 10 mg N=306 n (%)	Daridorexant 25 mg N=308 n (%)	PBO N=306 n (%)	RD Between 25 mg and PBO (%) (95% CI)	Daridorexant 25 mg N=618 n (%)	PBO N=615 n (%)	RD Between Pooled 25 mg and PBO (%) (95% CI)
Vascular disorders (SOC)	0	0	0	0 (0, 0)	0 (0, 0)	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Hypertensive crisis	0	0	0	0 (0, 0)	0 (0, 0)	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)

Source: adae.xpt; Software: R; CDS generated table

Treatment-emergent adverse events defined as the events occurred up to 30 days after double-blind study treatment, discontinuation, or until enrollment in the extension study
 Duration includes the double-blind treatment period and the placebo run-out period.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; PBO, placebo; RD, risk difference; SOC, system organ class

7.6.3. Dropouts and/or Discontinuations Due to Adverse Events, Trials ID-078A301 and ID-078A302

The overall rate of adverse events leading to discontinuation was no greater than that of placebo for all active treatment arms in both studies; see [Table 28](#). Consistent with a CNS mechanism of action, the AEs most commonly leading to discontinuation were in the Nervous system and Psychiatric system organ classes (SOCs). However, counts for any single PT or grouped FMQ term did not exceed two in any treatment arm for either study, and there was no imbalance of greater than two subjects for any SOC, obviating analysis of imbalances in AEs leading to discontinuation. See [Table 30](#) and [Table 31](#).

Table 30. Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term, Trials ID-078A301 and ID-078A302, Safety Population

System Organ Class	078A301					078A302				Pooled		
	Daridorexant 25 mg N=310 n (%)	Daridorexant 50 mg N=308 n (%)	PBO N=309 n (%)	RD Between 25 mg and PBO (%) (95% CI)	RD Between 50 mg and PBO (%) (95% CI)	Daridorexant 10 mg N=306 n (%)	Daridorexant 25 mg N=308 n (%)	PBO N=306 n (%)	RD Between 25 mg and PBO (%) (95% CI)	Daridorexant 25 mg N=618 n (%)	PBO N=615 n (%)	RD Between Pooled 25 mg and PBO (%) (95% CI)
Cardiac disorders (SOC)	0	1 (0.3)	1 (0.3)	-0.3 (-1.0, 0.3)	0 (-0.9, 0.9)	1 (0.3)	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Supraventricular extrasystoles	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 1)	0	0	0	0 (0, 0)	0	0	0 (0, 0)
Microvascular coronary artery disease	0	0	0	0 (0, 0)	0 (0, 0)	1 (0.3)	0	0	0 (0, 0)	0	0	0 (0, 0)
Atrial tachycardia	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	-0.3 (-1, 0.3)	0	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Ear and labyrinth disorders (SOC)	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	-0.3 (-1, 0.3)	0	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Tinnitus	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	-0.3 (-1, 0.3)	0	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Gastrointestinal disorders (SOC)	1 (0.3)	0	0	0.3 (-0.3, 1.0)	0 (0, 0)	0	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)
Colitis ulcerative	1 (0.3)	0	0	0.3 (-0.3, 1.0)	0 (0, 0)	0	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)
General disorders and administration site conditions (SOC)	0	0	0	0 (0, 0)	0 (0, 0)	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Discomfort	0	0	0	0 (0, 0)	0 (0, 0)	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Infections and infestations (SOC)	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	-0.3 (-1, 0.3)	0	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Anal abscess	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	-0.3 (-1, 0.3)	0	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.5, 0.2)

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System Organ Class Preferred Term	078A301					078A302				Pooled		
	Daridorexant 25 mg N=310 n (%)	Daridorexant 50 mg N=308 n (%)	PBO N=309 n (%)	RD Between 25 mg and PBO (%) (95% CI)	RD Between 50 mg and PBO (%) (95% CI)	Daridorexant 10 mg N=306 n (%)	Daridorexant 25 mg N=308 n (%)	PBO N=306 n (%)	RD Between 25 mg and PBO (%) (95% CI)	Daridorexant 25 mg N=618 n (%)	PBO N=615 n (%)	RD Between Pooled 25 mg and PBO (%) (95% CI)
	Injury, poisoning and procedural complications (SOC)	1 (0.3)	0	2 (0.6)	-0.3 (-1.4, 0.8)	-0.6 (-1.5, 0.2)	0	0	0	0 (0, 0)	1 (0.2)	2 (0.3)
Ankle fracture	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	-0.3 (-1, 0.3)	0	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Sedation	1 (0.3)	0	1 (0.3)	-0.0 (-0.9, 0.9)	-0.3 (-1, 0.3)	0	0	0	0 (0, 0)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.4)
Musculoskeletal and connective tissue disorders (SOC)	0	0	0	0 (0, 0)	0 (0, 0)	2 (0.7)	0	0	0 (0, 0)	0	0	0 (0, 0)
Musculoskeletal pain	0	0	0	0 (0, 0)	0 (0, 0)	1 (0.3)	0	0	0 (0, 0)	0	0	0 (0, 0)
Rheumatoid arthritis	0	0	0	0 (0, 0)	0 (0, 0)	1 (0.3)	0	0	0 (0, 0)	0	0	0 (0, 0)
Nervous system disorders (SOC)	4 (1.3)	0	3 (1.0)	0.3 (-1.3, 2.0)	-1 (-2.1, 0.1)	2 (0.7)	1 (0.3)	3 (1.0)	-0.7 (-1.9, 0.6)	5 (0.8)	6 (1.0)	-0.2 (-1.2, 0.9)
Amnesia	0	0	0	0 (0, 0)	0 (0, 0)	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Dizziness	2 (0.6)	0	0	0.6 (-0.2, 1.5)	0 (0, 0)	1 (0.3)	0	0	0 (0, 0)	2 (0.3)	0	0.3 (-0.1, 0.8)
Paraesthesia	0	0	0	0 (0, 0)	0 (0, 0)	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Poor quality sleep	1 (0.3)	0	0	0.3 (-0.3, 1.0)	0 (0, 0)	0	1 (0.3)	0	0.3 (-0.3, 1.0)	2 (0.3)	0	0.3 (-0.1, 0.8)
Restless legs syndrome	0	0	0	0 (0, 0)	0 (0, 0)	1 (0.3)	0	0	0 (0, 0)	0	0	0 (0, 0)
Sciatica	0	0	0	0 (0, 0)	0 (0, 0)	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Sleep paralysis	1 (0.3)	0	0	0.3 (-0.3, 1.0)	0 (0, 0)	0	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)
Migraine with aura	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	-0.3 (-1, 0.3)	0	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Syncope	0	0	2 (0.6)	-0.6 (-1.5, 0.2)	-0.6 (-1.5, 0.2)	0	0	0	0 (0, 0)	0	2 (0.3)	-0.3 (-0.8, 0.1)

505(b)1 NME NDA 214985
 Daridorexant (Quviviq) for Insomnia

System Organ Class Preferred Term	078A301					078A302				Pooled		
	Daridorexant 25 mg N=310 n (%)	Daridorexant 50 mg N=308 n (%)	PBO N=309 n (%)	RD Between 25 mg and PBO (%) (95% CI)	RD Between 50 mg and PBO (%) (95% CI)	Daridorexant 10 mg N=306 n (%)	Daridorexant 25 mg N=308 n (%)	PBO N=306 n (%)	RD Between 25 mg and PBO (%) (95% CI)	Daridorexant 25 mg N=618 n (%)	PBO N=615 n (%)	RD Between Pooled 25 mg and PBO (%) (95% CI)
	Psychiatric disorders (SOC)	1 (0.3)	0	2 (0.6)	-0.3 (-1.4, 0.8)	-0.6 (-1.5, 0.2)	1 (0.3)	4 (1.3)	3 (1.0)	0.3 (-1.4, 2.0)	5 (0.8)	5 (0.8)
Apathy	0	0	0	0 (0, 0)	0 (0, 0)	0	1 (0.3)	0	0.3 (-0.3, 1.0)	1 (0.2)	0	0.2 (-0.2, 0.5)
Depressed mood	1 (0.3)	0	0	0.3 (-0.3, 1.0)	0 (0, 0)	0	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)
Depression	0	0	0	0 (0, 0)	0 (0, 0)	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Hallucinations, mixed	0	0	0	0 (0, 0)	0 (0, 0)	0	1 (0.3)	0	0.3 (-0.3, 1.0)	1 (0.2)	0	0.2 (-0.2, 0.5)
Hypervigilance	0	0	0	0 (0, 0)	0 (0, 0)	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Irritability	0	0	0	0 (0, 0)	0 (0, 0)	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Nightmare	0	0	0	0 (0, 0)	0 (0, 0)	0	1 (0.3)	0	0.3 (-0.3, 1.0)	1 (0.2)	0	0.2 (-0.2, 0.5)
Schizophrenia	0	0	0	0 (0, 0)	0 (0, 0)	0	1 (0.3)	0	0.3 (-0.3, 1.0)	1 (0.2)	0	0.2 (-0.2, 0.5)
Suicidal ideation	0	0	0	0 (0, 0)	0 (0, 0)	1 (0.3)	0	0	0 (0, 0)	0	0	0 (0, 0)
Insomnia	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	-0.3 (-1, 0.3)	0	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Panic attack	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	-0.3 (-1, 0.3)	0	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Renal and urinary disorders (SOC)	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 1)	0	0	0	0 (0, 0)	0	0	0 (0, 0)
Renal impairment	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 1)	0	0	0	0 (0, 0)	0	0	0 (0, 0)

Source: adae.xpt; Software: R; CDS generated table

Treatment-emergent adverse events defined as the events occurred up to 30 days after double-blind study treatment, discontinuation, or until enrollment in the extension study
 Duration includes the double-blind treatment period and the placebo run-out period.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; PBO, placebo; RD, risk difference; SOC, system organ class

Table 31. FDA MedDRA Queries Leading to Discontinuation, Trials ID-078A301 and ID-078A302, Safety Population

System Organ Class	078A301					078A302				Pooled		
	Daridorexant 25 mg N=310 n (%)	Daridorexant 50 mg N=308 n (%)	PBO N=309 n (%)	RD Between 25 mg and PBO (%) (95% CI)	RD Between 50 mg and PBO (%) (95% CI)	Daridorexant 10 mg N=306 n (%)	Daridorexant 25 mg N=308 n (%)	PBO N=306 n (%)	RD Between 25 mg and PBO (%) (95% CI)	Daridorexant 25 mg N=618 n (%)	PBO N=615 n (%)	RD Between Pooled 25 mg and PBO (%) (95% CI)
Cardiac disorders (SOC)												
Arrhythmia	0	1 (0.3)	1 (0.3)	-0.3 (-1.0, 0.3)	0 (-0.9, 0.9)	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.5, 0.2)	
Tachycardia	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	-0.3 (-1, 0.3)	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.5, 0.2)	
Musculoskeletal and connective tissue disorders (SOC)												
Arthritis	0	0	0	0 (0, 0)	0 (0, 0)	1 (0.3)	0	0 (0, 0)	0	0	0 (0, 0)	
Back pain	0	0	0	0 (0, 0)	0 (0, 0)	0	1 (0.3)	-0.3 (-1.0, 0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)	
Nervous system disorders (SOC)												
Dizziness	2 (0.6)	0	0	0.6 (-0.2, 1.5)	0 (0, 0)	1 (0.3)	0	0 (0, 0)	2 (0.3)	0	0.3 (-0.1, 0.8)	
Paraesthesia	0	0	0	0 (0, 0)	0 (0, 0)	0	1 (0.3)	-0.3 (-1.0, 0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)	
Headache	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	-0.3 (-1, 0.3)	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.5, 0.2)	
Somnolence	1 (0.3)	0	1 (0.3)	-0.0 (-0.9, 0.9)	-0.3 (-1, 0.3)	0	0	0 (0, 0)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.4)	
Syncope	0	0	2 (0.6)	-0.6 (-1.5, 0.2)	-0.6 (-1.5, 0.2)	0	0	0 (0, 0)	0	2 (0.3)	-0.3 (-0.8, 0.1)	
Psychiatric disorders (SOC)												
Depression	1 (0.3)	0	0	0.3 (-0.3, 1.0)	0 (0, 0)	0	1 (0.3)	-0.3 (-1.0, 0.3)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.4)	
Irritability	0	0	0	0 (0, 0)	0 (0, 0)	0	1 (0.3)	-0.3 (-1.0, 0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)	
Parasomnia	1 (0.3)	0	0	0.3 (-0.3, 1.0)	0 (0, 0)	0	1 (0.3)	0.3 (-0.3, 1.0)	2 (0.3)	0	0.3 (-0.1, 0.8)	
Psychosis	0	0	0	0 (0, 0)	0 (0, 0)	0	2 (0.6)	0.6 (-0.2, 1.5)	2 (0.3)	0	0.3 (-0.1, 0.8)	

505(b)1 NME NDA 214985
 Daridorexant (Quviviq) for Insomnia

System Organ Class	078A301					078A302				Pooled		
	Daridorexant 25 mg N=310 n (%)	Daridorexant 50 mg N=308 n (%)	PBO N=309 n (%)	RD Between 25 mg and PBO (%) (95% CI)	RD Between 50 mg and PBO (%) (95% CI)	Daridorexant 10 mg N=306 n (%)	Daridorexant 25 mg N=308 n (%)	PBO N=306 n (%)	RD Between 25 mg and PBO (%) (95% CI)	Daridorexant 25 mg N=618 n (%)	PBO N=615 n (%)	RD Between Pooled 25 mg and PBO (%) (95% CI)
FMQ (Narrow)												
Anxiety	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	-0.3 (-1, 0.3)	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	0	2 (0.3)	-0.3 (-0.8, 0.1)
Insomnia	1 (0.3)	0	1 (0.3)	-0.0 (-0.9, 0.9)	-0.3 (-1, 0.3)	0	1 (0.3)	0	0.3 (-0.3, 1.0)	2 (0.3)	1 (0.2)	0.2 (-0.4, 0.7)

Source: Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as the events occurred up to 30 days after double-blind study treatment, discontinuation, or until enrollment in the extension study
 Duration includes the double-blind treatment period and the placebo run-out period.

Abbreviations: AE, adverse event; CI, confidence interval; FDA, Food and Drug Administration; FMQ, FDA MedDRA query; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event; PBO, placebo; PT, preferred term; RD, risk difference

7.6.4. Treatment-Emergent Adverse Events, Trials ID-078A301 and ID-078A302

Headache and Nasopharyngitis were the only common (i.e., rate $\geq 5\%$) TEAEs occurring at a rate greater than placebo in an active treatment arm ([Table 32](#)).

- **Headache:** The pattern of headache AEs across trials suggested a shallow dose-response for risk of headache with rates of 4% for placebo, 5% for 10 to 25 mg, and 6% for 50 mg. Although no specific causal pathway is evident, headache is a generally plausible adverse reaction for a CNS-active medication.
- **Nasopharyngitis:** Although rates of nasopharyngitis were higher than placebo for some active treatment arms there was no consistent pattern and relatively large variability in the rates such that it does not appear supported to consider this daridorexant-related.

Table 32. Treatment-Emergent Adverse Events¹ Occurring in $\geq 5\%$ of a Treatment Arm and With Higher Frequency in Treatment Arm Than Comparator Arm, Trials ID-078A301 and ID-078A302, Phase 3 Safety Population

	078A301			078A302			Pooled		
	Darido- rexant 25 mg N=310 Preferred Term n (%)	Darido- rexant 50 mg N=308 n (%)	PBO N=309 n (%)	Darido- rexant 10 mg N=306 n (%)	Darido- rexant 25 mg N=308 n (%)	PBO N=306 n (%)	Darido- rexant 25 mg N=618 n (%)	PBO N=615 n (%)	RD Between 25 mg and PBO (%) (95% CI)
Headache	17 (5.5)	20 (6.5)	12 (3.9)	14 (4.6)	15 (4.9)	11 (3.6)	32 (5.2)	23 (3.7)	1.4 (-0.9, 3.7)
Nasopharyngitis	28 (9.0)	24 (7.8)	24 (7.8)	35 (11.4)	13 (4.2)	19 (6.2)	41 (6.6)	43 (7.0)	-0.4 (-3.2, 2.5)

Source: adae.xpt; Software: R

Duration includes the double-blind treatment period and the placebo run-out period.

Treatment-emergent adverse events defined as the events occurred up to 30 days after double-blind study treatment, discontinuation, or until enrollment in the extension study

Coded as MedDRA preferred terms.

Abbreviations: CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects; n, number of subjects with adverse event; PBO, placebo; PT, preferred term; RD, risk difference

Other relatively common TEAES evidencing potentially unfavorable balance compared to placebo included Fatigue, Somnolence, Dizziness, Diarrhea, and Nausea ([Table 33](#)). Fatigue, Somnolence, and Dizziness are discussed later under evaluation of psychomotor impairment/CNS-depressant effects (Sections [7.7.1](#); [7.7.1.1](#) and [7.7.1.3](#)).

Nausea and diarrhea did not exhibit consistent rate patterns across trials that would indicate a dose-response, and the risk difference with placebo ranged from -1 to 1.3 across treatment arms. Although nausea is a generally plausible treatment-related AE for an orally administered drug, there is minimal evidence for such an effect here. Likewise, there is little evidence for diarrhea being a drug effect rather than a chance occurrence related to other environmental exposures.

Table 33. Treatment-Emergent Adverse Events Occurring at ≥2% Frequency in Any Dose Arm and Greater (≥1%) Than Placebo Arm, Trials ID-078A301 and ID-078A302, Safety Population

Preferred Term	078A301			078A302			Pooled		
	Darido- rexant 25 mg N=310 n (%)	Darido- rexant 50 mg N=308 n (%)	PBO N=309 n (%)	Darido- rexant 10 mg N=306 n (%)	Darido- rexant 25 mg N=308 n (%)	PBO N=306 n (%)	Darido- rexant 25 mg N=618 n (%)	PBO N=615 n (%)	RD Between 25 mg and PBO (%) (95% CI)
Fatigue	7 (2.3)	8 (2.6)	2 (0.6)	8 (2.6)	11 (3.6)	2 (0.7)	18 (2.9)	4 (0.7)	2.3 (0.8, 3.7)
Somnolence	11 (3.5)	6 (1.9)	7 (2.3)	7 (2.3)	10 (3.2)	4 (1.3)	21 (3.4)	11 (1.8)	1.6 (-0.2, 3.4)
Headache	17 (5.5)	20 (6.5)	12 (3.9)	14 (4.6)	15 (4.9)	11 (3.6)	32 (5.2)	23 (3.7)	1.4 (-0.9, 3.7)
Dizziness	6 (1.9)	7 (2.3)	2 (0.6)	4 (1.3)	7 (2.3)	5 (1.6)	13 (2.1)	7 (1.1)	1.0 (-0.4, 2.4)
Diarrhoea	8 (2.6)	2 (0.6)	4 (1.3)	4 (1.3)	3 (1.0)	4 (1.3)	11 (1.8)	8 (1.3)	0.5 (-0.9, 1.9)
Nausea	1 (0.3)	8 (2.6)	4 (1.3)	4 (1.3)	4 (1.3)	3 (1.0)	5 (0.8)	7 (1.1)	-0.3 (-1.4, 0.8)
Nasopharyngitis	28 (9.0)	24 (7.8)	24 (7.8)	35 (11.4)	13 (4.2)	19 (6.2)	41 (6.6)	43 (7.0)	-0.4 (-3.2, 2.5)

Source: adae.xpt; Software: R

Duration includes the double-blind treatment period and the placebo run-out period.

Treatment-emergent adverse events defined as the events occurred up to 30 days after double-blind study treatment, discontinuation, or until enrollment in the extension study

Coded as MedDRA preferred terms.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; PBO, placebo; RD, risk difference.

Evaluation of pooled TEAEs using FDA standard MedDRA queries ([Table 34](#)) detected several potential signals:

- **CNS-depressant effects (Somnolence, Fatigue, Confusional State, Dizziness, Syncope, and Vertigo)** -- These are reviewed (albeit sometimes under slightly different groupings) in Section [7.7.1](#) and are considered likely to reflect real drug effects. It should be noted, however, that the Syncope FMQ signal here is primarily derived from the inclusion of dizziness, rather than actual syncopal events, for which there was no signal.
- **Parasomnia** – This signal, that belongs to an established class effect and is considered likely to reflect a true drug effect, is reviewed in Section [7.7.2](#).
- **Psychosis** -- The signal from the Psychosis FMQ derives entirely from events that, on investigation of verbatim reports and where appropriate/available, narratives are attributable to hypnagogic or hypnopompic phenomena. Thus, they do not represent a signal for psychotogenic effects of daridorexant, but rather contribute to the small signal for the known class-effect of parasomnia. These are discussed further in Section [7.7.2](#) under the rubric of Parasomnia.
- **Depression** -- The Depression FMQ signal is discussed in Section [7.7.3](#) and is considered likely to reflect a real drug effect, based on pharmacology and class effects.
- **Headache** –The signal from the Headache FMQ parallels, and is primarily driven by, the Headache PT signal. No PTs unlikely to reflect the true construct of ‘headache’ were captured under the group query ‘headache’ (in contrast, e.g., to the results for the group query for syncope), and thus, the group query is considered by the clinical reviewer to be more appropriate for reporting in labeling than the individual PT Headache.
- **Cough**—This signal is small, deriving from a very small number of subjects and does not have a clear causal link to active treatment. Review of other DORA labels finds cough reported as occurring in 2% of drug and 1% of placebo-treated subjects for suvorexant, but it is not reported at all in the label for lemborexant. Thus, there is no clear evidence of a class effect that would support interpretation of this minimal signal as attributable to a true drug effect.

- **Arthritis and Arthralgia**—These FMQs are largely overlapping and thus discussed together. In each study, rates were higher for doses ≥ 25 mg than for placebo and presented evidence for a very shallow dose response when using pooled placebo and 25-mg dose rates. These event classes are not reported in the labels for other DORAs but are reported among “Other Reactions Observed During the Premarketing Evaluation” for a number of z-drugs. It is conceivable that a slight imbalance of joint pain and similar adverse events might result from more sustained positioning in joint-stressing postures during sleep as a result of deeper sleep and higher thresholds for arousal due to physical discomfort with sedative hypnotic medications. Because such effects, if in fact attributable to drug, are not considered to have clinically significant implications in the dosing range proposed for labeling, labeling of this small potential signal is not warranted.

Table 34. FDA MedDRA Queries¹ Occurring at Higher Frequency in Treatment Arm Than Comparator Arm With Pooled Risk-Difference for 25 mg vs. Placebo $\geq 0.6\%$, Trials ID-078A301 and ID-078A302, Phase 3 Safety Population

FDA MedDRA Query, Broad	078A301			078A302			Pooled		
	Daridorexant 25 mg N=310 n (%)	Daridorexant 50 mg N=308 n (%)	PBO N=309 n (%)	Daridorexant 10 mg N=306 n (%)	Daridorexant 25 mg N=308 n (%)	PBO N=306 n (%)	Daridorexant 25 mg N=618 n (%)	PBO N=615 n (%)	RD Between 25 mg and PBO (%) (95% CI)
Somnolence (FMQ)	20 (6.5)	14 (4.5)	11 (3.6)	15 (4.9)	23 (7.5)	6 (2.0)	43 (7.0)	17 (2.8)	4.2 (1.8, 6.6)
Fatigue	7 (2.3)	8 (2.6)	2 (0.6)	8 (2.6)	11 (3.6)	2 (0.7)	18 (2.9)	4 (0.7)	2.3 (0.8, 3.7)
Somnolence	11 (3.5)	6 (1.9)	7 (2.3)	7 (2.3)	10 (3.2)	4 (1.3)	21 (3.4)	11 (1.8)	1.6 (-0.2, 3.4)
Hypersomnia	1 (0.3)	0	0	0	2 (0.6)	0	3 (0.5)	0	0.5 (-0.1, 1.0)
Lethargy	0	0	0	0	1 (0.3)	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Sedation	1 (0.3)	0	2 (0.6)	0	0	0	1 (0.2)	2 (0.3)	-0.2 (-0.7, 0.4)
Fatigue (FMQ)	18 (5.8)	14 (4.5)	9 (2.9)	15 (4.9)	21 (6.8)	6 (2.0)	39 (6.3)	15 (2.4)	3.9 (1.6, 6.1)
Fatigue	7 (2.3)	8 (2.6)	2 (0.6)	8 (2.6)	11 (3.6)	2 (0.7)	18 (2.9)	4 (0.7)	2.3 (0.8, 3.7)
Somnolence	11 (3.5)	6 (1.9)	7 (2.3)	7 (2.3)	10 (3.2)	4 (1.3)	21 (3.4)	11 (1.8)	1.6 (-0.2, 3.4)
Asthenia	1 (0.3)	0	0	1 (0.3)	0	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Lethargy	0	0	0	0	1 (0.3)	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Confusional state (FMQ)	15 (4.8)	6 (1.9)	7 (2.3)	9 (2.9)	11 (3.6)	5 (1.6)	26 (4.2)	12 (2.0)	2.3 (0.3, 4.2)
Somnolence	11 (3.5)	6 (1.9)	7 (2.3)	7 (2.3)	10 (3.2)	4 (1.3)	21 (3.4)	11 (1.8)	1.6 (-0.2, 3.4)
Disturbance in attention	3 (1.0)	0	0	2 (0.7)	1 (0.3)	1 (0.3)	4 (0.6)	1 (0.2)	0.5 (-0.2, 1.2)
Confusional state	1 (0.3)	0	0	0	0	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Headache (FMQ)	19 (6.1)	21 (6.8)	15 (4.9)	14 (4.6)	16 (5.2)	11 (3.6)	35 (5.7)	26 (4.2)	1.4 (-1.0, 3.9)
Headache	17 (5.5)	20 (6.5)	12 (3.9)	14 (4.6)	15 (4.9)	11 (3.6)	32 (5.2)	23 (3.7)	1.4 (-0.9, 3.7)
Head discomfort	2 (0.6)	1 (0.3)	1 (0.3)	0	0	0	2 (0.3)	1 (0.2)	0.2 (-0.4, 0.7)
Migraine with aura	0	0	1 (0.3)	0	1 (0.3)	0	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.4)
Tension headache	0	1 (0.3)	0	0	0	0	0	0	0 (0, 0)
Migraine	0	1 (0.3)	1 (0.3)	0	0	0	0	1 (0.2)	-0.2 (-0.5, 0.2)

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 Daridorexant (Quviviq) for Insomnia

FDA MedDRA Query, Broad	078A301			078A302			Pooled		
	Daridorexant 25 mg N=310 n (%)	Daridorexant 50 mg N=308 n (%)	PBO N=309 n (%)	Daridorexant 10 mg N=306 n (%)	Daridorexant 25 mg N=308 n (%)	PBO N=306 n (%)	Daridorexant 25 mg N=618 n (%)	PBO N=615 n (%)	RD Between 25 mg and PBO (%) (95% CI)
	Depression (FMQ)	4 (1.3)	4 (1.3)	2 (0.6)	5 (1.6)	6 (1.9)	1 (0.3)	10 (1.6)	3 (0.5)
Overdose	1 (0.3)	1 (0.3)	0	2 (0.7)	2 (0.6)	0	3 (0.5)	0	0.5 (-0.1, 1.0)
Apathy	1 (0.3)	2 (0.6)	0	0	1 (0.3)	0	2 (0.3)	0	0.3 (-0.1, 0.8)
Depressed mood	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	0	2 (0.3)	0	0.3 (-0.1, 0.8)
Depressive symptom	0	0	0	0	1 (0.3)	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Feeling of despair	1 (0.3)	0	0	0	0	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Suicidal ideation	0	0	0	1 (0.3)	1 (0.3)	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Dysphoria	0	0	1 (0.3)	1 (0.3)	0	0	0	1 (0.2)	-0.2 (-0.5, 0.2)
Depression	0	0	1 (0.3)	0	0	1 (0.3)	0	2 (0.3)	-0.3 (-0.8, 0.1)
Arthritis (FMQ)	5 (1.6)	5 (1.6)	1 (0.3)	4 (1.3)	6 (1.9)	5 (1.6)	11 (1.8)	6 (1.0)	0.8 (-0.5, 2.1)
Arthralgia	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.6)	1 (0.3)	4 (0.6)	2 (0.3)	0.3 (-0.5, 1.1)
Joint swelling	0	2 (0.6)	0	0	2 (0.6)	0	2 (0.3)	0	0.3 (-0.1, 0.8)
Cervicobrachial syndrome	0	0	0	0	1 (0.3)	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Neck pain	2 (0.6)	1 (0.3)	0	1 (0.3)	0	1 (0.3)	2 (0.3)	1 (0.2)	0.2 (-0.4, 0.7)
Spinal osteoarthritis	1 (0.3)	0	0	0	0	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Spinal pain	0	0	0	0	1 (0.3)	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Osteoarthritis	0	1 (0.3)	0	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.4)
Rheumatoid arthritis	0	0	0	1 (0.3)	0	0	0	0	0 (0, 0)
Arthropathy	0	0	0	0	0	1 (0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Joint range of motion decreased	0	0	0	0	0	1 (0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Musculoskeletal stiffness	0	1 (0.3)	0	0	0	1 (0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)

505(b)1 NME NDA 214985
 Daridorexant (Quviviq) for Insomnia

FDA MedDRA Query, Broad	078A301			078A302			Pooled		
	Daridorexant 25 mg N=310	Daridorexant 50 mg N=308	PBO N=309	Daridorexant 10 mg N=306	Daridorexant 25 mg N=308	PBO N=306	Daridorexant 25 mg N=618	PBO N=615	RD Between 25 mg and PBO (%) (95% CI)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Cough (FMQ)	1 (0.3)	2 (0.6)	0	3 (1.0)	5 (1.6)	1 (0.3)	6 (1.0)	1 (0.2)	0.8 (-0.0, 1.6)
Cough	1 (0.3)	2 (0.6)	0	3 (1.0)	3 (1.0)	1 (0.3)	4 (0.6)	1 (0.2)	0.5 (-0.2, 1.2)
Allergic cough	0	0	0	0	1 (0.3)	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Haemoptysis	0	0	0	0	1 (0.3)	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Dizziness (FMQ)	7 (2.3)	9 (2.9)	5 (1.6)	4 (1.3)	8 (2.6)	5 (1.6)	15 (2.4)	10 (1.6)	0.8 (-0.8, 2.4)
Dizziness	6 (1.9)	7 (2.3)	2 (0.6)	4 (1.3)	7 (2.3)	5 (1.6)	13 (2.1)	7 (1.1)	1.0 (-0.4, 2.4)
Vertigo	1 (0.3)	2 (0.6)	2 (0.6)	1 (0.3)	1 (0.3)	0	2 (0.3)	2 (0.3)	-0.0 (-0.6, 0.6)
Labyrinthitis	0	0	1 (0.3)	0	0	0	0	1 (0.2)	-0.2 (-0.5, 0.2)
Psychosis (FMQ)	2 (0.6)	1 (0.3)	0	1 (0.3)	4 (1.3)	1 (0.3)	6 (1.0)	1 (0.2)	0.8 (-0.0, 1.6)
Hypnagogic hallucination	0	0	0	0	2 (0.6)	0	2 (0.3)	0	0.3 (-0.1, 0.8)
Hallucination, visual	1 (0.3)	0	0	0	0	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Hallucinations, mixed	0	0	0	0	1 (0.3)	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Schizophrenia	0	0	0	0	1 (0.3)	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Paraesthesia	1 (0.3)	1 (0.3)	0	1 (0.3)	0	1 (0.3)	1 (0.2)	1 (0.2)	-0.0 (-0.5, 0.4)
Syncope (FMQ)	7 (2.3)	8 (2.6)	4 (1.3)	6 (2.0)	7 (2.3)	5 (1.6)	14 (2.3)	9 (1.5)	0.8 (-0.7, 2.3)
Dizziness	6 (1.9)	7 (2.3)	2 (0.6)	4 (1.3)	7 (2.3)	5 (1.6)	13 (2.1)	7 (1.1)	1.0 (-0.4, 2.4)
Hypotension	1 (0.3)	0	0	1 (0.3)	0	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Syncope	0	1 (0.3)	2 (0.6)	1 (0.3)	0	0	0	2 (0.3)	-0.3 (-0.8, 0.1)
Vertigo (FMQ)	7 (2.3)	9 (2.9)	5 (1.6)	4 (1.3)	8 (2.6)	5 (1.6)	15 (2.4)	10 (1.6)	0.8 (-0.8, 2.4)
Dizziness	6 (1.9)	7 (2.3)	2 (0.6)	4 (1.3)	7 (2.3)	5 (1.6)	13 (2.1)	7 (1.1)	1.0 (-0.4, 2.4)
Vertigo	1 (0.3)	2 (0.6)	2 (0.6)	1 (0.3)	1 (0.3)	0	2 (0.3)	2 (0.3)	-0.0 (-0.6, 0.6)
Labyrinthitis	0	0	1 (0.3)	0	0	0	0	1 (0.2)	-0.2 (-0.5, 0.2)

505(b)1 NME NDA 214985
 Daridorexant (Quviviq) for Insomnia

FDA MedDRA Query, Broad	078A301			078A302			Pooled		
	Daridorexant 25 mg N=310 n (%)	Daridorexant 50 mg N=308 n (%)	PBO N=309 n (%)	Daridorexant 10 mg N=306 n (%)	Daridorexant 25 mg N=308 n (%)	PBO N=306 n (%)	Daridorexant 25 mg N=618 n (%)	PBO N=615 n (%)	RD Between 25 mg and PBO (%) (95% CI)
Arthralgia (FMQ)	4 (1.3)	4 (1.3)	1 (0.3)	2 (0.7)	5 (1.6)	4 (1.3)	9 (1.5)	5 (0.8)	0.6 (-0.5, 1.8)
Arthralgia	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.6)	1 (0.3)	4 (0.6)	2 (0.3)	0.3 (-0.5, 1.1)
Joint swelling	0	2 (0.6)	0	0	2 (0.6)	0	2 (0.3)	0	0.3 (-0.1, 0.8)
Cervicobrachial syndrome	0	0	0	0	1 (0.3)	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Neck pain	2 (0.6)	1 (0.3)	0	1 (0.3)	0	1 (0.3)	2 (0.3)	1 (0.2)	0.2 (-0.4, 0.7)
Spinal pain	0	0	0	0	1 (0.3)	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Arthropathy	0	0	0	0	0	1 (0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Joint range of motion decreased	0	0	0	0	0	1 (0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Musculoskeletal stiffness	0	1 (0.3)	0	0	0	1 (0.3)	0	1 (0.2)	-0.2 (-0.5, 0.2)

FDA MedDRA Query, Broad	078A301			078A302			Pooled		
	Daridorexant 25 mg N=310 n (%)	Daridorexant 50 mg N=308 n (%)	PBO N=309 n (%)	Daridorexant 10 mg N=306 n (%)	Daridorexant 25 mg N=308 n (%)	PBO N=306 n (%)	Daridorexant 25 mg N=618 n (%)	PBO N=615 n (%)	RD Between 25 mg and PBO (%) (95% CI)
Parasomnia (FMQ)	4 (1.3)	5 (1.6)	4 (1.3)	3 (1.0)	5 (1.6)	1 (0.3)	9 (1.5)	5 (0.8)	0.6 (-0.5, 1.8)
Sleep paralysis	1 (0.3)	1 (0.3)	0	0	2 (0.6)	0	3 (0.5)	0	0.5 (-0.1, 1.0)
Hypnagogic hallucination	0	0	0	0	2 (0.6)	0	2 (0.3)	0	0.3 (-0.1, 0.8)
Nightmare	2 (0.6)	0	1 (0.3)	0	1 (0.3)	1 (0.3)	3 (0.5)	2 (0.3)	0.2 (-0.5, 0.9)
Periodic limb movement disorder	0	0	0	0	1 (0.3)	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Rapid eye movement sleep behaviour disorder	0	0	0	0	1 (0.3)	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Rapid eye movements	0	3 (1.0)	0	0	0	0	0	0	0 (0, 0)
sleep abnormal	0	1 (0.3)	0	1 (0.3)	0	0	0	0	0 (0, 0)
Restless legs syndrome	0	1 (0.3)	0	1 (0.3)	0	0	0	0	0 (0, 0)
Abnormal dreams	1 (0.3)	0	2 (0.6)	2 (0.7)	0	0	1 (0.2)	2 (0.3)	-0.2 (-0.7, 0.4)
Somnambulism	0	0	1 (0.3)	0	0	0	0	1 (0.2)	-0.2 (-0.5, 0.2)

Source: Clinical reviewer extract from CDS generated table. adae.xpt; Software: R
 Duration includes the double-blind treatment period and the placebo run-out period.

Treatment-emergent adverse events defined as the events occurred up to 30 days after double-blind study treatment, discontinuation, or until enrollment in the extension study
 Coded as MedDRA preferred terms.

Abbreviations: FDA, Food and Drug Administration; MedDRA, Medical Dictionary for Regulatory Activities; FMQ, FDA MedDRA query; N, number of subjects in group; n, number of subjects with adverse event; PBO, placebo; PT, preferred term; RD, risk difference; CI, confidence interval

Clinical Reviewer Comment: It is worth noting that there was no concerning evidence of a signal for hypersensitivity reactions to daridorexant. However, it should also be noted (because of potential pharmacological plausibility) that an AE of increased intraocular pressure was reported for a single subject in the Applicant's integrated summary of safety. This AE was treatment emergent on 25 mg daridorexant and rated as mild. Because of the isolated nature of this event, no reliable conclusion can be drawn regarding relatedness to daridorexant and labeling of the event is not warranted. However, postmarketing surveillance should monitor the DORA class for an imbalance of such events.

7.6.5. Duration of Treatment-Emergent Adverse Events of Moderate to Severe Intensity, Trials ID-078A301 and ID-078A302

For the 50-mg dose in Trial ID-078A301, AEs with intensity ratings suggesting clinical meaningfulness (i.e., moderate to severe) were numerically more common than for placebo and had longer median duration resulting in a larger total number of AE days than placebo. For the 25-mg dose in both Trial ID-078A301 and Trial ID-078A302, rates were lower than placebo on each of these metrics. Thus, although the overall and serious AE rates for 25 and 50 mg doses appear very similar, examination of AE intensity and duration suggests that clinically meaningful AE rates do exhibit an overall positive dose-response relationship in the 25 to 50 mg dosing range. While not studied directly, this suggests that it is plausible that a dose reduction from 50 mg to 25 mg in case of poor tolerability of the 50 mg dose could improve tolerability while retaining some efficacy.

Table 35. Duration of Moderate and Severe Adverse Events During Double-Blind and Run-Out Periods, Trials ID-078A301 and ID-078A302, Safety Population

Parameter	078A301			078A302			Pooled	
	Daridorexant 25 mg N=310 n (%)	Daridorexant 50 mg N=308 n (%)	PBO N=309 n (%)	Daridorexant 10 mg N=306 n (%)	Daridorexant 25 mg N=308 n (%)	078A302 PBO N=306 n (%)	Daridorexant 25 mg N=618 n (%)	PBO N=615 n (%)
No. of Subjects with Moderate or Severe AEs	45 (14.5)	57 (18.5)	51 (16.5)	51 (16.7)	48 (15.6)	52 (17.0)	93 (15.0)	103 (16.7)
No. of Moderate or Severe AEs	53	93	80	71	68	77	121	157
Mean No. of Moderate or Severe AEs per Subject with any	1.2	1.6	1.6	1.4	1.4	1.5	1.3	1.5
Duration of Moderate or Severe AEs (days), Missing Imputed								
Mean (SD)	20.5 (28.1)	21.0 (23.5)	20.2 (28.0)	15.6 (20.9)	18.1 (23.9)	19.2 (23.9)	19.1 (25.8)	19.7 (26.0)
Median (Q1, Q3)	7 (2, 25)	11 (5, 33)	9 (2, 24)	8 (3, 18)	8 (2, 25)	8 (4, 24)	7 (2, 25)	8 (3, 24)
Min, Max	1, 92	1, 89	1, 110	1, 111	1, 100	1, 117	1, 100	1, 117
Total duration (days)	1087	1954	1612	1111	1229	1481	2316	3093
Duration of Moderate or Severe AEs (days), Missing Imputed								
Mean (SD)	10.4 (16.0)	16.6 (19.3)	14.1 (24.8)	12.9 (19.3)	12.3 (17.2)	13.4 (17.3)	11.5 (16.7)	13.8 (21.3)
Median (Q1, Q3)	4 (2, 11)	10 (3, 22)	6 (2, 10)	7 (3, 15)	5 (1, 19)	7 (3, 21)	5 (1, 16)	7 (2, 15)
Min, Max	1, 89	1, 89	1, 110	1, 111	1, 100	1, 117	1, 100	1, 117
Total duration (days)	425	1264	918	802	687	871	1112	1789
N(%) of AEs with Missing (End Date)	12 (22.6)	17 (18.3)	15 (18.8)	9 (12.7)	12 (17.6)	12 (15.6)	24 (19.8)	27 (17.2)

Source: adae.xpt; Software: SAS

For an adverse event with missing end date, the analysis end date for the adverse event is imputed as end date of runout period; if both end date for adverse event and end date of runout period were missing, then the analysis end date is imputed as the date of day 91 (84 days of double-blind treatment and 7 days of runout period) since the date of receiving the first dose of study drug

Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; PBO, placebo; Q1, first quartile; Q3, third quartile; SD, standard deviation

7.6.6. Laboratory Findings, Trials ID-078A301 and ID-078A302

With the exception of total cholesterol (high-density lipoprotein and low-density lipoprotein cholesterol values were not obtained by the Applicant) and TSH, there was no indication of a potential effect of daridorexant on laboratory values (blood cell counts, liver function tests, serum chemistry, other serum lipids). Although differences between drug and placebo were also small for cholesterol and TSH, these differences warrant closer inspection because a potentially causal role is supported by the pharmacology (see clinical reviewer comment 2, below) and toxicological findings (Sections [7.1.3](#) and [7.1.5](#)) for daridorexant.

Cholesterol

For total cholesterol, there were imbalances between drug and placebo rates of treatment-emergent level 2 and 3 hypercholesterolemia without a clear dose-response pattern (see [Table 36](#)).

Examination of changes in clinical category of cholesterol from baseline ([Table 37](#)) also presented a somewhat inconsistent pattern. Among those with normal baseline cholesterol (≤ 200 mg/dL) overall rates of shift to elevated cholesterol differed only minimally between arms in both Trial ID-078A301 and ID-078A302. However, changes from normal (≤ 200 mg/dL) or elevated cholesterol (> 200 to ≤ 225 mg/dL) to the highest level of elevated cholesterol (> 225 mg/dL) were appreciably more common for active treatment than placebo in Trial ID-078A301 but less consistently so in Trial ID-078A302.

Thus, there is a potential signal for clinically significant cholesterol elevation with daridorexant compared to placebo.

Table 36. Patients With One or More Lipids Analyte Values Outside Specified Levels, Trials ID-078A301 and ID-078A302, Safety Population

Laboratory Parameter	078A301			078A302			Pooled		
	Daridorexant 25 mg N=310 n (%)	Daridorexant 50 mg N=308 n (%)	PBO N=309 n (%)	Daridorexant 10 mg N=306 n (%)	Daridorexant 25 mg N=308 n (%)	PBO N=306 n (%)	Daridorexant 25 mg N=618 n (%)	PBO N=615 n (%)	Risk Difference (95% CI)
Cholesterol, total, high (mg/dL)									
Level 1 (>200)	205/298 (68.8)	202/303 (66.7)	195/300 (65.0)	221/301 (73.4)	199/295 (67.5)	202/298 (67.8)	404/593 (68.1)	397/598 (66.4)	1.67 (-5.90, 9.24)
Level 2 (>210)	183/298 (61.4)	184/303 (60.7)	155/300 (51.7)	199/301 (66.1)	174/295 (59.0)	173/298 (58.1)	357/593 (60.2)	328/598 (54.8)	9.06 (1.17, 16.95)
Level 3 (>225)	150/298 (50.3)	149/303 (49.2)	115/300 (38.3)	152/301 (50.5)	141/295 (47.8)	129/298 (43.3)	291/593 (49.1)	244/598 (40.8)	10.84 (2.97, 18.71)
Triglycerides, high (mg/dL)									
Level 1 (>150)	128/298 (43.0)	117/303 (38.6)	116/300 (38.7)	135/301 (44.9)	110/295 (37.3)	126/298 (42.3)	238/593 (40.1)	242/598 (40.5)	-0.05 (-7.83, 7.72)
Level 2 (>300)	24/298 (8.1)	22/303 (7.3)	25/300 (8.3)	28/301 (9.3)	20/295 (6.8)	22/298 (7.4)	44/593 (7.4)	47/598 (7.9)	-1.07 (-5.35, 3.21)
Level 3 (>500)	2/298 (0.7)	5/303 (1.7)	5/300 (1.7)	1/301 (0.3)	2/295 (0.7)	4/298 (1.3)	4/593 (0.7)	9/598 (1.5)	-0.02 (-2.06, 2.02)

Source: CDS generated table ad b.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration includes the double-blind treatment period and the placebo run-out period.

Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, number of subjects in treatment arm; n, number of subjects meeting criteria; PBO, placebo

Table 37. Postbaseline Shift of Total Cholesterol and Triglyceride From Each Baseline Categories, Trials ID-078A301 and ID-078A302, Safety Population

Laboratory Test	Baseline	Maximum Postbaseline	078A301			078A302			Pooled	
			Daridorexant 25 mg N=310 n (%)	Daridorexant 50 mg N=308 n (%)	PBO N=309 n (%)	Daridorexant 10 mg N=306 n (%)	Daridorexant 25 mg N=308 n (%)	PBO N=306 n (%)	Daridorexant 25 mg N=618 n (%)	PBO N=615 n (%)
Cholesterol (mg/dl)	≤200		128	137	146	112	130	133	258	279
	≤200		84 (65.6)	90 (65.7)	95 (65.1)	73 (65.2)	86 (66.2)	90 (67.7)	170 (65.9)	185 (66.3)
	>200 - ≤210		18 (14.1)	13 (9.5)	27 (18.5)	11 (9.8)	16 (12.3)	13 (9.8)	34 (13.2)	40 (14.3)
	>210 - ≤225		12 (9.4)	15 (10.9)	15 (10.3)	17 (15.2)	14 (10.8)	17 (12.8)	26 (10.1)	32 (11.5)
	>225		14 (10.9)	19 (13.9)	9 (6.2)	11 (9.8)	14 (10.8)	13 (9.8)	28 (10.9)	22 (7.9)
	>200 - ≤210		29	28	29	22	31	27	60	56
	≤200		4 (13.8)	9 (32.1)	5 (17.2)	2 (9.1)	8 (25.8)	0	12 (20.0)	5 (8.9)
	>200 - ≤210		2 (6.9)	4 (14.3)	6 (20.7)	5 (22.7)	5 (16.1)	7 (25.9)	7 (11.7)	13 (23.2)
	>210 - ≤225		6 (20.7)	5 (17.9)	6 (20.7)	7 (31.8)	6 (19.4)	14 (51.9)	12 (20.0)	20 (35.7)
	>225		17 (58.6)	10 (35.7)	12 (41.4)	8 (36.4)	12 (38.7)	6 (22.2)	29 (48.3)	18 (32.1)
	>210 - ≤225		33	45	44	49	48	52	81	96
	≤200		3 (9.1)	2 (4.4)	2 (4.5)	1 (2.0)	1 (2.1)	5 (9.6)	4 (4.9)	7 (7.3)
	>200 - ≤210		1 (3.0)	1 (2.2)	6 (13.6)	3 (6.1)	4 (8.3)	9 (17.3)	5 (6.2)	15 (15.6)
	>210 - ≤225		6 (18.2)	12 (26.7)	15 (34.1)	18 (36.7)	11 (22.9)	9 (17.3)	17 (21.0)	24 (25.0)
	>225		23 (69.7)	30 (66.7)	21 (47.7)	27 (55.1)	32 (66.7)	29 (55.8)	55 (67.9)	50 (52.1)
	>225		108	93	81	118	86	86	194	167
	≤200		2 (1.9)	0	3 (3.7)	4 (3.4)	1 (1.2)	1 (1.2)	3 (1.5)	4 (2.4)
	>200 - ≤210		1 (0.9)	0	1 (1.2)	3 (2.5)	0	0	1 (0.5)	1 (0.6)
	>210 - ≤225		9 (8.3)	3 (3.2)	4 (4.9)	5 (4.2)	2 (2.3)	4 (4.7)	11 (5.7)	8 (4.8)
	>225		96 (88.9)	90 (96.8)	73 (90.1)	106 (89.8)	83 (96.5)	81 (94.2)	179 (92.3)	154 (92.2)
Missing		12	5	9	5	13	8	25	17	

Laboratory Test	Baseline	Maximum Postbaseline	078A301			078A302			Pooled	
			Daridorexant 25 mg N=310 n (%)	Daridorexant 50 mg N=308 n (%)	PBO N=309 n (%)	Daridorexant 10 mg N=306 n (%)	Daridorexant 25 mg N=308 n (%)	PBO N=306 n (%)	Daridorexant 25 mg N=618 n (%)	PBO N=615 n (%)
Triglycerides (mg/dL)	≤150		236	249	247	224	234	229	470	476
	≤150		165 (69.9)	181 (72.7)	179 (72.5)	160 (71.4)	180 (76.9)	164 (71.6)	345 (73.4)	343 (72.1)
	>150 - ≤300		66 (28.0)	63 (25.3)	61 (24.7)	56 (25.0)	51 (21.8)	59 (25.8)	117 (24.9)	120 (25.2)
	>300 - ≤500		4 (1.7)	4 (1.6)	6 (2.4)	8 (3.6)	3 (1.3)	5 (2.2)	7 (1.5)	11 (2.3)
	>500		1 (0.4)	1 (0.4)	1 (0.4)	0	0	1 (0.4)	1 (0.2)	2 (0.4)
	>150 - ≤300		58	50	44	69	57	61	115	105
	≤150		5 (8.6)	5 (10.0)	5 (11.4)	4 (5.8)	5 (8.8)	7 (11.5)	10 (8.7)	12 (11.4)
	>150 - ≤300		38 (65.5)	31 (62.0)	30 (68.2)	49 (71.0)	37 (64.9)	44 (72.1)	75 (65.2)	74 (70.5)
	>300 - ≤500		15 (25.9)	11 (22.0)	9 (20.5)	16 (23.2)	14 (24.6)	8 (13.1)	29 (25.2)	17 (16.2)
	>500		0	3 (6.0)	0	0	1 (1.8)	2 (3.3)	1 (0.9)	2 (1.9)
	>300 - ≤500		4	4	7	8	4	8	8	15
	≤150		0	0	0	2 (25.0)	0	1 (12.5)	0	1 (6.7)
	>150 - ≤300		0	1 (25.0)	0	2 (25.0)	2 (50.0)	1 (12.5)	2 (25.0)	1 (6.7)
	>300 - ≤500		3 (75.0)	2 (50.0)	5 (71.4)	3 (37.5)	1 (25.0)	5 (62.5)	4 (50.0)	10 (66.7)
	>500		1 (25.0)	1 (25.0)	2 (28.6)	1 (12.5)	1 (25.0)	1 (12.5)	2 (25.0)	3 (20.0)
	>500		0	0	2	0	0	0	0	2
	≤150		0	0	0	0	0	0	0	0
	>150 - ≤300		0	0	0	0	0	0	0	0
	>300 - ≤500		0	0	0	0	0	0	0	0
	>500		0	0	2 (100.0)	0	0	0	0	2 (100.0)
Missing			12	5	9	5	13	8	25	17

Source: CDS generated table ad b.xpt; Software: R
 Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).
 Duration includes the double-blind treatment period and the placebo run-out period.
 Abbreviations: PBO, placebo

This signal is partially supported by mean changes from baseline that are greater for daridorexant than placebo (see [Table 38](#)). In the 4-week dose-ranging Study 201, all daridorexant-treated arms showed small increases from baseline to end of treatment (4 weeks) in cholesterol compared to placebo or active control (zolpidem 10 mg) without a clear dose-response pattern. In Trial ID-078A301, results were similar, but with some evidence of dose response for 50 mg versus 25 mg. In Trial ID-078A302 on the other hand change from baseline for 25 mg and for placebo differed only slightly, and 10 mg showed a decrease relative to placebo.

Table 38. Change From Baseline in Mean Total Serum Cholesterol, Study 201, Trials ID-078A301 and ID-078A302

Total Cholesterol	Placebo	Daridorexant 5 mg	Daridorexant 10 mg	Daridorexant 25 mg	Daridorexant 50 mg	Zolpidem 10 mg
Study 201 change from baseline to Visit 5, 2nd PSG morning						
Randomized N	N=60	N=60	N=58	N=60	N=61	N=60
Analysis n	57	58	53	57	58	59
Mean (mmol/L)	-0.06	0.1	0.03	0.03	0.04	-0.08
SD	0.62	0.65	0.58	0.61	0.44	0.5
Difference from placebo	0	0.16	0.09	0.09	0.1	-0.02
Difference from placebo in mg/dL	0	6.2	3.5	3.5	3.9	-0.8
Trial ID-078A301 change from baseline to last value in randomized double-blind treatment period						
Randomized N	309	--	--	310	308	--
% treated at baseline with HMG-CoA reductase inhibitor	10.7%	--	--	11.6%	7.8%	--
Analysis n	300	--	--	295	302	--
Mean (mmol/L)	-.05			.01	.04	
SD	.60			.82	.65	
Difference from placebo	0			.06	.09	
Difference from placebo in mg/dL	0			2.3	3.5	
Trial ID-078A302 change from baseline to last value in randomized double-blind treatment period						
Randomized N	306	--	306	308	--	--
% treated at baseline with HMG-CoA reductase inhibitor	11.1%	--	9.2%	7.1%	--	--
Analysis n	298	--	298	294	--	--
Mean (mmol/L)	.04		-.08	.05		
SD	.73		.72	.71		
Difference from placebo	0		-.12	.01		
Difference from placebo in mg/dL	0		-4.64	.39		

Source: Clinical Reviewer extract from Applicant generated table, Study 201 CSR page 893/1109. SD = Standard Deviation Output: T_LABCGTPB_SAF.rtf, Produced by RA on 15JAN2018 14:40 (GMT), Data Extraction Date: 13JUL2017 Program: bio02p.sas Page 27 of 69; 301 CSR & 302 CSR: Table 15.3.4-4.1 - Clinical Chemistry: Observed value and change from baseline to last value in the double-blind study period Safety Set and Table 15.1.6-2.1 Double-blind study treatment concomitant therapies at baseline by anatomical therapeutic chemical class and preferred name, Safety Set. Program: T_LB_CHEM_DESC_LASTDB_SS.sas and Program: T_CM_ATC_PN_ATBL_SS.sas
 Clinical reviewer converted units to mg/dL (multiplying by 38.67 ref: Haney EM, Huffman LH, Bougatsos C, et al. Screening for Lipid Disorders in Children and Adolescents [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2007 Jul. (Evidence Syntheses, No. 47.) Appendix 2. Units of Measure Conversion Formulas. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK33478/>)

Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; SD, standard deviation

Thus, there is some evidence for effects on total cholesterol from clinical studies involving at least 4-week dosing of daridorexant.

***Clinical Reviewer Comment:** Imbalance in baseline statin use is noted generally favoring placebo in Trials ID-078A301 and ID-078A302. The impact of this imbalance on the changes from baseline in cholesterol observed is unknown but would not be expected to lead to an overestimate of the effect of daridorexant on cholesterol.*

This modest signal for a cholesterol increasing effect of daridorexant should be considered in the additional context of findings in mice and rats suggestive of dose-dependent increases in cholesterol and triglycerides (Section [7.1.5](#)):

- *General pharmacological plausibility given the role of orexins in metabolic homeostasis*
- *Finding of a strongly dose-related increase in serum cholesterol for another DORA, suvorexant: 5 mg/dL versus placebo at the 10-mg dose, 6 mg/dL at the 20-mg dose, 7 mg/dL at the 40-mg dose, and 10 mg/dL at the 80-mg dose after 4 weeks of treatment, compared to a 4 mg/dL decrease for placebo (findings from dose-ranging Study 006, as noted in the product label section 6.1 and the medical review p.29)*
- *Uniformly smaller differences from placebo in mean changes in serum cholesterol from baseline for daridorexant than those observed for suvorexant and lack of a consistent dose response pattern*

Conclusion

There is meaningful evidence of a *potential* for daridorexant to cause increases in total cholesterol. However, the clinical data support at most a small effect. This potential harm, if it exists at the proposed doses, appears unlikely to be clinically meaningful, is monitorable, and would be remediable if clinically significant (e.g., through dietary change or use of a statin). The extent of drug effect does not warrant inclusion in the product label.

Thyroid Function

In Trial ID-078A301, treatment-emergent markedly elevated thyrotropin values on laboratory assessment (i.e., >6.6 mIU/L, and not >6.6 present at baseline) were reported for 13 subjects: 6 (25 mg), 6 (50 mg), and 1 (placebo) [information extracted from Trial ID-078A301 CSR section 12.4.7].

In addition, three subjects had TEAEs of Blood thyroid stimulating hormone increased without prior TSH elevation (two on 50-mg dose and one on 25-mg dose), and one had a TEAE with a verbatim of “worsening of hypothyroidism” (50-mg dose). The Applicant reported that for the four subjects with TEAEs of TSH elevation, three had similarly elevated TSH at baseline as well, with TSH changes from baseline to time of AE of 4.4 to 5.8, 5.5 to 6.2, and 5.4 to 4.4, respectively.

In Trial ID-078A302, seven subjects had TEAEs of Hypothyroidism or Blood thyroid stimulating hormone increased: three in the 10 mg arm, one in the 25 mg arm, and one in the

placebo arm. In addition, 61 subjects with normal baseline TSH lab values experienced high TSH lab values during double-blind treatment: 25 (8.3%) in the 10 mg arm, 14 (4.7%) in the 25 mg arm, and 22 (7.4%) in the placebo arm [source: extracted by clinical reviewer from Trial ID-078A302 CSR table 15.3.4-8.1].

Examination of mean changes from baseline in TSH in Trials ID-078A301 and ID-078A302 showed a mean change >0 only for the 25 mg arm in Trial ID-078A301. Thus, there was no consistent pattern or evidence of a dose response in mean change from baseline in TSH.

Conclusion

The nonclinical toxicology studies suggest elevated metabolism of thyroid hormone could cause elevations in TSH (Section 7.1.3). In Trial ID-078A301 there was an imbalance of AEs and laboratory abnormalities following a dose response pattern (consistent with a metabolic induction mechanism) although events were infrequent overall. In Trial ID-078A302 no such pattern was observed. Examination of mean changes in TSH did not provide supportive evidence in relation to AE findings. Evidence for induction of TSH elevations by clinically relevant doses of daridorexant is weak and likely reasonably addressed by postmarketing surveillance, as these events are monitorable and of unclear clinical significance in and of themselves.

7.6.7. Vital Signs Findings, Trials ID-078A301 and ID-078A302

There was no evidence of adverse effects of daridorexant on heart rate, blood pressure, or body weight. Examination of changes from baseline in heart rate and systolic and diastolic blood pressure showed small decrements for all treatment arms. There was no evidence for a drug effect on body weight. There was no indication of treatment-by-age or treatment-by-sex interactions affecting these parameters.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. CNS-Depressant Effects (Symptoms of Hypo-Arousal)

Issue

Induction of symptoms related to hypo-arousal are a primary concern for sedative-hypnotic medications, including DORAs.

These symptoms can be grouped under the following headings:

- Somnolence/sedation AEs: These describe events of decreased wakefulness (e.g., fatigue, sedation) or increased sleep drive (e.g., somnolence).
- Cognitive impairment AEs: These describe events related to decreased wakefulness as manifested by suppression of normal cognitive function when alert (e.g., feeling foggy, hungover, or confused).

- Fall risk AEs (syncope, dizziness, and disturbances of balance or coordination): These describe psychomotor manifestations that may occur in states of suppressed arousal (e.g., dizziness).
- Fall and injury AEs: These describe sequelae of hypo-arousal and its associated impairments in vigilance and psychomotor planning that may be expected to result in a greater likelihood of accidental injury.

Further, it is important to understand if these risks are persistent throughout treatment or are particularly associated with treatment initiation in order to guide patient and prescriber vigilance for adverse effects in this domain.

Background

The serious risk to patients and others posed by hypo-arousal in terms of increased risk for accidents and injuries is self-evident. Further, when not desired or situationally appropriate, symptoms of hypo-arousal are distressing in and of themselves.

Assessment of this risk in the context of treatment of insomnia disorder is complicated by the potentially competing effects of an effective treatment (Morin et al. 2020). Insomnia disorder involves less than sufficient sleep typically resulting in symptoms of sleep-deprivation and symptoms of hypo-arousal during intended wake periods. Effective treatment would therefore be expected to reduce those symptoms. Thus, although the drug could cause hypo-arousal for some, if effective, the net effect should be a reduction of its manifestations. Indeed, in the registration trials we see that the risk for falls and injuries in the placebo groups over the course of the entire trial was greater than or equal to the risk in active treatment groups. To parse out drug-effect driven symptoms of hypo-arousal from those attributable to insomnia itself, time-to-event analysis could be useful if drug effects are most evident at the beginning of treatment and patients adjust to the drug. Indeed, the driving study findings support this hypothesis see Section [17.2](#)).

Assessment

7.7.1.1. Somnolence/Sedation

The standard FDA MedDRA query “Somnolence” captured AEs occurring in Trials ID-078A301 and ID-078A302 with the PTs Fatigue, Somnolence, Hypersomnia, Sedation, and Lethargy.

- (1) *Is there a drug effect?* The pharmacology of daridorexant supports the conclusion that the crude rate differences indicating higher rates for Somnolence AEs with drug than placebo for all active treatment arms in both registration trials results from a true drug effect.
- (2) *Is there a treatment initiation effect?* Time-to-event analysis for the first occurrence of an AE with any of these PTs shows a small treatment initiation effect with separation from placebo (equal for 25 and 50-mg doses) in the first 1 to 2 days of treatment in Trial ID-078A301 ([Figure 7](#)) and a larger treatment initiation effect for the 25-mg dose in Trial ID-078A302 ([Figure 8](#)).
- (3) *Is the drug effect limited to the initiation period or are Somnolence AEs attributable to drug liable to continue accruing over time?* Events continued to accrue over the entire course of treatment in all arms, but the accrual rates tended to decline over time,

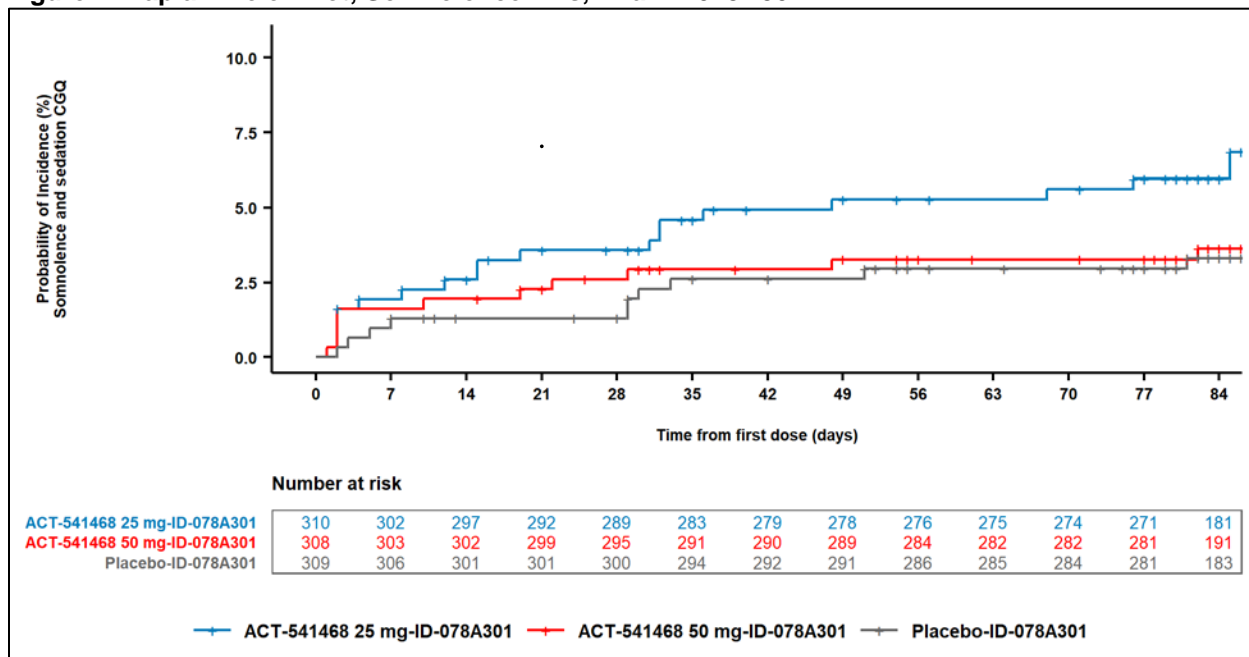
consistent with progressive improvement from baseline in insomnia observed for all treatment arms. In Trial ID-078A301 there was little evidence of difference between arms in the rate of event accrual beyond Day 28. Because rates in the active treatment arms can be considered as deriving from drug-attributable events plus insomnia attributable events minus drug-prevented events, observed equality with placebo is consistent with potential for continued accrual of drug-attributable events over the course of treatment. This interpretation is consistent with the observation of greater mean slope from Day 28 to 84 of treatment for both drug arms compared to placebo in Trial ID-078A302.

- (4) *Are Somnolence AEs attributable to drug dose-dependent in the 25 to 50 mg dosing range?* In Trial ID-078A301, the rates of Somnolence-type AEs were consistently no higher for 50 mg than for 25 mg over time, and the total crude rates were lower (4.5% for 50 mg versus 6.5% for 25 mg). This is contrary to the positive dose-response observed for Somnolence rates with 25 mg versus 10 mg versus placebo in Trial ID-078A302 but consistent with the numerically greater observed efficacy of 50 mg than 25 mg in treating insomnia that might support a higher rate of prevention of insomnia-attributable Somnolence AEs.

The 10-mg dose in Trial ID-078A302 had minimal separation from placebo in treatment response for objective sleep endpoints, such that its effects in producing Somnolence AEs is unlikely to be substantially masked by efficacy over placebo. Nonetheless, a clear separation in the survival curves for Somnolence between placebo and 10 mg can be observed. This finding and the clear separation of the 25 mg dose survival curve from both 10 mg and placebo suggests that the observation in Trial ID-078A301 of a lower rate of Somnolence AEs for 50 mg than 25 mg and a nearly equal rate to placebo after the 1st month of treatment is either a spurious finding (attributable to uncertainty of estimation in the context of a low overall event rate) or due to masking of adverse drug effects by efficacy effects.

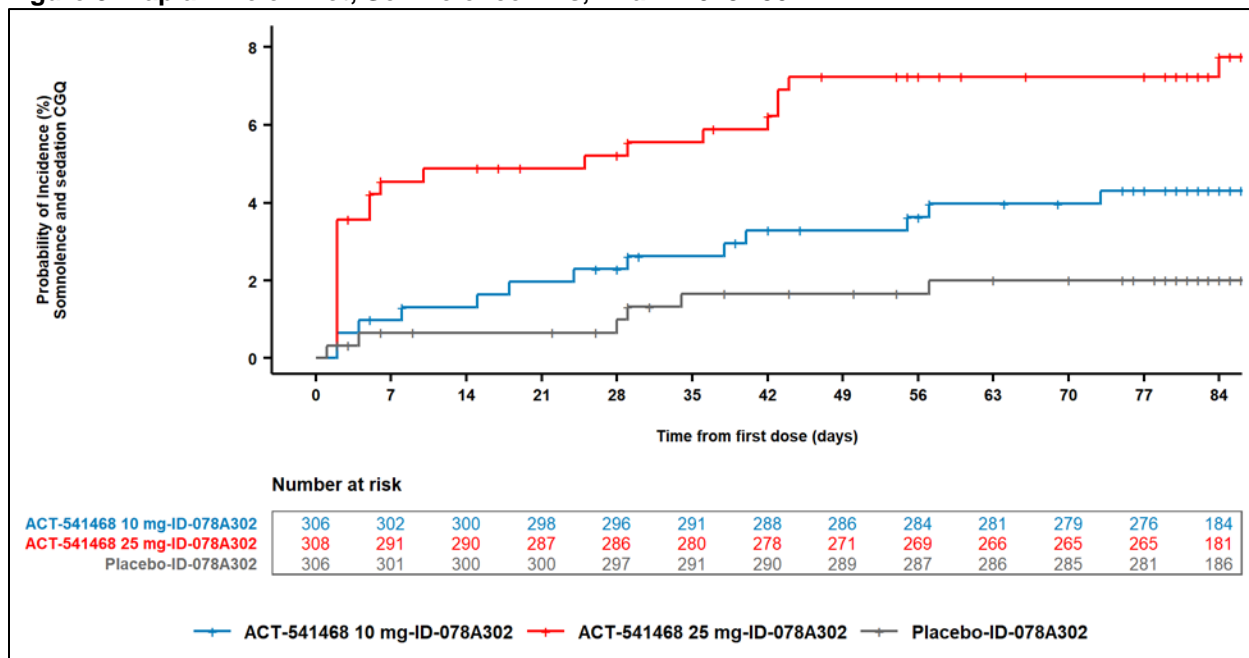
The lower rate of Somnolence AEs for 50 than 25 mg is consistent with the broad confidence intervals for these AE rates and cannot likely be explained by competing prevention of Somnolence AEs by the 50-mg dose. Thus, the observation of higher rates in the 25 mg arm than the 50 mg arm appears likely to be a spurious point estimate occurring in the context of fairly low event rates.

Figure 7. Kaplan-Meier Plot, Somnolence AEs, Trial ID-078A301



Source: CDS generated figure. adsl.xpt, adae.xpt; Software: R
 Abbreviations: AE, adverse event; CGQ, custom group query

Figure 8. Kaplan-Meier Plot, Somnolence AEs, Trial ID-078A302



Source: CDS generated figure. adsl.xpt, adae.xpt; Software: R
 Abbreviations: AE, adverse event; CGQ, custom group query

Clinical Reviewer Comment: The clinical reviewer performed supplementary analyses in JMP on the pooled data from Trial ID-078A301 and ID-078A302 to evaluate the influence of demographic factors on the Somnolence-group AEs on a pooled adae.xls-derived dataset with Somnolence-group AE flags provided by the clinical data scientist. Logistic regression models were run with demographic factors including continuous age

and treatment arm and demographic by treatment arm interactions. In all models tested, treatment arm and age had p-values <0.05 for associations with increased AEs in the Somnolence group. This provides additional support for a causal role of daridorexant in these AEs and indicates subjects' risk for these AEs increased with age, independent of treatment assignment. However, there was no indication in this analysis of an interaction effect between age and treatment to indicate that elderly subjects were more sensitive to adverse sedative effects of daridorexant.

On the other hand, cross tabulation across Trials ID-078A301 and ID-078A302 indicates these AEs occurred at a higher rate in all active treatment arms for subjects 65 years of age or older than for subjects younger than 65 years, whereas for placebo the rate was (minimally) lower in older subjects. The difference in rates between age groups was more pronounced for 25 mg than 50 mg or 10 mg. Because the sample size for the (combined) 25 mg arm in the cross tabulation is roughly twice that for 10 mg and 50 mg arms, the 25 mg arm may be considered to provide a more reliable estimate of the rates. Thus, there is some evidence of potentially increased sensitivity of elderly subjects to adverse sedative effects of daridorexant.

Table 39. Occurrence of Somnolence Group AEs by Age and Dose across Trials ID-078A301 and ID-078A302

	Daridorexant 10 mg		Daridorexant 25 mg		Daridorexant 50 mg		Placebo	
	Age Group		Age Group		Age Group		Age Group	
Somnolence Group AE	<65 years n (%)	≥65 years n (%)	<65 years n (%)	≥65 years n (%)	<65 years n (%)	≥65 years n (%)	<65 years n (%)	≥65 years n (%)
No	177 95.68%	114 94.21%	358 95.21%	217 89.67%	181 95.77%	113 94.96%	362 97.05%	236 97.52%
Yes	8 4.32%	7 5.79%	18 4.79%	25 10.33%	8 4.23%	6 5.04%	11 2.95%	6 2.48%

Source: Clinical reviewer generated table, CDS generated SAS dataset: AESI; Source: ADSL and others (ADAE, FDA FMQ broad dictionary, FDA FMQ narrow dictionary, CGQ dictionary, PT recoding dictionary); Study: 301 and 302; Population: Safety population; Variables added: SOMN_CGQ (Somnolence and Sedation CGQ), NAUS_FM QB (Nausea FMQ Broad), HEAD_FM Q (Headache FMQ narrow); 0 = no-event (if not 1 for those subjects with at least 1 dose of study drugs), 1 = event (if occurred during double-blind treatment and runout period); Cross reference: CDS STF Report (e.g., Tables 14, 26, 2; Table CGQ).
 Abbreviations: n, number of subjects meeting criteria

7.7.1.2. Cognitive impairment

The following AE PTs were grouped as representing adverse events of cognitive impairment:

- Confusional state, Cognitive disorder, Disturbance in attention, Hangover, Feeling abnormal, Psychomotor retardation, Memory impairment, and Amnesia.

Other PTs that could be considered as falling under the rubric of cognitive impairment did not occur in the data. PTs included under the rubric of Somnolence that could also be interpreted as involving reduced or impaired cognition were excluded to ensure independence of these analyses. Hangover was included because review of verbatim descriptions indicated that these events were attributed to treatment by patients/investigators, and cognitive effects are prominent in subjective reports of hangover (Stephens et al. 2008), whereas other more readily describable hangover symptoms (e.g., headache, nausea) appear more likely to be coded by the corresponding AE terms (i.e., headache, nausea, etc.).

- (1) *Is there a drug effect?* The pharmacology of daridorexant supports the conclusion that the crude rate differences indicating higher rates for cognitive impairment AEs with drug than placebo might result from a true drug effect. Cognitive impairment effects were observed in the SAD Study 101 and MAD Study 102 in a dose dependent manner. However, these effects were observed in the context of acute daytime ingestion by healthy subjects, with observed effects correlating with drug concentration (see Sections [14.2.1](#) and [14.2.2](#)).

Table 40. Treatment-Emergent Cognitive Impairment Events, Trials ID-078A301 and ID-078A302

Trial	Arm	PT	Subject ID	Subject	
				Age (years)	Time to First Event (Days)
301	Daridorexant 25 mg	Disturbance in attention	ID-078A301-	(b) (6) 27	7
301	Daridorexant 25 mg	Confusional state	ID-078A301-	25	9
301	Daridorexant 25 mg	Memory impairment	ID-078A301-	62	42
301	Daridorexant 25 mg	Disturbance in attention	ID-078A301-	33	52
301	Daridorexant 50 mg	Hangover	ID-078A301-	67	2
301	Placebo	Feeling abnormal	ID-078A301-	66	3
301	Placebo	Memory impairment	ID-078A301-	66	3
301	Placebo	Feeling abnormal	ID-078A301-	61	8
302	Daridorexant 10 mg	Hangover	ID-078A302-	65	2
302	Daridorexant 10 mg	Hangover	ID-078A302-	45	11
302	Daridorexant 10 mg	Cognitive disorder	ID-078A302-	41	18
302	Daridorexant 10 mg	Disturbance in attention	ID-078A302-	76	21
302	Daridorexant 25 mg	Psychomotor retardation	ID-078A302-	72	2
302	Daridorexant 25 mg	Feeling abnormal	ID-078A302-	59	10
302	Daridorexant 25 mg	Disturbance in attention	ID-078A302-	36	37
302	Daridorexant 25 mg	Cognitive disorder	ID-078A302-	38	82
302	Placebo	Amnesia	ID-078A302-	22	11

Source: Clinical reviewer generated table. adsl.xpt, adae.xpt; MAED
 Abbreviations: PT, preferred term

As seen in [Table 40](#) there was an imbalance of cognitive impairment AEs with low rates over all and lower rates for placebo than active treatment. However, the conditional maximum likelihood estimates rate ratio, stratifying by study and pooling events per subject-years of exposure of 1.6, 95%CI [0.6 to 5.8], did not indicate a significant difference between drug and placebo.⁴ Thus, evidence for a drug effect on cognitive impairment in the day following bedtime use of the drug is less robust and suggests that such adverse reactions are uncommon.

- (2) *Is there a treatment initiation effect?* Time-to-event analysis for the first occurrence of an AE with any of these PTs shows no evidence of a treatment initiation effect as events occurring early in treatment (i.e., <2 weeks or <1 week) appeared to occur at equal rates for drug and placebo.
- (3) *Is the drug effect limited to the initiation period or are Cognitive impairment AEs attributable to drug liable to continue accruing over time?* Events occurring later in treatment (≥ 2 weeks after initiation) were only observed in the active treatment arms,

⁴ Source of calculation: Clinical reviewer analysis using data extracted from Applicant CSRs, Results from OpenEpi, Version 3, open source calculator--PersonTime2 <http://openepi.com/PersonTime2/PersonTime2.htm>.

with a wide range of times to first event. Thus, it is possible that cognitive impairment AEs attributable to drug may continue to accrue.

- (4) *Is there indication of a dose response for Cognitive impairment AEs?* There was no indication of a dose-response relationship nor were events concentrated among subjects 65 years of age or older (subjects who might be considered at greater risk for both spontaneous and drug-induced AEs in this class).

7.7.1.3. Fall, Accident, and Injury Risk Factors (Sensory-Motor Impairments)

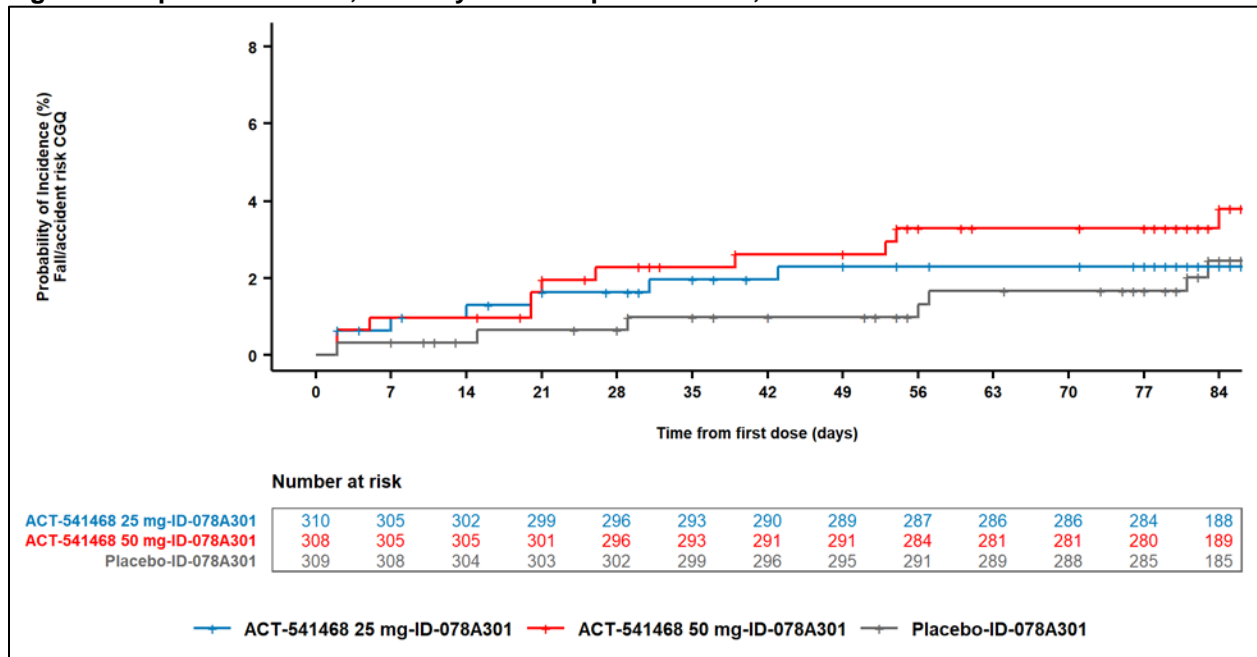
7.7.1.3.1. Evidence From Registration Trials

Sensory-motor symptoms posing increased risk for falls, accidents and injuries were grouped under two grouped queries: the FDA MedDRA query *Dizziness* (comprising PTs Dizziness, Vertigo, and Labyrinthitis), and the clinical reviewer-generated custom grouped query *Disorders of balance and coordination* (comprising PTs Gait disturbance, Coordination abnormal, Tandem Gait test abnormal, and Ataxia, based on rational grouping of observed AEs in Trials ID-078A301 and ID-078A302). Effects on body sway were observed in the SAD Study 101 and MAD Study 102 in a dose-dependent manner. However, these effects were observed in the context of acute daytime ingestion by healthy subjects, with observed effects correlating with drug concentration (see Sections [14.2.1](#) and [14.2.2](#)).

- For *Dizziness*, in Trial ID-078A301, 7 subjects (2.3%) in the 25 mg arm, 9 (2.9%) in the 50 mg arm, and 5 (1.6%) in the placebo arm had treatment-emergent events. In Trial ID-078A302, 4 subjects (1.3%) in the 10 mg arm, 8 (2.6%) in the 25 mg arm, and 5 (1.6%) in the placebo arm had treatment-emergent events.
- For *Disorders of balance and coordination*, in Trial ID-078A301, 0 subjects in the 25 mg arm, 2 (0.6%) in the 50 mg arm, and 1 (0.3%) in the placebo arm had treatment-emergent events. In Trial ID-078A302, 3 subjects (1.0%) in the 10 mg arm, 3 (1.0%) in the 25 mg arm, and 1 (0.3%) in the placebo arm had treatment-emergent events.

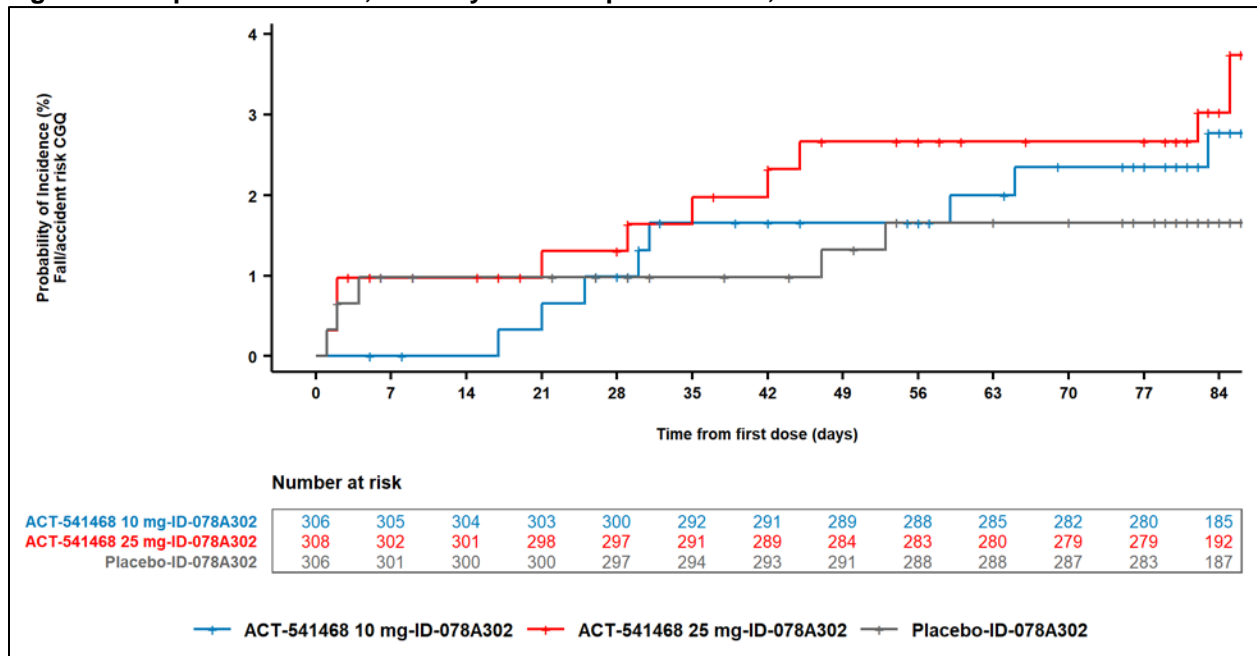
Combining these queries and examining time-to-event suggested a potential dose response for combined sensory motor impairment but no meaningful evidence for a treatment initiation effect (see [Figure 9](#) and [Figure 10](#)).

Figure 9. Kaplan-Meier Plot, Sensory-Motor Impairment GQ, Trial ID-078A301



Source: CDS generated figure adsl.xpt, adae.xpt; Software: R
 Abbreviations: CGQ, custom group query

Figure 10. Kaplan-Meier Plot, Sensory-Motor Impairment GQ, Trial ID-078A302



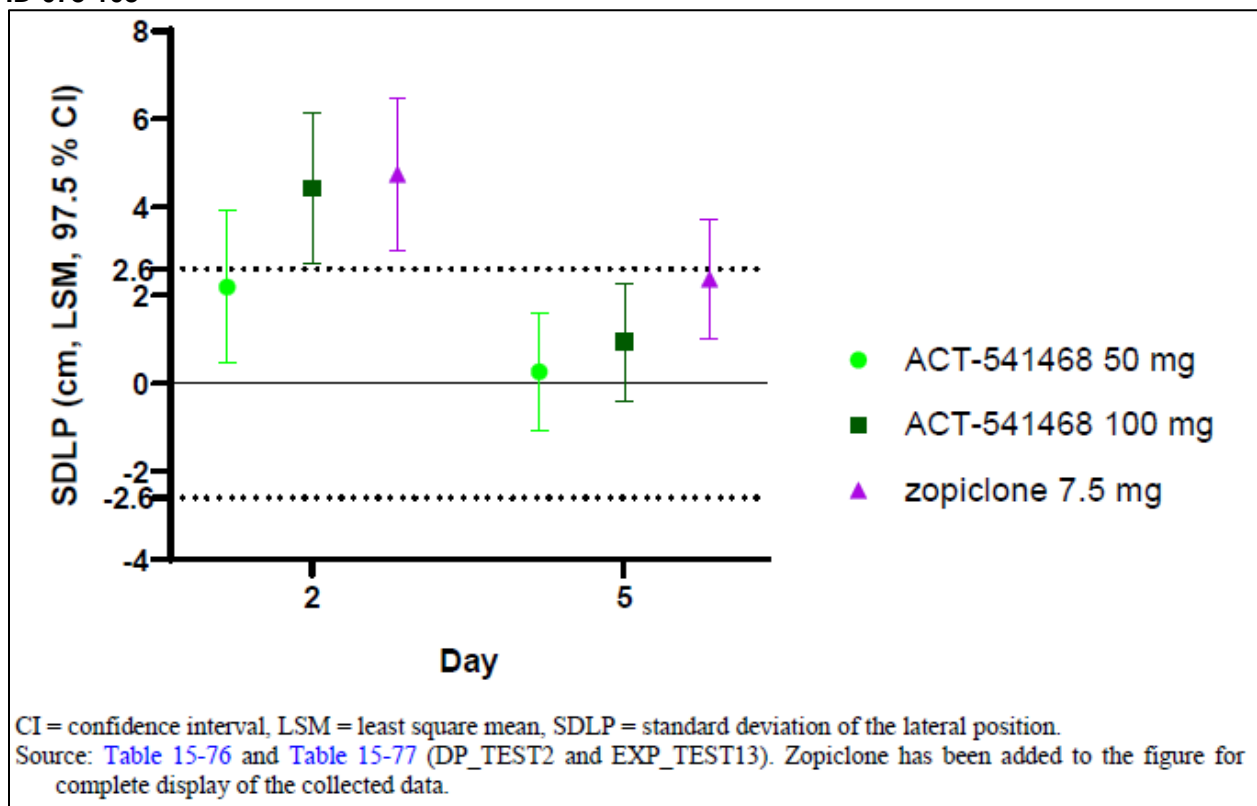
Source: CDS generated figure adsl.xpt, adae.xpt; Software: R
 Abbreviations: CGQ, custom group query

Consistent with the SAD/MAD study observations, sensory motor impairment may be associated with daridorexant, but next day AEs in this domain in the context of appropriate bedtime use were uncommon.

7.7.1.3.2. Evidence From Driving Study

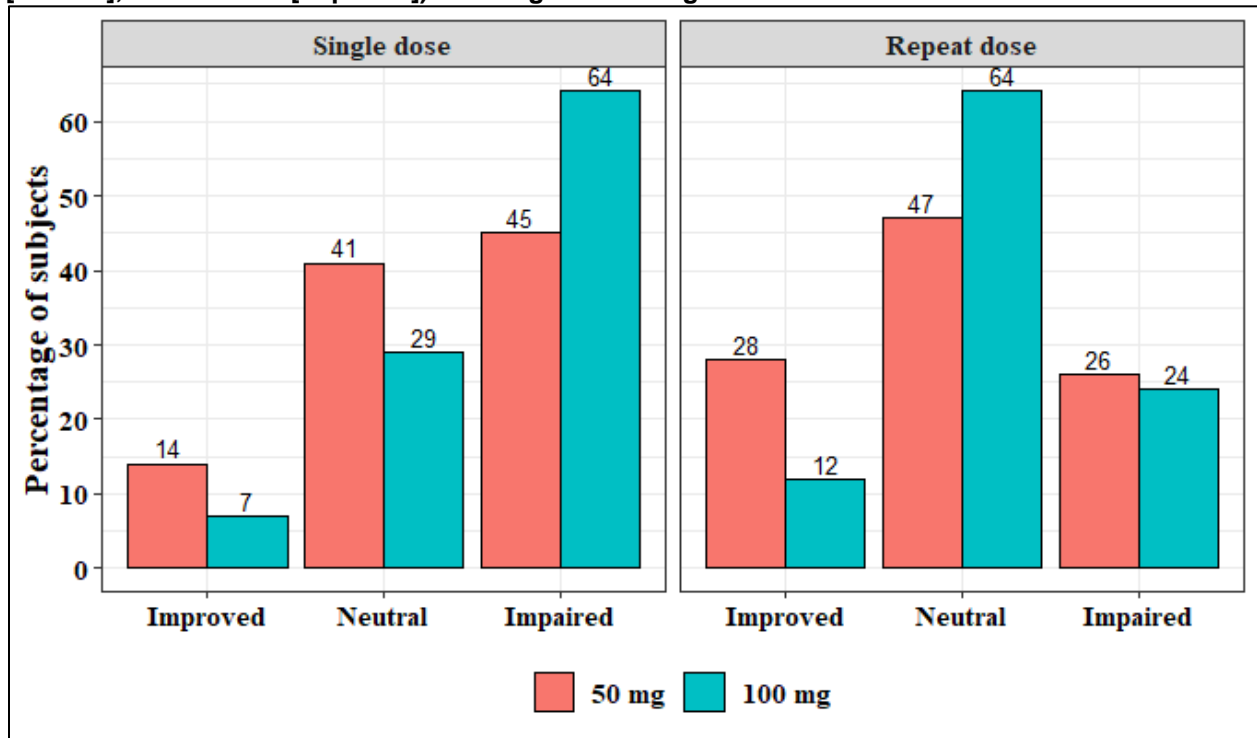
The next-day driving ability of healthy adults (50 to 64 years) and elderly subjects (65 to 80 years) was evaluated in Study ID-078-108 by assessment of the mean standard deviation of the lateral position (SDLP) using driving simulator in the morning following a single dose and multiple doses of daridorexant (50 and 100 mg) administered at bedtime. Both Δ SDLP and symmetry analyses suggested dose-dependent impairment of next-day driving performance after first dose of daridorexant 50 mg and 100 mg (Figure 11 and Figure 12). The study results suggested a potential for next-day residual effects on driving in some patients taking 50 mg daridorexant. For more details, please refer to Section 17.2.

Figure 11. Primary Driving Endpoint: LSM Estimates of Placebo-Corrected SDLP (cm, 97.5% CI) for Daridorexant 50 mg, 100 mg, and Zopiclone on Day 2 and Day 5 (Driving Performance Set), Study ID-078-108



Source: Applicant's CSR, Page 101

Figure 12. Proportion of Subjects With SDLP Changes (<-2.6 cm [Improved], -2.6 to 2.6 cm [Neutral], and >2.6 cm [Impaired]) in 50 mg and 100 mg Daridorexant.



Source: OCP Reviewer's analysis, dm.xpt, xp.xpt, pc.xpt; Software:R

Clinical Reviewer Comment: There was no evidence in this study for greater impairment among elderly than nonelderly subjects. However, this may be attributable to a selection bias for the driving study, such that elderly persons less susceptible to impairment than the general population of the elderly with insomnia might be more likely to volunteer for a driving study.

7.7.1.4. Fall, Accident, and Injury

Falls and injuries were more common among placebo-treated than daridorexant-treated subjects in Trial ID-078A301 and nearly equal in rates of occurrence in Trial ID-078A302 (see [Error! Not a valid bookmark self-reference.](#)).

Table 41. Treatment-Emergent Accidents and Injuries, Trials ID-078A301 and ID-078A302, Safety Population

Grouped Query Term	078A301					078A302				Pooled		
	Daridorexant 25 mg N=310 n (%)	Daridorexant 50 mg N=308 n (%)	PBO N=309 n (%)	RD Between 25 mg and PBO (%) (95% CI)	RD Between 50 mg and PBO (%) (95% CI)	Daridorexant 10 mg N=306 n (%)	Daridorexant 25 mg N=308 n (%)	PBO N=306 n (%)	RD Between 25 mg and PBO (%) (95% CI)	Daridorexant 25 mg N=618 n (%)	Pooled PBO N=615 n (%)	RD Between 25 mg and PBO (%) (95% CI)
Falls	4	5	14	-3.2	-2.9	8	10	9	0.3	14	23	-1.5
Accidents and Injuries GQ	(1.3)	(1.6)	(4.5)	(-5.9, -0.6)	(-5.6, -0.2)	(2.6)	(3.2)	(2.9)	(-2.4, 3.0)	(2.3)	(3.7)	(-3.4, 0.4)

Source: adae.xpt; Software: R

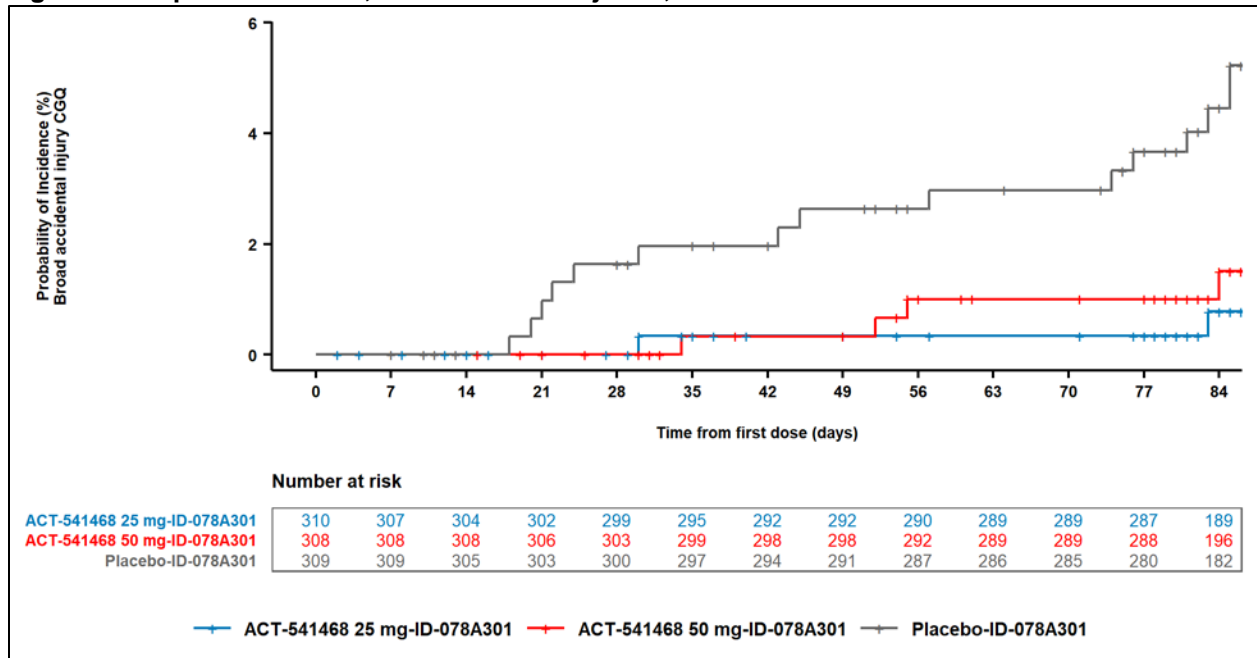
Accidents and injuries GQ comprises the PTs Joint injury, Contusion, Fall, Syncope, Upper limb fracture, R b fracture, Skin laceration, Joint dislocation, Limb injury, Radius fracture, Ankle fracture, Post-traumatic neck syndrome, Ligament sprain, Foot fracture, Spinal column injury, Face injury, Tooth fracture, Hand fracture, Meniscus injury, Road traffic accident, Skin abrasion, Muscle rupture, Muscle strain

Abbreviations: CI, confidence interval; GQ: Grouped Query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PBO, placebo; RD, risk difference

Time-to-event analysis did not indicate any treatment initiation effects (see [Figure 13](#) and [Figure 14](#)).

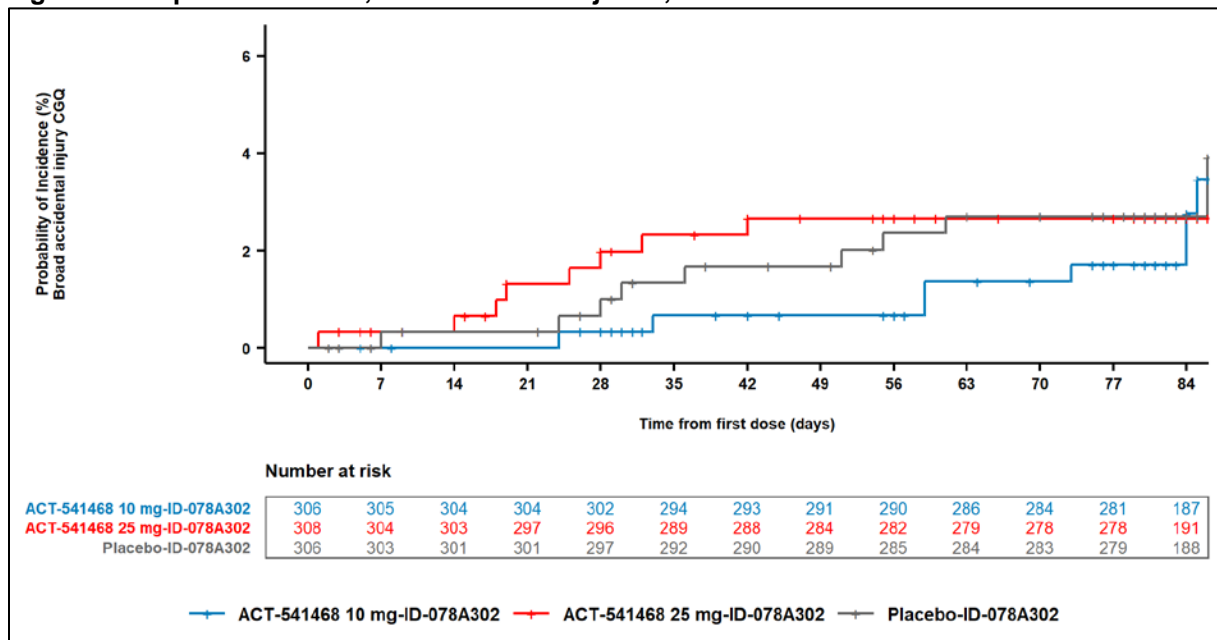
Clinical Reviewer Comment: Higher rates of falls, accidents, and injuries in placebo than active treatment arms in Trial ID-078A301 appear surprising, particularly in the context of evidence suggesting higher rates of AEs indicative of the conditions that would contribute to falls, accidents, and injuries for drug. This finding could (a) be spurious, attributable to uncertain point estimates in the context of low overall event rates, or (b) it could be attributable to prevention of such AEs by treatment of insomnia and reduction in impairments associated with sleep deficit. The degree of efficacy needed to support (b) appears unrealistic, however. Thus, explanation (a) appears best.

Figure 13. Kaplan-Meier Plot, Accidents and Injuries, Trial ID-078A301



Source: CDS generated figure. adsl.xpt, adae.xpt; Software: R
 Abbreviations: CGQ, custom group query

Figure 14. Kaplan-Meier Plot, Accidents and Injuries, Trial ID-078A302



Source: CDS generated figure. adsl.xpt, adae.xpt; Software: R
 Abbreviations: CGQ, custom group query

7.7.1.5. Effect of Age on Susceptibility to CNS-Depressant Effects

Normal aging is associated with reduced processing speeds and large-scale network function (Damoiseaux et al. 2008). It might therefore be expected that elderly patients would be more

vulnerable to CNS-depressant effects of daridorexant than younger ones. Because overall rates of CNS-depressant effects were low, precluding reliable comparisons of rates between treatment arms and age groups because of small cell sizes, overall AE rates and AE-rates in the SOCs most associated with CNS-depressant effects were examined by age group. Examination of [Table 42](#) shows no consistent increases in AE rates associated with older age nor a dose response pattern for differences in rates between younger and older subjects. Only injury, poisoning and procedural complication AEs occurred relatively substantially more frequently in the 50 mg group than the 25 mg group among subjects ≥ 65 years of age. However, the 50 mg rate was also approximately equal to the placebo rate, undercutting a dose response interpretation of the small absolute difference from the 25 mg rate. Results of the analysis presented in [Table 42](#) are broadly consistent with the supplementary analyses of Somnolence group AEs discussed in [Section 7.7.1.1](#).

Thus, there is modest evidence from Trial ID-078A301 or ID-078A302 that older patients are at increased risk for daridorexant-associated AEs than younger ones, regardless of dose. But evidence regarding a dose response for the strength of this relationship is minimal. There is no indication in the data that a 25-mg dose presents less risk in this domain than a 50-mg dose.

Table 42. Overall and CNS-Depressant Related SOC TEAEs by Age Group, Trial ID-078A301 and ID-078A302

System Organ Class	078A301			078A302			Pooled	
	Daridorexant 25 mg N1=121 N2=189 n (%)	Daridorexant 50 mg N1=119 N2=189 n (%)	PBO N1=122 N2=187 n (%)	Daridorexant 10 mg N1=121 N2=185 n (%)	Daridorexant 25 mg N1=121 N2=187 n (%)	PBO N1=120 N2=186 n (%)	Daridorexant 25 mg N1=242 N2=376 n (%)	PBO N1=242 N2=373 n (%)
Any Events (age ≥65)	44 (36.4)	43 (36.1)	43 (35.2)	55 (45.5)	58 (47.9)	48 (40.0)	102 (42.1)	91 (37.6)
Any Events (age 18-64)	84 (44.4)	77 (40.7)	71 (38.0)	76 (41.1)	68 (36.4)	62 (33.3)	152 (40.4)	133 (35.7)
Nervous system disorders (age ≥65)	18 (14.9)	11 (9.2)	11 (9.0)	10 (8.3)	16 (13.2)	12 (10.0)	34 (14.0)	23 (9.5)
Nervous system disorders (age 18-64)	25 (13.2)	25 (13.2)	17 (9.1)	20 (10.8)	21 (11.2)	9 (4.8)	46 (12.2)	26 (7.0)
General disorders and administration site conditions (age ≥65)	7 (5.8)	8 (6.7)	2 (1.6)	7 (5.8)	10 (8.3)	3 (2.5)	17 (7.0)	5 (2.1)
General disorders and administration site conditions (age 18-64)	6 (3.2)	7 (3.7)	6 (3.2)	6 (3.2)	8 (4.3)	2 (1.1)	14 (3.7)	8 (2.1)
Injury, poisoning and procedural complications (age ≥65)	4 (3.3)	8 (6.7)	8 (6.6)	9 (7.4)	9 (7.4)	4 (3.3)	13 (5.4)	12 (5.0)
Injury, poisoning and procedural complications (age 18-64)	8 (4.2)	9 (4.8)	15 (8.0)	9 (4.9)	12 (6.4)	11 (5.9)	20 (5.3)	26 (7.0)

Source: clinical reviewer generated table from CDS generated tables Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as the events occurred up to 30 days after double-blind study treatment, discontinuation, or until enrollment in the extension study
 Duration includes the double-blind treatment period and the placebo run-out period.

Abbreviations: CNS, central nervous system; N1, number of subjects aged ≥65 years in treatment arm; N2, number of subjects aged 18 to <65 years in treatment arm; n, number of subjects with adverse event; PBO, placebo; SOC, system organ class; TEAE, treatment-emergent adverse event

***Clinical Reviewer Comment:** Other subject characteristics with sufficiently balanced distributions to allow for potentially meaningful subgroup analysis of common AEs were also checked. These were sex and study region. CNS depressant effects (Somnolence group query) did not differ by sex or study region, nor was there evidence of a sex-by-dose or region-by-dose interaction effect on likelihood of CNS depression. Other common AE groups were also checked. Across Trial ID-078A301 and ID-078A302, female subjects were more likely than males to experience nausea, and non-US subjects were more likely to experience headaches overall. However, there was no evidence of a sex-by-dose or region-by-dose interaction effect.*

Summary

An overall trend for induction of symptoms related to hypo-arousal in comparison to placebo was observed with a modest dose response in the effective dosing range of 25 to 50 mg. The clearest effects occurred for AEs representing most directly an exaggerated pharmacology of daridorexant, namely somnolence and sedation, and a treatment initiation effect was observed in this but not in other domains. It is likely, given the SAD, MAD, and driving study findings, that, were events in other domains more common, treatment initiation effects would have been observed in cognitive and psychomotor domains as well. AEs in all of these domains were not limited to the treatment initiation period, however, and continued to occur over the course of treatment. For the lower rate of falls and injuries observed for drug than placebo-treated patients to be explicable by competing prevention of falls and injuries by treatment of insomnia, unrealistic assumptions (that are not supported by the clinical efficacy data) need to be made about the magnitude of the efficacy of drug. Thus, although no direct signal of fall risk was observed, class labeling warning about potential risk of fall with treatment remains appropriate in light of clear evidence (from the SAD/MAD studies) of the potential for daridorexant to cause psychomotor impairments that increase risk for falls, accidents, and injuries and observation of imbalance in such AEs unfavorable to daridorexant in the registration trials.

Conclusion

Psychomotor impairment can occur with daridorexant, and dose does not appear to interact with age in terms of risk. Class warnings and precautions pertaining to psychomotor impairment remain appropriate for this product. Specific reporting in section 6.1 of the product label is indicated for the Somnolence and Dizziness group queries. Specific labeling of a safety-motivated dosing modification for elderly patients solely on the basis of age is not indicated.

7.7.2. Parasomnias

Issue

Parasomnias have been reported with sedative hypnotics including DORAs labeled for the treatment of insomnia.

Symptoms similar to mild cataplexy have been reported with dual orexin receptor antagonists, including daridorexant, in a dose-dependent manner (e.g., in the daridorexant SAD/MAD clinical studies and nonclinical studies with dogs).

Thus, evaluation of parasomnia risk(s) is warranted for daridorexant.

Background

Parasomnias, including sleep paralysis (an inability to move or speak for up to several minutes during sleep-wake transitions) and hypnagogic/hypnopompic hallucinations (including vivid and disturbing perceptions) can cause patients significant distress and even fear of going to sleep (potentially worsening insomnia).

Parasomnias involving complex sleep behaviors pose the danger of accidental injury to self or others as patients are not fully aware of their surroundings when engaging in such behaviors and may fail to complete behavioral sequences as needed (e.g., not turning off stove after sleep cooking).

Narcolepsy-cataplexy-like symptoms involve sudden transitions to from wake to sleep states during normal activity or provoked by strong emotional states such as fear, excitement, or laughter, posing danger of accidental injury to self or others (e.g., if the person experiencing such symptoms is operating machinery).

Assessment

7.7.2.1. Parasomnias Other Than Narcolepsy/Cataplexy-Like Events

As seen in [Table 43](#), for parasomnias as a whole, differences between drug and placebo were minimal in Trial ID-078A301 and small in Trial ID-078A302. It is notable, however, that the specific parasomnias of sleep paralysis and hypnagogic hallucination occurred only in the 25 and 50 mg treatment arms. In Trial ID-078A303, one event consistent with parasomnias under the above grouping was reported; it occurred in a subject receiving daridorexant 50 mg.

The overall event rates were so low that the general class labeling in section (b) (4) of the proposed product label noting that these events “can occur with QUVIVIQ” is appropriate.

Table 43. Treatment-Emergent Parasomnia FDA Medical Query (Broad), and Preferred Term, Trials ID-078A301 and ID-078A302, Safety Population

	078A301					078A302				Pooled		
	Daridorexant 25 mg N=310 n (%)	Daridorexant 50 mg N=308 n (%)	PBO N=309 n (%)	RD Between 25 mg and PBO (%) (95% CI)	RD Between 50 mg and PBO (%) (95% CI)	Daridorexant 10 mg N=306 n (%)	Daridorexant 25 mg N=308 n (%)	PBO N=306 n (%)	RD Between 25 mg and PBO (%) (95% CI)	Daridorexant 25 mg N=618 n (%)	PBO N=615 n (%)	RD Between 25 mg and PBO (%) (95% CI)
Parasomnia (FMQ)	4 (1.3)	5 (1.6)	4 (1.3)	-0.0 (-1.8, 1.8)	0.3 (-1.6, 2.2)	3 (1.0)	5 (1.6)	1 (0.3)	1.3 (-0.3, 2.8)	9 (1.5)	5 (0.8)	0.6 (-0.5, 1.8)
Rapid eye movements sleep abnormal	0	3 (1.0)	0	0 (0, 0)	1 (-0.1, 2.1)	0	0	0	0 (0, 0)	0	0	0 (0, 0)
Restless legs syndrome	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 1)	1 (0.3)	0	0	0 (0, 0)	0	0	0 (0, 0)
Sleep paralysis	1 (0.3)	1 (0.3)	0	0.3 (-0.3, 1.0)	0.3 (-0.3, 1)	0	2 (0.6)	0	0.6 (-0.2, 1.5)	3 (0.5)	0	0.5 (-0.1, 1.0)
Hypnagogic hallucination	0	0	0	0 (0, 0)	0 (0, 0)	0	2 (0.6)	0	0.6 (-0.2, 1.5)	2 (0.3)	0	0.3 (-0.1, 0.8)
Periodic limb movement disorder	0	0	0	0 (0, 0)	0 (0, 0)	0	1 (0.3)	0	0.3 (-0.3, 1.0)	1 (0.2)	0	0.2 (-0.2, 0.5)
Rapid eye movement sleep behaviour disorder	0	0	0	0 (0, 0)	0 (0, 0)	0	1 (0.3)	0	0.3 (-0.3, 1.0)	1 (0.2)	0	0.2 (-0.2, 0.5)
Nightmare	2 (0.6)	0	1 (0.3)	0.3 (-0.8, 1.4)	-0.3 (-1, 0.3)	0	1 (0.3)	1 (0.3)	-0.0 (-0.9, 0.9)	3 (0.5)	2 (0.3)	0.2 (-0.5, 0.9)
Somnambulism	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	-0.3 (-1, 0.3)	0	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.5, 0.2)
Abnormal dreams	1 (0.3)	0	2 (0.6)	-0.3 (-1.4, 0.8)	-0.6 (-1.5, 0.2)	2 (0.7)	0	0	0 (0, 0)	1 (0.2)	2 (0.3)	-0.2 (-0.7, 0.4)

Source: CSD generated table. adae.xpt; Software: R

Treatment-emergent adverse events defined as the events occurred up to 30 days after double-blind study treatment, discontinuation, or until enrollment in the extension study

Duration includes the double-blind treatment period and the placebo run-out period.

Abbreviations: CI, confidence interval; FMQ, FDA Medical Query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PBO, placebo; RD, risk difference

7.7.2.2. Narcolepsy/Cataplexy-Like Events

No events in the registration studies were adjudicated as representing narcolepsy cataplexy-like events. In Trial ID-078A303, one subject experienced somnolence adjudicated as representing a narcolepsy-like event:

- Subject (b) (6) (daridorexant 25 mg): This 57-year-old Caucasian female subject experienced nonserious, moderate somnolence (verbatim “sleepiness”) with reported onset on Day 44 and resolution on Day 93, assessed as related to study treatment by the investigator. The subject reported falling asleep during the daytime less than or once per day (“several times, she fell asleep for a few minutes at work”). She had not experienced similar symptoms prior to entering the study. [source: Trial ID-078A303 CSR p.154]

7.7.2.3. Complex Sleep Behaviors

Complex sleep behaviors were only reported for one subject in the registration trials (a subject in the placebo arm of Trial ID-078A301 with an AE of somnambulism) and none in Trial ID-078A303.

Conclusion

Parasomnias in general, and particularly narcolepsy/cataplexy-like events, appear to be a potential effect of daridorexant based on individual reports and pharmacological plausibility but appear uncommon in the submitted data. No risk signal was detected for complex sleep behaviors. Current class labeling without enumeration is therefore appropriate for labeling risk of parasomnias with daridorexant.

Clinical Reviewer Comment: It is worth noting that in a representative community sample of 4972 people in the United Kingdom, reported rates of hypnopompic and hypnogogic hallucinations more than an order of magnitude higher than those observed in the AE reports for Trials ID-078A301, ID-078A302, and ID-078A303 (Ohayon et al. 1996). Even if selection bias were accounted for, given the high rate of survey participation, the reported community rates are much higher than those observed in the daridorexant studies. Further, psychiatric disorders including insomnia were associated with increased odds ratios for these events in the survey sample. Lifetime rates of sleep paralysis are also high (Sharpless and Barber 2011). This suggests that spontaneous AE reporting of parasomnias as relied upon in the registration trials is insensitive and may be unreliable or poorly represent the association between the product and the events. However, because these events are potentially distressing but not otherwise intrinsically harmful or dangerous additional formal study is not necessary.

Complex sleep behaviors present a clinically significant risk on the other hand. The 12-month prevalence of somnambulism in adults is approximately 1.5% (Stallman and Kohler 2016) and of polysomnographically determined REM sleep behavior disorder, approximately 1% (Haba-Rubio et al. 2018). With 206 patient years of exposure to daridorexant 25 to 50 mg in Trials ID-078A301 and ID-078A302 approximately ≥ 2 events would be expected based on general population rates. Both the 0-event rate observed in the active arms and the 1-event rate observed in the placebo arms are consistent with this expected rate.

7.7.3. Worsening of Depression/Suicidal Ideation

Issue

Sedative-hypnotic medications carry a class warning that “In primarily depressed patients treated with sedative-hypnotics, worsening of depression, including suicidal thoughts and actions (including completed suicides), have been reported.” Daridorexant belongs to this class and so this risk should be evaluated.

Background

Orexin signaling is directly involved in reward processing and appetitive behavior such that orexin antagonism may be expected to have the potential to produce depressive (particularly anhedonic) symptoms. Further, both DORAs indicated for the treatment of insomnia reported specific association with suicidal ideation (SI). Suvorexant labeling reports a dose-dependent incidence of SI observed in its registration trials, and lemborexant labeling reports a very low incidence of SI that was numerically higher than placebo in its clinical studies.

Assessment of the risk for depressive and suicidal symptoms is complicated by competing causal pathways. In addition to insomnia being a symptom of depression, primary insomnia appears to be a risk factor for depression (Riemann and Voderholzer 2003) and insomnia symptoms independently increase risk for suicide (Geoffroy et al. 2021). These complicating factors highlight the relevance of the class warning regarding potential to exacerbate symptoms among primarily depressed patients, despite their exclusion from studies for the treatment of primary insomnia. In clinical practice the insomnia disorder and mood and anxiety disorder populations are liable to converge to a meaningful extent.

Assessment

As seen in [Table 44](#), TEAEs of depressive symptoms were not frequent in the registration trials. Nonetheless, across both studies each drug arm reported rates higher than any placebo arm. This holds even if events of overdose (which may have had nondepressive motivation) are excluded from the rate calculations, yielding rates of 1%, 1%, 0.9%, and 1.3% for daridorexant 25 mg (Trial ID-078A301), 50 mg, 10 mg, and 25 mg (Trial ID-078A302), respectively).

Table 44. Depression FDA Medical Query (Broad), and Preferred Term, Trials ID-078A301 and ID-078A302, Safety Population

FMQ (Broad) Preferred Term	078A301					078A302				Pooled		
	Darido- rexant 25 mg N=310 n (%)	Darido- rexant 50 mg N=308 n (%)	PBO N=309 n (%)	RD Between 25 mg and PBO (%) (95% CI)	RD Between 50 mg and PBO (%) (95% CI)	Darido- rexant 10 mg N=306 n (%)	Darido- rexant 25 mg N=308 n (%)	PBO N=306 n (%)	RD Between 25 mg and PBO (%) (95% CI)	Darido- rexant 25 mg N=618 n (%)	PBO N=615 n (%)	RD Between 25 mg and PBO (%) (95% CI)
Depression (FMQ)	4 (1.3)	4 (1.3)	2 (0.6)	0.6 (-0.9, 2.2)	0.7 (-0.9, 2.2)	5 (1.6)	6 (1.9)	1 (0.3)	1.6 (-0.0, 3.3)	10 (1.6)	3 (0.5)	1.1 (-0.0, 2.3)
Apathy	1 (0.3)	2 (0.6)	0	0.3 (-0.3, 1.0)	0.6 (-0.2, 1.5)	0	1 (0.3)	0	0.3 (-0.3, 1.0)	2 (0.3)	0	0.3 (-0.1, 0.8)
Depressed mood	1 (0.3)	1 (0.3)	0	0.3 (-0.3, 1.0)	0.3 (-0.3, 1)	1 (0.3)	1 (0.3)	0	0.3 (-0.3, 1.0)	2 (0.3)	0	0.3 (-0.1, 0.8)
Overdose	1 (0.3)	1 (0.3)	0	0.3 (-0.3, 1.0)	0.3 (-0.3, 1)	2 (0.7)	2 (0.6)	0	0.6 (-0.2, 1.5)	3 (0.5)	0	0.5 (-0.1, 1.0)
Depressive symptom	0	0	0	0 (0, 0)	0 (0, 0)	0	1 (0.3)	0	0.3 (-0.3, 1.0)	1 (0.2)	0	0.2 (-0.2, 0.5)
Feeling of despair	1 (0.3)	0	0	0.3 (-0.3, 1.0)	0 (0, 0)	0	0	0	0 (0, 0)	1 (0.2)	0	0.2 (-0.2, 0.5)
Suicidal ideation	0	0	0	0 (0, 0)	0 (0, 0)	1 (0.3)	1 (0.3)	0	0.3 (-0.3, 1.0)	1 (0.2)	0	0.2 (-0.2, 0.5)
Depression	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	-0.3 (-1, 0.3)	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	0	2 (0.3)	-0.3 (-0.8, 0.1)
Dysphoria	0	0	1 (0.3)	-0.3 (-1.0, 0.3)	-0.3 (-1, 0.3)	1 (0.3)	0	0	0 (0, 0)	0	1 (0.2)	-0.2 (-0.5, 0.2)

Source: CSD generated table. adae.xpt; Software: R

Treatment-emergent adverse events defined as the events occurred up to 30 days after double-blind study treatment, discontinuation, or until enrollment in the extension study

Duration includes the double-blind treatment period and the placebo run-out period.

Abbreviations: FMQ, FDA Medical Query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PBO, placebo; RD, risk difference

No suicidal ideation or behavior was captured in the Columbia-Suicide Severity Rating Scale assessments in either Trial ID-078A301 or ID-078A302. In Trial ID-078A303, one subject receiving placebo and one receiving daridorexant 50 mg experienced treatment-emergent suicidal ideation. As in Trials ID-078A301 and ID-078A302, there were no treatment-emergent suicide attempts recorded.

***Clinical Reviewer Comment:** The observed rate of suicidal ideation is surprisingly low in the registration studies. For example, the general population rate of SI with at least some intent was 3.3% in 2001-2003 (Kessler et al. 2005), and since then suicide rates have increased substantially (Hedegaard et al. 2018). Thus, it is expected that the rate of any suicidal ideation in the registration trials should be appreciably >0, particularly with capture by a structured clinical interview, such as the Columbia-Suicide Severity Rating Scale. In this context, the small imbalance in treatment-emergent SI observed combined with the larger imbalance for depressive symptoms more broadly, a speculative but plausible mechanistic link, and evidence of association with SI for at least one other DORA suggests that the broad class labeling regarding SI and Depression in section 5 remains appropriate, and that labeling of the rates of depressive symptoms as captured by the broad Depression FMQ query for Trial ID-078A301 (which presents the most pertinent safety data) should be reported here as well (as was done with suicidal ideation events for suvorexant and lemborexant).*

Finally, it is noted that the treatment efficacy of daridorexant for insomnia could, by reducing this predisposing symptom, partially mask some of its potential depressive symptom causing effects. However, given the overall low (near noise-level) event rates observed such an effect could not be distinguished from chance as the expected difference of such an effect would be less than one additional subject (in light of previously discussed calculations).

Conclusion

In the context of pharmacological plausibility and similar effects observed for other DORAs, there is evidence of a signal for treatment-associated depressive symptoms when looking at a broad grouping of depressive symptoms. However, the overall incidence of depressive symptoms is low, reported in approximately 1 to 1.5% in the treated population compared with 0.3 to 0.6% in the placebo population. The class warning in Section 5 is adequate to describe the potential risk of worsening of depressive symptoms.

7.7.4. Abuse and Dependence

Issue

Because drugs with sedative and hypnotic effects are commonly abused, the extent of abuse potential and consequent risks of abuse of daridorexant warrant evaluation.

Background

With the exceptions of the barbiturate sedative hypnotics (Schedule III – high abuse potential) and ramelteon (unscheduled--no abuse potential), drugs labeled for the treatment of insomnia, including the currently labelled DORAs, are scheduled under Drug Enforcement Administration

Schedule IV as having abuse potential. Thus, it is expected that daridorexant will have some abuse potential as well.

On the other hand, antagonism of the orexin 1 receptor has been investigated as a potential treatment for substance use disorders because of its role in appetitive reward seeking (James et al. 2017). A search of the literature by the clinical reviewer found no case reports of suvorexant abuse, whereas abuse of benzodiazepine and z-drug sedative hypnotics is relatively common (Schifano et al. 2019). However, market penetration of DORAs is much smaller, and it is also possible that a DORA with a short elimination half-life could lead to daytime sensitization of orexin 1 signaling and thus, increase rather than decrease susceptibility to substance abuse and dependence. Thus, careful evaluation of daridorexant abuse potential is warranted.

7.7.4.1. Evidence Regarding Risk for Daridorexant Abuse

7.7.4.1.1. Abuse-Related AEs in Trials ID-078A301, ID-078A302, and ID-078A303

The Applicant performed a broad search for a predefined set of terms considered to be related to abuse potential based on the ‘Drug abuse, dependence and withdrawal’ SMQ, together with other PTs denoting euphoria, mood changes, psychosis, hallucinations, cognitive, attention, and mental disorders, substance abuse, and addiction. However, most of the AEs occurring in the study under this group query were descriptive of negative or aversive affective states (e.g., hangover, panic attack, etc.). The terms most notably suggestive of abuse of/abuse potential for daridorexant in the registration trials were AEs of overdose, either unintentional or unspecified. In each trial multiple subjects had repeat overdose AEs; however, the large proportion of these overdoses appear to have been single-tablet overdoses.

Rates of overdose during double-blind (Trials ID-078A301 and ID-078A302) treatment and in Trial ID-078A303 (open-label and double-blind treatment) were greater than placebo in all active treatment arms in each registration trial as well as Trial ID-078A303 (each subject counted once). The conditional maximum likelihood estimates rate ratio stratifying by study and pooling events per subject-years of exposure to daridorexant (any dose) versus placebo across all three trials was 2.0 (95% CI [0.9, 4.5]).⁵ The unstratified (crude) values for this calculation are presented in [Table 45](#).

⁵ Source of calculation: Clinical reviewer analysis using data extracted from Applicant CSRs, Results from OpenEpi, Version 3, open source calculator--PersonTime2 <http://openepi.com/PersonTime2/PersonTime2.htm>. Note that 1 subject with overdose AE in Trial ID-078A303 on 25 mg daridorexant also had overdose AE on placebo in the parent study. This subject’s events were included for both placebo and drug rates in the rate ratio calculation.

Table 45. Crude Pooled Treatment -Emergent Overdose Events by Exposure Category and Time, Trials ID-078A301, ID-078A302, and ID-078A303

Treatment-Emergent Overdose Cases	Exposed to Daridorexant	Not Exposed (Subjects on Placebo)	Total
n	39	8	47
% of total cases	83%	17%	100%
Person-Time (years)	692.8	210.9	903.7
% of total person-time	76.7%	23.3%	100%

Source: Clinical reviewer generated table, data extracted from CSRs Trials ID-078A301, ID-078A302, and ID-078A303, and Table 26

Abbreviations: n, number of subjects with adverse event

These findings present an equivocal picture for observed abuse in the clinical trials for daridorexant. In the context of single tablet overdoses primarily occurring singly or sparsely, the higher rates of overdose for drug than placebo may be attributable to cognitive effects of drug (i.e., forgetting drug was taken) rather than abuse of drug.

7.7.4.1.2. Withdrawal Syndrome Symptoms in the Run-Out Periods of Trials ID-078A301 and ID-078A302

There were no meaningful differences in group level change in scores on the Benzodiazepine Withdrawal Symptom Questionnaire from last on treatment assessment to either Visit 9 (1 day after single blind switch to placebo) or Visit 10 (1 week after).

However, compared to sleep at the end of active treatment, in Trial ID-078A301, patients switched to placebo from 50 mg of daridorexant experienced worsening of next-night sleep. These acute discontinuation effects were substantial, with worsening of WASO ([Table 46](#)), LPS ([Table 47](#)), and sTST ([Table 48](#)) following single blind switch of active treatment to placebo that followed a dose response pattern for WASO (switch of higher active dose to placebo resulted in greater increases in WASO than lower dose switch to placebo). The switch from 50 mg to placebo resulted in mean WASO equal to baseline (see [Figure 15 A and B](#)). Placebo-treated subjects did not experience substantial change in mean values of WASO or LPS from Month 3 to run-out assessment.

Visual inspection of eCDFs of change in WASO and LPS indicated a >10% absolute increase compared to placebo in the rate of subjects experiencing at least 1 hour increase in WASO following switch to placebo from daridorexant 50 mg, and indicated an approximately 5% absolute increase compared to placebo in the rate of subjects experiencing at least 1 hour increase in LPS following switch to placebo from daridorexant 50 mg or 25 mg. See [Section 16.3](#).

Results for 25 mg in Trial ID-078A302 were similar to and intermediate between those for 25 mg and 50 mg in Trial ID-078A301.

Table 46. Summary of WASO (min) at Month 3 and Run-Out by Study, Trial ID-078A301 and ID-078A302

Trial ID-078A301	Daridorexant	Daridorexant	
Endpoint: WASO (min)	25 mg	50 mg	Placebo
Month 3			
Median [min., max.]	65.75 [5.75, 257.00]	56.50 [8.50, 259.50]	79.88 [17.75, 266.75]
Mean (SE)	72.5 (2.3)	65.2 (2.3)	86.4 (2.6)
Run-out - Visit 9			
Median [min., max.]	80.25 [5.00, 275.50]	84.75 [7.50, 304.00]	77.75 [7.00, 234.50]
Mean (SE)	89.6 (3.2)	92.6 (3.4)	82.8 (2.7)
Change from Month 3 to run-out			
LS mean (SE)	18.86 (2.6)	25.30 (2.6)	2.82 (2.7)
[95% CI]	[13.7, 24.0]	[20.1, 30.5]	[-2.5, 8.1]
Change from Month 3 to run-out difference vs. Placebo			
LS mean (SE) [95% CI]	16.04 (3.7)	22.48 (3.8)	-
[95% CI]	[8.7, 23.4]	[15.1, 29.9]	-
Trial ID-078A302			
Endpoint: WASO (min)	Daridorexant	Daridorexant	Placebo
	10 mg	25 mg	
Month 3			
Median [min., max.]	79.75 [12.00, 322.00]	72.00 [7.50, 396.50]	81.50 [8.00, 326.25]
Mean (SE)	87.4 (2.9)	79.6 (2.9)	90.6 (2.8)
Run-out - Visit 9			
Median [min., max.]	76.00 [9.00, 335.50]	84.50 [9.50, 406.50]	73.00 [6.50, 376.00]
Mean (SE)	92.2 (3.7)	99.4 (3.9)	80.9 (3.3)
Change from Month 3 to Run-out			
LS mean (SE)	7.06 (3.2)	19.54 (3.1)	-5.49 (3.2)
[95% CI]	[0.8, 13.3]	[13.4, 25.7]	[-11.7, 0.7]
Change from Month 3 to run-out difference vs. placebo			
LS mean (SE)	12.55 (4.4)	25.03 (4.4)	-
[95% CI]	[3.9, 21.2]	[16.3, 33.7]	-

Source: Applicant generated table (response to 8/24/2021 IR)

ANCOVA model: Change from Month 3 to Run-out = Month 3 value + age group (<65; ≥65 years) + treatment.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; LS Mean, least squares mean; max., maximum; min., minimum; SE, standard error; WASO, wake after sleep onset.

Table 47. Summary of LPS (min) at Month 3 and Run-Out by Study

Trial ID-078A301	Daridorexant	Daridorexant	
Endpoint: LPS (min)	25 mg	50 mg	Placebo
Month 3			
Median [min., max.]	26.75 [0.75, 308.75]	24.00 [1.25, 163.25]	33.00 [1.25, 182.25]
Mean (SE)	35.7 (2.0)	30.3 (1.4)	42.9 (2.0)

Trial ID-078A301	Daridorexant	Daridorexant	
Endpoint: LPS (min)	25 mg	50 mg	Placebo
Run-out - Visit 9			
Median [min., max.]	34.00 [0.00, 480.00]	36.00 [0.00, 480.00]	28.50 [0.00, 329.00]
Mean (SE)	50.0 (3.2)	48.1 (2.9)	39.9 (2.3)
Change from Month 3 to run-out			
LS mean (SE)	14.86 (2.7)	15.88 (2.7)	0.71 (2.7)
[95% CI]	[9.6, 20.1]	[10.6, 21.2]	[-4.6, 6.0]
Change from Month 3 to run-out difference vs. placebo			
LS mean (SE) [95% CI]	14.15 (3.8)	15.17 (3.8)	-
[95% CI]	[6.7, 21.6]	[7.7, 22.7]	-
Trial ID-078A302	Daridorexant	Daridorexant	
Endpoint: LPS (min)	10 mg	25 mg	Placebo
Month 3			
Median [min., max.]	32.25 [0.00, 277.75]	30.00 [1.25, 300.00]	35.50 [2.00, 344.75]
Mean (SE)	44.1 (2.5)	38.9 (2.2)	49.2 (2.7)
Run-out - Visit 9			
Median [min., max.]	31.50 [0.00, 480.00]	33.00 [0.00, 480.00]	34.25 [0.00, 480.00]
Mean (SE)	50.2 (3.8)	55.5 (4.1)	52.6 (3.8)
Change from Month 3 to run-out			
LS mean (SE)	7.08 (3.7)	15.55 (3.7)	6.29 (3.7)
[95% CI]	[-0.1, 14.3]	[8.3, 22.8]	[-0.9, 13.5]
Change from Month 3 to run-out difference vs. placebo			
LS mean (SE)	0.79 (5.2)	9.26 (5.2)	-
[95% CI]	[-9.3, 10.9]	[-0.9, 19.4]	-

Source: Applicant generated table (response to 8/24/2021 IR)

ANCOVA model: Change from Month 3 to Run-out = Month 3 value + age group (<65; ≥65 years) + treatment.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; LPS, latency to persistent sleep; LS Mean, least squares mean; max., maximum; min., minimum; SE, standard error

Table 48. Summary of sTST (min) at Month 3 and Run-Out by Study

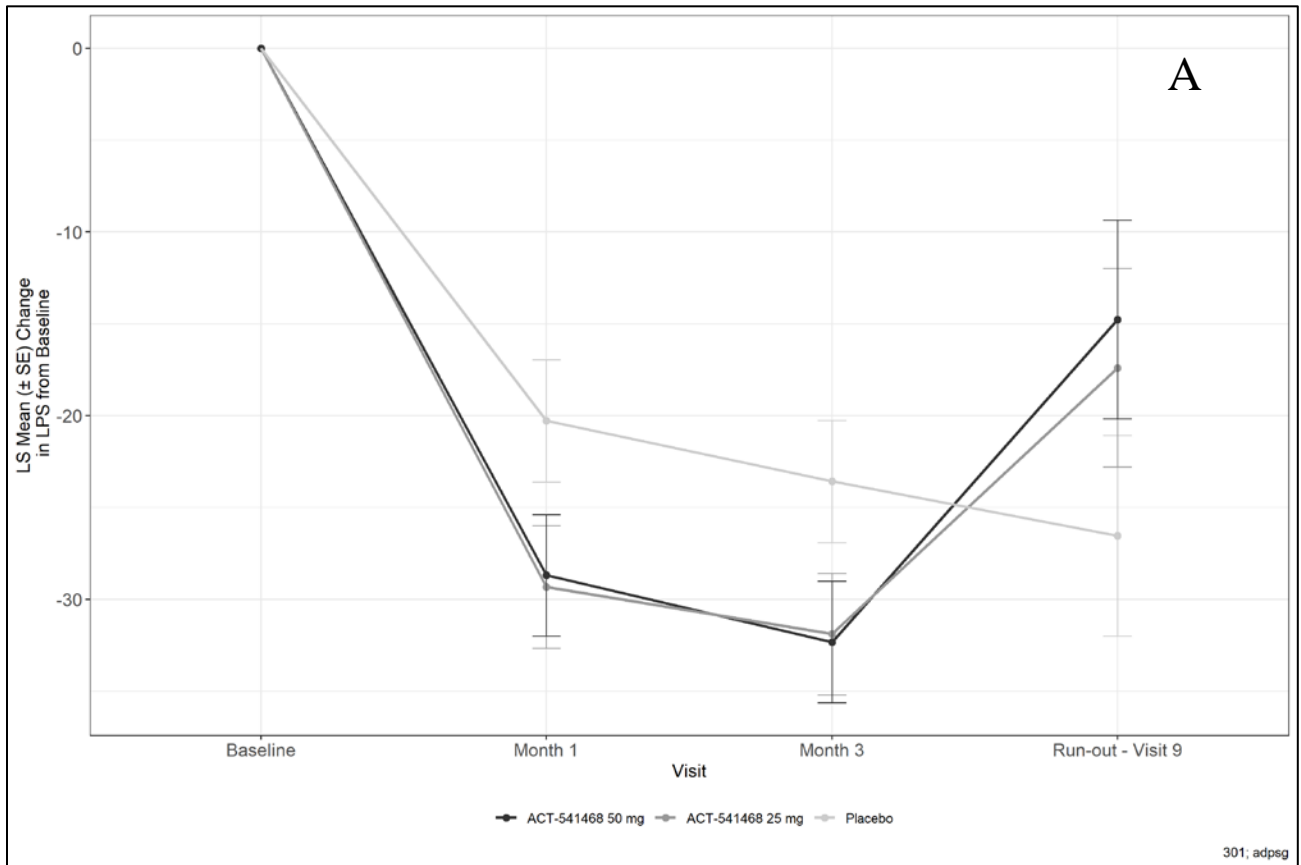
Trial ID-078A301	Daridorexant	Daridorexant	
Endpoint: sTST (min)	25 mg	50 mg	Placebo
Month 3			
Median [min., max.]	366 [137, 508]	373 [33, 600]	360 [56, 531]
Mean (SE)	358.4 (4.2)	371.8 (4.6)	354.5 (4.3)
Run-out			
Median [min., max.]	360 [105, 491]	366 [38, 560]	360 [133, 563]
Mean (SE)	352.6 (4.2)	356.7 (4.4)	359.5 (4.1)
Change from Month 3 to Run-out			
LS mean (SE)	-6.83 (2.0)	-13.55 (2.0)	2.27 (2.0)
[95% CI]	[-10.7, -3.0]	[-17.4, -9.7]	[-1.6, 6.2]
Change from Month 3 to run-out difference vs. placebo			
LS mean (SE)	-9.10 (2.8)	-15.83 (2.8)	-
[95% CI]	[-14.6, -3.6]	[-21.3, -10.4]	-
Trial ID-078A302	Daridorexant	Daridorexant	
Endpoint: sTST (min)	10 mg	25 mg	Placebo
Month 3			
Median [min., max.]	362 [99, 569]	371 [157, 540]	353 [129, 531]
Mean (SE)	360.4 (3.8)	365.5 (4.1)	347.0 (3.8)
Run-out			
Median [min., max.]	356 [90, 525]	360 [120, 503]	359 [133, 496]
Mean (SE)	351.6 (4.0)	355.5 (4.0)	352.1 (3.7)
Change from Month 3 to run-out			
LS mean (SE)	-8.07 (2.0)	-8.44 (2.0)	2.28 (2.1)
[95% CI]	[-12.1, -4.1]	[-12.5, -4.4]	[-1.8, 6.3]
Change from Month 3 to run-out difference vs. placebo			
LS mean (SE)	-10.35 (2.9)	-10.72 (2.9)	-
[95% CI]	[-16.0, -4.7]	[-16.4, -5.0]	-

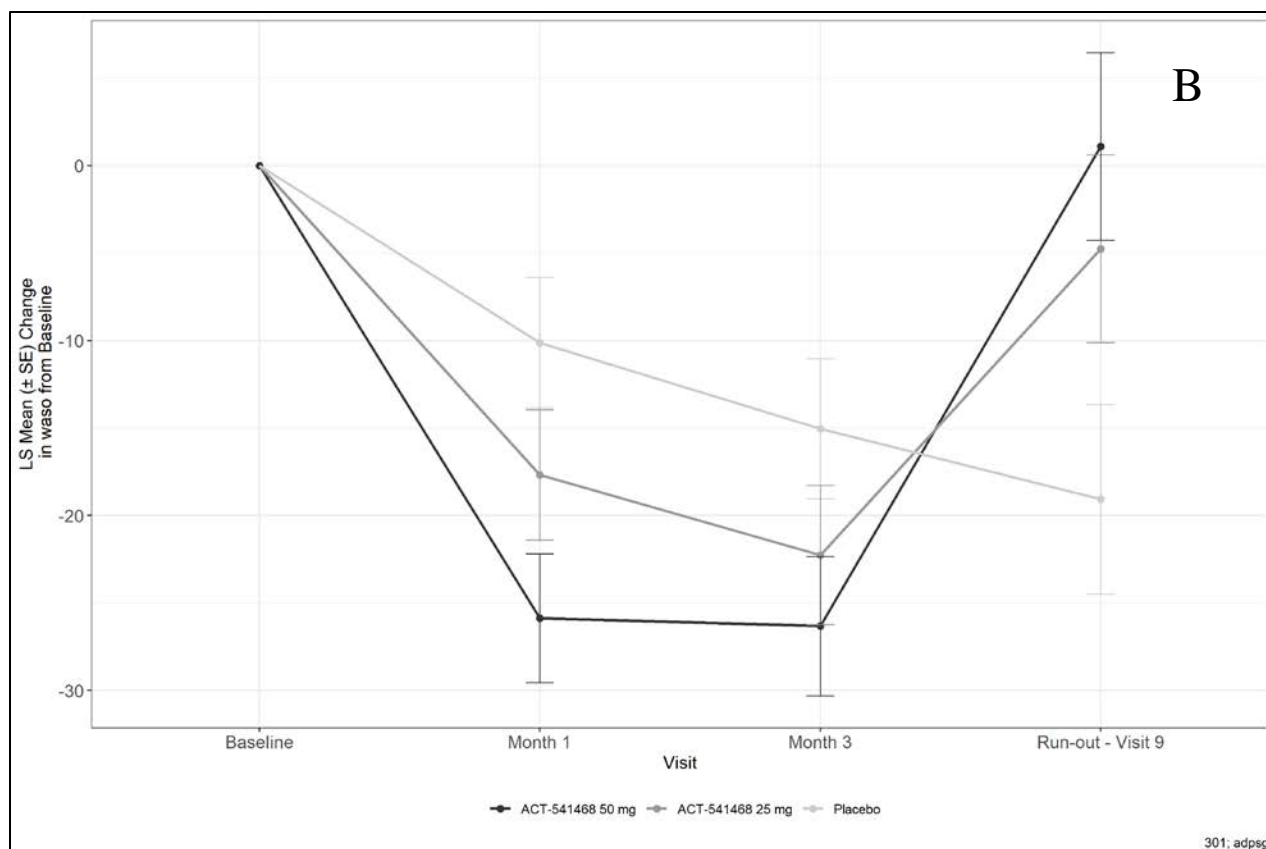
Source: Applicant generated table (response to 8/24/2021 IR)

ANCOVA model: Change from Month 3 to Run-out = Month 3 value + age group (<65; ≥65 years) + treatment.

Abbreviations; ANCOVA, analysis of covariance; CI, confidence interval; LS Mean, least squares mean; max., maximum; min., minimum; SE, standard error; sTST, subjective total sleep time

Figure 15. Trial ID-078A301 LPS (A) and WASO (B), Change Over Time From Baseline to Placebo Run-Out Visit 9





Source: FDA statistical reviewer, adpsg.xpt.

Abbreviations: LPS, latency to persistent sleep; LS mean, least squares mean; SE, standard error; WASO, wake after sleep onset

Clinical Reviewer Comment: It is notable that the degree of worsening of sleep on each of these parameters is approximately double the treatment effect at Month 3 in absolute magnitude. Drug withdrawal effect analysis of change in patient sleep parameters differs from assessment of rebound effects (Section [7.7.4.1.3](#)) in that rebound is defined as an outcome worse than study baseline, rather than end of treatment. However, worsening from end of treatment is clinically relevant from a patient-experience perspective because, with chronic treatment, a patient's frame of reference is liable to shift to their current status rather than remain their baseline status at start of treatment. These findings also are pertinent to interpretation of the primary trial estimands, as discussed in Section [6.2.1.3](#).

7.7.4.1.3. Rebound Insomnia in the Run-Out Periods of Trials ID-078A301 and ID-078A302

Increases in insomnia symptoms *above* baseline following runout period switch to single blind placebo in Trials ID-078A301 and ID-078A302 were greater for daridorexant than for placebo.

The Applicant analysis of rebound insomnia examined mean changes from study baseline to placebo runout. Although the global mean for WASO was not increased for any treatment arm compared to study baseline, when examined by age-group, subjects 65 years of age or older *on average* experienced rebound insomnia of 20 minutes WASO for 50 mg (with 95% CI excluding zero) and 6 minutes for 25 mg in Trial ID-078A301, with similar effects in Trial ID-078A302.

Subjects receiving placebo in either age group, and subjects younger than 65 years, did not experience mean increases from baseline in WASO. This suggests risk for dependence on daridorexant, and a robust risk of rebound for elderly patients. As there is not currently a standard approach for assessing and defining rebound insomnia in clinical trials, [REDACTED] (b) (4) [REDACTED] the Division will give further consideration to the appropriate approach for assessing rebound insomnia in clinical trials for insomnia drugs, including in the elderly. .

Table 49. Change From baseline in WASO (min) to Run-Out by Age Group

Age Group		<65 years					≥ 65 years				
Study		LS					LS				
Treatment	N	n	Mean	SE	95% CL	N	n	Mean	SE	95% CL	
Study ID-078A301 ^a											
Daridorexant 25 mg	73	173	-18.235	3.504	[-25.113, -11.357]	113	111	5.697	4.376	[-2.892, 14.287]	
Daridorexant 50 mg	174	172	-20.555	3.543	[-27.510, -13.600]	112	111	19.663	4.379	[11.068, 28.259]	
Placebo	67	166	-27.253	3.572	[-34.264, -20.242]	113	113	-4.032	4.378	[-12.625, 4.561]	
Study ID-078A302 ^a											
Daridorexant 10 mg	166	164	-24.543	4.125	[-32.641, -16.446]	116	109	6.59	5.06	[-3.342, 16.523]	
Daridorexant 25 mg	171	170	-11.069	4.051	[-19.020, -3.118]	113	106	3.717	5.138	[-6.369, 13.802]	
Placebo	172	171	-31.147	4.02	[-39.039, -23.255]	113	104	-15.772	5.174	[-25.929, -5.616]	
Pooled ^b											
Daridorexant 25 mg (pooled)	344	343	-15.42	2.657	[-20.634, -10.206]	226	217	4.184	3.334	[-2.358, 10.726]	
Placebo (pooled)	339	337	-29.886	2.667	[-35.119, -24.652]	226	217	-10.525	3.347	[-17.092, -3.957]	

Source: Applicant generated Table: iss-5.1.3-1.1 - Rebound insomnia: Analysis for change from baseline in WASO (min) to run-out by age group 1 Combined Treatment Withdrawal Set. Program: T_WASO_BTW_RO_SUB1_CTWS.sas

^a, ANCOVA model: Change from baseline = Baseline + Treatment + age group + age group x Treatment.

^b, ANCOVA model: Change from baseline = Baseline + Treatment + Study + age group + age group x Treatment

Abbreviations: LS Mean, least squares mean; N, number of subjects in treatment arm; n, number of subjects with adverse event; SE, standard error of the mean; CL, confidence limit

7.7.4.1.4. Integration With HAP Study Findings

The human abuse potential (HAP) study results indicated that abusers of sedative hypnotic medications had similar preference responses to suprathreshold doses of daridorexant as to active comparator (but lower rates of euphoric responses). See [17.3.1.3.1](#). Thus, patients with a history of substance abuse may also be at risk for abuse of daridorexant.

Almost no patients with a history of remitted substance use disorder were included in Trials ID-078A301 and ID-078A302. Thus, the risk in this population is unknown. Evidence of rapid recurrence of insomnia with treatment discontinuation and an imbalance of overdose events among phase 3 study subjects receiving active treatment suggest the possibility of elevated risk of abuse of daridorexant or relapse precipitation in insomnia patients with a history of substance use disorder.

7.7.4.2. Evidence Regarding Risk From Daridorexant in the Context of Daridorexant Abuse

7.7.4.2.1. Risk From Suprathreshold Doses of Daridorexant

Studies 101 and 102 provide evidence regarding effects of suprathreshold doses (i.e., >50 mg) and of daytime drug administration. No SAEs or deaths were observed, but AEs of somnolence and sedation were prominent and AEs potentially reflecting narcolepsy/cataplexy-like events were also observed, and these together represent the primary source of significant risk that would be associated with abuse of daridorexant. This represents the most likely major risk deriving from daridorexant abuse.

Chronic abuse of high or very high dose daridorexant may be unlikely but could result in significant morbidity. Extrapolation from animal data is uncertain, but it appears that death attributable to chronic overdosing would likely require repeated consumption of doses at least 10 times the proposed recommended/maximum dose of 50 mg. See Section [13](#).

Thus, although there is no indication of a dangerous withdrawal syndrome, the risks from daridorexant abuse appear meaningful, based on the expected CNS-depressant effects, and are likely to be otherwise similar in overall severity to risks from abuse of other Schedule IV sedative or hypnotic drugs indicated for the treatment of insomnia.

7.7.4.2.2. Implications of Respiratory Study Findings for Interpretation of Abuse-Associated Risk

Studies of effects of daridorexant on respiratory function (Section [17.1](#)) in patients at risk for and from respiratory suppression were generally reassuring but inconclusive. Thus, concern for respiratory suppression resulting from abuse of daridorexant is not high. However, it is not wholly obviated because, among abusers, high doses, which were not studied for respiratory depressant effects, may be used, and it is possible that at high doses, respiratory suppression could be observed in vulnerable subjects; although in SAD Study 101, in healthy males, single doses up to and including 200 mg (n=6 subjects) did not result in any AE reports consistent with respiratory suppression.

7.7.4.2.3. Implications of DDI Study Findings for Interpretation of Abuse Potential

Super-additive effects were not observed in the DDI studies. Thus, abuse of daridorexant is not considered to amplify risk in the context of concomitant abuse of alcohol or therapy with citalopram. Other DDI studies with other DORAs have not indicated an increase of the respiratory suppressing effects of opiates, however, these findings may not be applicable to daridorexant. Daridorexant abuse does not appear likely to alter the risk profile of GABA-ergic substance abuse or interfere with the safety of concomitant antidepressant treatment that patients with substance use disorders are liable to receive.

7.7.4.2.4. Implications of Hepatic Impairment Study Findings for Interpretation of Abuse Potential

Patients with a history of opiate or alcohol use disorders are more likely to have concurrent hepatic impairment. The hepatic impairment study suggests that the sedating effects of daridorexant increases with level of hepatic impairment. Lower doses of daridorexant would be needed to achieve abuse-motivating effects in this population. Given the absence of evidence of hepatotoxicity for daridorexant these findings do not indicate increased concern for harm from daridorexant were it abused in this population.

Conclusion

As with other DORAs, the HAP study indicates potential for abuse based on drug liking by sedative hypnotic abusers. The other available clinical data did not indicate risk for significant abuse of daridorexant. However, worsening of sleep following discontinuation of daridorexant could be associated with the potential for dependence. Thus, FDA considers it appropriate to recommend Drug Enforcement Administration scheduling under Schedule IV, as was recommended for other DORAs.

Because there appears to be little harm associated with long term use of daridorexant in the clinical data in the development program based on exposures of up to approximately 1 year, and insomnia is often a chronic condition, continued use of this product is expected and not a major concern. The absence of substantial withdrawal symptoms suggests that dependence on product consisting of return of insomnia with product discontinuation would not unduly interfere with product discontinuation were it indicated for a patient under 65 years of age. However, the observation of substantial rebound insomnia for patients aged 65 years and older, most prominently with the 50-mg dose is of concern. The concern is augmented by the increased likelihood of need for discontinuation of daridorexant with increasing age as comorbidities tend

to increase with age, and because there is some evidence of increased risk for CNS depressant AEs among older patients as well.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Renal Impairment

In a dedicated renal impairment study (ID-078-115), single-dose administration of 25 mg daridorexant in subjects with severe renal impairment versus healthy subjects led to similar C_{max} , t_{max} , and $t_{1/2}$. Based on these results, daridorexant can be administered to patients with renal impairment without the need for dose adjustment.

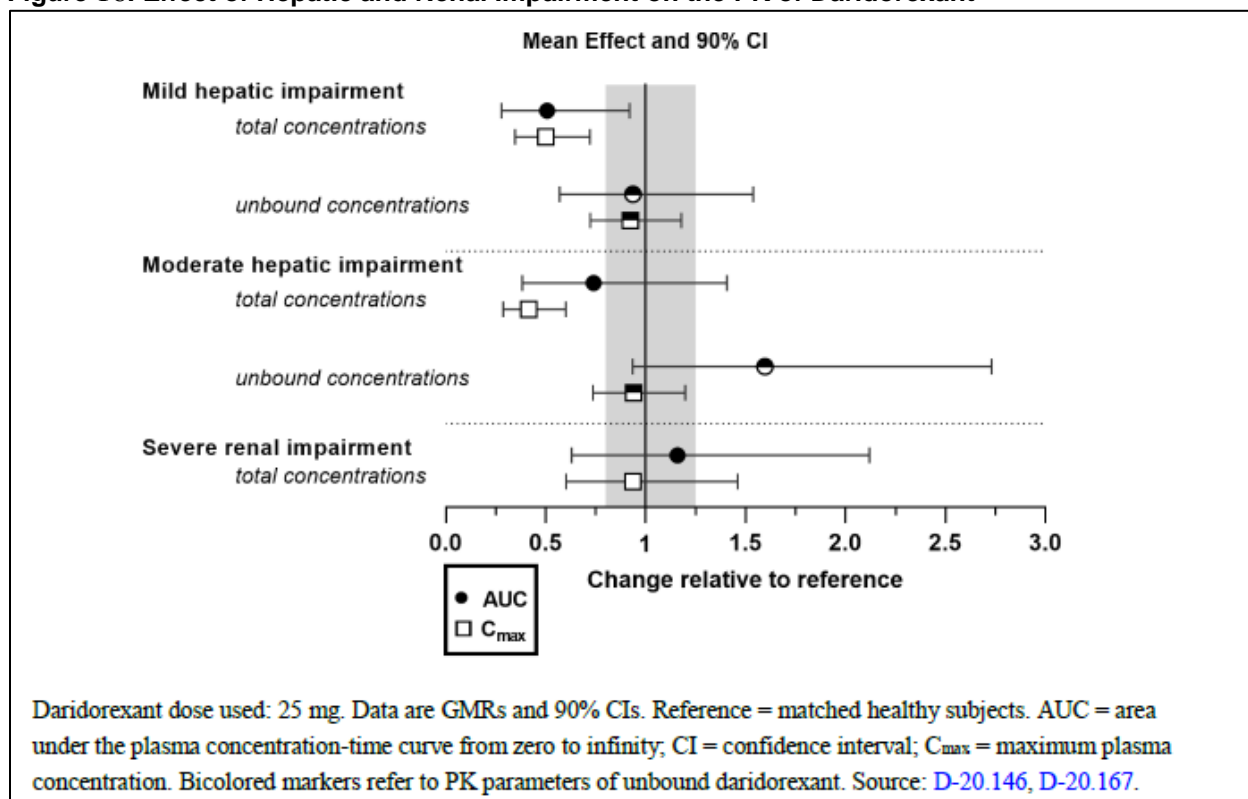
- Mild, moderate, and severe renal impairment = no dose-adjustment

Hepatic Impairment

In a dedicated hepatic impairment study (ID-078-112), the exposure of daridorexant was compared in healthy subjects versus subjects with hepatic impairment (mild and moderate). The exposure of daridorexant (i.e., unbound C_{max} and AUC) was similar in subjects with mild hepatic impairment compared to healthy controls. However, exposure was higher (i.e., 60% increase in unbound C_{max}) with a 2-fold increase in $t_{1/2}$ in subjects with moderate hepatic impairment compared to healthy controls. Subjects with severe hepatic impairment were not studied. Based on these results, the following dose-adjustments are recommended:

- Subjects with mild hepatic impairment = no dose-adjustment
- Subjects with moderate hepatic impairment = maximum dose of 25 mg
- Subjects with severe hepatic impairment = daridorexant is not recommended

Figure 16. Effect of Hepatic and Renal Impairment on the PK of Daridorexant



Source: 2.7.2. Summary of clinical pharmacology, fig 3-4, page-94.

Other Intrinsic Factors: Age, Sex, Race, Body Size, etc.

Based on population PK analysis, sex and race are not covariates on daridorexant PK. Age and body size (lean body weight, fat mass) are covariates in the population PK model. However, compared to a reference subject (age 60 years, fat mass 20 kg, lean body weight 55 kg) daridorexant C_{max} and AUC₀₋₂₄ are expected to decrease by as much as -8% or increase by up to +20% for extreme values of age and body size.

Based on a graphical assessment there is no apparent relationship between age and efficacy (change from baseline WASO or LPS) in phase 3 Trials ID-078A301 and ID-078A302. See Section [14.6.2](#) for details.

8.2. Drug Interactions

Effect of Other Drugs on the PK of Daridorexant

CYP3A4 inhibitors: In healthy subjects, coadministration of daridorexant 25 mg with the moderate CYP3A4 inhibitor diltiazem (240 mg) increased daridorexant AUC and C_{max} by 2.4 times and 1.4 times, respectively. Based on the clinically observed effect of diltiazem (a moderate CYP3A inhibitor) on daridorexant PK and the physiological-based PK (PBPK) model predicted effect of strong CYP3A inhibitors on daridorexant PK, the strong CYP3A inhibitors

are expected to result in daridorexant AUC increases greater than 5-fold. Based on these results, the following dose-adjustments are recommended:

- Mild CYP3A4 inhibitor = no dose-adjustment
- Moderate CYP3A4 inhibitor = maximum dose of 25 mg
- Strong CYP3A4 inhibitor = daridorexant is not recommended

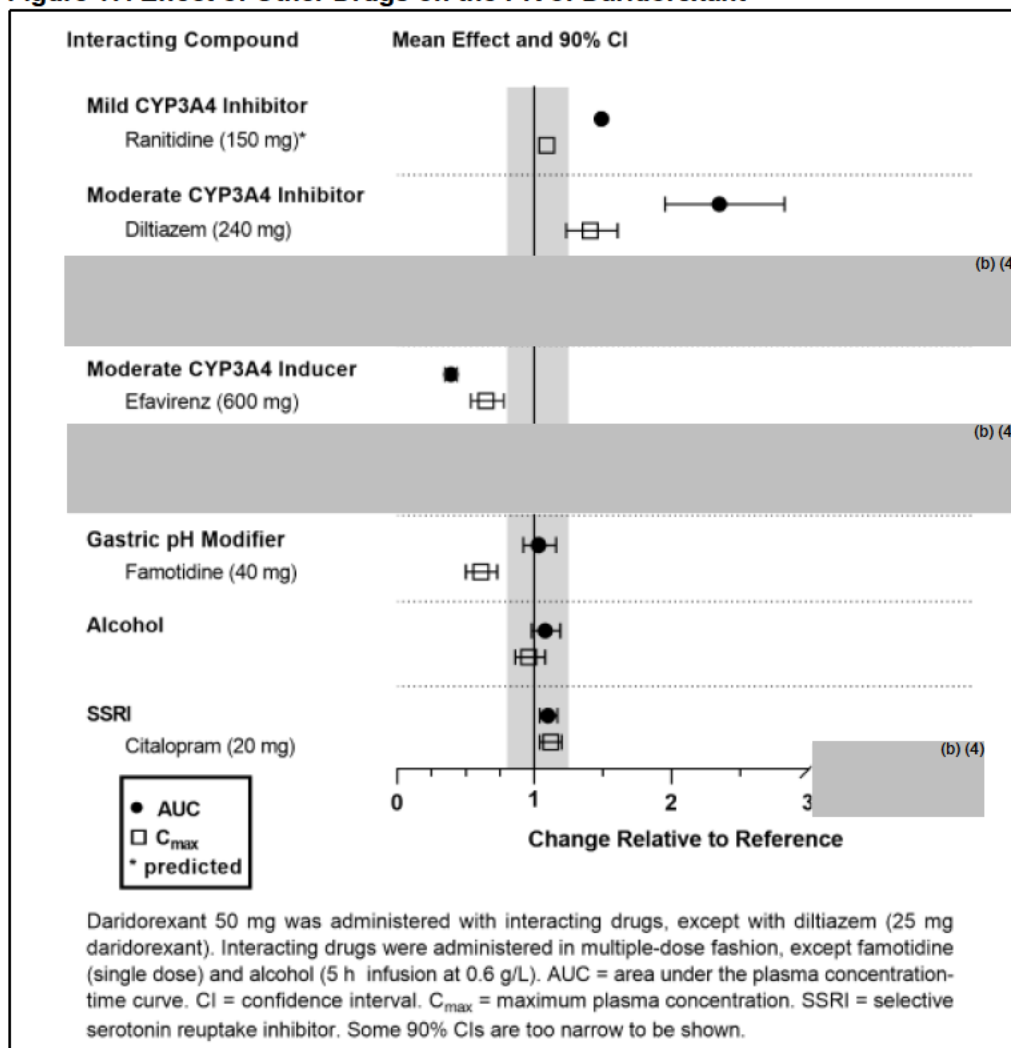
CYP3A4 inducers: In healthy subjects, coadministration with efavirenz (600 mg once daily), a moderate CYP3A4 inducer, decreased daridorexant exposure parameters AUC and C_{max} by 61% and 35%, respectively. Based on the clinically observed effect of efavirenz (a moderate CYP3A inducer) on daridorexant PK and the PBPK model predicted effect of strong CYP3A inducers on daridorexant PK, the strong inducers are expected to result in daridorexant AUC ratios of less than 0.5. Based on these results, the following dose-adjustments are recommended:

- Moderate and strong CYP3A4 inducer = daridorexant is not recommended

Citalopram: In healthy subjects, coadministration of 20 mg citalopram (a selective serotonin re-uptake inhibitor) did not have any clinically relevant effect on the PK of 50 mg daridorexant. No dose adjustment is recommended when daridorexant is used concomitantly with citalopram.

Gastric pH Modulators: In healthy subjects, coadministration with 40 mg of famotidine (an inhibitor of gastric acid secretion) caused no change in the AUC of daridorexant but decreased the C_{max} by approximately 39% and increased the T_{max} by 0.5 hr. Because there was no change in AUC coupled with clinically insignificant changes in C_{max} and T_{max} , no dose adjustment is recommended when daridorexant is used concomitantly with drugs that reduce gastric acidity.

Figure 17. Effect of Other Drugs on the PK of Daridorexant



Source: Applicant proposed label, fig-1.

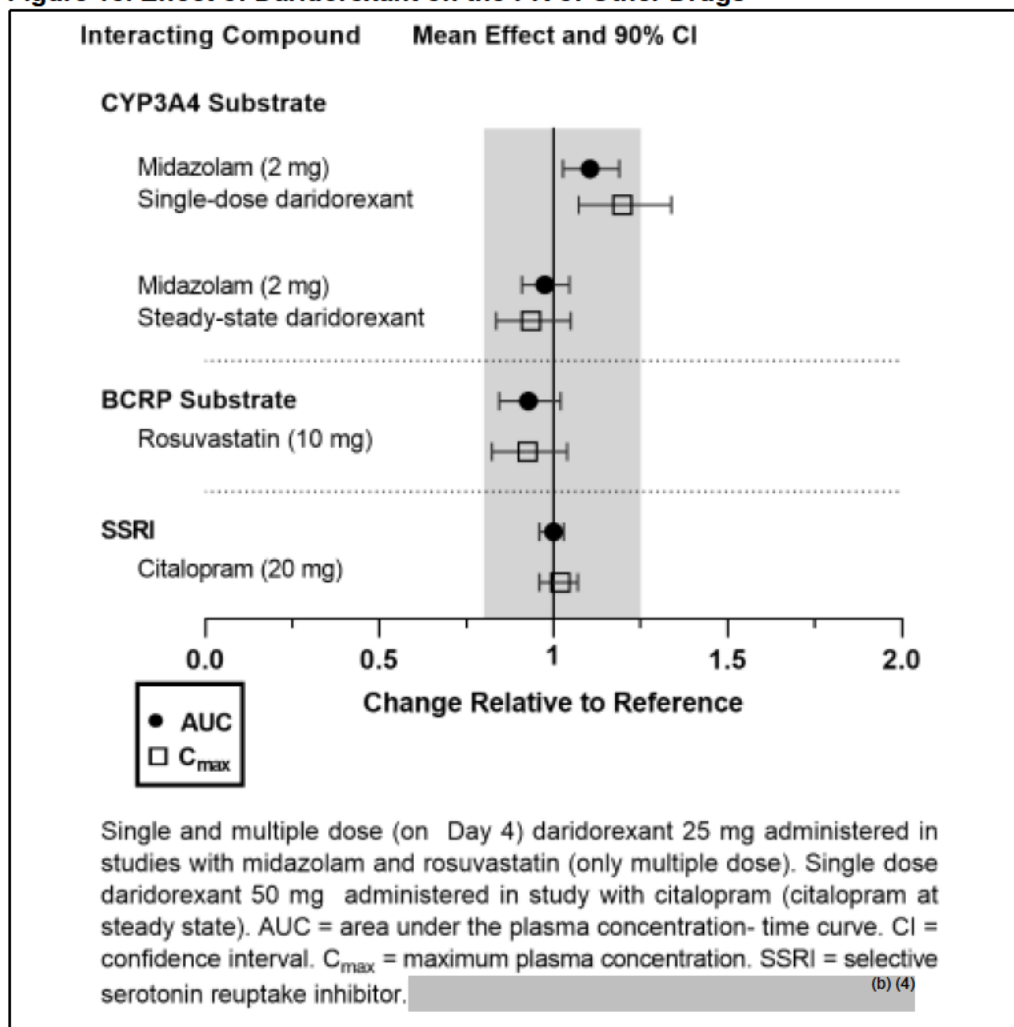
Effect of Daridorexant on the PK of Other Drugs

CYP3A4 Substrates: In healthy subjects receiving daridorexant and midazolam (a sensitive CYP3A4 substrate), daridorexant at a dose of 25 mg did not affect the PK of midazolam, indicating the absence of CYP3A4 induction or inhibition. PBPK modeling showed that similar results can be expected with a dose of 50 mg; therefore, CYP3A4 substrates can be administered with daridorexant without any dose adjustment.

BCRP Substrate: In healthy subjects receiving daridorexant and rosuvastatin (a BCRP Substrate), daridorexant at a dose of 25 mg did not affect the PK of rosuvastatin indicating an absence of inhibition of BCRP. PBPK modeling showed that similar results can be expected with a dose of 50 mg; therefore, BCRP substrates can be administered with daridorexant without dose adjustment.

Citalopram: In healthy subjects, the PK of citalopram at steady state was not affected by coadministration of 50 mg daridorexant.

Figure 18. Effect of Daridorexant on the PK of Other Drugs



Source: Applicant proposed label, fig-2.

8.3. Plans for Pediatric Drug Development

Insomnia disorder is common in the pediatric population aged 10 years and older (Johnson et al. 2006), and there is a lack of approved medications for this demographic.

On March 9, 2020 an agreed iPSP was submitted, and on March 24, 2020 Initial agreement issued.

In alignment with the agreed iPSP, the Applicant is proposing the following studies for the pediatric development of daridorexant:

- (5) A dose-finding (b) (4) study (b) (4) (in children aged from 10 to <18 years) (b) (4) subjects with insomnia disorder

- (6) A (b) (4) study (b) (4), which will be conducted in pediatric subjects (aged from 10 to <18 years) with insomnia disorder (b) (4) to evaluate the efficacy and safety of daridorexant (b) (4)

- (7) (b) (4)

- (8) A waiver for studies in pediatric subjects below 10 years of age was requested the grounds that such studies would be highly impractical.

Clinical Reviewer Comment:

(b) (4)

8.3.1. Juvenile Animal Study

Daridorexant was administered orally to juvenile rats from postnatal day (PND) 21 through PND 84 at doses of 0, 50, 150, and 450 mg/kg/day. Daridorexant at 450 mg/kg/day delayed sexual maturation in males (~2 days) without affecting reproductive performance or sperm parameters. Sexual maturation and reproductive capacity in females were not affected. Learning and memory in the juvenile animals were not affected by daridorexant in either sex.

In addition, daridorexant caused hepatocellular hypertrophy in the liver in both sexes with correlative increases in GGT levels (3x and 8x in males and females, respectively) and increased liver weight at 450 mg/kg/day and follicular cell hypertrophy in the thyroid with correlative increases in thyroid weight at ≥ 150 mg/kg/day. Findings in the liver and thyroid gland were similar to those observed in studies in adult rats at the same or comparable doses.

Based on the delay in sexual maturation in males and the liver findings, the NOAEL for juvenile toxicity is 150 mg/kg/day in both sexes.⁶

8.4. Pregnancy and Lactation

Pregnancy

Pregnant women were excluded from clinical trials with daridorexant, and no pregnancy exposure cases have been reported. Animal studies do not suggest an increased risk for embryo-fetal toxicity. Pregnancy labeling will include a statement that there are no available data on daridorexant use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

Daridorexant will be indicated for a condition that would be expected to be seen in females of reproductive potential and during pregnancy. Therefore, a postmarketing requirement (PMR) will be issued for the applicant to conduct a pregnancy exposure registry and a complimentary study of a different design. The pregnancy labeling will also include contact information for the pregnancy exposure registry study.

8.4.1. Embryofetal Developmental Toxicity

Daridorexant was administered orally to pregnant rats during the period of organogenesis at doses of 30, 100, and 300 mg/kg/day, which are approximately 1, 3, and 8 times the MRHD of 50 mg respectively, based on AUC. Daridorexant did not cause any maternal or embryofetal toxicities or fetal malformation at doses up to 300 mg/kg/day. The NOAEL for maternal and fetal toxicity is 300 mg/kg/day, which is approximately 8 times the MRHD of 50 mg, based on AUC.

Daridorexant was administered orally to pregnant rabbits during the period of organogenesis at doses of 30, 60, and 120 mg/kg/day, which are approximately 3, 4, and 10 times the MRHD of 50 mg, respectively, based on AUC. Daridorexant decreased maternal weight gain (-40%) and food consumption (-15%) at the dose of 120 mg/kg/day but did not cause any fetal toxicities or malformation at doses up to 120 mg/kg/day. The NOAELs for maternal and fetal toxicity are 60 and 120 mg/kg/day respectively, which are approximately 4 and 10 times the MRHD of 50 mg, respectively, based on AUC.

8.4.2. Pre- and Postnatal Developmental Toxicity

Daridorexant was administered orally to pregnant rats during gestation and lactation at doses of 50, 100, and 300 mg/kg/day, which are approximately 1, 3, and 9 times the MRHD of 50 mg, respectively, based on AUC. Daridorexant did not cause any maternal or developmental toxicities at doses up to 300 mg/kg/day. Sexual maturation, learning and memory, and reproductive performance in the offspring were not affected. The NOAEL for maternal and developmental toxicity is 300 mg/kg/day, which is approximately 9 times the MRHD of 50 mg, based on AUC. Daridorexant was present in the offspring plasma on postnatal days 4 and 20.

⁶ Safety margins for the juvenile study was not calculated because the pediatric clinical dose has not been determined yet.

In lactating rats (postpartum day 14), after a single oral administration of daridorexant at 30 mg/kg, daridorexant and its M1, M3, and M10 metabolites were present in the milk within 1-hour postdose. These data suggest that daridorexant and its metabolites will likely be present in human milk and lactational exposure of the drug to breastfeeding infants will likely occur.

Lactation

Lactating women were excluded from clinical trials with daridorexant, and no lactation exposure cases have been reported. There are no available data on the presence of daridorexant in human milk, the effects on the breastfed infant, or the effects on milk production. Daridorexant and its metabolites are present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Lactation labeling will include these conclusions as well as a statement consistent with labeling for other drugs in class that infants exposed to daridorexant through breast milk should be monitored for excess sedation. The following risk/benefit statement will also be included: “the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Quviviq and any potential adverse effects on the breastfed infant from Quviviq or from the underlying maternal condition.”

Daridorexant will be 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 (such as molecular weight less than 800 Daltons), it is possible that the drug will also be present in human milk. Therefore, a PMR will be issued for the applicant to conduct a clinical lactation study.

9. Product Quality

The Office of Pharmaceutical Quality Review team has assessed NDA 214985 with respect to chemistry, manufacturing, and controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such the Office of Pharmaceutical Quality recommends approval of this NDA from a quality perspective.

The proposed 24-month expiry is acceptable when stored at 20 to 25°C.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

There were no good clinical practice compliance concerns or data quality concerns that affected interpretation of safety or efficacy. See section 20 for additional information about the results of

the clinical site inspections. No investigators reported any financial conflicts of interest requiring disclosure.

11. Advisory Committee Summary

An advisory committee was not held during this marketing application review. This drug is not first in its class, the clinical trial designs are similar to those for previously approved products in the class, evaluation of the data did not raise significant safety or efficacy issues that were unexpected for a drug in this class, and outside expertise was not necessary.

III. Appendices

12. Summary of Regulatory History

This product was developed by IDORSIA PHARMACEUTICALS LTD under IND 128789 opened May 27, 2016.

- (1) December 1, 2015 PreIND meeting request withdrawn January 21, 2016 prior to receipt of preliminary comments on January 23, 2016
- (2) February 29, 2016 PreIND meeting held (minutes March 21, 2016) to discuss and gain agreement on the adequacy of the nonclinical program to support the drug development program, the opening of an IND with a phase 2 study in adults with insomnia disorder, a proposed phase 2 study in elderly subjects with insomnia disorder, ^{(b) (4)}

- (3) June 24, 2016 Study May proceed for IND-opening phase 2 dose-finding study
- (4) April 19, 2017 Special Protocol Assessment Carcinogenicity Study protocol submitted
- (5) July 19, 2017 Sponsorship transferred from Actelion to Idorsia Pharmaceuticals, Ltd.
- (6) November 16, 2017 End of Phase 2 Type B meeting held (minutes December 14, 2017) to gain agreement on the following:

Nonclinical program to support the NDA at a maximum human dose of 50 mg

With respect to drug discrimination studies, FDA indicated that the Sponsor should make a good faith effort to train the animals to suvorexant and would like to see the data if the Sponsor believes it is not possible to do so. If it is not possible to train the animals to discriminate suvorexant from vehicle, the Sponsor can train the animals to a ^{(b) (4)} as suggested in the original protocol. FDA also indicated that that the Sponsor should conduct a dose response curve to inform their training dose.

Clinical pharmacology program to support an NDA for daridorexant in insomnia disorder

With respect to the clinical pharmacology program, FDA provided advice on pharmacokinetic (PK) studies, which was not further discussed at the meeting, indicated the need for a thorough QT study, which the Sponsor agreed to conduct, discussed their driving study plan, including 50% target enrollment of elderly subjects.

Phase 3 development program to support an NDA for daridorexant in insomnia disorder

With respect to dose-selection, the Division expressed concern with respect to use of the same doses in nonelderly adult and elderly patients, and inquired about the selection of 50 mg as the maximum dose given preliminary evidence suggestive of greater potential

efficacy at 75 mg. The Sponsor explained that they selected the phase 3 doses [10 mg, 25 mg, and 50 mg] based on safety and efficacy data from phase 2 studies. In the phase 1 studies, the 75-mg dose of daridorexant demonstrated exaggerated pharmacodynamic (PD) effects in some patients, and the Sponsor thinks that this dose might cause more next-day residual effects. Furthermore, higher doses were associated with two cases of sleep paralysis or narcolepsy-like symptoms. Regarding the use of the 50-mg dose in elderly patients, the Sponsor presented slides summarizing adverse events (AEs) of delusional disorder, gait disturbance, and feeling abnormal in elderly patients enrolled in Study AC-078A202. Most these events were reported from a single site, and the gait disturbance event reporting was potentially triggered following the institution of protocol-mandated neurological examinations. The independent study board did not adjudicate these events to be adverse events of special interest. The Sponsor will continue to require neurological examinations in the phase 3 studies. The Division agreed with the proposed dosages for the phase 3 studies.

With respect to the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ), the Division indicated

(b) (4)

(7) January 22, 2018 Type C teleconference (minutes February 07, 2018) to discuss the IDSIQ with COA staff.

COA noted concerns regarding the (b) (4) of the “energetic” item, and wording of the “clear headed” item

The Agency requested that the Sponsor also submit reliability results for the instrument as well as responsiveness analyses using known groups (e.g., insomnia patients versus good sleepers) as subgroups for the analyses. The Sponsor agreed to submit these results to the Agency for review.

The Agency stated that the Sponsor should prespecify thresholds for clinically meaningful improvement in scores for each prespecified endpoint.

The Agency provided additional comments regarding the Sleep Diary Questionnaire. The Agency had concerns regarding use of the subjective total sleep time as the first-ranked secondary endpoint, in addition to the objective polysomnography (PSG) endpoint. The Agency recommended that the Sponsor re-examine their qualitative data to determine what is most important to patients in terms of improvement from treatment (e.g., latency to sleep, total time awake, number of awakenings, etc.). The Sponsor indicated that they selected the subjective total sleep time as the key secondary endpoint because it was sensitive to treatment in phase 2 studies and the IDSIQ had not been used in phase 2/3 studies yet. The Sponsor agreed to provide a summary report in support of their sleep diary endpoint(s) as a separate submission for Agency review and comment.

- (8) February 11, 2019 Type C telecon (minutes March 11, 2019) to discuss and obtain agreement on additional statistical sensitivity analyses proposed to further assess validation of the human abuse potential (HAP) Study ID-078-107
- (9) December 19, 2019 Type C meeting (minutes December 23, 2019) to obtain FDA input and guidance on the acceptability and sufficiency of the nonclinical and clinical data package for the NDA submission

Extensive comment on drug-drug interaction (DDI) and physiological-based PK (PBPK) data to be submitted was provided

The Sponsor clarified that Phase II enzymes are involved in further biotransformation of a minor downstream metabolite of daridorexant, not the identified major metabolites nor daridorexant itself. The Agency agreed that the Sponsor is not required to submit pertinent study reports on this aspect.

With regard to safety data, the Sponsor clarified that Trial ID-078A303 is placebo-controlled and described a rerandomization plan for patients receiving placebo during Trials ID-078A301 or ID-078A302. We agreed that the Trial ID-078A303 data will be separate from the pooled data from Trials ID-078A301 and ID-078A302.

With regard to subjective Total Sleep Time (sTST), the Sponsor agreed to submit the meaningful change threshold (range) estimate prior to data unblinding. We agreed with the likely generalizability of the [first 200 subjects in Trial ID-078A301] sample's demographics. The Sponsor planned to repeat the analyses of clinically meaningful within patient change by analyzing the entire population of Trial ID-078A301. This proposal was deemed acceptable.

- (10) September 29, 2020 Type B PreNDA meeting (minutes October 27, 2020)

With regard to the proposed indication, the Division indicated that an indication

“for the treatment of insomnia” may be acceptable. This Division did not agree that “(b) (4)” is appropriate. However, the Division indicated “(b) (4)”

With regard to the IDSIQ, after receipt of our preliminary comments, the Sponsor decided to keep the domain name “sleepiness” (b) (4). We suggested that the NDA include a dossier explain the domains in a way that confers confidence in the Sponsor’s proposed analyses of the IDSIQ. The Agency commented that there are (b) (4). We suggested that the Sponsor submit qualitative and quantitative evidence to support the domain structure and names with their NDA. The Sponsor requested permission to submit the IDSIQ datasets within 30 days of submitting their NDA and the Division agreed.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the Investigational New Drug Application

13.1.1. Pharmacology

13.1.1.1. Primary Pharmacology

Daridorexant is a dual orexin receptor antagonist and is hypothesized to treat insomnia disorder by inhibiting the actions of the orexin neuropeptides orexin-A and orexin-B at orexin receptors 1 (OX1R) and 2 (OX2R).

The Applicant conducted in vitro and in vivo studies to investigate the pharmacology of daridorexant and its three major human metabolites (M1, M3, and M10). Findings are summarized below:

In Vitro

In in vitro assays using calcium release as a marker for orexin receptor activation, daridorexant competed against the endogenous agonist, orexin A, and inhibited the recombinant orexin receptors with slightly higher potency for OX1R over OX2R in all three species (human, rat, and dog, [Table 50](#), Study B-14.010). The receptor occupancy half-life for daridorexant was 8 minutes at the human OX1R and 4 minutes at the human OX2R (Study B-20.019).

Table 50. Inhibitory Potency of Daridorexant on Recombinant Human, Rat, and Dog OX1R and OX2R

Species	Apparent K_b (nM)	
	OX1R	OX2R
Human	0.47	0.93
Rat	1.1	1.7
Dog	0.33	0.66

Source: Study B-14.010

Abbreviations: K_b , equilibrium dissociation constant

Compared to the parent drug, the three metabolites M1, M3, and M10 had lower potency than daridorexant at the recombinant human OX1R and OX2R ([Table 51](#), Study B-17.052).

Table 51. Inhibitory Potency of Daridorexant and its Metabolites on Recombinant Human OX1R and OX2R

Test system	Recombinant CHO cells expressing human OX1R or OX2R.	
Assay	Inhibition of orexin-A–induced calcium mobilization, measured as increase in fluorescence of calcium-sensitive dye.	
Compound	Apparent K_b (nM)	
	OX1R	OX2R
Daridorexant	0.77	0.95
M1 (ACT-776537)	63	45
M3 (ACT-776063)	31	7.8
M10 (ACT-1016-3307)	1190	527

Source: Study B-17.052
 Abbreviations: K_b , equilibrium dissociation constant

In Vivo

In male Wistar rats (Study B-14.036), after a single oral administration at doses of 0, 10, 30, 100, or 300 mg/kg, daridorexant caused dose-dependent decreases in time awake and home cage activities and increases in rapid eye movement (REM) and nonREM sleep time. Similar dose-dependent sleep-promoting effects were observed in male beagle dogs after oral administration of daridorexant at doses of 10, 30, and 90 mg/kg (Study B-14.056). In both the rat and dog, the general sleep architecture (the relative proportion of the time spent in nonREM and REM sleep) was not affected by daridorexant.

In male Wistar rats (Study B-20.029), a single oral administration of daridorexant at doses up to 100 mg/kg did not affect motor function in rotarod and grip strength tests after forced awakening at 30 to 150 minutes postdose. In comparison, zolpidem, a positive GABA_A receptor modulator, caused dose- and time-dependent impairment in motor function at up to 2 hours postdose.

13.1.1.2. Secondary Pharmacology

In secondary pharmacology screening assays (Studies B-20.056, B-20.057, B-14.063, B-14.069, B-17.064, B-17.065, and B-17.066), daridorexant and its M1 and M3 metabolites exhibited a few off-target activities, including weak inhibitory activity of daridorexant at the human dopamine transporter ($IC_{50}=14.3\mu M$), adrenergic β_3 receptor ($IC_{50}=16.7\mu M$), and phosphodiesterase PDE 4 (81% inhibition at $10\mu M$); weak inhibitory activity of the M1 metabolite at the AT1 (angiotensin II type 1), tachykinin NK3, and opiate κ receptors ($IC_{50}=24, 20, \text{ and } 14.6\mu M$ respectively); and weak inhibitory activity of the M3 metabolite at the human dopamine transporter (68% inhibition at $10\mu M$).

The M10 metabolite did not show appreciable binding to any of the tested targets ($IC_{50}>10\mu M$).

At therapeutically relevant levels, the impact of these off-target activities is expected to be limited for the following reasons:

- At the maximum recommended human dose (MRHD) of 50 mg daridorexant, the C_{max} levels of daridorexant and M1, M3, and M10 metabolites were 1006, 251, 553, and

99.1 ng/mL,⁷ respectively (~2.2, 0.5, 1, and 0.2 μ M, respectively). Considering the high plasma protein binding of daridorexant and its metabolites (~99% for daridorexant, M1, and M3 and ~95% for M10), the levels of free/unbound daridorexant and its metabolites are significantly lower than the reported IC₅₀ values needed for meaningful off-target activities.

- M3 is a strong Pgp substrate; therefore, its brain concentration at therapeutically relevant levels is expected to be low.
- M10 had lower exposure levels and negligible secondary pharmacology activity.

13.1.1.3. Safety Pharmacology

At therapeutically relevant levels, no adverse effects of daridorexant were observed on the central nervous system (CNS), cardiovascular, and respiratory systems.

CNS Safety Pharmacology

In male Wistar rats (Study T-13.223, good laboratory practice [GLP]), a single oral administration of 100, 300, and 1000 mg/kg daridorexant caused transient and reversible dose-dependent decreases in activity and arousal and rectal temperature (decreased up to 2.1°C, relative to controls). These effects were related to the drug pharmacology. The no observed adverse effect level (NOAEL) for CNS safety pharmacology is 1000 mg/kg.

Cardiovascular Safety Pharmacology

In an in vitro hERG assay (Study T-14.012, GLP), daridorexant induced weak inhibition of the potassium current with an IC₂₀ of 7.4 μ M (~3400 ng/mL) and IC₅₀ of 25 μ M (~11500 ng/mL), respectively. Considering the clinical C_{max} of ~1000 ng/mL and the high protein binding of daridorexant (>99%), the risk for hERG inhibition at therapeutically relevant levels is reasonably low.

In conscious male and female beagle dogs (Study T-13.252, GLP), after a single oral administration at 10, 30, and 100 mg/kg, daridorexant caused a slight decrease in heart rate (-23 bpm) and a slight increase in PR, resting rate, and QT interval at $\geq$ 30 mg/kg, which were secondary to the decrease in heart rate and are not considered to be adverse. The arterial blood pressure, QTc interval, QRS complex, or body temperature were not affected during the 24-hour postdose period. The NOAEL for cardiovascular safety pharmacology is 100 mg/kg and the plasma levels of daridorexant at this dose were C_{max} of 8900 and 9550 ng/mL (19736 and 21178nM) in males and females, respectively.

In male Wistar rats (Study B-14.057, nonGLP), after a single oral administration at 300 mg/kg, daridorexant decreased heart rate (-42 bpm), body temperature (-0.3°C), and locomotor activity (-55%) relative to vehicle controls (0.5% methylcellulose). These effects are likely due to the pharmacology of the drug. No effects were observed on PR, QRS, resting rate interval or cardiac rhythm (QT). C_{max} was achieved at 2 hours postdose and ranged between 3440 and 6820 ng/mL (7629 and 15124nM). In male spontaneously hypertensive rats (Study B-14.058, nonGLP), after

⁷ Human exposure data of daridorexant and its major human metabolite M1, M3, and M10 are from the Clinical Study AC-078-105 (Study D-18.155)

a single oral administration of daridorexant at 300 mg/kg, similar effects were observed, including slightly decreases in the heart rate (-40 bpm), body temperature (-0.5°C) and locomotor activity (-63%). In addition, mean arterial pressure was reduced (-8 mm Hg).

In anesthetized guinea pigs (Study B-14.059, nonGLP), intravenous (IV) infusion of daridorexant at 3, 10, and 30 mg/kg did not have any meaningful effects on mean arterial pressure, heart rate, or electrocardiogram (ECG) parameters (QRS, resting rate, QT, or QTc). The plasma level of daridorexant at the 30 mg/kg IV dose was 23265 ng/mL (51593nM).

Respiratory Safety Pharmacology

In male Wistar rats (Study T-13.222, GLP), after a single oral administration of daridorexant at 100, 300, and 1000 mg/kg, no significant changes in respiratory parameters were observed. The NOAEL for respiratory safety pharmacology is 1000 mg/kg.

13.1.2. Pharmacokinetics/ADME/Toxicokinetics

The bioanalytical methods for the determination of daridorexant and its M1, M3, and M10 metabolites were validated for the range of 10 to 10000 ng/mL in plasma samples from the rat, dog, mouse, and rabbit ⁸ (Studies BA-13.013, 13.014, 14.018, 17.029, 17.030, 17.031, 18.023, 19.100).

Daridorexant is a lipophilic weak base with limited solubility under physiologically relevant conditions. The absorption, distribution, metabolism, and excretion (ADME) profiles of daridorexant and/or its major human metabolites M1, M3, and M10 are summarized below.

13.1.2.1. Absorption

In MDCKII wildtype cells (Study B-17.067), daridorexant was highly permeable with comparable apical-to-basolateral and basolateral-to-apical permeability coefficient (P_{app}) values (19 to 30 and 14 to 20 $\times 10^{-6}$ cm/s respectively). In mammalian cells that express various human transporters (Studies B-17.067 and 19.052), daridorexant was not a substrate of Pgp; M1 was a weak Pgp substrate; M3 and M10 were significant substrates of Pgp and therefore unlikely to penetrate into the brain. Neither daridorexant nor the metabolites M1, M3, and M10 were substrates of BCRP. Daridorexant was not a substrate of OATP1B1 or OATP1B3.

The in vivo PK profile of daridorexant was evaluated (Study B-13.116, nonGLP) after a single IV injection of 0.1, 0.3, and 1 mg/kg in male rats and 0.3 mg/kg in female rats (n=5/group); a single IV injection of 0.3, 1, and 3 mg/kg in male dogs (n=4/group); a single oral administration of 3, 10, and 30 mg/kg in male rats and 10 mg/kg in female rats (n=5/group); or a single oral administration of 1, 3, 10, and 30 mg/kg under fasted condition and 10 mg/kg under fed condition in male dogs (n=4/group). In addition, the effects of (b) (4) and salt form (compared to free base) were investigated in fasted dogs after a single oral administration of daridorexant by comparing the PK profile between formulations of (b) (4).

⁸ The bioanalytical methods for the determination of daridorexant levels in the rat and dog plasma were also validated for the range of 1 to 1000 ng/mL (Study BA-13.013 and 13.014).

(b) (4) at the dose of 30 mg/capsule/dog
(n=4/group).

Following oral administration, daridorexant was quickly absorbed with T_{max} values of 0.3 hours in rats, 0.8 to 2 hours in dogs under fasted condition, and 2.5 hours in dogs under fed condition. In dogs, compared to the fasted condition, the drug exposure levels (both C_{max} and AUC) were slightly higher under fed condition (1.3-fold relative to fasted condition). Plasma clearance was also quick in both rats and dogs, with a terminal half-life $T_{1/2}$ of 0.5 to 2.1 and 2.5 to 4.1 hours, respectively.

In rats, drug exposure (AUC) increased slightly more than dose proportionally whereas in dogs, drug exposure increased dose proportionally. Oral bioavailability was 10 to 30% and 31 to 58% in rats and dogs, respectively. The clearance in female rats was slightly lower than males, leading to higher exposure levels and higher oral bioavailability (30%) than male rats (~15%).

(b) (4) did not significantly affect the AUC ($\leq 10\%$ difference) but increased the C_{max} (+63%) in fasted dogs. The exposure levels (AUC) of daridorexant did not change significantly between the (b) (4) of the salt form and the (b) (4) form in the dog whereas the (b) (4) formulation yielded a slightly lower exposure (~24% decrease) relative to the (b) (4) of the HCl salt with (b) (4).

13.1.2.2. Distribution

13.1.2.2.1. Plasma Protein Binding

The protein binding of daridorexant is high in both animal and human plasma samples (>95% bound in the mouse, rat, dog, and rabbit plasma; and >97% bound in human plasma, [Table 52](#); Studies B-13.202 and 17.061). In human samples, saturation of protein binding of daridorexant was observed at concentrations ≥ 15 $\mu\text{g/mL}$, which was likely due to saturable binding to the $\alpha 1$ -acid glycoprotein ($\alpha 1\text{AGP}$, 98.1%, 93.3% and 65.7% bound at 1.5, 5, and 15 $\mu\text{g/mL}$ daridorexant concentrations, respectively). However, it should be noted that at the proposed MRHD of 50 mg, the clinical C_{max} of daridorexant was ~ 1 $\mu\text{g/mL}$; therefore, the saturable binding is unlikely to occur at clinically relevant levels. This was further supported by findings from the ex vivo assay using samples collected from the clinical study (Study AC-078-101), in which consistently high protein binding (99.7 to 99.9%) was observed without saturation in samples collected from the 25-mg and 200-mg dose groups.

Similarly, the protein binding of the M1 and M3 metabolites was high in both animal (mouse, rat, dog, and rabbit) and human samples. The protein binding of the M10 metabolite was relatively lower than that of daridorexant or the M1 and M3 metabolites in animal species (~70 to 80% bound) but remained to be relatively high in human samples (>92% bound, [Table 52](#)).

Table 52. Protein Binding of Daridorexant and its M1, M3, and M10 Metabolites in the Mouse, Rat, Rabbit, Dog, and Human Plasma Samples

concentration (µg/mL)	rat (%)	mouse (%)	rabbit (%)	dog (%)	man (%)
daridorexant					
0.5	2.8	2.6	0.5	2.4	0.3
1.5	2.8	3.0	1.4	3.0	0.3
5	3.3	2.5	2.7	4.3	0.5
15	4.2	2.9	3.1	5.0	1.6
50	4.1	3.6	3.4	5.4	2.3
200	4.8	4.2	4.4	5.4	2.9
M1 (ACT-776537)					
0.5	n.d.	n.d.	n.d.	n.d.	0.1
1.5	0.5	1.3	n.d.	1.2	0.1
5.0	0.4	1.3	n.d.	1.4	0.3
15	0.6	1.1	n.d.	1.5	n.d.
M3 (ACT-776063)					
0.5	n.d.	n.d.	n.d.	n.d.	0.4
1.5	6.2	6.9	n.d.	5.8	0.5
5.0	8.2	8.9	n.d.	11	1.4
15	12	11	n.d.	17	n.d.
M10 (ACT-1016-3307)					
0.5	n.d.	n.d.	n.d.	n.d.	4.0
1.5	31	21	n.d.	21	4.4
5.0	31	21	n.d.	29	7.8
15	31	19	n.d.	39	n.d.

Source: Studies B-13.202 and B-17.061

13.1.2.2.2. In Vivo Tissue Distribution

In male albino rats (Wistar, Study B-16.005), after a single oral administration of ¹⁴C-radiolabeled daridorexant at 10 mg/kg in a vehicle of 0.5% methylcellulose (w/w), drug-related radioactivity was rapidly absorbed and broadly distributed in all tissues within 0.5 hours postdose. Tissues/organs with high radioactivity levels included the gastrointestinal mucosa, liver, kidney, adrenal gland, brown fat, and myocardium. Tissues with relatively low radioactivity levels included in the white fat, nasal mucosa, bone surface, uveal tract/retina, and choroid plexus. Radioactivity in the brain was only observed at 0.5 hours postdose and reached 34% of the respective levels in the blood. Radioactivity levels declined rapidly and were below the limit of quantification at 24 hours postdose in most tissues except the liver and gastrointestinal mucosa, suggesting rapid clearance.

In male pigmented rats (Lister Hooded, Study B-16.005), after a single oral administration of ¹⁴C-radiolabeled daridorexant at 10 mg/kg in a vehicle of 0.5% methylcellulose (w/w), the distribution of radioactivity into tissues was generally similar to that observed in albino rats.

There was no significant distribution/accumulation of radioactivity in the uveal tract/retina, pigmented skin, or meninges of the brain, suggesting that daridorexant does not bind to melanin.

In lactating Wistar rats (postpartum day 14, Study B-20.022), after a single oral administration at 30 mg/kg in a vehicle of 0.5% methylcellulose (w/w), daridorexant and its M1, M3, and M10 metabolites were present in the milk within 1-hour postdose. The concentration of daridorexant in the milk significantly exceeded that in the plasma with a milk-to-plasma ratio of ~14 to 20, whereas the levels of metabolites were comparable between the milk and plasma (milk-to-plasma ratio of 0.6 to 1.4). These data suggest that daridorexant and its metabolites will likely be present in human milk and lactational exposure of the drug to breastfeeding infants will likely occur.

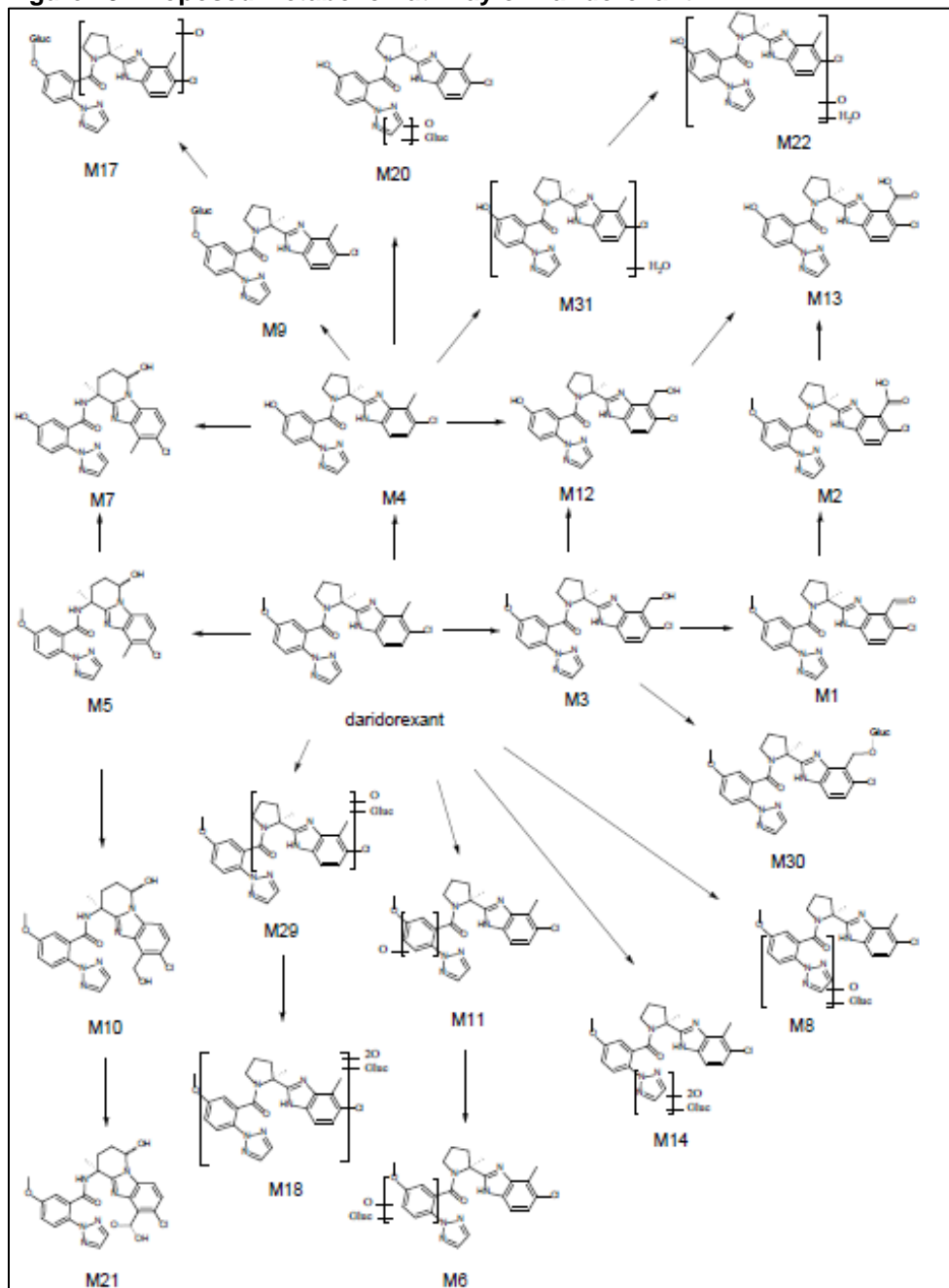
13.1.2.3. Metabolism

Daridorexant was extensively metabolized in vitro in primary hepatocytes and/or liver microsomes (Study B-14.019) and in vivo after oral administration in animals (mouse, rat, and dog) and humans (Studies B-14.054, 15.042, and 16.062). The in vitro and in vivo metabolic pathways were generally similar. CYP3A4 was identified as the major CYP enzyme involved in the metabolism, accounting for ~89% of the total turn-over in vitro with minor contributions from CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 (Study B-15.073).

Despite some minor differences in the metabolism between the animals and humans, there were no unique or disproportional human metabolites of daridorexant. Three major human metabolites (M1, M3, and M10) were identified in vivo ([Figure 19](#), Study B-15.042). All three metabolites were present at adequate levels in the rat, rabbit, and dog and were adequately qualified in pivotal nonclinical safety studies.⁹

⁹ The exposure levels of the M1, M3, and M10 metabolites in pivotal nonclinical studies in the rat, rabbit, and dog were equal to or higher than human exposure levels at the MRHD of 50 mg.

Figure 19. Proposed Metabolic Pathway of Daridorexant



Source: Study B-15.042

13.1.2.3.1. In Vitro Metabolism

In liver microsomes and primary hepatocytes from animal species (mouse, rat, rabbit, dog, and monkey) and humans, daridorexant was metabolized via three primary metabolic pathways: aliphatic hydroxylation of the methyl group at the benzimidazole moiety to generate M3, demethylation of the methoxy group to generate M4, and hydroxylation of the methylpyrrolidine moiety to generate M5. Secondary metabolism generates M7 from M5, M1, M2, and M10 from M3, and the glucuronide M9 from M4 (Study B14.019).

Although there were some species differences in the in vitro metabolism of daridorexant, there was no unique human metabolite. All three major human metabolites (M1, M3, and M10) were generated in the liver microsomes or primary hepatocytes from the rat and dog.

13.1.2.3.2. In Vivo Metabolism

After oral and IV administration at 10 and 1 mg/kg, respectively, daridorexant was extensively metabolized in the rat (Study B-14.054). The major in vivo metabolic pathways were generally similar to those identified in the in vitro assays. Additional minor in vivo metabolic pathways included aromatic hydroxylation of the anisole ring to generate M11 and a possible combined hydroxylation in the phenyl triazole moiety and subsequent glucuronidation to generate M8.

13.1.2.4. Excretion

Excretion of daridorexant after oral and IV administration was evaluated as part of the metabolic profiling study in the rat (Study B-14.054). Most radioactivity following oral and IV administration of daridorexant was measured in biliary secretion, which accounted for close to 90% of the dose and less than 2% of the dose was excreted via the urine.

13.1.2.5. Drug-Drug Interaction

13.1.2.5.1. Enzyme Inhibition Potential of Daridorexant and/or its Metabolites

In in vitro assays, daridorexant and the M1 metabolite weakly inhibited several CYP enzymes, whereas no significant inhibitory activity was observed with the M3 and M10 metabolites.

In human liver microsomes (for CYP1A2, 2B6, 2C8, 2C9, 2D6, and 3A) or insect cells expressing human CYP2C19 (Studies B-14.018, 17.055, and 20.034), daridorexant inhibited CYP2C8, 2C9, 2C19, and 3A4 with IC_{50} values of 18, 19, 8.2, and 7.3 to 15 μ M, respectively. The M1 metabolite inhibited CYP2C8, 2C9, 2C19, and 3A4 with IC_{50} values of 17, 26, 11, and 26 μ M, respectively. The inhibition of CYP3A4 by daridorexant and M1 metabolite was time- and NADPH-dependent whereas other inhibitions were not time-dependent. At therapeutically relevant concentrations, daridorexant had negligible inhibitory activity on CYP1A2, 2A6, 2B6, and 2D6 ($IC_{50} \geq 50 \mu$ M); M1 had negligible inhibitory activity on CYP1A2, 2B6, and 2D6 ($IC_{50} > 44 \mu$ M); M3 and M10 had negligible inhibitory activity on all CYP enzymes tested ($IC_{50} \geq 26 \mu$ M and 88 μ M, respectively).

13.1.2.5.2. Enzyme Induction Potential of Daridorexant and/or its Metabolites

In in vitro assays, both daridorexant and its M1, M3, and M10 metabolites induced multiple CYP enzymes.

In mammalian cells (CV-1 cell) that express the human pregnane X receptor (PXR) (Studies B-14.064 and 17.063), both daridorexant and its metabolites induced dose-dependent activation of the human PXR. For daridorexant and M3, the EC_{50} values were 3 and 2.4 μ M, respectively. For M1 and M10, EC_{50} values could not be determined due to cytotoxic effect at concentrations $\geq 3 \mu$ M for M1 or absence of a plateau at the highest tested concentration of 30 μ M for M10. Nevertheless, M1 at 1 μ M increased PXR activation by 4-fold relative to vehicle controls and M10 at 30 μ M increased PXR activation by 2.4-fold.

In primary human hepatocytes (Studies D-17.063 and 14.064), daridorexant dose-dependently increased the mRNA expression of CYP2B6, 2C9, and 3A4. M1 and M3, but not M10, dose-dependently increased mRNA expression of CYP2B6. None of the three metabolites induced mRNA expression of CYP1A.¹⁰ In liver samples collected from the 4-week studies in the rat (Study T-13.221) and dog (Study T-13.220), repeat treatment of daridorexant dose-dependently increased the mRNA of CYP3A1, 2B1, 2B2, UGT1a1, UGT1a6, and UGT2b1 in the rat and CYP3A12 in the Dog (Study B-14.065).

13.1.2.5.3. Transporter Inhibition Potential of Daridorexant and its Metabolites

In *in vitro* assays, both daridorexant and its M1, M3, and M10 metabolites showed relatively weak inhibitory activity against multiple transporters.

In mammalian cells that express various human transporters (Studies B-14.061, 17.049 and 19.069), daridorexant inhibited BCRP, MATE1, MATE2, OATP1B1, OATP1B3, OAT3, OCT1, and P-gp/MDR1 with IC₅₀ values of 3.0, 9.7, 8.4, 11, 16, 39, 71, and 24/21 μM, respectively. The M1 metabolite inhibited OATP1B1, P-gp, BCRP, OCT1, and MATE1 transporters with IC₅₀ values of 4.5, 31, 10, 0.5, and 16 μM, respectively. The M3 metabolite weakly inhibited P-gp, BCRP, OCT1, MATE1, and MATE2K transporters with IC₅₀ values of ~94, 21, 8, 23, and 100 μM, respectively. The M10 metabolite weakly inhibited OCT1 and MATE1 transporters with IC₅₀ values of 180 and 230 μM. No other significant transporter inhibition potential was observed with daridorexant and/or its metabolites.

13.1.3. General Toxicology Studies

The nonclinical program of daridorexant includes an adequate battery of genotoxicity studies; repeat dose general toxicology studies in the mouse for up to 28 days, rat for up to 26 weeks, and dog for up to 39 weeks; 2-year and 6-month carcinogenicity studies in the rat and Tg.rasH2 mouse, respectively; a complete battery of reproductive and developmental toxicology studies in the rat and/or rabbit; juvenile rat toxicology study; special toxicology studies; and studies to qualify impurities. All pivotal toxicology studies were conducted under GLP. The major human metabolites of daridorexant (M1, M3, and M10) are adequately qualified in nonclinical studies because the exposure levels in the nonclinical species (general toxicology studies in rat and dog, carcinogenicity study in the rat, and embryofetal toxicity studies in the rat and rabbit) were equal to or higher than the clinical exposure at the MRHD of 50 mg.

Main safety findings, target organs, and their clinical relevance are summarized and discussed in Section [7.1](#). Findings from individual toxicological studies are summarized below:

¹⁰ The induction of CYP3A4 and CYP2C9 by the M1, M3, and M10 metabolites were not evaluated *in vitro* because no CYP3A4 or 2C9 induction was observed in the clinical DDI study.

13.1.3.1. Rat

13.1.3.1.1. 26-Week Rat Study: ACT-541468A-26-Week Oral (Gavage) Toxicity Study in the Rat Followed by an 8-Week Treatment - Free Period (Study T-15.076)¹¹

Table 53. Study T-15.076 Information

GLP compliance:	Yes
Methods	
Dose and frequency of dosing:	0 (vehicle control), 50 (LD), 150 (MD), and 450 (HD) mg/kg/day, once daily
Route of administration:	oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Wistar Rats: RccHan from (b) (4)
Number/Sex/Group:	Main study: n=20/sex/group Recovery: n=5/sex/group TK: n=6/sex/group
Age:	~6 weeks at treatment initiation
Unique design:	Thyroid hormone levels (T3, T4, and TSH) were measured at Weeks 13 and 26 (n=10/sex/group)
Deviation from study protocol affecting interpretation of results:	There were multiple minor quality-related issues; however, they did not affect the GLP status or the overall conclusion of the study (See Overall assessment on GLP Compliance and Data Quality)

Source: Summarized from the Applicant's Study Reports

Abbreviations: HD, high dose; LD, low dose; MD, mid dose; TK, toxicokinetic; n, number of subjects with given characteristic; TSH, thyroid-stimulating hormone

¹¹ This study also served as the dose range finding study for the 2-year rat carcinogenicity study.

Table 54. Observations and Results, Study T-15.076

Major Drug-Related Findings^a	
Mortality	Potentially drug-related mortality at 450 mg/kg/day
CNS	Pharmacology-related, dose-dependent CNS depression (decreased activity) at ≥ 50 mg/kg/day. Exaggerated-pharmacology-related, clinical signs of “lateral decubitus, contraction/stiffness of limbs for approximately 30 seconds to a few minutes, then the animal stand up but with a decreased activity for a few minutes” in one female at 450 mg/kg/day on multiple days, which led to early termination of this animal.
Liver	Dose-dependent increases in the incidence and/or severity of centrilobular hepatocellular hypertrophy at ≥ 150 mg/kg/day with correlative increases in the liver weight ($\uparrow \sim 60\%$ and 120% in HDM and HDF, respectively), cholesterol ($\uparrow 86\%$ in HDF), triglycerides ($\uparrow 29\%$ and 91% in HDM and HDF, respectively), and GGT ($\uparrow 4x$ and $2x$ in HDM and HDF, respectively). Changes in the liver were partially reversible and are likely due to the enzyme induction effects of the drug.
Thyroid	Dose-dependent increases in the incidence and/or severity of follicular cell hypertrophy in the thyroid at ≥ 150 mg/kg/day with correlative increases in the thyroid weight ($\uparrow \sim 30\%$ in HDM and HDF) and plasma TSH levels ($\uparrow 2x$ in HDM and HDF). These changes are likely secondary to the liver enzyme induction and increased metabolism of thyroid hormones; nevertheless, the histopathology changes persisted after recovery.
Kidney	Tubular hyaline casts in the kidney in HDF with correlative increases in the kidney weight ($\uparrow \sim 20\%$ in HDF) and increased leucocytes and proteins in the urine (trace to marked levels in HDF), which persisted after recovery.

Source: Summarized from the Applicant’s Study Reports

^a, adequate histopathology evaluation conducted at the terminal and recovery necropsy without peer review

Abbreviations: CNS, central nervous system; GGT, gamma-glutamyl transferase; HDF, high dose female; HDM, high dose male; TSH, thyroid-stimulating hormone

NOAEL and Safety Margin

Based on the cataplexy-like clinical signs and increased gamma-glutamyl transferase (GGT) levels, the NOAEL is 150 mg/kg/day in both males and females in the 26-week rat study. The corresponding exposure levels of daridorexant after 26 weeks of treatment were AUC of 16.8 and 26.5 $\mu\text{g}\cdot\text{hr}/\text{mL}$ and C_{max} of 5.8 and 6.6 $\mu\text{g}/\text{mL}$ in males and females, respectively, which provide a safety margin of 6 and 3 relative to the MRHD of 50 mg, based on C_{max} and AUC, respectively (Table 55).

Table 55. Exposure Levels of Daridorexant and its Metabolites at the NOAEL in the 26-Week Rat Study and Corresponding Safety Margins

Doses (mg/kg/day)	Daridorexant		M1 (ACT-776537)				M3 (ACT-776063)				M10 (ACT-1016-3307)					
	C_{max}		C_{max}		C_{max}		C_{max}		C_{max}		C_{max}		C_{max}			
	($\mu\text{g}/\text{mL}$)	($\mu\text{g}\cdot\text{hr}/\text{mL}$)	($\mu\text{g}/\text{mL}$)	($\mu\text{g}\cdot\text{hr}/\text{mL}$)	($\mu\text{g}/\text{mL}$)	($\mu\text{g}\cdot\text{hr}/\text{mL}$)	($\mu\text{g}/\text{mL}$)	($\mu\text{g}\cdot\text{hr}/\text{mL}$)	($\mu\text{g}/\text{mL}$)	($\mu\text{g}\cdot\text{hr}/\text{mL}$)	($\mu\text{g}/\text{mL}$)	($\mu\text{g}\cdot\text{hr}/\text{mL}$)	($\mu\text{g}/\text{mL}$)	($\mu\text{g}\cdot\text{hr}/\text{mL}$)		
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
NOAEL (150)	5.8	6.6	16.8	26.5	2.9	4.0	12.8	11.5	3.3	5.8	15.4	28.9	0.9	0.7	4.0	5.0
Human exposure ^a	1		6.3		0.25		3.7		0.55		5.9		0.1		1.1	
Safety Margin ^b	6/60 x		3/30 x		12/120 x		3/30 x		6/60 x		3/30 x		7/70 x		4/40 x	

Source: Summarized from the Applicant’s Study Reports

^a, human exposure levels are based on clinical study AC-078-105, AUC of 6300 $\text{ng}\cdot\text{hr}/\text{mL}$ and C_{max} of 1006 ng/mL

^b, safety margins calculated based on total exposures and the free fraction after adjustment for protein binding

Abbreviations: AUC, area under the concentration-time curve; C_{max} , maximum plasma concentration

13.1.3.1.2. 13-Week Rat Study: Daridorexant: 13-Week Oral (Gavage) Administration Toxicity Study in the Rat Followed by a 4-Week Treatment-free Period (Study T-14.068)¹²

Table 56. Study T-14.068 Information

GLP compliance:	Yes
Methods	
Dose and frequency of dosing:	0 (vehicle control), 50 (LD), 150 (MD), and 450 (HD) mg/kg/day, once daily
Route of administration:	oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Wistar Rats: RccHan from (b) (4)
Number/Sex/Group:	Main study: n=10/sex/group Recovery: n=5/sex/group TK: n=6/sex/group
Age:	~5 to 6 weeks at treatment initiation
Unique design:	Thyroid hormone levels (T3, T4, and TSH) were measured at the terminal and recovery necropsy.
Deviation from study protocol affecting interpretation of results:	None that significantly affected the interpretation of study outcome

Source: Summarized from the Applicant's Study Reports

Abbreviations: HD, high dose; LD, low dose; MD, mid dose; n, number of subjects with given characteristic; TK, toxicokinetic

Table 57. Observations and Results, Study T-14.068

Major Drug-Related Findings^a

CNS	Pharmacology-related, dose-dependent CNS depression (decreased activity, subdued or sluggish behavior) at ≥50 mg/kg/day
Liver	Dose-dependent centrilobular hepatocellular hypertrophy at ≥150 mg/kg/day, which correlated with liver enlargement, increased liver weight (↑ up to 53% and 97% in HDM and HDF, respectively), and increased cholesterol level (~2x in HDF). These changes were reversible.
Thyroid	Dose-dependent follicular cell hypertrophy in the thyroid, which correlated with enlarged thyroid gland, increased thyroid weight (↑ up to 28% and 52% in HDM and HDF, respectively), and increased TSH levels (↑8.4x and 2.2 x in HDM and HDF, respectively). These changes were reversible.

Changes in the liver and thyroid are likely due the enzyme induction effects of the drug and the increased metabolism of thyroid hormones.

Source: Summarized from the Applicant's Study Reports

^a, adequate histopathology evaluation conducted at the terminal and recovery necropsy without peer review

Abbreviations: CNS, central nervous system; HDF, high dose female; HDM, high dose male; TSH, thyroid-stimulating hormone

NOAEL and Safety Margin

Given the mild, adaptive, and reversible nature of the changes in the liver and thyroid, they are not considered to be adverse. The NOAEL for the 13-week rat study is 450 mg/kg/day in both sexes. The corresponding exposure levels of daridorexant after 13 weeks of treatment was AUC

¹² This study was also used to support qualification of impurities.

of 34.5 and 52.1 $\mu\text{g}\cdot\text{hr}/\text{mL}$ in males and females, respectively, which provides a ~5-fold safety margin relative to the MRHD of 50 mg, based on AUC.¹³

13.1.3.1.3. Nonpivotal Studies in the Rat

The nonpivotal short-term (3 days to 4 weeks) studies in the rat primarily served as dose range finding studies for pivotal studies during the course development. Findings were generally similar to those observed in the pivotal studies and the CNS, liver, and thyroid gland were the primary target organs.

4-Week Repeat Dose Study (Study T-13.221, GLP)

In a 4-week study, Wistar rats were orally treated with daridorexant at doses of 0 (vehicle control, 0.5% w/v methylcellulose), 100 (low dose [LD]), 300 (mid dose [MD]), and 1000 (high dose [HD]) mg/kg/day (n=10/sex/group). A 4-week recovery period (n=5/sex/group) was included. Toxicokinetic (TK) analysis was conducted on Days 1 and 28 (n=6/sex/group¹⁴)

The high dose of 1000 mg/kg/day exceeded the maximum tolerated dose (MTD) and caused premature deaths in 6 out of 10 females. At this dose, daridorexant also caused centrilobular hepatocellular hypertrophy with correlative increases in liver weight and higher serum levels of triglycerides (2x in high dose males [HDM] and high dose females [HDF]), cholesterol (2x in HDF), and GGT (6x and 11x in HDM and HDF, respectively) and alanine aminotransferase (ALT) (2x in HDF). Follow-up mechanistic studies showed that the deaths were potentially caused by hypothermia associated with daridorexant treatment at the dose of 1000 mg/kg/day (Studies T-14.060 and T-14.064, nonGLP); nevertheless, the hypothermia effects of daridorexant were not due to activation of the transient receptor potential cation channel subfamily V member 1 (TRPV1, Study T-14.052, nonGLP).

At ≤ 300 mg/kg/day, drug-related findings were largely similar to those observed in the 26- and 13-week pivotal studies, including

- Dose-dependent pharmacology-related CNS depression (decreased activity).
- Adaptive changes in the liver and thyroid (hepatocellular hypertrophy in the liver and follicular cell hypertrophy in the thyroid) with correlative increases in liver and thyroid weight.

The NOAEL for the 4-week rat study is 300 mg/kg/day in both sexes. The corresponding exposure levels of daridorexant was AUC of 32.1 and 54.6 $\mu\text{g}\cdot\text{hr}/\text{mL}$ in males and females, respectively, which provides a ~5-fold safety margin relative to the MRHD of 50 mg, based on AUC.

¹³ The exposure levels in male rats at the NOAEL was used to calculate the safety margin because it provided a more conservative margin.

¹⁴ For HD TK group, one female was transferred to the recovery group. Therefore, the number of females in the HD recovery and TK groups was 6 and 5, respectively.

2-Week Repeat Dose Study (Study T-13.163, nonGLP)

In a 2-week study, Wistar rats were orally treated with daridorexant at doses of 0 (vehicle control, 0.5% methylcellulose), 100, 300, 600 (female only), and 1000 mg/kg/day (n=5/sex/group). TK analysis of daridorexant was conducted on Day 13 (n=3/sex/group). Drug-related findings were generally similar to those observed in the pivotal studies at the same or similar doses, including:

- Dose-dependent CNS depression
- Increased liver weight with correlative increases in GGT levels in both sexes and cholesterol level (females) at ≥ 600 mg/kg/day
- Increased thyroid weight in males at 1000 mg/kg/day

3-Day Repeat Dose Study (Study T-13.144, nonGLP)

In a 3-day study, Wistar rats were orally treated with daridorexant at 1000 mg/kg/day. Drug-related findings included decreased activity, cytoplasmic vacuolation in the liver with correlative increases in serum GGT (both sexes), ALT (females), and ALP (males) levels.

13.1.3.2. Dog

13.1.3.2.1. 39-Week Dog Study: Daridorexant - 39-Week Toxicity Study by the Oral (Gavage) Route in the Beagle Dog Followed by an 8-Week Treatment-Free Period (Study T-16.017)

Table 58. Study T-16.017 Information

GLP compliance:	Yes
Methods	
Dose and frequency of dosing:	0 (vehicle control), 10 (LD), 30 (MD), and 100 (HD) mg/kg/day, once daily
Route of administration:	oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Beagle dogs from (b) (4)
Number/Sex/Group:	Main study: n=4/sex/group Recovery: n=3/sex for control and HD
Age:	10-11 months at treatment initiation
Unique design:	Thyroid hormone levels (T3, T4, and TSH) were measured in all animals at Weeks 26, 39 (terminal necropsy) and 47 (recovery necropsy)
Deviation from study protocol affecting interpretation of results:	There were multiple minor quality-related issues; however, they did not affect the GLP status or the overall conclusion of the study (See Overall assessment on GLP Compliance and Data Quality).

Source: Summarized from the Applicant's Study Reports

Abbreviations: HD, high dose; LD, low dose; MD, mid dose; n, number of subjects with given characteristic.

Table 59. Observations and Results, Study T-16.017

Major Drug-Related Findings^a	
CNS	Exaggerated-pharmacology related, <i>cataplexy-like clinical signs</i> (lying down, loss of balance, unsteady gait, clumsy movement, unable to stand, subdued and/or immobility) <i>after positive stimulation</i> at ≥ 30 mg/kg/day
Liver	Hepatomegaly (increased size and volume of hepatocytes) at 100 mg/kg/day with correlative increases in the liver weight ($\uparrow \sim 30\%$ and 65% in HDM and HDF, respectively), liver enlargement, and increased ALT ($\uparrow 10x$), GLDH ($\uparrow 19x$), AST ($\uparrow 3x$), GGT ($\uparrow 3x$), and ALP ($\uparrow 3x$) in some animals. These changes were reversible after recovery.
Gallbladder	Dose-dependent increases in luminal secretory material in the gallbladder at ≥ 30 mg/kg/day. These changes were reversible after recovery.

Source: Summarized from the Applicant's Study Reports

^a, adequate histopathology evaluation conducted at the terminal and recovery necropsy without peer review

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, central nervous system; GGT, gamma-glutamyl transferase; GLDH glutamate dehydrogenase; HDF, high dose female; HDM, high dose male; TSH, thyroid-stimulating hormone

NOAEL and Safety Margin

Based on the cataplexy-like clinical signs and increased liver enzyme levels, the NOAEL is considered to be 10 mg/kg/day in both males and females in the 39-week dog study. The corresponding exposure levels of daridorexant, after 39 weeks of treatment, were AUC of 9100 and 17500 ng*hr/mL and C_{max} of 1830 and 3530 ng/mL in males and females, respectively, which provided a safety margin of ~ 1.5 -fold relative to the proposed MRHD of 50 mg, based on both C_{max} and AUC.¹⁵

¹⁵ Because cataplexy is primarily C_{max} driven whereas liver changes were AUC related, safety margin were calculated based on both C_{max} and AUC. At the MRHD of 50 mg, the exposure levels in humans were C_{max} of 1004 (ng/ml) and AUC of 6300 ng*hr/mL. Exposure levels in male dogs at the NOAEL were used because they provided a more conservative safety margin.

13.1.3.2.2. 13-Week Dog Study: Daridorexant – 13-Week Oral (Gavage) Administration Toxicity Study in the Dog Followed by a 4-Week Treatment-Free Period (Study T-14.067, GLP¹⁶)

Table 60. Study T-14.067 Information

GLP compliance:	Yes
Methods	
Dose and frequency of dosing:	0 (vehicle control), 20 (LD), 50 (MD), and 150 (HD) mg/kg/day, once daily
Route of administration:	oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Beagle dogs from (b) (4)
Number/Sex/Group:	Main study: n=4/sex/group Recovery: n=2/sex for control and HD
Age:	~7 months at treatment initiation
Unique design:	Thyroid hormone levels (T3, T4, and TSH) were measured in all animals at Weeks 6, 13 (terminal necropsy) and 17 (recovery necropsy).
Deviation from study protocol affecting interpretation of results:	None that significantly affected the interpretation or conclusion of the study

Source: Summarized from the Applicant's Study Reports

Abbreviations: HD, high dose; LD, low dose; MD, mid dose; n, number of subjects with given characteristic

Table 61. Observations and Results, Study T-14.067

Major Drug-Related Findings ^a

CNS	Exaggerated-pharmacology related, cataplexy-like clinical signs (fainting) <i>after positive stimulation</i> at ≥50 mg/kg/day; decreased activity at 150 mg/kg/day
Body weight and food consumption	Decreased body weight (↓~10%), weight gain (↓~15%), and food consumption (↓~40%) at 150 mg/kg/day. These changes were reversible during the recovery period.
Liver	Increased liver weight (↑up to ~50%) at ≥50 mg/kg/day; increased ALT (↑3x) and GLDH (↑85%) levels in 2/4 females and increased ALP (↑4x) in 1/4 male at 150 mg/kg/day. These changes were reversible after recovery.
Gallbladder	Dark and thick material in the gallbladder at 150 mg/kg/day. These changes were reversible after recovery.

Source: Summarized from the Applicant's Study Reports

^a, adequate histopathology evaluation conducted at the terminal and recovery necropsy without peer review

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; CNS, central nervous system; GLDH glutamate dehydrogenase

NOAEL and Safety Margin

Based on the cataplexy-like clinical signs, the NOAEL is considered to be 20 mg/kg/day in both males and females in the 13-week dog study. The corresponding exposure levels of daridorexant, after 13 weeks of treatment, were AUC of 34100 and 19700 ng*hr/mL and C_{max} of 4500 and

¹⁶ This study was also used to support qualification of impurities.

3500 ng/mL in males and females, respectively, which provided a safety margin of ~3.5-fold relative to the proposed MRHD of 50 mg, based on C_{max} .¹⁷

13.1.3.2.3. Nonpivotal Studies in the Dog

The nonpivotal short-term (3 days to 4 weeks) studies in the dog primarily served as dose range finding studies for pivotal studies during the course development. Findings were generally similar to those observed in the pivotal studies and the CNS, liver, and gallbladder were the primary target organs.

4-Week Repeat Dose Dog Study (Study T-13.220, GLP)

In a 4-week study, beagle dogs were orally treated with daridorexant at doses of 0 (vehicle control, 0.5% w/v methylcellulose), 30 (LD), 100 (MD), and 300/200 (HD) mg/kg/day (n=3/sex/group). A 4-week recovery period (n=2/sex) was included for control and HD groups. TK analysis was conducted on Days 1 and 28 (n=6/sex/group)

The high dose of 300 mg/kg/day was not tolerated, caused severe weight loss, and led to a 5-day dose cessation and subsequent dose reduction to 200 mg/kg/day from Day 11. However, 200 mg/kg/day also exceeded the MTD and caused repeated tremors in both sexes and continued weight loss in females.

Other drug-related findings were largely similar to those observed in the 13- and 39-week dog studies, including centrilobular hepatocellular hypertrophy in the liver with correlative increases in the liver weight (~60%) and ALP levels (2x), follicular cell hypertrophy with correlative increases in the thyroid weight at ≥ 100 mg/kg/day, and increased luminal secretory material in the gallbladder at $\geq 300/200$ mg/kg/day.

The NOAEL for the 4-week dog study is 30 mg/kg/day in both sexes. The corresponding exposure levels of daridorexant after 4 weeks of treatment were C_{max} of 7270 and 6110 ng/mL and AUC of 41500 and 36700 ng*hr/mL in males and females, respectively, which provides a ~6-fold safety margin relative to the MRHD of 50 mg, based on AUC.

3-Day and 2-Week Dose Range Finding Study in the Dog (Study T-13.172, nonGLP)

Beagle dogs were orally treated with daridorexant at increasing doses of 30, 100, 300, and 1000 mg/kg/day for 3 consecutive days with a 4-day washout period in between (n=1/sex). At ≥ 300 mg/kg/day, daridorexant caused dose-dependent vomiting, weight loss, and decreased food consumption.

Beagle dogs were orally treated with daridorexant at 600 mg/kg/day for 2 weeks (n=2/sex). At 600 mg/kg/day, daridorexant caused weight loss and decreased food consumption, increased inflammatory cell infiltrate and/or accumulation of secretory material in the gall bladder with correlative bile duct hyperplasia, and inflammatory cell infiltration in the liver with increased liver enzymes.

¹⁷ Because cataplexy is primarily C_{max} driven, safety margin was calculated based on C_{max} .

13.1.3.3. Mouse

13.1.3.3.1. 4-Week Mouse Study: Daridorexant: 28-Day Repeated Dose Oral Toxicity and Toxicokinetic Study in CByB6F1 Mice (Study T-17.009)¹⁸

Table 62. Study T-17.009 Information

GLP compliance:	Yes
Methods	
Dose and frequency of dosing:	0 (vehicle control), 100 (LD), 300 (MD), and 1500 ¹⁹ (HD) mg/kg/day, once daily
Route of administration:	oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	CByB6F1 wildtype litter mates from (b) (4)
Number/Sex/Group:	Main study: n=10/sex/group TK: n=20/sex/group for daridorexant treated groups; n=5/sex for vehicle control group
Age:	~5-6 weeks at treatment initiation
Unique design:	None
Deviation from study protocol affecting interpretation of results:	None that significantly impacted data interpretation or conclusion

Source: Summarized from the Applicant's Study Reports

Abbreviations: HD, high dose; LD, low dose; MD, mid dose; n, number of subjects with given characteristic; TK, toxicokinetic

Table 63. Observations and Results, Study T-17.009

Major Drug-Related Findings^a

Liver	At 300 mg/kg/day, adaptive changes in the liver including centrilobular hepatocellular hypertrophy in the liver with correlative liver enlargement and increased liver weight. At 1500 mg/kg/day, focal necrosis (clusters of necrotic cells) in the liver.

Source: Summarized from the Applicant's Study Report

^a, adequate histopathology evaluation conducted at the terminal and recovery necropsy without peer review

NOAEL and Safety Margin

Based on the liver findings (focal necrosis), the NOAEL for the 4-week mouse study is 300 mg/kg/day. The corresponding exposure levels of daridorexant, after 4 weeks of treatment, were C_{max} of 3280 and 893 ng/mL and AUC of 5530 and 2210 ng*hr/mL in males and females, respectively, which provide a safety margin of ~0.5 fold based on AUC.

Although the safety margin is relatively small. The low drug exposure in the mouse study does not affect the safety assessment of daridorexant because adequate exposure levels of daridorexant and its major human metabolites M1, M3, and M10 have been characterized in the rat and dog.

¹⁸ This study also served as dose range finding study for the 6-month carcinogenicity study in Tg rash2 mice.

¹⁹ For the high dose group, animals were titrated at 500 mg/kg/day for the first 2 days, 1000 mg/kg/day on Days 3 and 4, and 1500 mg/kg/day for the rest of the treatment period.

13.1.3.3.2. Nonpivotal Studies in the Mouse

The Applicant conducted a few 2-week studies in different mouse strains, the findings were generally similar to those observed in the 4-week mouse study with the liver as the main target organ. The findings are summarized below.

B6C3F1 mice were orally treated with daridorexant at 0 (vehicle control, 0.5% methylcellulose), 100 (LD), 300 (MD), and 1000/600 (HD) mg/kg/day for 2 weeks (n=9/sex/group, Study T-16.019, nonGLP). TK was conducted in satellite TK animals (n=12/sex/group). The 1000 mg/kg/day dose exceeded MTD, caused severe CNS depression, and led to dose reduction to 600 mg/kg/day. Main drug-related findings included increased liver weight (~25% to 30%) and histopathology of diffuse hepatocellular hypertrophy at all doses.

CD-1 mice were orally treated with daridorexant at 0 (vehicle control, 0.5% methylcellulose, 5/sex), 1000 (LD, 7/sex), and 2000 (HD, 3 per sex treated at 1000 mg/kg/day from Day 1 to 4, and then 1000 mg/kg twice daily [BID] 6 hours apart, from Day 5 to Day 14) for 2 weeks (Study T-16.054, nonGLP). The liver was the target organ as evidenced by centrilobular to pan-lobular hepatocellular hypertrophy with correlative increases in the liver weight, increased ALT and glutamate dehydrogenase levels in both sexes (~3x and 2x, respectively), and increased aspartate aminotransferase level in males (2x) at 2000 mg/kg/day.

CByB6F1 mice were orally treated with daridorexant at 0 (vehicle control, 0.5% w/v methylcellulose, 5 mice/sex), 1000 (LD, 7 mice/sex), and 2000 (HD, 7 mice per sex treated at 1000 mg/kg/day from Day 1 to 4 and then 1000 mg/kg BID from Day 5 to Day 14) for 2 weeks (Study T-16.061, nonGLP). Drug-related findings included dose-dependent increases in liver weight (30% to 65%) with correlative histopathology of minimal to moderate hepatocellular hypertrophy.

13.1.4. Genetic Toxicology

Daridorexant was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay, clastogenic in the in vitro mammalian chromosome aberration assay in human lymphocytes, or in the in vivo rat bone marrow micronucleus assay.

The genotoxicity studies with daridorexant are summarized below.

Table 64. Daridorexant Genotoxicity, Study T-14.007

Study Title	<i>Daridorexant: Salmonella typhimurium reverse mutation assay (Study T-14.007, GLP)</i>
Tester Strains:	Tester strains: TA98, TA100, TA1535, TA1537, and TA102
Concentrations:	Doses tested: ± S9, 3, 10, 33, 100, 333, 1000, 2500, and 5000 µg/plate
Study Validity	The study is valid. The tester strain, dose selection, and metabolic activation were adequate. The positive and negative controls generated expected results and the values were within the historical control range at the test facility.
Study Conclusion:	Daridorexant was not mutagenic in a valid in vitro bacterial Ames assay.

Source: Summarized from the Applicant's Study Reports

Table 65. Daridorexant Genotoxicity, Study T-14.008

<i>Daridorexant: In vitro Chromosome Aberration Test in Human Lymphocytes (Study T-14.008, GLP)</i>	
Study Title	<i>Daridorexant: In vitro Chromosome Aberration Test in Human Lymphocytes (Study T-14.008, GLP)</i>
Cell line	Peripheral Human Blood Lymphocytes
Concentrations in the definitive test	+S9, 4-hour incubation: 17.1, 29.9, and 52.2 µg/mL*; +S9, 22-hour incubation: 17.1, 29.9, and 52.2 µg/mL*; -S9, 22-hour incubation: 29.9, 52.2, and 91.4 µg/mL#; *, high dose selected based on precipitation. #, high dose selected based on cytotoxicity and precipitation.
Study Validity	This study is valid. The dose selection was adequate. The positive and negative controls generated expected results and the values were within the historical control range at the test facility.
Study Conclusion:	Daridorexant was not clastogenic in a valid in vitro chromosomal aberration assay in human lymphocytes.

Source: Summarized from the Applicant's Study Reports

Table 66. Daridorexant Genotoxicity, Study T-14.010

<i>Daridorexant: Micronucleus Assay in Bone Marrow Cells of the Rat (Study T-14.010, GLP)</i>	
Study Title	<i>Daridorexant: Micronucleus Assay in Bone Marrow Cells of the Rat (Study T-14.010, GLP)</i>
Rat Strain	Wistar rats (RccHan: Wistar, from (b) (4))
Treatment Duration:	twice (short-term study)
Doses tested	0 (vehicle control, 0.5% methylcellulose), 125 (LD), 500 (MD), and 2000 (HD). High dose was selected based on limit dose.
Study Validity	This study is valid. The dose selection was adequate. Adequate exposure to daridorexant and its major metabolites (M1, M3, and M10) was confirmed by TK. The positive and negative controls generated expected results and the values were within the historical control range at the test facility.
Study Conclusion:	Daridorexant was negative in a valid in vivo micronucleus assay in the rat bone marrow.

Source: Summarized from the Applicant's Study Reports
Abbreviations: HD, high dose; LD, low dose; MD, mid dose; TK, toxicokinetic

13.1.5. Reproductive Toxicology

13.1.5.1. Fertility and Early Embryonic Development Study

13.1.5.1.1. Fertility Toxicity Study by the Oral Route (Gavage) Administration in the Female Rat (Study T-16.004)

Table 67. Study T-16.004 Information

GLP compliance:	Yes
Methods	
Dose and frequency of dosing:	0 (control), 30 (LD), 100 (MD), and 300 (HD) mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose 400 cps
Species/Strain:	Wistar rats Crl: WI (Han)
Number/Sex/Group:	Main study: n=22/group TK: n=6/group for LD, MD, and HD; n=3 for control
Study design:	Female rats were orally treated for 2 weeks prior to and throughout mating with untreated males and until GD 7. On GD 13, all females were sacrificed. Parameters of evaluation included mortality, clinical conditions, body temperature, body weights and food consumption, estrous cycle, and cesarean data. In addition, TK analysis was conducted in TK animals on treatment Day 1 and GD 7. The high dose of 300 mg/kg/day was selected based on the minimal maternal toxicity observed in the embryofetal developmental toxicity study whereas 1000 mg/kg/day caused maternal deaths in pregnant rats.
Deviation from study protocol affecting interpretation of results:	None that significantly impacted data interpretation.

Source: Summarized from the Applicant's Study Reports

Abbreviations: GD, gestation day; HD, high dose; LD, low dose; MD, mid dose; n, number of subjects with given characteristic; TK, toxicokinetic

Table 68. Observations and Results, Study T-16.004

Major Drug-Related Findings	
Clinical signs	Pharmacology-related CNS depression (partially closed eyes, slow breathing and lying down) at ≥ 100 mg/kg/day; no change in body temperature
Mating and Fertility	No drug-related changes in mating and fertility index
Necropsy findings Cesarean section data	At ≥ 100 mg/kg/day, the number of implantation sites was slightly decreased (11.1 and 10.7 in MD and HD, respectively, compared to 11.8 in controls) and the pre-implantation loss was slightly increased (15.2% and 19.2% in MD and HD groups, respectively, compared to 13.3% in controls)

Source: Summarized from the Applicant's Study Reports

Abbreviations: CNS, central nervous system; HD, high dose; MD, mid dose

NOAEL and Safety Margin

Given the dose-relationship and the correlative decreases in the implantation sites and increases in pre-implantation loss, these effects are considered to be drug-related. The magnitude of changes in HD animals was relatively large and is conservatively considered to be adverse. Therefore, the NOAEL for female fertility is 100 mg/kg/day. The corresponding exposure level (AUC) on Gestation Day 7 was 17800 ng*hr/mL, which provided a 3-fold safety margin relative to the MRHD of 50 mg, based on AUC.

13.1.5.1.2. Fertility Toxicity Study by the Oral Route (Gavage) in the Male Rat (Study T-16.003)

Table 69. Study T-16.003 Information

GLP compliance:	Yes
Methods	
Dose and frequency of dosing:	0 (control), 50 (LD), 150 (MD), and 450 (HD) mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Wistar rats Crl: WI (Han)
Number/Sex/Group:	n=22/group
Study design:	Males were treated 14 days before and throughout mating (with untreated females) and up to the day before scheduled necropsy (a total of 7 weeks of treatment). Females were sacrificed on gestation day 13 and were examined for pregnancy status, number of corpora lutea, intrauterine implantations and intrauterine deaths (resorption sites). Sperm analysis (sperm motility, sperm counts, and sperm morphology) were conducted. In addition, TK analysis was conducted in the first 6 males/group on Days 1 and 39.
	Dose selection was based on the 13-week repeat dose studies, in which 450 mg/kg/day was tolerated with findings of hepatocellular hypertrophy and increased liver weight and follicular hypertrophy in the thyroid with correlative changes in thyroid hormones. Therefore, 450 mg/kg/day was selected as the high dose for the male fertility study.
Deviation from study protocol affecting interpretation of results:	None that significantly impacted data interpretation.

Source: Summarized from the Applicant's Study Reports
 Abbreviations: HD, high dose; LD, low dose; MD, mid dose; n, number of subjects with given characteristic; TK, toxicokinetic

Table 70. Observations and Results, Study T-16.003

Major Drug-related Findings	
Clinical signs	Pharmacology-related, dose dependent CNS depression (partially closed eyes, slow breathing and lying down at all doses)
Mating and Fertility	No drug-related changes in male fertility parameters or sperm analysis.

Source: Summarized from the Applicant's Study Reports
 Abbreviations: CNS, central nervous system

NOAEL and Safety Margin

Given the minimal finding, the NOAEL for male fertility is 450 mg/kg/day. The corresponding exposure level of daridorexant after 6 weeks of repeat treatment in males was 46700 ng.hr/mL, which provided an ~7-fold safety margin relative to the MRHD of 50 mg, based on AUC.

13.1.5.2. Embryofetal Developmental Toxicity Study

13.1.5.2.1. Embryo-Fetal Toxicity Study by the Oral Route (Gavage) in the Rat (Study T-14.017)

Table 71. Study T-14.017 Information

GLP compliance:	Yes
Methods	
Dose and frequency of dosing:	0 (vehicle control), 30 (LD), 100 (MD), and 300 (HD) mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Wistar rats (from (b) (4))
Number/Sex/Group:	Main study: n=22/group TK: n=6/group for LD, MD, and HD; n=3 for control
Study design:	Pregnant rats were orally treated with daridorexant at doses of 0 (vehicle control), 30 (LD), 100 (MD), and 300 (HD) mg/kg/day from GD 6 to 17. Cesarean examination was performed on GD 20. Maternal parameters of evaluation included mortality, clinical signs, body weight, and food consumption. Fetal parameters included litter size, live/dead fetuses, fetal weight, sex, and external, skeletal, and visceral malformations and variations. TK analyses of daridorexant and its major metabolites M1, M3, and M10 were conducted on GDs 6 and 17 (Study T-17.042 and BA-17.048). Dose selection was based on a dose range finding (DRF) study (Study T-14.016), in which pregnant rats were orally treated with daridorexant at 100, 300, and 1000 mg/kg/day from GDs 6 to 17. At 1000 mg/kg/day, daridorexant treatment exceeded the MTD and caused maternal deaths. At 300 mg/kg/day, daridorexant caused slight decreases in food consumption (without changes in weight gain) and clinical signs of decreased activity and piloerection. Therefore, 300 mg/kg/day was selected as the high dose for the definitive study.
Deviation from study protocol affecting interpretation of results:	None that significantly impacted study quality or data interpretation

Source: Summarized from the Applicant's Study Reports

Abbreviations: DRF, dose range finding; GD, gestation day; HD, high dose; LD, low dose; MD, mid dose; MTD, maximum tolerated dose; n, number of subjects with given characteristic; TK, toxicokinetic

Table 72. Observations and Results, Study T-14.017

Major Drug-related Findings	
Maternal	Slight decreases in food consumption (↓7%) without changes in weight gain at 300 mg/kg/day, which is not considered to be adverse; no other maternal toxicities were observed. ²⁰
Embryofetal	No drug-related embryofetal toxicities and no fetal malformation were observed at doses up to 300 mg/kg/day.

Source: Summarized from the Applicant's Study Reports

NOAEL and Safety Margin

Based on the minimal findings, the NOAEL for maternal and embryofetal toxicity is 300 mg/kg/day in this study. The corresponding exposure levels (AUC) of daridorexant and the M1, M3, and M10 metabolites on GD 17 were 51600, 77100, 34500, and 7880 ng*hr/mL, respectively, which provided a safety margin of ~8-fold relative to the proposed MRHD of 50 mg, based on AUC of daridorexant.

It should be noted that compared to nonpregnant female rats at the same doses of 100 and 300 mg/kg/day (Study T-13.163), the exposure levels of daridorexant in pregnant rats were higher on GD 6 (~2 to 3-fold) and slightly higher on GD 17 (~50 to 60%).

²⁰ Hypersalivation was observed in the dams at ≥ 100 mg/kg/day without any other clinical signs. This was most likely due to the taste of the drug formulation rather than a direct toxic effect.

13.1.5.2.2. Embryo-Fetal Toxicity Study by the Oral Route (Gavage) in the Rabbit (Study T-14.015)

Table 73. Study T-14.015 Information

GLP compliance:	Yes
Methods	
Dose and frequency of dosing:	0 (vehicle control), 30 (LD), 60 (MD), and 120 (HD) mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	New Zealand White Rabbit
Number/Sex/Group:	N=22/group
Study design:	Pregnant rabbits were orally treated with daridorexant at doses of 0 (vehicle control), 30 (LD), 60 (MD), and 120 (HD) mg/kg/day from GDs 6 to 19. Cesarean examination was performed on GD 29. Maternal parameters of evaluation included mortality, clinical signs, body weight, and food consumption. Fetal parameters included litter size, live/dead fetuses, fetal weight, sex, and external, skeletal, and visceral malformations and variations. TK analyses of daridorexant and its major metabolites M1, M3, and M10 were conducted in 6 animals/group on GDs 6 and 19 (Studies T-18.073 and BA-18.034) Dose selection was based on the DRF studies. In nonpregnant rabbits (Study T-14.013), doses tested were 30, 100, 200, and 300 mg/kg/day. Daridorexant at ≥ 200 mg/kg/day was not tolerated and caused severe body weight loss ($\downarrow$ up to 276 g) and reduced food consumption ($\downarrow$ up to 50%). In pregnant rabbits (Study T-14.014), doses tested were 30, 60, and 120 mg/kg/day. Daridorexant was tolerated at 120 mg/kg/day and slightly decreased food consumption ($\downarrow 9\%$, without changes in body weight). No embryofetal toxicities were observed at doses up to 120 mg/kg/day. Therefore, 120 mg/kg/day was selected as the high dose for the definitive study.
Deviation from study protocol affecting interpretation of results:	None that significantly affected study quality or data interpretation.

Source: Summarized from the Applicant's Study Reports

Abbreviations: DRF, dose range finding; HD, high dose; LD, low dose; MD, mid dose; N, number of subjects; TK, toxicokinetic

Table 74. Observations and Results, Study T-14.015

Major Drug-related Findings	
Maternal	Decreased weight gain ($\downarrow 40\%$) and food consumption ($\downarrow 15\%$) at 120 mg/kg/day during the first week of treatment; the effects were reversible.
Embryofetal	No drug-related embryofetal toxicities or fetal malformation were observed at doses up to 120 mg/kg/day.

Source: Summarized from the Applicant's Study Reports

NOAEL and Safety Margin

Based on decreased maternal weight gain and food consumption, the NOAEL for maternal toxicity is 60 mg/kg/day. The corresponding exposure levels of daridorexant and the M1, M3,

and M10 metabolites on GD 19 were 24500, 3280, 3730, and 517 ng*hr/mL, respectively, which provided a safety margin of 4-fold relative to the MRHD of 50 mg based on AUC of daridorexant.

Based on the minimal findings, the NOAEL for embryofetal toxicity is 120 mg/kg/day. The corresponding exposure levels of daridorexant and the M1, M3, and M10 metabolites on GD 19 were 62000, 5170, 8000, and 591 ng*hr/mL, respectively, which provided a safety margin of 10-fold relative to the MRHD of 50 mg based on AUC of daridorexant.

13.1.5.3. Juvenile Animal Toxicity Study

13.1.5.3.1. Study Number/ Title: Daridorexant: A 9-Week Juvenile Toxicity Study by Oral (Gavage) in Rats With a 4-Week Recovery Period (Study T-19.049)

Table 75. Study T-19.049 Information

GLP compliance:	Yes
Methods	
Dose and frequency of dosing:	0 (vehicle control), 50 (LD), 150 (MD), and 450 (HD) mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Wistar Han (Rcc Han: WIST)
Number/Sex/Group:	Main study: n=10/sex/group Recovery: n=6/sex/group Reproductive: n=20/sex/group TK: n=9/sex/group

Study design:	Juvenile rats were orally treated with daridorexant at doses of 0 (vehicle control), 50 (LD), 150 (MD), and 450 (HD) mg/kg/day from PND 21 to PND 84. A 4-week recovery subset was included to assess the reversibility of the drug effects. A reproductive subset was included to assess potential drug effects on reproductive performance after recovery. Parameters evaluated included mortality, clinical signs, growth (body weight, weight gain, and food consumption, sexual maturation, and bone density), neurobehavioral assessment (motor activity, acoustic startle, functional observation battery, and learning and memory (Y-water maze)), reproductive capacity (estrus cycle, mating, pregnancy, and sperm evaluation), clinical chemistry, gross pathology, organ weight, and histopathology (including detailed brain histopathology). In addition, TK analyses of daridorexant and its major metabolites M1, M3, and M10 were conducted on Days 1, 22, and 57. Dose selection was based on a 2-week DRF study (Study T-18.097), in which juvenile rats were orally treated with daridorexant at 0, 50, 150, and 450 mg/kg/day from PNDs 21 to 35. Drug-related findings were limited to increased GGT levels and increased liver weight at 450 mg/kg/day without correlative histopathology findings. In previous repeat dose studies in adult rats, daridorexant, at the same doses of 50, 150, and 450 mg/kg/day, caused dose-dependent increases in the incidence of hepatocellular hypertrophy in the liver with correlative increases in GGT levels and liver weight, and follicular cell hypertrophy in the thyroid. Therefore, 450 mg/kg/day was selected as the high dose.

Deviation from study protocol affecting interpretation of results:	None that significantly affected study quality or data interpretation

Source: Summarized from the Applicant's Study Reports

Abbreviations: DRF, dose range finding; GGT, gamma-glutamyl transferase; HD, high dose; LD, low dose; MD, mid dose; n, number of subjects with given characteristic; PND, postnatal day; TK, toxicokinetic

Table 76. Observations and Results, Study T-19.049

Major Drug-related Findings

Sexual maturation	Daridorexant at 450 mg/kg/day slightly delayed sexual maturation in males (2 days late relative to controls) without affecting sperm parameters or male fertility. Females were not affected.
Liver and thyroid gland	Daridorexant at 450 mg/kg/day caused hepatocellular hypertrophy in the liver in both sexes with correlative increases in GGT (↑3x and 8x in HDM and HDF, respectively) and liver weight. Daridorexant at ≥150 mg/kg/day caused follicular cell hypertrophy in the thyroid with correlative increases in thyroid weight. These changes were reversible or partially reversible after recovery.
CNS	No effects on learning and memory or other neurobehavioral parameters at doses up to 450 mg/kg/day

Source: Summarized from the Applicant's Study Reports

Abbreviations: GGT, gamma-glutamyl transferase; HDF, high dose female; HDM, high dose male

NOAEL and Safety Margin

Based on the delay in sexual maturation in males and liver findings in both sexes at the high dose, the NOAEL is 150 mg/kg/day in both sexes. After 9 weeks of repeat treatment, the corresponding exposure (AUC) levels of daridorexant and the M1, M3, and M10 metabolites were 16700/15300 (M/F), 10700/17600 (M/F), 29300/48500 (M/F), and 4300/3490 (M/F) ng*hr/mL, respectively.²¹

13.2. Individual Reviews of Studies Submitted to the New Drug Application

13.2.1. Carcinogenicity Studies

13.2.1.1. Rat Carcinogenicity Study

13.2.1.1.1. Study Title: Daridorexant - 104-Week Carcinogenicity Study by the Oral (Gavage) Route in the Rat

Table 77. Study T-16.060 Information

Study no.:	T-16.060
Study report location:	EDR, SDN-1
Study initiation date:	May 5, 2017
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	Daridorexant; RH03L117A1; 99.35%
Prior Exec CAC Dose Concurrence:	Y
Basis for Dose Selection:	Dose selection was based on a 26-week study, in which rats were orally treated with daridorexant at 0 (0.5% methylcellulose), 50, 150, and 450 mg/kg/day. Drug-related deaths occurred at 450 mg/kg/day. Other drug-related findings included dose-dependent increases in the clinical signs of CNS suppression; 2) dose-dependent increases in hepatocellular hypertrophy in the liver and follicular cell hypertrophy in the thyroid with correlative increases in organ weights and clinical chemistry parameters in both sexes; 3) tubular hyaline casts in the kidney in high dose females with correlative increases in the kidney weight and urine levels of leucocytes and protein. Based on the mortality at 450 mg/kg/day, 150 mg/kg/day was selected as the high dose. 15 and 50 mg/kg/day were selected as the low- and mid-doses based on approximately one third AUC spacing.

Source: Summarized from the Applicant's Study Reports

Abbreviations: AUC, area under the concentration-time curve; CNS, central nervous system

Reviewer Carcinogenicity Conclusion (negative/ positive): Negative

²¹ Safety margins for the juvenile study was not calculated

(b) (4)

ECAC Carcinogenicity Conclusion (negative/ positive): Negative

Key Findings:

- Daridorexant did not increase the incidence of tumors in rats treated for 2 years at oral doses of 15, 50, and 150 mg/kg/day. The high dose of 150 mg/kg/day is approximately 3 times the MRHD of 50 mg, based on AUC.
- Daridorexant at 150 mg/kg/day caused adaptive changes in the liver and the thyroid and/or pituitary gland, including
 - in females: bile duct hyperplasia, karyocytomegaly or multinucleated hepatocytes, centrilobular hepatocellular hypertrophy and sinusoidal angiectasis (vessel dilation) in the liver, and cystic follicles in the thyroid gland.
 - in males: hepatocellular vacuolation in the liver, hyperplasia in the *pars distalis* of the pituitary gland, and follicular hyperplasia, and numerically increased (not statistically significant) adenoma/carcinoma in the thyroid.

These changes were likely due to the enzyme induction effects of daridorexant, which led to increased metabolism of thyroid hormones and overactivation of the hypothalamus-pituitary-thyroid axis.

Table 78. Methods, Study T-16.060

Doses:	0 (water control), 0 (vehicle control), 15 (LD), 50 (MD), and 150 (HD) mg/kg/day
Frequency of dosing:	Once daily
Number/Sex/Group:	Main study: n=50/sex/group TK: n=6/sex/group (except water control)
Dose volume:	10 mL/kg
Formulation/Vehicle:	0.5% methylcellulose (from (b) (4)), Batch Nos: SLBQ0373V and SLBR9863V
Route of administration:	ORAL GAVAGE
Species:	RAT
Strain:	WISTAR HAN from (b) (4)
Age:	Approximately 5 weeks of age at treatment initiation
Comment on Study Design and Conduct:	A water control group was included in addition to the vehicle control group (0.5% methylcellulose). In general, there were no significant differences between the vehicle and water controls in the parameters evaluated. Therefore, the 0.5% methylcellulose vehicle did not affect data interpretation and was used for tumor data comparison. There were multiple minor quality-related issues; however, they did not affect the GLP status or the overall conclusion of the study (See Overall assessment on GLP Compliance and Data Quality)
Dose Adjustments or Early Termination:	No dose adjustment or early termination was initiated during the study.
Dosing Solution Analysis:	The concentrations and homogeneity of the dosing formulation were within the acceptable range, except for one LD sample collected in Week 97 (-19% of nominal value). Considering the single incidence, it is not expected to affect the quality of the study or data interpretation.

Source: Summarized from the Applicant's Study Reports

Abbreviations: GLP, good laboratory practice; LD, low dose; n, number of subjects with given characteristic; TK, toxicokinetic

Observations and Results

Mortality

Compared to the vehicle or water control, there were no statistically significant dose-response relationships in mortality in either sex. At the terminal necropsy, there were 33 (66%), 40 (80%), 33 (66%), 33 (66%), and 33 (66%) males and 29 (58%), 22 (44%), 33 (66%), 31 (62%), and 28 (56%) females in the water control, vehicle control, LD, MD, and HD groups, respectively (Table 79).

Table 79. Mortality in the 2-Year Rat Carcinogenicity Study

Dose (mg/kg/day)	Male					Female				
	0 (water)	0 (vehicle)	15 (LD)	50 (MD)	150 (HD)	0 (water)	0 (vehicle)	15 (LD)	50 (MD)	150 (HD)
number per group	50	50	50	50	50	50	50	50	50	50
Found dead	4	3	5	3	3	0	4	1	1	2
Sac moribund	13	7	12	14	14	21	24	16	18	20
Total mortality	17	10	17	17	17	21	28	17	19	22
Survived to terminal necropsy	33	40	33	33	33	29	22	33	31	28
Survival rate (%)	66%	80%	66%	66%	66%	58%	44%	66%	62%	56%

Source: Summarized from the Applicant's Study Reports
Abbreviations: HD, high dose; LD, low dose; MD, mid dose

Clinical Signs

Clinical observations were performed daily before dosing and at least once after dosing. Additional clinical observations were recorded once daily (QD) during the first week of dosing and between 2 and 3 hours after dosing from Weeks 31 to 80.

Compared to the water or vehicle controls, drug-related clinical signs included hypersalivation immediately after dosing at all doses, which also correlated with abnormal foraging and pedaling at MD and HD. These are likely due to the taste of the drug formulation rather than a direct pharmacological or toxicological effect of the drug.

One HDM (No. 301) was moribund on Day 331 with clinical signs of labored breathing and lying down. Postmortem necropsy identified lesions in the trachea and lung, indicating that the death was due to gavage error rather than a direct drug effect.

Body Weights and Food Consumption

Body weight and food consumption were measured weekly for the first 16 weeks and then at least once every 4 weeks thereafter.

During the treatment period, compared to the water or vehicle controls, HDM had slightly increased body weight (7%) and weight gain (11%) without any changes in food consumption. Considering the small magnitude of the changes, they are not expected to affect the tumor data interpretation. Other groups were not affected.

Ophthalmology

Ophthalmology was conducted in all main study animals at pretreatment baseline and in the first 25 animals of the controls and HD groups during Weeks 52 and 103.

Compared to the water or vehicle control, there were no drug-related ophthalmic changes in HD animals after 52 and 103 weeks of treatment. The incidence of corneal opacities was similar between HD and controls. Given the lack of findings in HD, LD and MD were not evaluated.

Palpable Mass

All animals were examined for grossly visible or palpable masses once every 4 weeks up to Week 26 and then once every 2 weeks between Weeks 27 and 51, and weekly from Week 52.

During the treatment period, compared to water or vehicle controls, there were no drug-related changes in the incidence or distribution of palpable mass.

Most of the palpable masses were located in the thoracic and abdominal regions (ventral/dorsal) and to a lower extent in the urogenital region. However, the incidence was comparable across all groups without any drug-related differences.

Gross Pathology

At the unscheduled necropsy (for premature deaths) or terminal necropsy, main study animals were examined for gross pathology. An adequate list of organ/tissue weights was recorded.

Compared to water or vehicle controls, males had dose-dependent increases in the incidence of gross findings in the kidney, including irregular surface, and enlarged and/or pale appearance ([Table 80](#)). These findings correlated with the histopathology of chronic progressive nephropathy (CPN). Females were not affected.

CPN is a well-known spontaneous lesion mostly in male rats and is often exacerbated with various drug treatment, particularly in long-term studies. In the absence of other correlative findings, the toxicological relevance appears limited.

Table 80. Drug-Related Gross Pathology Findings in the Kidney in the 2-Year Rat Carcinogenicity Study

Dose (mg/kg/day)	Male					Female				
	0 (water)	0 (vehicle)	15 (LD)	50 (MD)	150 (HD)	0 (water)	0 (vehicle)	15 (LD)	50 (MD)	150 (HD)
number per group	50	50	50	50	50	50	50	50	50	50
Irregular Surface	3	4	2	10	14	2	1	2	1	1
Enlarged	4	5	1	9	12	0	0	2	0	0
Pale, Pale/raised focus	5	2	2	8	6	1	1	0	1	2

Source: Summarized from the Applicant's Study Reports
Abbreviations: HD, high dose; LD, low dose; MD, mid dose

Organ Weight

At the terminal necropsy, compared to water or vehicle controls, the liver and thyroid weight was increased dose dependently in MD and HD males and females.

Increased liver weight correlated with the histopathology of bile duct hyperplasia, increased karyocytomegaly/multinucleated hepatocytes, and centrilobular hepatocellular hypertrophy in HDF and increased incidence of hepatocellular vacuolation in HDM.

Increased thyroid weight correlated with the numerical increases (without statistical significance) in the incidence of follicular adenomas and carcinoma in HDM and cystic follicles in HDF.

Table 81. Drug-Related Organ Weight Changes in the 2-Year Rat Carcinogenicity Study

	Males			Females		
Dose (mg/kg/day)	15	50	150	15	50	150
Liver						
% Change in Absolute Weight						
compared to vehicle control	↑4%	↑9%*	↑26%*	↑14%*	↑10%*	↑42%*
compared to water control	↑2%	↑7%	↑23%	↑14%	↑10%	↑41%
% Change in Relative Weight (to BW)						
compared to vehicle control	↑3%	↑8%*	↑15%*	↑13%	↑15%*	↑38%*
compared to water control	=	↑5%	↑11%	↑13%	↑15%	↑37%
Thyroid						
% Change in Absolute Weight						
compared to vehicle control	=	↑8%	↑38%*	↑1%	↑10% ^a	↑23%*
compared to water control	↑4%	↑12%	↑43%	↓3%	↑6% ^a	↑19%
% Change in Relative Weight (to BW)						
compared to vehicle control	↓1%	↑9%	↑27%*	↓1%	↑15% ^a	↑20%*
compared to water control	↑1%	↑11%	↑29%	↓5%	↑11% ^a	↑16%

Source: Summarized from the Applicant's Study Reports

Notes: =, <1% difference; *, p<0.05 compared to vehicle controls; statistical analysis was not conducted between drug-treated groups and water control; however, the same trend was observed; a, one MDF (No. 264) was excluded from the analysis due to an abnormally high value of the absolute (3.22 g) and relative (0.82) weight of the thyroid gland

Abbreviations: BW, body weight

Histopathology

Peer Review Conducted: Yes

Historical Control Provided for Tumor Incidence: The test site did not have enough studies to generate the historical control for RccHan:Wistar rats. The Applicant provided a few published literatures of neoplastic and non-neoplastic changes in Wistar rats.

There was no statistically significant difference in the neoplastic or non-neoplastic histopathology changes between the vehicle and water controls. However, there were numerical differences in the incidence of the follicular adenoma and adenoma plus carcinoma in the thyroid gland between the water and vehicle controls, which led to different statistical outcomes when the treatment groups were compared to the two control groups separately (see Neoplastic Section below).

Neoplastic

Thyroid Gland

Compared to the vehicle control, there were no drug-related statistically significant differences in the incidence of neoplastic tumors by either trend analysis or pairwise comparisons. HDM had numerically increased incidence of follicular adenoma and combined adenoma and carcinoma in the thyroid gland and adenoma in the pituitary gland ([Table 82](#)). However, the difference did not reach statistical significance when analyzed by either trend analysis ($p>0.005$) or pairwise comparison ($p>0.01$).

Compared to the water control, there was a significant positive dose response relationship in the incidences of follicular adenoma ($p=0.0032<0.005$) and combined follicular adenoma and carcinoma ($p=0.0027<0.005$) in the thyroid gland. HDM also had a significant increase in the incidence of the follicular adenoma ($p=0.0039<0.01$) and combined adenoma and carcinoma ($p=0.0033<0.01$) in the thyroid gland in the pairwise comparison relative to the water control ([Table 83](#)).

Pituitary Gland

HDM had numerically increased incidence of adenoma in the pars distalis in the pituitary gland; however, it did not reach statistical significance when compared to either the vehicle or water control ([Table 82](#) and [Table 83](#)).

No difference in the tumor incidence was observed in females when compared to either the water or vehicle controls.

The difference in the statistical outcomes was due to the small numerical difference in the incidence of follicular adenoma/adenoma plus carcinoma in the thyroid between the water and vehicle control groups (2/3 out of 50 in the water control compared to 4/5 out of 50 in the vehicle control). The test site did not have an adequate number of studies to generate the historical control range for RccHan:Wistar rats. However, follicular adenoma and/or carcinoma in the thyroid gland is an age-related spontaneous tumor in Wistar rats, particularly in the male. According to the literature, the incidence of spontaneous follicular adenoma and carcinoma in RccHan:Wistar rats goes up to 12% and 9%, respectively (Weber 2017). The vehicle used in the current study (0.5% w/v methylcellulose) is relatively common in nonclinical studies. The tumor incidence of the vehicle control and water control in the current study was within the historical control range from the literature. Therefore, despite the numerical differences from the water control, the 0.5% methylcellulose vehicle control itself was not carcinogenic and is not expected to affect tumor data interpretation. It is appropriate to compare the treatment groups to the vehicle control for the current study. *Because no statistical significance was achieved by either trend analysis or pairwise comparison relative to the vehicle control, daridorexant treatment did not increase the incidence of follicular adenoma or carcinoma in the thyroid in this study.* The numerical increases in follicular adenoma and carcinoma in the thyroid in HDM were likely secondary to the liver enzyme induction effects of daridorexant treatment rather than a direct carcinogenic effect of the drug (see the non-neoplastic section for more information).

Table 82. Tumor Types With Statistical Analysis for Comparisons Between Vehicle Control and Treated Groups, Male Rats

Organ Name	Tumor Name	0 mg/kg/day	15 mg/kg/day	50 mg/kg/day	150 mg/kg/day
		Vehicle (N=50)	Low (N=50)	Med (N=50)	High (N=50)
		P-value - Trend	P-value - Vehicle vs. Low	P-value - Vehicle vs. Med	P-value - Vehicle vs. High
Pituitary gland	Adenoma	5/50 (46) 0.0164	10/50 (44) 0.1099	6/50 (40) 0.4004	14/50 (44) 0.0141
Thyroid glands	Follicular adenoma	4/50 (46) 0.0080	6/50 (44) 0.3412	6/50 (41) 0.2977	12/50 (43) 0.0178
Thyroid glands	C_follicular adenoma+carcinoma	5/50 (46) 0.0061	8/50 (45) 0.2610	6/50 (41) 0.4178	14/50 (43) 0.0121

Source: Study T16.060; Table excerpted from Dr. Miao Zhuang's statistical review of the rat carcinogenicity study
 Abbreviations: N, number of subjects

Table 83. Tumor Types With Statistical Analysis for Comparisons Between Water Control and Treated Groups, Male Rats

Organ Name	Tumor Name	0 mg/kg/day	15 mg/kg/day	50 mg/kg/day	150 mg/kg/day
		Water (N=50)	Low (N=50)	Med (N=50)	High (N=50)
		P-value - Trend	P-value - Water vs. Low	P-value - Water vs. Med	P-value - Water vs. High
Pituitary gland	Adenoma	7/50 (43) 0.0475	10/50 (44) 0.3135	6/50 (40) 0.6767	14/50 (44) 0.0740
Thyroid glands	Follicular adenoma	2/50 (42) 0.0032	6/50 (44) 0.1482	6/50 (41) 0.1245	12/50 (43) 0.0039
Thyroid glands	C_follicular adenoma+carcinoma	3/50 (42) 0.0027	8/50 (45) 0.1208	6/50 (41) 0.2292	14/50 (43) 0.0033

Source: Study T16.060; Table excerpted from Dr. Miao Zhuang's statistical review of the rat carcinogenicity study
 Abbreviations: N, number of subjects

Non-Neoplastic

Liver

Compared to the vehicle and water control groups, HDF had increased incidence and/or severity of bile duct hyperplasia, karyocytomegaly/multinucleated hepatocytes, centrilobular hepatocellular hypertrophy, and sinusoidal angiectasis (Table 84). HDM had increased incidence of hepatocellular vacuolation (Table 84). These changes correlated with increased liver weight in HDM&F and were likely due to induction of liver enzymes in response to repeat daridorexant treatment. These findings are also consistent with previous repeat dose studies in the rat at the same or comparable doses.

Table 84. Drug-Related Non-Neoplastic Changes in the Liver in the 2-Year Rat Carcinogenicity Study

Group	Males					Females				
	1	2	3	4	5	1	2	3	4	5
Dose (mg/kg/day)	0	15	50	150	0	0	15	50	150	0
Rats per Group	50	50	50	50	50	50	50	50	50	50
Bile duct hyperplasia	4	3	4	0	3	6	13	14	25	14
minimal	2	3	4	0	3	6	6	10	21	9
slight	1	0	0	0	0	0	7	4	3	4
moderate	0	0	0	0	0	0	0	0	0	1
marked	1	0	0	0	0	0	0	0	1	0
Increased karyocytomegaly/ multinucleated hepatocytes	0	0	0	0	0	0	1	4	25	1
minimal	0	0	0	0	0	0	1	4	22	1
slight	0	0	0	0	0	0	0	0	3	0
Hepatocellular hypertrophy, centrilobular	1	0	1	1	0	1	0	2	9	0
minimal	0	0	1	0	0	1	0	2	9	0
slight	1	0	0	1	0	0	0	0	0	0
Angiectasis	3	5	1	6	7	2	1	3	10	0
minimal	3	5	1	5	7	2	1	3	10	0
slight	0	0	0	1	0	0	0	0	0	0
Hepatocellular vacuolation, increased	10	15	10	25	13	7	3	7	5	7
minimal	3	11	5	17	10	5	3	6	4	5
slight	3	3	5	6	2	2	0	1	1	2
moderate	4	0	0	2	1	0	0	0	0	0
marked	0	1	0	0	0	0	0	0	0	0

Source: Study T16.060
 Groups 1, 2, 3, 4, 5: vehicle control, LD, MD, HD, and water control groups, respectively
 Abbreviations: HD, high dose; LD, low dose; MD, mid dose

Kidney

Compared to the vehicle and water control groups, HDF had increased incidence of CPN (Table 85). In addition, mid dose males (MDMs) and HDMs had slightly increased incidence and severity of urothelial hyperplasia in the calyx (Table 85).

CPN is a well-known spontaneous lesion in rats, particularly in the males (as evidenced by the higher incidence in all male groups in the current study), whereas females generally are less affected. Similarly, urothelial hyperplasia is a spontaneous change commonly associated with

CPN. In the current study, the increased incidence in CPN in HDF and urothelial hyperplasia in HDM suggested drug-induced exacerbation of these spontaneous lesions. Nevertheless, because there is no human counterpart of CPN (Greaves 2011), and given the relative mild severity of urothelial hyperplasia (mainly minimal to slight), the clinical relevance of these histopathology changes appears to be limited.

Table 85. Drug-Related Non-Neoplastic Changes in the Kidney in the 2-Year Rat Carcinogenicity Study

Group	Males					Females				
	1	2	3	4	5	1	2	3	4	5
Dose (mg/kg/day)	0	15	50	150	0	0	15	50	150	0
Rats per Group	50	50	50	50	50	50	50	50	50	50
Chronic Progressive Nephropathy	42	35	33	48	42	15	14	11	35	6
minimal	25	18	13	17	17	13	11	9	25	4
slight	8	10	5	8	13	1	1	1	9	0
moderate	4	4	6	12	6	0	0	0	1	0
marked	3	0	2	6	1	1	2	0	0	1
severe	2	3	7	5	5	0	0	1	0	1
Urothelial Hyperplasia, Calyx	2	3	9	12	3	6	7	11	12	14
Minimal	2	1	4	7	2	6	6	10	11	11
Slight	0	1	3	5	1	0	1	1	0	2
Moderate	0	1	2	0	0	0	0	0	1	1

Source: Study T16.060
 Groups 1, 2, 3, 4, 5: vehicle control, LD, MD, HD, and water control groups, respectively
 Abbreviations: HD, high dose; LD, low dose; MD, mid dose

Pituitary Gland

Compared to the vehicle and water control groups, HDM had increased incidence of hyperplasia in the pars distalis of the pituitary gland (Table 86), which correlated with the numerically (but not statistically significant) increased incidence of pituitary adenomas in HDM (See the neoplastic section).

Table 86. Drug-Related Non-Neoplastic Changes in the Pituitary Gland in the 2-Year Rat Carcinogenicity Study

Group	Males					Females				
	1	2	3	4	5	1	2	3	4	5
Dose (mg/kg/day)	0	15	50	150	0	0	15	50	150	0
Rats per Group	50	50	50	50	50	50	50	50	50	50
Hyperplasia, Pars Distalis	4	6	7	9	3	6	9	12	6	4
Minimal	2	3	3	5	1	1	4	3	2	4
Slight	0	1	1	3	2	2	5	5	4	0
Moderate	2	2	3	1	0	3	0	4	0	0

Source: Study T16.060
 Groups 1, 2, 3, 4, 5: vehicle control, LD, MD, HD, and water control groups, respectively
 Abbreviations: HD, high dose; LD, low dose; MD, mid dose

Thyroid Gland

Compared to the vehicle and water control groups, HDF had increased incidence of cystic follicles in the thyroid gland. MDM and HDM had slightly increased incidence and/or severity of follicular hyperplasia in the thyroid (Table 87). Other groups were not affected.

Table 87. Drug-Related Non-Neoplastic Changes in the Thyroid Gland in the 2-Year Rat Carcinogenicity Study

Group	Males					Females				
	1	2	3	4	5	1	2	3	4	5
Dose (mg/kg/day)	0	15	50	150	0	0	15	50	150	0
Rats per Group	50	50	50	50	50	50	50	50	50	50
Hyperplasia, Follicular	0	0	2	2	1	0	0	0	0	0
Minimal	0	0	2	0	1	0	0	0	0	0
Moderate	0	0	0	2	0	0	0	0	0	0
Cystic Follicles, Present	13	6	7	6	4	3	3	5	10	3

Source: Study T16.060

Groups 1, 2, 3, 4, 5: vehicle control, LD, MD, HD, and water control groups, respectively

Abbreviations: HD, high dose; LD, low dose; MD, mid dose

Ovaries

Compared to the vehicle and water control groups, HDF had increased incidence of ovarian cysts (14/50 compared to 4/50 in vehicle and water controls). Other groups were not affected.

In the current study, proliferative histopathology changes were observed in multiple endocrine organs/tissues, including the pituitary and thyroid gland in both sexes and the ovaries in females. This is likely due to the enzyme induction effects of daridorexant. Daridorexant has been shown to activate PXR *in vitro* and upregulate mRNA expression of multiple CYP enzymes both *in vitro* and *in vivo*. Increased CYP enzyme levels led to increased metabolism of endocrine hormones and subsequent activation of the hypothalamus-pituitary-thyroid or -ovarian axis, which led to proliferative changes in the corresponding tissues. Rats are known to be more sensitive to such mechanisms. This is further supported by findings from the 6-month repeat dose study in the rat, in which daridorexant at ≥ 150 mg/kg/day decreased T4 hormone levels and/or increased thyroid stimulating hormone levels with correlative histopathology of follicular hypertrophy in the thyroid gland.

The numerical increase in follicular adenoma and carcinoma in the thyroid and adenoma in the pituitary gland in HDM is likely a continuum of proliferative changes due to prolonged overactivation of the hypothalamic-pituitary-thyroid axis. Given the difference in the metabolism of thyroid hormones between the rat and human, the clinical relevance of these findings appears limited.

Toxicokinetics

On Days 1 and 176, blood samples were collected from TK animals at 1, 2, 3, 5, 8, and 24 hours postdose. TK profiles of daridorexant and its metabolites M1, M3, and M10 were determined.

Daridorexant

On both sampling days, after oral administration, daridorexant was quickly absorbed with T_{max} values between 1 and 3 hours. The exposure levels of daridorexant increased greater than dose proportionally. Females generally had higher daridorexant exposures than males, with a female-to-male ratio of 1.6 to 2.1 ([Table 88](#)).

Table 88. Summary of TK Parameters of Daridorexant in the 2-Year Rat Carcinogenicity Study

Dose (mg/kg/day)	Day	Sex	T _{max} (h)	C _{max} (ng/mL)	AUC _{last} (h*ng/mL)
15	1	F	1	294	693
15	1	M	1	150	366
15	176	F	1	748	1450
15	176	M	1	338	743
50	1	F	1	2150	5280
50	1	M	2	1390	3260
50	176	F	1	3260	7820
50	176	M	1	1550	4200
150	1	F	2	5780	31300
150	1	M	3	3770	19100
150	176	F	1	8460	35000
150	176	M	2	3910	16800

Source: Study T16.060

Abbreviations: AUC_{last}, area under the curve to last measurable collection; C_{max}, maximum plasma concentration; t_{max}, time to maximum concentration

M1 Metabolite (ACT-776537)

After oral administration of daridorexant, the T_{max} of M1 ranged between 2 and 8 hours postdose. The M1 exposure levels increased close to or slightly greater than dose proportionally. There were no significant sex differences in M1 exposure levels. The exposure levels of M1 were generally higher than that of the parent drug, with a metabolite-to-parent ratio of 1.2 to 2.5 in females and 1.7 to 4.6 in males. Repeat administration of daridorexant led to increased M1 exposure levels in LD but not in MD or HD ([Table 89](#)).

M3 Metabolite (ACT-776063)

After oral administration of daridorexant, the T_{max} of the M3 metabolite ranged between 1 and 5 hours postdose. The M3 exposure levels increased greater than dose proportionally. Females had higher M3 exposure levels than males, with a female-to-male ratio of 1.6 to 2.4. The exposure levels of M3 were similar to or slightly lower than that of the parent drug, with a metabolite-to-parent ratio of 0.6 to 1.2. Repeat administration of daridorexant led to slightly increased M3 exposure levels in LD and MD but not in HD ([Table 90](#)).

M10 Metabolite (ACT-1016-3307)

After oral administration of daridorexant, the T_{max} of the M10 metabolite ranged between 1 and 8 hours postdose. The M10 exposure levels increased greater than dose proportionally. There were no significant sex differences in M10 exposure levels. The M10 exposure levels were lower than that of the parent drug, with a metabolite-to-parent ratio of 0.08 to 0.4. Repeat administration of daridorexant led to increased M10 exposure levels ([Table 91](#)).

Table 89. Summary of TK Parameters of the M1 Metabolite (ACT-776537) in the 2-Year Rat Carcinogenicity Study

Dose (mg/kg/day)	Day	Sex	T _{max} (h)	C _{max} (ng/mL)	AUC _{last} (h*ng/mL)
15	1	F	2	322	1710
15	1	M	2	356	1420
15	176	F	3	302	3040
15	176	M	2	434	3400
50	1	F	5	1080	9620
50	1	M	2	1330	8370
50	176	F	8	930	12200
50	176	M	3	997	10600
150	1	F	8	6020	40400
150	1	M	8	5100	40500
150	176	F	8	4180	43200
150	176	M	3	2260	28400

Source: Study T16.060

Abbreviations: AUC_{last}, area under the curve to last measurable collection; C_{max}, maximum plasma concentration; t_{max}, time to maximum concentration

Table 90. Summary of TK Parameters of the M3 Metabolite (ACT-776063) in the 2-Year Rat Carcinogenicity Study

Dose (mg/kg/day)	Day	Sex	T _{max} (h)	C _{max} (ng/mL)	AUC _{last} (h*ng/mL)
15	1	F	1	236	667
15	1	M	1	115	300
15	176	F	1	595	1670
15	176	M	1	326	743
50	1	F	1	1110	3810
50	1	M	2	939	2310
50	176	F	1	1700	6740
50	176	M	1	1010	3220
150	1	F	5	2880	19100
150	1	M	3	1950	12000
150	176	F	1	5100	35600
150	176	M	1	2690	14600

Source: Study T16.060

Abbreviations: AUC_{last}, area under the curve to last measurable collection; C_{max}, maximum plasma concentration; t_{max}, time to maximum concentration

Table 91. Summary of TK Parameters of the M10 Metabolite (ACT-1016-3307) in the 2-Year Rat Carcinogenicity Study

Dose (mg/kg/day)	Day	Sex	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (h*ng/mL)
15	1	F	2	23.9	77.1
15	1	M	2	40.6	82.8
15	176	F	1	64.4	304
15	176	M	1	115	328
50	1	F	3	80.3	410
50	1	M	2	160	467
50	176	F	3	179	1060
50	176	M	1	303	1200
150	1	F	8	536	1810
150	1	M	8	544	2650
150	176	F	2	546	3880
150	176	M	1	702	3570

Source: Study T16.060

Abbreviations: AUC_{last}, area under the curve to last measurable collection; C_{max}, maximum plasma concentration; t_{max}, time to maximum concentration

13.2.1.2. Mouse Carcinogenicity Study

13.2.1.2.1. Study Title: Daridorexant: A 26-Week Oral Oncogenicity Study in CByB6F1-Tg(HRas)2Jic Mice

Table 92. Study T-18.041 Information

Study no.:	T-18.041
Study report location:	EDR, SDN-1, NDA 214985
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	Daridorexant; RH03L117A1; 99.35%
Prior Exec CAC Dose Concurrence:	Y
Basis for Dose Selection:	Dose selection was based on the 14-day and 28-day dose range finding studies in the wild-type litter mate CByB6F1 mice. In the 28-day study, doses tested were 0 (vehicle control), 100 (LD), 300 (MD), and 1500 (HD) mg/kg/day. There was no mortality or any drug-related changes in body weight or weight gain. Minimal to mild liver focal- and single cell-necrosis were observed in both sexes at 1500 mg/kg/day, suggesting that the MTD was exceeded at this dose. Adaptive changes in the liver were observed at ≥ 300 mg/kg/day, including liver enlargement, increased liver weight, and hepatocellular hypertrophy. Similar adaptive liver changes were observed in the 14-day study in both sexes dosed at 1000 and 2000 (1000, BID) mg/kg/day. In both studies, repeat administration of daridorexant led to significantly decreased drug exposure in both sexes. Based on these findings, 1000 mg/kg/day was selected as the high dose based on MTD. The mid and low doses were selected to provide approximately one third AUC spacing.

Source: Summarized from the Applicant's Study Reports

Abbreviations: AUC, area under the concentration-time curve; HD, high dose; LD, low dose; MD, mid dose; MTD, maximum tolerated dose

Reviewer Carcinogenicity Conclusion (negative/ positive): Negative

ECAC Carcinogenicity Conclusion (negative/ positive): Negative

Key Findings:

- Daridorexant did not increase the incidence of tumors in Tg.rasH2 mice treated for 26 weeks at oral doses of 100, 300, and 1000 mg/kg/day in males and 100, 200, and 1000 mg/kg/day in females.
- Daridorexant dose-dependently increased the incidence and severity of hepatocellular hypertrophy in the liver in males at all doses and in females at 1000 mg/kg/day.

Table 93. Methods, Study T-18.041

Doses:	0 (vehicle control), 100 (LD), 300/200 (M/F, MD), and 1000 (HD) mg/kg/day
Frequency of dosing:	Once daily
Number/Sex/Group:	Main study: n=25/sex/group Positive control: n=10/sex TK: n=38/sex/group for daridorexant groups; n=8/sex for vehicle control in wild type mice
Dose volume:	10 mL/kg
Formulation/Vehicle:	0.5% methylcellulose (from (b) (4) , Batch No. SLCB1319)
Route of administration:	ORAL GAVAGE
Species:	MOUSE
Strain:	CB6F1-TgN (RasH2)
Age:	~6.5 weeks at treatment initiation
Comment on Study Design and Conduct:	A positive control (n=10/sex) was included, in which animals were treated with a single intraperitoneal administration of NMU at 75 mg/kg. TK was conducted in a satellite group of wild type mice (n=8/sex for control and n=38/sex/group for treatment groups).
Dosing Comments (Dose Adjustments or Early Termination):	No dose adjustment or early termination in the study
Dosing Solution Analysis:	Dosing formulation analysis was conducted in samples collected at Weeks 1, 8, 15, 22, and 26. The concentration and homogeneity were within the acceptable range. The stability of the dosing formulation was previously established.

Source: Summarized from the Applicant's Study Reports

Abbreviations: HD, high dose; LD, low dose; MD, mid dose; n, number of subjects with given characteristic; NMU, N-nitroso-N-methylurea; TK, toxicokinetic

Observations and Results

Mortality

Compared to controls, there was no drug-related mortality. At the scheduled necropsy, there were 23 (92%), 25 (100%), 23 (92%), and 24 (96%) males and 23 (92%), 25 (100%), 25 (100%), and 22 (88%) females in the control, LD, MD, and HD groups, respectively. Nine out of 10 (90%) males and 7/10 (70%) females in the positive control group survived until terminal necropsy.

The premature deaths were either due to spontaneous tumors or undetermined (no macroscopic or microscopic findings) ([Table 94](#)).

Table 94. Unscheduled Deaths in the 6-Month Carcinogenicity Study in Tg.rasH₂ Mice

Animal No./Sex	Dose Level (mg/kg)	Fate/Animal Disposition	Fate Day	Cause of Death/Euthanasia
1015/M	0	EE	154	Undetermined
1018/M	0	FD	142	Spleen hemangiosarcoma
2008/M	75 NMU	EE	158	Stomach, squamous cell carcinoma
5009/M	300	FD	145	Undetermined
5020/M	300	FD	128	Undetermined
6006/M	1000	EE	140	Undetermined
1515/F	0	FD	112	Undetermined
1518/F	0	EE	127	Uterus, carcinoma
2505/F	75 NMU	EE	106	Skin, carcinoma
2507/F	75 NMU	EE	152	Multicentric lymphoma
2509/F	75 NMU	EE	133	Undetermined
6510/F	1000	EE	111	Bone hemangiosarcoma
6522/F	1000	EE	156	Multicentric lymphoma
6525/F	1000	EE	183	Skin hemangiosarcoma

M-Male; F-Female; EE-Euthanized in extremis; FD-Found Dead
Source: Study B-18.041

Clinical Signs

Clinical observations, including observations for palpable or abnormal masses, were conducted weekly.

Compared to vehicle controls, there were no drug-related abnormal clinical signs or palpable masses. One LDM (No. 3520) had a convulsion on Day 181. No other abnormal findings (clinical signs or microscopic findings) were observed in this animal. Considering the single incidence and absence of similar findings at higher doses, this convulsion is considered incidental.

As expected, animals in the positive control group had nodules and palpable masses, which correlated with microscopic findings of tumors.

Body Weights and Food Consumption

Body weight and food consumption were measured weekly during the first 14 weeks and once every two weeks thereafter.

Compared to vehicle controls, MDM and HDM had slightly decreased body weight and/or weight gain (~6% to 9%) starting from Day 80; no correlative changes in food consumption were observed. Given the small magnitude and lack of correlative changes, the decreases in body weight are not expected to affect tumor data interpretation. Females were not affected.

Gross Pathology

At the terminal necropsy, all animals were examined for gross pathology. An adequate list of organ/tissue weights was recorded.

Compared to vehicle controls, there were no drug-related gross pathology findings.

Organ Weight

Compared to vehicle controls, MDM, HDM, and HDF had increased absolute and relative liver weight, which correlated with histopathology of hepatocellular hypertrophy in the liver ([Table 95](#)).

Table 95. Drug-Related Changes in Liver Weight in the 6-Month Carcinogenicity Study in Tg.rasH₂ Mice

Group	Males				Females			
	1	3	5	6	1	3	4	6
Dose (mg/kg)	0	100	300	1000	0	100	200	1000
No. animals per group	23	25	23	24	23	25	25	22
Liver (No. weighed)	(23)	(25)	(23)	(24)	(23)	(25)	(25)	(22)
Absolute value (g)	1.6843	+5.8	+15.6 ^a	+39.1 ^{b, d}	1.2451	+4.6 ^d	+7.6 ^d	+48.5 ^{b, c}
Relative to body weight	5.31724	+8.3 ^b	+21.2 ^{b, d}	+55.0 ^{b, d}	5.50194	+3.9	+5.8	+46.9 ^{b, c}
Relative to brain weight	3.57686	+6.6	+17.3 ^b	+42.0 ^{b, d}	2.56300	+4.8 ^d	+7.6 ^d	+52.7 ^{b, d}

Source: Study T-18.041

All values presented as percent difference from the vehicle group; Group 1: vehicle control; Group 3, LDM and LDF; Group 4, MDF; Group 5, MDM; Group 6, HDM and HDF; a, p<0.05 relative to the vehicle control; b, p<0.01 relative to the vehicle control; c, p<0.05 relative to the positive control; d, p<0.01 relative to the positive control

Histopathology

Peer Review Conducted: Yes

Historical Control Provided for Tumor Incidence: Yes

Neoplastic

Compared to the vehicle controls, there were no drug-related neoplastic changes. The tumor incidences were comparable across all daridorexant treatment groups and vehicle controls.

The positive control group, as expected, had significant increases in the incidence of tumors in the lung, skin, and stomach in males and in the skin and stomach in females ([Table 96](#)).

Table 96. Tumor Findings in the Positive Control Group in the 6-Month Carcinogenicity Study in Tg.rasH₂ mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	Positive (N=10) P-value - Vehicle vs. Positive
		Male	
Lungs	C_ALVEOLAR- BRONCHIOLAR ADENOMA+CARCINOMA	1/25 (24)	3/10 (8) 0.0393
Skin	PAPILLOMA, BENIGN	1/25 (24)	4/10 (9) 0.0133
Stomach	PAPILLOMA, BENIGN	0/25 (24)	8/10 (10) <0.001
Female			
Skin	PAPILLOMA, BENIGN	0/25 (24)	5/10 (10) <0.001
Stomach	PAPILLOMA, BENIGN	0/25 (24)	7/10 (10) <0.001

Source: Study T-18.041; Table excerpted from Dr. Miao Zhuang's statistical review of the Tg.rasH₂ mouse carcinogenicity study
 Abbreviations: N, number of subjects

Non-Neoplastic

Compared to the vehicle controls, the incidence and severity of hepatocellular hypertrophy were increased dose dependently in males at all doses and in HDF (Table 97), which correlated with increased liver weight. These changes are consistent with the enzyme induction effects of daridorexant treatment in the animals and are considered adaptive.

Table 97. Drug-Related Hepatocellular Hypertrophy in the 6-Month Carcinogenicity Study in Tg.rasH₂ Mice

Group	Males				Females			
	1	3	5	6	1	3	4	6
Dose (mg/kg)	0	100	300	1000	0	100	200	1000
No. animals examined	25	25	25	25	25	25	25	25
Liver (No. Examined)	(25)	(25)	(25)	(25)	(25)	(25)	(25)	(25)
Hypertrophy, hepatocellular, centrilobular	0	15	21	24	0	0	0	11
Minimal	0	14	7	0	0	0	0	5
Mild	0	1	13	7	0	0	0	6
Moderate	0	0	1	16	0	0	0	0
Marked	0	0	0	1	0	0	0	0

Source: Study T-18.041

Toxicokinetics

Blood samples were collected from wildtype TK animals at 1, 2, 3, 4, 8, and 24 hours postdose on Days 1 and 182 (3 animals/sex/group/time point).²² The TK profiles of daridorexant and its M1, M3, and M10 metabolites were determined.

After oral administration, daridorexant was quickly absorbed and converted to the M1, M3, and M10 metabolites with T_{max} values of 1 to 4 hours for both daridorexant and the metabolites. The exposure (AUC) levels of daridorexant and the M1, M3, and M10 metabolites increased greater than dose proportionally. Repeat administration led to decreased exposure levels of daridorexant and the metabolites, with Day 182-to-Day 1 ratio of 0.1 to 0.5 for daridorexant, 0.03 to 0.2 for

²² For control TK, blood samples were only collected at 1 hour post-dose.

M1, 0.05 to 0.7 for M3, and 0.04 to 0.3 for M10, which was likely due to enzyme induction and increased metabolism/elimination of the drug. No significant sex differences in the exposure levels were observed on Day 1; however, on Day 182, females had lower exposure levels of daridorexant and the metabolites relative to males, with the female-to-male ratio of 0.4 to 0.6 for daridorexant, 0.2 to 0.3 for M1 and M3, and 0.1 to 0.2 for M10 ([Table 98](#), [Table 99](#), [Table 100](#), and [Table 101](#))

Table 98. TK Parameters of Daridorexant in the 6-Month Carcinogenicity Study in Tg.rasH₂ Mice

Dosing (mg/kg)	Day	Sex	T _{max} (h)	C _{max} (ng/mL)	C _{max} /D (ng/mL)/(mg/kg)	AUC _{last} (ng [*] h/mL)	AUC _{last} /D (ng [*] h/mL)/(mg/kg)	T _{last} (h)
100	1	F	1	516	5.16	1470	14.7	8
100	1	M	1	517	5.17	765	7.65	4
100	182	F	1	152	1.52	245	2.45	4
100	182	M	1	184	1.84	403	4.03	4
200	1	F	1	1600	7.98	3270	16.3	4
200	182	F	1	244	1.22	668	3.34	8
300	1	M	1	3890	13.0	5840	19.5	8
300	182	M	1	1010	3.38	2170	7.23	8
1000	1	F	1	13900	13.9	38500	38.5	8
1000	1	M	2	9610	9.61	31800	31.8	24
1000	182	F	1	559	0.559	1970	1.97	8
1000	182	M	2	832	0.832	4730	4.73	8

Source: Study T-18.041

Abbreviations: AUC_{last}, area under the curve to last measurable collection; C_{max}, maximum plasma concentration; TK, toxicokinetic; T_{last}, time of last collection; T_{max}, time to maximum concentration

Table 99. TK Parameters of the M1 Metabolite in the 6-Month Carcinogenicity Study in Tg.rasH₂ Mice

Dosing (mg/kg)	Day	Sex	T _{max} (h)	C _{max} (ng/mL)	C _{max} /D (ng/mL)/(mg/kg)	AUC _{last} (ng [*] h/mL)	AUC _{last} /D (ng [*] h/mL)/(mg/kg)	T _{last} (h)
100	1	F	1	240	2.40	663	6.63	8
100	1	M	1	263	2.63	584	5.84	8
100	182	F	1	19.8	0.198	28.1	0.281	2
100	182	M	1	67.5	0.675	124	1.24	4
200	1	F	3	646	3.23	2180	10.9	8
200	182	F	1	39.0	0.195	141	0.707	8
300	1	M	1	755	2.52	2790	9.29	8
300	182	M	1	204	0.681	474	1.58	4
1000	1	F	4	2790	2.79	17300	17.3	24
1000	1	M	4	3100	3.10	17700	17.7	24
1000	182	F	1	190	0.19	547	0.547	8
1000	182	M	1	419	0.419	2000	2.00	8

Source: Study T-18.041

Abbreviations: AUC_{last}, area under the curve to last measurable collection; C_{max}, maximum plasma concentration; TK, toxicokinetic; T_{last}, time of last collection; T_{max}, time to maximum concentration

Table 100. TK Parameters of the M3 Metabolite in the 6-Month Carcinogenicity Study in Tg.rasH₂ Mice

Dosing (mg/kg)	Day	Sex	Tmax (h)	Cmax (ng/mL)	Cmax/D (ng/mL)/(mg/kg)	AUClast (ng*h/mL)	AUClast/D (ng*h/mL)/(mg/kg)	Tlast (h)
100	1	F	1	206	2.06	323	3.23	4
100	1	M	1	219	2.19	311	3.11	4
100	182	F	1	29.5	0.295	69.4	0.694	4
100	182	M	1	80.3	0.803	227	2.27	8
200	1	F	1	636	3.18	1530	7.64	8
200	182	F	1	43.3	0.217	159	0.796	8
300	1	M	1	1650	5.51	2440	8.12	8
300	182	M	2	142	0.473	592	1.97	8
1000	1	F	1	4000	4.00	13300	13.3	24
1000	1	M	2	3680	3.68	13800	13.8	24
1000	182	F	1	185	0.185	644	0.644	8
1000	182	M	4	532	0.532	2630	2.63	8

Source: Study T-18.041

Abbreviations: AUC_{last}, area under the curve to last measurable collection; C_{max}, maximum plasma concentration; TK, toxicokinetic; T_{last}, time of last collection; T_{max}, time to maximum concentration

Table 101. TK Parameters of the M10 Metabolite in the 6-Month Carcinogenicity Study in Tg.rasH₂ Mice

Dosing (mg/kg)	Day	Sex	Tmax (h)	Cmax (ng/mL)	Cmax/D (ng/mL)/(mg/kg)	AUClast (ng*h/mL)	AUClast/D (ng*h/mL)/(mg/kg)	Tlast (h)
100	1	F	1	134	1.34	186	1.86	4
100	1	M	1	109	1.09	149	1.49	4
100	182	F	1	13.7	0.137	6.86	0.0686	1
100	182	M	1	34.5	0.345	50.2	0.502	3
200	1	F	1	283	1.42	668	3.34	4
200	182	F	1	32.0	0.16	101	0.505	8
300	1	M	1	528	1.76	870	2.90	4
300	182	M	1	86.8	0.289	209	0.697	4
1000	1	F	1	1170	1.17	4550	4.55	8
1000	1	M	2	1100	1.10	4860	4.86	24
1000	182	F	1	106	0.106	268	0.268	8
1000	182	M	1	219	0.219	1090	1.09	8

Source: Study T-18.041

Abbreviations: AUC_{last}, area under the curve to last measurable collection; C_{max}, maximum plasma concentration; TK, toxicokinetic; T_{last}, time of last collection; T_{max}, time to maximum concentration

13.2.2. Reproductive and Developmental Toxicology

13.2.2.1. Prenatal and Postnatal Development

13.2.2.1.1. Study Title: Pre- and Postnatal Development Study of Daridorexant by the Oral (Gavage) Route in the Rat (Segment III)

Table 102. Study T-19.005 Information

Study no.:	T-19.005
Study report location:	EDR, SDN-1
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	Daridorexant (Daridorexant); RH03L117A1; 99.6%
Enhanced PPND Study:	N

Source: Summarized from the Applicant's Study Reports

Key Findings:

- Oral administration of daridorexant at doses up to 300 mg/kg/day did not cause any maternal or developmental toxicity in the rat.
- The NOAEL for maternal and developmental toxicity is 300 mg/kg/day. The corresponding maternal exposure levels of daridorexant on lactation Day 20 were C_{max} of 11200 ng/mL and AUC of 55600 ng*hr/mL, which provided a safety margin of ~9-fold relative to the MRHD of 50 mg, based on AUC.
- The offspring were exposed to daridorexant likely via lactational exposure.

At 300 mg/kg/day, the body weight and weight gain in the offspring were slightly lower than the controls. However, the magnitude was small (~5%) and it did not affect other parameters, such as sexual maturation, learning and memory, or reproductive performance. Therefore, in the absence of correlative findings, the slight decreases are not considered to be adverse.

Table 103. Methods, Study T-19.005

Doses:	0 (vehicle control), 50 (LD), 100 (MD), and 300 (HD) mg/kg/day
Frequency of dosing:	Once daily
Number/Sex/Group:	n=20/group
Dose volume:	10 mL/kg
Formulation/Vehicle:	0.5% (w/v) methylcellulose in water
Route of administration:	ORAL GAVAGE
Species:	Rat
Strain:	Wistar (Crl: WI Han)
Comment on Study Design and Conduct:	Pregnant rats were orally treated with daridorexant at 0, 50, 100, and 300 mg/kg/day from GD 6 through weaning (Lactation Day/LacD 20). F0 dams were evaluated for mortality, clinical signs, body weight, and food consumption, parturition, lactation, and gross pathology at the scheduled necropsy. F1 offspring were evaluated for viability, clinical signs, body weight and food consumption, sexual maturation, neurobehavioral assessment (sensory and motor activity, learning and memory), reproductive capacity, and gross pathology. Dose selection was based on a DRF study in pregnant rats, in which the dose of 1000 mg/kg/day exceeded MTD and caused maternal deaths whereas the next lower dose of 300 mg/kg/day only caused mild decreases in food consumption. In addition, the 26-week general toxicology study in nonpregnant rats, daridorexant at 450 mg/kg/day caused cataplexy-like clinical signs in one female. Based on the maternal death and cataplexy-like clinical signs, 300 mg/kg/day was selected as the high dose for the current study, which is acceptable, although 450 mg/kg/day could have been selected and tested as the high dose. Several operational deviations were identified at the test facility; however, they did not affect the entire course of the study conduct, and unlikely would affect the data interpretation (see Overall Assessment on GLP Compliance and Data Quality for details).
Dosing Solution Analysis:	The concentration and stability of the dosing formulation were within the acceptable range.

Source: Summarized from the Applicant's Study Reports

Abbreviations: DRF, dose range finding; GD, gestation day; HD, high dose; LD, low dose; MD, mid dose; MTD, maximum tolerated dose; n, number of subjects with given characteristic

Observations and Results

F0 Dams

Mortality

All animals were observed twice daily for mortality. Cage-side clinical signs were observed daily. Detailed clinical observation was conducted on each weighing day for the dams.

There was no drug-related mortality.

One mid dose female (MDF) (No. 42) was euthanized on Day 24 due to moribund condition (cold to touch, pale, piloerection, red vaginal discharge, and decreased activity). Postmortem necropsy showed total litter resorption. One HDF (No. 69) had total litter death on Lactation Day 2 and therefore was euthanized (not due to adverse conditions of the dam). Although the two premature deaths only occurred in the drug-treated animals (one MD and one HD, each),

other animals at the same doses did not have any clinical signs or similar findings, given the single incidence, they are not considered to be drug related.

Two control females (No. 4 and 14) and one MDF (No. 55) were not pregnant and therefore were euthanized on Day 26 or 27.

Clinical Signs

During the treatment period, compared to controls, there were no drug-related adverse clinical signs.

Hypersalivation, associated with occasional foraging and/or pedaling, was observed immediately after dosing at all dose levels during both the gestational and lactational periods. These are most likely due to the taste of the drug formulation, rather than a pharmacological or toxicological effect.

Occasional piloerection was observed in 8/20 HDF. However, since there were no other correlative clinical signs observed in this group, they are not considered adverse.

Body Weight and Food Consumption

Maternal body weights were recorded on Days 0, 6, 9, 12, 15, 18, and 20 of the gestation period and on Days 1, 4, 7, 10, 17, and 21 of the lactation period.

During gestation, compared to controls, body weight gain was slightly increased between GD 9 and 12 in MD and HD (27% and 28%, respectively). However, food consumption was slightly decreased in HD between GDs 6 and 12 (up to 17%). These changes were transient and were not present during other periods of treatment. The cumulative weight gain during the gestation period was only slightly higher in MD and HD (9% and 5%, respectively) without affecting the overall health of the dams. Therefore, these changes are not considered to be adverse.

Parturition and Litter Observations

There were 18 (90%), 20 (100%), 18 (90%), and 20 (100%) pregnant females in the control, LD, MD, and HD groups, respectively. The mean gestation duration was comparable across all groups (~22 days).

Compared to controls, there were no drug-related changes in the parturition or litter parameters. The postimplantation loss, litter size, live birth, and viability indices were comparable across all groups.

One out of 18 MD (No. 43) and 3/20 HD (No. 65, 69, and 76) had one stillborn pup in each litter (a total of one and three stillborn pups in MD and HD, respectively). The live birth indices (99.5% and 98.5% in MD and HD, respectively) were within the historical control range (96% to 100%) and the stillborn only affected a single pup in each litter; therefore, they are considered incidental.

Of the three HD females that had stillborn pups, one HD female (No. 69) lost its entire litter on postnatal day (PND) 3 (see mortality). This female had 1 stillborn pup and 8 live pups at parturition. The pup weight on Lactation Day 1 from this dam appeared to be lower than average (6.6 g males and 5.3 g female, compared to 7 g male and 6.7 g females to group mean values), which could have potentially contributed to the total litter loss on PND 3. Nevertheless, because

the overall values in the HD group were comparable to the controls and were within the historical control range, this single incidence is not considered to be drug related.

Pup Observations (Clinical Signs, Weight, and Sex Ratio)

Compared to controls, there were no abnormal clinical signs in the pups associated with maternal dosing. Sex ratio of the pups (at birth or at weaning) was not affected by daridorexant.

HD pup weight was slightly lower at birth (4.6% for males and 5.3% for females, respectively) and continued to be lower at weaning (7.5% for males and 6.5% for females, respectively). These decreases are considered drug related; however, the values were still within the historical range at the test facility. Given the small magnitude and lack of correlative adverse observations (such as clinical signs, growth, sexual maturation, etc.), they are not considered to be adverse.

Necropsy

At the scheduled necropsy, compared to controls, there were no drug-related abnormal macroscopic findings in the dam or in the pups that were culled on Lactation Day 4.

F1 Generation

Mortality

Offspring were examined daily for mortality.

There was no mortality in the F1 offspring.

Clinical Signs

Cage-side clinical signs were observed daily; detailed clinical examination was conducted once weekly.

Compared to controls, there were no abnormal clinical signs in the F1 offspring.

Body Weight and Food Consumption

Body weight and food consumption for the F1 offspring were measured weekly.

Compared to controls, HD F1 offspring had slightly lower body weight and weight gain in males (~4 to 5% up to Day 77) and females (2 to 7% up to Day 56), which correlated with slightly lower food consumption (~5%). However, the sexual maturation and general health status were not affected. Given the small magnitude and lack of correlative findings, the slight decreases in body weight and food consumption are not considered to be adverse.

Sexual Maturation

Sexual maturation was determined by the day of vaginal opening or balanopreputial separation.

Compared to controls, there were no drug-related changes in sexual maturation.

The mean occurrence of balanopreputial separation of all groups, including the concurrent controls, were out of the historical range (50.1 to 53.5 days in the current study, relative to 41.7 to 47.5 days in the historical range). However, the values in the drug-treated groups were

comparable to the concurrent controls. Therefore, male sexual maturation in the F1 offspring was not affected by maternal drug treatment.

Female sexual maturation in the F1 offspring was not affected by maternal drug treatment. The occurrence of vaginal opening was comparable across all groups and were within the historical control range.

Motor Activity and Acoustic Startle response

Locomotor activity and acoustic startle response were evaluated in F1 offspring at approximately 10 weeks of age.

Compared to controls, both ambulatory and fine movements were increased during the first interval (10 minutes) in all drug-treated groups. However, the increase was transient and only occurred in the first trial. The Applicant stated that the animals were placed for acquisition in group order, which likely led to a longer acclimatization period and less exploratory movement in a novel environment for the control group. Therefore, the increases in the initial ambulatory movement in the treatment groups was most likely due to an artifact in the acquisition procedure and not a drug effect.

Compared to controls, the acoustic startle response in the F1 offspring was not affected by maternal drug treatment.

Learning and Memory (Multiple-T Watermaze)

At approximately 8 and 9 weeks of age, learning and memory were evaluated in F1 offspring using a multiple-T watermaze.

Compared to controls, learning and memory in the F1 offspring were not affected by maternal drug treatment.

Reproductive Capacity

Compared to controls, the reproductive performance and fertility in the F1 offspring were not affected by maternal drug treatment. The precoital interval, mating and fertility indices, and caesarean parameters (the number of corpora lutea and viable embryos, pre- and postimplantation loss) were all comparable to or better than²³ the concurrent controls.

Necropsy

At the scheduled necropsy, there were no abnormal macroscopic findings in the offspring associated with maternal drug treatment.

One control male (No. 209) had small seminal vesicles, left testes, epididymides, and prostate. This control male failed to mate or inseminate the paired control female. It is not considered to be drug-related since it was in the control group.

²³ 3, 1, 2, and 1 female were not pregnant in the control, LD, MD, and HD groups, respectively, which led to a slightly higher copulation and fertility index in the drug-treated groups relative to concurrent controls. Nevertheless, the values were within the historical range and are not considered to be drug related.

Toxicokinetics and Lactation (Exposures)

Blood samples were collected from the dams at 1, 2, 3, 5, 8, and 24 hours postdose on Lactation Days 4 and 20 (n=3/group/time point). Blood samples were collected from all culled pups on Lactation Day 4 (n=6 litters/group, pooled) and from all the pups not selected for reproductive assessment on Lactation Day 20 (3 pups/sex/litter from 6 litters/group) at 2 hours after dosing the dam. Blood levels of daridorexant were determined.

Maternal Exposure

On both sampling days, after oral administration, daridorexant was quickly absorbed in the dams with a T_{max} of 1 hour. In general, daridorexant exposure increased dose proportionally. The exposure was comparable between Lactation Days 4 and 20 ([Table 104](#)).

Table 104. Maternal Exposure of Daridorexant in the Pre- and Postnatal Development Toxicity Study in the Rat

Dose (mg/kg)	Lactation Day	T_{max} (h)	C_{max} (ng/mL)	C_{max}/D (ng/mL)/(mg/kg)	AUC_{0-24h} (h*ng/mL)	AUC_{0-24h}/D (ng*h/mL)/(mg/kg)
50	4	1	2300	46.1	6680	134
50	20	1	3010	60.2	8490	170
100	4	1	5250	52.5	20400	204
100	20	1	5790	57.9	21100	211
300	4	1	8360	27.9	60900	203
300	20	1	11200	37.2	55600	185

Source: Study T-19.005

Abbreviations: AUC_{0-24h} , area under the curve from 0 to 24 hours; C_{max} , maximum plasma concentration; T_{max} , time to maximum concentration

Offspring Exposure

On both sampling days, at 2 hours postdose in the dams, daridorexant was present in the blood of F1 offspring. The exposure levels in the offspring were lower than those in the dams, with a maternal-to-offspring ratio of ~100 on Lactation Day 4 and ~250 on Lactation Day 20 ([Table 105](#)). Although no direct exposure measurement was conducted in the milk, the presence of daridorexant in the offspring at both Lactation Day 4 and Lactation Day 20 suggest that **daridorexant and its metabolites are likely present in the rat milk.**

Table 105. Offspring Exposure of Daridorexant in the Pre- and Postnatal Developmental Toxicity Study in the Rat

Dose (mg/kg)	PND/ Lactation Day	Dams	Pups	Dam/Pup Ratio
50	4	2020	19.4	104
50	20	2720	10.6	256
100	4	3410	49.0	70
100	20	4830	18.6	260
300	4	7410	57.9	128
300	20	7250	28.6	253

Source: Study T-19.005

unit: ng/mL

Abbreviations: PND, postnatal day

13.2.3. Special Toxicology Studies

13.2.3.1. Phototoxicity

In BALB/c 3T3 cell lines (Study T-14.009, GLP), daridorexant did not show any phototoxic effects whereas the positive control, chlorpromazine, caused expected phototoxic response.

13.2.3.2. Other Toxicity Studies

In female Wistar rats (Study B-14.060, nonGLP), after a single oral administration at 1000 mg/kg, daridorexant increased stomach content (111% relative to vehicle controls) without affecting the mean small intestine transit.

In primary mouse hepatocytes (Study T-16.030, nonGLP), daridorexant at concentrations up to 50 μ M did not cause any cytotoxicity. At 100 and 300 μ M, daridorexant caused cytotoxicity as evidenced by increased LDH leakage (by ~3 and 5-fold, respectively, relative to control). Similarly, in primary human hepatocytes (Study T-16.030, nonGLP), daridorexant at concentrations up to 50 μ M did not cause any cytotoxicity. At 100 and 300 μ M, daridorexant was toxic and increased LDH leakage by 1.7 and 7.5-fold, respectively. It should be noted that the noncytotoxic dose of 50 μ M is approximately 22 and 7500 times the total and free ²⁴ plasma concentration of daridorexant at the MRHD of 50 mg. Therefore, the cytotoxicity at $\geq 100\mu$ M has limited clinical relevance.

13.2.4. Safety Evaluation of Impurities and Excipients

13.2.4.1. Excipients

There are no novel excipients of safety concern in the drug product. All excipients comply with United States Pharmacopeia or National Formulary monograph.

²⁴ Calculation based on > 97% protein binding in human plasma in the in vitro assay (Study B-13.202 and 17.061)

13.2.4.2. Impurities

13.2.4.2.1. Safety Assessment of Mutagenic Impurities

In Silico (Q)SAR

The Applicant conducted in silico quantitative structure-activity relationship ((Q)SAR, Derek and Leadscope) to evaluate the mutagenic potential of 11 daridorexant-related impurities. An independent (Q)SAR analysis was conducted by the FDA computational toxicology group. Findings from the Agency's analyses are consistent with the Applicant's conclusion and a total of 7 mutagenic impurities were identified ([Table 106](#)).

Table 106. (Q)SAR Evaluation of Daridorexant-Related Impurities

No.	Chemical Name	Bacterial Mutagenicity Expert Prediction*
1	(b) (4)	-
2	(b) (4)	-
3	(b) (4)	-
4	(b) (4)	+
5	(b) (4)	+
6	(b) (4)	+
7	(b) (4)	+
8	(b) (4)	+
9	(b) (4)	+
10	(b) (4)	+
11	(b) (4)	-

Source: (Q)SAR Analysis Report from the FDA Computational Toxicology Consultation Service
Abbreviations: +, positive; -, negative

Ames Study

The Applicant conducted Ames studies to assess the genotoxicity of 9 process-related impurities, including (b) (4), and ACT-699581 (Studies T-13.155, 13.156, 13.157, 13.158, 13.159, 13.160, 15.065, 20.004, and 18.087). All studies were conducted with the pre-incubation method under GLP with appropriate positive and negative controls and are considered adequate studies. Key study information and findings are summarized in [Table 107](#).

Table 107. Summary of Ames Studies Conducted With Process-Related Impurities

Study ID	Impurity	Tester Strains	Doses Tested (µg/plate)	Findings
T-13.155 ^a	(b) (4)	TA1535, TA1537, TA98, TA100, and TA102	(b) (4)	positive (in TA98 with S9)
T-13.156 ^a				negative
T-13.157 ^a				negative
T-13.158 ^a				Equivocal or weakly positive in TA100
T-13.159 ^a				negative
T-13.160 ^a				positive (in all 5 test strains ± S9)
T-15.065 ^a				negative
T-18.087 ^a	ACT-699581A			negative
T-20.004 ^b	(b) (4)			negative

Source: Summarized from the Applicant's Study Reports

^a, test facility: (b) (4)

^b, test site: (b) (4)

^c, all studies conducted under GLP and are considered to be adequate with appropriate negative and positive controls

Out of the 9 tested impurities, (b) (4) and (b) (4) were positive and (b) (4) showed equivocal or weakly positive signal in the Ames study. Therefore, these three impurities are considered mutagenic (Class 2).

The rest of the impurities ((b) (4) ACT-699581A, (b) (4)) were negative in the Ames study and are considered nonmutagenic impurities (Class 5).

(b) (4) are no longer used in the synthesis of daridorexant and their potential formation is excluded. Therefore, no additional safety assessment is needed for these impurities.

Control of Mutagenic Impurities

Based on the in silico (Q)SAR and in vitro Ames studies, the following mutagenic impurities were identified:

- Positive in in silico (Q)SAR analysis (Class 3): (b) (4)
- Positive in Ames studies or known mutagen (Class 2): (b) (4) (Ames positive), (b) (4) (Ames positive), and (b) (4);
- Known mutagenic carcinogens (Class 1): (b) (4) and (b) (4).

For (b) (4), the Applicant proposed a specification limit of (b) (4) $\mu\text{g}/\text{day}$, which is consistent with the compound specific acceptable intake (AI) value for oral route of administration per International Conference on Harmonisation (ICH) M7(R1) guidance. For (b) (4), the compound specific AI value is (b) (4) $\mu\text{g}/\text{day}$ for oral route. (b) (4). The Applicant proposed no routine testing for these impurities per ICH M7(R1) option 4, which is considered acceptable by the CMC review team.

For impurities (b) (4), the Applicant proposed to limit the total amount of impurities to (b) (4) ppm, which is (b) (4) $\mu\text{g}/\text{day}$.²⁵ The proposed threshold is acceptable per ICH M7(R1) guidance ($<5 \mu\text{g}/\text{day}$ for total amount of mutagenic impurities). In addition, The Applicant tested six consecutive batches of (b) (4) active pharmaceutical ingredient manufactured and the amounts of (b) (4) were all below the limit of detection for each individual compound.²⁶ Therefore, the Applicant proposed no routine testing for these impurities per ICH M7(R1) option 4, which is considered acceptable by the CMC review team.

13.2.4.2.2. Safety Assessment of Nonmutagenic Impurities

For impurities (b) (4), the Applicant proposed a specification limit of $\leq$ (b) (4), respectively, in the drug substance. In addition, (b) (4) is also a degradation product and the Applicant proposed the same (b) (4)% specification limit in the drug product. At these proposed specification limits, the estimated daily amount of these impurities is $\leq$ (b) (4) mg, respectively, at the MRHD of 50 mg.

Impurities (b) (4) were predicted to be negative for mutagenic potential in adequate in silico (Q)SAR analyses. In addition, (b) (4) were present in the nonclinical batches used in previous nonclinical toxicology studies, including the in vivo micronucleus study in the rat, general toxicology studies in the rat and dog, and carcinogenicity studies in the mouse and rat (Table 108). Findings from these nonclinical studies do not indicate a substantial mutagenic or

²⁵ (b) (4) $< 5 \mu\text{g}/\text{day}$ based on MRHD of 50 mg/day daridorexant (b) (4)

²⁶ The limit of detection (LOD) for (b) (4) is (b) (4) ppm, respectively.

carcinogenic risk of these impurities at the proposed specification limit. Given the negative (Q)SAR findings and lack of mutagenic or carcinogenic signals in previous nonclinical studies (Table 108), these impurities are considered nonmutagenic, and no additional genotoxicity testing is needed.

Table 108. Impurity Content in the Nonclinical Batches Used in Nonclinical Toxicology Studies

API Batch	Tox study for qualification	Impurity in %
RH01L117A0	T-13.220 (4 weeks dog)	(b) (4)
	T-13.221 (4 weeks rat)	
	T-14.010 (micronucleus test rat)	
RH01L117A1	T-14.068 (13 weeks rat)	
	T-14.067 (13 weeks dog)	
RH02L117A1	T-15.076 (26 weeks rat)	
	T-16.017 (39 weeks dog)	
RH03L117A1	T-16.060 (carcinogenicity rat)	
	T-18.041 (carcinogenicity in transgenic mice)	

API = active pharmaceutical ingredient; n.d. = not detected.
 Source: Summarized from the Applicant's Study Reports

For (b) (4), the proposed specification limit of (b) (4) % is below the qualification threshold per ICHQ3(A). Therefore, no additional nonclinical studies are needed to qualify (b) (4). For impurities (b) (4), the proposed specification limits of ≤ (b) (4) respectively, are adequately qualified based on their presence in the nonclinical batches used in previous general toxicology studies (Table 109), including the 13-week rat and dog studies (Batch RH01L17A1) and the 26-week rat and 39-week dog studies (Batch RH02L117A1).

Table 109. Qualification of Impurities: (b) (4)

Nonclinical Batch RH01L117A1 (Used in the 13-Week Rat and Dog Studies)						
Impurity	Levels in the Nonclinical Batch (%)	Amount (mg/kg/day) at the NOAEL of 20 mg/kg/day	Human Equivalent Dose (Human 60 kg, Based on mg/m ²)		Proposed Limit (%)	Qualified?
			mg per day	% of 50 mg		
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Yes
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Yes
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	No
Nonclinical Batch RH02L117A1 (Used in the 26-Week Rat and 39-Week Dog Studies)						
Impurity	Levels in the Nonclinical Batch (%)	Amount (mg/kg/day) at the NOAEL of 10 mg/kg/day	Human Equivalent Dose (Human 60 kg, Based on mg/m ²)		Proposed Specification (%)	Qualified?
			mg per day	% of 50 mg		
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Yes
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Yes
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Yes

Source: Summarized from the Applicant's Study Reports
 Abbreviations: NOAEL, no observed adverse effect level

For impurities (b) (4) in the drug substance, the Applicant proposed a specification limit of $\leq$ (b) (4)%; for impurity (b) (4) in the drug product, the Applicant proposed a specification limit of $\leq$ (b) (4)%. These proposed specification limits are lower than the identification and/or qualification threshold per ICHQ3(A) and Q3(B) guidelines; therefore, no additional nonclinical studies are needed to qualify these impurities.

13.2.4.2.3. Qualification for the Enantiomer ACT-699581A

ACT-699581A is an enantiomer of daridorexant. The Applicant has proposed a (b) (4)% release specification limit. To support the proposed limit, the Applicant conducted the bacterial Ames study (Study T-18.087), an in vitro chromosome aberration test (Study T-18.088), and a 4-week general toxicity study (Study T-18.085) to qualify this enantiomer.

ACT-699581A was negative in the in vitro Ames study and the chromosomal aberration study in human lymphocytes; therefore, it is considered nongenotoxic. In the 4-week repeat dose study, rats were orally treated with ACT-699581A at doses of (b) (4), and (b) (4) mg/kg/day, which correspond to approximately (b) (4) and (b) (4)% of ACT-699581A at the MRHD of 50 mg for a 60 kg human, based on mg/m². Exposure to the compound was confirmed in satellite TK animals on Days 1 and 28. Daily oral administration of ACT-699581A did not cause any adverse toxicity at doses up to (b) (4) mg/kg/day. The no observed effect level (NOEL)/NOAEL was (b) (4) mg/kg/day. The corresponding exposure levels after 28 days of repeat treatment were AUC of (b) (4) ng*hr/mL in males and (b) (4) ng*hr/mL in females.

Collectively, these data provide adequate nonclinical safety support for the proposed (b) (4)% specification limit for ACT-699581A in the final drug product at the MRHD of 50 mg. The Ames study is summarized in [Table 107](#). The in vitro chromosome aberration study and the 4-week repeat dose study are reviewed below.

13.2.4.2.4. Study Title: ACT-699581A: Chromosome Aberration Test in Human Lymphocytes In Vitro

Table 110. Study T-18.088 Information

Study no.:	T-18.088
Study report location:	EDR, SDN-1, NDA 214985
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	ACT-699581A; ELN023-3002.1; 99.4%

Source: Summarized from the Applicant's Study Reports

Abbreviations: GLP, good laboratory practice

Key Findings:

- ACT-699581A was not clastogenic in a valid in vitro chromosomal aberration assay.

Table 111. Methods, Study T-18.088

Cell line:	Human lymphocytes															
Basis of concentration selection:	+S9 4-hour incubation: high dose of (b) (4) µg/mL was selected (b) (4); in addition, at (b) (4) µg/mL, slight cytotoxicity was observed (mitotic index of 58.7%) -S9 22-hour incubation: high dose of (b) (4) µg/mL was selected based on cytotoxicity (52.8% mitotic index at (b) (4) µg/mL and 0% mitotic index at the next higher dose of (b) (4) µg/mL)															
Negative control:	DMSO (dimethyl sulfoxide)															
Positive control:	-S9: ethylmethane sulfonate (600/825 µg/mL) +S9: cyclophosphamide (7.5 µg/mL)															
Formulation/Vehicle:	DMSO															
Doses and Incubation & Sampling Time:	<table border="1"> <thead> <tr> <th>Treatment Condition</th> <th>Treatment Time</th> <th>Recovery Time</th> <th>Drug Concentration</th> </tr> </thead> <tbody> <tr> <td>+S9</td> <td>4 hr</td> <td>18 hr</td> <td>(b) (4) µg/mL</td> </tr> <tr> <td rowspan="2">-S9</td> <td>4 hr</td> <td>18 hr</td> <td>(b) (4) µg/mL</td> </tr> <tr> <td>22 hr</td> <td>0 hr</td> <td>(b) (4), and (b) (4) µg/mL</td> </tr> </tbody> </table>	Treatment Condition	Treatment Time	Recovery Time	Drug Concentration	+S9	4 hr	18 hr	(b) (4) µg/mL	-S9	4 hr	18 hr	(b) (4) µg/mL	22 hr	0 hr	(b) (4), and (b) (4) µg/mL
Treatment Condition	Treatment Time	Recovery Time	Drug Concentration													
+S9	4 hr	18 hr	(b) (4) µg/mL													
-S9	4 hr	18 hr	(b) (4) µg/mL													
	22 hr	0 hr	(b) (4), and (b) (4) µg/mL													
Comment on Study Validity:	The study is valid: appropriate positive and negative controls were included and generated expected results; dose selection based on precipitation and/or cytotoxicity was adequate; adequate number of cells and two replicates per condition were evaluated															

Source: Summarized from the Applicant's Study Reports
 Abbreviations: DMSO, dimethyl sulfoxide

Results

Both the positive and negative controls generated expected results and the values were within the historical control range at the test facility.

Compared to controls, there were no significant drug-related increases in the percent of cells with chromosomal aberration. Under one test condition (4 hours incubation at (b) (4) µg/mL with S9), the value was slightly higher than the concurrent controls (3.3% relative to 0 to 3.2% in vehicle controls); however, this value was within the historical control range (0 to 3.3%) at the test facility and no increase was observed at the next higher dose of (b) (4) µg/mL. Therefore, this finding is considered incidental.

13.2.4.2.5. Study Title: A 4-Week Repeated-dose Toxicity Study of ACT-699581A by the Oral (gavage) Route in the Rat

Table 112. Study T-18.085 Information

Study no.:	T-18.085
Study report location:	EDR, SDN-1, NDA 214985
Conducting laboratory and location:	(b) (4)
Duration:	4
Duration Units:	weeks
GLP compliance:	Y
Drug, lot #, and % purity:	ACT-699581A; ELN-23-3002.1; 98.9% to 99.4% ²⁷

Source: Summarized from the Applicant's Study Reports

Abbreviations: GLP, good laboratory practice

Key Findings:

- Oral administration of ACT-699581A at doses of (b) (4), and (b) (4) mg/kg/day for 4 weeks did not cause any toxicity in rats. The NOEL/NOAEL is (b) (4) mg/kg/day. The corresponding exposure levels after 4 weeks of oral administration were C_{max} of (b) (4) and (b) (4) ng/mL and AUC of (b) (4) and (b) (4) ng*h/mL in males and females, respectively.

Table 113. Methods, Study T-18.085

Doses:	0 (vehicle control), (b) (4) (LD), (b) (4) (MD), and (b) (4) (HD) mg/kg/day
Frequency of dosing:	Once daily
Number/Sex/Group:	Main study: n=10/sex/group TK: n=6 (control) or 3 (treatment)/sex/group
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.05% methylcellulose (400 cps)
Route of administration:	ORAL GAVAGE
Species:	RAT
Strain:	WISTAR HAN
Age / Sexual Maturity:	~6 weeks old at treatment initiation
Comment on Study Design and Conduct:	None

Dosing Solution Analysis: Dosing formulation analysis was conducted with samples collected at the beginning and end of the study. The homogeneity and concentration generally were within the acceptable range, except for one HD sample collected during Week 4, which had a 121.2% of the nominal concentration. This single deviation is unlikely to affect data interpretation.

Source: Summarized from the Applicant's Study Reports

Abbreviations: HD, high dose; LD, low dose; MD, mid dose; TK, toxicokinetic; n, number of subjects with given characteristic

²⁷ The purity of the same batch was 99.4% at the beginning of the study and 98.9% at the end of the study.

Observations and Results

Mortality

Animals were observed for general health and mortality at least twice daily. Cage-side clinical observation was performed once daily. Detailed clinical observation was conducted weekly.

There was no drug-related death in the study.

On Day 28, two TK MDF died (No. 123 and 124). These two animals appeared agitated during the blood sampling procedure and postmortem necropsy identified dark mandibular lymph nodes with congestion or hemorrhages, suggesting that the deaths were likely procedure-related rather than due to drug effects.

Clinical Signs

Compared to vehicle controls, there were no drug-related clinical signs.

Body Weights and Food Consumption

Body weight and food consumption were measured twice weekly.

Compared to vehicle controls, there were no drug-related changes in body weight, weight gain, or food consumption.

Ophthalmoscopy

Ophthalmic examinations were conducted at pretreatment baseline and during Week 4 in controls and HD.

Compared to vehicle controls, there were no drug-related ophthalmic findings in the HD group (LD and MD were not evaluated in the absence of any findings in HD).

Hematology, Coagulation, and Clinical Chemistry

At the terminal necropsy, blood samples were collected from all main study animals (fasted) under anesthesia. An adequate battery of hematology, coagulation, and clinical chemistry parameters was evaluated.

Compared to vehicle controls, there were no abnormal drug-related changes in hematology, coagulation, or clinical chemistry parameters.

Urinalysis

Urine samples were collected from main study animals for 6 hours during the night prior to scheduled necropsy. An adequate battery of urinalysis parameters was evaluated.

Compared to vehicle controls, there were no abnormal or drug-related changes in urinalysis parameters.

Gross Pathology, Organ Weights, and Histopathology

At the scheduled necropsy, all main study animals were evaluated for gross pathology, organ weights, and histopathology.

Compared to vehicle controls, there were no drug-related gross pathology findings.

Toxicokinetics

On Days 1 and 28 at 1, 2, 3, 5, 8, and 24 hours postdose, blood samples were collected from TK animals. The TK profile of ACT-699581 were determined.

After oral administration, ACT-699581 was quickly absorbed with T_{max} values of 1 to 2 hours. The exposure to ACT-699581 increased greater than dose proportionally. Repeat administration led to slightly increased drug exposure, with the Day28-to-Day 1 ratio of 1.3 to 1.6. Females had higher exposure compared to males with the female-to-male ratio of ~4.

Table 114. Summary of TK Parameters of ACT-699581 in the 4-Week Rat Study

Dose (mg/kg)	Day	Sex	Tmax (h)	Cmax (ng/mL)	Cmax/D (ng/mL)/(mg/kg)	AUClast (ng*h/mL)	AUClast/D (ng*h/mL)/(mg/kg)	Tlast (h)
(b) (4)	1	F	2	(b) (4)	(b) (4)	(b) (4)	(b) (4)	3
		M	1					3
	28	F	1					3
		M	1					3
	1	F	1					3
		M	1					3
	28	F	1					3
		M	1					3
	1	F	1					8
		M	1					8
	28	F	2					24
		M	1					8

Source: Study T-18.085

Abbreviations: AUC_{last}, area under the curve to last measurable collection; C_{max}, maximum plasma concentration; TK, toxicokinetic; T_{last}, time of last collection; T_{max}, time to maximum concentration

13.3. Overall Assessment on GLP Compliance and Data Quality

During the IND and NDA review, multiple deviations were identified/reported in pivotal nonclinical studies conducted at the (b) (4) site, including:

- (b) (4)

Given the relatively high incidence of deviations, the review Division and the Office of Study Integrity and Surveillance requested an audit of the above studies and a site inspection at the test facility, which were performed by the (b) (4)

The inspection confirmed the identified deviations. Nevertheless, the observations were considered to be minor and did not affect the GLP status or the overall conclusion of the studies. Therefore, these studies are considered adequate to support the NDA application. For detailed information, see Document Archiving, Reporting, and Regulatory Tracking System record dated (b) (4) under NDA 214985.

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

Plasma Protein Binding of Daridorexant and its Metabolites- M1, M3, and M10

The extent of daridorexant and its metabolites binding to animal and human plasma proteins was investigated ex vivo in plasma samples using rapid equilibrium dialysis. Daridorexant was highly bound to plasma proteins in all species but showed significant species differences in unbound fraction. At the lowest concentration of 0.5 µg/mL, rat, mouse, and dog exhibited unbound fractions in the range of 2.4 to 2.8%, while lower unbound fractions of 0.5 and 0.3% were observed for plasma of rabbit and human. Saturation of plasma protein binding at low daridorexant concentrations was evident in all species. Similar to parent daridorexant, all three metabolites displayed significant species differences in the extent of plasma protein binding. Binding to human plasma proteins was generally higher compared to any of the animal species.

Metabolic Profiling of Daridorexant

The objective of this study was the determination and comparison of daridorexant metabolic profiles in vitro using liver microsomes and hepatocytes from human and various animal species. These studies were conducted with liver microsomes and liver hepatocytes. Samples were analyzed by high performance liquid chromatography coupled to ¹⁴C-radioactivity and ultraviolet detection. Metabolite structures were identified using MS and the aid of chemical references.

Incubation of daridorexant with human liver microsomes led to the formation of three primary metabolites, i.e., the aliphatic alcohol M3, the phenol M4, and the rearranged piperidinol M5. These three metabolites were consistently observed with liver microsomes of all species. The metabolism of daridorexant with human hepatocytes was investigated using two batches of freshly prepared, and one batch of cryopreserved, hepatocytes. Ten metabolites were observed across all batches. A control experiment in the absence of cells confirmed that all products were indeed daridorexant metabolites. Beyond the three primary metabolites M3 to M5 observed with liver microsomes, a number of downstream products were observed in human hepatocytes. The aliphatic alcohol M3 was further oxidized to the corresponding aldehyde M1 and the acid M2. The phenol M4 was glucuronidated to M9. The piperidinol M5 was hydroxylated at the methyl group of the benzimidazole moiety to yield M10. The cross-product M7 resulted from either hydroxylation of M4 or oxidative demethylation of M5. Metabolites M6 and M8 were downstream products, both resulting from combined oxidation and glucuronidation.

Cytochrome P450 Enzymes Involved in Metabolism of Daridorexant

The nature of human P450 enzymes involved in daridorexant metabolism was investigated using two complementary approaches: (1) incubation with human liver microsomes in the presence of specific chemical inhibitors for the different P450 isoforms, and (2) incubation with recombinant P450 enzymes. For this purpose, daridorexant was incubated with human liver microsomes and

recombinant CYP2C9, CYP2C19, CYP2D6, and CYP3A4 over a concentration range up to 100 μ M. Due to the complexity of the metabolic pattern, enzyme kinetic parameters, K_m and V_{max} , were determined based on substrate depletion rather than metabolite formation rates. Intersystem scaling factors and the abundance of individual P450 enzymes in human liver were used to quantify the contribution of each enzyme to overall metabolic clearance. Additional experiments were performed with recombinant P450 enzymes and the chemical references of metabolites M1 (ACT-776537), M2 (ACT776353), M3 (ACT-776063), M4 (ACT774170), and M5 (ACT-1006-2069) in order to identify the P450 enzymes involved in the secondary metabolism of daridorexant. Samples were analyzed by liquid chromatograph with tandem mass spectrometry (LC-MS/MS) or high performance liquid chromatography coupled to ^{14}C -radiodetection.

CYP3A4 is the major P450 enzyme involved in daridorexant metabolism, accounting for 89% of total turnover in vitro. Minor contributions, each individually below 3%, come from CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. Specifically, CYP3A4 is the only P450 enzyme catalyzing formation of M5, and the major enzyme responsible for formation of M3 and M4. M3 is also formed by CYP2C19, while CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 produce M4.

Human Cytochrome P450 Inhibition by Daridorexant and its Metabolites

The objective of this study was to (a) assess the potential of daridorexant to inhibit the human cytochrome P450 isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, (b) assess the time-dependent inhibition of daridorexant on CYP2C19 activity, and (c) to assess the potential of its three major metabolites M1 (ACT-776537), M3 (ACT-776063), and M10 (ACT-1016-3307) to inhibit the human cytochrome P450 isoforms CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.

The effect of daridorexant and its three major metabolites on the inhibition of human P450 enzymes was tested in vitro using either human liver microsomes and P450 isoform-specific marker transformations or recombinant P450 enzymes expressed in baculovirus-infected Sf9 cells for CYP2C19. For the determination of IC_{50} values, substrates were used at concentrations around their respective K_m values, while inhibitor concentrations up to 100 μ M were used. Control inhibitors with known inhibitory outcome were run in parallel for each P450 enzyme. Metabolite formation and residual inhibitor concentrations at the end of the experiment were quantified with LC-MS/MS. Nonspecific binding to equipment and liver microsomes was determined by rapid equilibrium dialysis.

Daridorexant was a weak inhibitor of a number of P450 enzymes, including CYP1A2, CYP2A6, CYP2B6, and CYP2D6, with IC_{50} values of about 50 μ M or higher. A more pronounced inhibition was observed on the three members of the CYP2C family, i.e., CYP2C8, CYP2C9, and CYP2C19, with IC_{50} values in the range of 8.2 to 19 μ M. Inhibition of CYP3A4 was assessed using midazolam and testosterone as enzyme specific probes. The inhibition pattern was consistent for both markers with IC_{50} and K_i values of 7.3 μ M and 4.6 to 4.8 μ M, respectively. The inhibition potential of the metabolites showed a similar pattern but was generally weaker compared to parent drug, likely reflecting their more polar nature.

Human Cytochrome P450 Induction by Daridorexant and its Metabolites

The objective of this study was to (a) assess the potential of daridorexant to induce the expression of the major human cytochrome P450 isoforms, i.e., CYP3A4, CYP2C9, CYP1A2, and CYP2B6, and (b) investigate the potential of the three major metabolites of daridorexant to activate human PXR in CV-1 cells and to induce human CYP2B6 and CYP1A2 mRNA in primary human hepatocytes. Daridorexant was tested for its potential to activate human PXR in a transcriptional activation assay in CV-1 cells, and to modulate the CYP3A4, CYP2C9, CYP1A2, and CYP2B6 mRNA expression in three different batches of primary human hepatocytes .

The potential of daridorexant and its three major metabolites to induce P450 enzymes in vitro was initially investigated by probing for the activation of human PXR in a reporter gene assay. Human PXR was expressed in green monkey CV-1 cells and activation of the nuclear receptor investigated in a concentration range from 0.03 to 30 μ M. Rifampin was used as a positive control. The unbound fractions in these experiments were determined by rapid equilibrium dialysis.

Daridorexant and its metabolites elicited a concentration-dependent activation of human PXR. EC₅₀ values for daridorexant and M3 were 3.0 μ M and 2.4 μ M, while E_{max} values were 6.6- and 6.2-fold above vehicle control, respectively. No complete concentration-response curves were obtained for metabolites M1 and M10 due to cytotoxicity above 3 μ M for M1, and the absence of a plateau at the highest concentration of 30 μ M for M10.

Drug Transporter Substrate Studies with Daridorexant

The objective of the study was to investigate whether daridorexant is a substrate of the human uptake transporters OATP1B1 and OATP1B3 and human efflux transporters P-gp and BCRP. Cellular uptake of daridorexant was determined in CHO cells overexpressing OATP1B1 or OATP1B3 and compared to the uptake into wild-type CHO cells, using daridorexant at three concentrations: 0.1, 1, and 10 μ M. Experiments were done in the presence and absence of the OATP inhibitor cyclosporin A over a period up to 3 min. Atorvastatin acid was used as a positive control to verify cellular functionality. Total radioactivity was quantified by liquid scintillation counting.

The uptake ratio of daridorexant into OATP1B1- and OATP1B3-expressing cells and the respective CHO wildtype cells was around unity and not different in the presence of the OATP inhibitor cyclosporin A. The uptake ratios of the positive control atorvastatin acid range between 2.5 to 9.6, and decreased to values close to unity in the presence of cyclosporin A. The data suggest that daridorexant is not a substrate of OATP1B1 and OATP1B3.

Evaluation of Whether Metabolites M1, M3, and M10 of Daridorexant are Substrates of Human P-gp and BCRP

To assess whether the three major daridorexant metabolites are substrates of BCRP, bidirectional transport experiments were performed with BCRP-expressing and the respective wildtype MDCKI cells. P_{app} values were determined for both cell types at a single concentration of 1 μ M in (A-B) and (B-A) direction. Experiments were performed in the presence and absence of the

BCRP inhibitor Ko143. Lucifer yellow was used to verify cell layer integrity. Metabolite concentrations in both transwell chambers were quantified by LC-MS/MS.

Metabolites M1 and M3 had high P_{app} in both transport directions and an (A-B)/(BA) ratio of 0.8 and 2.5 in MDCKI cells, respectively. No relevant change in (A-B) or (B-A) P_{app} values was observed in the presence of the BCRP inhibitor Ko143. M10 exhibited large differences between both P_{app} values resulting in an (A-B)/(B-A) ratio of 34. This ratio was, however, unaffected by Ko143, indicating that M10 is not a BCRP substrate. The polarized flux is likely the result of the activity of endogenous canine P-gp/MDR1 in the MDCKI cells.

Potential of Daridorexant and the 3 Major Daridorexant Metabolites M1, M3, and M10 as Inhibitor of Transporters

Inhibition of the uptake transporters OATP1B1, OATP1B3, OAT1, OAT3, OCT1, and OCT2, and the efflux transporters MATE1, MATE2-K, P-gp/MDR1, and BCRP by daridorexant and its metabolites was assessed using MDCKII, CHO, and HEK293 cells overexpressing the transport proteins together with respective wildtype cells. The effect on OATP, OAT, OCT, and MATE transport was investigated by measuring the cellular uptake of transporter-specific model substrates in the presence of increasing concentrations of inhibitor. For P-gp/MDR1, the inhibitory potential was assessed by measuring changes in the bidirectional transport of digoxin and colchicine in a transwell assay. BCRP inhibition was assessed using BCRP-expressing Sf9 membrane vesicles. OATP inhibition experiments were performed with a 30 min pre-incubation period. Concentrations of daridorexant and its metabolites up to 300 μ M were used together with known inhibitors of each transport protein. The concentrations of model substrates were determined by LC-MS/MS. Nonspecific binding in these inhibition experiments was determined by rapid equilibrium dialysis.

Daridorexant inhibited the uptake of model substrates by several drug transport proteins. The strongest inhibition was observed on BCRP and MATE transport with IC_{50} values ranging from 3.0 to 9.7 μ M. Inhibition of OATP, OAT3, OCT1, and P-gp/MDR1 was less pronounced, with IC_{50} values ranging from 11 to 71 μ M. IC_{50} values on OAT1 and OCT2 transport were above the highest tested concentration of 300 μ M. The daridorexant metabolites were generally weaker transport inhibitors with few notable exceptions. M1 inhibited atorvastatin uptake into OATP1B1 expressing cells with an IC_{50} of 4.5 μ M. M1 and M3 inhibited OCT1-mediated uptake of metformin with IC_{50} values of 0.5 μ M and 8.0 μ M, respectively.

Time-Dependent Inhibition Potential of Daridorexant and its 3 Major Metabolites M1, M3, and M10 on CYP1A2 and CYP2B6 Activity

Time-dependent inhibition by daridorexant and its metabolites was investigated for the same set of P450 enzymes, using human liver microsomes and the same P450 markers as for the competitive inhibition assays. Control inhibitors with known inhibitory outcomes were run in parallel for each P450 enzyme. Metabolite formation and residual inhibitor concentrations at the end of the experiment were quantified with LC-MS/MS. Nonspecific binding to equipment and liver microsomes was determined by rapid equilibrium dialysis.

With the exception of CYP3A4, daridorexant and its metabolites showed no time-dependent inhibition of any P450 enzyme. Small but consistent effects were elicited by daridorexant and M1 on CYP3A4 activity, which were NADPH-dependent and increased with rising concentrations and pre-incubation time. Enzyme kinetic parameters for CYP3A4 inactivation, i.e., K_i and the maximal rate of inactivation, were determined for both compounds.

14.2. In Vivo Studies

14.2.1. Single-Ascending Dose (SAD) Study (AC-078-101)

This was a single-center, double-blind, randomized, placebo-controlled study to evaluate the PK, PD, safety, and tolerability of single-ascending dose (SAD) of daridorexant in healthy male subjects. Daridorexant at single oral doses of 5, 25, 50, 100, and 200 mg or placebo was administered in the morning to 40 healthy male subjects (6:2 active:placebo, at each dose level). PK assessments of daridorexant included the determination of C_{max} , t_{max} , $t_{1/2}$, AUC, and the assessment of dose proportionality across daridorexant doses. PD included objective measurements (saccadic peak velocity [SPV], speed of eye movements), adaptive tracking (hand-eye coordination task measuring vigilance and attention), body sway (postural stability), and subjective measurements (Bond and Lader visual analog scale [VAS] for subjective alertness, mood, and calmness). Safety evaluations comprised the collection of AEs and serious adverse events (SAEs), physical examination, vital signs, body weight, body temperature, clinical laboratory tests, 12-lead ECG, and narcolepsy questionnaires.

Results

PK: Across doses, daridorexant was absorbed with a median t_{max} of 0.80 to 2.75 h, and the geometric mean $t_{1/2}$ was between 5.9 and 8.8 h. Results from the power model showed that the exposure increased less than proportionally to the dose administered (i.e., neither for C_{max} [0.61 to 0.77] nor for AUC_{0-inf} [0.77 to 0.98] was the 90% CI for the slope completely within the critical interval of 0.81 to 1.19). However, at the lower doses (25 and 50 mg) the increase in exposure parameters was dose proportional.

PD: At doses of 25 mg and higher, the PD assessments revealed reduced vigilance and attention, reduced visuomotor coordination indicated by decreased SPV and adaptive tracking performance, and reduced postural stability indicated by increased body sway. The onset of effect started within 1 h after administration and the maximum effect occurred around t_{max} (i.e., 1.5 h following treatment intake for doses up to 100 mg). At 200 mg, the maximum effect generally occurred after 2 h.

Safety: No SAEs, severe AEs, or AEs leading to study discontinuation were reported. The most frequently reported AEs (in >10% of subjects) were: somnolence, (23/40 subjects), fatigue (9/40), disturbance in attention (7/40), and headache (6/40). The incidence of somnolence increased with increasing dose.

Table 115. PK Parameters of Daridorexant in Healthy Subjects After Administration of Single Dose of 5-200 mg, Study AC-078-101

Parameter [unit]	5 mg (N = 6)	25 mg (N = 6)	50 mg (N = 6)	100 mg (N = 6)	200 mg (N = 6)
C_{max} [ng/mL]	160 122, 208	632 516, 774	1231 963, 1576	1557 1245, 1946	1869 1179, 2962
t_{max} [h]	0.80 0.50, 2.00	1.00 0.80, 2.50	2.00 0.70, 3.00	2.50 1.50, 3.50	2.75 1.50, 4.00
AUC_{0-24} [ng·h/mL]	894 556, 1439	2568 1612, 4092	6947 4838, 9976	10998 8488, 14248	17864 10891, 29302
$t_{1/2}$ [h]	6.5 4.8, 8.9	6.1 4.1, 9.1	5.9 4.8, 7.4	7.5 5.3, 10.5	8.8 6.6, 11.8

Data are geometric means (and 95% CI) or for t_{max} the median (and range). AUC_{0-24} = area under the plasma concentration-time curve from time zero to 24 h; CI = confidence interval; C_{max} = maximum plasma concentration; HGC = hard gelatin capsule; N = number of subjects; PK = pharmacokinetic(s); $t_{1/2}$ = terminal half-life; t_{max} = time to reach maximum plasma concentration. Source: D-15.653.

Source: Summary of Clinical Pharmacology (2.7.2), 6.3, Page- 150.

Conclusions

The PK of daridorexant were characterized by quick absorption and elimination in the anticipated clinical dose range up to 50 mg, and dose-related effects on the CNS were observed, indicating a suitable PK/PD profile for a sleep-promoting agent. The dose-dependent incidence of somnolence as the most common AE was consistent with the observed PD effects and the pharmacological class of orexin receptor antagonists. Taken together, the results of the first-in-human study provided good indications about the therapeutic dose range of daridorexant and supported the design of the subsequent multiple-ascending dose (MAD) study in healthy male and female subjects, in which a dose range of 10 to 75 mg was explored.

14.2.2. Multiple-Ascending Dose Study (AC-078-102)

This was a single-center, double-blind, randomized, placebo-controlled study to evaluate the PK, PD, safety, and tolerability of daridorexant in healthy male and female subjects. MAD oral doses of daridorexant (10, 25, and 75 mg) or placebo were administered once daily for 5 days in the morning to 31 healthy male or female adults (8:2 active:placebo at each dose level, 1:1 sex ratio). PK assessments of daridorexant included the determination of C_{max} , t_{max} , $t_{1/2}$, and AUC as well as the assessment of dose proportionality and accumulation across daridorexant doses. PD assessments included objective measurements (SPV, adaptive tracking, body sway, digit symbol substitution [assesses visual perception and other cognitive functions including attention, short-term memory, and psychomotor speed] and simple reaction time to measure reaction time) and subjective measurements (Leeds sleep evaluation questionnaire, Bond and Lader VAS, Bowdle VAS [for psychedelic effects], and Karolinska Sleepiness Scale to assess next-day alertness).

The study also evaluated PK differences between healthy young adults and healthy elderly subjects after multiple doses.

Safety evaluations comprised the collection of AEs and SAEs, physical examination, vital signs, body weight, body temperature, clinical laboratory tests, 12-lead ECG, and narcolepsy questionnaires.

Results

PK: Across doses, daridorexant in healthy adult subjects was absorbed with a median t_{max} of 1.00 to 1.98 h, and $t_{1/2}$ on Day 5 was between 5.6 and 8.5 h. Results from the power model showed that the exposure increased proportionally to the dose administered, while C_{max} showed a less than dose-proportional increase. Based on AUC_{0-24} Day 5/Day 1, the accumulation index was 1.1 across all 3 doses tested.

Table 116. PK Parameters of Daridorexant in Healthy Subjects After Administration of Single and Repeat Doses of 10 to 75 mg, Study AC-078-102

Study/ Time point	Daridorexant dose	N	C_{max} [ng/mL]	t_{max} [h]	AUC_{0-24} [ng·h/mL]	$t_{1/2}$ [h]	AI (AUC_{0-24} Day 5/Day 1)
AC-078-102 (Part A)/ Day 1 (single dosing)	10 mg	8	256 (224, 294)	1.00 (0.50, 1.00)	1156 (962, 1388)	5.9 (4.5, 7.6)	-
	25 mg	8	614 (466, 810)	1.17 (1.00, 3.00)	3502 (2413, 5084)	5.9 (4.8, 7.3)	-
	75 mg	7	1225 (766, 1960)	1.98 (1.00, 4.00)	8583 (5797, 12707)	9.2 (6.3, 13.6)	-
AC-078-102 (Part A)/ Day 5 (5-day dosing)	10 mg	8	280 (214, 366)	1.00 (0.50, 1.10)	1293 (1069, 1563)	5.6 (4.2, 7.4)	1.13 (0.18)
	25 mg	8	616 (445, 852)	1.00 (1.00, 4.00)	3805 (2695, 5371)	6.7 (5.1, 8.8)	1.10 (0.16)
	75 mg	7	1308 (885, 1933)	1.07 (1.00, 1.10)	8940 (6441, 12410)	8.5 (6.8, 10.8)	1.07 (0.23)

Source: Summary of Clinical Pharmacology (2.7.2), Table 3-2, Page- 77

Abbreviations: AUC_{0-24h} , area under the curve from 0 to 24 hours; C_{max} , maximum plasma concentration; N, number of subjects; $T_{1/2}$, terminal half-life; T_{max} , time to maximum concentration

Safety: No SAEs, severe AEs, or AEs leading to study treatment discontinuation were reported. The most frequently reported AE across active dose groups was somnolence, reported by 1, 5, and 6 subjects (out of 8 per dose group) treated with 10, 25, and 75 mg, respectively. Other reported AEs in the MAD part included headache, sudden onset of sleep, and dizziness.

Conclusions

The PK of daridorexant was characterized by quick absorption and elimination with no or minimal accumulation after multiple dosing. Elimination was slightly prolonged in the elderly compared to young adults, reflected by a $t_{1/2}$ of approximately 6 to 8 h and 8 to 10 h in adults and elderly, respectively. Dose-related effects on the CNS were observed following multiple dosing to healthy young adults.

14.2.3. PK of Daridorexant in Japanese vs. Caucasian Subjects (ID-078-105)

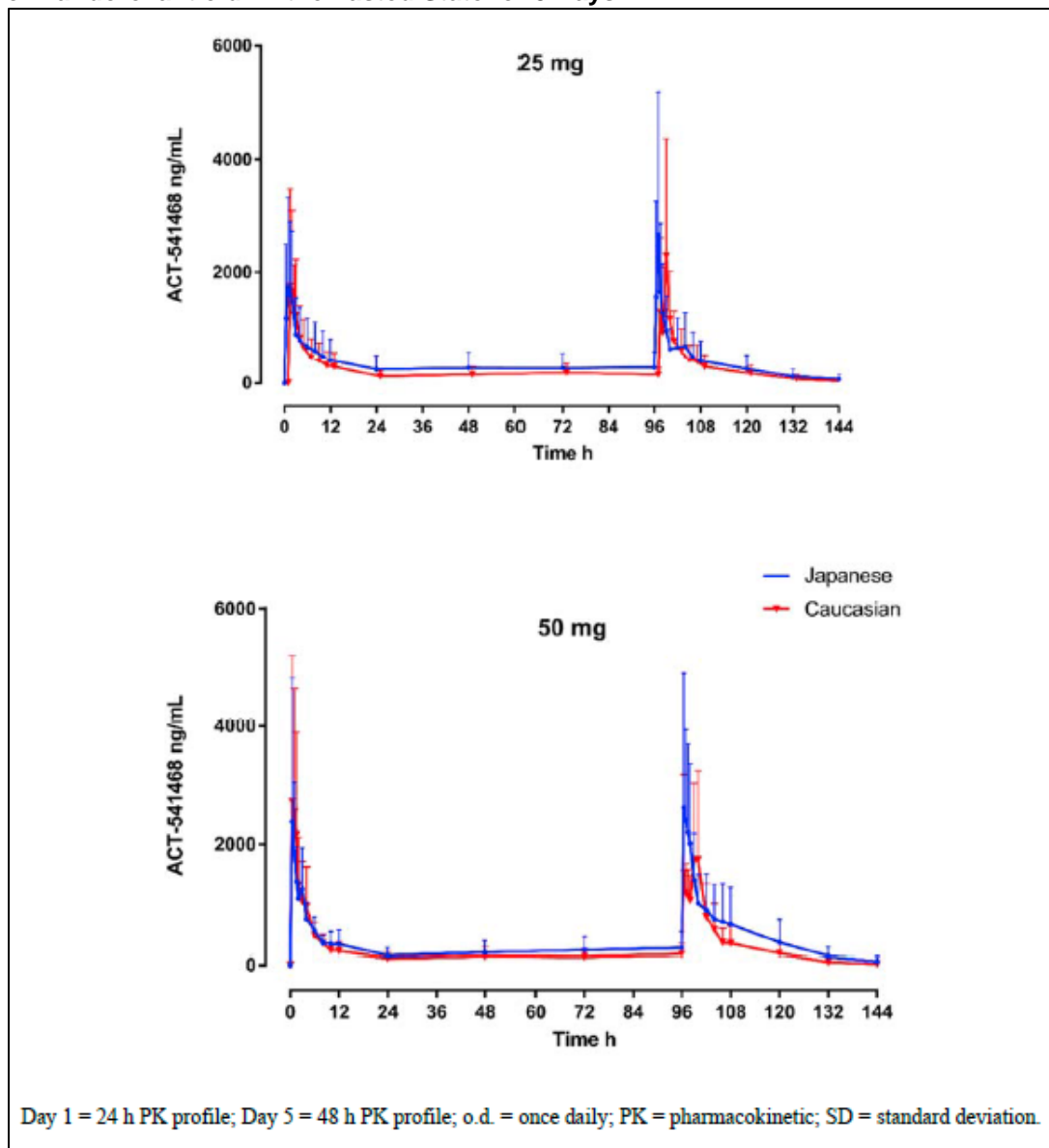
This was a single-center, double-blind, placebo-controlled, randomized study to evaluate the PK, PD, tolerability, and safety of single- and repeated-dose daridorexant in Caucasian and Japanese healthy male and female subjects. Repeated oral doses of daridorexant (25 or 50 mg) were

administered for 5 days in the morning to 41 healthy male and female subjects (21 Japanese and 20 Caucasian, 8:2 active:placebo at each dose level, 1:1 sex ratio).

Results

No relevant effect of ethnicity was observed on Day 1 in any of the PK Parameters. On Day 5, exposure parameters C_{max} and AUC_{0-24} at 50 mg (not at 25 mg) were higher in Japanese subjects, indicated by a GMR (90% CI) Japanese/Caucasian of 1.40 (1.15 to 1.69) and 1.31 (1.02 to 1.69), respectively. PK parameters of metabolites M1, M3, and M10 at steady state (Day 5) were similar in both ethnic groups and in line with previous observations in Study AC-078-104. As observed in Caucasian subjects, dose-dependent effects on the objective PD variables (SPV, adaptive tracking, and body sway) were observed in Japanese subjects. At 25 mg, when compared with Caucasian subjects, the maximum effect occasionally occurred earlier (1 h in Japanese subjects versus 2 h in Caucasian subjects) and was larger in Japanese subjects. At 50 mg, effects were similar between the two ethnic groups.

Figure 20. Arithmetic Mean ($\pm$ SD) Plasma Concentration Versus Time PK Profiles of Daridorexant in Healthy Young Japanese and Caucasian Subjects Following Administration of 25 mg and 50 mg of Daridorexant o.d. in the Fasted State for 5 Days



Source: Clinical Study Report (AC-078-105), Fig 11-1, page 89

Conclusions

Overall, the small differences in PD characteristics (slightly earlier maximum effect at 25 mg) and the observed AE profile of daridorexant at 25 and 50 mg in healthy Japanese and Caucasian subjects suggest that Japanese subjects may be more sensitive to the effects of daridorexant. The slightly higher exposure (at 50 mg) in Japanese subjects did not translate into stronger PD effects or higher AE incidence.

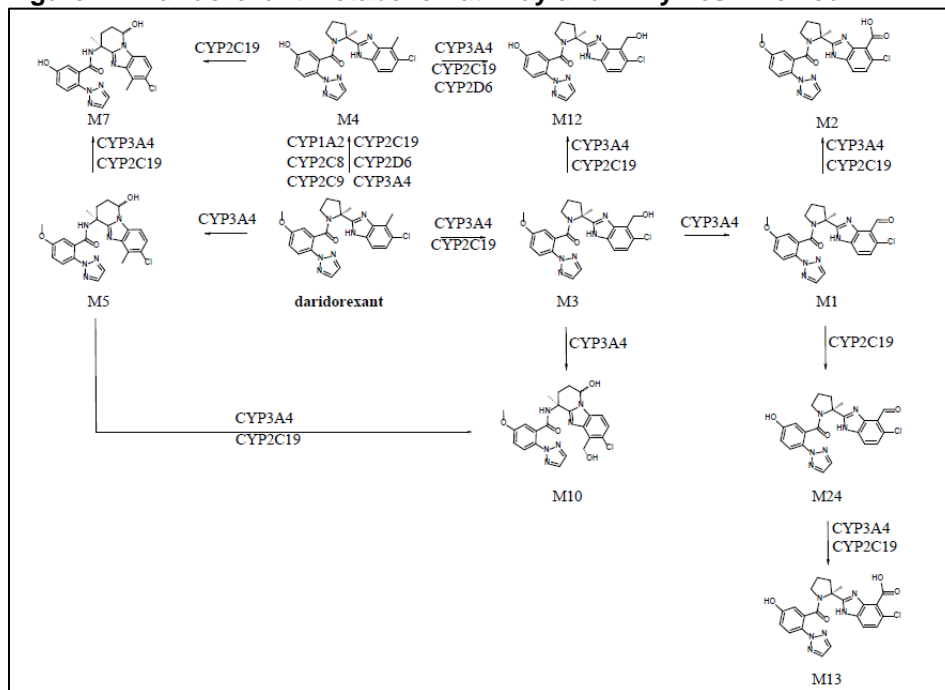
14.2.4. Mass Balance and Absolute Bioavailability (ID-078-101)

The ADME and absolute bioavailability (BA) characteristics of daridorexant were investigated as part of Study AC-078-101. For the ADME/mass balance, a single oral dose of a ^{14}C -radiolabeled daridorexant microtracer was given simultaneously with a single oral dose of daridorexant 50 mg to investigate mass balance, metabolism, and excretion pathways. For the absolute BA, a single short IV infusion of a ^{14}C -radiolabeled daridorexant microtracer was given at the expected t_{max} of the orally administered nonradiolabeled daridorexant (100 mg, HGC).

Mass Balance Results

The arithmetic mean (95% CI) cumulative recovery of radioactivity from urine and feces was 84.5% (78.3 to 90.6), with fecal excretion of radioactivity being the major route of elimination (95% CI of 56.6% [49.6 to 63.5]). Only traces of unchanged parent compound (0.3% of the dose administered) were recovered in urine and feces. In general, the metabolic profile of daridorexant was similar in animal species versus human. In human plasma, three major circulating metabolites were found: M1, M3 and M10. Compared to the parent compound, C_{max} values of all three metabolites were lower. Additionally, based on nonclinical data, all three metabolites showed 8-to 1500-fold lower potency compared to parent. Therefore, the major metabolites are not expected to contribute to pharmacological effect of daridorexant.

Figure 21. Daridorexant Metabolic Pathway and Enzymes Involved



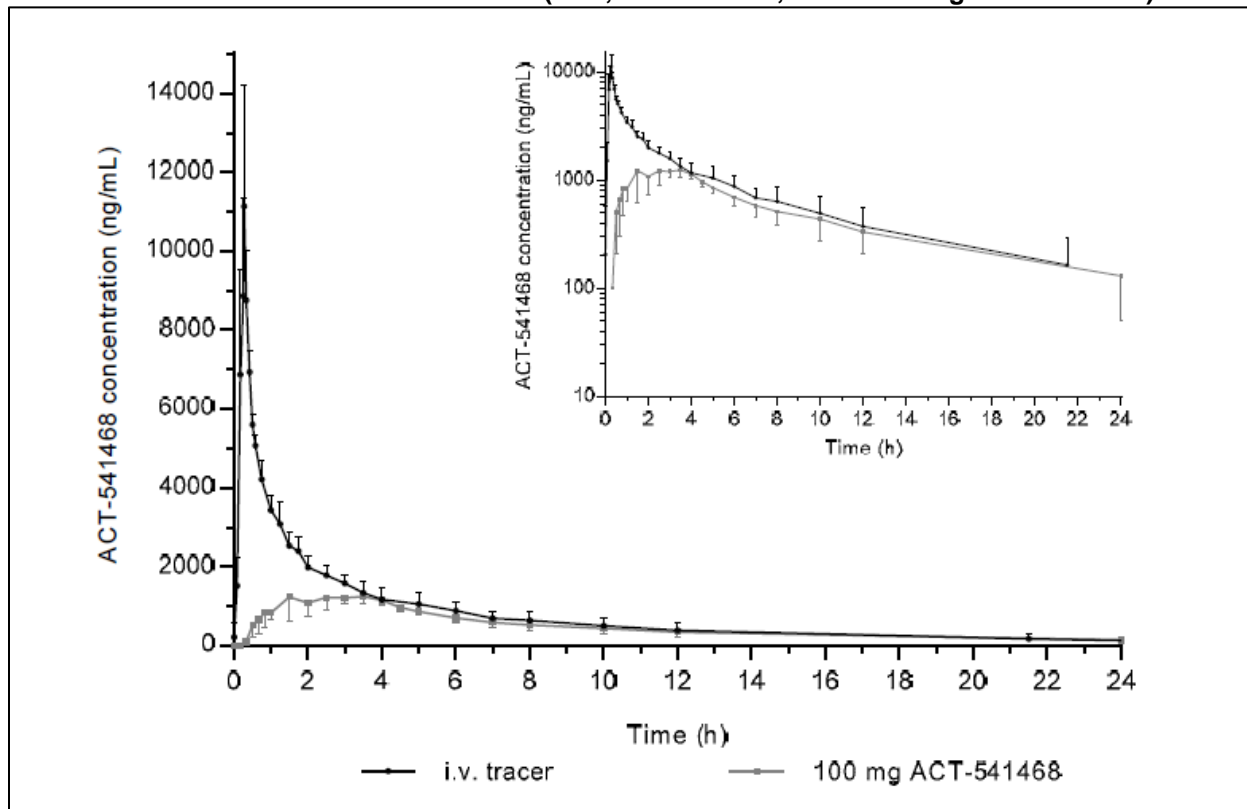
Source: Module 1.11.3, Fig 1, Page 7, Applicant response on April 6th, 2021 to FDA- IR

Absolute BA Results

After IV administration, ^{14}C -daridorexant was quickly distributed and eliminated. There were no marked differences in $t_{1/2}$ between IV (^{14}C -radiolabeled daridorexant) and oral (nonradiolabeled

daridorexant) administration. Daridorexant had a geometric mean (95% CI) absolute BA of 62.1% (95% CI: 51.6 to 74.8), CL of 4.97 L/h (3.04 to 8.11), and V_{ss} of 31.0 L (95% CI: 26.3 to 36.5).

Figure 22. Mean Plasma Concentration-Time Profile of p.o. Daridorexant (Cold) vs. Dose-Adjusted, IV Administered ¹⁴C-Labeled Daridorexant (+SD, Linear Scale, Inset Semilogarithmic Scale)



Source: Clinical Study Report (AC-078-101), Fig 11-8, page 107
Abbreviations: IV, intravenous; p.o., orally

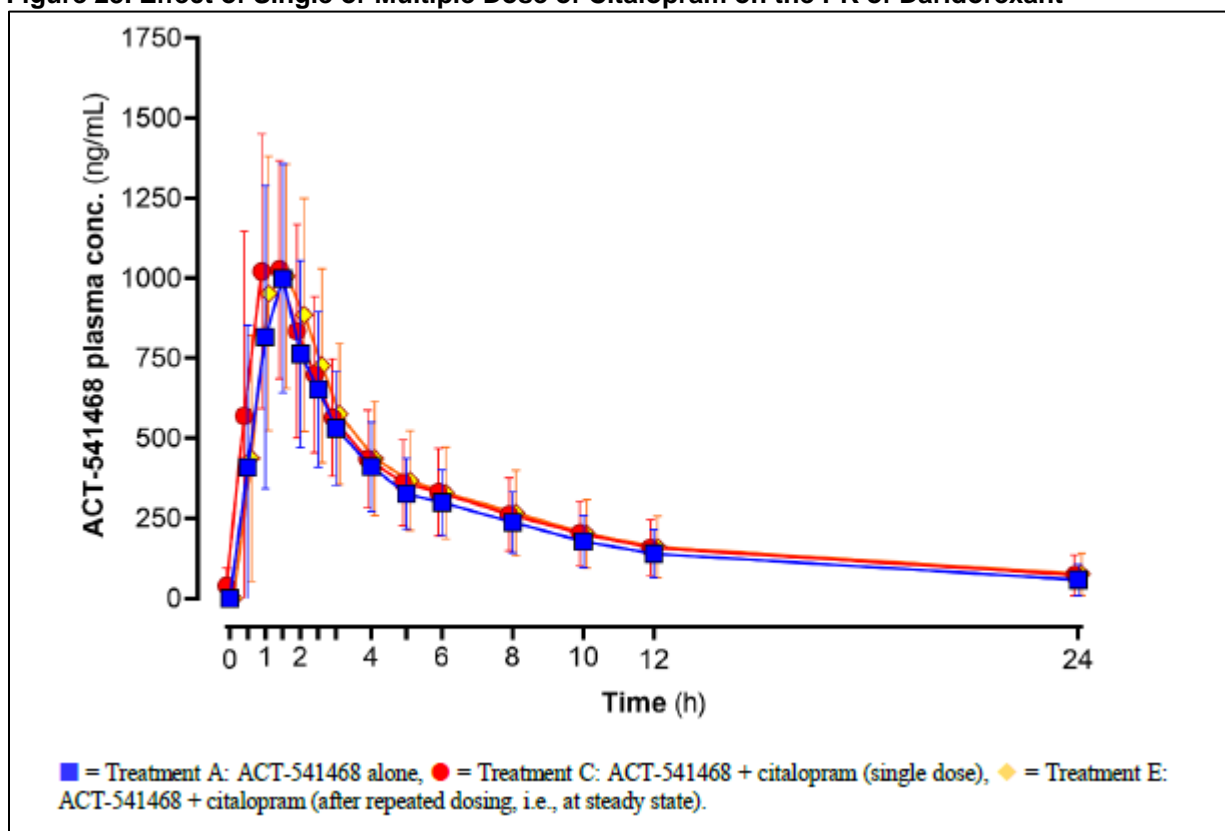
14.2.5. PK and PD Interactions Between Daridorexant and the SSRI Citalopram (ID-078-114)

This was a single-center, single-blind, randomized, placebo-controlled, sequential design study with the inclusion of two double-blind nested crossover parts to evaluate the PK and PD interaction between single-dose daridorexant (tablet) and both single and repeated once daily doses of the selective serotonin reuptake inhibitor, citalopram, in healthy male and female subjects. In addition, the safety and tolerability of daridorexant and citalopram alone, and when administered concomitantly, were assessed. A total of 24 healthy male and female subjects (1:1 sex ratio) were randomized. PD assessments included objective measurements (SPV, unstable tracking, body sway, simple reaction time, and digit symbol substitution) and subjective measurements (Bond and Lader VAS and the Karolinska Sleepiness Scale). Safety evaluations comprised the collection of AEs and SAEs, physical examination, vital signs, body weight, clinical laboratory tests, 12-lead ECG, narcolepsy questionnaires, and suicidal ideation.

Results

When administered concomitantly at citalopram steady state, the daridorexant geometric mean ratio (GMR) (90% CI) for C_{max} , AUC_{0-24} , and $t_{1/2}$ was 1.12 (1.04 to 1.20), 1.10 (1.04 to 1.17), and 1.14 (1.08 to 1.20), respectively, while t_{max} remained unchanged. At citalopram steady state, single-dose daridorexant did not affect the C_{max} and AUC_{0-24} of citalopram as indicated by GMR (90% CI) of 1.02 (0.96 to 1.07) and 1.00 (0.96 to 1.03), respectively.

Figure 23. Effect of Single or Multiple Dose of Citalopram on the PK of Daridorexant



Source: Clinical Study Report (ID-078-114), Fig 11-1, page 95
Abbreviations: PK, pharmacokinetic

Conclusions

The PK of daridorexant was not affected in a relevant way by coadministration with citalopram. The effects on objective and subjective PD assessments following coadministration of daridorexant and citalopram were mainly driven by the expected CNS effects of daridorexant. While the incidence of AEs was highest when both drugs were coadministered, as expected based on the known safety profile of both daridorexant and citalopram, the overall tolerability was acceptable. In summary, the results show that doses up to 50 mg of daridorexant can be administered concomitantly with citalopram without dose adjustment.

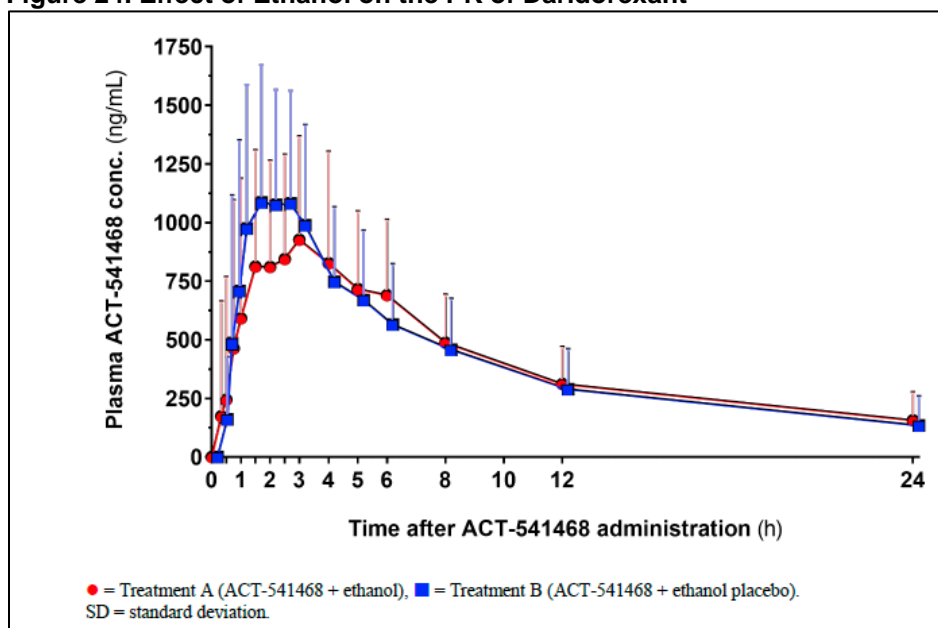
14.2.6. PK and PD Interactions Between Daridorexant and Ethanol (ID-078-111)

This was a single-center, double-blind, randomized, placebo-controlled, double-dummy, 4-way crossover study to evaluate the PK and PD interaction between single-dose daridorexant (tablet) and single-dose ethanol in healthy male and female subjects. In addition, the safety and tolerability of daridorexant, ethanol, and their concomitant administration were assessed. A total of 22 healthy male and female subjects (1:1 sex ratio) were randomized.

Results

When administered concomitantly with ethanol, daridorexant C_{max} , AUC_{0-inf} , and $t_{1/2}$ remained unchanged, i.e., GMR (90% CI) was 0.96 (0.86 to 1.08), 1.08 (0.98 to 1.19), and 1.09 (1.01 to 1.18), respectively, compared to daridorexant alone. Absorption of daridorexant was delayed as indicated by a median difference (90% CI) for t_{max} of 1.25 h (0.51 to 1.78). Daridorexant did not alter the total dose of ethanol required to maintain the 0.6 g/L clamp compared to ethanol administered alone as indicated by GMR (95% CI) of 1.00 (0.97, 1.02). Daridorexant administered together with ethanol did not lead to marked differences compared to the administration of either daridorexant or ethanol alone for VAS mood and calmness. Similarly, coadministration did not further decrease smooth pursuit or VAS alcohol intoxication compared to ethanol alone. However, coadministration led to a numerically greater impairment on SPV, body sway, VAS alertness, and adaptive tracking compared to daridorexant alone.

Figure 24. Effect of Ethanol on the PK of Daridorexant



Source: Clinical Study Report (ID-078-111), Fig 11-1, page 87
Abbreviations: PK, pharmacokinetic

Conclusions

No relevant changes in daridorexant PK parameters were observed following coadministration with ethanol, apart from a shift in t_{max} . Coadministration of daridorexant and ethanol led to

reinforced drug actions, which were at most indicative of an additive effect. No supra-additive effects of daridorexant and ethanol were found on any of the PD parameters. All treatments were generally well tolerated, considering the expected occurrence of CNS-related AEs following morning administration of daridorexant and/or ethanol.

14.2.7. Food Effect Study (ID-078-113)

In the food effect Study ID-078-113, subjects received a single oral dose of 50 mg daridorexant in the formulation used in the clinical phase 3 studies and intended to be commercially used (film-coated tablets). This was a single-center, open-label, randomized, two-way crossover, phase 1 study to investigate the effect of food (high-fat and high-calorie meal) on the PK of Daridorexant after administration of a single dose. This study included 20 healthy male subjects.

Results

The high-fat and high-calorie meal had a minimal effect on the PK of daridorexant with ~10% decrease in AUC and ~16% decrease in C_{max} . The results of this study were in line with a previous food effect study performed with daridorexant (AC-078-104, 25 mg, administered as a HGC), in which a similar decrease in C_{max} and prolongation in t_{max} , and no modification of $t_{1/2}$ and AUC was reported, indicating matching PK properties between the two formulations.

Table 117. Effect of Food on the PK of Daridorexant

Parameter [unit]	Effect of food on daridorexant PK*	
	AC-078-104 (N = 20, 25 mg HGC)	ID-078-113 (N = 19, 50 mg Tablet)
C_{max}	0.76 (0.69, 0.83)	0.84 (0.73, 0.98)
t_{max} [h]	1.88 (1.38, 2.39)	1.28 (0.50, 2.31)
AUC ₀₋₂₄	1.03 (0.99, 1.08)	0.91 (0.83, 1.00)
$t_{1/2}$	0.97 (0.89, 1.07)	0.88 (0.83, 0.94)

*Data are GMRs (Fed/Fasted; 90% CI) except for t_{max} , for which data are median differences (Fed-Fasted; 90% CI). AUC₀₋₂₄ = area under the plasma concentration-time curve from zero to 24 h; C_{max} = maximum plasma concentration; HGC = hard gelatin capsule; N = Number of subjects in the population; $t_{1/2}$ = terminal half-life; t_{max} = time to reach maximum plasma concentration. Source: D-17.098 and D-19.130.

Source: Summary of Clinical Pharmacology (2.7.2), Table 3-14, Page- 96
Abbreviations: PK, pharmacokinetic

Conclusions

Food had a minimal effect on the absorption and the overall exposure of daridorexant. Thus, daridorexant can be administered with or without food, but its sleep-promoting effect could be delayed when administered with or soon after a meal, specifically when a high-fat high-calorie meal is consumed.

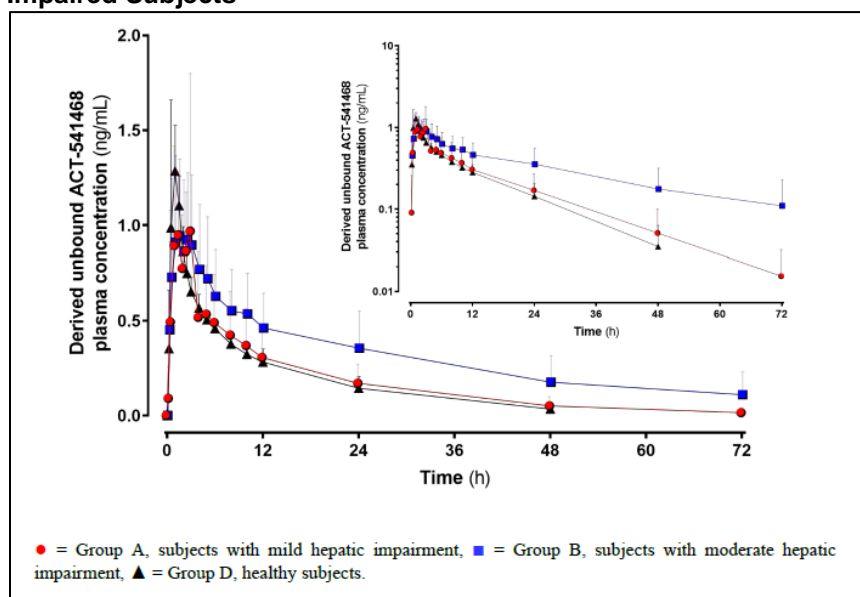
14.2.8. Daridorexant in Subjects With Hepatic Impairment (ID-078-112)

This was a single-center, open-label study to evaluate the PK, safety, and tolerability of single-dose daridorexant in subjects with mild and moderate hepatic impairment due to liver cirrhosis compared to healthy subjects. A total of 24 subjects in 3 groups (Group A: mild hepatic impairment; Group B: moderate hepatic impairment; Group D: healthy subjects) were treated with a single oral dose of daridorexant 25 mg in the morning. Healthy subjects were matched to subjects with moderate hepatic impairment based on sex, age (± 10 years), body weight and height ($\pm 15\%$) at screening.

Results

PK parameters of unbound daridorexant (i.e., C_{max} , $AUC_{0-\infty}$, and CL_u/F) in healthy subjects and subjects with mild hepatic impairment were unchanged following administration of 25 mg daridorexant. Unbound C_{max} in subjects with moderate hepatic impairment was similar to healthy subjects, while unbound $AUC_{0-\infty}$ increased by 1.6-fold and the $t_{1/2}$ increase by 2-fold.

Figure 25. Mean Concentration (Unbound) Versus Time Profile for Daridorexant in Hepatic Impaired Subjects



Source: Clinical Study Report (ID-078-112), Fig 11-2, page 86

Conclusions

A dose adjustment is not required in subjects with mild hepatic impairment. In subjects with moderate hepatic impairment, a maximum dose of 25 mg is recommended based on the anticipated higher extent of accumulation upon repeated-dose administration. Daridorexant is not recommended in subjects with severe hepatic impairment.

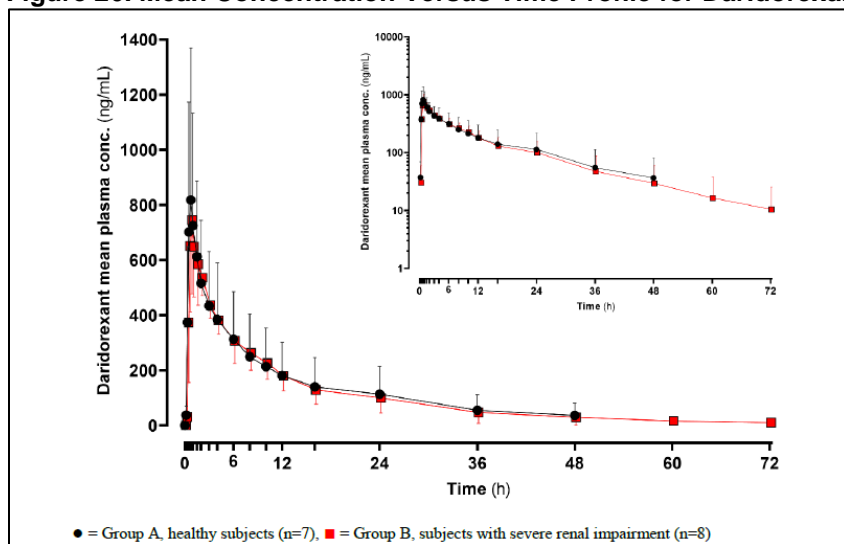
14.2.9. Daridorexant in Subjects With Severe Renal Impairment (ID-078-115)

This was a single-center, open-label study to evaluate the PK, safety, and tolerability of single-dose daridorexant in subjects with severe renal function impairment compared to healthy subjects. A total of 15 subjects in 2 groups (Group A: 7 healthy subjects; Group B: 8 subjects with severe renal function impairment) were treated with a single oral dose of daridorexant 25 mg in the morning. Healthy subjects were matched to renal impairment subjects based on sex, age (± 10 years), and body weight ($\pm 15\%$) at screening.

Results

Compared to healthy subjects, subjects with severe renal function impairment showed similar PK parameters as indicated by GMR (90% CI) for C_{max} and $t_{1/2}$ of 0.94 (0.60, 1.46) and 0.99 (0.66, 1.48), respectively, while median t_{max} was reached at 0.75 h in both groups. A slightly lower CL/F (by 13%) and V_z/F (by 15%) and an increase in $AUC_{0-\infty}$ by 1.16-fold was observed in subjects with severe renal function impairment compared to healthy subjects. Plasma protein binding was similar between the two groups, with mean C_u/C values ranging from 0.20 to 0.24% measured 1 and 3 h postdose. No SAEs, severe AEs, or AEs leading to study discontinuation were reported. No clinically relevant effects following administration of daridorexant were detected on physical examination, vital signs, body weight, clinical laboratory tests, 12-lead ECG, and narcolepsy questionnaires.

Figure 26. Mean Concentration Versus Time Profile for Daridorexant in Renal Impaired Subjects



Source: Clinical Study Report (ID-078-115), Fig 11-1, page 71

Conclusions

No dose adjustments are required in patients with any degree of renal function impairment, mild, moderate, or severe.

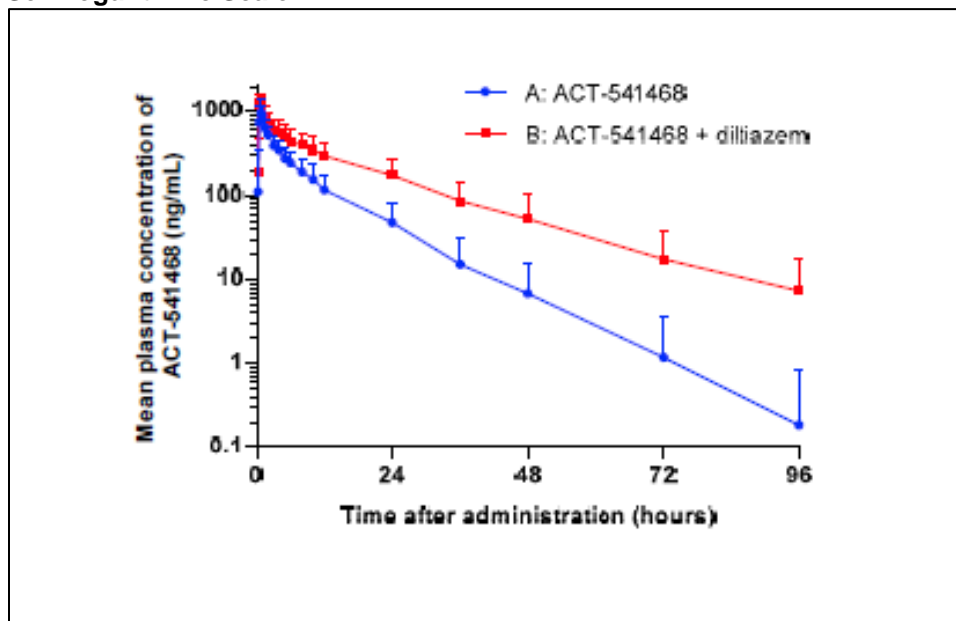
14.2.10. Effect of the Moderate CYP3A4 Inhibitor Diltiazem on the PK of Daridorexant (AC-078-103)

This was a single-center, open-label, randomized, 2-way crossover study to evaluate the effect of repeated-dose treatment with the moderate CYP3A4 inhibitor diltiazem on the PK of single-dose daridorexant in healthy male subjects. In addition, the safety and tolerability of daridorexant, of diltiazem, and when administered concomitantly were assessed. A total of 14 healthy male subjects were randomized in a 1:1 ratio to 1 of 2 possible treatment sequences (AB or BA) and received the following two treatments in two different periods, separated by a washout period of 10 to 14 days:

- **Treatment A:** Single oral dose of daridorexant 25 mg on Day 1.
- **Treatment B:** Repeated oral doses of diltiazem 240 mg o.d. for 7 days (from Day 1 to Day 7) with a single oral dose of daridorexant 25 mg concomitantly on Day 4 (i.e., at diltiazem steady state).

PK: When administered concomitantly with diltiazem, daridorexant C_{max} increased with a GMR (90% CI) of 1.41 (1.23, 1.61) compared to daridorexant administered alone. Absorption of daridorexant was slightly more rapid as indicated by the median difference (90% CI) t_{max} of -0.24 h (-0.38 to -0.11). Daridorexant exposure ($AUC_{0-\infty}$) and $t_{1/2}$ increased with a GMR (90% CI) of 2.35 (1.96, 2.83) and 1.76 (1.63, 1.91), respectively.

Figure 27. Arithmetic Mean (+SD) Plasma Concentration-Time Profile of Daridorexant After Administration of 25 mg Daridorexant Alone (A) and Concomitantly With Diltiazem (B) on Semilogarithmic Scale



Source: Clinical Study Report (ID-078-103), Fig 11-1, page 60

Safety: No SAEs or AEs leading to study treatment discontinuation were reported. The most frequently reported AEs were somnolence (13/14 subjects) and headache (7/14 subjects). No clinically relevant effects following the administration of study treatments were detected on

physical examination, vital signs, body weight, clinical laboratory tests, 12-lead ECG, and narcolepsy questionnaires.

Conclusions

These results reflect a moderate inhibition of daridorexant metabolism as defined by the FDA guidance, i.e., ≥ 2 -fold but < 5 -fold increase in AUC. A dose of 25 mg (i.e., half of the recommended 50-mg dose) of daridorexant is recommended when administered concomitantly with a moderate CYP3A4 inhibitor.

14.2.11. Effect of Moderate CYP3A4 Inducer Efavirenz or Gastric pH-Modifier Famotidine on the PK of Daridorexant (AC-078-120)

This was a single-center, open-label, randomized study including a crossover subpart to evaluate the effect of single-dose famotidine on the relative BA of single-dose daridorexant (tablet), and a 1-sequence crossover subpart to evaluate the influence of repeated doses of the moderate CYP3A4 inducer efavirenz on the PK of single-dose daridorexant in healthy male subjects. In addition, the safety and tolerability of daridorexant, famotidine, efavirenz, and when administered concomitantly (daridorexant plus efavirenz or daridorexant plus famotidine) were assessed.

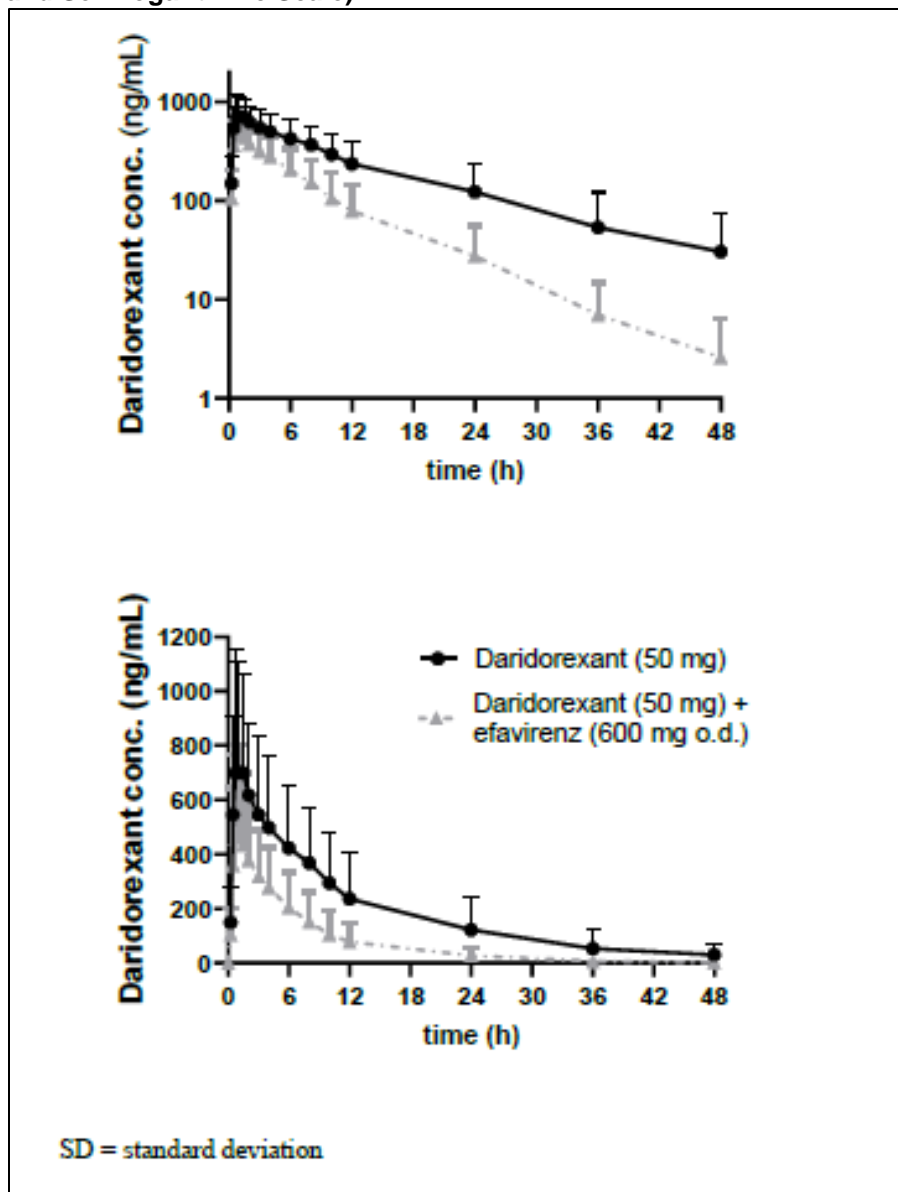
A total of 24 healthy male subjects were randomized in a 1:1 ratio to 1 of 2 possible treatment sequences (ABCD or BACD):

- **Treatment A:** Single oral dose of daridorexant 50 mg on Day 1 or 3.
- **Treatment B:** Single oral dose of famotidine 40 mg followed 3 h later by a single oral dose of daridorexant 50 mg on Day 1 or 3.
- **Treatment C:** Repeated oral doses of efavirenz 600 mg o.d. in the evening of Days 5 to 14.
- **Treatment D:** Single oral dose of daridorexant 50 mg in the morning of Day 15 followed by a single oral dose of 600 mg efavirenz in the evening of Days 15 and 16.

Results

When daridorexant was administered concomitantly with efavirenz at steady state, daridorexant C_{max} , AUC_{0-48} , and $t_{1/2}$ decreased with GMR (90% CI) of 0.65 (0.54 to 0.78), 0.41 (0.36 to 0.45), and 0.65 (0.58 to 0.72), respectively, compared to daridorexant alone. T_{max} remained unaffected by efavirenz as median difference (90% CI) was 0.00 h (-1.00 to 0.38).

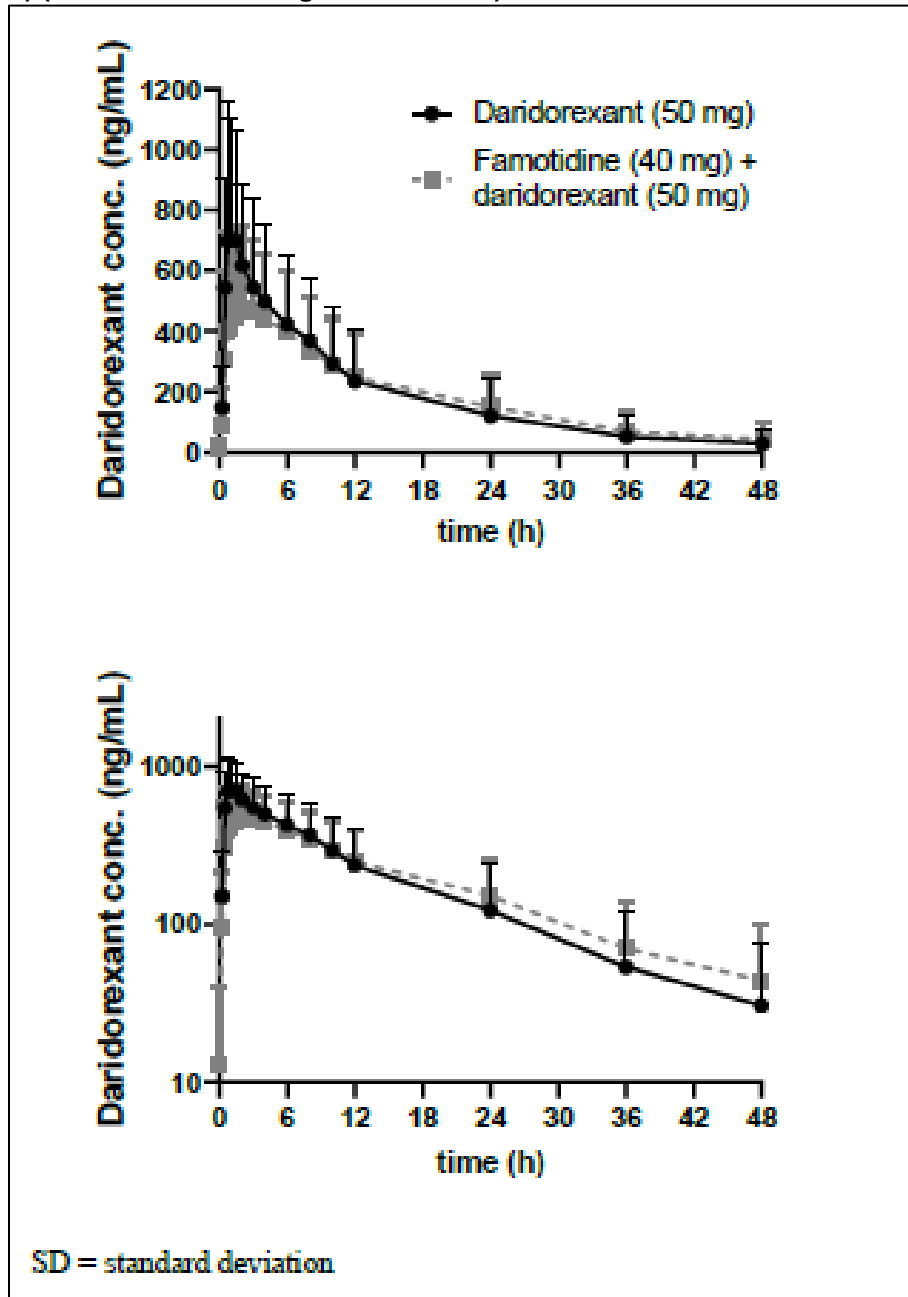
Figure 28. Mean Plasma Concentration ($\pm$ SD) Versus Time Profiles of Daridorexant After a Single Dose of 50 mg Alone (Treatment A) or With 600 mg Efavirenz at Steady State (Treatment D) (Linear and Semilogarithmic Scale)



Source: Clinical Study Report (ID-078-120), Fig 11-2, page 59

When daridorexant administration was preceded by the administration of a single dose of famotidine, daridorexant AUC_{0-48} remained unchanged, i.e., GMR (90% CI) was 0.99 (0.88 to 1.10). However, daridorexant's C_{max} decreased with a GMR (90% CI) of 0.61 (0.50 to 0.73) compared to daridorexant alone. In addition, absorption of daridorexant was delayed, indicated by a median difference (90% CI) for t_{max} of 0.50 h (-0.38 to 1.25), and $t_{1/2}$ was increased with a GMR (90% CI) of 1.27 (1.13 to 1.42).

Figure 29. Mean Plasma Concentration ($\pm$ SD) Versus Time Profiles of Daridorexant After a Single Dose of 50 mg Alone (Treatment A) or Preceded by a Single Dose of 40 mg Famotidine (Treatment B) (Linear and Semi-Logarithmic Scale)



Source: Clinical Study Report (ID-078-120), Fig 11-1, page 55

Conclusions

The results show that daridorexant can be administered concomitantly with medications increasing gastric pH without the need for dose adjustment. These results also confirm that daridorexant is a CYP3A4 substrate as AUC decreases upon administration of the moderate CYP3A4 inducer efavirenz is $\geq 50\%$ and $< 80\%$.

14.2.12. Effect of Daridorexant on the PK of the CYP3A4 Sensitive Index Substrate Midazolam (AC-078-104)

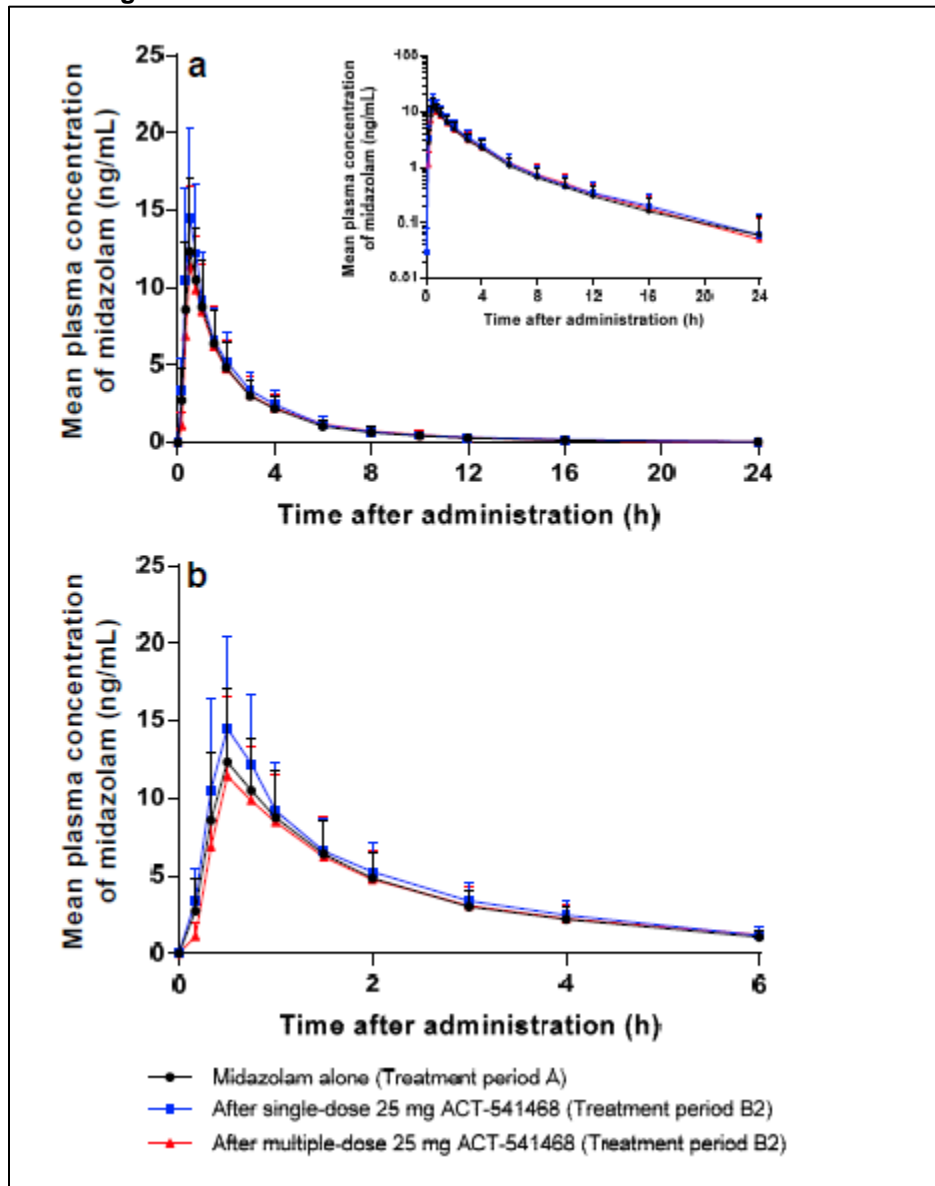
This was a single-center, open-label study to evaluate the effect of single-dose (CYP3A4 inhibition) and repeated-dose (CYP3A4 induction) daridorexant on the PK of single-dose midazolam and its metabolite 1-OH midazolam in healthy male subjects. A total of 20 healthy male subjects were included and received the treatments in the following fixed sequence:

- **Treatment A:** Single oral dose of midazolam 2 mg under fasted conditions on Day 1.
- **Treatment B:** Single oral dose of daridorexant 25 mg (Treatment B1) followed 1 h later by a single oral dose of midazolam 2 mg under fasted conditions on Day 2 (Treatment B2).

Results

When administered concomitantly with single-dose daridorexant, midazolam C_{max} , AUC_{0-24} , and $t_{1/2}$ were slightly higher when compared to midazolam alone with a GMR (90% CI) of 1.20 (1.07 to 1.34), 1.11 (1.03 to 1.19), and 1.05 (0.93 to 1.20), respectively. The median difference (90% CI) for t_{max} was 0.00 h (-0.13 to -0.00). Results were similar for 1-OH midazolam. When administered concomitantly with repeated-dose daridorexant, midazolam C_{max} , AUC_{0-24} , and $t_{1/2}$ were slightly lower when compared to midazolam alone with a GMR (90% CI) of 0.94 (0.83 to 1.05), 0.98 (0.91 to 1.05), and 0.88 (0.78 to 0.98), respectively. The median difference (90% CI) for t_{max} was 0.00 h (0.00 to 0.13). Results were similar for 1-OH midazolam

Figure 30. Arithmetic Mean (+SD) Plasma Concentration-Time Profile of Midazolam After Administration of Midazolam Alone (Treatment period A), 1h After Single Dosing of Daridorexant (Treatment Period B2), and After Multiple Dosing of Daridorexant (Treatment Period D2), on Linear & Semilogarithmic Scale.



Source: Clinical Study Report (ID-078-104), Fig 11-2, page 74

Conclusions

The 25 mg daridorexant dose did not inhibit nor induce CYP3A4 metabolism, indicating that CYP3A4 substrates can be administered concomitantly with daridorexant without dose adjustment.

14.2.13. Effect of Daridorexant on the PK of the BCRP Index Substrate Rosuvastatin (ID-078-106)

Study Objectives, Design, and Methodology

This was a single-center, open-label, 1-sequence, 2-treatment study to evaluate the effect of repeated-dose daridorexant at steady state on the PK of single-dose rosuvastatin in healthy male subjects. In addition, the safety, and tolerability of daridorexant and rosuvastatin (alone and in combination) were assessed.

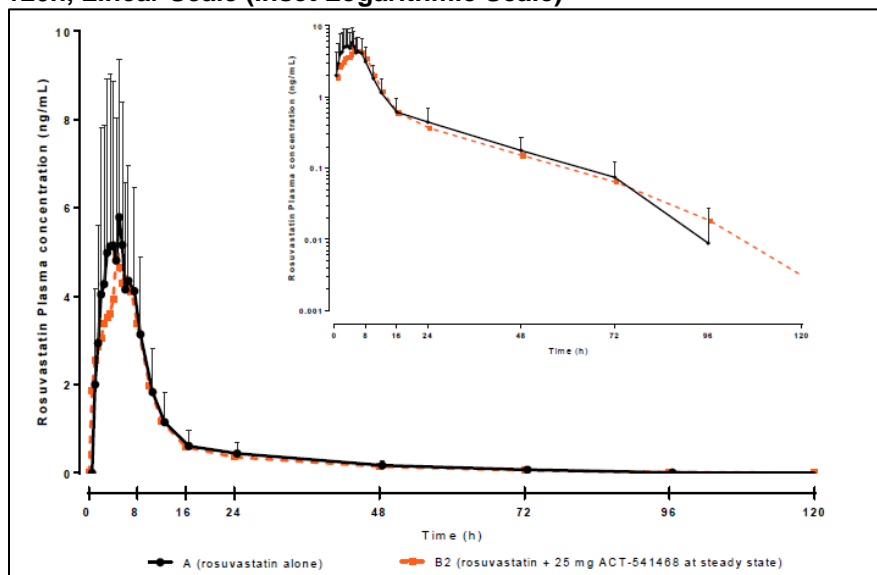
A total of 20 healthy male subjects were included and received the treatments in the following fixed sequence:

- **Treatment A:** Single oral dose of rosuvastatin 10 mg on Day 1.
- **Treatment B1:** Repeated oral doses of daridorexant 25 mg o.d. on Days 5 to 7.
- **Treatment B2:** Single oral dose of 10 mg rosuvastatin with oral dose of daridorexant 25 mg on Day 8. From Days 9 to 12, subjects received daridorexant 25 mg o.d.

Results

PK: When administered concomitantly with daridorexant at steady state, rosuvastatin C_{max} , AUC_{0-inf} , and $t_{1/2}$ remained essentially unchanged with a GMR (90% CI) of 0.93 (0.82 to 1.04), 0.93 (0.84 to 1.02), and 1.09 (0.92 to 1.29), respectively. Absorption of rosuvastatin was slightly delayed with a median difference (90% CI) for t_{max} of 0.75 h (0.25 to 1.50).

Figure 31. Arithmetic Mean ($\pm$ SD) Plasma Concentration-Time Profile After Administration of 10 mg Rosuvastatin Alone (A) and Concomitantly With 25 mg Daridorexant (B2) From Time 0 to 120h, Linear Scale (Inset Logarithmic Scale)



Source: Clinical Study Report (ID-078-106), Fig 11-1, page 61

Safety: No SAEs, severe AEs, or AEs leading to study treatment discontinuation were reported. Only three AEs were reported in 3/20 subjects: leukocytosis and headache after administration of

daridorexant alone, and insomnia after concomitant administration of rosuvastatin and daridorexant. No clinically relevant effects following the administration of study treatments were detected on physical examination, vital signs, body weight, clinical laboratory tests, 12-lead ECG, and narcolepsy questionnaires.

Conclusions

The results show that 25 mg daridorexant does not inhibit BCRP, indicating that BCRP substrates can be administered concomitantly with daridorexant without dose adjustment.

14.3. Bioanalytical Method Validation

Daridorexant was quantified in human plasma with a concentration range from 0.500 to 2000 ng/mL using a validated LC-MS/MS method, following protein precipitation. A further LC-MS/MS method was validated allowing for the simultaneous quantification of daridorexant and its metabolites M1, M3, and M10 in human plasma with a concentration range of 2.00 to 2000 ng/mL, following protein precipitation. The methods were successfully validated with respect to specificity/selectivity, precision and accuracy, postpreparative stability, short-term stability, long-term storage at $-20/-80^{\circ}\text{C}$, freeze-and-thaw stability, recovery, effect of sample dilution, matrix effect, re-injection reproducibility, maximum number of samples to be analyzed within a single batch, and stability of stock and working solutions at room temperature.

Table 118. Summary of Bioanalytical Method Performance

Bioanalytical method validation report name, amendments, and hyperlinks	BA-17.028 – Validation of an analytical method for the determination of ACT-541468 and its metabolites ACT-776063, ACT-776537 and ACT-1016-3307 in human plasma samples by LC-MS/MS No report amendments BA-17.028 Final Report
Method description	METH-077: Determination of ACT-541468 and its metabolites ACT-776063, ACT-776537 and ACT-1016-3307 in human plasma samples by LC-MS/MS
Materials used for standard calibration curve and concentration	Calibration curve prepared from working solutions prepared in acetonitrile/dimethyl sulfoxide (1:1, v/v), spiked in human plasma with a ratio of 1/50. Concentration of calibrators: 2.00, 5.00, 10.0, 25.0, 100, 500, 1600 and 2000 ng/mL
Validated assay range	2.00 to 2000 ng/mL
Material used for quality controls (QCs) and concentration	Quality controls prepared from working solutions prepared in acetonitrile/dimethyl sulfoxide (1:1, v/v), spiked in human plasma with a ratio of 1/50. Concentration of quality controls: QC _{LLOQ} : 2.00 ng/mL (used in validation study only), QC _L : 5.00 ng/mL, QC _M : 100 ng/mL, 1600 ng/mL and 10000 ng/mL (used to test effect of dilution)
Minimum required dilutions (MRDs)	Not applicable to this assay.
Sources and lot of reagents	Not applicable, no critical reagents.
Regression model and weighting	Quadratic weighted 1/x ²

Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8
	Cumulative accuracy (%bias) from LLOQ to ULOQ	ACT-541468: -4.9% to 2.3% ACT-776063: -3.4% to 4.8% ACT-776537: -3.1% to 1.7% ACT-1016-3307: -2.5% to 1.1%
	Cumulative precision (%CV) from LLOQ to ULOQ	ACT-541468: ≤ 5.3% ACT-776063: ≤ 7.6% ACT-776537: ≤ 4.8% ACT-1016-3307: ≤ 4.5%

Selectivity & matrix effect	6 lots tested. For matrix effect, bias: ACT-541468: QCL: 0.9%; QCH: -2.6% ACT-776063: QCL: 1.6%; QCH: 0.2% ACT-776537: QCL: 13.7%; QCH: 2.9% ACT-1016-3307: QCL: 1.8%; QCH: 1.8%
Interference & specificity	6 lots tested for specificity. Any peak present at the retention time of the analyte had an area < 20% of the average area of 6 QC_{LLOQ} samples. Any peak present at the retention time of the internal standard had an area < 5% of the average area of 6 QC_{LLOQ} samples <u>Midazolam Interference test (89.6 ng/mL)</u> ACT-776063: Bias: QCL: -7.6%; QC_M: -7.2%; QCH: -3.9% ACT-776537: Bias: QCL: -7.6%; QC_M: -2.3%; QCH: -10.2% ACT-1016-3307: Bias: QCL: 1.4%; QC_M: -8.0%; QCH: -8.8% No effect on quantification <u>Plasma arising from Japanese healthy subjects interference test (10 pooled subjects)</u> ACT-776063: Bias: QCL: -0.5%; QC_M: 4.2%; QCH: 4.4% ACT-776537: Bias: QCL: 1.0%; QC_M: 9.3%; QCH: 1.3% ACT-1016-3307: Bias: QCL: -1.1%; QC_M: 2.3%; QCH: -1.1% No effect on quantification <u>Plasma arising from subjects with mild and moderate hepatic impairment interference test (6 pooled subjects)</u> ACT-776063: Bias: QCL: 5.3%; QC_M: 1.2%; QCH: -4.4% mild Bias: QCL: 1.9%; QC_M: 4.3%; QCH: -2.5% moderate

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Hemolysis effect	ACT-541468: bias: QC _L : 2.2%; QC _H : -1.0% ACT-776063: bias: QC _L : -0.1%; QC _H : -1.4% ACT-776537: bias: QC _L : 15.0%; QC _H : 2.7% ACT-1016-3307: bias: QC _L : 5.7%; QC _H : 1.9%
Lipemic effect	ACT-541468: bias: QC _L : 6.2%; QC _H : 1.8% ACT-776063: bias: QC _L : 0.7%; QC _H : -0.8% ACT-776537: bias: QC _L : 11.9%; QC _H : 0.5% ACT-1016-3307: bias: QC _L : 6.9%; QC _H : 3.1%
Recovery (% mean)	ACT-541468: QCL: 107.8%, QCM: 104.6%, QCH: 108.1% ACT-776063: QCL: 108.0%, QCM: 101.5%, QCH: 108.9% ACT-776537: QCL: 104.5%, QCM: 101.5%, QCH: 103.9% ACT-1016-3307: QCL: 108.3%, QCM: 106.5%, QCH: 111.9%
Average recovery of drug (% mean)	ACT-541468: 106.8% ACT-776063: 106.1% ACT-776537: 103.3% ACT-1016-3307: 108.9%
Dilution linearity & hook effect	Tested concentration: 10000 ng/mL. Dilution factor: 10: ACT-541468: Bias: -9.3% ACT-776063: Bias: -5.9% ACT-776537: Bias: -5.2% ACT-1016-3307: Bias: -4.6%
Bench-top/process stability	Bench-top stability: 24 h at room temperature in human plasma Process stability: 67 h at 4 °C in sample extracts
Freeze-Thaw stability	5 cycles from nominally -20 °C and -80 °C for all analytes* * for ACT-541468, 8 cycles were also determined in study BA-16.032. Freeze-thaw stability considered for ACT-541468 at -80 °C: 8 cycles
Long-term storage	377 days at -20 °C and -80 °C for ACT-541468*, ACT-776063 and ACT-776537 378 days at -20 °C and -80 °C for ACT-1016-3307 * for ACT-541468, a stability of 381 days at -20 °C and -80 °C was also determined in validation study BA-15.004. Long term storage considered for ACT-541468: 381 days at -20 °C and -80 °C

Sources: Summary of Method Performance- METH 055 (Doc # D-21.119, pages 8-21. Summary of Method Performance- METH 077 (Doc # D-21.120, pages 6-16

Abbreviations: MRD, minimum required dilution; QC, quality control

14.4. Physiologically Based Pharmacokinetic (PBPK) Analysis Review

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's PBPK report, entitled "Daridorexant (Daridorexant): PBPK modeling to predict pharmacokinetic drug-drug interactions" to support the intended uses.

The Division of Pharmacometrics has reviewed the PBPK report and supporting modeling files and concluded the following.

- The daridorexant model is adequate to predict the daridorexant PK profiles following a single intravenous administration of 2 µg, which was given simultaneously with an oral dose of 100 mg, a single oral dose administration (5, 25 and 50 mg), or multiple oral dose administration (10 mg QD, 25 mg QD, and 75 mg QD) of daridorexant in healthy subjects.
- The daridorexant model is adequate to predict the effect of cimetidine or ranitidine on daridorexant PK following a single or multiple oral dose administration of daridorexant (25 mg or 50 mg) and multiple dose administration of cimetidine (400 mg BID) or ranitidine (150 mg BID) in healthy subjects. Model predicted daridorexant geometric mean AUC ratios were approximately 1.15 and 1.50 when coadministered with cimetidine or ranitidine in healthy subjects, respectively.
- The daridorexant model is adequate to predict the effect of verapamil, erythromycin, or fluconazole on daridorexant PK following a single or multiple oral dose administration of daridorexant (25 mg or 50 mg) and multiple dose administration of verapamil (80 mg three times a day), erythromycin (500 mg four times a day), or fluconazole (200 mg QD) in healthy subjects. Model predicted daridorexant geometric mean AUC ratios were approximately 2.90, 3.60 and 3.00 when coadministered with verapamil, erythromycin, or fluconazole in healthy subjects, respectively.
- The daridorexant model can be used to support the evaluation of the effect of strong CYP3A inhibitors (itraconazole 200 mg QD and ketoconazole 200 mg BID) on the PK of daridorexant. Based on the clinically observed inhibitory effect of diltiazem (a moderate CYP3A inhibitor) on daridorexant PK and the evaluation of DDI potential of daridorexant with strong CYP3A inhibitors using PBPK models, the strong CYP3A inhibitors are expected to result in daridorexant AUC ratios of greater than 5.
- The daridorexant model can be used to support the evaluation of the effect of strong CYP3A inducers (carbamazepine 400 mg BID and rifampicin 600 mg QD) on the PK of daridorexant. Based on the clinically observed induction effect of efavirenz (a moderate CYP3A inducer) on daridorexant PK and the evaluation of DDI potential of daridorexant with strong CYP3A inducers using PBPK models, the strong inducers are expected to result in daridorexant AUC ratios of less than 0.5.

Applicant's PBPK Modeling Effort

PBPK Software

Simcyp V17 (Simcyp Ltd, UK) was used to develop the daridorexant PBPK models and predict the PK of daridorexant with and without CYP3A modulators.

Model Development

Daridorexant

The absorption of daridorexant was modelled using the Advanced, Dissolution, Absorption, and Metabolism (ADAM) model in Simcyp. A solid immediate release formulation (b) (4) model were selected. The effective permeability in human jejunum (P_{eff}) (5.29×10^{-4} cm/s) was predicted based on the measured apparent permeability (P_{app}) values in MDCK-II wild-type cells and then translated into regional P_{eff} values using Mech P_{eff} predictor (mechanistic regional permeability predictor). The mass balance study indicated almost complete absorption of daridorexant from the gut, as evidenced by less than 1% of the oral dose excreted in feces as unchanged drug (D-15.653).

The controlled supersaturation experiments in fasted state simulated intestinal fluid (FaSSIF) indicated that daridorexant precipitated (b) (4) from supersaturated condition (ELB0238-2687). The solubility of (b) (4) daridorexant was assigned in the model as the intrinsic solubility of daridorexant. The critical supersaturation ratio was estimated from in vitro study and used as initial estimates for parameter estimation of the supersaturation ratio and precipitation rate constant from clinical data. The diffusion layer model scalar was estimated by simultaneous fitting of dissolution rate data of a 5 mg capsule in simulated gastric fluid, FaSSIF, and fed state simulated intestinal fluid (FeSSIF). The particle size distribution of the active pharmaceutical ingredient was entered as a log normal distribution. The biorelevant solubility was considered by estimating bile micellar distribution coefficients from FaSSIF, FeSSIF and aqueous solubilities in buffers in SIVA 3.0. After oral administration, daridorexant was quickly absorbed with a median T_{max} of 0.7 to 2 h for the 5, 25, and 50-mg doses, and 2.5 and 2.8 h for the 100 and 200-mg doses, respectively. The apparent terminal half-life was between 5.9 and 6.5 h for the 5, 25 and 50-mg doses and 7.5 h and 8.8 h for the 100 and 200-mg doses, respectively. The absolute bioavailability was 62%.

The full PBPK distribution model was used to describe the distribution of daridorexant. Daridorexant was highly bound to plasma proteins with fraction unbound in plasma of 0.003. The volume of distribution at steady state (0.41 L/kg) was estimated using the Method 3 in Simcyp and adjusted based on the clinical PK data (D-15.653) by applying a K_p scalar of 0.53. Perfusion-limited distribution was assumed for all organs.

Mass balance study indicated that the percentage of unchanged drug excreted in feces was less than 1% of the administered dose and in urine, no unchanged daridorexant was found. Therefore, daridorexant elimination was assumed to be governed by metabolic elimination only. In vitro study results suggested that the fraction of daridorexant metabolized by CYP3A4 was 89% of the metabolic intrinsic clearance, while the remaining 11% was ascribed to CYP2C19. The minor contribution of CYP2D6, CYP2C9, CYP2C8 and CYP1A2 was not considered in the model. The systemic clearance of daridorexant was 5 L/h, which was derived from an intravenous study (D-

15.653). The CYP3A4 (3.10 $\mu\text{L}/\text{min}/\text{pmol}$) and CYP2C19 (3.75 $\mu\text{L}/\text{min}/\text{pmol}$) intrinsic clearance were back-calculated using the total metabolic clearance (5 L/h). In human plasma, 3 major metabolites accounted for 28.9%, 12.7% and 9.0% of total radioactivity, respectively. Nonclinical study showed that the 3 major metabolites are not expected to contribute to the pharmacological effect of daridorexant.

In vitro obtained K_i value of daridorexant on CYP3A4 competitive inhibition (4.6 μM) and k_{inact} of 0.036 h^{-1} and K_{app} of 44 μM for time-dependent CYP3A4 inhibition were used in the model. Daridorexant mediated CYP3A4 induction was characterized using the in vitro obtained EC_{50} (0.31 μM) and E_{max} (14.3-fold) values, which were calibrated based on the EC_{50} and E_{max} values of rifampicin (positive control).

Victim Drug Models

The default PBPK models of diltiazem, midazolam, erythromycin, fluconazole, verapamil, itraconazole, ketoconazole, carbamazepine, rifampicin, efavirenz, cimetidine, and ranitidine in Simcyp were used for DDI prediction.

FDA's Assessment

- (1) This is a PBPK analysis where daridorexant PBPK model was verified using clinical DDI study results with a moderate CYP3A4 inhibitor and a moderate CYP3A4 inducer, and the model was used to evaluate the DDI potential of daridorexant with weak, moderate, or strong CYP3A4 inhibitors and strong CYP3A4 inducers. Daridorexant is a substrate of CYP3A4 and CYP2C19. The estimated fractions metabolized by CYP3A4 and CYP2C19 were 0.89 and 0.11, respectively, based on in vitro phenotyping studies, chemical inhibition study (Study B-15.073) and clinical DDI studies with a moderate CYP3A4 inhibitor (diltiazem, Study AC-078-103) and a moderate CYP3A4 inducer (efavirenz, Study ID-078-120). The f_m values obtained from DDI studies with a moderate inhibitor and inducer may result in uncertainties regarding the predicted exposure change with strong modulators, especially for drugs having a high f_m value (July 2021). In PBPK modeling practice, clinical data with strong modulators are usually used to anchor the PBPK model performance by accurately estimating fraction metabolized by a particular enzyme. In this case, the PBPK model validated using clinical data with moderate CYP3A4 modulators cannot be used to accurately predict the DDI extent with strong modulators, however, the model can be used to support the evaluation of the effect of strong CYP3A4 modulators on the PK of daridorexant.
- (2) The in vitro obtained kinetic parameter values for CYP3A4 inhibition (competitive inhibition and time-dependent inhibition) and induction by daridorexant were used in the model. Generally, there is an uncertainty with respect to the extrapolation of kinetic parameter values obtained from an in vitro system to in vivo, especially for kinetic parameters for drug-mediated enzyme induction effect. However, due to about 40 to 80-fold lower protein binding in vivo ($f_{u,p}=0.003$) as compared to those in in vitro systems ($f_{u,mic}=0.12$ and $f_{u,cell}=0.24$), along with the model validation with daridorexant PK data following a single and multiple dose administration (5, 25, and 50 mg) and DDI study results with midazolam (a sensitive CYP3A4 substrate), the Applicant's model

appears adequate to predict the daridorexant PK at doses lower than 50 mg and extrapolate the effect of a stronger modulator to a weaker modulator.

PBPK Model Application

The developed PBPK model was used to simulate the DDI for daridorexant in the following scenarios.

- To predict the effect of cimetidine and ranitidine (weak CYP3A inhibitors), and verapamil, erythromycin, and fluconazole (moderate CYP3A inhibitors) on the PK of daridorexant following oral administration in healthy subjects.
- To predict the effect of itraconazole and ketoconazole (strong CYP3A inhibitors) on the PK of daridorexant following oral administration in healthy subjects.
- To predict the effect of carbamazepine and rifampicin (strong CYP3A inducers) on the PK of daridorexant following oral administration in healthy subjects.

Results

(1) Can daridorexant PBPK model describe daridorexant PK in healthy subjects?

Yes. The daridorexant model was able to capture the observed daridorexant PK profiles following a single intravenous administration of 2 µg, which was given simultaneously with an oral dose of 100 mg, a single oral dose administration (5, 25 and 50 mg), or multiple oral dose administration (10 mg QD, 25 mg QD, and 75 mg QD) in healthy subjects. However, the plasma concentration of daridorexant appeared to be underpredicted at higher doses of 100 mg and 200 mg ([Figure 32](#) and [Table 119](#)).

(2) Can daridorexant PBPK model predict the effect of cimetidine and ranitidine (weak CYP3A inhibitors), and verapamil, erythromycin, and fluconazole (moderate CYP3A inhibitors) on the PK of daridorexant?

Yes. The daridorexant model validated using clinical data with diltiazem (a moderate CYP3A inhibitor) and efavirenz (a moderate CYP3A inducer) was adequate to predict the effect of moderate CYP3A inhibitors (verapamil, erythromycin, and fluconazole) and weak CYP3A inhibitors (cimetidine and ranitidine) on the PK of daridorexant following a single dose administration of daridorexant and multiple dose administration of modulators in healthy subjects ([Table 120](#)).

In addition, the reviewer's analyses suggested no significant difference in the effect of aforementioned moderate or weak inhibitors on the PK of daridorexant following a single dose or multiple dose administration of daridorexant.

(3) Can daridorexant PBPK model provide supportive information on the evaluation of the effect of itraconazole and ketoconazole (strong CYP3A inhibitors) on the PK of daridorexant following oral administration in healthy subjects?

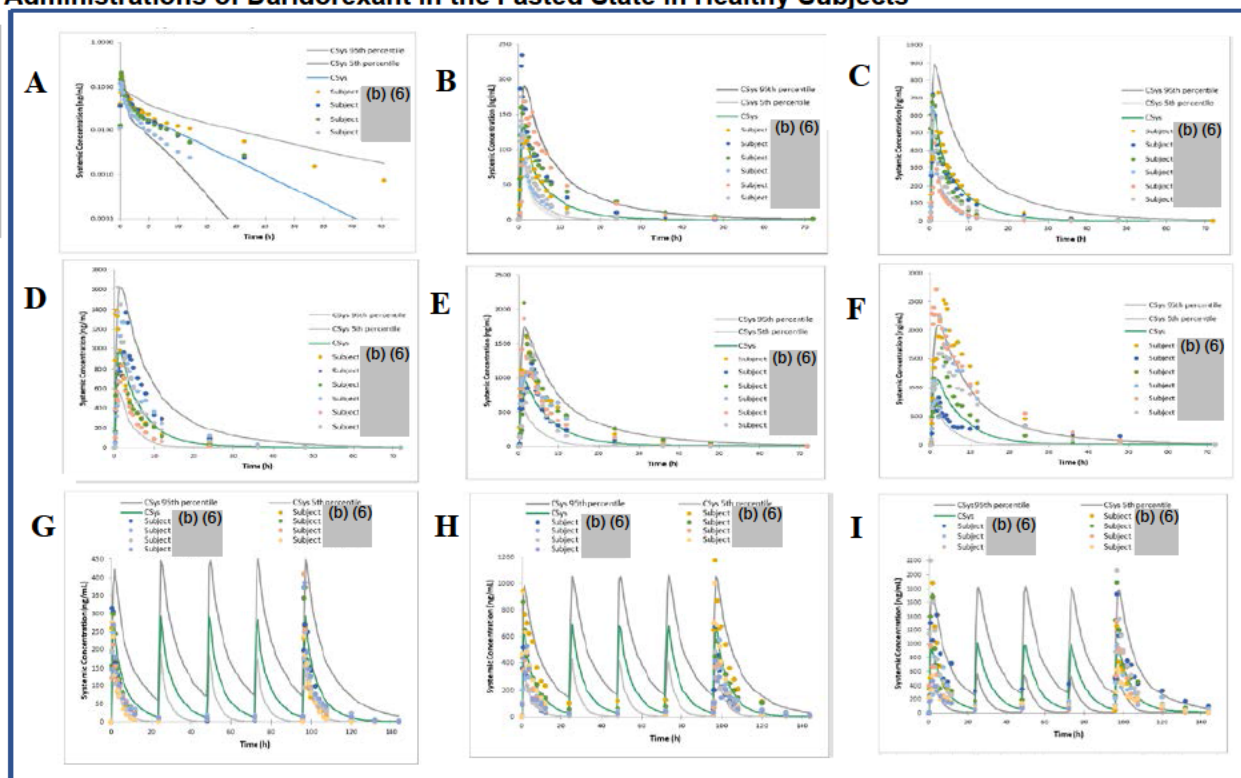
Yes. Due to the uncertainties when extrapolating the study results from a less sensitive study to a more sensitive study, the daridorexant model validated using clinical data with a moderate CYP3A inhibitor can be used to support the evaluation of the effect of strong CYP3A inhibitors (itraconazole and ketoconazole) on the PK of daridorexant. Refer to "FDA's assessment" for the

details. Based on the clinically observed inhibitory effect of diltiazem on daridorexant PK, its high fraction metabolized by CYP3A4 of 89% and the DDI potential estimation with strong CYP3A inhibitors by using the current PBPK model (Table 120), the strong inhibitors are expected to result in daridorexant AUC ratios of greater than 5.

(4) Can daridorexant PBPK model provide supportive information on the evaluation of the effect of carbamazepine and rifampicin (strong CYP3A inducers) on the PK of daridorexant following oral administration in healthy subjects?

Yes. Due to the uncertainties when extrapolating the study results from a less sensitive study to a more sensitive study, the daridorexant model validated using clinical data with a moderate CYP3A inducer can be used to support the evaluation of the effect of strong CYP3A inducers (carbamazepine and rifampicin) on the PK of daridorexant. Refer to “FDA’s assessment” for the details. Based on the clinically observed induction effect of efavirenz on daridorexant PK, its high fraction metabolized by CYP3A4 of 89% and the DDI potential estimation with strong inducers by using the current PBPK model (Table 120), the strong inducers are expected to result in daridorexant AUC ratios of less than 0.5.

Figure 32. Observed (Dots) and Simulated (Lines) Daridorexant Concentration-Time Profiles Following a Single Intravenous Dosing (2 mg, A)¹, a Single Oral (5 mg, B; 25 mg, C; 50 mg, D; 100 mg, E and 200 mg, F) or Multiple Oral (10 mg QD, G; 25 mg QD, H, 75 mg QD, I) Dose Administrations of Daridorexant in the Fasted State in Healthy Subjects²



Source: Simulated data were from the Applicant’s PBPK report (B-20.042). Observed data were from Study AC-078-101(A, B, C, D, E, and F) and AC-078-102 (G, H, and I).

¹ Given simultaneously with an oral dose of 100 mg daridorexant

² Green line represents the simulated median PK profiles of daridorexant. The upper and lower lines represent the 95th and the 5th percentile, respectively. The dots are individual observed plasma concentrations.

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Table 119. Observed and Simulated Daridorexant Geometric Mean C_{max} and AUC and C_{max} and AUC Ratios Following a Single (IV or Oral) or Multiple Oral Dose Administration of Daridorexant.

Dose, Route	AUC (ng*h/mL)	C _{max} (ng/mL)	Study #
	Observed/Predicted/ R _{Pred/Obs}	Observed/Predicted/ R _{Pred/Obs}	
2 mg, IV, SD ¹	0.31/0.33/1.06	0.15/0.14/0.93	
5 mg, oral, SD, fasted	971/873/0.90	160/138/0.86	
25 mg, oral, SD, fasted	2703/4300/1.59	632/640/1.01	AC-078-
50 mg, oral, SD, fasted	7417/7329/0.99	1231/1011/0.82	101
100 mg, oral, SD, fasted	12338/9076/0.74	1557/1065/0.68	
200 mg, oral, SD, fasted	22906/12171/0.53	1869/1204/0.64	
25 mg, oral, SD, fasted	4252/4146/0.98	716/667/0.93	
25 mg, oral, SD, fed	4388/4780/1.09	542/598/1.10	AC-078-
50 mg, oral, SD, fed	6858/8004/1.16	800/1088/1.36	104
10 mg, Oral, QD, fasted, day 1	1156/1864/1.61	256/286/1.12	
10 mg, Oral, QD, fasted, day 5	1293/1986/1.54	280/301/1.08	
25 mg, Oral, QD, fasted, day 1	3502/4565/1.30	614/679/1.11	AC-078-
25 mg, Oral, QD, fasted, day 5	3805/4725/1.24	616/708/1.15	102
75 mg, Oral, QD, fasted, day 1	8583/7647/0.89	1225/997/0.81	
75 mg, Oral, QD, fasted, day 5	8940/7868/0.88	1308/1046/0.80	

Source: Simulated data were from the Applicant's PBPK report (B-20.042). Observed data were from Study AC-078-101, AC-078-104 and AC-078-102.

¹ Given simultaneously with an oral dose of 100 mg daridorexant

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; IV, intravenous; QD, once daily; SD, single dose

Table 120. Predicted and Observed Effects of CYP3A4 Index Inhibitors and Inducers on the Pharmacokinetics of 25 and 50 mg Daridorexant.

DDI perpetrator	Daridorexant (mg)		GMR (90% CI of the ratio)	
			AUC _{0-t} (ng·h/mL)	C _{max} (ng/mL)
CYP3A4 inhibition				
cimetidine (weak)	25	predicted	1.15 (1.15-1.15)	1.09 (1.09-1.09)
	50	predicted	1.14 (1.14-1.14)	1.09 (1.09-1.09)
ranitidine (weak)	25	predicted	1.49 (1.47-1.50)	1.08 (1.08-1.08)
	50	predicted	1.49 (1.47-1.50)	1.09 (1.09-1.09)
diltiazem (moderate)	25	observed	2.33 (1.94-2.81)	1.41 (1.23-1.61)
	25	predicted	2.43 (2.39-2.46)	1.22 (1.21-1.22)
	50	predicted	2.41 (2.37-2.44)	1.24 (1.23-1.24)
verapamil (moderate)	25	predicted	2.93 (2.88-2.99)	1.27 (1.26-1.27)
	50	predicted	2.89 (2.83-2.94)	1.29 (1.28-1.29)
erythromycin (moderate)	25	predicted	3.63 (3.55-3.70)	1.32 (1.31-1.33)
	50	predicted	3.56 (3.49-3.64)	1.35 (1.34-1.35)
fluconazole (moderate)	25	predicted	3.08 (3.06-3.11)	1.31 (1.31-1.32)
	50	predicted	3.05 (3.03-3.08)	1.34 (1.33-1.34)
itraconazole (strong)	25	predicted	5.90 (5.78-6.01)	1.43 (1.42-1.44)
	50	predicted	5.82 (5.71-5.94)	1.47 (1.46-1.48)
ketoconazole (strong)	25	predicted	5.50 (5.39-5.61)	1.42 (1.41-1.43)
	50	predicted	5.46 (5.35-5.57)	1.46 (1.45-1.48)
CYP3A4 induction				
efavirenz (moderate)	50	observed	0.41 (0.36-0.46)	0.65 (0.54-0.78)
	25	predicted	0.35 (0.35-0.36)	0.64 (0.64-0.65)
	50	predicted	0.36 (0.35-0.36)	0.64 (0.63-0.64)
carbamazepine (strong)	25	predicted	0.55 (0.55-0.55)	0.77 (0.76-0.77)
	50	predicted	0.55 (0.55-0.56)	0.76 (0.76-0.77)
rifampin (strong)	25	predicted	0.26 (0.26-0.27)	0.55 (0.55-0.56)
	50	predicted	0.26 (0.26-0.26)	0.55 (0.54-0.55)

Source: Summary of Clinical Pharmacology (D-20.204) and PBPK report (B-20.042)
 Perpetrator dosing information: cimetidine 400 mg BID; ranitidine 150 mg BID; diltiazem: 240 mg QD; verapamil 80 mg TID; erythromycin 500 mg QID; fluconazole 200 mg QD; itraconazole 200 mg QD; ketoconazole 200 mg BID; efavirenz 600 mg QD; carbamazepine 400 mg BID; rifampin 600 mg QD
 Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum plasma concentration

14.5. Population PK Review

The Applicant developed a population PK model to describe the pharmacokinetics of daridorexant, characterize the relationship between daridorexant PK with demographics and other covariates, and conduct PK simulations to inform the clinical relevance of covariates. The PK dataset includes healthy volunteers and subjects with insomnia disorder.

Summary of PK Data

In total, 1898 subjects provided 12,627 concentration measurements available for analysis. There data came from 17 clinical studies (13 phase 1, 2 phase 2, and 2 phase 3 studies):

- Phase 1: AC-078-101, -102, -104, -105;
- Phase 1: ID-078-106, -107, -108, -111, -112, -113, -114, -115, -117;
- Phase 2: AC-078A201, AC-078A202;
- Phase 3: ID-078A301, ID-078A302

Study details be found in [Table 3](#) in Section [3.2](#).

Population PK Model

Applicant's modeling approach utilized the rich PK data from phase 1 studies to generate the structural model and covariate selection (univariate forward inclusion, backward elimination). Next, the phase 1 data were pooled with phase 2 and phase 3 data for (re)estimation of model parameters. Applicant indicates that parameters for which phase 2 and phase 3 (sparse) data did not provide additional information (i.e., absorption parameters, intercompartmental drug transfer, related between subject variability and related covariate effects) were kept fixed according to the estimates from phase 1 data. Otherwise, the Applicant then assessed covariates once more on the pooled PK dataset of phase 1, phase 2, and phase 3 studies.

The final structural model utilized two compartments, first-order absorption, absorption lag, and nonlinear (Michaelis–Menten) elimination. The model is parameterized in terms of oral absorption rate constant (k_a), absorption lag (t_{lag}), volume of distribution of the central compartment (V_c), volume of distribution of the peripheral compartment (V_p), intercompartmental clearance (Q), maximum rate of elimination (V_m), concentration at which the rate of elimination is half the maximum rate (K_m), and oral bioavailability (F).

Allometric scaling: V_c and K_m scale with lean body weight normalized to 55 kg. V_p and Q scale with fat mass normalized to 20 kg. K_m scales with age normalized to 30 years. The normalization value originals from the typical covariate values in the phase 1 studies. In all allometry cases, a power model was utilized, and the coefficient was estimated.

Inter-individual variability: exponential

Inter-occasion variability: F , k_a , t_{lag}

Residual variability: Multiplicative (a.k.a. proportional) and additive

Covariates: Dose is a covariate on F . Food status is a covariate on t_{lag} and k_a . Time of day (morning versus evening) is a covariate on k_a . Lean body weight is a covariate on V_c and K_m . Fat mass is a covariate on V_p and Q . Age and alkaline phosphatase (ALP) are covariates on K_m .

The parameter estimates for the final model are shown in the tables below. Model 831 is the final model. Earlier models (lower model numbers) reflect the model development steps.

Table 121. Structural Parameter and Covariate Estimates for Selected Models (Model 831 is Final)

Parameter	Model (b) (4)	Model (b) (4)	Model (b) (4)	Model (b) (4)	Model (b) (4)	Model (b) (4)	Model (b) (4)	Model (b) (4)	Model (b) (4)	Model 831
										Est. RSE(%)
F										0.41
Dose										-0.47
t _{lag} (h)										0.41
Food: fasted										-0.51
Food: fed										0.62
k _a (1/h)										1.05
Food: fasted										0.09
Food: fed										-1.19
Morning admin.										1.05
V _c (L)										14.60
Lean body wt.										0.49 13.86
V _p (L)										13.70
Fat mass										0.47 13.83
Q (L/h)										3.58
Fat mass										1.47 6.48
V _m (mg/h)										6.94
K _m (ng/mL)										2.36
Age										0.30 6.87
ALP										0.34 10.54
Lean body weight										-0.20 25.95
CL (L/h)										

If no RSE value is reported, the population parameter was fixed rather than estimated.

ALP = alkaline phosphatase; CL = drug clearance; Est. = Parameter estimate; F = Bioavailability fraction; k_a = absorption rate constant; K_m = concentration at which the rate of elimination is half the maximum rate; PK = pharmacokinetic(s); Q = intercompartmental transfer rate; RSE = relative standard error; t_{lag} = Time lag between drug intake and start of absorption; V_c = volume of distribution of the central compartment; V_m = maximum rate of elimination; V_p = volume distribution of the peripheral compartment.

Source: sequence 0001, module 5353, poppk.pdf, page 41 of 400

Table 122. Variability Parameter Estimates for Selected Models (Model 831 is Final)

Parameter	Model (b) (4)	Model (b) (4)	Model (b) (4)	Model (b) (4)	Model (b) (4)	Model (b) (4)	Model (b) (4)	Model (b) (4)	Model (b) (4)	Model 831
										Est. RSE(%)
SD(F)										0.42
SD(t _{lag})										0.26
SD(k _a)										0.59
SD(V _c)										0.17
SD(V _p)										0.23
SD(Q)										0.50
SD(V _m)										0.09
SD(K _m)										0.36
SD(CL)										
IOV(F)										0.20
IOV(t _{lag})										0.42
IOV(k _a)										0.66
Additive error										17.59 1.97
Multiplicative error										0.16 1.34

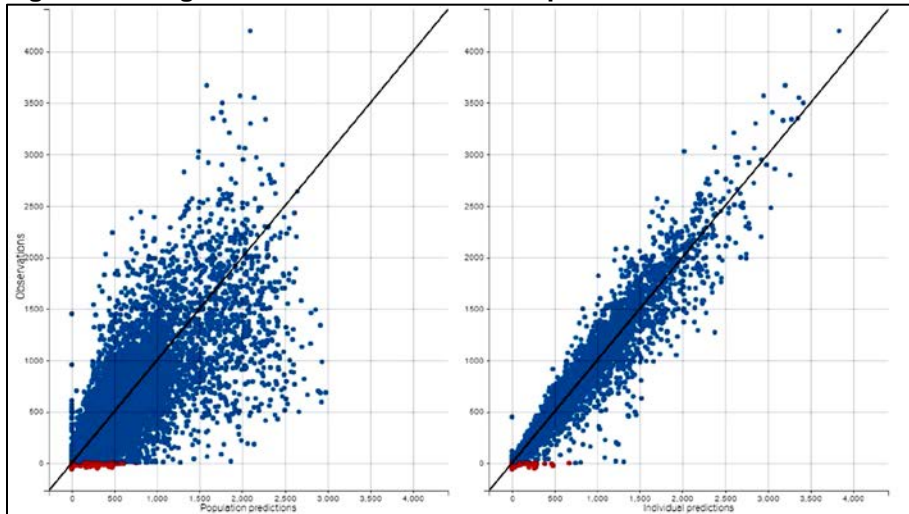
If no RSE value is reported, the population parameter was fixed rather than estimated.

CL = drug clearance; Est. = Estimate; F = Bioavailability fraction; IOV = inter-occasion variability; k_a = absorption rate constant; K_m = concentration at which the rate of elimination is half the maximum rate; PK = pharmacokinetic(s); Q = intercompartmental transfer rate; RSE = relative standard error; SD = standard deviation; t_{lag} = Time lag between drug intake and start of absorption; V_c = volume of distribution of the central compartment; V_p = volume distribution of the peripheral compartment; V_m = maximum rate of elimination.

Source: sequence 0001, module 5353, poppk.pdf, page 42 of 400

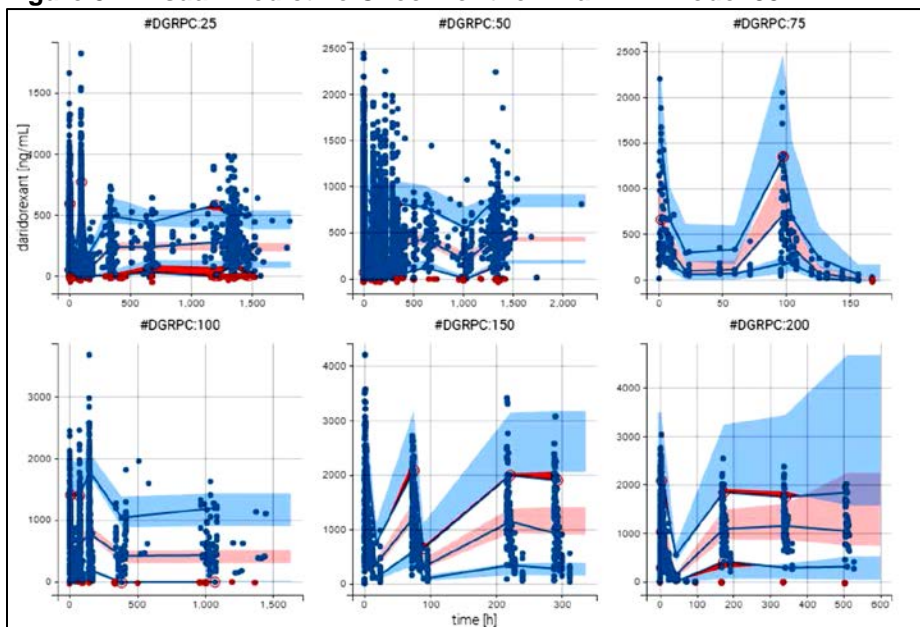
The model diagnostics are presented in [Figure 33](#) and [Figure 34](#).

Figure 33. Diagnostic Plots for the Final Population PK Model 831



Source: sequence 0001, module 5353, poppk.pdf, page 43 of 400
Blue: data points, Red: censored data points, Line: line of identity. Units: ng/mL

Figure 34. Visual Predictive Check for the Final PPK Model 831



Source: sequence 0001, module 5353, poppk.pdf, page 45 of 400
Dose groups (mg) are indicated in the titles of the panels. Blue dots, observations; red dots, censored observations; blue lines, empirical 10th, 50th, and 90th percentiles; blue and pink areas, 90% range of simulated 10th, 50th, and 90th percentiles; red areas, empirical percentiles outside simulated percentile range

The Applicant conducted PK simulations to assess the effect of varying covariates on PK. Due to the half-life of ~8 hours, the Day 3 scenario represents steady-state simulated PK (see [Table 123](#)).

Table 123. PK Simulations of Covariate Effects on Day 1 and Day 3

Covariate	Exposure metric	Day 1									Day 3				
		Covariate values			Absolute exposure			Relative exposure change (%)			Absolute exposure			Relative exposure change (%)	
		Low (5%)	Reference	High (95%)	Low	Reference	High	Low	High	Low	Reference	High	Low	High	
Age	AUC _{0-24h}	23	60	74	6665.34	7930.70	8216.12	-15.95	3.60	7736.68	9981.47	10550.7	-22.49	5.70	
Age	C _{max}	23	60	74	790.44	817.00	822.43	-3.25	0.67	869.93	954.68	976.02	-8.88	2.24	
Age	C _{8h}	23	60	74	317.44	381.10	394.70	-16.71	3.56	372.93	483.95	510.91	-22.94	5.57	
Age	t _{max}	23	60	74	2.03	2.10	2.12	-3.33	0.95	2.02	2.09	2.1	-3.35	0.48	
Fat mass	AUC _{0-24h}	39.1	20	13.1	7339.46	7930.70	8266.69	-7.45	4.24	9758.76	9981.47	10115.4	-2.23	1.34	
Fat mass	C _{max}	39.1	20	13.1	646.72	817.00	898.10	-20.84	9.93	806.63	954.68	1020.49	-15.51	6.89	
Fat mass	C _{8h}	39.1	20	13.1	364.75	381.10	408.98	-4.30	7.31	483.3	483.95	503.46	-0.14	4.03	
Fat mass	t _{max}	39.1	20	13.1	1.81	2.10	2.29	-13.81	9.05	1.79	2.09	2.27	-14.35	8.61	
Lean body weight	AUC _{0-24h}	69.1	55	36.2	7535.79	7930.70	8678.55	-4.98	9.43	9522.3	9981.47	10873.4	-4.60	8.94	
Lean body weight	C _{max}	69.1	55	36.2	752.13	817.00	946.72	-7.94	15.88	884.63	954.68	1095.6	-7.34	14.76	
Lean body weight	C _{8h}	36.2	55	69.1	367.56	381.10	405.26	-3.56	6.33	467.06	483.95	515.3	-3.49	6.48	
Lean body weight	t _{max}	36.2	55	69.1	1.99	2.10	2.17	-5.24	3.33	1.98	2.09	2.15	-5.26	2.87	
ALP	AUC _{0-24h}	38	60	99	7239.24	7930.70	8704.22	-8.72	9.75	8701.61	9981.47	11583.9	-12.82	16.05	
ALP	C _{max}	38	60	99	803.01	817.00	831.37	-1.71	1.76	906.5	954.68	1014.6	-5.05	6.28	
ALP	C _{8h}	38	60	99	347.10	381.10	417.32	-8.93	9.49	421.73	483.95	558.95	-12.86	15.50	
ALP	t _{max}	38	60	99	2.06	2.10	2.14	-1.90	1.91	2.05	2.09	2.12	-1.91	1.44	
Food status	AUC _{0-24h}	fed	light meal/uncontrolled	fasted	7398.71	7930.70	7969.83	-6.71	0.49	9772.95	9981.47	9994.27	-2.09	0.13	
Food status	C _{max}	fed	light meal/uncontrolled	fasted	523.15	817.00	839.62	-35.97	2.77	665.57	954.68	977.34	-30.28	2.37	
Food status	C _{8h}	fasted	light meal/uncontrolled	fed	371.94	381.10	443.60	-2.41	16.39	473.32	483.95	561.92	-2.20	16.11	
Food status	t _{max}	fasted	light meal/uncontrolled	fed	1.84	2.10	4.48	-12.38	113.33	1.83	2.09	4.26	-12.44	103.83	
Admin.	AUC _{0-24h}	evening	evening	morning	7930.66	7930.70	8085.55		1.95	9981.47	9981.47	10079.7		0.98	
Admin.	C _{max}	evening	evening	morning	816.98	817.00	1053.60		28.96	954.68	954.68	1191.71		24.83	
Admin.	C _{8h}	morning	evening	evening	360.12	381.10	381.13	-5.51		459.83	483.95	483.95	-4.99		
Admin.	t _{max}	morning	evening	evening	1.25	2.10	2.10	-40.48		1.24	2.09	2.09	-40.67		

AUC_{0-24h}: ng/mL*h, C_{max} and C_{8h} ng/mL, t_{max} h.
 ALP = alkaline phosphatase; AUC_{0-24h} = area under the curve over a dosing interval; C_{max} = maximum concentration; C_{8h} = concentration 8 h after dosing; t_{max} = time of maximum concentration.

Source: sequence 0022, module 1, clin-info-amend.pdf, page 4 of 5

Top section of table refers to intrinsic factors. Bottom section of table includes the effect of the time of day for administration as well as the effect of meals. Shaded portion presents % change for low covariate value and % change for high covariate value versus reference covariate value on Day 1 and Day 3 (steady-state), respectively

Reviewer comment: The goodness-of-fit plots do not suggest the presence of systemic bias. The visual predictive check indicates that the model can represent the distribution of daridorexant exposures reasonably well for the proposed dose levels of 25 mg and 50 mg once daily.

The visual predictive check indicates that the model exhibits increasingly large uncertainty in predictions of the highest exposures as the dose level increases above 50 mg once daily. **Overall, the model is acceptable.**

The PK simulations shown in Table 123 indicate that variations in intrinsic factors (age, fat mass, lean body weight, ALP) are expected, as a worst-case scenario, to cause reductions in PK of up to 23% or cause increases in PK of up to 16%. Changes in these values are not expected to be clinically relevant and do not warrant a dose adjustment.

Though the model predicted food effect appears to reduce exposure by ~36% and increase T_{max} by up to 113%, the in vivo food effect study (ID-078-113) demonstrated a lower magnitude effect and is expected to be more reliable than the population PK-based estimate. Please refer to Section 14.2.7 for details.

The C_{max} value is up to 29% higher when administered in the morning versus administered in the evening. However, the proposed evening administration time is consistent with the evening administration time utilized in the phase 3 program. Thus, there is no need to further assess the possibility of changing administration time to morning.

14.6. Exposure-Response Review

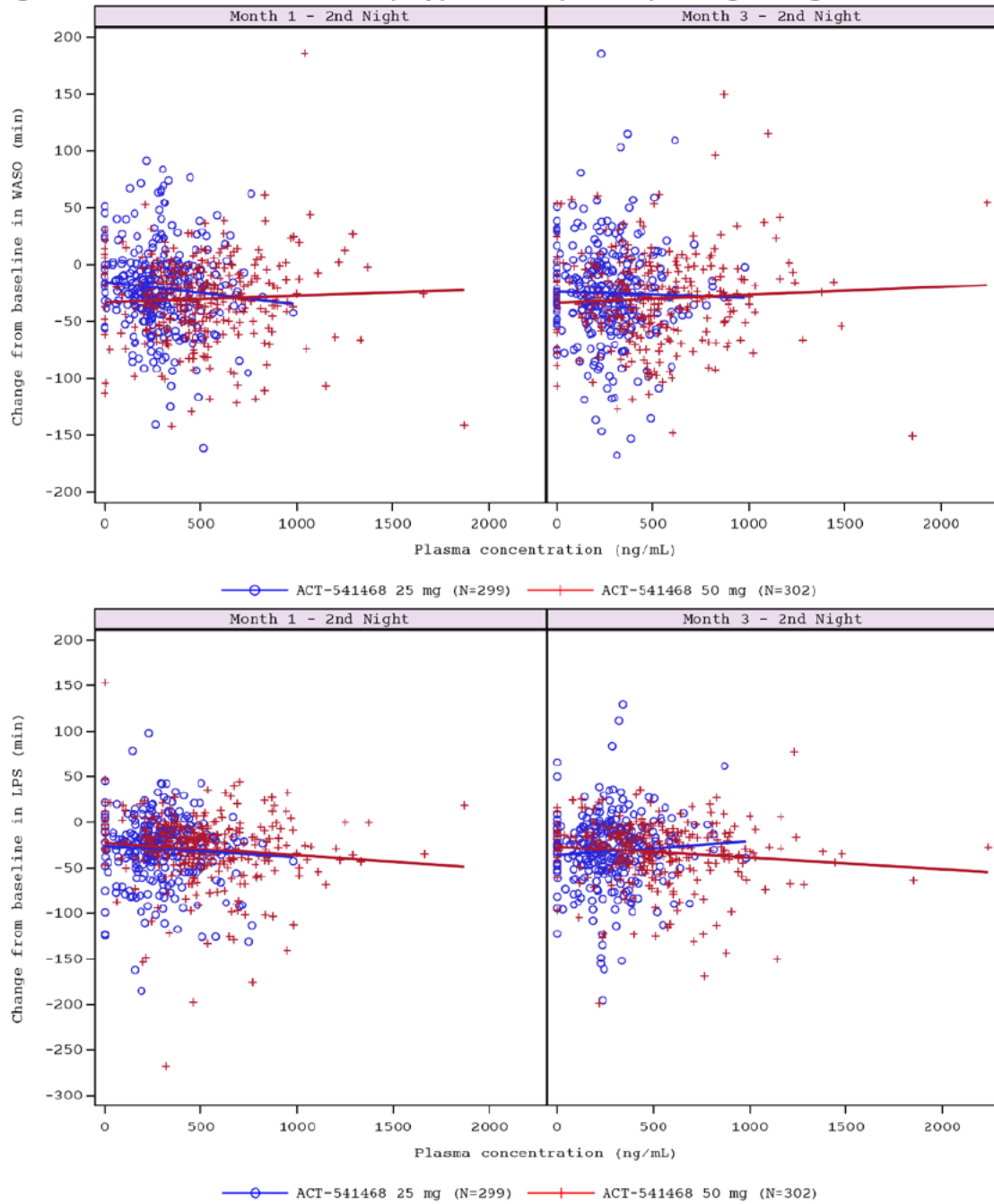
14.6.1. Applicant's Exposure-Response Analyses

The Applicant conducted exposure-response (E-R) analyses for safety using data from Studies ID-078-107 (human abuse potential study), ID-078-108 (driving study), and ID-078-117 (QT interval effect study). These three studies are discussed in Section [17](#) of this review.

The Applicant conducted graphical exposure-response analyses for efficacy using data from treatment and placebo arms of phase 3 Trials ID-078A301 and ID-078A302. The phase 3 trial data were analyzed separately from one another. The change from baseline values for numerous efficacy endpoints (wake after sleep onset [WASO], latency to persistent sleep [LPS], sTST, and IDSIQ sleepiness domain score; VAS quality of sleep, depth of sleep, daytime alertness, and daily ability to function) at Month 1 and Month 3 were compared with PK samples. The PK samples utilized in these comparisons were collected at 9 to 10 hours postdose (morning after the second PSG night at Visits 6 and 8).

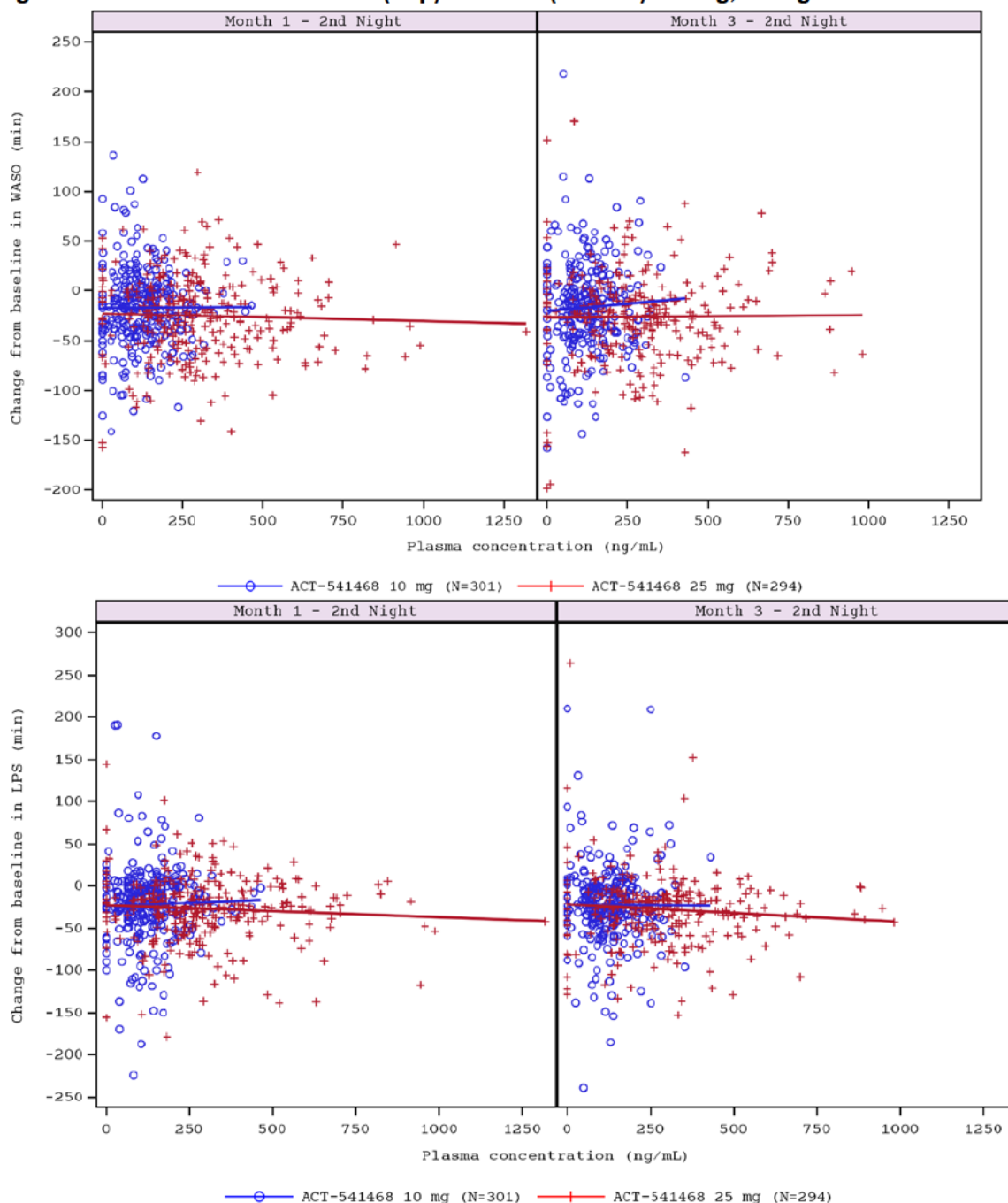
The resulting plots for these graphical exposure-response analyses for the primary efficacy endpoints (WASO and LPS) are shown in [Figure 35](#) and [Figure 36](#).

Figure 35. Trial ID-078A301 WASO (Top) and LPS (Bottom): 25 mg, 50 mg



Source: sequence 0001, module 5351, id-078a301-e3-15.pdf, pages 1065 and 1066
The points represent the observed efficacy endpoint measured during the night and the next day daridorexant plasma concentration value
Abbreviations: LPS, latency to persistent sleep; WASO, wake after sleep onset

Figure 36. Trial ID-078A302 WASO (Top) and LPS (Bottom): 10 mg, 25 mg



Source: sequence 0001, module 5351, id-078a302-e3-15.pdf, pages 1085 and 1086
The points represent the observed efficacy endpoint measured during the night and the next day daridorexant plasma concentration value

Abbreviations: LPS, latency to persistent sleep; N, number of subjects; WASO, wake after sleep onset

The Applicant provided the following conclusions:

- No correlation between daridorexant plasma concentration and change from baseline in the selected endpoints was observed. This reflects that the exposure to daridorexant

measured the next morning does not have an obvious correlation to the efficacy assessed during the previous night.

- Establishing PKPD relationships for the efficacy of sleep-promoting drugs is notoriously challenging, due to the multiple sleep stage changes during the night, the fact that efficacy may depend more on changes in drug concentration than on absolute values, and the internight variability, to mention just a few factors.

Reviewer Comment: *The reviewer highlights the following observations regarding the exposure-response results for WASO and LPS:*

Comparing E-R for 25-mg dose level across phase 3 studies:

- *For WASO, E-R slope is negative except for Month 3 in Trial ID-078A302 (where slope is nearly flat)*
- *For LPS, E-R slope is negative except for Month 3 in Trial ID-078A301 (where slope is positive)*

Comparing E-R Across Dose Levels:

- *In Trial ID-078A301, for WASO, the E-R slope is positive for 50 mg and negative for 25 mg (at Month 1 and Month 3)*
- *In Trial ID-078A301, for LPS the E-R slope is positive for 25 mg and negative for 50 mg (at Month 3)*
- *In Trial ID-078A302, for WASO, the E-R slope is positive for 10 mg and nearly flat for 25 mg (at Month 3)*
- *In Trial ID-078A302, for LPS, the E-R slope is positive for 10 mg and negative for 25 mg (at Month 1 and Month 3)*

Overall, the observed E-R relationship does not appear to be consistent across studies or across the dose levels for either of the primary efficacy endpoints, WASO or LPS. The additional endpoints included in such graphical analyses (sTST and IDSIQ; id-078a301-e3-15.pdf pages 1067-1068, and id-078a302-e3-15.pdf pages 1087-1088; figures not shown in review) present similar inconsistencies in E-R slope across study and dose level.

The reviewer agrees with the Applicant that the daridorexant PK sample measured the next morning does not have an obvious correlation to the change-from-baseline efficacy endpoints assessed during the previous night.

One factor affecting these results is the time difference between efficacy measurement and the PK sample in the context of daridorexant PK. The daridorexant plasma half-life is approximately 8-hours. The Applicant reports that the study medication was administered 30±5 min before the PSG recordings. The PSG recording duration is 480 minutes (8 hours). The PK sample was collected at 9 to 10 hours postdose. Thus, PSG completion time and PK sample time both occur at ~1 half-life after the PSG beginning. If an exposure-response relationship exists for these efficacy endpoints, it is expected that such E-R relationships would be flatter when using a PK sample collected 9 to 10 hours

postdose compared to an E-R relationship that uses C_{max} (as T_{max} is ~2.09 h, and thus expected to occur during the PSG recording period). However, considering the PK variability reported (i.e., percent coefficient of variation ranged from 63 to 137% and from 32 to 61%, in Studies AC-078-101 and AC-078-102, respectively), it is not clear that the individual C_{max} values (expected to occur during the PSG session) for subjects in phase 3 studies analyses can be reliably inferred for use in E-R analyses.

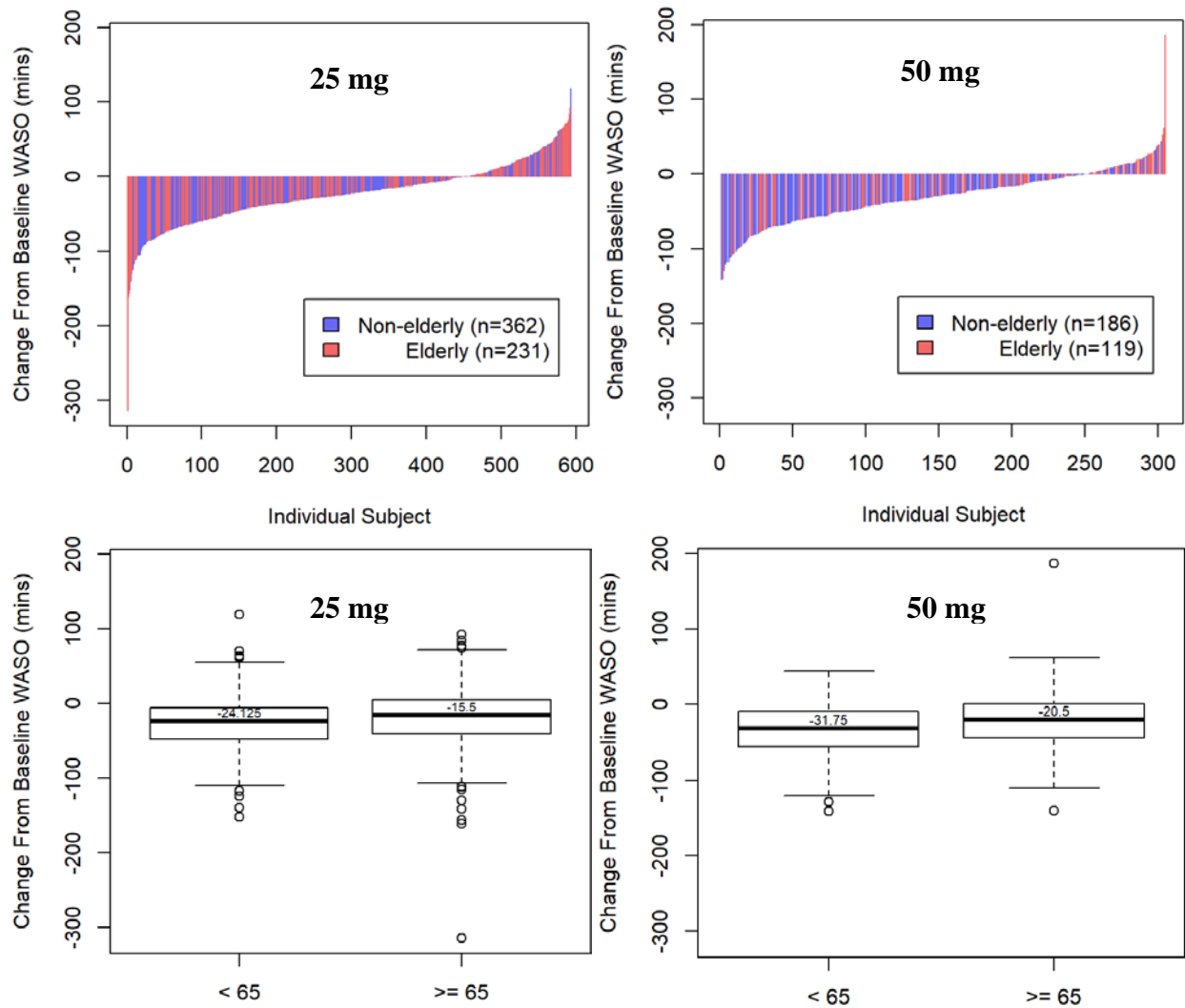
Overall, considering the high PK variability, and that subjects in phase 3 trials provided a single PK sample, occurring after PSG completion (obtained 9 to 10 hours postdose, over 1 half-life), it is not clear whether the PK profile for individual patients during the PSG can be reliably predicted.

14.6.2. Reviewer's Exposure-Response Analyses

A graphical assessment was conducted to assess the apparent relationship between age and efficacy outcomes. The WASO and LPS change from baseline values were pooled from both phase 3 trials ID-078A301 and ID-078A302 and were arranged from lowest (greatest improvement) to highest by subject and plotted with stratification by age ("waterfall plot" of elderly versus nonelderly; <65 years versus $\geq$ 65 years of age). Separate plots were generated by dose level (25 mg versus 50 mg) and time of efficacy assessment (Month 1 versus Month 3). [Figure 37](#), [Figure 38](#), [Figure 39](#), and [Figure 40](#).

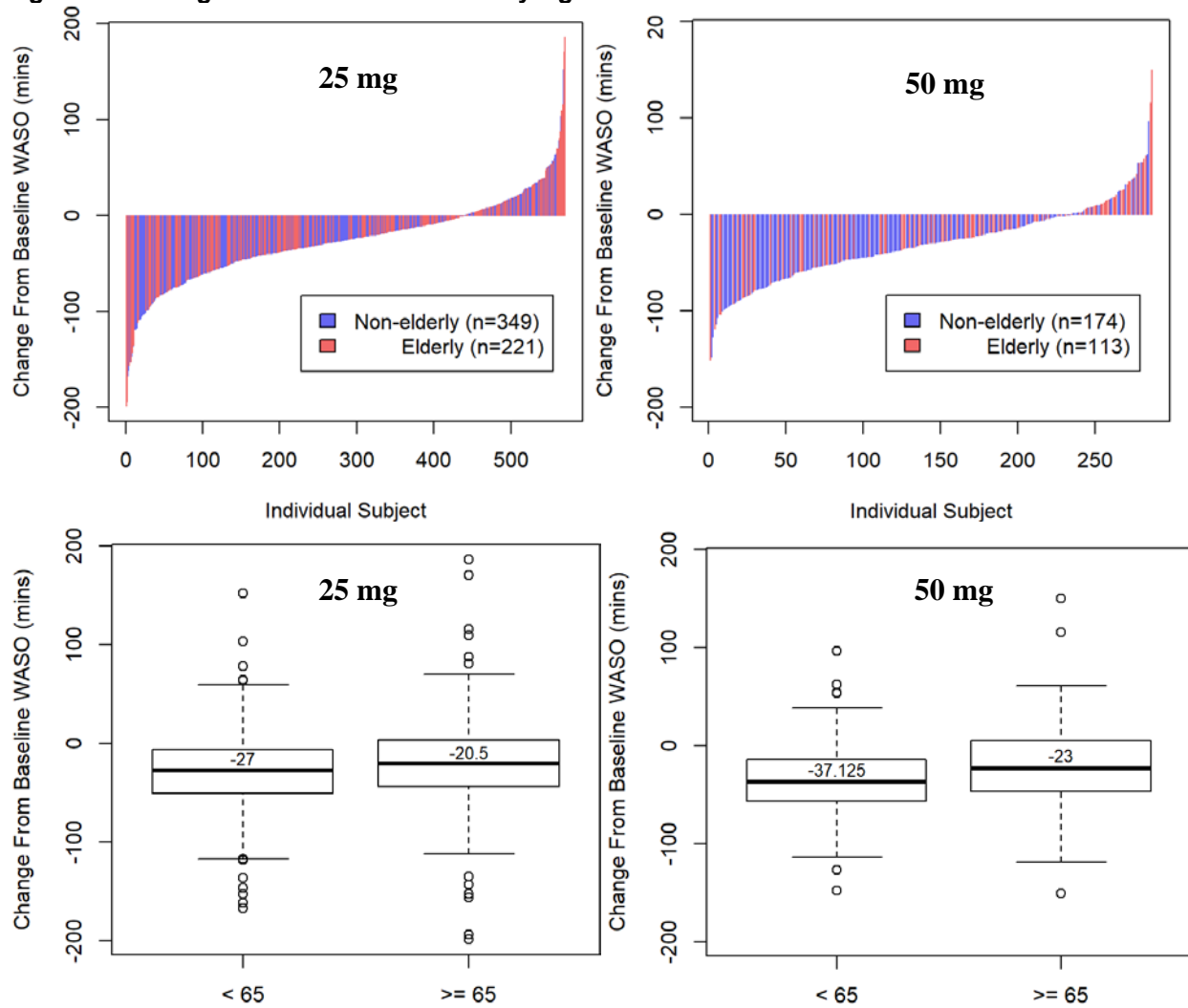
show the waterfall plots as well as boxplots of the elderly versus nonelderly population for WASO and LPS change from baseline values, for 25 mg and 50 mg, at Month 1 and Month 3.

Figure 37. Change From Baseline WASO by Age at Month 1, Trials ID-078A301 and ID-078A302



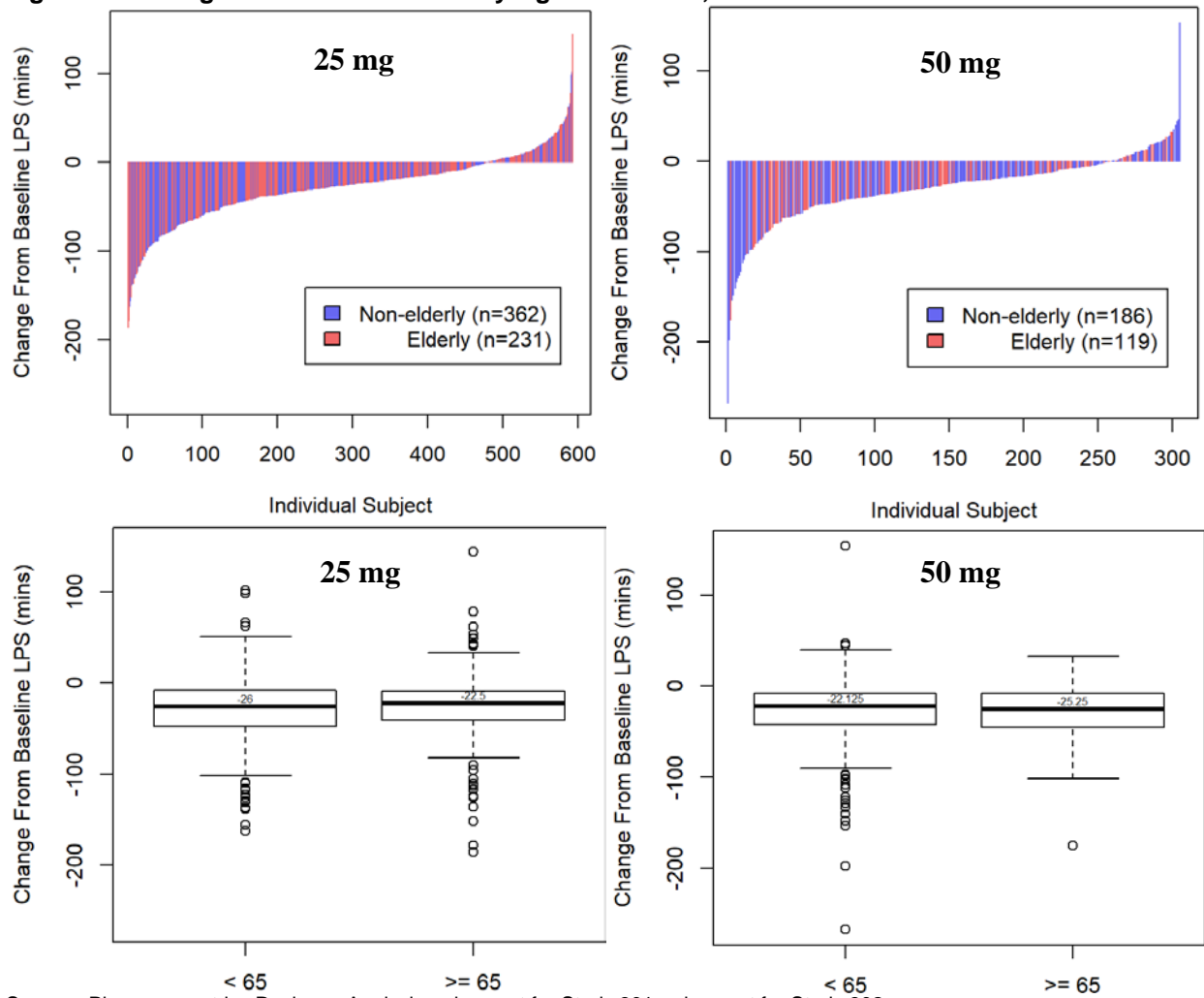
Source: Pharmacometrics Reviewer Analysis; adpsg.xpt for Study 301, adpsg.xpt for Study 302
 The number displayed at the center of the boxplot is the median
 Abbreviations: n, number of subjects in group; WASO, wake after sleep onset

Figure 38. Change From Baseline WASO by Age at Month 3 in Trials ID-078A301 and ID-078A302



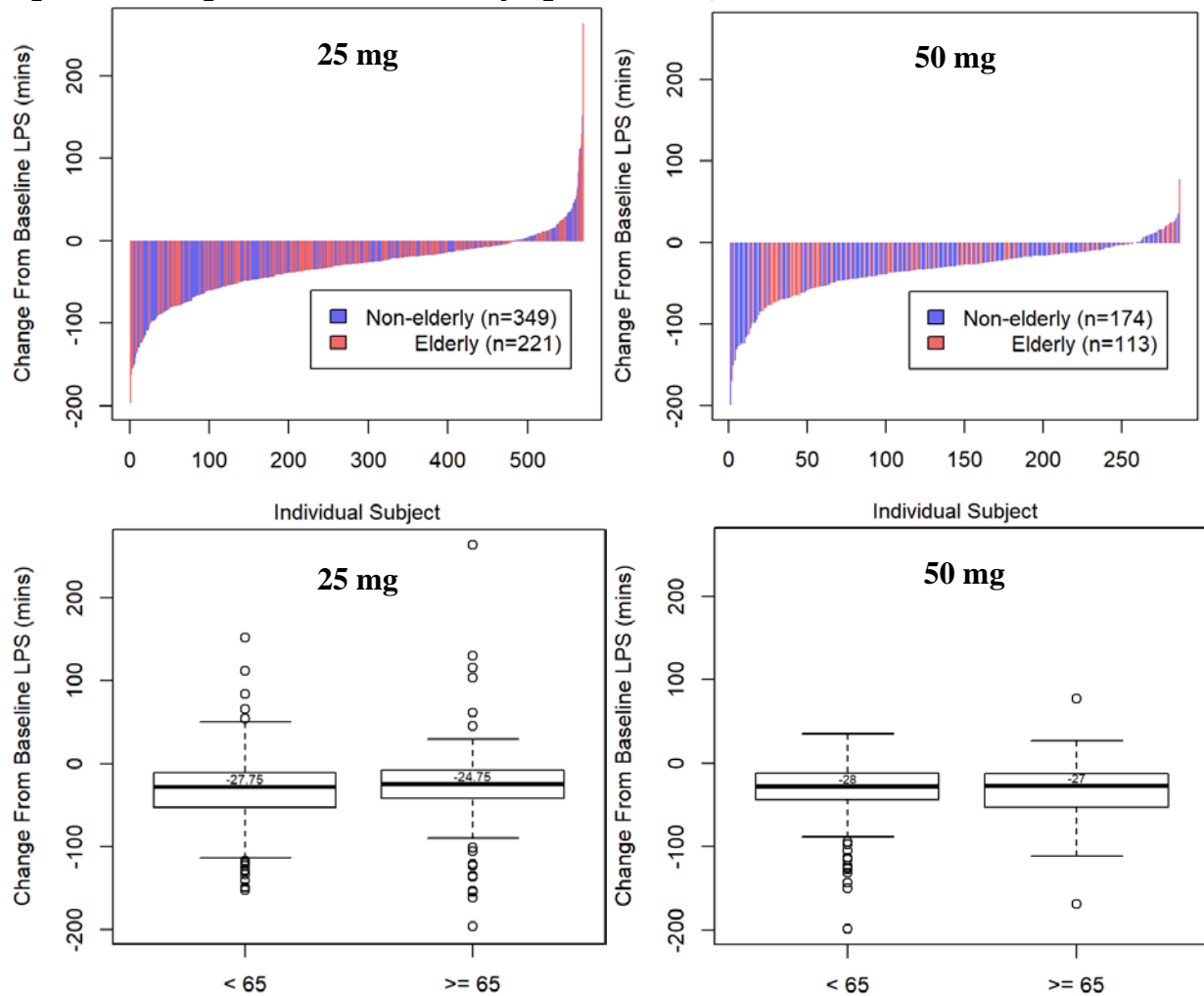
Source: Pharmacometrics Reviewer Analysis; adpsg.xpt for Study 301, adpsg.xpt for Study 302
 The number displayed at the center of the boxplot is the median
 Abbreviations: n, number of subjects in group; WASO, wake after sleep onset

Figure 39. Change From Baseline LPS by Age at Month 1, Trials ID-078A301 and ID-078A302



Source: Pharmacometrics Reviewer Analysis; adpsg.xpt for Study 301, adpsg.xpt for Study 302
 The number displayed at the center of the boxplot is the median
 Abbreviations: LPS, latency to persistent sleep; n, number of subjects in group

Figure 40. Change From Baseline LPS by Age at Month 3, Trials ID-078A301 and ID-078A302



Source: Pharmacometrics Reviewer Analysis; adpsg.xpt for Study 301, adpsg.xpt for Study 302
The number displayed at the center of the boxplot is the median
Abbreviations: LPS, latency to persistent sleep; n, number of subjects in group

Overall, any apparent numerical differences between elderly and nonelderly efficacy in phase 3 trials are modest relative to the variability in the response. Overall, there is no apparent relationship between age and efficacy on WASO or LPS.

15. Trial Design: Additional Information and Assessment

See Section [6.2.1.1](#) for assessment of the trial design of ID-078A301 and ID-078A302. The trial designs are adequate for the intended labeling claims.

16. Efficacy: Additional Information and Assessment

16.1. Supplementary Information on Sample Characteristics for Trials ID-078A301 and ID-078A302

Additional analysis for Section [6.2.2.1](#).

Table 124. Previous Medical Conditions (Medical History) in Psychiatric Disorders by Preferred Term, Trials ID-078A301 and ID-078A302, Safety Population

System Organ Class Preferred Term	078A301			078A302			Pooled	
	Daridorexant 25 mg N=310	Daridorexant 50 mg N=308	PBO N=309	Daridorexant 10 mg N=306	Daridorexant 25 mg N=308	PBO N=306	Daridorexant 25 mg N=618	PBO N=615
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Psychiatric disorders (SOC)	19 (6.1)	22 (7.1)	13 (4.2)	25 (8.2)	18 (5.8)	19 (6.2)	37 (6.0)	32 (5.2)
Depression	8 (2.6)	10 (3.2)	6 (1.9)	18 (5.9)	10 (3.2)	9 (2.9)	18 (2.9)	15 (2.4)
Tobacco abuse	2 (0.6)	6 (1.9)	1 (0.3)	0	1 (0.3)	2 (0.7)	3 (0.5)	3 (0.5)
Major depression	3 (1.0)	2 (0.6)	2 (0.6)	2 (0.7)	3 (1.0)	3 (1.0)	6 (1.0)	5 (0.8)
Alcoholism	0	1 (0.3)	0	1 (0.3)	0	2 (0.7)	0	2 (0.3)
Anxiety	1 (0.3)	1 (0.3)	2 (0.6)	3 (1.0)	2 (0.6)	2 (0.7)	3 (0.5)	4 (0.7)
Depressed mood	0	1 (0.3)	0	0	0	0	0	0
Perinatal depression	0	1 (0.3)	1 (0.3)	1 (0.3)	0	0	0	1 (0.2)
Post-traumatic stress disorder	1 (0.3)	1 (0.3)	0	0	0	0	1 (0.2)	0
Stress	1 (0.3)	1 (0.3)	0	0	0	0	1 (0.2)	0
Suicidal ideation	0	1 (0.3)	0	0	1 (0.3)	0	1 (0.2)	0
Adjustment disorder with depressed mood	1 (0.3)	0	0	1 (0.3)	0	0	1 (0.2)	0
Attention deficit/hyperactivity disorder	0	0	1 (0.3)	0	0	0	0	1 (0.2)
Burnout syndrome	0	0	0	0	2 (0.6)	1 (0.3)	2 (0.3)	1 (0.2)
Delirium	1 (0.3)	0	0	0	0	0	1 (0.2)	0
Generalised anxiety disorder	0	0	0	0	0	1 (0.3)	0	1 (0.2)
Hypnagogic hallucination	0	0	0	0	1 (0.3)	0	1 (0.2)	0
Mixed anxiety and depressive disorder	1 (0.3)	0	0	0	0	0	1 (0.2)	0

System Organ Class Preferred Term	078A301			078A302			Pooled	
	Daridorexant 25 mg N=310 n (%)	Daridorexant 50 mg N=308 n (%)	PBO N=309 n (%)	Daridorexant 10 mg N=306 n (%)	Daridorexant 25 mg N=308 n (%)	PBO N=306 n (%)	Daridorexant 25 mg N=618 n (%)	PBO N=615 n (%)
Nicotine dependence	1 (0.3)	0	0	0	0	0	1 (0.2)	0
Panic attack	0	0	0	0	1 (0.3)	0	1 (0.2)	0
Panic disorder	0	0	1 (0.3)	1 (0.3)	0	0	0	1 (0.2)

Source: CDS generated table. admh.xpt; Software: SAS

Medical histories are those procedures or diagnoses which are not ongoing when the informed consent is obtained

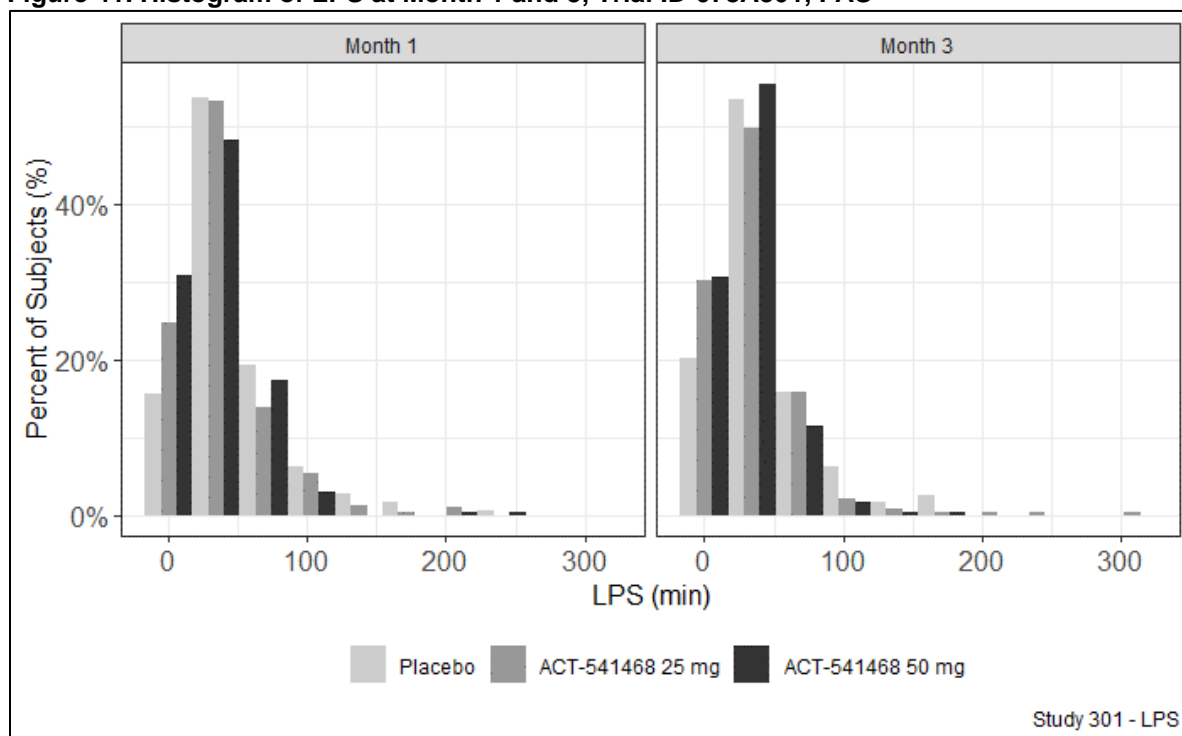
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with at least one event; SOC, system organ class

16.2. Statistical Model Assumptions Assessment

The primary endpoints (LPS and WASO) were observed to have a skewed distribution, see [Figure 41](#), [Figure 42](#), [Figure 43](#), and [Figure 44](#). The prespecified mixed model for repeated measures (MMRM) model assumed a normal error distribution. When the assumption of normal error distribution is violated, the model standard errors may be overestimated. While overestimation of the standard error does not inflate the type I error, the statistical power may be impacted. FDA is less concerned about type II errors; however, in this case, the clinical team was concerned about insufficient evidence to support the LPS endpoint.

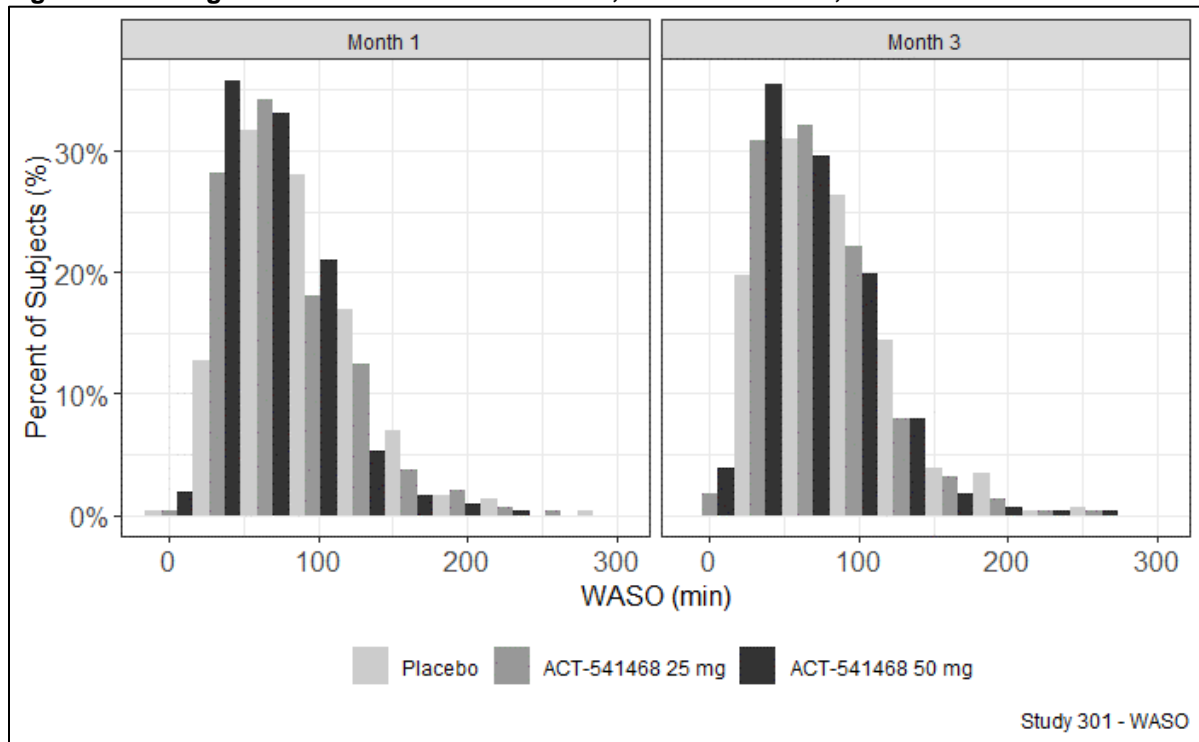
To explore if there is evidence for violation of the normality assumption, quantile-quantile plots (Q-Q plot) for each MMRM model's residuals were visually inspected. In a normal Q-Q plot, normally distributed residuals will fall on a 45-degree line. Deviations from this diagonal line indicate lack of normality in the residuals. In [Figure 45](#), the residuals for the prespecified MMRM analysis (Trial ID-078A302, LPS endpoint) deviate from the 45-degree line. For points with a theoretical residual with a predicted quantile greater than 1, the observed residuals are greater than the theoretical residual. This pattern suggests that a log transformation or similar data transformation may provide a better model fit. In [Figure 46](#), a Q-Q plot for the residuals from a MMRM analysis with log-transformed LPS in Trial ID-078A302 indicates a better model fit because the residuals fall on a 45-degree line. Similar results are seen for the Trial ID-078A301 LPS endpoint and both WASO endpoints. While the model fit is improved by log transforming the outcome data, all statistical inference should be made on the originally specified normal outcome distribution in order to protect the type I error because the log transformation is made after seeing the data.

Figure 41. Histogram of LPS at Month 1 and 3, Trial ID-078A301, FAS



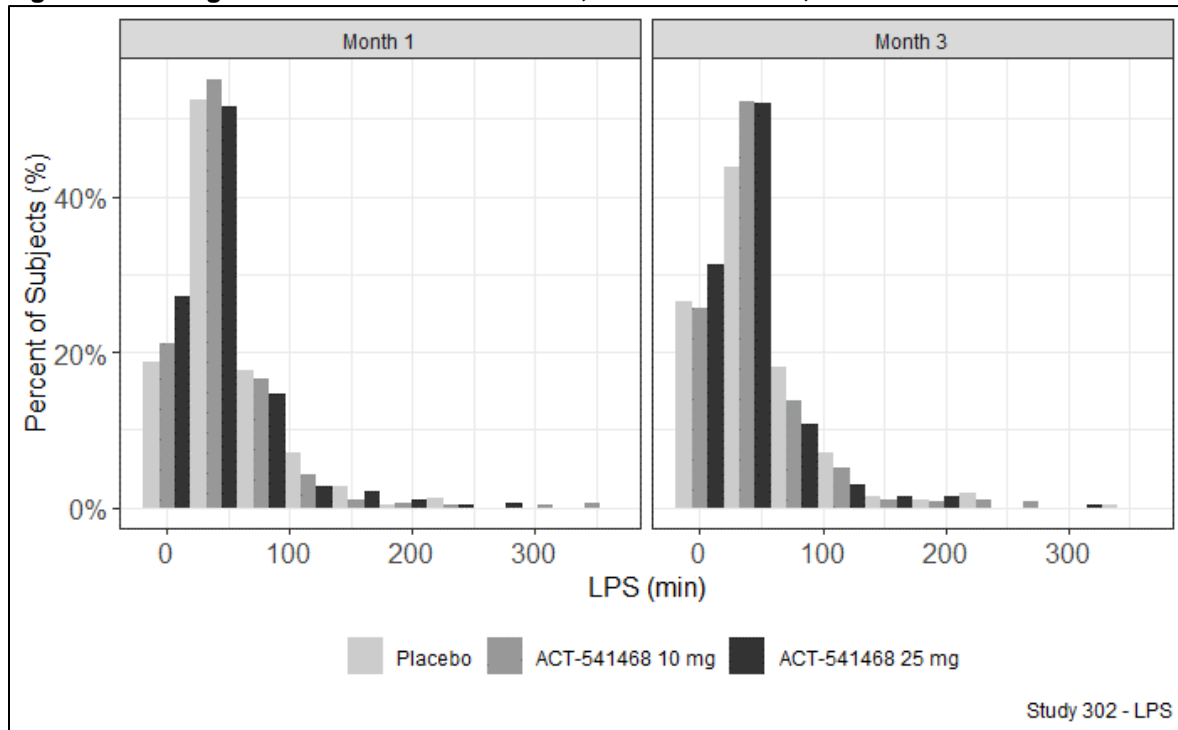
Source: Statistical Reviewer; adpsg.xpt
Abbreviations: FAS, full analysis set; LPS, latency to persistent sleep

Figure 42. Histogram of WASO at Month 1 and 3, Trial ID-078A301, FAS



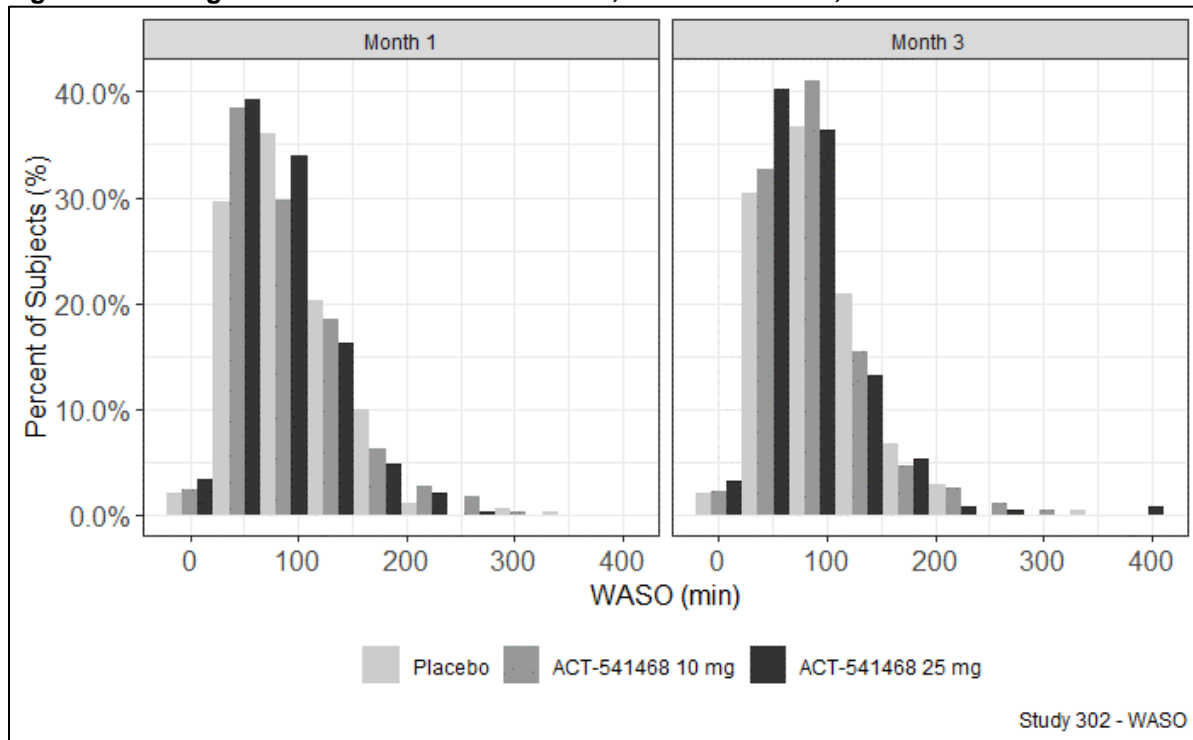
Source: Statistical Reviewer; adpsg.xpt
Abbreviations: FAS, full analysis set; WASO, wake after sleep onset

Figure 43. Histogram of LPS at Month 1 and 3, Trial ID-078A302, FAS



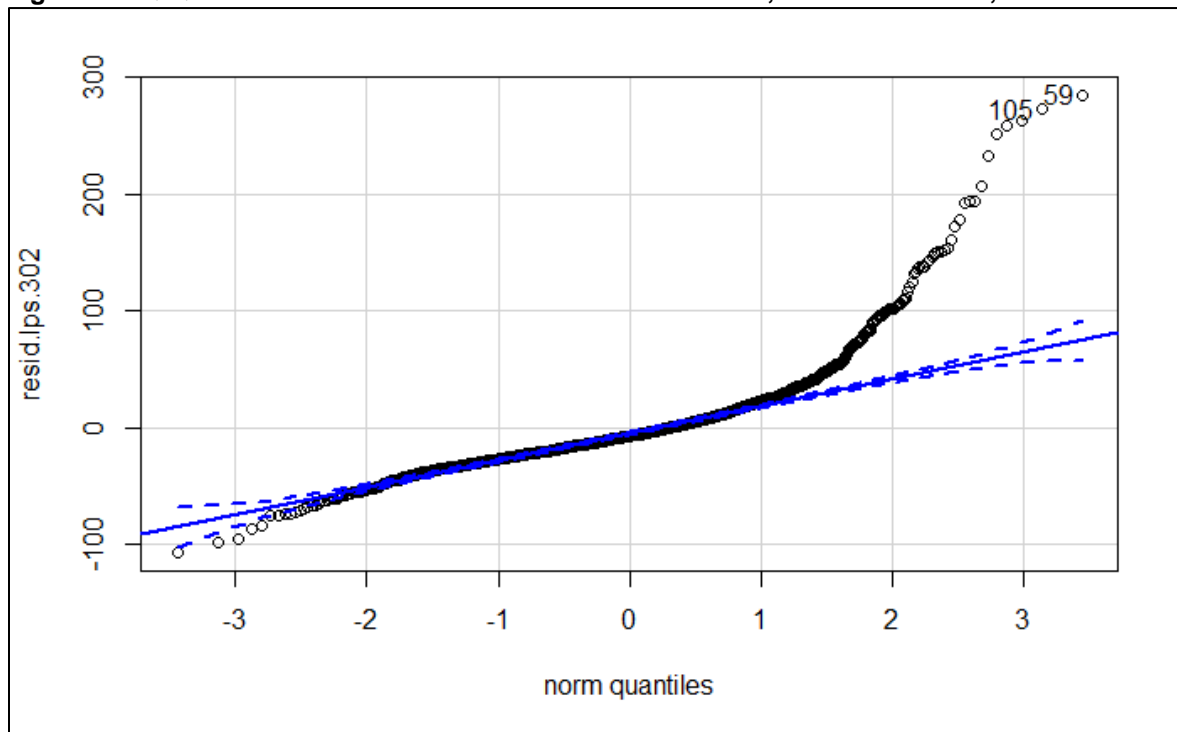
Source: Statistical Reviewer; adpsg.xpt
Abbreviations: FAS, full analysis set; LPS, latency to persistent sleep

Figure 44. Histogram of WASO at Month 1 and 3, Trial ID-078A302, FAS



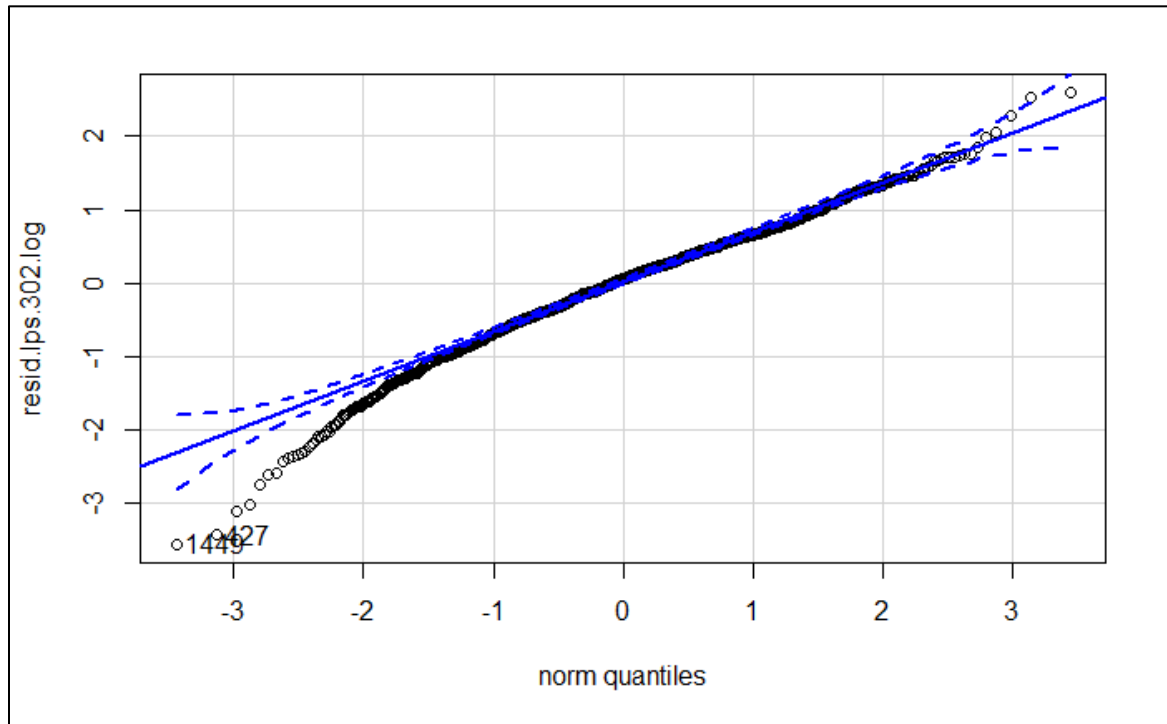
Source: Statistical Reviewer; adpsg.xpt
Abbreviations: FAS, full analysis set; WASO, wake after sleep onset

Figure 45. Q-Q Plot of Residuals From MMRM Model for LPS, Trial ID-078A302, FAS



Source: Statistical Reviewer; adpsg.xpt.
Numbers indicate the index of the outlying observations.

Figure 46. Q-Q Plot of Residuals From Log-Transformed MMRM Model for LPS, Trial ID-078A302, FAS

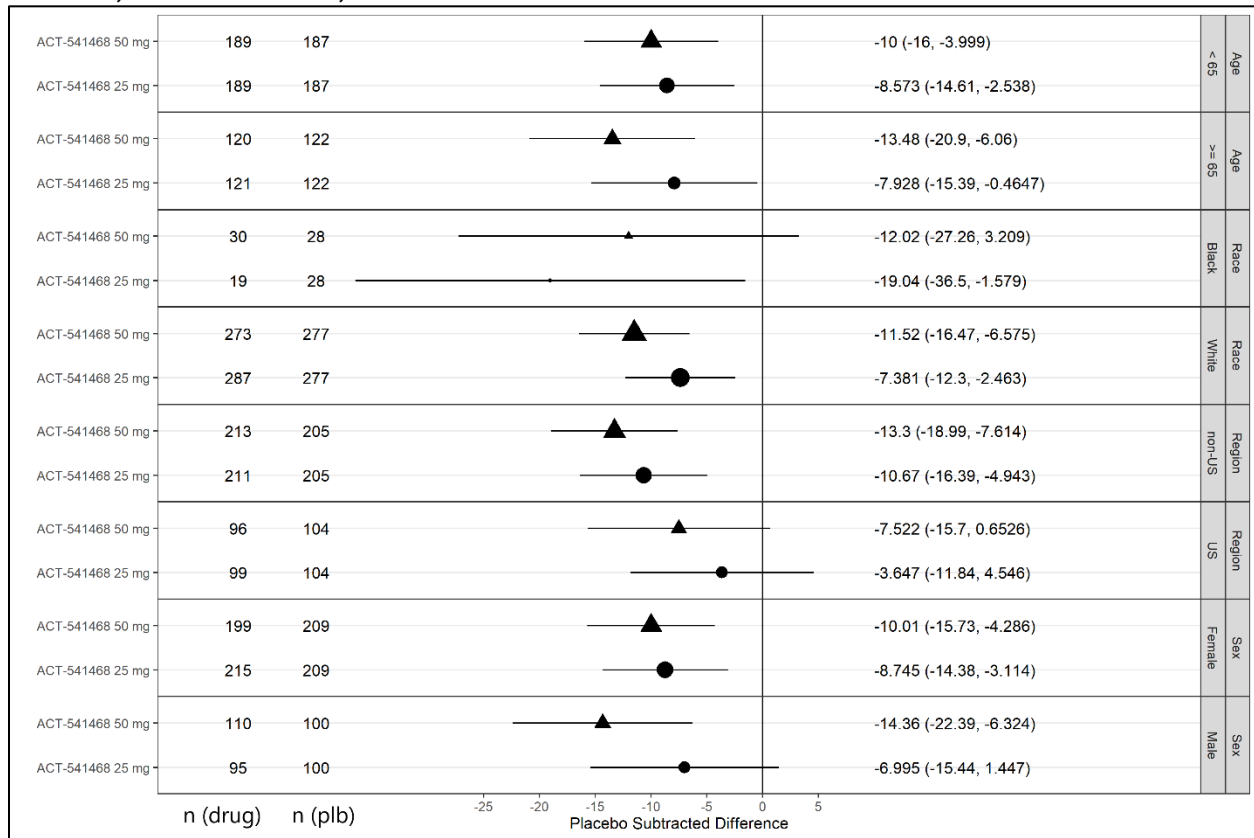


Source: Statistical Reviewer; adpsg.xpt.

16.3. Analyses of Treatment Effects by Patient Baseline Characteristics in Trials ID-078A301 and ID-078A302

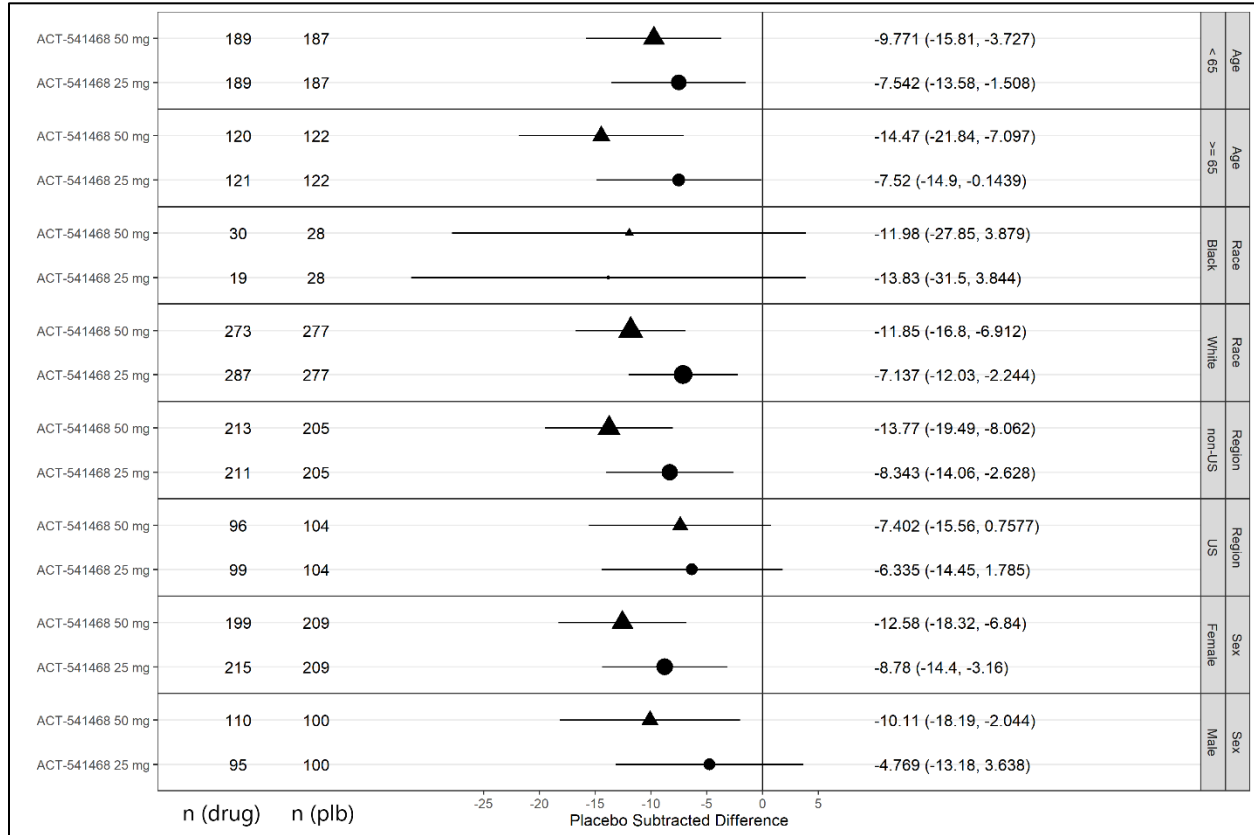
See discussion in Section [6.2.2.5](#). All differences are in minutes.

Figure 47. Forest Plot of LPS Treatment Effects by Subgroup at Month 1 With 95% Confidence Intervals, Trial ID-078A301, FAS



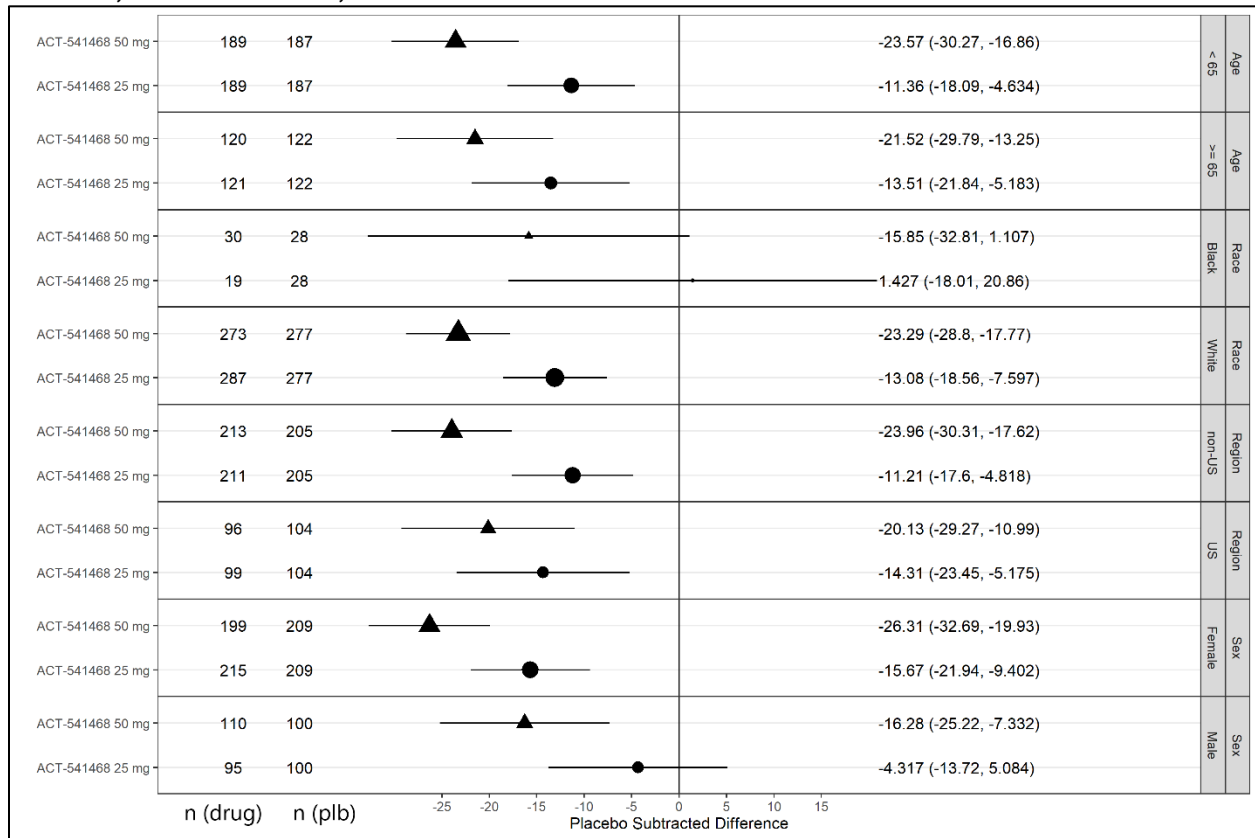
Source: Statistical Reviewer; adpsg.xpt, adsl.xpt
 Abbreviations: FAS, full analysis set; LPS, latency to persistent sleep; n, number of subjects in group; US, United States

Figure 48. Forest Plot of LPS Treatment Effects by Subgroup at Month 3 With 95% Confidence Intervals, Trial ID-078A301, FAS



Source: Statistical Reviewer; adpsg.xpt, adsl.xpt
 Abbreviations: FAS, full analysis set; LPS; latency to persistent sleep; n, number of subjects in group; US, United States

Figure 49. Forest Plot of WASO Treatment Effects by Subgroup at Month 1 With 95% Confidence Intervals, Trial ID-078A301, FAS



Source: Statistical Reviewer; adpsg.xpt

Abbreviations: FAS, full analysis set; n, number of subjects in group; US, United States; WASO, wake after sleep onset

Figure 50. Forest Plot of WASO Treatment Effects by Subgroup at Month 3 With 95% Confidence Intervals, Trial ID-078A301, FAS

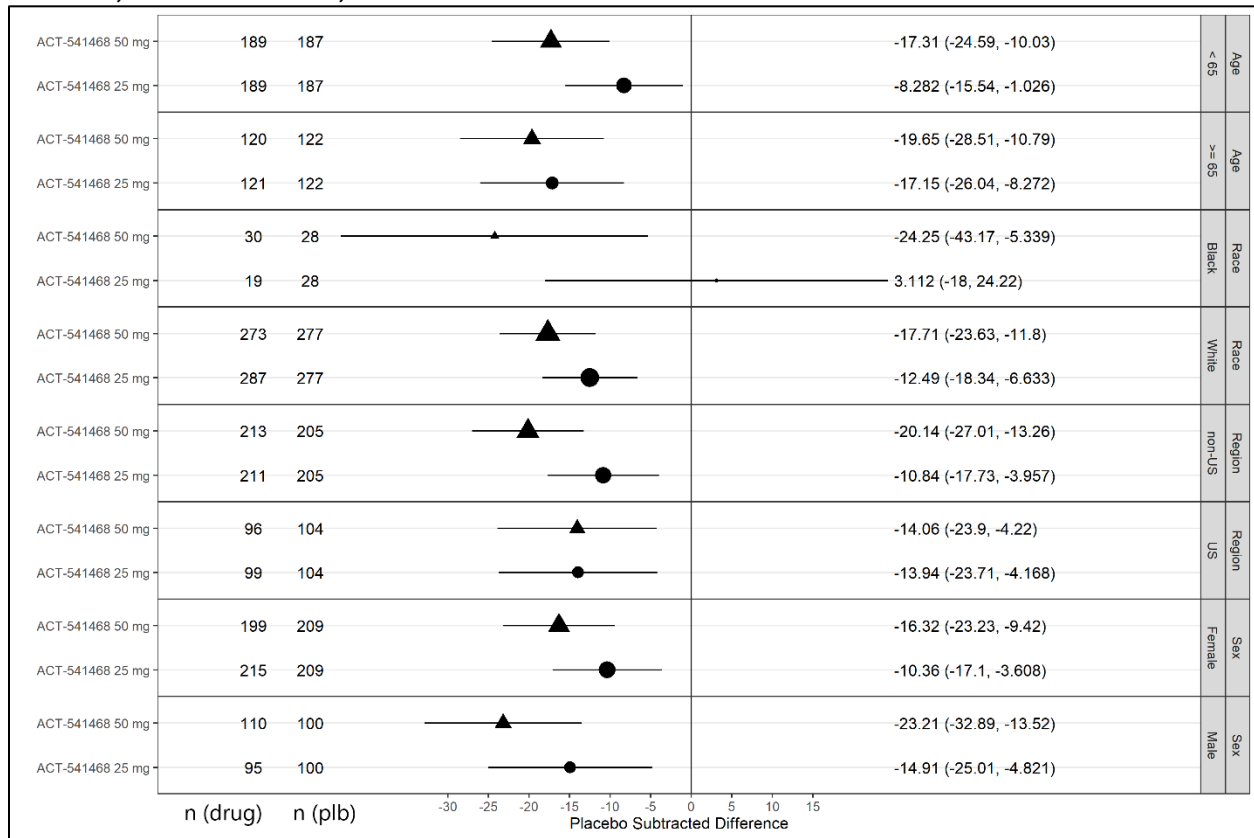
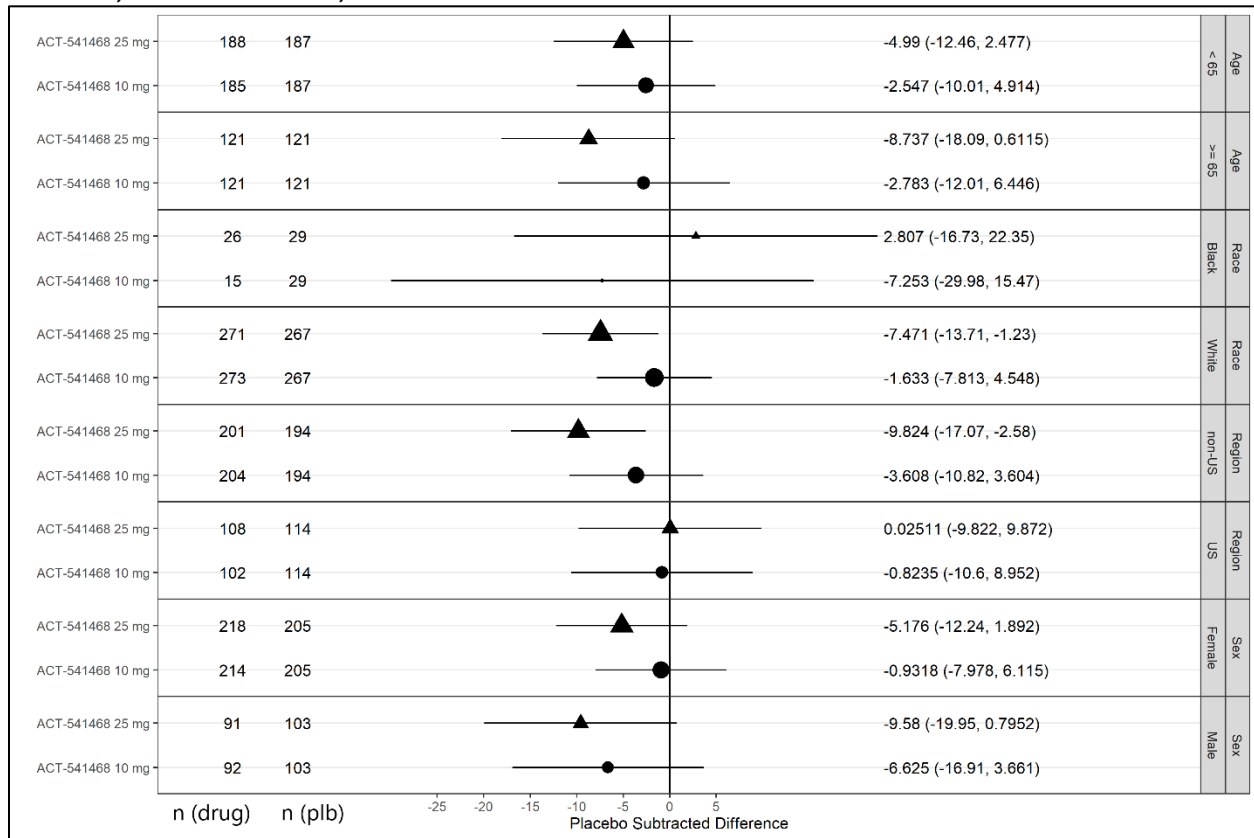
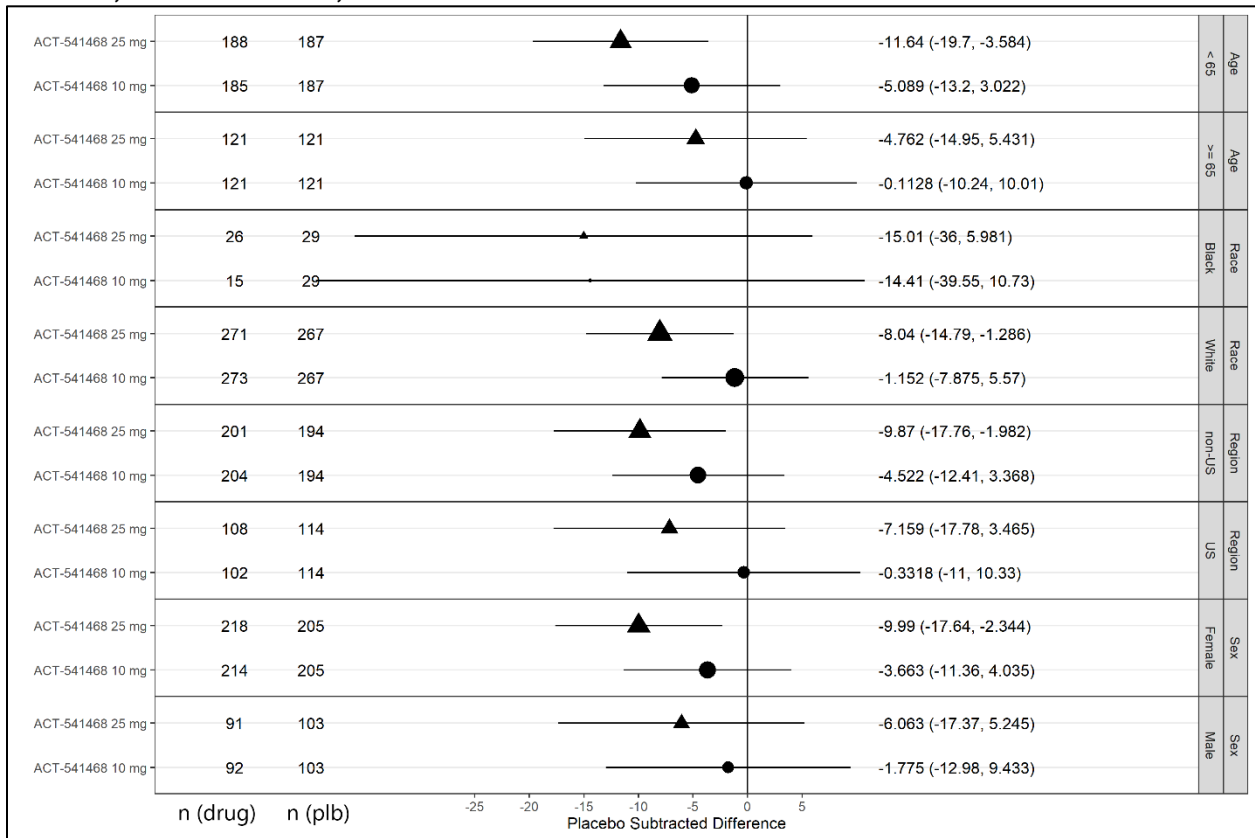


Figure 51. Forest Plot of LPS Treatment Effects by Subgroup at Month 1 With 95% Confidence Intervals, Trial ID-078A302, FAS



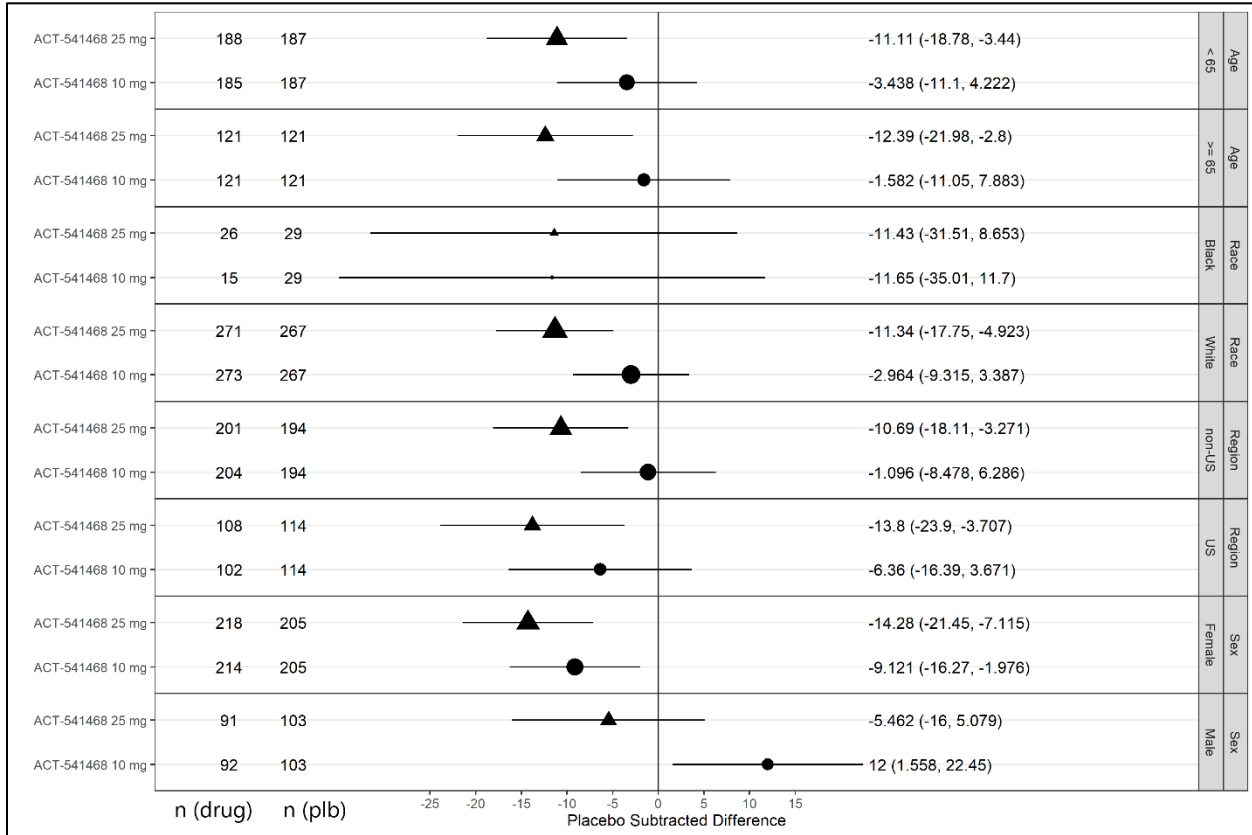
Source: Statistical Reviewer; adpsg.xpt, adsl.xpt
 Abbreviations: FAS, full analysis set; LPS, latency to persistent sleep; n, number of subjects in group; US, United States

Figure 52. Forest Plot of LPS Treatment Effects by Subgroup at Month 3 With 95% Confidence Intervals, Trial ID-078A302, FAS



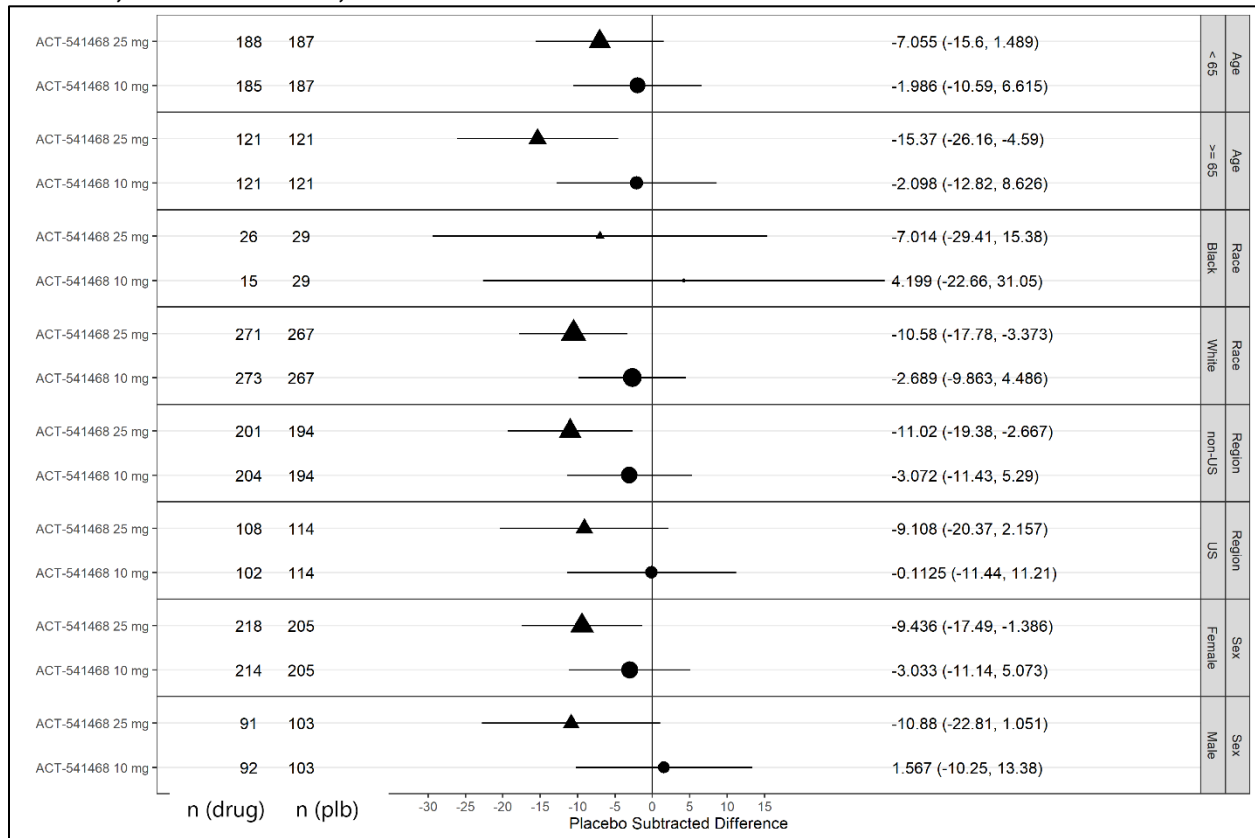
Source: Statistical Reviewer; adpsg.xpt, adsl.xpt
 Abbreviations: FAS, full analysis set; LPS, latency to persistent sleep; n, number of subjects in group; US, United States;

Figure 53. Forest Plot of WASO Treatment Effects by Subgroup at Month 1 With 95% Confidence Intervals, Trial ID-078A302, FAS



Source: Statistical Reviewer; adpsg.xpt, adsl.xpt
 Abbreviations: FAS, full analysis set; n, number of subjects in group; US, United States; WASO, wake after sleep onset

Figure 54. Forest Plot of WASO Treatment Effects by Subgroup at Month 3 With 95% Confidence Intervals, Trial ID-078A302, FAS

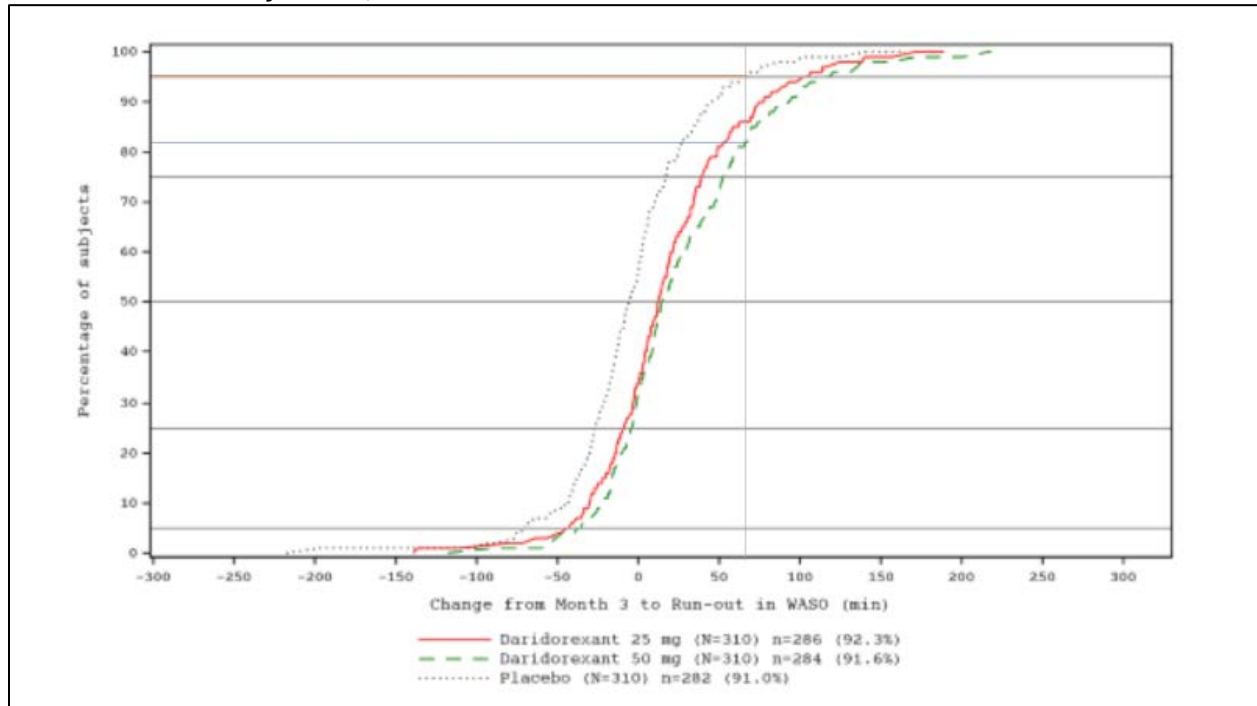


Source: Statistical Reviewer; adpsg.xpt, adsl.xpt
 Abbreviations: FAS, full analysis set; n, number of subjects in group; US, United States; WASO, wake after sleep onset

16.4. eCDFs of Sleep Parameter Change During Placebo Run-Out Period

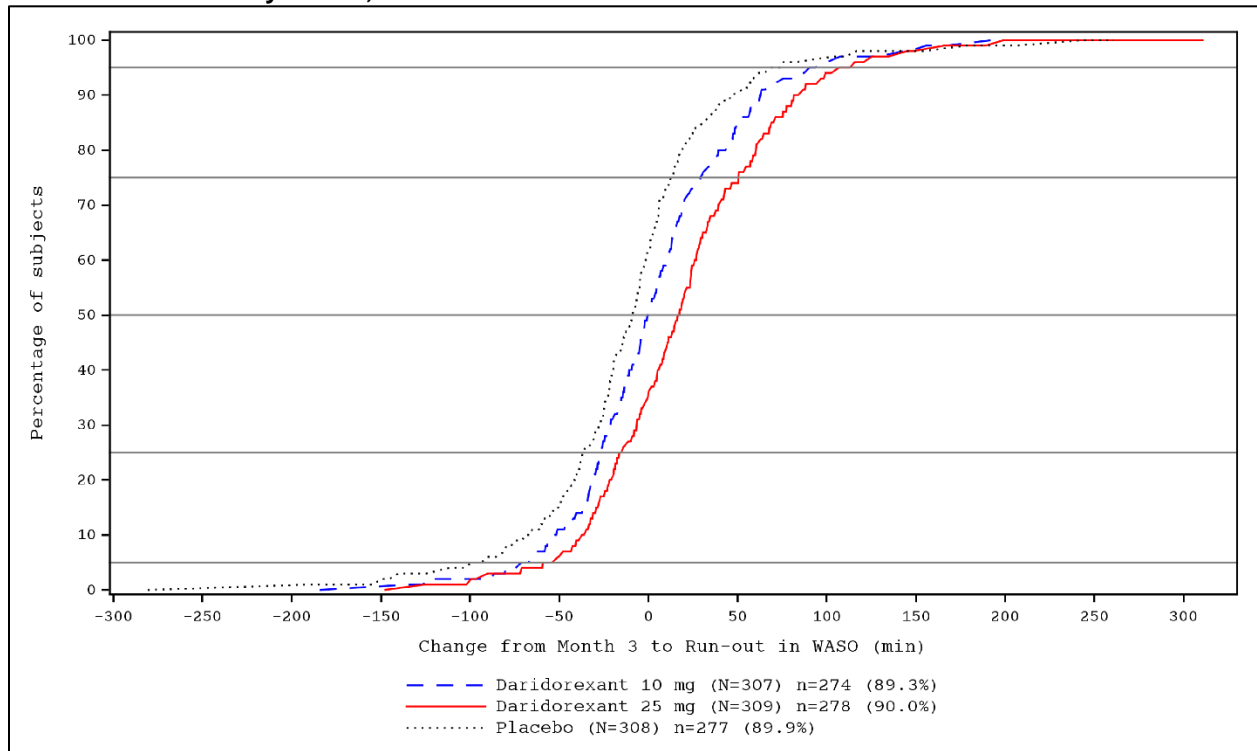
Analyses supporting discussion in Section [7.7.4.1.2](#).

Figure 55. Empirical Cumulative Distribution Function of the Change From Month 3 in WASO (min) to Run-Out Full Analysis Set, Trial ID-078A301



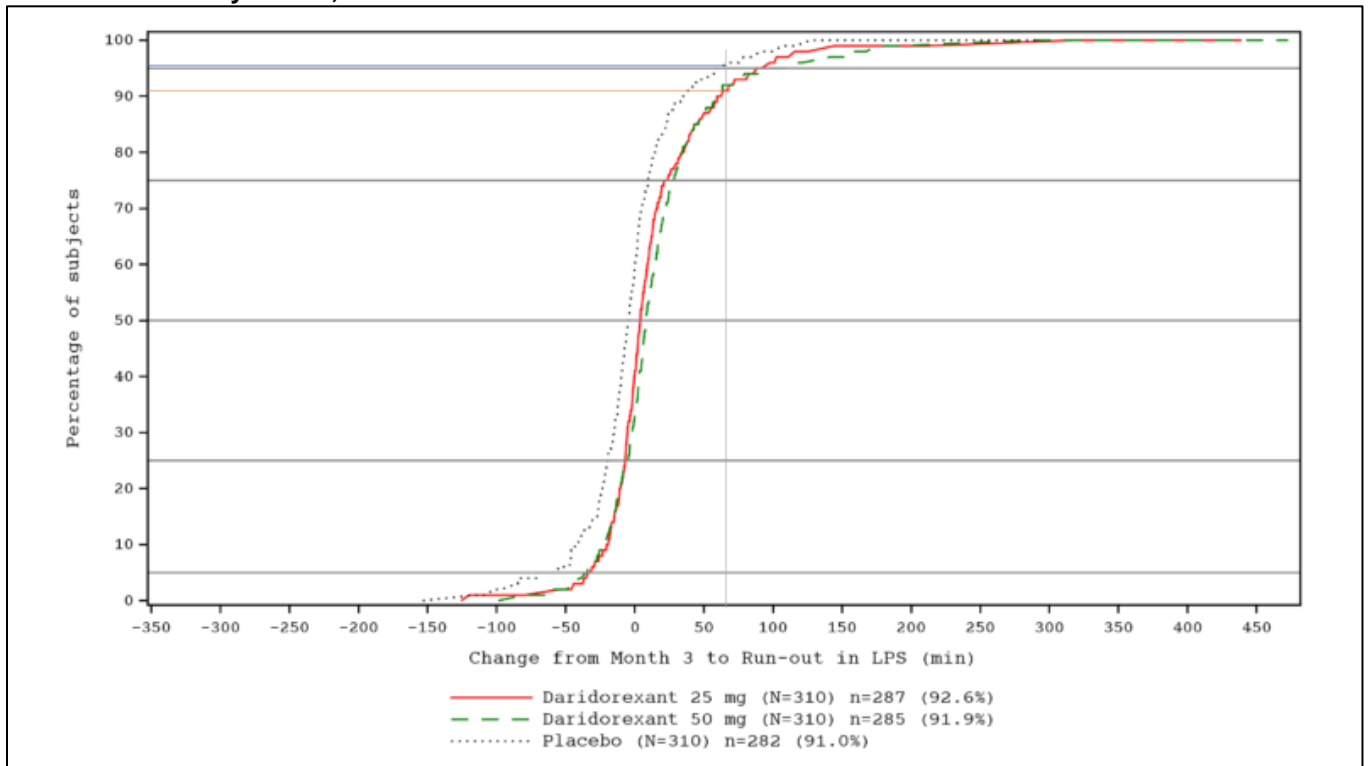
Source: Applicant generated figure, D-21.235: Response to 17 August 2021 Information Request - n is the number of subjects with no missing values. Program: F_FDA_REQ23_WASO_ECDF_FAS.sas. Visual inspection marker lines added by clinical reviewer
Abbreviations: N, number of subjects; n, number of subjects with no missing values; WASO, wake after sleep onset

Figure 56. Empirical Cumulative Distribution Function of the Change From Month 3 to Run-out Full Analysis Set, Trial ID-078A302



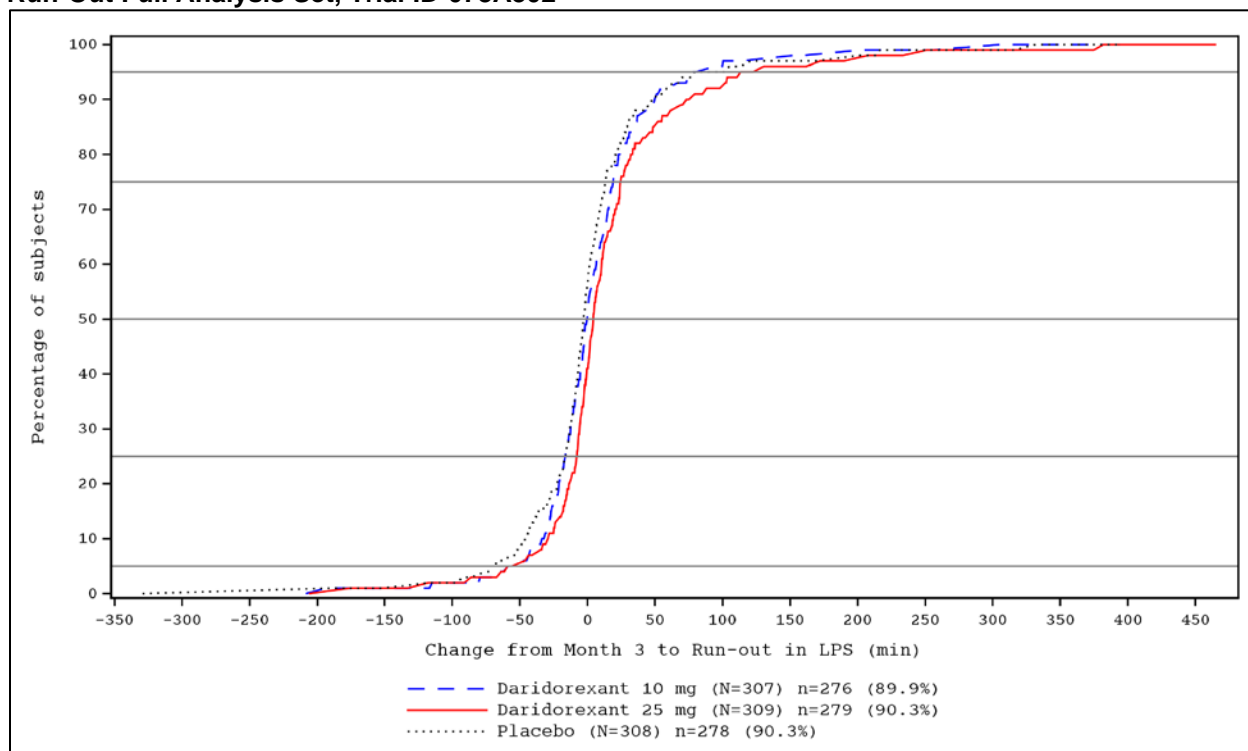
Source: Applicant generated figure, D-21.235: Response to 17 August 2021 Information Request - n is the number of subjects with no missing values. Program: F_FDA_REQ23_WASO_ECDF_FAS.sas
Abbreviations: N, number of subjects; n, number of subjects with no missing values; WASO, wake after sleep onset

Figure 57. Empirical Cumulative Distribution Function of the Change From Month 3 in LPS (min) to Run-Out Full Analysis Set, Trial ID-078A301



Source: Applicant generated figure, D-21.235: Response to 17 August 2021 Information Request - n is the number of subjects with no missing values. Program: F_FDA_REQ23_WASO_ECDF_FAS.sas. Visual inspection marker lines added by clinical reviewer
Abbreviations: LPS, latency to persistent sleep; N, number of subjects; n, number of subjects with no missing values

Figure 58. Empirical Cumulative Distribution Function of the Change From Month 3 in LPS (min) to Run-Out Full Analysis Set, Trial ID-078A302



Source: Applicant generated figure, D-21.235: Response to 17 August 2021 Information Request - n is the number of subjects with no missing values. Program: F_FDA_REQ23_WASO_ECDF_FAS.sas
Abbreviations: LPS, latency to persistent sleep; N, number of subjects; n, number of subjects with no missing values

17. Clinical Safety: Additional Information and Assessment

17.1. Respiratory Function

17.1.1. COPD

Description

Study ID-078-109 was a randomized, double-blind, placebo-controlled, two treatment period crossover study, with 5-night treatment periods, conducted to investigate the effects of daridorexant on nighttime respiratory function in patients with moderate chronic obstructive pulmonary disease (COPD). The randomized population comprised 28 male and female subjects with a body mass index $<35 \text{ kg/m}^2$, $40\% \leq \text{FEV1} < 80\%$, wakeful $\text{SaO}_2 > 90\%$ and not $< 85\%$ for > 5 minutes while asleep, and no acute exacerbations of COPD within 2 months prior to screening. Each treatment period lasted 5 nights: on Night 1, subjects were randomized to daridorexant or placebo and underwent in-clinic PSG; Nights 2 to 4 involved self-administration at home; Night 5 involved in-clinic PSG. Between each treatment period, there was a 1 to 2-week washout period. The primary efficacy endpoint was the mean SaO_2 during total sleep time (TST) after multiple-dose administration (Night 5), measured by pulse oximetry and PSG. Other

endpoints included the effect of single dose (Night 1) and multiple dose (Night 5) daridorexant on the apnea-hypopnea index (AHI), safety and tolerability, PK parameters, and other nonrespiratory sleep parameters.

Results - Efficacy

The primary endpoint was evaluated in the multiple-dose set, which the Applicant defined as subjects, “who complied with the protocol sufficiently to be likely to exhibit the multiple-dose treatment effects,” (ID-078-109 Clinical Study Report p. 9). Of note, this set excluded two subjects who experienced desaturations after receiving their first dose of investigation product, thus violating the intent-to-treat principle:

- Subject (b) (6) desaturated to <90% for >10% TST after receiving daridorexant on Period 1, Night 1
- Subject (b) (6) desaturated to <85% for >5 minutes after receiving daridorexant on Period 1, Night 5

One additional subject was excluded from the multiple-dose set after receiving both daridorexant and placebo, because of equipment malfunction on Night 5. The Applicant prespecified that for the purposes of their primary efficacy analysis, a drop in SaO₂ ≥2.0% was considered clinically meaningful, i.e., that a mean treatment difference ≥2.0% (daridorexant – placebo) would signify a true treatment difference.

The Applicant reports the following point estimates for the primary endpoint:

Table 125. Summary of Mean SaO₂ During TST After Multiple-Dose Administration of 50 mg Daridorexant (Treatment A) or Placebo (Treatment B)

Parameter [unit]	Statistics	Treatment A N = 25	Treatment B N = 25
Mean SaO ₂ during TST [%]	n/miss	25/0	25/0
	Arithmetic mean	91.77	91.55
	95% CI of arithmetic mean	91.03, 92.51	90.86, 92.25

Treatment: A = Multiple dose of 50 mg ACT-541468, B = Placebo.
CI = confidence interval, miss = number of subjects with missing observations, N = number of subjects treated, n = number of subjects in the considered situation, SaO₂ = oxygen saturation, TST = total sleep time.

Source: Idorsia, Clinical Study Report ID-078-109, Table 11-1

[Table 125](#) demonstrates that there was no numerically significant difference in the point estimates for mean SaO₂ between treatment and placebo in the multiple-dose set. The Applicant also reported that when viewed as a between-treatment difference, the point estimate is 0.18 (90% CI [-0.21 to 0.57], p<0.0001), in which the lower limit of the confidence interval was greater than the 2.0% change threshold. In addition, in a post hoc sensitivity analysis that incorporated the two subjects excluded from the multiple-dose set and imputed last observation carried forward, the point estimate for difference between treatments was 0.11 (90% CI [-0.28 to 0.49], p<0.0001), in which the lower limit of the confidence interval surpassed the significance threshold of 2.0% decrease in SaO₂.

Among the secondary endpoints examined in the multiple-dose set, there was a numeric trend associated with % TST during which SaO₂ was <90%, <85%, and <80% favoring placebo, although this trend did not meet statistical significance. Finally, daridorexant, when compared to placebo, exerted a small, statistically significant change on AHI, as demonstrated in [Table 126](#) below:

Table 126. Effect of Multiple-Dose Administration of 50 mg Daridorexant on AHI During TST

Parameter [unit]	Statistics	
AHI during TST [events/h]	n/miss	25/0
	Difference (A-B)	1.81
	90% CI of the difference	0.85, 2.77
	p-value	0.0036

Treatment: A = Multiple dose of 50 mg ACT-541468, B = Placebo.
AHI = apnea/hypopnea index, CI = confidence interval, miss = number of subjects with missing values in both treatments, n = number of subjects with available value in at least one treatment, TST = total sleep time.

Source: Idorsia, Clinical Study Report ID-078-109, Table 11-12

This treatment difference was not considered clinically significant because it did not exceed the minimal clinically important difference (MCID) for AHI of 5, as outlined by the Applicant.

Results – Safety

Overall, there was a low incidence of treatment-emergent adverse events (TEAEs) in Study 078-109. There were no SAEs or deaths. The treatment discontinuations of Subjects ^{(b) (6)} and ^{(b) (6)} were not handled as AEs; therefore, the Applicant reported no TEAE resulting in treatment discontinuation. Aside from one episode of moderate dyspnea following daridorexant administration, the majority of TEAEs were mild in severity, with the most frequent including gastroenteritis, nasopharyngitis, and headache. Incidences were balanced between treatment and placebo arms, and no significant differences in vital signs or lab values were detected.

Assessment

Although the overall safety and efficacy data from Study 078-109 are generally reassuring, there are several important limitations to interpretation of the results.

- The sample size was small.
- The population was limited to patients with only moderate COPD. Findings cannot be extrapolated to patients with severe COPD, and, although we would expect patients with mild COPD to be at lower risk than those with worse disease, there is no data available for that cohort, limiting the generalizability of the results.
- The short duration treatment period provides insights into short-term safety, but it cannot eliminate the theoretical risk of respiratory depression in populations at high risk for respiratory compromise when used chronically, as intended by the Applicant.
- When taken together, there are trends in the data that could signify a possible safety issue. In the evaluations of the secondary endpoints, % TST <90% and AHI, there was a

pattern of worsening respiratory function in daridorexant versus placebo. For % TST this did not achieve statistical significance, and for AHI, this difference was only 1.81, where 5.0 represents the usual MCID. While neither of these findings represent obvious clinically meaningful changes, it is impossible to predict how these parameters might behave in subjects exposed to longer duration of treatment or with more severe underlying disease or during an exacerbation.

- The two study subjects who discontinued treatment following clinically meaningful desaturations warrant concern for possible adverse reactions. Since the Applicant did not prespecify how intercurrent events, such as desaturations, would be handled, the impact of these two events is only available as a post hoc sensitivity analysis, in which inclusion of those values does push the lower limit of the confidence interval below the threshold for meaningful change in SaO₂.
- Finally, SaO₂ and AHI are noninvasive measurements that are well-understood by prescribers, but SaO₂ can be relatively insensitive to changes in ventilation (i.e., respiratory depression), especially in patients with moderate COPD. These measurements have, however, previously supported labeling claims for other drugs in this class.

In conclusion, there are several limitations to interpreting the data in this small and short trial, and caution should still be used by prescribers when considering daridorexant in patients with mild and moderate COPD. Given the lack of any data in patients with severe COPD, daridorexant should not be prescribed in that population unless additional data becomes available postmarketing.

17.1.2. OSA

Description

Study ID-078-110 was a randomized, double-blind, placebo-controlled, two treatment period crossover study, with 5-night treatment periods, conducted to investigate the effects of daridorexant on nighttime respiratory function in patients with mild to moderate obstructive sleep apnea (OSA). The randomized population comprised 28 male and female subjects with a body mass index <35 kg/m², 5 ≤ AHI <30 events/h on both pre-enrollment and screening PSG, SaO₂ ≥90% during normal respirations and not <85% for >5 minutes while asleep, and “no need for continuous positive airway pressure (CPAP) or a dental appliance for the treatment of OSA.” Each treatment period lasted five nights: on Night 1, subjects were randomized to daridorexant or placebo and underwent in-clinic PSG; Nights 2 to 4 involved self-administration at home; Night 5 involved in-clinic PSG. Between each treatment period, there was a one- to two-week washout period. The primary efficacy endpoint was the AHI during TST after multiple-dose administration (Night 5). Definitions of apneas and hypopneas and scoring of PSGs were consistent with the American Academy of Sleep Medicine guidelines. Other endpoints included the effect of single dose (Night 1) daridorexant on AHI, AHI during different sleep phases (REM versus nonREM), mean SaO₂ during TST, % TST during which SaO₂ was <90%, <85% and <80%, and other nonrespiratory sleep parameters.

Results – Efficacy

The primary endpoint was evaluated in the multiple-dose set, as defined in Study 078-109. This set also violated the intent-to-treat principle: three subjects were excluded from it after receiving one or more doses of placebo or daridorexant:

- Subject (b) (6) had an increase in AHI from 10.6 to 27.9 after receiving placebo on Period 1 Night 1
- Subject (b) (6)'s AHI went from 29.9 to 50.2 after receiving daridorexant on Period 1 Night 5
- Subject (b) (6)'s AHI went from 28.2 to 53.3 events after receiving placebo on Period 1 Night 1

None of these subjects experienced a desaturation, prompting amendment 2 to the protocol, which revised individual subject treatment discontinuation criteria such that subjects discontinued treatment only if an increase in AHI >10 was accompanied by a mean decrease in SaO₂ >4% or a mean nonapneic SaO₂ <85% for >5 minutes. Once again, the AHI MCID was set at 5.

The Applicant reports the following point estimates for the primary endpoint:

Table 127. Summary of AHI During TST After Multiple-Dose Administration of 50 mg Daridorexant (Treatment A) or Placebo (Treatment B)

Parameter [unit]	Statistics	Treatment A N = 25	Treatment B N = 25
AHI during TST [events/h]	n/miss	25/0	25/0
	Arithmetic mean	15.11	14.23
	95% CI of arithmetic mean	11.97, 18.24	11.06, 17.40

Treatment: A = Multiple dose of 50 mg ACT-541468, B = Placebo.
 AHI = apnea/hypopnea index, CI = confidence interval, miss = Number of subjects with missing observations, N = Number of subjects treated, n = Number of subjects in the considered situation, TST = total sleep time.

Source: Idorsia, Clinical Study Report, ID-078-110, Table 11-1

[Table 127](#) demonstrates that there was no numerically significant difference in the point estimates for AHI between treatment and placebo in the multiple-dose set. In support of this finding, the Applicant also reported that when viewed as a between-treatment difference, the point estimate was 0.74 (90% CI [-1.43 to 2.92], p=0.0014), in which the confidence interval remained under the MCID of 5. In a post hoc sensitivity analysis, which incorporated the three subjects excluded from the multiple-dose set and imputed maximum bias, the point estimate for difference between treatments was 2.38 (90% CI [0.22 to 4.97], p≤0.0484), in which the upper limit of the confidence interval nearly approached the MCID of 5.

Among the secondary endpoints examined in the multiple-dose set, none demonstrated a statistically significant difference between treatment and placebo. There was a small numeric trend in the AHI during REM phase sleep favoring placebo, which did not reach statistical or clinical significance. Finally, the Applicant performed a linear regression model, which did not

demonstrate a strong association between severity of OSA and the point estimate for treatment difference (daridorexant – placebo) during TST after multiple doses (R^2 : 0.0034, $p=0.7809$).

Results – Safety

Overall, there was a low incidence of TEAEs in Study 078-110. There were no SAEs or deaths. The treatment discontinuations of Subjects (b) (6) and (b) (6) were not handled as AEs; therefore, the Applicant reported no TEAEs resulting in treatment discontinuation. The majority of TEAEs were mild in severity, with the most frequent being hangover and cystitis. Incidences were balanced between treatment and placebo arms, and no significant difference in vital signs or lab values were detected.

Assessment

The overall safety and efficacy data from Study 078-110 are generally reassuring, but there are several important limitations to interpretation of the results, as in Study 078-109:

- The sample size was small.
- The population was limited to patients with mild to moderate OSA not using CPAP or a dental appliance at baseline. Findings cannot be extrapolated to patients with severe OSA or those who require treatment of their OSA with CPAP or a dental appliance, limiting the generalizability of the results. As the Applicant pointed out, however, many patients with OSA are either undiagnosed or noncompliant with CPAP and other devices; therefore, observations from this study may provide useful insights regarding real world usage. In addition, one might expect any potential deleterious effect on AHI or SaO₂ from daridorexant to be more easily detected without the protective effects of CPAP or an oral appliance, thus providing some reassurance regarding the safety profile observed in this study.
- The short duration treatment period provides insight into short-term safety, but it cannot eliminate the theoretical risk of respiratory depression in populations at high risk for respiratory compromise when used chronically, as intended by the Applicant.
- The three study subjects who discontinued treatment following a clinically meaningful increase in AHI warrant concern for possible adverse reactions. Since the Applicant did not prespecify how such intercurrent events would be handled, the impact of these events is only available as a post hoc sensitivity analysis. In the maximum bias sensitivity analysis, the upper limit of the confidence interval nearly reaches the MCID of 5. One might argue, however, that amendment 2, which permitted the continued treatment of patients with an increase in AHI without concomitant desaturation, would be more likely to skew safety results against the treatment, for which reason the results of Study 078-110 provide additional reassurance.

In conclusion, there are several limitations to interpreting the data in this small and short trial, and caution should still be used by prescribers when considering daridorexant in patients with mild and moderate OSA. Given the lack of any data in patients with severe OSA and those requiring CPAP or dental appliance treatment at baseline, daridorexant should not be prescribed in that population unless additional data becomes available postmarketing.

17.2. Next Day Psychomotor Effects (Driving Study)

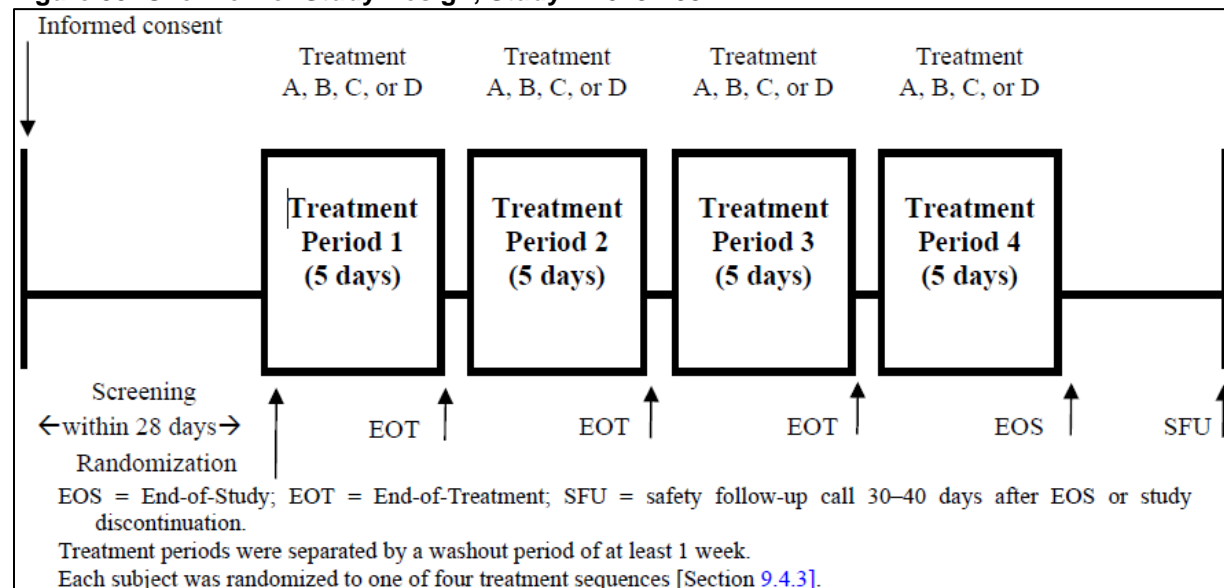
Background

The next-day driving ability of healthy adults (50 to 64 years) and elderly subjects (65 to 80 years) was evaluated in Study ID-078-108 by assessment of the mean standard deviation of the lateral position (SDLP) using a driving simulator in the morning following a single dose and multiple doses of daridorexant (50 and 100 mg) administered at bedtime.

Study Design

Figure 59 shows the design features of the driving study. It was a randomized, double-blind, placebo- and active-controlled, 4-way crossover study. Randomization was stratified by age group (adult: 50 to 64 years versus elderly: 65-80 years) and sex in a 1:1 ratio. All subjects received placebo and zopiclone 7.5 mg (positive control), daridorexant 50 mg (therapeutic dose) and daridorexant 100 mg (supratherapeutic dose). In each treatment period, subjects received study treatment each evening on Days 1 to 4, at least 3 h after the last meal and 10 minutes before the bedtime. Zopiclone 7.5 mg was given only at Days 1 and Days 4 of the respective treatment period; subjects received placebo on Days 2 and 3 to avoid development of tolerance.

Figure 59. Overview of Study Design, Study ID-078-108



Source: Applicant's CSR, Page 48.

Abbreviations: A, daridorexant 50 mg; B, daridorexant 100 mg; C, zopiclone 7.5 mg; D, Placebo

Blood concentrations of daridorexant were measured at predose on Days 2 to 4 and at 8 h post dose (i.e., in the morning) on Days 2 to 5. The relationship between daridorexant concentrations and driving performance was evaluated. The driving assessment was conducted in the morning on Days 2 (i.e., the first dose of study drug) and Days 5 (i.e., after subjects had taken a dose for 4 consecutive nights at bedtime).

All subjects were trained on the driving simulator during screening, with training conducted by the study coordinator or a technician. At each driving simulation session, subjects were instructed to drive for 1 h with a steady lateral position in the right lane in a dual-carriageway highway at a mean speed of 95 km/h.

Study Endpoints

Primary Endpoint

Driving performance as measured by the SDLP (difference from placebo, Δ SDLP, cm) on Days 2 and 5 at 9 h post dose.

Secondary Endpoints

Measured on Days 2 and 5, at 9 h post dose:

- Mean Lateral Position (MLP)
- Mean speed (km/h).
- SD of the mean speed.
- Number of lapses (i.e., short periods of inattention and reduced alertness; defined as a change from the steady lateral position of ≥ 100 cm for ≥ 4 s).
- Subjective driving quality and effort scale.

Pharmacokinetic/Pharmacodynamic Endpoint

Plasma concentrations of daridorexant at predose on Days 2 to 4 and at 8 h post dose on Days 2 to 5.

Analysis Methodology

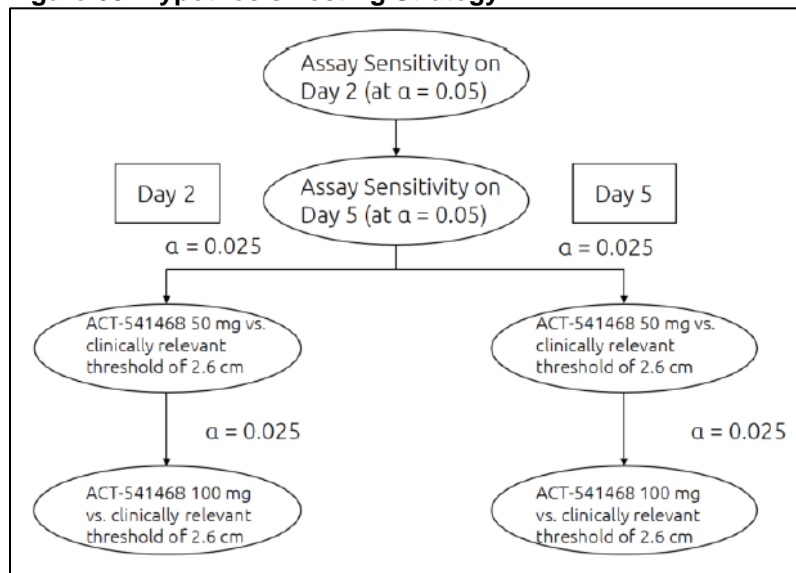
Study 108 had six primary hypothesis tests for the driving endpoint. The first two tests assessed assay sensitivity through comparing zopiclone to placebo at Day 2 and Day 5. The next family of tests assessed both 50 mg and 100 mg daridorexant versus placebo at Day 2 and Day 5. In [Figure 60](#), the Applicant's multiple comparison procedure tested assay sensitivity at $\alpha = 0.05$ sequentially. If both tests reject, then testing proceeded to testing of daridorexant versus placebo. All daridorexant to placebo hypothesis tests are of the form:

Does the test drug (ACT-541468 50 and 100 mg) produce effects similar to placebo?

H₀: The mean difference of ACT-541468 – placebo in SDLP on Day 2 and 5 is ≥ 2.6 cm.

H₁: The mean difference of ACT-541468 – placebo in SDLP on Day 2 and 5 is < 2.6 cm.

Figure 60. Hypothesis Testing Strategy



Source: Applicant's CSR, Page 80.

The assay sensitivity and the primary driving endpoint were analyzed based on an MMRM with treatment, study day, period, sex, age group (50 to 64 and 65 to 80 years), and the interaction of treatment by study day as fixed effects, and subject as a random effect. An unstructured covariance matrix was used to account for the correlation between repeated measurements from the same subject. The model effects were estimated from the least square mean differences for each of the hypotheses (i.e., for H₀, the difference in the least square means between daridorexant [50 and 100 mg] and placebo on Days 2 and 5, based on the same MMRM). The least squares mean, difference in least square means of each daridorexant dose compared to placebo, 95% confidence intervals, and p-values were calculated.

Statistical Reviewer Comment: *The Applicant used an equivalence test to compare daridorexant to placebo. An equivalence test places the hypothesis of no difference in the alternative hypothesis. In this construction, rejection of the null hypothesis implies no difference between drug and placebo.*

Symmetry Analysis

The SDLP was also analyzed by symmetry on the driving performance set, to evaluate whether there was a difference in the number of subjects with an increase in SDLP >2.6 cm (impairment) compared to placebo versus the number of subjects with a decrease in SDLP <-2.6 cm (improvement) compared to placebo. The two frequencies (impaired versus improved) were compared using McNemar's test. The p-value for the two proportions of subjects with impairment (e.g., increase in SDLP >2.6 cm from active treatment over placebo) and subjects with improvement (decrease in SDLP >2.6 cm from active treatment over placebo) were calculated using an exact binomial test.

Statistical Reviewer Comment: (b) (4)

A
 significant *p*-value can support a conclusion that there is a treatment difference. However, a nonsignificant *p*-value can only support the conclusion that there is not enough evidence to reject the assumption of no treatment difference. The symmetry analysis is not a proper analysis for the purpose of the study.

Results

Assay Sensitivity

On both Day 2 and Day 5, zopiclone separated from placebo demonstrating assay sensitivity. The *p*-values are both <0.0001, see [Table 128](#).

Table 128. Assay Sensitivity Analysis: Difference in SDLP (cm) Between Zopiclone and Placebo (Driving Performance Set)

Sched. Treatment	period	day	n	LSM	95% CI of LSM	SE	----- Difference to placebo -----			p-value for threshold 0 cm (one-sided)
							LSM	95% CI of LSM	SE	
Day 2										
Zopiclone			57	42.13	40.06, 44.21	1.056	4.75	3.23, 6.26	0.770	<.0001*
Placebo			58	37.39	35.32, 39.46	1.053				
Day 5										
Zopiclone			56	38.94	36.97, 40.91	1.001	2.37	1.19, 3.56	0.602	<.0001*
Placebo			58	36.56	34.60, 38.52	0.997				

CI = confidence interval, LSM = least square mean, n = number of subjects, SE = standard error. The null hypothesis that the mean difference of zopiclone - placebo in SDLP on Day 2 and 5 is ≤ 0 cm was tested at the 1-sided 2.5% significance level. Analysis was performed using mixed-effect model for repeated measurements (MMRM). Source: [Table 15-71](#) (Table DP_TEST1). Production date: 14Nov2019.

Source: Applicant's CSR, Page 100.

Analysis for Primary Endpoint

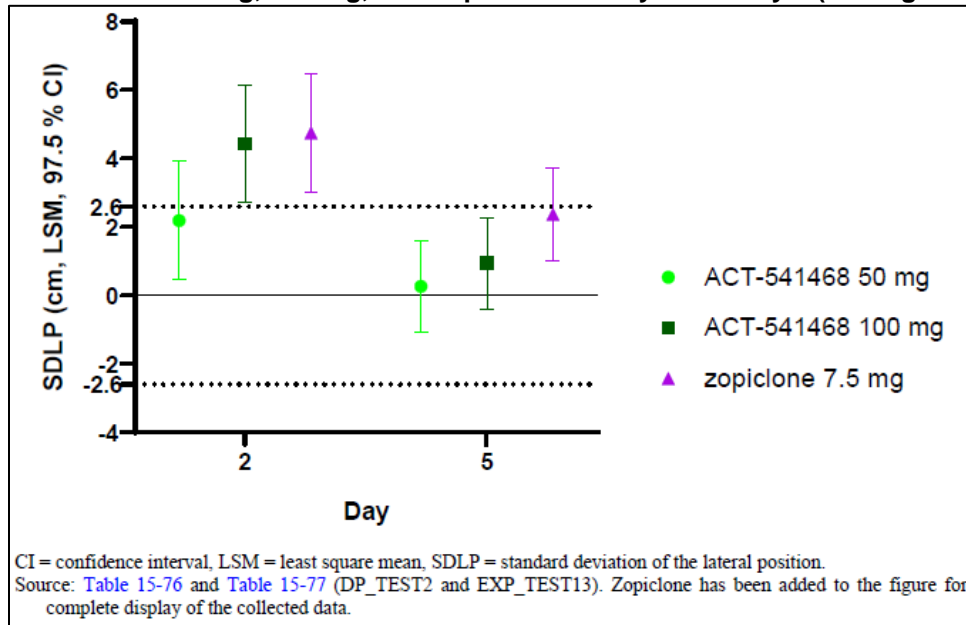
On Day 2, the test for the 50-mg dose of daridorexant failed to reject (*p*=0.2991) the null hypothesis that daridorexant had at least a Δ SDLP ≥ 2.6 cm, see [Table 129](#) and [Figure 61](#). The 50-mg dose had an increase in SDLP of 2.19 cm (97.5% CI: 0.46 to 3.93) compared to placebo. The Day 2 testing stopped at this point. The 100-mg dose had an increase in SDLP of 4.43 cm (97.5% CI: 2.72 to 6.15) compared to placebo.

On Day 5, the test for the 50-mg dose of daridorexant rejected (*p*<0.0001) the null hypothesis that daridorexant had at least a Δ SDLP ≥ 2.6 cm, see [Table 129](#) and [Figure 61](#). The 50-mg dose had an increase in SDLP of 0.26 cm (97.5% CI: -1.08 to 1.59) compared to placebo. Continuing down the testing hierarchy, the test for the 100-mg dose of daridorexant rejected (*p*=0.0027) the

null hypothesis that daridorexant had at least a Δ SDLP ≥ 2.6 cm. The 100-mg dose had an increase in SDLP of 0.94 cm (97.5% CI: -0.40 to 2.27) compared to placebo.

Therefore, daridorexant has a similar effect on next day driving performance to placebo at Day 5. However, we have insufficient evidence to conclude that daridorexant is equivalent to placebo on next day driving performance at Day 2. The observed increase in mean Δ SDLP on Day 2 suggests next day driving impairment.

Figure 61. Primary Driving Endpoint: LSM Estimates of Placebo-Corrected SDLP (cm, 97.5% CI) for Daridorexant 50 mg, 100 mg, and Zopiclone on Day 2 and Day 5 (Driving Performance Set)



Source: Applicant's CSR.

Table 129. Primary Driving Endpoint: Difference in SDLP (cm) Between Daridorexant, Zopiclone, and Placebo on Day 2 and Day 5 (Driving Performance Set)

Sched. period Treatment	day	n	LSM	97.5% CI		SE	----- Difference to placebo -----			p-value for threshold 2.6 cm (one-sided)
				of LSM	SE		LSM	97.5% CI of LSM	SE	
Day 2										
ACT-541468 50 mg	57	39.58	37.21, 41.96	1.055	2.19	0.46, 3.93	0.772		0.2991	
ACT-541468 mg	100	59	41.82	39.46, 44.19	1.051	4.43	2.72, 6.15	0.763	0.9917	
Zopiclone	57	42.13	39.76, 44.51	1.056	4.75	3.01, 6.48	0.770		0.9972	
Placebo	58	37.39	35.02, 39.76	1.053						
Day 5										
ACT-541468 50 mg	59	36.82	34.58, 39.06	0.995	0.26	-1.08, 1.59	0.595		<.0001*	
ACT-541468 mg	100	59	37.50	35.26, 39.74	0.995	0.94	-0.40, 2.27	0.594	0.0027*	
Zopiclone	56	38.94	36.68, 39.74	1.001	2.37	1.02, 3.73	0.602		0.3533	
Placebo	58	36.56	34.32, 38.81	0.997						

CI = confidence interval, LSM = least square mean, SE = standard error. The null hypothesis that the mean difference of ACT-541468 – placebo in SDLP on Day 2 and 5 is ≥ 2.6 cm was tested at the 1-sided 1.25% significance level.
 *Statistically significant p-value. Source: Table 15-76 (Table DP TEST2) Production date: 14NOV2019. Zopiclone has been added to the table for complete display of the collected data. Source: Table 15-77 (Table EXP_TEST13) Production date: 01JUN2020.

Source: Applicant's CSR.

Analysis for Secondary Endpoint

Symmetry Analysis for SDLP

The symmetry analysis compared those subjects whose SDLP improved (subjects with a change from placebo in SDLP < -2.6 cm) to those whose SDLP showed impairment (subjects with a change from placebo in SDLP > 2.6 cm, or where the driving test was stopped, regardless of SDLP).

On both Day 2 and Day 5, zopiclone had more subjects impaired than on their placebo Day 2. Therefore, the symmetry analysis also showed assay sensitivity, see Table 130. On Day 2, the symmetry analysis suggested that more subjects had driving impairment on daridorexant compared to placebo for both doses. On Day 5, there was insufficient evidence to conclude that daridorexant impairs driving compared to placebo.

Table 130. Symmetry Analysis of SDLP (cm) on Day 2 and Day 5 (Overall) (Driving Performance Set)

Contrast	Sched. period day	Threshold [cm]	Impaired subjects n (%)	Improved subjects n (%)	Neutral subjects n (%)	McNemar statistic	p-value
Zopiclone vs Placebo	Day 2	2.6	35 (62.5%)	3 (5.4%)	18 (32.1%)	26.95	<.0001*
	Day 5	2.6	28 (50.0%)	7 (12.5%)	21 (37.5%)	12.60	0.0005*
ACT-541468 50 mg vs Placebo	Day 2	2.6	24 (43.6%)	8 (14.5%)	23 (41.8%)	8.00	0.0070*
	Day 5	2.6	15 (25.9%)	16 (27.6%)	27 (46.6%)	0.03	1.0000
ACT-541468 100 mg vs Placebo	Day 2	2.6	38 (65.5%)	4 (6.9%)	16 (27.6%)	27.52	<.0001*
	Day 5	2.6	14 (24.1%)	7 (12.1%)	37 (63.8%)	2.33	0.1892

Impaired subjects = subjects with increase in SDLP from corresponding treatment over placebo > threshold. Improved subjects = subjects with decrease in SDLP from corresponding treatment over placebo > threshold. Neutral subjects = subjects with SDLP between 2.6 and -2.6 cm from corresponding treatment over placebo. P-value was calculated using an exact binomial test. *Statistically significant p-value. Source: Table 15-84 (Table DP_SYM). Production date 14Nov2019

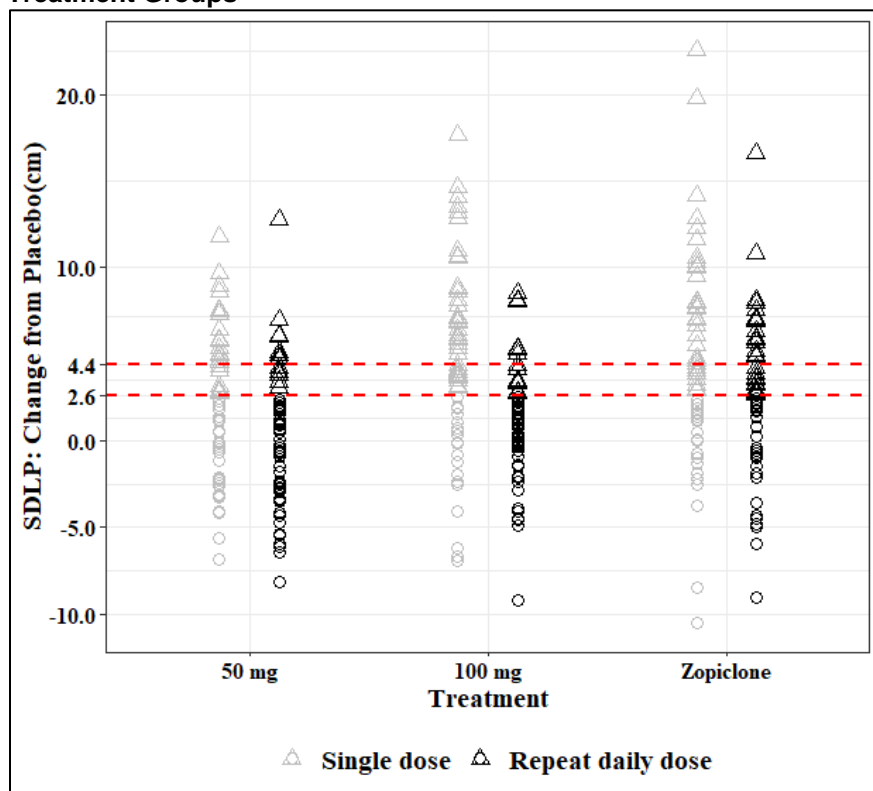
Source: Applicant's CSR, Page 109.

Figure 62. ΔSDLP After Single Dose (on Day 2) and Repeat Daily Dose (on Day 5) Across Treatment Groups

shows the distribution of ΔSDLP on Day 2 (after single dose) and Day 5 (after 4 repeat dose) across treatment groups. Subjects with blood alcohol concentration of 0.5 and 0.8 g/L have been reported to show ΔSDLP of 2.6 cm and 4.4 cm, respectively. Table 131 summarizes the number of subjects exceeding the ΔSDLP threshold of 2.6 cm and 4.4 cm across treatment groups after single and repeat dosing. After the first dose, 25 subjects in 50 mg and 38 subjects in 100 mg had ΔSDLP >2.6 cm, which indicates dose-dependent next-day driving impairment potential of daridorexant. On repeat dosing, 15 subjects in 50 mg and 14 subjects in 100 mg had ΔSDLP >2.6 cm. Similar trends were observed for ΔSDLP threshold of 4.4 cm. It should be noted that no subjects in daridorexant group prematurely stopped driving in the study.

In terms of number of lapses, the Applicant analysis showed more lapses on Day 2 across all 3 active treatments compared to placebo (74, 72, 72, and 48 lapses with zopiclone, daridorexant 50 and 100 mg, and placebo treatment, respectively), whereas on Day 5, the number of lapses were similar across treatments (51, 55, 47, and 53 lapses with zopiclone, daridorexant 50 and 100 mg, and placebo treatment, respectively).

Figure 62. Δ SDLP After Single Dose (on Day 2) and Repeat Daily Dose (on Day 5) Across Treatment Groups



Source: FDA OCP Reviewer's analysis

The reference line at 2.6 cm and 4.4 cm refer to Δ SDLP changes at alcohol limit of 0.5 and 0.8 g/L

Abbreviations: SDLP, standard deviation of the lateral position

Table 131. Number of Subjects Exceeding Δ SDLP of 2.6 cm and 4.4 cm After Single Dose (on Day 2) and Repeat Daily Dose (on Day 5) Across Treatment Groups

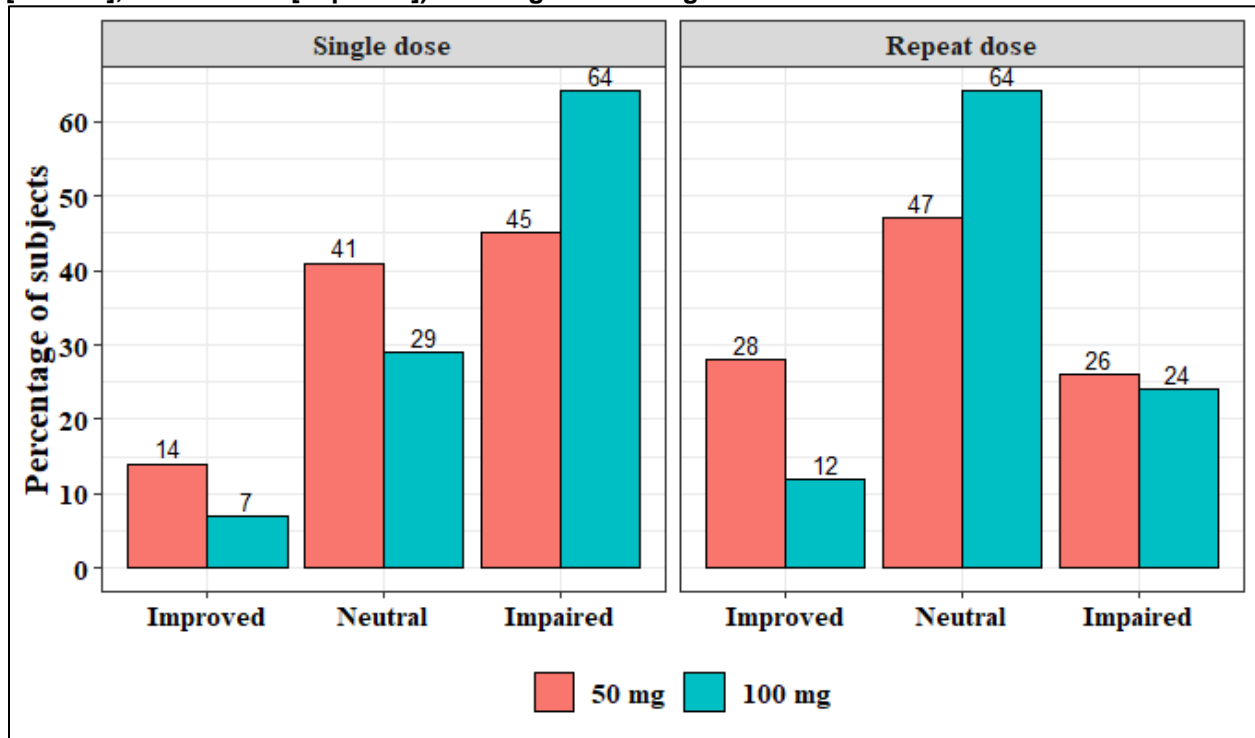
Treatment Group	Single dose		Repeat dose	
	Δ SDLP >2.6 cm	Δ SDLP >4.4 cm	Δ SDLP >2.6 cm	Δ SDLP >4.4 cm
Daridorexant 50 mg	25	16	15	9
Daridorexant 100 mg	38	27	14	6
Zopiclone 7.5 mg	36	27	28	16

Source: FDA OCP Reviewer's analysis

Abbreviations: SDLP, standard deviation of the lateral position

Error! Reference source not found. shows the proportion of improved, neutral, and impaired subjects after single dose and repeat dosing. There were more impaired subjects than improved subjects after a single dose in both the 50 mg and 100 mg treatment groups as well as after repeat dosing of the 100-mg dose, which suggested driving-impairment potential of daridorexant.

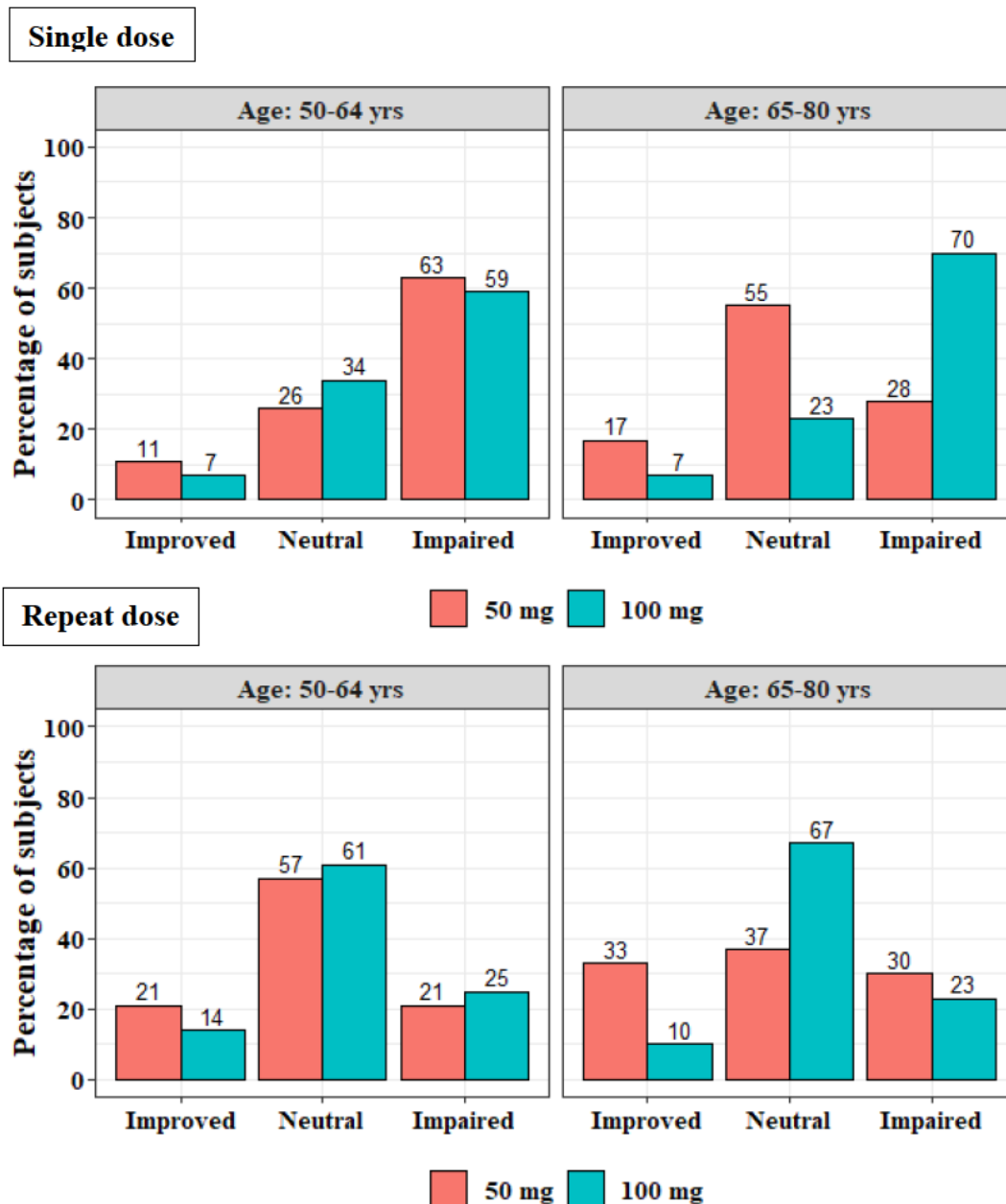
Figure 63. Proportion of Subjects With SDLP Changes (<-2.6 cm [Improved], -2.6 to 2.6 cm [Neutral], and >2.6 cm [Impaired]) in 50 mg and 100 mg Daridorexant



Source: FDA OCP Reviewer's analysis
Abbreviations: SDLP, standard deviation of the lateral position

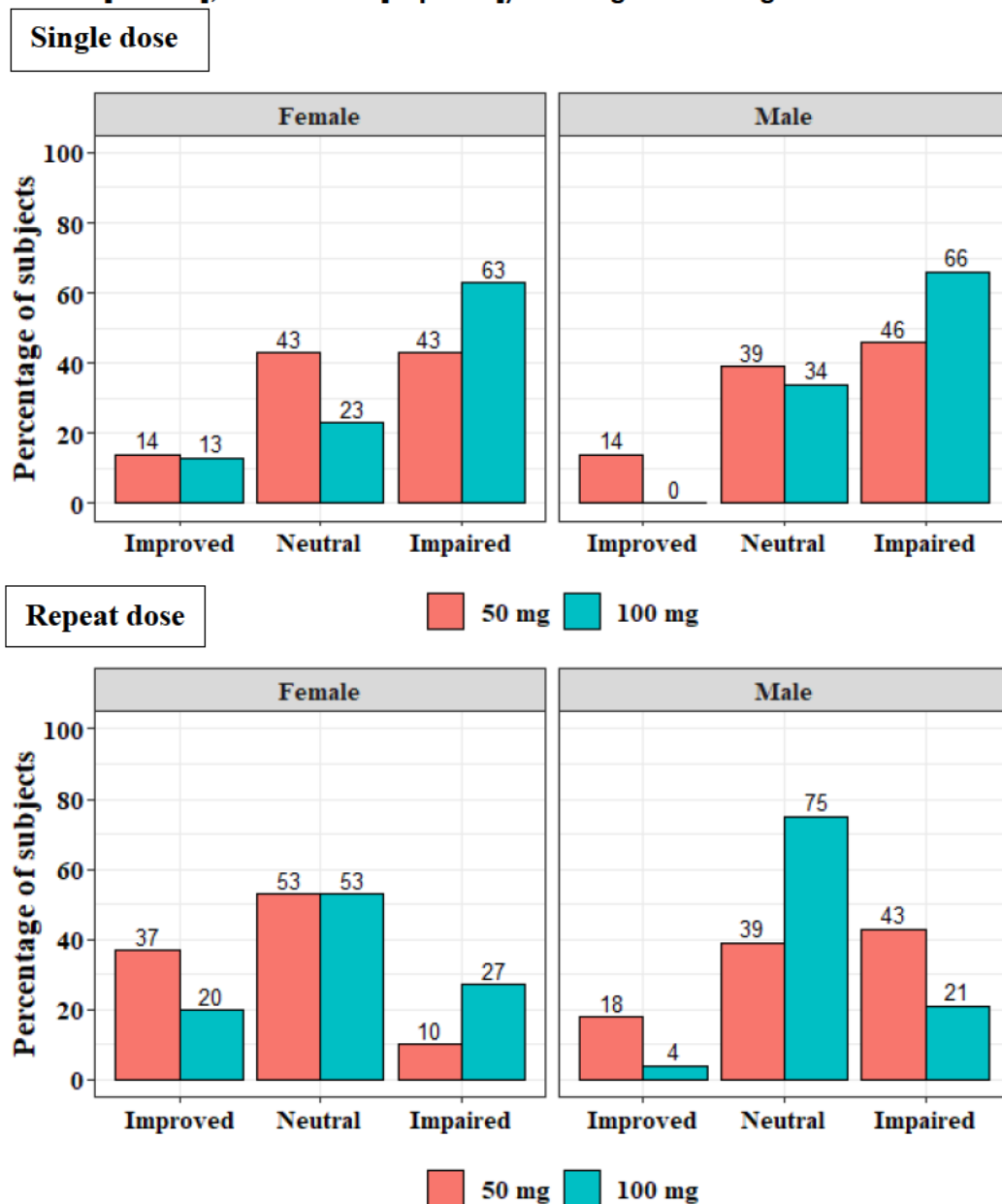
Error! Reference source not found. was then further stratified by age and sex to evaluate any impact of age and sex on driving impairment potential of daridorexant. No relationship between dose and proportion of impaired subjects with SDLP >2.6 cm by age was observed on Day 2 and Day 5 in [Figure 64](#). Similarly, no relationship between dose and proportion of impaired subjects with SDLP >2.6 cm in male and female subjects can be observed on Day 2 and Day 9 in [Figure 65](#).

Figure 64. Proportion of Nonelderly (50-64 yrs.) and Elderly (>65 yrs.) Subjects With SDLP Changes (<-2.6 cm [Improved], -2.6 to 2.6 cm [Neutral], and >2.6 cm [Impaired]) in 50 mg and 100 mg Daridorexant.



Source: FDA OCP Reviewer's analysis
Abbreviations: SDLP, standard deviation of the lateral position

Figure 65. Proportion of Male and Female Subjects With SDLP Changes (<-2.6 cm [Improved], -2.6 to 2.6 cm [Neutral], and >2.6 cm [Impaired]) in 50 mg and 100 mg Daridorexant

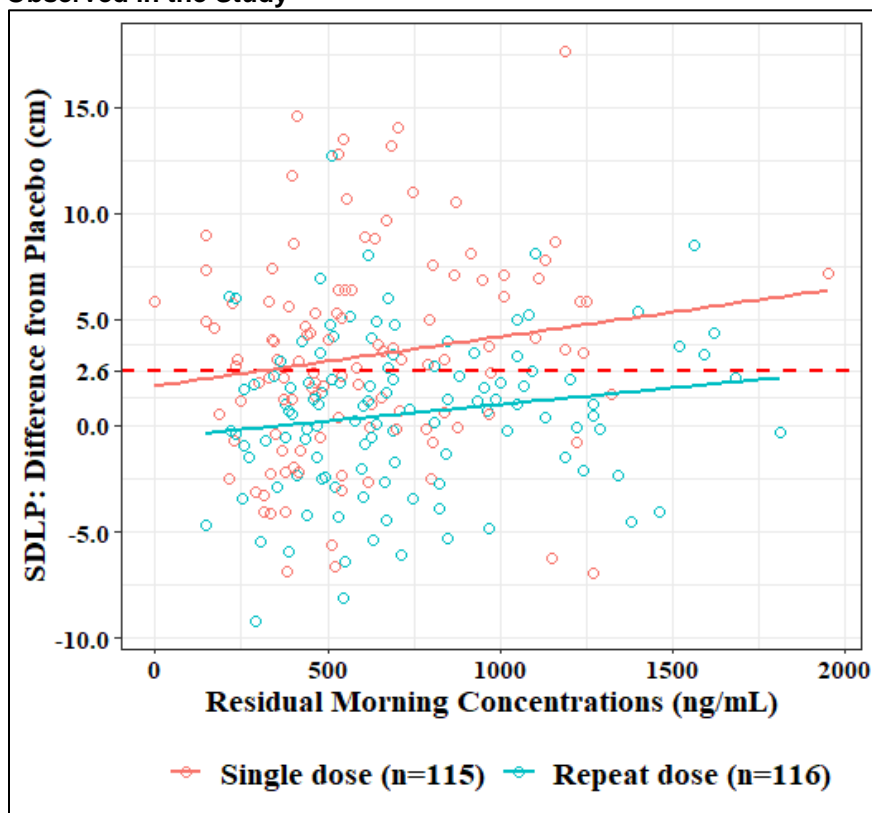


Source: FDA OCP Reviewer's analysis
 Abbreviations: SDLP, standard deviation of the lateral position

Pharmacokinetic/Pharmacodynamic Analysis

[Error! Reference source not found.](#) shows the findings of linear regression analysis of the relationship between next-day residual concentrations of daridorexant and Δ SDLP. The 95% CI of the slope includes zero indicating a lack of statistically significant relationship ([Error! Reference source not found.](#)). [Error! Reference source not found.](#) shows that some subjects have Δ SDLP >2.6 cm or 4.4 cm across next-day residual daridorexant concentrations indicating the presence of inter subject variability in the driving test.

Figure 66. Relationship Between Next-Day Residual Concentrations of Daridorexant and Δ SDLP Observed in the Study



Source: FDA OCP Reviewer's analysis
 Abbreviations: SDLP, standard deviation of the lateral position

Table 132. Intercept and Slope Estimates Obtained From Linear Regression of Next-Day Residual Concentration - Δ SDLP Data

Dosing Frequency	Intercept (cm)		Slope (cm per ng/mL)	
	Mean	95% CI	Mean	95% CI
Single dose	1.866	-0.032, 3.764	0.0023	-0.0004, 0.0051
Repeat dose	-0.585	-2.071, 0.900	0.0016	-0.0002, 0.0034

Source: FDA OCP Reviewer's analysis

Discontinuations

No subjects prematurely stopped during the driving assessment. Two subjects (i.e., Subject ^{(b) (6)} after 50-mg dose due to positive alcohol breath test, and Subject ^{(b) (6)} after placebo due to adverse events of “joint dislocation of the left shoulder”) prematurely discontinued the trial.

Office of Clinical Pharmacology Reviewer Comments: Both Δ SDLP and symmetry analyses suggest a dose-dependent impairment of next-day driving performance after the first dose of daridorexant 50 mg and 100 mg. The label should mention that there is a potential for next-day residual effects in some patients taking 50 mg daridorexant.

17.3. HAP study

17.3.1. Human Abuse Potential Study With Daridorexant (Study ID-078-107)

This HAP study was a randomized, double-blind, double-dummy, placebo- and active-controlled, 6-way cross-over study to evaluate the abuse potential of single oral doses of daridorexant. The study consisted of four phases: screening, qualification, treatment, and follow-up.

The primary objective of the study was to determine the abuse potential of daridorexant using placebo as a control and suvorexant and zolpidem as positive controls. The secondary objectives consisted of assessing the safety and tolerability of daridorexant at therapeutic and supratherapeutic single doses.

Subjects were healthy male or female adults, 18 to 55 years of age who have used sedatives for recreational purposes at least 10 times in their lives and at least once in the 12 weeks before screening. A total of 72 subjects were randomized to the treatment phase and 63 subjects completed the study.

17.3.1.1. Qualification Phase

The qualification phase was a double-blind cross-over drug discrimination test in which subjects were asked to discriminate between the effects of a single oral dose of 150 mg suvorexant (CIV), 30 mg zolpidem, and placebo. Subjects were dosed on Day 1 of the study with each treatment being dosed approximately 3 days apart. Subjects received the study drugs on test days following a fasting period of at least 8 hours. Subjects were required to continue fasting during the test session for at least 4 hours after treatment administration. The qualification criteria consisted of:

- The ability to distinguish orally administered suvorexant (150 mg) and zolpidem (30 mg) from placebo on the bipolar Drug Liking ('at this moment') VAS. A Drug Liking score ≥ 15 points higher, relative to placebo, on this scale was necessary.
- Acceptable placebo response based on Drug Liking (score between 40 and 60 points, inclusive).
- Ability to complete the PD assessments and acceptable overall responses, as judged by the investigator or designee.
- Ability to tolerate doses of positive control drugs as judged by the investigator or designee based on available safety data.
- General behavior suggested that the subject could successfully complete the study, as judged by the research site staff.

17.3.1.2. Treatment Phase

The washout period between the last treatment of the qualification phase and the first treatment of the treatment phase was three days. Eligible subjects (as determined by the qualification phase) entered the treatment phase and remained as inpatients in the clinical research unit.

Subjects were randomized to receive each of the six treatments in a randomized, double-blind, double-dummy fashion:

- Placebo
- 50 mg daridorexant
- 100 mg daridorexant
- 150 mg daridorexant
- 30 mg zolpidem
- 150 mg suvorexant

Each subject received five overencapsulated tablets and three tablets of daridorexant or its matching placebo.

For each treatment, subjects were fasted for at least 10 hours predose and for 4 hours postdose. Study drug administration in each treatment period was separated by a minimum washout interval of 3 days. Thus, a sufficiently long washout period was used in this study.

The proposed highest therapeutic dose of daridorexant is 50 mg once/day, therefore the Applicant used this dose as their lowest dose and included doses 2- to 3-fold higher as suprathreshold doses.

Subjective and Cognitive Measures

The T_{max} of zolpidem, suvorexant, and daridorexant is 1 hour after dosing. The assessment times varied depending on the endpoint to be measured, however, they covered the length of the study and PD assessments were conducted at the appropriate times. The pharmacodynamic measures included the use of VAS, safety endpoints, and observer's assessments, and were conducted at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose. All other assessments for PK were conducted at 0, 0.25, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose.

The primary measure was:

- Drug Liking ('at this moment') VAS Emax (Bipolar) (Emax)

The secondary measures included:

- Drug Liking VAS ("at this moment"), (Emin, TEmax, TEmin, TA_AUE)
- Overall Drug Liking VAS (Emax and Emin)
- Take Drug Again VAS (Emax and Emin)
- High VAS (Emax and Emin)
- Good Drug Effects VAS (Emax, TEmax, TA_AUE)
- Bad Drug Effects VAS (Emax, TEmax, TA_AUE)
- Drug Similarity scale (Emax)
- Drowsiness/Alertness VAS (Emax, Emin, TEmax, TA_AUE)
- Bowdle VAS (Emax) – psychedelic effect
- Any effects VAS (Emax, TEmax, TA_AUE)

The Applicant also assessed observer-rated measures of sedation and cognitive/psychomotor impairment:

- Observer assessment of alertness/sedation scale
- Reaction time task (RTT)
 - RTT five-choice error score
- Paired Associates Learning
- Rapid visual information processing
 - Rapid visual information processing median response latency

Pharmacokinetic Endpoints:

- C_{max}
- T_{max}
- AUC_{0-t}
- Half-life

Safety Endpoints:

- Incidence, frequency, and severity of AEs
- Vital signs (blood pressure, respiratory rate, heart rate, and oral temperature)
- Electrocardiograms (ECGs)
- Clinical laboratory test results (clinical chemistry, hematology, urinalysis)
- Physical examination findings
- Columbia-Suicide Severity Rating Scale

17.3.1.3. Results

The data below were drawn from the Statistical Review and Evaluation of the present HAP study, as conducted by Dr. Ling Chen, FDA Office of Biostatistics VI. The primary measure of Drug Liking ('at this moment'), as well as the secondary measures Take Drug Again and Overall Drug Liking in response to zolpidem, suvorexant, daridorexant, and placebo were evaluated for statistically significant differences by Dr. Chen as well as the Applicant.

Subjects in the qualification phase had a maximum mean drug liking (bipolar VAS, E_{max}) score of 84.7 ± 1.38 for suvorexant, 82.9 ± 1.3 for zolpidem, and 50.2 ± 0.1 for placebo. The mean difference in these scores between drug treatment and placebo was 34.6 ± 1.4 for suvorexant and 32.7 ± 1.4 for zolpidem indicating that subjects were able to discriminate between drug treatment and placebo and moved to the treatment phase of the study. However, the drug treatment scores were higher than those presented in Table 133, which is data gathered from a modified completer population (MCP). The MCP is defined as completers who do not satisfy the following criteria for the primary endpoint, Drug Liking (E_{max}).

- (1) The difference between maximum and minimum of E_{max} scores for all treatments is smaller than or equal to 5 (that is, similar E_{max} scores across all treatments including placebo).
- (2) $E_{max}(P) > 60$ and $E_{max}(P) - E_{max}(Z30) \geq 5$ (or $E_{max}(P) - E_{max}(S150) \geq 5$).

This analysis removed five subjects from the completer population (Subject numbers [REDACTED] (b) (6) [REDACTED]) generating an MCP that contains 58 subjects compared to the N=63 analyzed by the Applicant. Importantly, this change to the completer population did not change the statistical outcome, between the Applicant and the Agency, of the primary or secondary measures analyzed in Table 133.

The subjective measures of Drug Liking, Take Drug Again, and Overall Drug Liking are bipolar scales ranging from 0 to 100 with 50 as neutral, and an a priori defined acceptable placebo range of 40 to 60.

The data in Table 133 indicate that the positive comparators, suvorexant and zolpidem, were significantly different from placebo for the primary measure of Drug Liking, validating the study. The positive comparators were also significantly different from placebo in the secondary measures of Take Drug Again and Overall Drug Liking. Also, doses of 100 and 150 mg daridorexant did not produce less drug liking than the positive comparators, and this was repeated in the secondary measures of Take Drug Again and Overall Drug Liking. However, the lower dose of 50 mg daridorexant was significantly different from the positive comparators in the primary measure of Drug Liking. The 50-mg dose of daridorexant was significantly different from placebo in the secondary measure of Overall Drug Liking. Taken together, these data indicate that the abuse potential of daridorexant is not significantly different from zolpidem and suvorexant.

Table 133. Effects of Oral Placebo, Zolpidem 30 mg, Suvorexant 150 mg, and Daridorexant (50, 100, and 150 mg) on Key Subjective Measures (VAS) - E_{max} Scores (Scale 0-100, Mean ± SD) Using the Modified Completer Population

Measure	Placebo	Zolpidem 30 mg	Suvorexant 150 mg	Daridorexant 50 mg	Daridorexant 100 mg	Daridorexant 150 mg
Drug Liking ^A (at this moment) (bipolar) (N=58)	52.8±1.2	80.1±1.9*	80.3±2.0*	72.0±2.2* ^{ZS}	79.1±2.2	80.6±1.9
Take Drug Again ^A (bipolar) (N=58)	53.4±1.8	79.8±2.3*	81.6±2.3*	74.3±2.9	79.5±2.5	81.7±2.4
Overall Drug Liking ^A (bipolar) (N=58)	53.8±1.4	78.6±2.3*	81.3±2.2*	73.1±2.6*	79.2±2.5	80.6±2.3

Source: Reviewer generated table from study report for Study ID-078-107

^A data based on a modified completer population: subjects (b) (6) were removed from the analysis

* significantly different from placebo with a p-value<0.0001

^Z significantly different from zolpidem (30 mg) with a p-value<0.0001

^S significantly different from suvorexant (150 mg) with a p-value<0.0001

Abbreviations: N, number of subjects

The Applicant also assessed several other secondary measures. The measures Good Drug Effects, High, and Bad Drug Effects are unipolar scales ranging from 0 to 100 with 0 as neutral and an acceptable placebo range of 0 to 20. The measures of Good Drug Effects and High were close to neutral for the placebo group while all of the other treatment groups were significantly higher (Table 134). Similar to the primary measure (i.e., Drug Liking), the 50 mg daridorexant treatment was significantly lower than the positive controls and the 100 and 150 mg treatments were not significantly different from the positive comparators. The measurement of Bad Drug effects was statistically significantly different between the drug treatment groups and placebo, however, the overall magnitude of the responses was very low, and it is unclear whether this would be a significant effect in an abuse setting. The results for Any Effects and Alertness/Drowsiness scales presented in Table 134 are indicative of the therapeutic indication of the drugs used in the study (e.g., insomnia) and indicate that all of the drugs produce sedative effects compared to placebo. The Applicant also measured the internal and external perceptions of psychedelic effects of daridorexant using a Bowdle VAS. The positive comparators and all doses of daridorexant produced statistically higher perceptions of psychedelic effects compared to placebo.

Table 134. Mean of Secondary Endpoints Zolpidem 30 mg, Suvorexant 150 mg, and Daridorexant (50, 100, and 150 mg)

Measure	Placebo	Zolpidem 30 mg	Suvorexant 150 mg	Daridorexant 50 mg	Daridorexant 100 mg	Daridorexant 150 mg
High (unipolar) (N=63)	5.5±16.6	60.2±32.6*	50.1±37.1*	38.2±36.2* ^{ZS}	48.4±38.2*	58.1±35.0*
Good Drug Effects (unipolar) (N=63)	7.7±19.3	60.4±29.4*	63.1±31.7*	45.0±34.2* ^{ZS}	59.0±33.1*	65.4±28.3*
Bad Drug Effects (unipolar) (N=63)	1.1±5.2	14.0±27.6*	11.8±23.3*	3.5±12.9	10.7±23.7*	10.5±20.9*
Any Drug Effects (unipolar) (N=63)	7.8±19.4	62.9±27.5*	70.9±29.1*	47.2±34.3* ^{ZS}	62.0±32.2*	68.5±26.1*
Alertness/Drowsiness (Emin) (unipolar) (N=63)	42.1±15.8	19.4±15.2*	12.1±12.2*	23.3±17.8* ^{ZS}	13.9±14.2*	9.3±10.4*

Source: Reviewer generated table from study report for Study ID-078-107

* significantly different from placebo with a p-value<0.0001

^Z significantly different from zolpidem (30 mg) with a p-value<0.0001

^S significantly different from suvorexant (150 mg) with a p-value<0.0001

Abbreviations: N, number of subjects

The Applicant also conducted a Drug Similarity VAS 12-hours postdosing. This VAS is a 0 to 100 scale where 0 equals definitely not and 100 equals definitely so in regard to comparison of the following drugs: amphetamine, barbiturates, benzodiazepines, cannabis, cocaine, ecstasy, ketamine, lysergic acid diethylamide, methamphetamine, opioids, phencyclidine, psilocybin, and sedatives. The data are presented in the review conducted by Dr. Ling Chen. In brief, the subjects found daridorexant to be most similar to sedatives (mean range: 43.3 to 83.3) and ketamine (CIII) (mean range: 66.0 to 75.0).

17.3.1.3.1. Adverse Events in Core Phase

The Applicant monitored for treatment-emergent AEs across all arms of the treatment phase of the study. All AEs, including abuse-related AEs were coded to a Medical Dictionary for Regulatory Activities (MedDRA) and the MedDRA system organ class and preferred term (PT). The abuse related AEs are summarized in [Table 135](#) and indicate that suprathreshold doses of daridorexant (i.e., 100 and 150 mg) produce a similar number and percent of AEs to the positive comparator drugs. A notable difference being the reports of Euphoric Mood which were lower in the daridorexant treatment arms compared to the positive comparators.

Table 135. Abuse-Related Treatment-Emergent Adverse Events Reported During the Treatment Phase of HAP Study ID-078-107, Expressed as N (%)

Drug	Daridorexant (mg)			Suvorexant (mg)	Zolpidem (mg)	Placebo
	50 (N=67)	100 (N=69)	150 (N=67)	150 (N=67)	30 (N=69)	0 (N=66)
Abnormal Dreams	1 (1.5)	1 (1.4)	--	2 (3.0)	--	--
Affect Lability	--	--	--	--	1 (1.4)	--
Confusional State	1 (1.5)	--	1 (1.5)	--	8 (11.6)	--
Disturbance in Attention	1 (1.5)	--	--	--	2 (2.9)	--
Dizziness	1 (1.5)	2 (2.9)	1 (1.5)	1 (1.5)	4 (5.8)	1 (1.5)
Euphoric Mood	2 (3.0)	4 (5.8)	3 (4.5)	6 (9.0)	14 (20.3)	1 (1.5)
Fatigue	2 (3.0)	3 (4.3)	4 (6.0)	2 (3.0)	2 (2.9)	--
Feeling Abnormal	1 (1.5)	1 (1.4)	1 (1.5)	3 (4.5)	10 (14.5)	--
Feeling Drunk	--	--	1 (1.5)	--	--	--
Hallucination, Visual	--	--	--	1 (1.5)	--	--
Illusion	--	--	1 (1.5)	--	2 (2.9)	--
Mental Impairment	--	--	--	--	2 (2.9)	--
Paresthesia	--	--	1 (1.5)	1 (1.5)	1 (1.4)	--
Somnolence	33 (58.2)	46 (79.7)	59 (88.1)	56 (83.6)	64 (92.8)	16 (24.2)

Source: Reviewer generated table from study report for Study ID-078-107
 Abbreviations: N, number of subjects

17.3.1.3.2. Pharmacokinetics

The majority of the peak PD effects produced by daridorexant were present within 1 to 2 hours of oral administration of the drug. These data are supported by the T_{max} of the drug, which is 1.1 hour. The duration of the PD effects was longer for suvorexant because of the longer half-life but was similar for zolpidem and daridorexant, lasting six to eight hours postdose.

Table 136. PK Parameters of Single Oral Doses of Daridorexant at 50, 100, and 150 mg in HAP Study ID-078-107

PK Parameters	Dose of Daridorexant (mg)		
	50	100	150
C _{max} (ng/mL)	1115.1	1653.4	1958.4
T _{max} (h)	1.1	1.1	1.1
AUC _{0-inf} (ng·h/mL)	7692.4	13847.6	18983.2
T _{1/2} (h)	7.2	8.4	8.6

Source: Reviewer generated table from study report for Study ID-078-107

Abbreviations: AUC_{0-inf}, area under the concentration-time curve extrapolated to infinity; C_{max}, maximum plasma concentration; PK, pharmacokinetic; T_{1/2}, terminal half-life; t_{max}, time to maximum concentration

17.3.1.4. Conclusion

The data from HAP Study ID-078-107 indicate that the abuse potential of daridorexant is similar to that of zolpidem and suvorexant, both of which are controlled in Schedule IV of the Controlled Substances Act. The data from the study indicate that the 50-mg dose of daridorexant produced significantly lower PD measures compared to the positive comparators, however, they were significantly greater than placebo. Notably, the 50-mg dose is the highest therapeutic dose of daridorexant, and it was compared to 3-fold and 7.5-fold suprathreshold doses of the positive comparators, 30 mg zolpidem and 150 mg suvorexant, respectively, the highest therapeutic doses approved by FDA. The daridorexant suprathreshold doses of 100 and 150 mg (2- to 3-fold the highest proposed therapeutic dose) produced PD measures that were not significantly different from those of the positive comparators used in this study. As a result, Study ID-078-107 is supportive evidence that daridorexant has abuse potential similar to the Schedule IV drugs zolpidem and suvorexant.

18. Mechanism of Action/Drug Resistance: Additional Information and Assessment

The relevant information regarding the mechanism of action of daridorexant is described in Sections [5](#) and [13.1](#).

19. Other Drug Development Considerations: Additional Information and Assessment

19.1. COA Review of sTST and IDSIQ

Analyses supporting evaluations are presented in Sections [6.3.1.2](#) (Efficacious dose; Secondary Endpoints) and [6.3.2.1](#) (IDSIQ Sleepiness Fitness for Purpose).

19.1.1. sTST

sTST was measured by Item 9 in the Sleep Diary Questionnaire, which is a daily eDiary completed in the morning between 6:00 am and 10:00 am with a recall period of “last night”.

9. In total, how long did you sleep last night? (This should just be your best estimate, based on when you went to bed and woke up, how long it took you to fall asleep, and how long you were awake. You do not need to calculate this by adding and subtracting; just give your best estimate.) _____ h _____ min

The secondary efficacy endpoints of Study ID-078A301 and Study ID-078A302 based on sTST were defined as:

- Change from baseline to Month 1 in sTST.
- Change from baseline to Month 3 in sTST.

The Applicant has taken several approaches to explore the thresholds of clinically meaningful within-patient change in sTST.

- Patient interviews (n=17)
 - 10 people indicated that an increase of at least 2 or 3 total hours asleep to 5 nights per week would be an important improvement in treating their insomnia
- Anchor-based analyses anchored on 2 category improvement in patient global impression of severity daytime symptoms scale using phase 2 data (open-label Study AC-078A203)
 - Approximately 1.4 weekly average sleep hours per day were estimated as clinical meaningful improvement for insomnia treatment Thresholds derived from the anchor-based analyses using phase 2 data for sTST should be confirmed using phase 3 data because of the following reasons:
 - Open-label study design of phase 2 Study AC-078A203
 - Shorter study period (2 weeks treatment) than phase 3 trials (12 weeks treatment)
 - Multiple anchor scales are available in phase 3 trials

To interpret study results on sTST endpoint, anchor-based analyses using pooled phase 3 trial data were requested. The requested anchor scales to be used in anchor-based analyses include patient global impression-severity and -change (PGI-S and PGI-C) nighttime symptoms as well as PGI-S and PGI-C daytime symptoms. The derived thresholds of clinically meaningful within patient change in sTST average weekly score (in minutes) at Month 1/Visit 6 and Month 3/Visit 8 from both phase 3 trials are summarized in [Table 137](#) and [Table 138](#) below.

Table 137. Anchor-Based Estimates of Thresholds of Clinical Meaningful Within Patient Change in sTST Average Weekly Score (in Minutes) Change From Baseline to Month 1 and Month 3, Study ID-078A301 (N=930)

Anchor Scales				
Anchor Category	PGA-S (Daytime Symptoms)		PGI-C (Daytime Symptoms)	
Considered Clinically Meaningful Improvement	2-Point Decrease	Moderately Better	PGI-S (Night-Time Symptoms) 2-Point Decrease	PGI-C (Night-Time Symptoms) Moderately Better
sTST average weekly score (in minutes) change from baseline to Month 1				
Median change	67.1	54.9	80.7	62.9
(95% CI)	(50.0, 78.0)	(46.4, 69.3)	(57.9, 94.3)	(52.9, 75.7)
sTST average weekly score (in minutes) change from baseline to Month 3				
Median change	66.6	74.3	83.2	75.7
(95% CI)	(57.8, 75.7)	(60.0, 87.2)	(72.1, 94.3)	(63.6, 84.0)

Source: COA reviewer table derived from Applicant IR response dated May 18, 2021, Table 10
 Abbreviations: CI, confidence interval; PGA-S, patient global assessment of severity; PGI-C, patient global impression-change; PGI-S, patient global impression-severity; sTST, subjective total sleep time

Table 138. Anchor-Based Estimates of Thresholds of Clinical Meaningful Within Patient Change in sTST Average Weekly Score (in Minutes) Change From Baseline to Month 1 and Month 3, Study ID-078A302 (N=924)

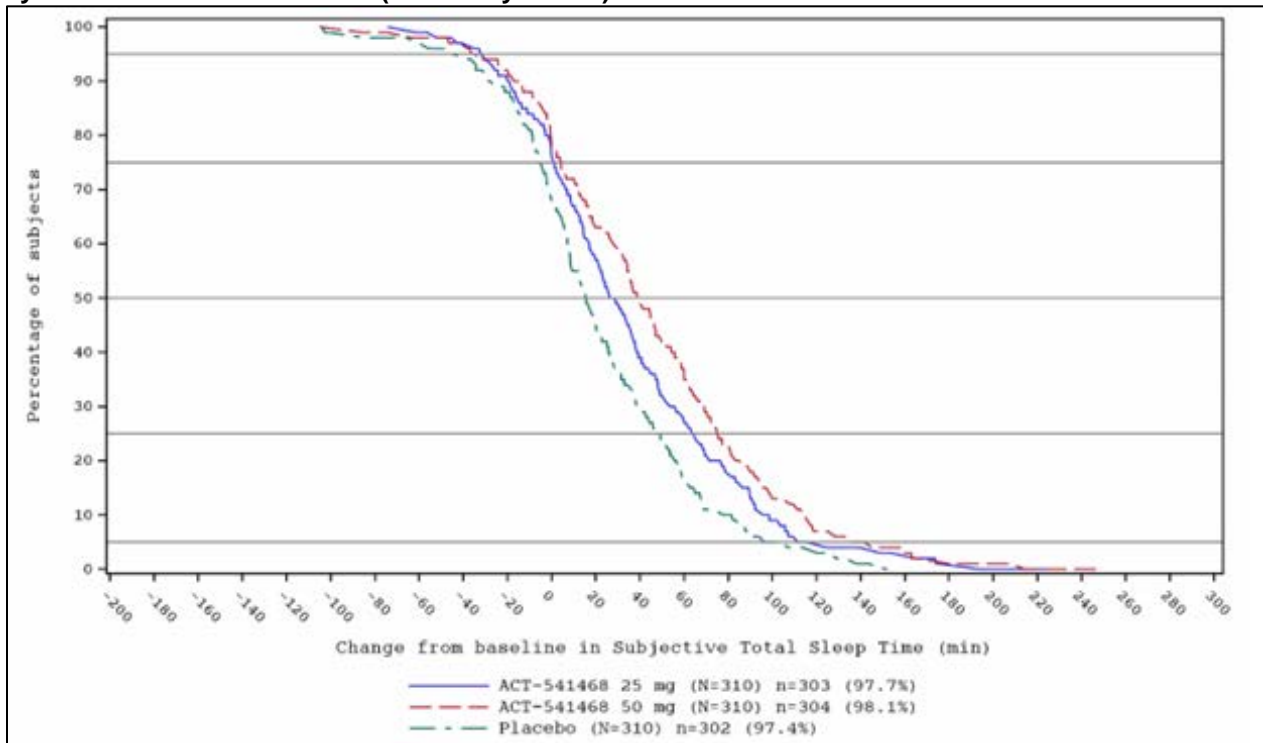
Anchor Scales				
Anchor Category	PGA-S (Daytime Symptoms)		PGI-C (Daytime Symptoms)	
Considered Clinically Meaningful Improvement	2-Point Decrease	Moderately Better	PGI-S (Night-Time Symptoms) 2-Point Decrease	PGI-C (Night-Time Symptoms) Moderately Better
sTST average weekly score (in minutes) change from baseline to Month 1				
Median change	66.8	67.1	81.8	60.0
(95% CI)	(55.9, 72.1)	(60.0, 77.1)	(67.9, 94.2)	(54.3, 73.0)
sTST average weekly score (in minutes) change from baseline to Month 3				
Median change	70.0	73.6	89.3	65.7
(95% CI)	(60.0, 79.2)	(64.0, 82.1)	(80.0, 100.0)	(59.3, 77.1)

Source: COA reviewer table derived from Applicant IR response dated May 18, 2021, Table 12
 Abbreviations: CI, confidence interval; PGA-S, patient global assessment of severity; PGI-C, patient global impression-change; PGI-S, patient global impression-severity; sTST, subjective total sleep time

Based on the anchor-based analyses above, the thresholds of clinical meaningful within patient change in sTST average weekly score (in minutes) range from 54.9 to 81.8 from baseline to Month 1 and from 65.7 to 89.3 from baseline to Month 3.

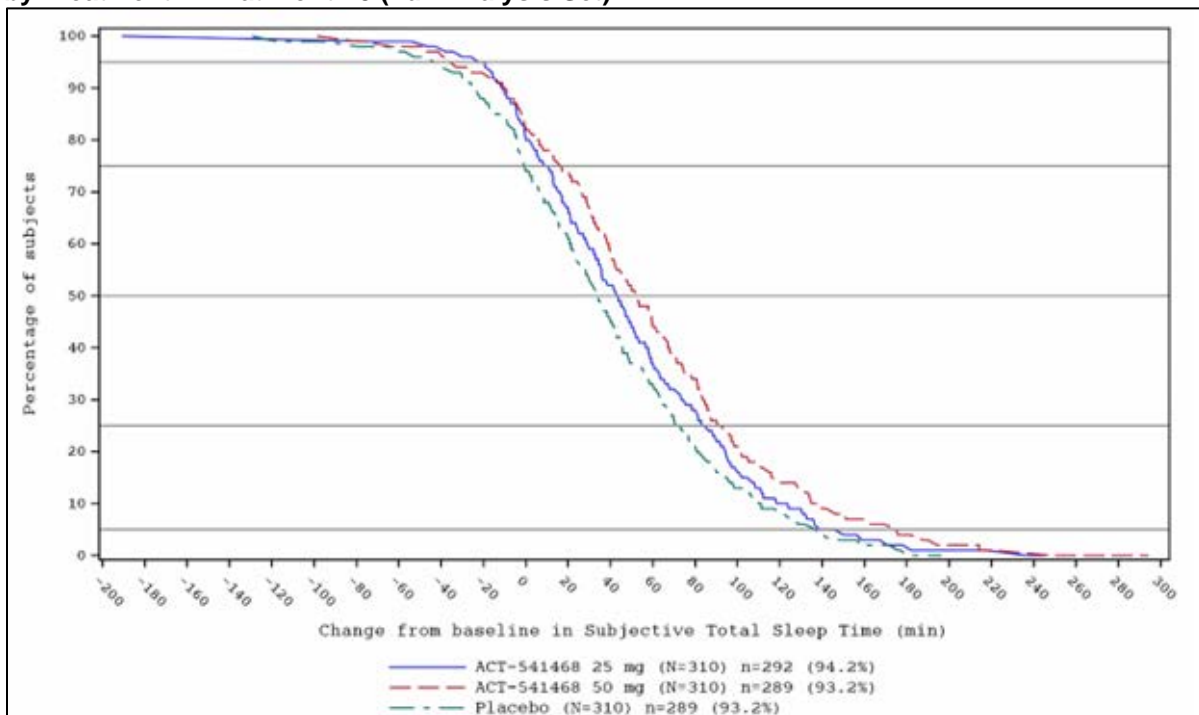
[Figure 67](#) through [Figure 70](#) below show empirical cumulative distribution function (eCDF) plots of change from baseline in sTST average weekly score (in minutes) by treatment arm at Month 1 and Month 3 for both Trial ID-078A301 and Trial ID-078A302.

Figure 67. Empirical Cumulative Distribution Function of the Change From Baseline in sTST (min) by Treatment Arm at Month 1 (Full Analysis Set)



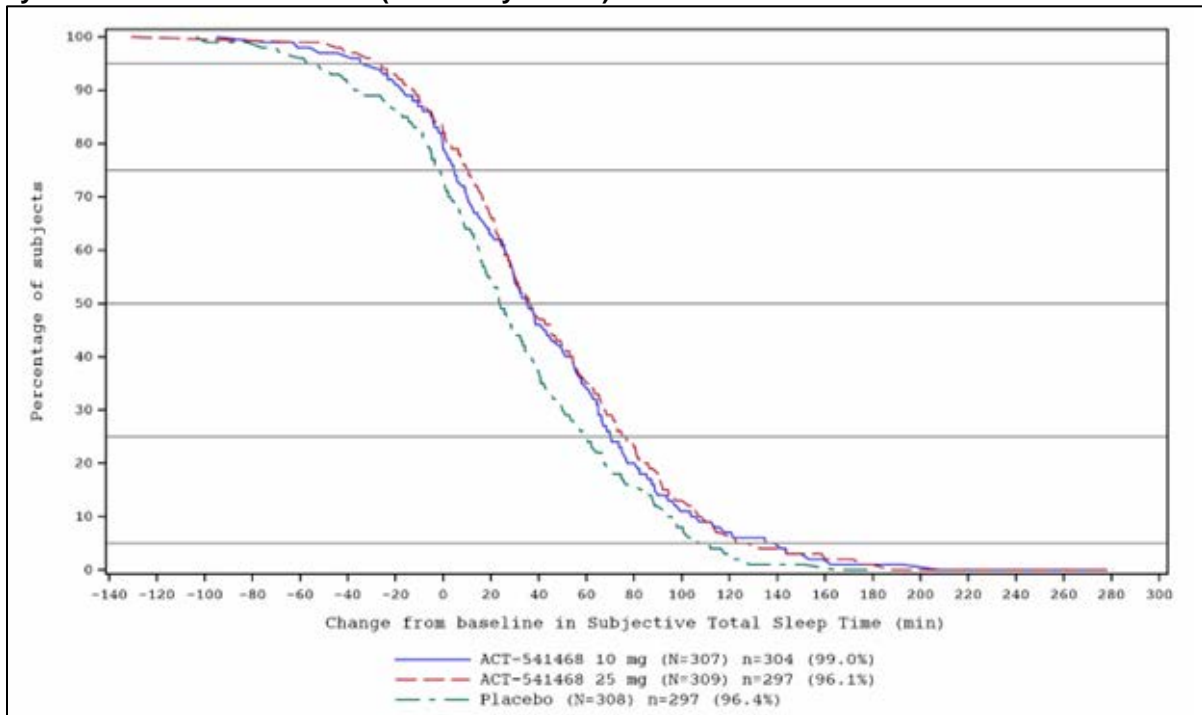
Source: ID-078A301, Figure 15.2.3-3.1
Abbreviations: N, number of subjects in treatment arm

Figure 68. Empirical Cumulative Distribution Function of the Change From Baseline in sTST (min) by Treatment Arm at Month 3 (Full Analysis Set)



Source: ID-078A301, Figure 15.2.3-3.1
Abbreviations: N, number of subjects in treatment arm; sTST, subjective total sleep time

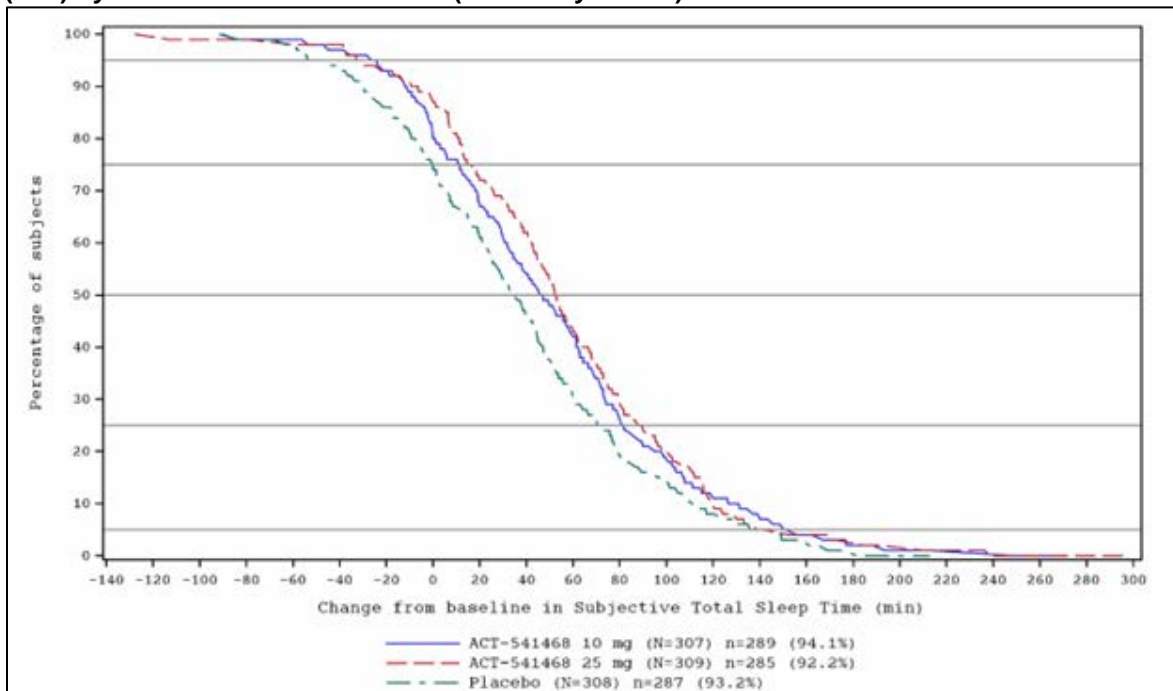
Figure 69. Empirical Cumulative Distribution Function of the Change From Baseline in sTST (min) by Treatment Arm at Month 1 (Full Analysis Set)



Source: ID-078A302, Figure 15.2.3-3.1

Abbreviations: N, number of subjects in treatment arm; sTST, subjective total sleep time

Figure 70. Empirical Cumulative Distribution Function Plots of the Change From Baseline in sTST (min) by Treatment Arm at Month 3 (Full Analysis Set)



Source: Applicant generated figure, ID-078A302, Figure 15.2.3-3.1

Abbreviations: N, number of subjects in treatment arm; sTST, subjective total sleep time

The eCDF plots by treatment arm for Trial ID-078A301 showed that there was a moderate separation of 50 mg treatment arm from placebo arm and a small separation of 25 mg treatment arm from placebo arm within the range of thresholds of clinically meaningful improvement (from 54.9 to 81.8 from baseline to Month 1 and from 65.7 to 89.3 from baseline to Month 3) in sTST average weekly score (in minutes) at both Month 1 and Month 3.

The eCDF plots by treatment arm for Trial ID-078A302 showed that there was a small separation of 25 mg treatment arm from placebo arm within the range of thresholds of clinically meaningful improvement (from 54.9 to 81.8 from baseline to Month 1 and from 65.7 to 89.3 from baseline to Month 3) in sTST average weekly score (in minutes) at both Month 1 and Month 3.

The anchor-based analyses results described above are consistent with the statistical analysis results Trial ID-078A301 and Trial ID-078A302 below:

Trial ID-078A301 results on sTST showed that:

- Changes from baseline were statistically significant at Month 1 and Month 3 for daridorexant 50 mg compared to placebo.
- For daridorexant 25 mg compared to placebo, changes from baseline were statistically significant at Month 1 and Month 3.

Trial ID-078A302 results on sTST showed that

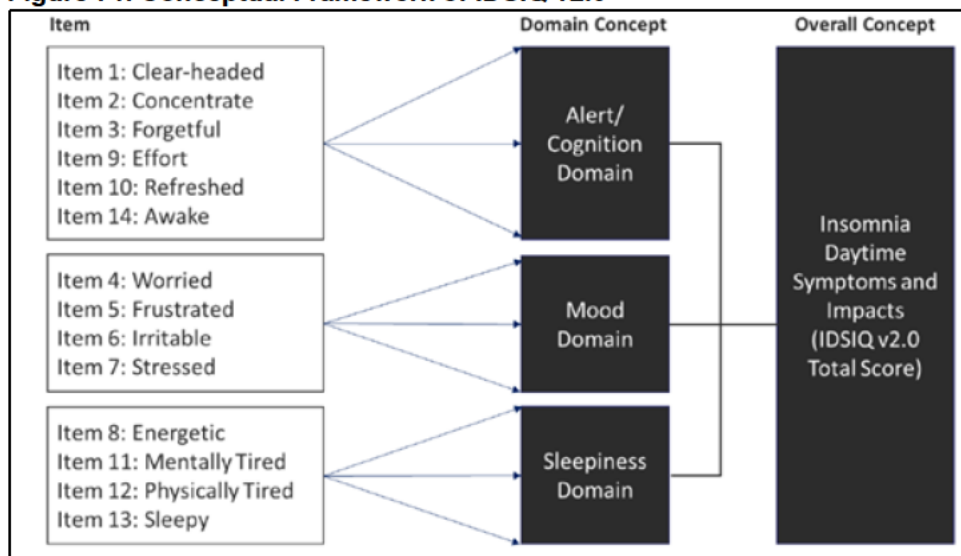
- For daridorexant 25 mg compared to placebo, changes from baseline were statistically significant both at Month 1 and Month 3

19.1.2. IDSIQ

The IDSIQ v2.0 was completed by the subject each evening from 8:00 pm to 11:59 pm using an electronic diary with a recall period of “today”. The concepts elicited during the development of IDSIQ describe the subjective experience of insomnia patients across the course of a day and the impact on daytime functioning.

The conceptual framework of IDSIQ is presented in [Figure 71](#).

Figure 71. Conceptual Framework of IDSIQ v2.0



Source: Applicant generated figure, IDSIQ evidence dossier, Figure 2
Abbreviations: IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire

The IDSIQ v2.0 has 3 domains assessing Alert/Cognition, Mood, and Sleepiness. For each domain, the item responses in the respective domains are summed to provide a domain score. A total score is obtained by summing across all item responses. Prior to summation, items 1, 2, 8, 10 and 14 are reverse scored. For Sleepiness domain, Daily domain score is the sum of Item 8*, Item 11, Item 12, and Item 13; Weekly Average is the mean of the daily domain score over 7 days. The Sleepiness domain score ranges from 0 to 40 with higher score indicating greater burden of illness.

Secondary efficacy endpoints of Trial ID-078A301 and Trial ID-078A302 based on IDSIQ were defined as:

- Change from baseline to Month 1 in IDSIQ sleepiness domain score
- Change from baseline to Month 3 in IDSIQ sleepiness domain score

The Applicant has taken several approaches to explore the thresholds of clinically meaningful within patient change in IDSIQ Sleepiness domain scores.

- (1) An exit interview study was conducted among 41 insomnia subjects exiting the phase 2 AC-078A203 study
 - 3.5 points change in Sleepiness domain using a 0 to 10 scale was reported to be clinically meaning
- (2) Anchor-based analyses were conducted to derive thresholds of clinical meaningful within patient change in IDSIQ v2.0 scores using phase 2 (AC-078A203) data.
 - (b) (4)
clinical meaningful improvement is typically considered to have at least 2-point improvement in PGI-S and “moderately better” in PGI-C.

- Thresholds derived from the anchor-based analyses using phase 2 data for IDSIQ are not appropriate because of the following reasons:
 - Open-label study design of phase 2 Study AC-078A203
 - (b) (4)
 - Shorter study period (2 weeks treatment) than phase 3 trials (12 weeks treatment)

To interpret study results on IDSIQ Sleep domain endpoint, anchor-based analyses using pooled phase 3 trial data were requested. The requested anchor scales to be used in anchor-based analyses include PGI-S and PGI-C nighttime symptoms as well as PGI-S and PGI-C daytime symptoms. The derived thresholds of clinical meaningful within patient change in IDSIQ Sleepiness domain score at Month 1/Visit 6 and Month 3/Visit 8 from both phase 3 trials were summarized in [Table 139](#) and [Table 140](#).

Table 139. Anchor-Based Analyses Estimates of Thresholds of Clinical Meaningful Within Patient Change in IDSIQ Average Weekly Sleepiness Domain Score Change From Baseline to Month 1 and Month 3, Study ID-078A301 (N=930)

Anchor Scales				
Anchor Category	PGA-S (Daytime Symptoms)		PGI-C (Daytime Symptoms)	
Considered Clinical Meaningful Improvement	2-Point Decrease	Moderately Better	PGI-S (Night-Time Symptoms) 2-Point Decrease	PGI-C (Night-Time Symptoms) Moderately Better
IDSIQ average weekly sleepiness domain score change from baseline to Month 1				
Median change	-5.9	-5.1	-6.4	-5.1
(95% CI)	(-7.3, -3.9)	(-6.6, -4.0)	(-9.4, -4.70)	(-6.5, -4.1)
IDSIQ average weekly sleepiness domain score change from baseline to Month 3				
Median change	-7.2	-6.7	-9.7	-6.6
(95% CI)	(-8.9, -6.3)	(-8.9, -5.4)	(-12.2, -8.6)	(-8.4, -5.3)

Source: COA reviewer table derived from Applicant IR response dated May 18, 2021, Table 3 and Table 4
 Abbreviations: CI, confidence interval; IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; PGA-S, patient global assessment of severity; PGI-C, patient global impression-change; PGI-S, patient global impression-severity

Table 140. Anchor-Based Analyses Estimates of Thresholds of Clinical Meaningful Within Patient Change in IDSIQ Average Weekly Sleepiness Domain Score Change From Baseline to Month 1 and Month 3, Study ID-078A302 (N=924)

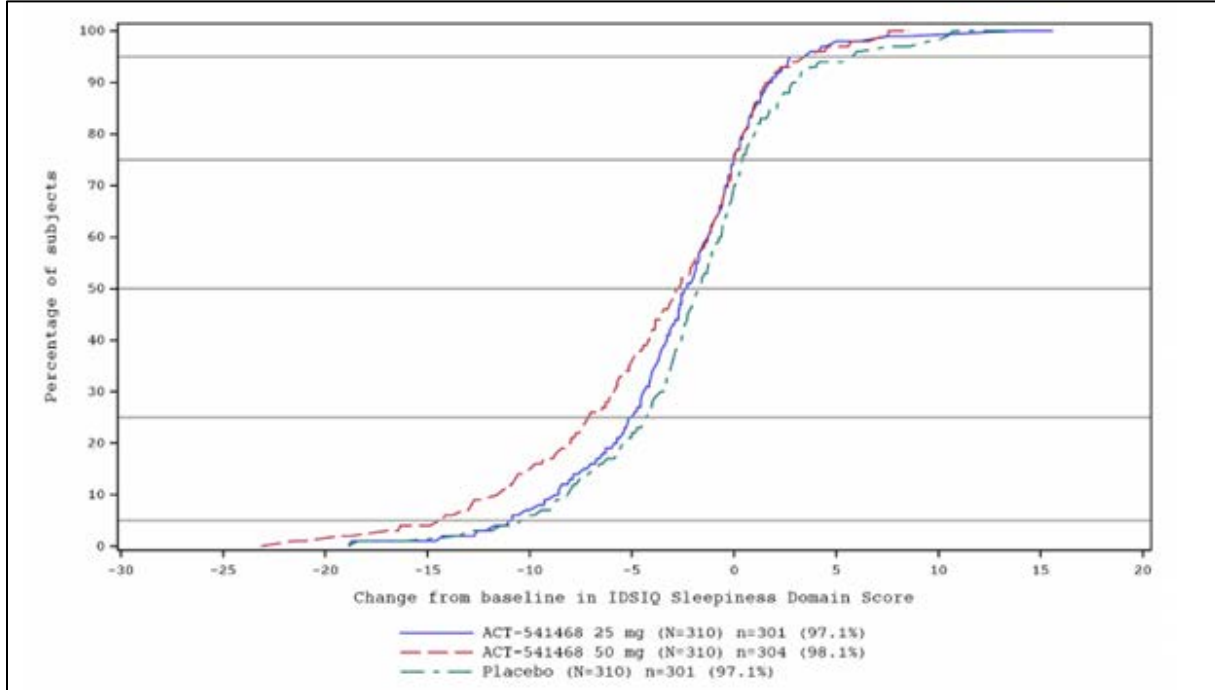
Anchor Scales				
Anchor Category	PGA-S (Daytime Symptoms)		PGI-C (Daytime Symptoms)	
Considered Clinical Meaningful Improvement	2-Point Decrease	Moderately Better	PGI-S (Night-Time Symptoms) 2-Point Decrease	PGI-C (Night-Time Symptoms) Moderately Better
IDSIQ average weekly sleepiness domain score change from baseline to Month 1				
Median change	-6.4	-5.6	-10.1	-6.3
(95% CI)	(-8.1, -4.4)	(-7.3, -4.3)	(-11.2, -7.4)	(-7.4, -4.3)
IDSIQ average weekly sleepiness domain score change from baseline to Month 3				
Median change	-7.2	-7.0	-10.9	-6.7
(95% CI)	(-8.4, -5.8)	(-8.6, -5.5)	(-12.0, -8.4)	(-8.0, -5.3)

Source: COA reviewer table derived from Applicant IR response dated May 18, 2021, Table 7 and Table 8
 Abbreviations: CI, confidence interval; IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; PGA-S, patient global assessment of severity; PGI-C, patient global impression-change; PGI-S, patient global impression-severity

Based on the anchor-based analyses above, the thresholds of clinical meaningful within patient change in IDSIQ average weekly Sleepiness domain score range from -5.1 to -10.1 from baseline to Month 1 and from -6.6 to -10.9 from baseline to Month 3.

Figure 72, Figure 73, Figure 74, and Figure 75 show eCDF of change from baseline in IDSIQ Sleepiness domain score by treatment arm at Month 1 and Month 3 for both Trial ID-078A301 and Trial ID-078A302.

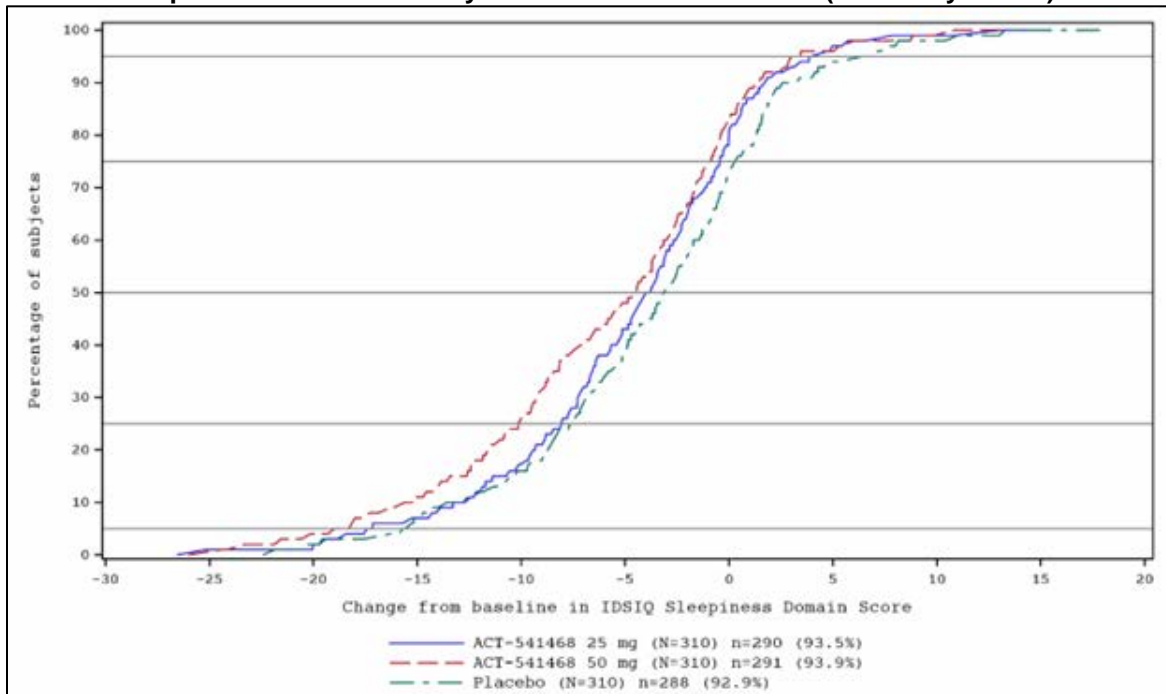
Figure 72. Empirical Cumulative Distribution Function (eCDF) Plots of the Change From Baseline in IDSIQ Sleepiness Domain Score by Treatment Arm at Month 1 (Full Analysis Set)



Source: ID-078A301 Figure 15.2.3-4.1

Abbreviations: IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; N, number of subjects in treatment arm; n, number of subjects with change from baseline in IDSIQ sleepiness domain score at month 1

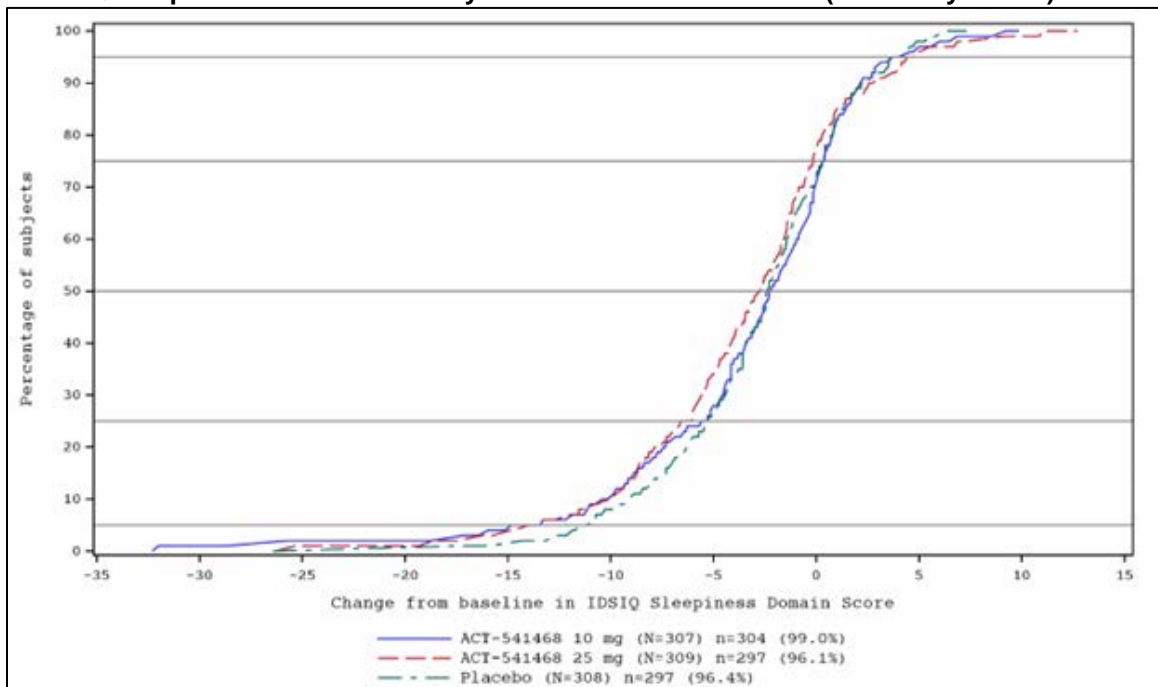
Figure 73. Empirical Cumulative Distribution Function (eCDF) Plots of the Change From Baseline in IDSIQ Sleepiness Domain Score by Treatment Arm at Month 3 (Full Analysis Set)



Source: ID-078A301 Figure 15.2.3-4.1

Abbreviations: IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; N, number of subjects in treatment arm; n, number of subjects with change from baseline in IDSIQ sleepiness domain score at month 3

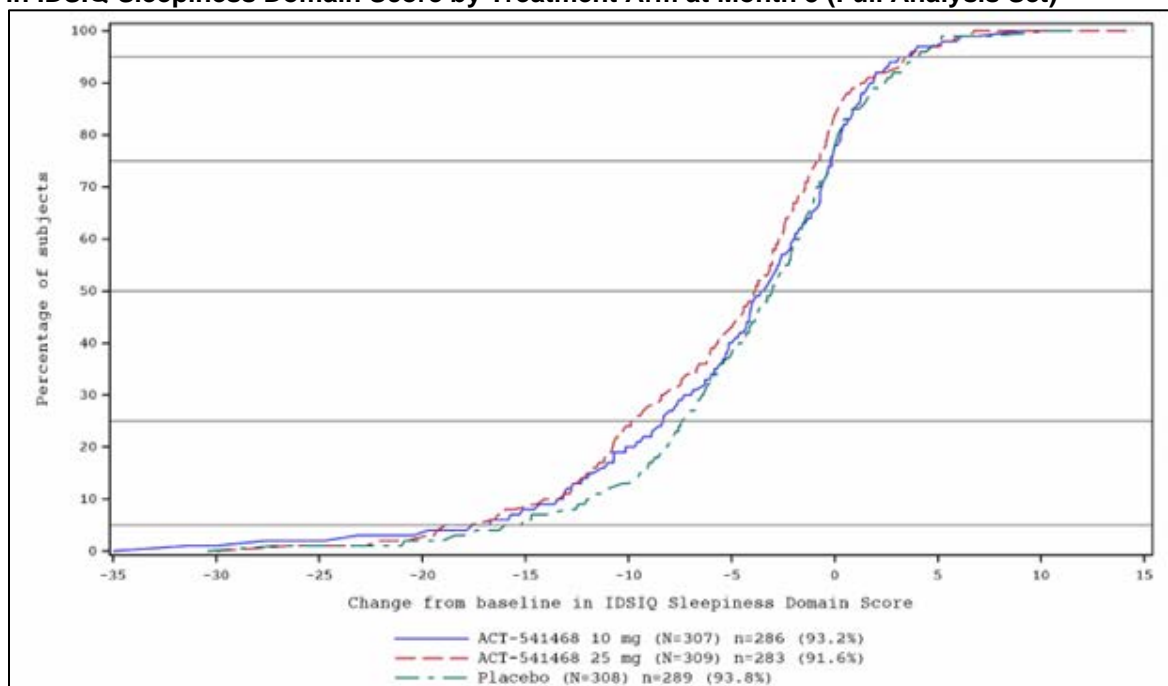
Figure 74. Empirical Cumulative Distribution Function (eCDF) Plots of the Change From Baseline in IDSIQ Sleepiness Domain Score by Treatment Arm at Month 1 (Full Analysis Set)



Source: ID-078A302 Figure 15.2.3-4.1

Abbreviations: IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; N, number of subjects in treatment arm; n, number of subjects with change from baseline in IDSIQ sleepiness domain score at month 1

Figure 75. Empirical Cumulative Distribution Function (eCDF) Plots of the Change From Baseline in IDSIQ Sleepiness Domain Score by Treatment Arm at Month 3 (Full Analysis Set)



Source: ID-078A302 Figure 15.2.3-4.1

Abbreviations: IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; N, number of subjects in treatment arm; n, number of subjects with change from baseline in IDSIQ sleepiness domain score at month 3

The eCDF plots by treatment arm for Trial ID-078A301 showed that there was a clear separation between 50 mg treatment arm and placebo arm within the range of thresholds of clinical meaningful improvement (from -5.1 to -10.1 from baseline to Month 1 and from -6.6 to -10.9 from baseline to Month 3) in IDSIQ Sleepiness domain score at both Month 1 and Month 3. However, there appears no separation between 25 mg treatment arm and placebo arm within these ranges of thresholds at neither Month 1 nor Month 3.

The eCDF plots by treatment arm for Trial ID-078A302 showed that there was a small separation of 25 mg treatment arm from placebo arm within the range of thresholds of clinical meaningful improvement (from -5.1 to -10.1 from baseline to Month 1 and from -6.6 to -10.9 from baseline to Month 3) in IDSIQ Sleepiness domain score at Month 1 and Month 3.

The anchor-based analyses results described above are consistent with the statistical analysis results Trial ID-078A301 and Trial ID-078A302 below:

Trial ID-078A301 results on IDSIQ sleepiness domain showed that:

- Changes from baseline were statistically significant at Month 1 and Month 3 for daridorexant 50 mg compared to placebo.
- For daridorexant 25 mg compared to placebo, a numerical trend for improvement was observed at Month 1 and Month 3 but changes were not statistically significant.

Trial ID-078A302 results on IDSIQ sleepiness domain showed that:

- For daridorexant 25 mg, differences to placebo were not statistically significant at Month 1 or Month 3 (two-sided p-values 0.0733 and 0.0120, respectively)

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

The clinical investigators (CIs), Drs. Gotfried, Heller, Ahmad, and Thein were inspected in support of this original New Drug Application (NDA 214985) for daridorexant for the treatment of insomnia [REDACTED] (b) (4) (Protocols ID-078A301 and ID-078A302).

Two complaints against Dr. Heller were investigated for Study ID-078A301 (Site #3575) and no evidence of subject safety or data integrity issues was identified to support the allegations. In response to an Agency request, the Applicant provided re-analysis of efficacy for all endpoints included in the Type I error control scheme for Study 301 with the data from Site # 3575 excluded. Statistical significance remained the same for all endpoints and exclusion of the results from Site #3575 did not alter conclusions regarding efficacy.

Overall, based on the results of these inspections, the conduct of the above studies was adequate, and the clinical data generated from these CI sites appear to be reliable in support of this NDA.

21. Labeling Summary of Considerations and Key Additional Information

[Table 141](#) summarizes high-level, significant changes to the proposed prescribing information made by FDA during the course of the review.

Table 141. Proposed Labeling Changes

SECTION	PROPOSED LABELING	REVISED LABELING
Highlights	Applicant proposed language for all required sections.	The Product Title was revised to add “[controlled substance schedule pending]” as the controlled substance schedule will not be completed prior to approval. Similarly, the following was added to the Initial U.S. Approval date “[pending controlled substance scheduling]” Other sections of HL were revised to align with the FPI.
Section 1 Indications and Usage	QUVIVIQ is indicated for the treatment of adult patients with insomnia (b) (4)	QUVIVIQ is indicated for the treatment of adult patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance.
Section 2 Dosage and Administration	2.1 Recommended Dosage The recommended dose of QUVIVIQ for adults is (b) (4)	2.1 Recommended Dosage The recommended dosage range is 25 to 50 mg of QUVIVIQ taken orally no more than once per night within 30 minutes of going to bed (with at least 7 hours remaining prior to planned awakening). Time to sleep onset may be delayed if taken with or soon after a meal.
	2.3 Dosage Recommendations for Concomitant Use with CYP3A4 Inhibitors Dosage and administration language was provided for use with moderate and strong CYP3A4 inhibitors.	2.3 Dosage Recommendations for Concomitant Use with CYP3A4 Inhibitors or CYP3A4 Inducers Language was added to include recommendations for concomitant use with strong or moderate CYP3A inducers (in alignment with revisions to Section 7 Drug Interactions).

SECTION	PROPOSED LABELING	REVISED LABELING
Section 3 Dosage Forms and Strengths	Applicant proposed language.	
Section 5 Warnings and Precautions		This section was revised according to class labeling considerations (hypnotic drugs; orexin receptor antagonists) and findings from the clinical review. 5.1 CNS-Depressant Effects and Daytime Impairment 5.2 Worsening of Depression/Suicidal Ideation 5.3 Sleep Paralysis, Hypnagogic/Hypnopompic Hallucinations, and Cataplexy-like Symptoms 5.4 Complex Sleep Behaviors 5.5 Patients with Comprised Respiratory Function 5.6 Need to Evaluate for Co-Morbid Diagnoses Further discussion below:
	5.1 CNS-Depressant Effect Applicant proposed language.	5.1 CNS-Depressant Effects and Daytime Impairment The section was revised to include language regarding the driving study and added a cross reference to Section 2. Also included language about concomitant use with alcohol (to align with Section 7) . The following statement was added to align with other drugs in the class: “Because QUVIVIQ can cause drowsiness, patients, particularly the elderly, are at a higher risk of falls.”

SECTION	PROPOSED LABELING	REVISED LABELING
	5.2 Sleep Paralysis, Hallucinations, and Cataplexy-like Symptoms Applicant proposed language.	5.2 Worsening of Depression/Suicidal Ideation The Applicant proposed “Worsening of Depression/Suicidal Ideation” as Section 5.3. The language was moved to Section 5.2 and revised to: Patients with psychiatric disorders, including insomnia, are at increased risk of suicide. In primarily depressed patients treated with hypnotics, worsening of depression and suicidal thoughts and actions (including completed suicides) have been reported. As with other hypnotics, QUVVIQ should be administered with caution in patients exhibiting symptoms of depression. Monitoring of suicide risk and protective measures may be required.
	5.3 Worsening of Depression/Suicidal Ideation Applicant proposed language.	5.3 Sleep Paralysis, Hypnagogic/Hypnopompic Hallucinations, and Cataplexy-like Symptoms The “Worsening of Depression/Suicidal Ideation” warning and precaution was moved to Section 5.2 and the Applicant’s proposal for Section 5.3 “Sleep Paralysis, Hallucinations, and Cataplexy-like Symptoms” was revised and moved to Section 5.3.

SECTION	PROPOSED LABELING	REVISED LABELING
	5.4 Patients with Compromised Respiratory Function Applicant proposed language stating that QUIVIQ ^{(b) (4)} [REDACTED].	5.4 Complex Sleep Behaviors Applicant's proposed "Patients with Compromised Respiratory Function" as Section 5.4 was moved to Section 5.5. Applicant did not include a Warning and Precaution for Complex Sleep Behaviors. The following language was added as Section 5.4: Complex sleep behaviors, including sleep-walking, sleep-driving, and engaging in other activities while not fully awake (e.g., preparing and eating food, making phone calls, having sex), have been reported to occur with the use of hypnotics including orexin ^{(b) (4)} [REDACTED] receptor antagonists such as QUVIVIQ. These events can occur in hypnotic-naïve as well as in hypnotic-experienced persons. Patients usually do not remember these events. Complex sleep behaviors may occur following the first or any subsequent use of QUVIVIQ, with or without the concomitant use of alcohol and other CNS depressants [see Drug Interactions (7.1)]. Discontinue QUVIVIQ immediately if a patient experiences a complex sleep behavior.

SECTION	PROPOSED LABELING	REVISED LABELING
		5.5 Patients with Compromised Respiratory Function The Applicant proposed “Patients with Compromised Respiratory Function” as Section 5.4. The warning and precaution was moved to Section 5.5 and revised to state that QUIVIQ was not studied in moderate OSA requiring CPAP, severe OSA, or severe COPD. The section recommends that HCPs consider respiratory function if prescribed to patients with compromised respiratory function and includes a reference to Section 8.7 Patients with Compromised Respiratory Function.
	Applicant did not propose a Warning and Precaution titled “Need to Evaluate for Co-morbid Diagnoses.”	5.6 Need to Evaluate for Co-morbid Diagnoses The following language was added as Section 5.6 to align with other drugs in the class: Because sleep disturbances may be the presenting manifestation of a medical and/or psychiatric disorder, treatment of insomnia should be initiated only after careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia or the emergence of new cognitive or behavioral abnormalities may be the result of an unrecognized underlying psychiatric or medical disorder and can emerge during the course of treatment with sleep-promoting drugs such as QUIVIQ.

SECTION	PROPOSED LABELING	REVISED LABELING
Section 6 Adverse Reactions	Applicant proposed language.	(b) (4) The Division determined that including safety results from Study ID-078A301 would best represent the safety findings because the study compared 25 mg and 50 mg to placebo, both of which are recommended dosage strengths. Study 2 compared 10 mg (an unapproved dosage strength) and 25 mg to placebo, but not 50 mg, and had similar incidence of common adverse reactions in the 25 mg and placebo groups to study ID-078A301. (b) (4) Some of the AR groupings were revised resulting in revisions to the AR table.
Section 7 Drug Interactions	Applicant provided language for 7.1 titled “ (b) (4)	The language was displayed in table format. Drug interaction information for Strong and moderate CYP3A4 inducers was added. We removed (b) (4)
Section 8 Use in Specific Populations	Applicant provided language for section 8 to include 8.1, 8.2, 8.4, 8.5, 8.6, 8.7 (b) (4)	

SECTION	PROPOSED LABELING	REVISED LABELING
		8.1 Pregnancy Consulted DPMH Added pregnancy exposure registry statement. DPMH recommended that patients report pregnancy exposures to the general PV contact number until the pregnancy registry study contact number is established to allow for pregnancy exposures from launch to registry establishment to be captured. The general Idorsia Pharmaceuticals Ltd PV contact number was added. Nonclinical added animal study information based MRHD.
	8.5 Geriatric Use Applicant proposed language.	8.5 Geriatric Use Included the following sentence to align with other drugs in the class "Because QUVIVIQ can increase somnolence and drowsiness, patients, particularly the elderly, are at higher risk of falls [see Warnings and Precautions (5.1)]."
	8.6 Hepatic Impairment Applicant proposed that QUVIVIQ is not for use in severe hepatic impairment (not studied); dosage reduction in moderate hepatic impairment, and no adjustment in mild hepatic impairment.	8.6 Hepatic Impairment Recommendations remained the same, but language was revised for better readability.

SECTION	PROPOSED LABELING	REVISED LABELING
	8.7 (b) (4) [REDACTED]	8.7 Patients with Compromised Respiratory Function (b) (4) [REDACTED] Section 8.7 was titled "Patients with Compromised Respiratory Function" DPACC was consulted and provided revised language for this section to include more specificity regarding the studies. The section includes information on both the OSA and COPD populations and notes that QUVVIQ has not been studied in patients with severe OSA or those requiring CPAP or those with severe COPD. A statement that clinically meaningful respiratory effects in patients with compromised respiratory function cannot be excluded with a reference to Section 5.5 was also included.
	(b) (4) Patients with Compromised Respiratory Function Applicant proposed language.	Moved to Section 8.7.
Section 9 Drug Abuse and Dependence	Applicant provided language.	Controlled substance staff was consulted and provided revised language. Controlled substance schedule is pending review by DEA, so language was added to Section 9.1 to note that, i.e., "Controlled substance schedule to be determined after review by the Drug Enforcement Administration."
Section 12 Clinical Pharmacology	12.1 Mechanism of Action Applicant provided language.	12.1 Mechanism of Action Language was revised to align with other drugs in the class.

SECTION	PROPOSED LABELING	REVISED LABELING
	12.2 Pharmacodynamics Applicant provided language.	12.2 Pharmacodynamics The statement, “Daridorexant binds to and inhibits the orexin receptors OX1R and OX2R (K _i =0.47 and 0.93nM, respectively)” was added to align with similar drugs in the class. QTIRT was consulted and Cardiac Electrophysiology language was revised as a result.
	12.3 Pharmacokinetics Applicant provided language.	12.3 Pharmacokinetics OCP recommended Forest plots (b) (4) for the Specific Populations (e.g., patients with renal or hepatic impairment) and Drug Interactions Studies sections.
13 Nonclinical Toxicology	13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Applicant provided language.	13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Applicant’s language was revised for clarity.
	13.2 Animal Toxicology and/or Pharmacology Applicant provided language.	13.2 Animal Toxicology and/or Pharmacology Applicant’s language was revised for clarity.

SECTION	PROPOSED LABELING	REVISED LABELING
14 Clinical Studies	Applicant provided language.	A clinically meaningful and statistically significant treatment effect was observed on WASO, LPS, and sTST; results for these endpoints were included (b) (4) (b) (4) Quantitative description of worsening of sleep parameters was added to inform prescribers and patients about the effects of product discontinuation after a period of regular use. (b) (4)
16 How Supplied/Storage and Handling	Applicant provided language.	Minor revisions.
17 Patient Counseling Information	Applicant provided language.	Some revisions to align with the PI.
Patient Labeling	(b) (4)	The document will be included as patient labeling (b) (4) a Medication Guide (MG) to align with other drugs in the class. The MG was revised to align with the final FPI.

22. Postmarketing Requirements and Commitments

The Division consulted the Division of Pediatric and Maternal Health (DPMH) for the review of this application. Daridorexant is indicated for a condition that would be expected to be seen in females of reproductive potential, during pregnancy, and during lactation. Therefore, DPMH recommends postmarketing requirements for the applicant to conduct a pregnancy exposure

registry, a complimentary study of a different design, and clinical lactation study. They are as follows:

Post Marketing Requirement (PMR) 4150-1

- Conduct a lactation study in lactating women who have received therapeutic doses of daridorexant using a validated assay to assess concentrations of daridorexant in breast milk using a validated assay [REDACTED] (b) (4).

PMR 4150-2

- Conduct a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to daridorexant 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.

PMR 4150-3

- 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) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to daridorexant during pregnancy compared to an unexposed control population.

Efficacy data for daridorexant indicate reduced WASO with 25 and 50 mg bedtime doses. However, it is important for persons to be arousable from sleep in cases of emergency, and once aroused to be able to function. Adverse events of dizziness and impairments in balance and coordination, and, to a lesser extent, cognition were common and observed at rates higher than placebo in a dose dependent manner. Thus, assessment of effects on balance and cognition after arousal from sleep are also warranted. It is useful to patients and clinicians to know what levels of impairment in arousability & post-middle-of-night arousal psychomotor function should be expected from use of this drug. Such information will enhance safety-informed decision-making regarding its use. The following PMR is recommended to provide the aforementioned information:

PMR 4150-4

- Middle of the Night Safety Study in Female and Male patients or healthy controls aged 18 to 65 and >65 years to assess the ability to awaken to sound in the middle of the night and postural stability and cognitive function following awakening.

Given that pediatric patients also experience insomnia, the Applicant proposed studies in the iPSP and has agreed to conduct the following studies in patients aged 10 to <18 years old:

Pediatric Research Equity Act (PREA) PMR 4150-5

- Dose-finding (b) (4) study

PREA PMR 4150-6

- Pediatric effectiveness and safety (b) (4) study

PREA PMR 4150-7

- (b) (4)

The Applicant has requested a waiver of pediatric assessments in children below 10 years of age. This is because assessing sleep in children below 10 years of age is complex and challenging, due to the high variability of sleep and napping time, both across the age range, and between children of the same age.

23. Financial Disclosure

Table 142. Covered Clinical Studies: Trial ID-078A301 and Trial ID-078A302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 85 for Trial ID-078A301; 92 for Trial ID-078A302; total =177		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): none		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: NA Significant payments of other sorts: NA Proprietary interest in the product tested held by investigator: NA Significant equity interest held by investigator: NA Sponsor of covered study: NA		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Request details from Applicant) Nothing to disclose per Applicant
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Request information from Applicant) NA per Applicant
Number of investigators with certification of due diligence (Form FDA 3454, box 3): NA		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from Applicant) NA

24. References

Bureau, UC, 2019, QuickFacts United States, United States Census Bureau, accessed August 31, 2021, <https://www.census.gov/quickfacts/fact/table/US/PST045219>.

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Daridorexant (Quviviq) for Insomnia

Chong, Y, CD Fryer, and Q Gu, 2013, Prescription sleep aid use among adults: United States, 2005-2010, NCHS Data Brief, (127):1-8.

Damoiseaux, JS, CF Beckmann, EJ Arigita, F Barkhof, P Scheltens, CJ Stam, SM Smith, and SA Rombouts, 2008, Reduced resting-state brain activity in the "default network" in normal aging, Cereb Cortex, 18(8):1856-1864.

DeCarlo, A and BC Samuels, 2020, Microinjection of orexin neuropeptide into the brainstem raphe pallidus elevates intraocular pressure, Investigative Ophthalmology & Visual Science, 61(7):1233-1233.

Geoffroy, PA, MA Oquendo, P Courtet, C Blanco, M Olfson, H Peyre, M Lejoyeux, F Limosin, and N Hoertel, 2021, Sleep complaints are associated with increased suicide risk independently of psychiatric disorders: results from a national 3-year prospective study, Mol Psychiatry, 26(6):2126-2136.

Greaves, P, 2011, Histopathology of Preclinical Toxicity, 4th edition: Academic Press.

Haba-Rubio, J, B Frauscher, P Marques-Vidal, J Toriel, N Tobback, D Andries, M Preisig, P Vollenweider, R Postuma, and R Heinzer, 2018, Prevalence and determinants of rapid eye movement sleep behavior disorder in the general population, Sleep, 41(2).

Harris, GC and G Aston-Jones, 2006, Arousal and reward: a dichotomy in orexin function, Trends Neurosci, 29(10):571-577.

Hedegaard, H, SC Curtin, and M Warner, 2018, Suicide Rates in the United States Continue to Increase, NCHS Data Brief, (309):1-8.

James, MH, SV Mahler, DE Moorman, and G Aston-Jones, 2017, A Decade of Orexin/Hypocretin and Addiction: Where Are We Now?, Curr Top Behav Neurosci, 33:247-281.

Johnson, EO, T Roth, L Schultz, and N Breslau, 2006, Epidemiology of DSM-IV insomnia in adolescence: lifetime prevalence, chronicity, and an emergent gender difference, Pediatrics, 117(2):e247-256.

NON-RESPONSIVE

Kaufmann, CN, R Mojtabai, RS Hock, RJ Thorpe, Jr., SL Canham, LY Chen, AM Wennberg, LP Chen-Edinboro, and AP Spira, 2016, Racial/Ethnic Differences in Insomnia Trajectories Among U.S. Older Adults, Am J Geriatr Psychiatry, 24(7):575-584.

Kessler, RC, P Berglund, G Borges, M Nock, and PS Wang, 2005, Trends in suicide ideation, plans, gestures, and attempts in the United States, 1990-1992 to 2001-2003, JAMA, 293(20):2487-2495.

Guideline for Industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions* (March 1995)

Morin, CM, E Altena, H Ivers, C Merette, M LeBlanc, J Savard, and P Philip, 2020, Insomnia, hypnotic use, and road collisions: a population-based, 5-year cohort study, Sleep, 43(8).

- Murphy, P, M Moline, D Mayleben, R Rosenberg, G Zammit, K Pinner, S Dhadda, Q Hong, L Giorgi, and A Satlin, 2017, Lemborexant, A Dual Orexin Receptor Antagonist (DORA) for the Treatment of Insomnia Disorder: Results From a Bayesian, Adaptive, Randomized, Double-Blind, Placebo-Controlled Study, *J Clin Sleep Med*, 13(11):1289-1299.
- Nattie, E and A Li, 2012, Respiration and autonomic regulation and orexin, *Prog Brain Res*, 198:25-46.
- Ohayon, MM, RG Priest, M Caulet, and C Guilleminault, 1996, Hypnagogic and hypnopompic hallucinations: pathological phenomena?, *Br J Psychiatry*, 169(4):459-467.
- Ratti, E, DJ Carpenter, S Zamuner, S Fernandes, L Squassante, H Danker-Hopfe, G Archer, J Robertson, R Alexander, DG Trist, and E Merlo-Pich, 2013, Efficacy of vestipitant, a neurokinin-1 receptor antagonist, in primary insomnia, *Sleep*, 36(12):1823-1830.
- Riemann, D and U Voderholzer, 2003, Primary insomnia: a risk factor to develop depression?, *J Affect Disord*, 76(1-3):255-259.
- Samuels, BC, N Hammes, C Bernabe, L Federici, A Molosh, S Bhatnagar, A Shekhar, and P Johnson, 2017, Stimulation of Hypothalamic Orexin Neurons using DREADD Technology Increases Intraocular Pressure, *Investigative Ophthalmology & Visual Science*, 58(8):1602-1602.
- Sargin, D, 2019, The role of the orexin system in stress response, *Neuropharmacology*, 154:68-78.
- Sateia, MJ, DJ Buysse, AD Krystal, DN Neubauer, and JL Heald, 2017, Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline, *J Clin Sleep Med*, 13(2):307-349.
- Schifano, F, S Chiappini, JM Corkery, and A Guirguis, 2019, An Insight into Z-Drug Abuse and Dependence: An Examination of Reports to the European Medicines Agency Database of Suspected Adverse Drug Reactions, *Int J Neuropsychopharmacol*, 22(4):270-277.
- Sharpless, BA and JP Barber, 2011, Lifetime prevalence rates of sleep paralysis: a systematic review, *Sleep Med Rev*, 15(5):311-315.
- Singareddy, R, AN Vgontzas, J Fernandez-Mendoza, D Liao, S Calhoun, ML Shaffer, and EO Bixler, 2012, Risk factors for incident chronic insomnia: a general population prospective study, *Sleep Med*, 13(4):346-353.
- Stallman, HM and M Kohler, 2016, Prevalence of Sleepwalking: A Systematic Review and Meta-Analysis, *PLoS One*, 11(11):e0164769.
- Stephens, R, J Ling, TM Heffernan, N Heather, and K Jones, 2008, A review of the literature on the cognitive effects of alcohol hangover, *Alcohol Alcohol*, 43(2):163-170.
- Van Dongen, HP, G Maislin, JM Mullington, and DF Dinges, 2003, The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation, *Sleep*, 26(2):117-126.
- Weber, K, 2017, Differences in Types and Incidence of Neoplasms in Wistar Han and Sprague-Dawley Rats, *Toxicol Pathol*, 45(1):64-75.

505(b)1 NME NDA 214985
 Daridorexant (Quviviq) for Insomnia

Xu, L, A Krishna, S Stewart, K Shea, R Racz, JL Weaver, DA Volpe, NR Pilli, S Narayanasamy, J Florian, V Patel, MK Matta, MB Stone, H Zhu, MC Davis, DG Strauss, and R Rouse, 2021, Effects of sedative psychotropic drugs combined with oxycodone on respiratory depression in the rat, Clin Transl Sci.

Zhang, B and YK Wing, 2006, Sex differences in insomnia: a meta-analysis, Sleep, 29(1):85-93.

25. Review Team

Table 143. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Jasmeet (Mona) Kalsi, PharmD signing on behalf of Latrice Wilson, PharmD (previous RPM)
Nonclinical Reviewer	Jia Yao, PhD
Nonclinical Team Leader	Aisar Atrakchi, PhD
Office of Clinical Pharmacology Reviewer(s)	Praveen Balimane, PhD Pharmacometrics – Michael Bewernitz, Vishnu Sharma PBPK – Jianghong Fan
Office of Clinical Pharmacology Team Leader(s)	Luning (Ada) Zhuang, PhD Pharmacometrics – Atul Bhattaram (TL) PBPK – Xinyuan (Susie) Zhang (TL)
Clinical Reviewer	Zimri Yaseen, MD
Clinical Team Leader	Pamela Horn, MD
Associate Director of Labeling	Kimberly Updegraff, PharmD
Statistical Reviewer	Andrew Potter, PhD
Statistical Team Leader	Peiling Yang, PhD
Cross-Disciplinary Team Leader	Pamela Horn, MD
Division Director (pharm/tox)	Lois Freed, PhD
Division Director (OCP)	Mehul Mehta, PhD
Division Director (OB)	Hsien Ming J Hung, PhD
Deputy Division Director (clinical)	Bernard Fischer, MD
Division Director (clinical)	Tiffany R. Farchione, MD
Office Director (or designated signatory authority)	Teresa Buracchio, MD, signing on behalf of Billy Dunn, MD

OCP = Office of Clinical Pharmacology
 OB = Office of Biostatistics

Table 144. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	ATL – Valerie Amspacher Drug Substance – Zhixing Shan Drug Product – Grace Chiou Process and Facilities – Yongming Lu; Yaodong (Tony) Huang Biopharm – Kaushal Dave; Ta-Chen Wu RBPM – Teshara Bouie
Microbiology	N/A
OPDP	Sam Fasanmi (reviewer); Aline Moukhtara (TL)
OSI	Jenn Sellers; Phillip Kronstein (TL)
OSE/DEPI	DEPI-1 TL – Kira Leishear DEPI-1 SE – Dinci Pennap DEPI-1 Drug Use TL – Nabila Sadiq DEPI-2 Non-Med Use (NMU) -2 TL – Rose Radin DEPI-2 NMU-1 TL – Tamra Meyer
OSE/DMEPA	DMEPA TL – Sevan Kolejian DMEPA SE – Loretta Holmes OSE PM – Phuong B Nguyen
OSE/DRISK	
Other	Edward Hawkins (CSS) Elisabeth Boulos (reviewer) and Kelly Stone (TL) – DPACC Julia Ju (Reviewer) – COA Kristie Baisden (reviewer) and Tamara Johnson (TL) - DPMH

OPQ = Office of Pharmaceutical Quality
 OPDP = Office of Prescription Drug Promotion
 OSI = Office of Scientific Investigations
 OSE = Office of Surveillance and Epidemiology
 DEPI = Division of Epidemiology
 DMEPA = Division of Medication Error Prevention and Analysis
 DRISK = Division of Risk Management

Table 145. Signatures of Reviewers

Table 145 Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical	Tiffany R. Farchione	OND/ON/DP	IA and ES ☐ Authored ☐ Contributed ☒ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Statistical	Andrew Potter	OB/DBIV	6.2, 6.3, 17.2, 7.7.4.1.2, 16.2, 16.3 ☒ Authored ☐ Contributed ☐ Approved
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Pharmacology/Toxicology	Lois Freed	OND/DPT-N	5.1, 7.1, 8.3, 8.4, 13.1 and 13.2 ☐ Authored ☐ Contributed ☒ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Pharmacology/Toxicology	Jia Yao	OND/DPT-N	5.1, 7.1, 8.3, 8.4, 13.1 and 13.2 ☒ Authored ☒ Contributed ☐ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	Mehul Mehta	OTS/OCP/DNP	5, 6, 7, 8, 14, 17 ☐ Authored ☐ Contributed ☒ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
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Clinical Pharmacology/Pharmacometrics	Atul Bhattaram	OTS/OCP/DPM	7.7.1.3.2, 17.2, 14.5 and 14.6 ☐ Authored ☐ Contributed ☒ Approved
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
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Reviewer	Signature: Jianghong Fan -S Digitally signed by Jianghong Fan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jianghong Fan -S, 0.9.2342.19200300.100.1.1=2001454698 Date: 2022.01.06 14:55:47 -05'00'		

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 Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

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/s/

PAMELA J HORN
01/07/2022 01:06:04 PM

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number: 214985/0001

Drug Name: Daridorexant (ACT-541468)

Indication: Treatment of insomnia

Study number: ID-078-107

Applicant: Idorsia Pharmaceuticals, Ltd.

Date(s): Date of Document: 01/08/2021
PDUFA date: 01/07/2022
Date of Consult: 03/04/2021
Completion date: 09/20/2021

Review Priority: Standard (12-month program for NME)

Biometrics Division: DB VI

Statistical Reviewer: Ling Chen, Ph.D., Expert Mathematical Statistician,
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Keywords: Crossover design; Human abuse potential study; Self-reported endpoint;
Stimulants

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1. Executive Summary

The applicant, Idorsia Pharmaceuticals, Ltd., submitted the results from the human abuse potential study ID-078-107 for the assessment of abuse potential of ACT-541468 (Name of finished product: Daridorexant).

Study ID-078-107 was a Phase 1 randomized, double-blind, double-dummy, placebo- and active-controlled, 6-way cross-over study to evaluate the abuse potential of single oral doses of ACT-541468 in healthy recreational drug users. The primary objective was to determine the abuse potential of ACT-541468 using placebo as control and suvorexant and zolpidem as active controls (positive controls). The study consisted of a 3-period Qualification Phase and a 6-period Core Phase (Treatment Phase).

There were six treatments in the Core Phase. These treatments were 30 mg zolpidem, 150 mg suvorexant, 50, 100 and 150 mg doses of ACT-541468, and placebo. In the Core Phase, 72 subjects were randomized, 71 subjects received at least one dose of study drug, and 63 subjects (87.5%) completed this phase of the study. Subjects discontinued in the Core Phase primarily for other reasons (5 subjects [6.9%]), such as family matters, while 3 subjects (4.2%) withdrew voluntarily, and 1 subject (1.4%) discontinued due to AEs.

The results from the reviewer's primary analysis on Drug Liking Emax and secondary analyses on Overall Drug Liking Emax and Take Drug Again Emax showed that 100 and 150 mg doses of ACT-541468 did not produce significantly smaller subject responses compared to both 30 mg zolpidem and 150 mg suvorexant ($p \geq 0.1955$), and 50 mg ACT-541468 produced significantly smaller subject responses than both positive control drugs ($p \leq 0.046$) except the comparison with 30 mg zolpidem for Take Drug Again Emax ($p = 0.1562$). The exploratory comparisons were performed between 50 mg ACT-541468 and placebo for Drug Liking Emax and Overall Drug Liking Emax. The results showed that 50 mg ACT-541468 produced significantly greater subject responses than placebo ($p \leq 0.0215$). The study was validated by the significant difference between each positive control and placebo for Drug Liking Emax with a test margin of 15 ($p = 0.0003$).

The reviewer conducted sensitivity analyses on Drug Liking Emax, Overall Drug Liking Emax and Take Drug Again Emax based on the modified completer population (MCP). The results from the sensitivity analyses were consistent of the findings from both primary and secondary analyses.

For other secondary endpoints: Emin scores of Alertness/Drowsiness and Observer's Assessment of Alertness/Sedation (composite score and sum score), Emax scores of Any Effects, Bad Effects, Good Effects, High, and Composite Score of Bowdle (external perception and internal perception), as well as Drug Similarity VAS the descriptive statistics are provided in Section 2.4.4.

In conclusion, the results from the HAP study ID-078-107 show that abuse potential of ACT-541468 is similar to those of zolpidem and suvorexant.

2. Review report on Study SEP360-101

2.1. Overview

This was a Phase 1 randomized, double-blind, double-dummy, placebo- and active-controlled, 6-way cross-over study to evaluate the abuse potential of single oral doses of ACT-541468 in healthy recreational drug users.

2.1.1. Objectives of the study

Primary Objective:

- To determine the abuse potential of ACT-541468 using placebo as control, and suvorexant and zolpidem as active comparators.

Secondary Objectives:

- To evaluate the safety and tolerability of ACT-541468 at therapeutic and supra-therapeutic single doses.
- To assess the pharmacokinetics (PK) of single oral doses of 50, 100, and 150 mg ACT-541468.
- To investigate the PK/pharmacodynamic (PD) relationship between ACT-541468 plasma concentrations (and/or PK parameters) and measures of abuse potential.

2.1.2. Study design

This was a Phase 1 randomized, double-blind, double-dummy, placebo- and active-controlled, 6-way cross-over study to evaluate the abuse potential of single oral doses of ACT-541468 in healthy recreational drug users.

The study consisted of a 3-period qualification phase (Part A) and a 6-period core phase (Part B). Each period started at the time of first administration (i.e., Day 1) and ended on the day of the last assessment related to the administration schedule. In each period of the core phase, a single-dose treatment was administered (ACT-541468, suvorexant, zolpidem, or placebo). The maximum total study duration per subject was approximately 9 weeks (from screening to End-of-Study [EOS]).

Schematic overviews of the qualification and core phases are given in Figure 9-1 and Figure 9-2, respectively, in the study report.

Figure 9-1 Study design: qualification phase (Part A)

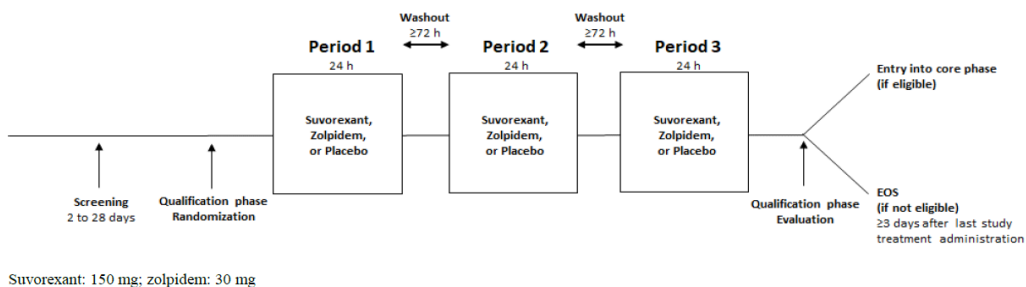
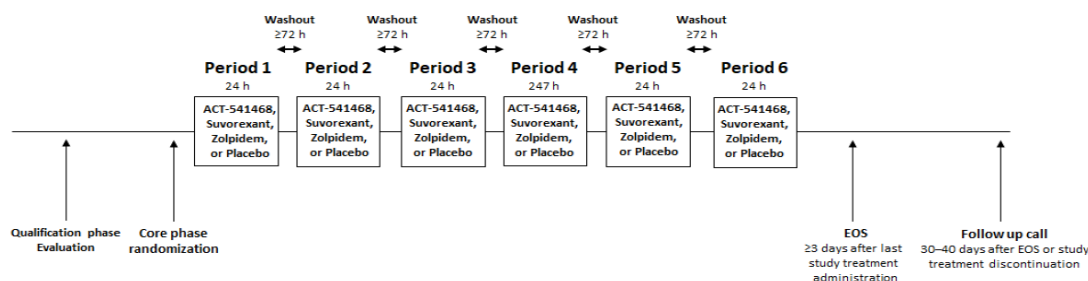


Figure 9-2 Study design: core phase (Part B)



ACT-541468: 50 mg, 100 mg, 150 mg; suvorexant: 150 mg; zolpidem: 30 mg.

2.1.3. Disposition of Subjects

A total of 72 subjects were randomized to the Core Phase and 71 subjects received at least 1 dose of study drug, and 63 (87%) subjects completed this phase of the study. Nine subjects (12.5%) discontinued prior to study completion, including 1 subject who was randomized but did not receive any dose of study drug in the core phase and 8 subjects who discontinued after receiving at least one dose of study drug. These subjects discontinued primarily for other reasons (5 subjects [6.9%]), such as family matters, while 3 subjects (4.2%) withdrew voluntarily, and 1 subject (1.4%) discontinued due to AEs.

2.1.4. Abuse potential endpoints

Primary endpoint

The Emax of the Drug Liking VAS ('at this moment') assessed repeatedly over 24 h post-dose during each treatment period was used as primary endpoint in this study. It is a bipolar VAS scale ranging from 0 (i.e., maximum disliking) to 100 points (i.e., maximum liking) with 50 points representing a neutral response.

Secondary endpoint

The following secondary PD endpoints were applied to assess the balance of effects as well as positive/negative, sedative, psychedelic, and other effects. In addition, some objective PD endpoints were applied.

Balance of effects

- Drug Liking VAS (bipolar): TEmax, Emin, TEmin, TA_AUE
- Overall Drug Liking VAS (bipolar): Emax, Emin
- Take Drug Again VAS (bipolar): Emax, Emin

Positive Effects

- Good Effects VAS (unipolar): Emax, TEmax, TA_AUE
- Feeling High VAS (unipolar): Emax, TEmax, TA_AUE

Negative Effects

- Bad Effects VAS (unipolar): Emax, TEmax, TA_AUE

Sedative and Other Effects

- Alertness/Drowsiness VAS (bipolar): Emin, TEmin, time-averaged area over the effect

curve (TA_AOE)

- Observer's Assessment of Alertness/Sedation (OAA/S) composite and sum scores (unipolar): Emin, TEmin, TA_AOE

Psychedelic effects

- Bowdle VAS (unipolar): Emax for Internal and External Perceptions composite scores

Other effects

- Drug Similarity VAS (unipolar): 12 h score
- Any Effects VAS (unipolar): Emax, TEmax, TA_AUE

Objective PD endpoints

- Reaction time task (RTI) median five-choice reaction time: Emax, area under the effect time curve (AUE)
- RTI median five-choice error score: Emax, AUE
- Paired Associates Learning (PAL): total errors adjusted Emax, AUE; total attempts Emax, AUE; first attempt memory score Emin
- Rapid visual information processing (RVP) target sensitivity (A' prime): Emin
- RVP median response latency: Emax, AUE

2.1.5. Statistical methodologies used in the Sponsor's analyses

The statistical hypotheses used were recommended in FDA 2017 Guidance. The test margins for the primary endpoint were prespecified at 15, 0, and 11 for the comparisons positive control versus placebo, positive control versus test drug, and test drug versus placebo, respectively. The significance level for each test was 0.05. Analyses for secondary and exploratory endpoints used one-sided tests for the comparisons between positive control and placebo, and between positive control and test drug at the significance level of 0.05. For the comparison between test drug and placebo, the two-sided test with the significance level of 0.10 was used. All tests for the secondary endpoints and exploratory endpoints are with a margin zero.

Analysis of primary and secondary endpoints were performed using a mixed-effect ANOVA model. The model was to include treatment, period, and treatment sequence as fixed effects, and baseline (pre-dose) measurement as a covariate where applicable, and subject nested within sequence as a random effect. A first-order direct carry-over effect from the treatment of the previous period was included in the model if it was found significant at 25% level. For the first treatment period, treatment 'A' was used for all subjects and all PD endpoints. From each model, least squares means and CIs were provided for each treatment; and difference in least squares mean, CIs of the difference, and p-values were provided for each treatment comparison.

The assumption of normal distribution of the data required for the ANOVA model was examined using a Shapiro-Wilk W normality test on the residuals from the mixed-effect model. Parameters were analyzed under the assumption of a normal distribution if the p-value of the test was ≥ 0.05 . Based on the Shapiro-Wilk W test, the model was decided through the steps described in Section 9.8.3 (note that this was a change to the planned analysis in the SAP).

Reviewer's comments: The sponsor stated in Section 9.8.3. that the t-test was only used if the distribution of the paired difference was normal or slightly skewed, i.e., upper-tailed = 0 to 0.5; lower-tailed = -0.5 to 0; two-tailed = -0.5 to 0.5.

If the probability value was <0.05 for the Shapiro Wilk W test, and the residuals appeared to be severely non-normal in distribution and the paired differences between treatments did not graphically appear to be moderately symmetric (are heavily skewed), then the endpoint was analyzed non-parametrically. The Sign test and the distribution-free confidence interval (CI) were used to evaluate treatment differences.

Reviewer's comments: In the Section 9.8.3. the sponsor stated:

For inferential analyses, if the result from the CI did not match the result from the p-value, i.e., the margin was not contained in the CI but the p-value was not significant, the CI and the p-value were set to 'not applicable'.

The confidence interval cannot always be used for making a conclusion for a statistical test, especially the Sign test and the distribution free CI are two different methodologies. The conclusion of a comparison should be based on the Sign test.

The sponsor's post-hoc analyses are also included in the Section 9.8.3.

2.1.6. Sponsor's summary of the pharmacodynamic evaluation and conclusions

The sponsor's pharmacodynamic results

1. Did the positive control drugs produce mean responses that showed greater abuse potential compared to placebo in order to claim study validity (hypothesis #1)?

The positive comparators (150 mg suvorexant and 30 mg zolpidem) produced responses that showed greater drug liking compared to placebo:

- 150 mg suvorexant was associated with a difference of 29.0 compared to placebo, with a lower bound of the CI of 26.0 ($p < 0.0001$), which was greater than the pre-specified margin of 15.
- 30 mg zolpidem showed a difference of 26.0 compared to placebo, with a lower bound of the CI of 22.0 ($p < 0.0001$), which was greater than the pre-specified margin of 15.

These data demonstrate that the overall study can be considered valid according to the pre-specified criteria.

2. Did the test drug ACT-541468 produce mean responses that showed less abuse potential compared to the positive control drugs (hypothesis #2)?

The test drug (ACT-541468) did not produce responses that showed less drug liking compared to the positive comparators at all dose levels:

- 150 mg suvorexant and 30 mg zolpidem – 50 mg ACT-541468 differences (lower bound of the CI) were 7.5 (4.1) and 6.6 (3.3), respectively ($p \leq 0.0007$).
- 150 mg suvorexant and 30 mg zolpidem – 100 mg ACT-541468 differences (lower bound of the CI) were 3.0 (-1.0) and 1.0 (-2.0), respectively ($p \geq 0.1958$).
- 150 mg suvorexant and 30 mg zolpidem – 150 mg ACT-541468 differences (lower bound of the CI) were -0.6 (-2.7) and -3.0 (-4.0), respectively ($p \geq 0.6583$).

Thus, ACT-541468 showed significantly less drug-liking at the 50 mg dose compared to both positive comparators, but not at the doses of 100 and 150 mg.

3. Did the test drug ACT-541468 produce mean responses that show similar abuse potential compared to placebo (hypothesis #3)?

As the test drug ACT-541468 was significantly different from both positive comparators only at the dose of 50 mg, but not at doses of 100 or 150 mg (see hypothesis #2), the p-values for comparisons between ACT-541468 and placebo are not shown. However, descriptive results showed differences and upper bounds of the CI that exceeded the pre-specified margin of 11, indicating that ACT-541468 did not produce responses that were similar to placebo.

Time course of Drug Liking effects

Suvorexant, zolpidem, and ACT-541468 showed a similar time to peak effects (i.e., T_{Emax}) typically occurring at 1.5 to 2 h post-dose. However, the duration of PD effects was slightly longer with suvorexant compared to zolpidem and all doses of ACT-541468, i.e., generally returning to baseline by 12 h post-dose for suvorexant vs 6–8 h post-dose for zolpidem and ACT-541468, respectively.

Secondary PD endpoints

Overall Drug Liking VAS, Take Drug Again VAS, Feeling High VAS, Good Effects VAS, Bad Effects VAS, Alertness/Drowsiness VAS, Any Effects VAS

Both suvorexant and zolpidem significantly differentiated from placebo with respect to each of these 7 VAS assessments. The 50 mg dose of ACT-541468 consistently showed scores that were significantly different from both suvorexant and zolpidem in favor of ACT-541468 50 mg. This was applicable to each of these PD VAS assessments except for the Take Drug Again VAS in comparison to zolpidem. However, no significant differences from comparator data were observed at the doses of 100 mg and 150 mg ACT-541468 for the majority of assessments.

Bowdle VAS for assessment of perceptual effects

Both suvorexant and zolpidem significantly differentiated from placebo with respect to Internal and External Perception composite scales. ACT-541468 showed significantly lower scores (i.e., less alterations of internal and external perception) compared to zolpidem at all doses and compared to suvorexant at the 50 mg and 100 mg doses. All doses of ACT-541468 differentiated from placebo.

Drug Similarity VAS

Based on Drug Similarity VAS data, the perceived effects of zolpidem, suvorexant, and ACT-541468 were consistently considered more similar to the effects of benzodiazepines and other sedatives than those of other psychoactive substances such as opioids and cannabis. These VAS values with respect to benzodiazepines and other sedatives were lowest at the 50 mg dose of ACT-541468 as compared to all other active treatments.

Observer's Assessment of Alertness/Sedation

Both suvorexant and zolpidem differentiated from placebo based on composite and sum scores of the OAA/S, i.e., indicating sedative effects greater than placebo. The lowest degree of sedation was

determined for the 50 mg dose of ACT-541468 as compared to all other active treatments. All doses of ACT-541468 differentiated from placebo.

Objective assessments of cognitive function (reaction time task, Rapid Visual Information Processing, Paired Associates Learning score)

Both suvorexant and zolpidem showed significant cognitive impairment with respect to the majority of endpoints, including RTI – five-choice reaction time, RVP – response latency, and PAL – total errors. Compared to zolpidem, ACT-541468 showed significantly less impairment at all doses with respect to these 3 endpoints. Compared to suvorexant, less impairment was noted for the 50 mg dose of ACT-541468. The doses of 100 mg and 150 mg ACT-541468 both differentiated from placebo, whereas at the 50 mg dose, this was only applicable for RVP – response latency.

Conclusion

- Study validity was achieved for both comparators, zolpidem and suvorexant, since the difference in Drug Liking VAS Emax between each positive comparator drug and placebo exceeded the pre-defined margin of 15 points.
- The primary endpoint analysis revealed a significantly lower Drug Liking VAS Emax of ACT-541468 compared to both suvorexant and zolpidem at 50 mg (i.e., highest dose in phase 3). No significant differences were determined at 100 and 150 mg.
- ACT-541468 showed lower effects on the majority of secondary endpoints (i.e., balance of effects, positive, negative, sedative, psychedelic, and any effects) compared to both suvorexant and zolpidem at the dose of 50 mg, but not at 100 mg or 150 mg.
- Equivalence of Drug Liking VAS Emax to placebo was not determined for any dose of ACT-541468.
- There was no PK/PD association between Cmax and Drug Liking VAS Emax after administration of ACT-541468.

2.3. Data Location

The datasets used in the reviewer’s analyses are located at

<\\CDSESUB1\evsprod\NDA214985\0001\m5>

2.4. Reviewer’s Assessment

In this report, the reviewer used the following notations for treatments in Study ID-078-107:

Z30 – 30 mg zolpidem

S150 – 150 mg suvorexant

T50 – 50 mg ACT-541468

T100 – 100 mg ACT-541468

T150 – 150 mg ACT-541468

P – Placebo

2.4.1. Primary Analysis

2.4.1.1. Descriptive statistics

The primary endpoint of this study is Drug Liking Emax. Table 1 summarizes the mean, standard deviation (SD), minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3), and maximum (Max) for Emax and TEmax of Drug Liking VAS for the 6 treatments in the study. The summary statistics for paired differences are also provided in the table.

Table 1: Summary statistics for Drug Liking Emax and Drug Liking TEmax (N=63)

Endpoint	TRT/TRT Diff	Mean	SD	Min	Q1	Med	Q3	Max
Drug Liking Emax	Z30	79.9	14.4	50	71	78	90	100
	S150	80.7	14.9	50	71	80	92	100
	T50	73.2	16.8	50	59	73	86	100
	T100	79.1	16.4	50	68	80	92	100
	T150	81.3	14.2	50	71	84	93	100
	P	55.1	12.2	50	50	50	50	100
	Z30-P	24.8	16.9	-14	12	26	37	50
	Z30-T50	6.6	15.6	-36	0	6	19	38
	Z30-T100	0.7	15.6	-50	-7	0	9	34
	Z30-T150	-1.4	15.0	-50	-7	0	6	39
	S150-P	25.7	16.8	-7	12	28	40	50
	S150-T50	7.5	16.2	-22	-4	3	19	50
	S150-T100	1.6	12.1	-37	-2	0	8	31
	S150-T150	-0.6	10.2	-26	-7	0	5	22
	T50-P	18.2	17.6	-20	1	20	29	50
	T100-P	24.1	19.4	-26	9	23	42	50
	T150-P	26.2	16.4	-8	16	25	39	50
	Drug Liking TEmax (hr)	Z30	2.7	3.4	0.25	1	2	3
S150		2.8	3.4	0.25	1.5	2	3	24
T50		2.3	2.0	0.25	1	2	3	12
T100		2.1	1.4	0.25	1.5	1.5	3	6
T150		2.7	3.5	0.25	1	1.5	3	24
P		0.7	1.4	0.25	0.25	0.25	0.25	8

The table shows the mean produced by 100 and 150 mg of ACT-541468 were similar to those by the positive controls. The median differences between these two doses of ACT-541416 and each positive control were zero. ACT-541468 50 mg produced smaller mean and median differences compared to each

positive control, but larger mean and median differences compared to placebo. The median TEmax produced by the positive controls and 50 mg ACT-541468 was at 2 hours post-dose. The median TEmax produced by 100 and 150 mg doses of ACT-541468 was 1.5 hours post-dose.

Figure 1 is the heat map display for Drug Liking Emax by treatment.



Figure 1: Heat Map by Treatment for Drug Liking Emax (N=63)

Note: The orange line on the heat map separates females from males.

The heat map shows that 11 (17.5%) subjects had Drug Liking Emax scores for placebo greater than 60. Subjects # (b) (6) # (b) (6) and # (b) (6) had Drug Liking Emax scores 93, 100 and 94 for placebo, respectively. Five (7.9%) subjects (# (b) (6), and # (b) (6)) and 7 (11.1%) subjects (# (b) (6), and # (b) (6)) had Drug Liking Emax scores smaller than 60 for 30 mg zolpidem and 150 mg suvorexant, respectively.

Figure 2 is the mean time course profiles by treatment for Drug Liking VAS. Data were collected at hours 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24. The peak mean responses produced by 50, 100 and 150 mg doses of ACT-541468 were 66.3, 73.4 and 75.3, respectively, and were reached at hour 1.5. The peak mean response produced by 30 mg zolpidem and 40 mg suvorexant were 70.2 and 75.5, and were reached at hours 3 and 2, respectively. The duration of liking effects was slightly longer with 150 mg suvorexant compared to 30 mg zolpidem and all doses of ACT-541468.

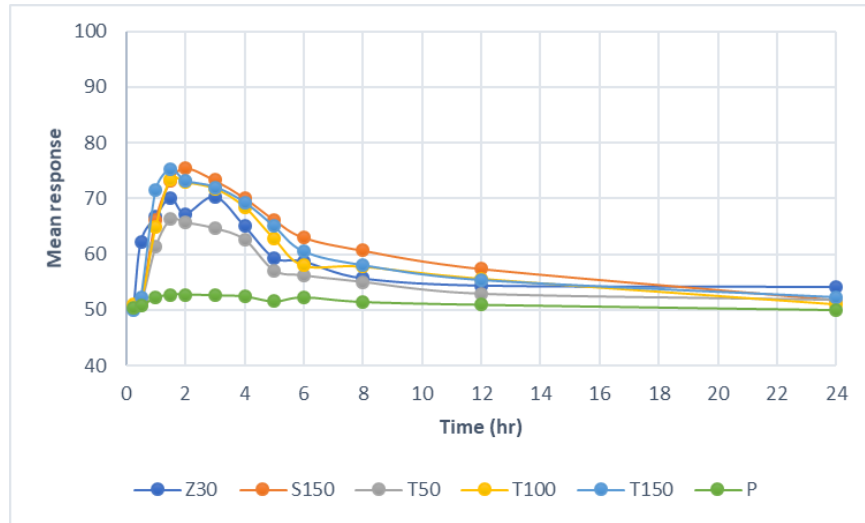


Figure 2: The mean time course profiles for Drug Liking VAS by treatment (N=63)

2.4.1.2. Statistical Testing

For the primary endpoint (1) at least one positive control must demonstrate significantly larger mean responses than placebo with a margin 15 to validate the study; (2) all doses of ACT-541468 must demonstrate significantly smaller mean responses than the validated positive control(s) to show that ACT-541468 produces less drug liking than positive control(s); (3) all doses of ACT-541468 must demonstrate the difference from placebo significantly smaller than 11 to show that ACT-541468 produces drug liking similar to placebo. In the sequential testing, an insignificant test will result in cessation of testing the following hypothesis. Therefore, no multiplicity adjustment for Type I error rate is required, and the significance level of each test is 5%. Figure 3 is the testing procedure.

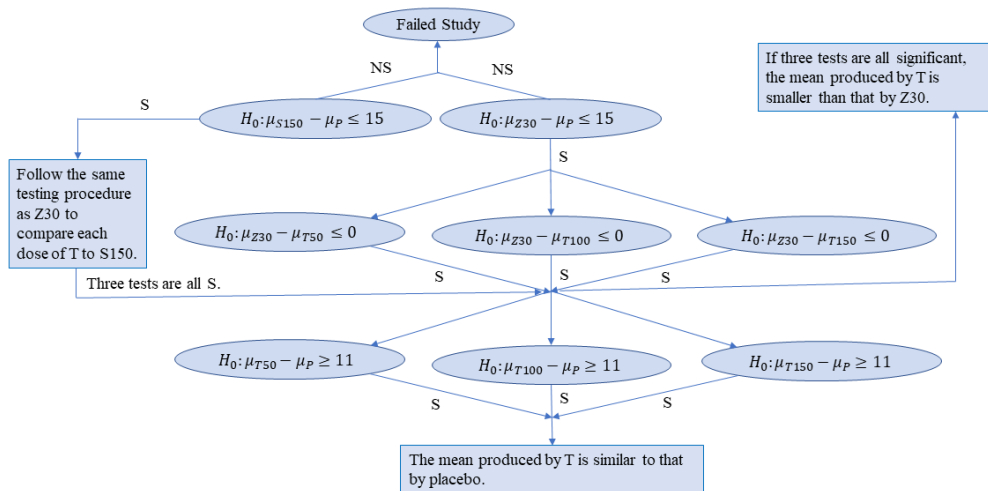


Figure 3: Testing procedure for the primary endpoint

Note: μ_{C1} and μ_{C2} denote means produced by 30 mg zolpidem and 150 mg suvorexant, respectively, and μ_{T50} , μ_{T100} and μ_{T150} denote means produced by 50, 100, and 150 mg doses of ACT-541468. S and NS denote the test is significant or not, respectively.

In the reviewer’s analysis, when any dose of ACT-541468 passed the comparison with both positive controls, the comparison between this dose of ACT-541468 and placebo was performed regardless of the significance in the comparisons between other doses of ACT-541468 and the positive controls. However, the result from this comparison can only be used for exploratory purpose. For decision making, one can pursue that ACT-541468 has similar abuse potential to placebo if and only if all doses of ACT-541468 passed the comparisons with all validated positive controls.

The statistical model used in the reviewer’s primary analysis was a mixed-effects model which included sequence, period, treatment and first-order-carryover effect as fixed effects, and subject as a random effect. For the primary endpoint, the W test on the residuals was significant ($p=0.0072$). Therefore, the normality of paired differences was further examined. Table 2 shows p-value of the W test and skewness for each paired difference for Drug Liking Emax.

Table 2: The W-Test results for the pairwise comparisons for Drug Liking Emax (N=63)

TRT Diff	skewness	P-value
Z30-P	-0.18	0.04404
Z30-T50	-0.57	0.06323
Z30-T100	-0.54	0.01502
Z30-T150	-0.31	0.00567
S150-P	-0.12	0.00387
S150-T50	0.51	0.07322
S150-T100	-0.31	0.01475
S150-T150	-0.15	0.23050
T50-P	0.23	0.03189
T100-P	-0.30	0.00498
T150-P	-0.09	0.00927

The p-value in red indicates that the W test was not significant at $\alpha = 0.05$ (prespecified in the protocol), and then the paired t test was used for these comparisons. Based on the sponsor’s changes on the planned analyses (Section 9.8 of the study report), the t-test was only used if the distribution of the paired difference was normal or slightly skewed, i.e., skewness=0 to 0.5 for upper-tailed test; skewness = -0.5 to 0 for lower-tailed test; and skewness= -0.5 to 0.5 for two-tailed test. The cases with blue skewness satisfied the rules. The Sign test was used for the rest of comparisons.

Table 3 shows the test results from the primary analysis. The p-value of a failed test is in red. Note that the comparisons between any dose of ACT-541468 and placebo was performed only when the comparisons between this dose and each positive control were significant.

Table 3: Primary analysis results on Drug Liking Emax (N=63)

TRT	C1	C2	T50	T100	T150	P	Comments
Mean (StdErr)	79.9 (1.8)	80.7 (1.9)	73.2 (2.1)	79.1 (2.1)	81.3 (1.8)	55.1 (1.5)	
Comparison	Mean/ Med Diff	StdErr/ (Q1, Q2)	Test value	p-value	95% CI		
					LCL	UCL	
Z30 vs. P	26.0	(12, 37)	15	0.0003	21.0	Infty	Z30 is validated
Z30 vs. T50	6.0	(0, 19)	0	0.0004	1.0	Infty	Drug liking produced by T is not less than that by Z30
Z30 vs. T100	0.0	(-7, 9)	0	0.5000	-1.0	Infty	
Z30 vs. T150	-1.4	1.9	0	0.7714	-4.6	Infty	
S150 vs. P	28.0	(23, 30)	15	0.0003	23.0	Infty	S150 is validated
S150 vs. T50	7.5	2.0	0	0.0003	4.1	Infty	Drug Liking produced by T is not less than that by S150
S150 vs. T100	0.0	(-1, 8)	0	0.1955	0.0	Infty	
S150 vs. T150	-0.6	1.3	0	0.6658	-2.7	Infty	
T50 vs. P	20.0	(1, 29)	11	0.9785	-Infty	22.0	Exploratory

*: The Sign test was performed for the comparisons in green. The median difference and the interquartile range as well as the distribution free 95% confidence interval of the median difference were listed.

The reviewer's primary analysis shows that for Drug Liking Emax:

1. The median difference between each positive control and placebo was significantly greater than 15 ($p = 0.0003$).
2. The mean or median differences between each positive control and each dose of ACT-541468 were not significantly greater than zero ($p \geq 0.1955$) except the comparison between each positive control and 50 mg ACT-541468 ($p \leq 0.0004$).
3. For exploratory purpose, the test for the comparison between 50 mg ACT-541468 and placebo was performed. The median difference between 50 mg ACT-541468 and placebo was not significantly smaller than 11 ($p = 0.9785$). This large p-value indicates that in fact, the median difference between 50 mg ACT-541468 and placebo was significantly greater than 11 with a p-value of 0.0215.

In conclusion, drug liking produced by ACT-541468 was not smaller than that produced by either 30 mg zolpidem or 40 mg suvorexant. The results were validated by the significant differences between both positive controls and placebo.

Note: Several mistakes were found in Tables 15-33, 15-34 and 15-35 in sponsor's report. The median of paired difference and (Q1, Q3) of paired difference in these tables were wrongly calculated using the difference in medians, difference in Q1, and difference in Q3 between treatments. These mistakes were also made in other tables for secondary endpoints.

2.4.2. Secondary Analyses

There were many secondary endpoints in this study. The protocol did not prespecify key secondary endpoints. After discussed with the CSS reviewer, Dr. Edward Hawkins, in the secondary analyses the reviewer analyzed Overall Drug Liking Emax and Take Drug Again Emax. For other secondary endpoints, descriptive statistics were presented in Section 2.4.4.

2.4.2.1. Descriptive Statistics

Table 4 summarizes the mean, standard deviation (SD), minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3), and maximum (Max) for the 6 treatments in the study for Overall Drug Liking Emax and Take Drug Again Emax.

Table 4: Summary statistics for Overall Drug Liking Emax, and Take Drug Again Emax (N=63)

Endpoint	TRT	Mean	SD	Min	Q1	Med	Q3	Max
Overall Drug Liking Emax	Z30	79.4	17.0	31	68	83	94	100
	S150	81.8	16.3	29	72	82	97	100
	T50	74.3	19.4	50	51	75	92	100
	T100	80.0	18.4	27	71	83	97	100
	T150	81.2	17.4	16	72	81	99	100
	P	55.7	13.3	50	50	50	50	100
Take Drug Again Emax	Z30	80.6	17.3	37	69	81	100	100
	S150	82.2	17.1	29	71	84	100	100
	T50	75.6	21.6	0	55	77	100	100
	T100	80.6	18.9	27	69	83	100	100
	T150	82.2	17.7	11	73	83	100	100
	P	56.2	16.8	0	50	50	50	100

Note that the mean scores and median scores produced by ACT-541468 were greater than or equal to 74.3 and 75, respectively, and Q3 scores produced by ACT-541468 were greater than or equal to 92.

Figure 4 is the heat map by treatment for Overall Drug Liking Emax.

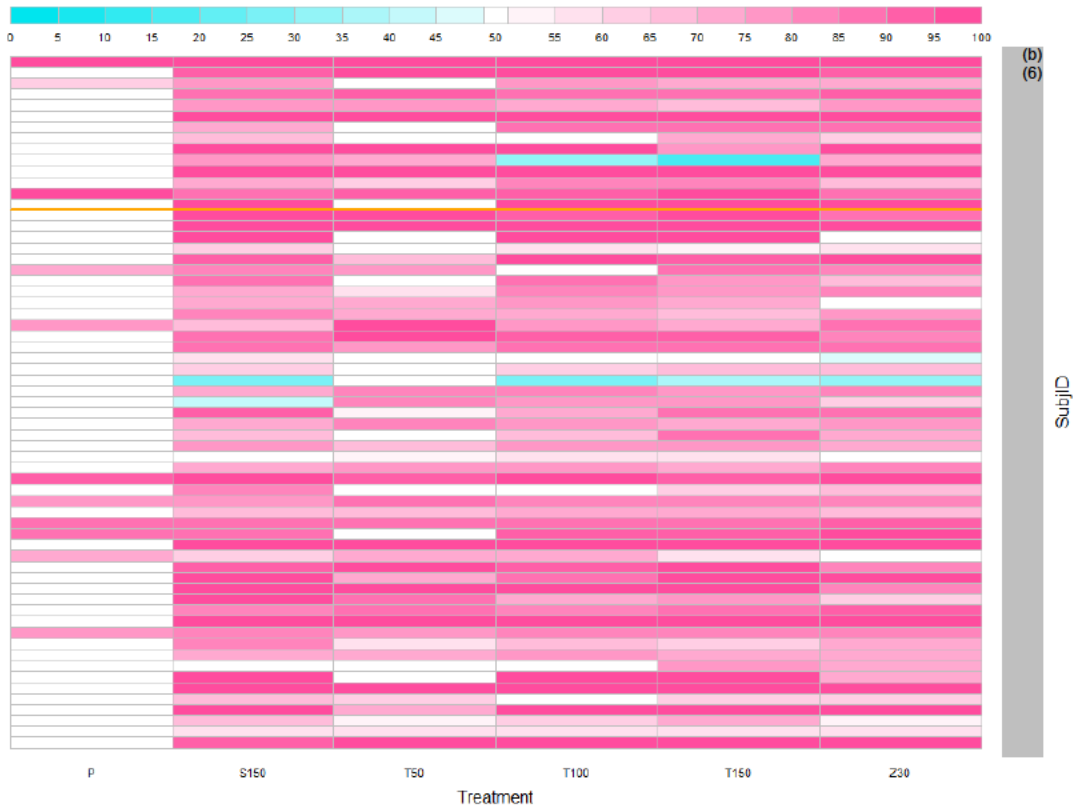


Figure 4: Heat map by treatment for Overall Drug Liking Emax

Eleven (17.5%) subjects in some degree overall liked placebo (Emax score >60). Subject # (b) (6) overall disliked two positive controls. Subject # (b) (6) overall disliked 150 mg suvorexant. Subject # (b) (6) had an Emax score 100 for all treatments including placebo.

Figure 5 is the heat map by treatment for Take Drug Again Emax. Two subjects (# (b) (6) and # (b) (6)) had an Emax score 100 for all treatments including placebo. Subject # (b) (6) had an Emax score 0 for placebo, which indicates the subject strongly did not want to take placebo again.

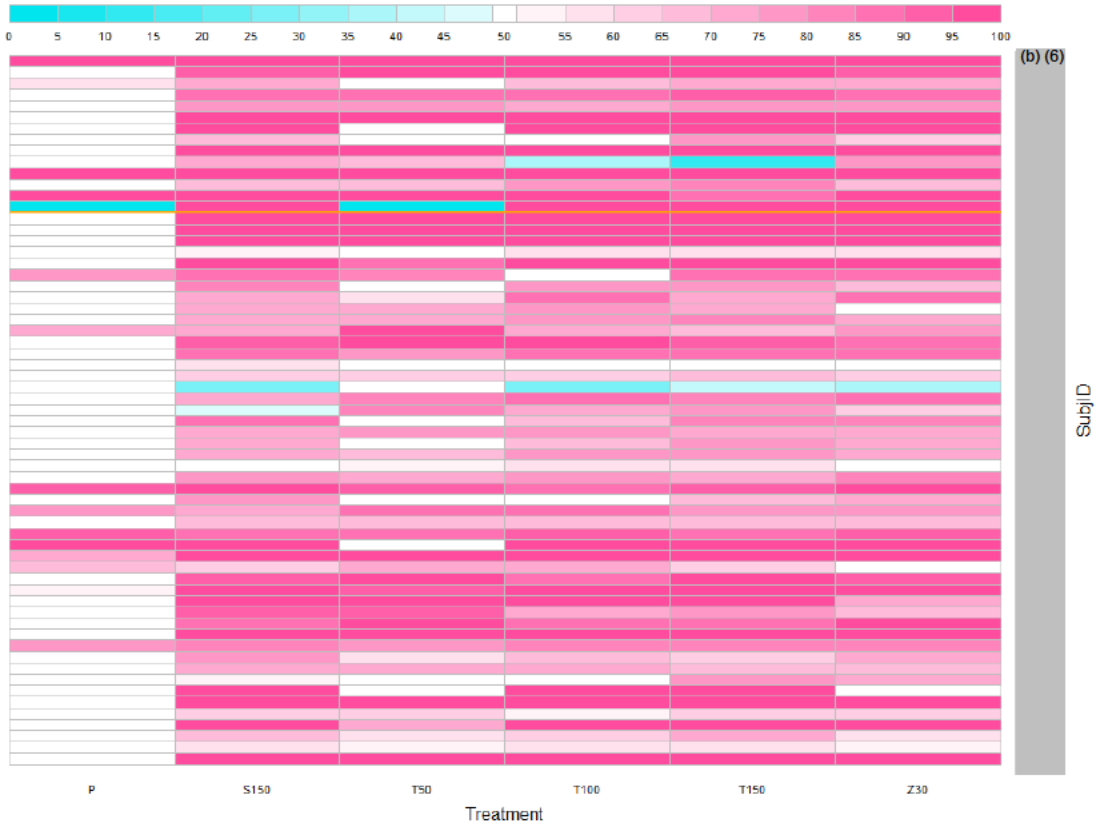


Figure 5: Heat map by treatment for Take Drug Again Emax

Figure 6 shows the means with SDs for Overall Drug Liking VAS and Take Drug Again VAS at hours 12 and 24 for each treatment.

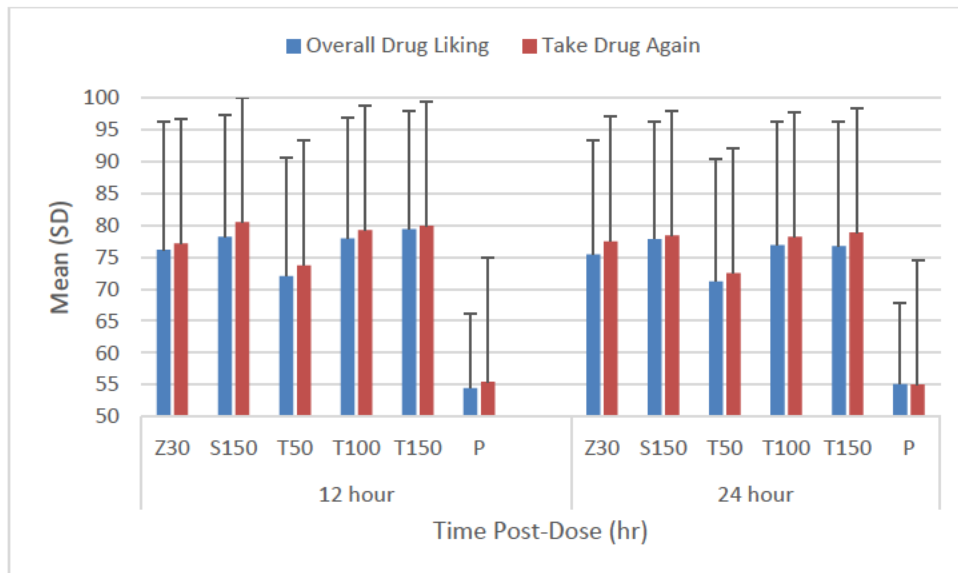


Figure 6: Means with SDs for Overall Drug Liking VAS and Take Drug Again VAS scores at hours 12 and 24 post dose for each treatment (N=63)

2.4.2.2. Statistical Testing

The statistical model used in the reviewer’s secondary analysis was a mixed-effects model which included sequence, period, treatment and first-order-carryover effect as fixed effects and subject as a random effect. The W test on residuals for both secondary endpoints were significant ($p \leq 0.0007$). Therefore, the normality of paired differences was further examined. Table 5 shows p-value of the W test and skewness for each paired difference for Overall Drug Liking Emax and Take Drug Again Emax.

Table 5: The W-Test results for the pairwise comparisons for Overall Drug Liking Emax and Take Drug Again Emax (N=63)

TRT Diff	Overall Drug Liking Emax		Take Drug Again Emax	
	skewness	p-value	skewness	p-value
Z30-P	-0.22	0.01060	0.56	0.00510
Z30-T50	0.62	0.00473	2.26	0.00000
Z30-T100	-0.23	0.00009	-0.18	0.00000
Z30-T150	0.67	0.00000	1.43	0.00000
S150-P	-0.37	0.00093	0.41	0.00223
S150-T50	0.55	0.00070	2.05	0.00000
S150-T100	1.16	0.00000	1.30	0.00000
S150-T150	1.84	0.00000	2.81	0.00000
T50-P	0.14	0.00008	-0.17	0.00004
T100-P	-0.36	0.00057	0.29	0.00410
T150-P	-0.53	0.00151	0.04	0.00805

From the Table values, one may see that the W tests for all comparisons were highly significant. Based on the sponsor’s changes on the planned analyses (Section 9.8 of the study report), the t-test was only used if the distribution of the paired difference was normal or slightly skewed, i.e., skewness=0 to 0.5 for upper-tailed test; skewness = -0.5 to 0 for lower-tailed test; and skewness=-0.5 to 0.5 for two-tailed test. The cases with blue skewness satisfied the rules. The Sign test was used for the rest of comparisons.

Table 6 shows the test results. The p-value of a failed test is in red. Note that the comparisons between any dose of ACT-541468 and placebo was performed, only when the comparisons between this dose and each positive control were significant. The comparison between 50 mg ACT-541468 and placebo was a two-tailed test. For this test, no difference between two treatments was in the null hypothesis. Therefore, the p-value in blue shows significant difference between 50 mg ACT-541468 and placebo.

Table 6: Analysis Results on Overall Drug Liking Emax and Take Drug Again Emax (N=63)

N=63	TRT	Z30	S150	T50	T100	T150	P
	Mean (StdErr)	79.4 (2.1)	81.8 (2.0)	74.3 (2.4)	80.0 (2.3)	81.2 (2.2)	55.7 (1.7)
Endpoint	Comparison	Med Diff	(Q1, Q3)	Test value	p-value	95% CI	
						LCL	UCL
Overall Drug Liking Emax	Z30 vs. P	25	(8, 40)	0	<0.0001	17	Infty
	Z30 vs. T50	1	(-2, 16)	0	0.0460	0	Infty
	Z30 vs. T100	0	(-4, 4)	0	0.5000	-1	Infty
	Z30 vs. T150	0	(-8, 4)	0	0.7121	-2	Infty
	S150 vs. P	25	(9, 45)	0	<0.0001	22	Infty
	S150 vs. T50	2	(-1, 15)	0	0.0088	0	Infty
	S150 vs. T100	0	(-3, 2)	0	0.5000	0	Infty
	S150 vs. T150	0	(-3, 2)	0	0.7200	-1	Infty
	T50 vs. P	17	(0, 36)	0	<0.0001	6	24
N=63	TRT	Z30	S150	T50	T100	T150	P
	Mean (StdErr)	80.6 (2.2)	82.2 (2.2)	75.6 (2.7)	80.6 (2.4)	82.2 (2.2)	56.2 (2.2)
Endpoint	Comparison	Mean/ Med Diff	StdErr/ (Q1, Q3)	Test value	p-value	95% CI	
						LCL	UCL
Take Drug Again Emax	Z30 vs. P	24	(7, 41)	0	<0.0001	17	Infty
	Z30 vs. T50	0	(-2, 9)	0	0.1562	0	Infty
	Z30 vs. T100	0	(-3, 3)	0	0.8144	-1	Infty
	Z30 vs. T150	0	(-4, 0)	0	0.967	-1	Infty
	S40 vs. P	26.0	2.7	0	<0.0001	21.4	Infty
	S150 vs. T50	0	(-2, 10)	0	0.0298	0	Infty
	S150 vs. T100	0	(-1, 2)	0	0.2612	0	Infty
	S150 vs. T150	0	(-3, 2)	0	0.5000	0	Infty

Note: 1) The Sign test was performed for the comparisons in green. In such a case, the median difference and interquartile range (Q1, Q3) of the difference as well as the distribution free 95% confidence interval of the median difference were listed.

The results show that for Overall Drug Liking Emax

1. The mean or median difference between each positive control and placebo was significantly greater than zero ($p < 0.0001$).
2. The median differences between each positive control and each dose of ACT-541468 were not significantly greater than 0 ($p \geq 0.5000$) except the comparisons between each positive control and 50 mg ACT-541468 ($p \leq 0.0460$).
3. For exploratory purpose, the test for the comparison between 50 mg ACT-541468 and placebo was performed. The median difference between 50 mg ACT-541468 and placebo was significantly

The statistical testing procedure and the statistical model used for the sensitivity analyses were the same as those used in the primary and secondary analyses. Results for checking assumptions of the statistical model and the W test results for paired comparisons are not presented here. Table 8 shows the results from the sensitivity analyses.

Table 8: Results from the Reviewer’s Sensitivity Analyses (N=58)

Endpoint	Comparison	Mean/ Med Diff	StdErr/ (Q1, Q3)	Test value	p-value	95% CI	
						LCL	UCL
Drug Liking Emax	Z30 vs. P	26	(20, 39)	15	<0.0001	22.0	Infy
	Z30 vs. T50	8.2	1.9	0	<0.0001	4.9	Infy
	Z30 vs. T100	0	(-3, 5)	0	0.5000	0.0	Infy
	Z30 vs. T150	0	(-5, 6)	0	0.5562	-3.0	Infy
	S150 vs. P	28	(17, 40)	15	<0.0001	26.0	Infy
	S150 vs. T50	8.4	2.1	0	0.0001	4.8	Infy
	S150 vs. T100	0	(-4, 8)	0	0.2758	0.0	Infy
	S150 vs. T150	-0.2	1.3	0	0.5670	-2.4	Infy
	T50 vs. P	20	(0, 31)	11	>0.9999	-Infy	24
Overall Drug Liking Emax	Z30 vs. P	25	(11, 40)	0	<0.0001	19.0	Infy
	Z30 vs. T50	5.5	2.2	0	0.0079	1.8	Infy
	Z30 vs. T100	0	(-4, 4)	0	0.5000	-1.0	Infy
	Z30 vs. T150	0	(-9, 4)	0	0.7646	-2.0	Infy
	S150 vs. P	27.5	2.5	0	<0.0001	23.4	Infy
	S150 vs. T50	3	(0, 20)	0	0.0055	0.0	7.0
	S150 vs. T100	0	(-2, 3)	0	0.5000	0.0	Infy
	S150 vs. T150	0	(-3, 4)	0	0.2712	-5.0	Infy
	T50 vs. P	19	(0, 36)	0	<0.0001	0.0	4.0
Take Drug Again Emax	Z30 vs. P	26.5	2.75	0	<0.0001	21.9	Infy
	Z30 vs. T50	0	(-2, 10)	0	0.1456	0.0	Infy
	Z30 vs. T100	0	(-3, 4)	0	0.6224	0.0	Infy
	Z30 vs. T150	0	(-5, 0)	0	0.9808	-2.0	Infy
	S150 vs. P	28.2	2.8	0	<0.0001	23.6	Infy
	S150 vs. T50	1	(-1, 11)	0	0.0179	0.0	Infy
	S150 vs. T100	0	(-1, 3)	0	0.2498	0.0	Infy
	S150 vs. T150	0	(-3, 2)	0	0.6254	0.0	Infy

Note: 1) The Sign test was performed for the comparisons in green. In such a case, the median difference and interquartile range (Q1, Q3) of the difference as well as the distribution free 95% confidence interval of the median difference were listed.

The p-value in red shows the test was not significant. The p-value in blue shows that the median difference between 50 mg ACT-541468 and placebo was significantly greater than zero for Overall Drug Liking Emax. The results from the sensitivity analyses were consist of those from the primary and secondary analyses (See Tables 3 and 6).

2.4.4. Descriptive statistics for other secondary endpoints

Table 10 summarizes the mean, standard deviation (SD), minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3), and maximum (Max) for the 6 treatments in the study for secondary endpoints: Alertness/Drowsiness Emin, Any Effects Emax, Bad Effects Emax, Good Effects Emax and Feeling High Emax. Note that Alertness/Drowsiness VAS is a bipolar scale. Instead of reporting results based on the change from predose response for this measure, the reviewer reported the results from predose and post-dose separately. In addition, predose responses of all subjects to Feeling High VAS were 0 except one subject whose score was 1. Therefore, summary statistics for Feeling High Emax were based on post-dose responses.

Table 9: Summary Statistics of secondary endpoints: Alertness/Drowsiness Emin, Any Effects Emax, Bad Effects Emax, Good Effects Emax and Feeling High Emax (N=63)

Endpoint	TRT	Mean	SD	Min	Q1	Med	Q3	Max
Alertness /Drowsiness Emin	Z30	19.4	15.2	0	1	21	29.5	50
	S150	12.1	12.2	0	0.75	8.5	18.25	50
	T50	23.3	17.8	0	8	21	38	50
	T100	13.9	14.2	0	0	11.5	24	50
	T150	9.3	10.4	0	0	5	16	36
	P	42.1	15.8	0	39	50	50	50
Alertness /Downiness predose	Z30	50	0	50	50	50	50	50
	S150	51.4	7.8	49	50	50	50	100
	T50	50.0	0.1	49	50	50	50	50
	T100	50.7	5.5	50	50	50	50	94
	T150	50.3	2.3	50	50	50	50	68
	P	50.7	6.4	43	50	50	50	100
Any Effects Emax	Z30	62.9	27.5	0	45	64	85	100
	S150	70.9	29.1	0	52	78	100	100
	T50	47.2	34.3	0	9	50	77	100
	T100	62.0	32.2	0	38	68	92	100
	T150	68.5	26.1	9	55	75	89	100
	P	7.8	19.4	0	0	0	0	77
Feeling Bad Drug Effects	Z30	14.0	27.6	0	0	0	16	100
	S150	11.8	23.3	0	0	0	12	100

Emax	T50	3.5	12.9	0	0	0	0	78
	T100	10.7	23.7	0	0	0	3	100
	T150	10.5	20.9	0	0	0	11	82
	P	1.1	5.2	0	0	0	0	36
Feeling Good Drug Effects Emax	Z30	60.4	29.4	0	41	67	86	100
	S150	63.1	31.7	0	38	72	88	100
	T50	45.0	34.2	0	12	46	75	100
	T100	59.0	33.1	0	38	63	91	100
	T150	65.4	28.3	0	48	66	89	100
	P	7.7	19.3	0	0	0	0	79
Feeling High Emax	Z30	60.2	32.6	0	32	69	89	100
	S150	50.1	37.1	0	9	58	80	100
	T50	38.2	36.2	0	0	34	73	100
	T100	48.4	38.2	0	8	54	89	100
	T150	58.1	35.0	0	26	65	86	100
	P	5.5	16.6	0	0	0	0	77

Compared to all active treatments in the study, 50 mg ACT-541468 produced lower effects according to these endpoints. However, the effects produced by 50 mg ACT-541468 were larger than placebo. ACT-541468 150 mg produced largest drowsiness compared to other active treatments.

The predose responses were included in the dataset for Composite Score of Observer's Assessment of Alertness/Sedation, Sum Score of Observer's Assessment of Alertness/Sedation, Composite Score of VAS Bowdle-External Perception, and Composite Score of VAS Bowdle-External Perception. However, the predose responses from subjects were a constant. For example, for Composite Score of Observer's Assessment of Alertness/Sedation and Sum Score of Observer's Assessment of Alertness/Sedation predose responses were 5 and 20, respectively for all subjects. The 5 and 20 were the maximum scores on these two scales, respectively. It appears that the predose was not collected from subjects during the study rather manually added later. Therefore, the summary statistics in Tables 11 and 12 were based on subjects' post-dose responses.

Table 10: Summary Statistics of secondary endpoints based on Bowdle VAS (N=63)

Endpoint	TRT	Mean	SD	Min	Q1	Med	Q3	Max
Composite Score Emin	Z30	3.3	1.1	0	3	4	4	5
	S150	3.6	1.1	0	3	4	4	5
	T50	4.0	1.0	0	4	4	5	5
	T100	3.8	0.9	0	3	4	4	5
	T150	3.7	1.0	0	3	4	4	5
	P	4.7	0.7	0	5	5	5	5
Sum Score Emin	Z30	15.9	2.2	12	14	16	17	20
	S150	16.4	2.6	11	15	16	18	20
	T50	18.0	2.1	11	17	19	20	20
	T100	17.0	2.2	11	15.75	17	19	20
	T150	16.5	2.2	12	15.5	16	18	20
	P	19.6	1.1	14	20	20	20	20

Table 11: Summary Statistics of secondary endpoints based on Observer's Assessment of Alertness/Sedation (N=63)

Endpoint	TRT	Mean	SD	Min	Q1	Med	Q3	Max
Composite Score Emin	Z30	3.3	1.1	0	3	4	4	5
	S150	3.6	1.1	0	3	4	4	5
	T50	4.0	1.0	0	4	4	5	5
	T100	3.8	0.9	0	3	4	4	5
	T150	3.7	1.0	0	3	4	4	5
	P	4.7	0.7	0	5	5	5	5
Sum Score Emin	Z30	15.9	2.2	12	14	16	17	20
	S150	16.4	2.6	11	15	16	18	20
	T50	18.0	2.1	11	17	19	20	20
	T100	17.0	2.2	11	15.75	17	19	20
	T150	16.5	2.2	12	15.5	16	18	20
	P	19.6	1.1	14	20	20	20	20

Note that based on Observer's Assessment of Alertness/Sedation, 150 mg ACT-541468 produced similar sedative effect compared to other active treatments.

Figures 7 -15 are the mean time course profiles by treatment for these secondary measures. The vertical axis is based on the range of each scale except bipolar Alertness/Drowsiness, in which 0-60 is used for the

vertical axis. Note that all five active treatments produced peak mean for bad drug effects less than 7 on a unipolar scale.

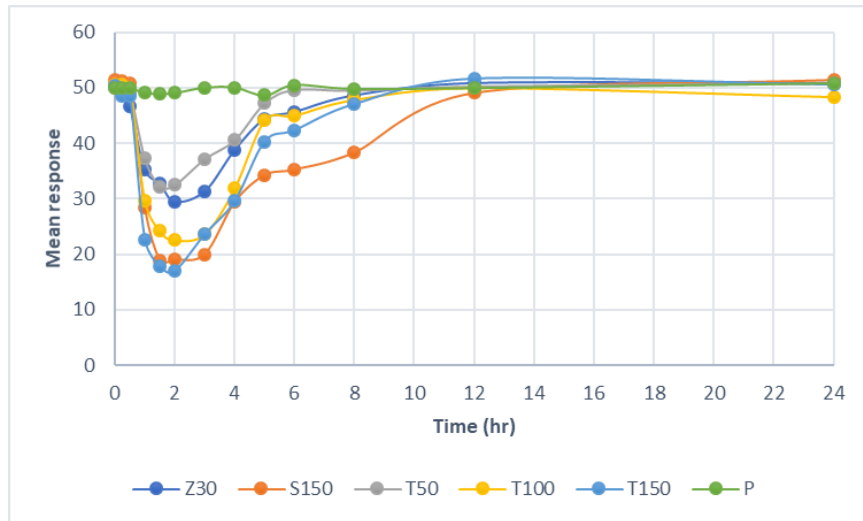


Figure 7: The mean time course profiles by treatment for Alertness/Drowsiness VAS (N=63)

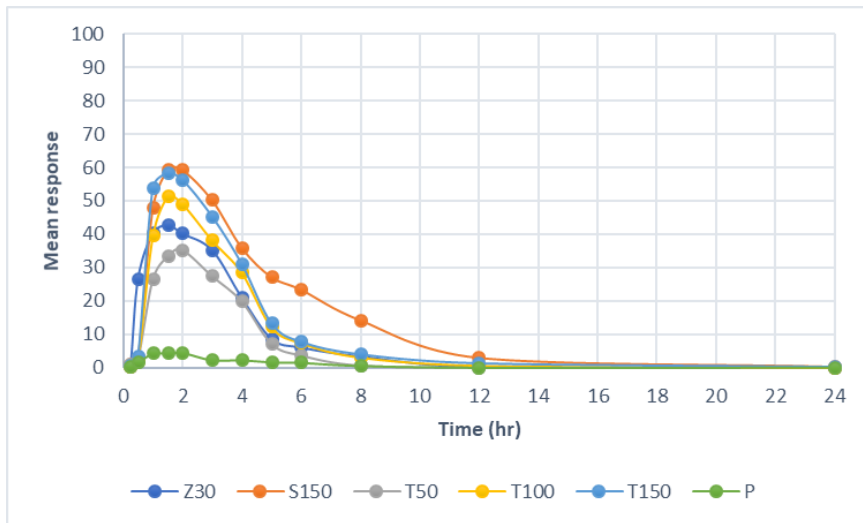


Figure 8: The mean time course profiles by treatment for Any Effects VAS (N=63)

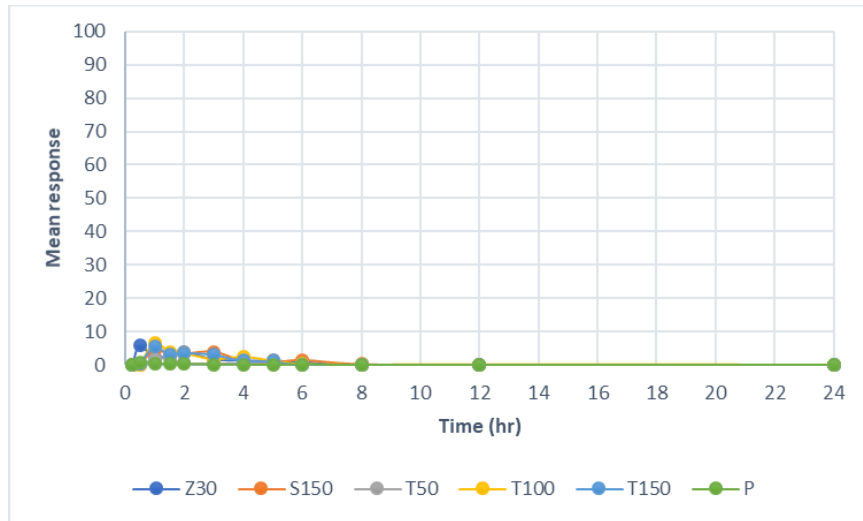


Figure 9: The mean time course profiles by treatment for Feeling Bad Drug Effects VAS (N=63)

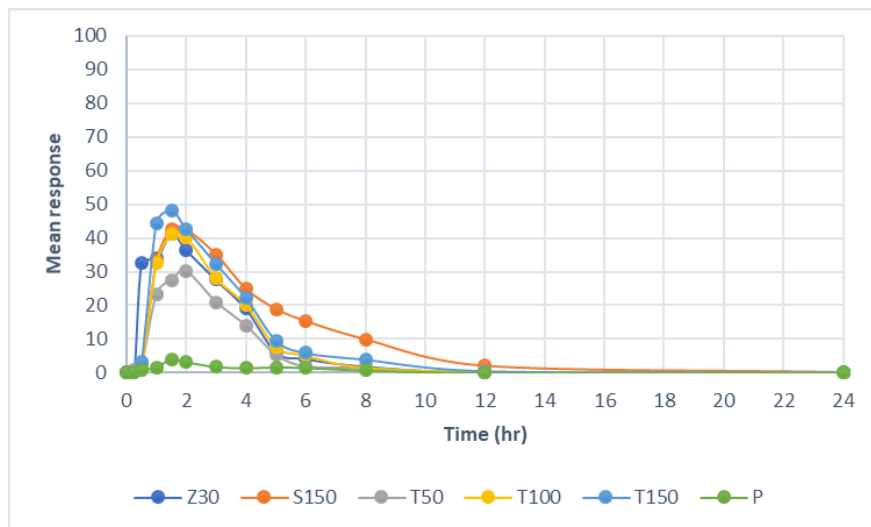


Figure 10: The mean time course profiles by treatment for Feeling Good Drug Effects VAS (N=63)

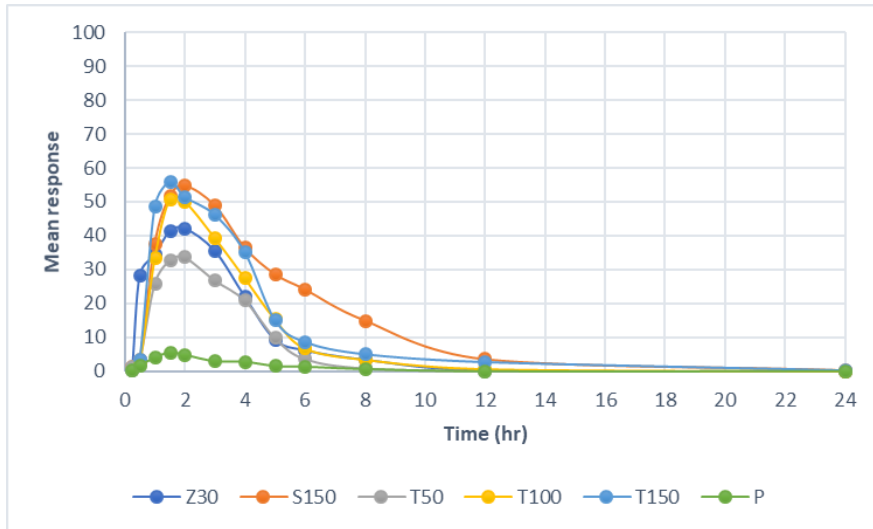


Figure 11: The mean time course profiles by treatment for Feeling High VAS (N=63)

It appears that the effects (Alertness/Drowsiness VAS, Any Effects VAS, Good Effects VAS, Filing High VAS) produced by 150 mg suvorexant lasted longer than any of other active treatments.

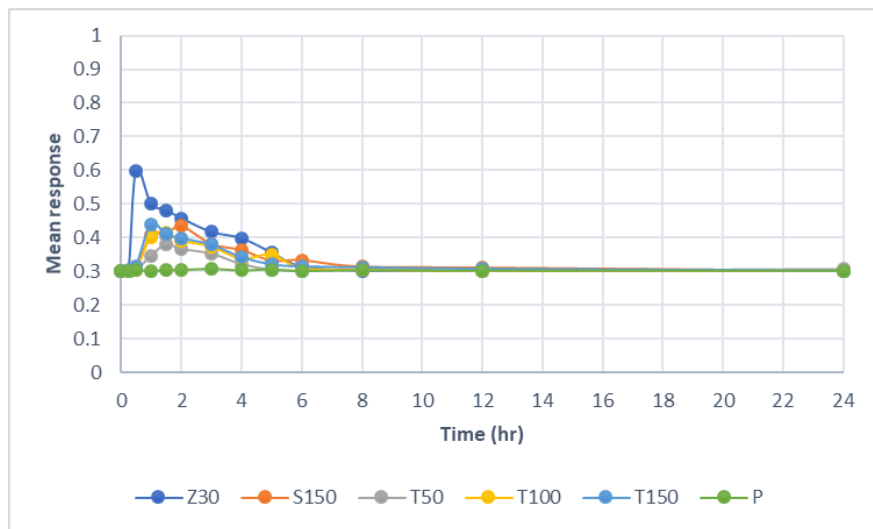


Figure 12: The mean time course profiles by treatment for Composite Score of Bowdle VAS External Perception (N=63)

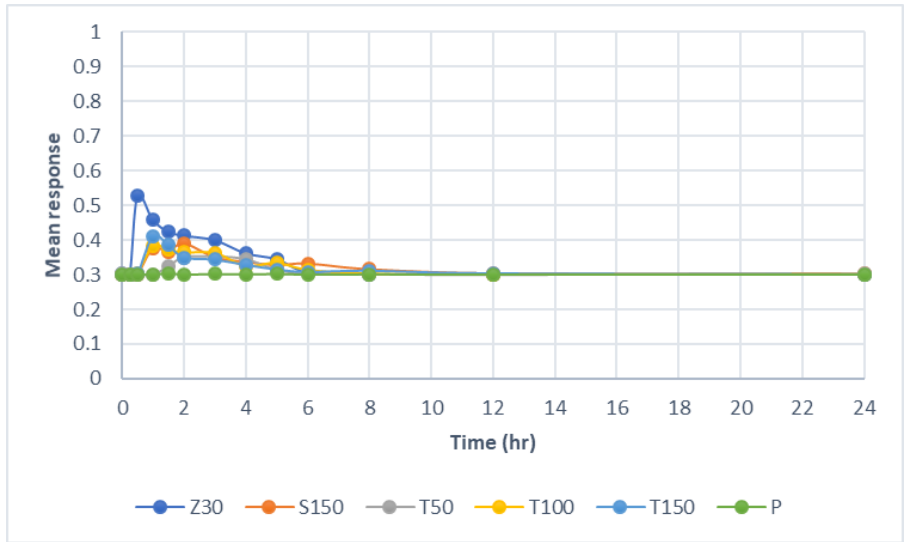


Figure 13: The mean time course profiles by treatment for Composite Score of Bowdle VAS, Internal Perception (N=63)

Based on Bowdle VAS, it appears the peak mean psychedelic effects produced by 30 mg zolpidem was larger and occurred earlier compared to other active treatments.

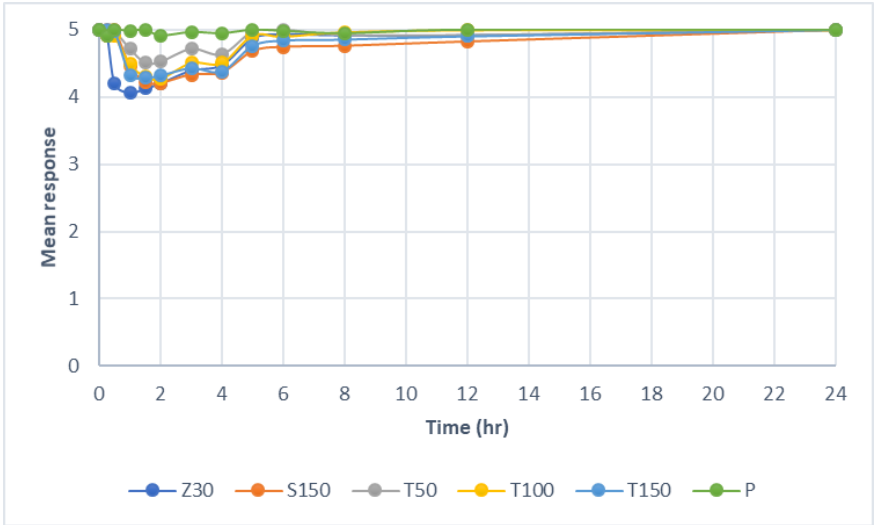


Figure 14: The mean time course profiles by treatment for Composite Score of Observer's Assessment of Alertness/Sedation (N=63)

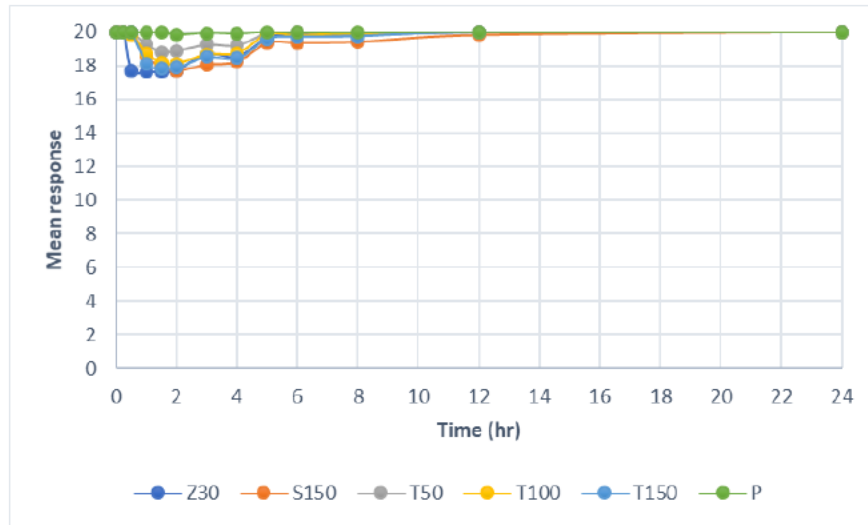


Figure 15: The mean time course profiles by treatment for Sum Score of Observer’s Assessment of Alertness/Sedation (N=63)

Drug Similarity VAS is a unipolar scale (0: definitely not, 100: definitely so). The data for Drug Similarity VAS were collected at hour 12 post-dose. Drugs in the comparisons with each treatment in the study were amphetamine, barbiturates, benzodiazepines, cannabis, cocaine, ecstasy, ketamine, lysergic acid diethylamide, methamphetamine, opioids, phencyclidine, psilocybin, and sedatives. Table 13 shows summary statistics for subjects’ responses to the comparisons between each treatment and each drug. The N denotes the number of subjects who gave a response for such a comparison. For example, compared to amphetamine 12 subjects gave responses to all treatments. Compared to barbiturates only one subject gave a zero response to all treatments. Because 0 denotes “definitely not”, the N for each treatment compared to each drug should be 63. It is not clear to this reviewer, how the investigator instructed subjects to respond to questionnaires for Drug Similarly VAS, and why Ns are not all equal to 63. Nevertheless, almost all subjects responded to all treatments when compared to benzodiazepines. Because the Ns may be different, drug to drug comparisons for these summary statistics for a treatment is not meaningful. For example, only one subject compared 150 mg suvorexant to ketamine with a similarity score 84, and the mean score is 84 (84/1). Comparing 84 to the mean similarity score of 61.8 based on 63 subjects who compared 150 mg suvorexant to benzodiazepines is not meaningful.

Table 12: Summary Statistics for Drug Similarity VAS at hour 12 (N=63)

Drug	TRT	N	Mean	SD	Min	Q1	Med	Q3	Max
Amphetamine	Z30	12	1.1	2.0	0	0	0	2.25	5
	S150	12	1.2	2.3	0	0	0	2.25	7
	T50	12	1.6	3.1	0	0	0	2.25	8
	T100	12	1.0	2.0	0	0	0	1.5	6
	T150	12	1.0	1.8	0	0	0	3	4
	P	12	0.6	2.0	0	0	0	0	7

Barbiturates	Z30	1	0.0	0.0	0	0	0	0	0
	S150	1	0.0	0.0	0	0	0	0	0
	T50	1	0.0	0.0	0	0	0	0	0
	T100	1	0.0	0.0	0	0	0	0	0
	T150	1	0.0	0.0	0	0	0	0	0
	P	1	0.0	0.0	0	0	0	0	0
Benzodiazepines	Z30	63	52.8	34.1	0	19	63	83	100
	S150	62	61.8	32.8	0	37.5	68.5	87.75	100
	T50	63	43.6	39.1	0	0	44	83	100
	T100	63	53.3	36.6	0	16	66	85	100
	T150	63	56.5	32.5	0	22	64	86	100
	P	63	11.5	28.0	0	0	0	0	100
Cannabis	Z30	60	28.6	29.0	0	1	21.5	47.5	100
	S150	59	29.6	28.2	0	5	22	50	100
	T50	60	20.8	28.6	0	0	3	40.75	100
	T100	60	25.0	29.3	0	0	10	46	100
	T150	60	26.7	27.8	0	5	14.5	45	95
	P	60	7.6	22.5	0	0	0	0	100
Cocaine	Z30	41	2.2	5.1	0	0	0	2	24
	S150	40	3.5	7.6	0	0	0	3	35
	T50	41	2.3	5.1	0	0	0	2.5	22
	T100	41	4.4	15.4	0	0	0	0.5	90
	T150	41	3.9	6.5	0	0	0	6.5	25
	P	41	0.7	2.5	0	0	0	0	14
Ecstasy	Z30	29	5.5	8.9	0	0	0	7	30
	S150	28	8.0	14.3	0	0	0	12.75	64
	T50	29	2.3	3.7	0	0	0	4.5	15
	T100	29	4.9	10.3	0	0	0	4	44
	T150	29	6.3	11.8	0	0	0	7.5	46
	P	29	1.1	3.9	0	0	0	0	20
Ketamine	Z30	1	65.0	0.0	65	65	65	65	65
	S150	1	84.0	0.0	84	84	84	84	84
	T50	1	75.0	0.0	75	75	75	75	75
	T100	1	55.0	0.0	55	55	55	55	55
	T150	1	66.0	0.0	66	66	66	66	66
	P	1	0.0	0.0	0	0	0	0	0
Lysergic acid	Z30	7	6.4	11.3	0	0	0	7	31

diethylamide	S150	7	3.9	7.1	0	0	0	9	18
	T50	7	1.9	4.1	0	0	0	2	11
	T100	7	3.1	6.4	0	0	0	5	17
	T150	7	3.1	8.3	0	0	0	0	22
	P	7	0.0	0.0	0	0	0	0	0
Methamphetamine	Z30	4	0.0	0.0	0	0	0	0	0
	S150	4	0.0	0.0	0	0	0	0	0
	T50	4	0.0	0.0	0	0	0	0	0
	T100	4	0.0	0.0	0	0	0	0	0
	T150	4	0.0	0.0	0	0	0	0	0
	P	4	0.0	0.0	0	0	0	0	0
Opioids	Z30	49	30.3	29.2	0	7.5	16	52	96
	S150	49	40.3	30.3	0	16.5	34	68	100
	T50	49	26.9	31.0	0	0	19	46	100
	T100	49	33.8	31.5	0	7	22	63.5	100
	T150	49	40.6	31.0	0	9.5	36	68	100
	P	49	6.0	19.6	0	0	0	0	95
Phencyclidine	Z30	6	20.7	27.5	0	0	7	50	65
	S150	6	26.0	26.7	0	0	26	49	58
	T50	6	12.0	22.2	0	0	1	24.5	56
	T100	6	23.8	30.0	0	0	10.5	56	71
	T150	6	33.0	34.1	0	0	33	65.5	67
	P	6	11.3	26.3	0	0	0	18.5	65
Psilocybin	Z30	4	6.3	12.5	0	0	0	18.75	25
	S150	3	10.3	17.9	0	0	0	31	31
	T50	4	0.8	1.5	0	0	0	2.25	3
	T100	4	1.3	2.5	0	0	0	3.75	5
	T150	4	6.0	12.0	0	0	0	18	24
	P	4	0.0	0.0	0	0	0	0	0
Sedatives	Z30	7	74.7	33.9	7	61	90	99	100
	S150	7	85.3	18.5	48	79	92	100	100
	T50	7	43.3	44.7	0	0	32	91	100
	T100	7	72.4	26.2	35	36	81	90	100
	T150	7	83.4	10.5	70	73	83	92	100
	P	7	5.3	14.0	0	0	0	0	37

3. Conclusion

The results from the reviewer's primary analysis on Drug Liking Emax showed that 100 and 150 mg doses of ACT-541468 did not produce less drug liking compared to both 30 mg zolpidem and 150 mg suvorexant. The results from secondary analyses on Overall Drug Liking Emax and Take Drug Again Emax supported the primary findings, and showed that compared to both positive controls, overall, subjects did not like 100 and 150 mg doses of ACT-541468 less and did not have less interest to take 100 mg and 150 mg doses of ACT-541468 again. In conclusion, the results from the HAP study ID-078-107 showed that abuse potential of ACT-541468 was similar to those of zolpidem and suvorexant.

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