CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

220860Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Original NDA
Application Number	220860
Priority or Standard	Priority
Submit Date(s)	12/10/2025
Received Date(s)	12/10/2025
PDUFA Goal Date	8/10/2026
Division/Office	Division of Psychiatry/Office of Neuroscience
Review Completion Date	8/5/2026
Established Name	Oveporexton tablets
Trade Name	Orzeyful
Pharmacologic Class	Orexin receptor 2 (OX2R) agonist
Code name	TAK-861
Applicant	Takeda Pharmaceuticals U.S.A., Inc.
Dosage form	Tablets
Applicant proposed Dosing Regimen	1 to 2 mg twice daily (take the first dose after awakening and second dose 3 to 5 hours later).
Applicant Proposed Indication(s)/Population(s)	Treatment of narcolepsy type 1 in patients (b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	60380001 | Narcolepsy
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of narcolepsy type 1 in adult patients
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	60380001 | Narcolepsy
Recommended Dosing Regimen	1 to 2 mg twice daily (take the first dose after awakening and second dose 3 to 5 hours later).

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Glossary

AASM	American Academy of Sleep Medicine
ABPM	ambulatory blood pressure monitoring
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BC-CCI-E	British Columbia Cognitive Complaints Inventory Expanded Version
BID	twice daily
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CGI-C	Clinical Global Impressions of Change
CMC	chemistry, manufacturing, and controls
CPAL	continuous paired associate learning
CRO	contract research organization
CSF	Cerebrospinal Fluid
CSS	Controlled Substances Staff
C-SSRS	Columbia Suicide Severity Rating Scale
CYP450	Cytochrome P450
DBL	Database lock
DCOA	Division of Clinical Outcome Assessment
DDS	Deputy Director of Safety
DHN	Division of Hepatology and Nutrition
DILI	Drug-Induced Liver Injury
DMC	data monitoring committee
DNS	disturbed/disrupted night sleep
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DUOG	Division of Urology, Obstetrics, and Gynecology
ECG	electrocardiogram
EDC	electronic data capture
eDiary	electronic patient-reported diary
EDS	Excessive Daytime Sleepiness
EQ-5D-5L	EuroQol-5 Dimensions 5-Levels
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
FINI	Functional Impacts of Narcolepsy Instrument
GBH	Gamma-Hydroxybutyric Acid
GCP	good clinical practice
GD	gestation day
GLP	Good Laboratory Practices
GGT	gamma-glutamyltransferase

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H3	Histamine-3
HDL	high density lipoprotein
HI	hepatic impairment
HLA	Human Leukocyte Antigen
ICF	Informed Consent Form
ICSD-3	International Classification of Sleep Disorders, Third Edition
iDSST-s	International Digit Symbol Substitution Test—symbols
IRB	Institutional Review Board
IRT	interactive response technology
ISS	integrated summary of safety
ITT	intent to treat
KSS	Karolinska Sleepiness Scale
LDL	low density lipoprotein
LSEC	Liver Safety Evaluation Committee
LOEL	Lowest Observed Effect Level
LTE	long-term extension
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
mIPSS	modified International Prostate Symptom Score
MRHD	Maximum Recommended Human Dose
mITT	modified intent to treat
MSLT	Multiple Sleep Latency Testing
MWT	maintenance of wakefulness test
NDA	new drug application
NME	new molecular entity
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NSS-CT	narcolepsy severity scale for clinical trials
NT1	Narcolepsy Type 1
NT2	Narcolepsy Type 2
ONB	one back test
OPQ	Office of Pharmaceutical Quality
OX1R	Orexin Type-1 Receptor
OX2R	Orexin Type-2 Receptor
OSA	Obstructive Sleep Apnea
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PAP	Positive Airway Pressure
PD	pharmacodynamics
PGI-C	Patient Global Impression of Change
PK	pharmacokinetic
PMC	postmarketing commitment
PMR	postmarketing requirement
PLLR	Pregnancy and Lactation Labeling Rule

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PO	oral
PRO	patient reported outcome
PSG	polysomnography
PVT	psychomotor vigilance test
QOL	Quality of Life
(Q)SAR	quantitative structure-activity relationship
QT/IRT	Interdisciplinary Review Team for QT Studies
REM	Rapid Eye Movement
REMS	risk evaluation and mitigation strategy
RI	renal impairment
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SF-36	36-Item Short Form Survey Instrument
SL	sleep latency
SOREMPs	Sleep-Onset REM Periods
TEAE	treatment emergent adverse event
TK	Toxicokinetics
TSQM	treatment satisfaction questionnaire for medication
WCR	weekly cataplexy rate

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1 Executive Summary

1.1. Product Introduction

Oveporexton is a selective oral orexin receptor 2 (OX2R) agonist proposed for the treatment of narcolepsy type 1 (NT1; narcolepsy with cataplexy) in patients (b) (4). Of note, NT1 is an orphan indication. Oveporexton would be available as 0.5 mg, 1 mg, and 2 mg oral tablets. The proposed dosing regimen is 1 mg or 2 mg twice daily, with the first dose taken upon awakening and the second dose taken 3 to 5 hours later. Oveporexton can be taken with or without food. Oveporexton is a new molecular entity (NME) that has not been marketed anywhere in the world and would be first in its pharmacological class approved for the proposed indication. The proposed proprietary name for oveporexton in this application is Orzeyful.

The NDA includes results from Studies TAK-861-3001 and TAK-861-3002, two randomized, double-blind, placebo-controlled efficacy and safety studies in participants 16 years of age or older with NT1, and from the ongoing long-term extension (LTE) Study TAK-861-2003. The application also includes data from phase 1 pharmacokinetic (PK) studies, phase 2 dose-finding studies in NT1 and NT2, and updated safety information from the 90-day safety update in the LTE.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided substantial evidence of effectiveness for oveporexton as a treatment for NT1. The application included data from two adequate and well-controlled efficacy and safety studies, TAK-861-3001 and TAK-861-3002, both randomized, double-blind, placebo-controlled trials conducted in adults with NT1. Both studies yielded highly statistically significant results on the primary efficacy endpoint—change from Baseline to Week 12 in mean sleep latency on the Maintenance of Wakefulness Test (MWT)—as well as on all secondary endpoints included in the pre-specified multiple testing procedure. The magnitude of effect was large across both studies, and the results were robust to sensitivity analyses addressing missing data and modeling assumptions.

The Applicant sought an indication for NT1 as a whole, rather than a symptom-specific indication such as excessive daytime sleepiness (EDS) or cataplexy in narcolepsy. This approach required demonstration of a meaningful treatment effect across all five core components of the NT1 symptom pentad: EDS, cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and disturbed/disrupted nighttime sleep (DNS). The review team assessed the evidence from both studies and recommends approval for NT1.

Across both pivotal studies, oveporexton demonstrated robust, statistically significant, and clinically meaningful improvements on objective and subjective measures of EDS, including the MWT and the Epworth Sleepiness Scale (ESS). A statistically significant and clinically meaningful reduction in weekly cataplexy rate was observed in both studies, with a greater than 60% reduction relative to placebo in Study TAK-861-3001 and a 75% reduction in Study

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TAK-861-3002. Statistically significant reductions in the frequency and distress of hypnagogic and hypnopompic hallucinations and sleep paralysis were demonstrated in both the overall study populations and in symptomatic subgroups, with consistent and large effect sizes across studies. With respect to DNS—the most complex domain given the wakefulness-promoting mechanism of action of oveporexton—the evidence, including significant improvements in polysomnography-measured REM latency (replicated across both studies with highly consistent effect sizes of approximately 70 to 72 minutes versus placebo), subjective sleep quality, and sleep-related quality of life measures, supports a meaningful treatment benefit on this pentad domain. The numerical increase in objectively measured nocturnal awakenings observed in both studies is consistent with the drug's pharmacology and does not, in the judgment of the review team, detract from the overall conclusion of a beneficial effect on nighttime sleep.

A concern is that the studies were mainly conducted outside of the United States; the North American subgroup consisted of 33 subjects from the United States and Canada. This subgroup did not reach nominal significance for the low-dose arm for the primary outcome (excessive daytime sleepiness), though nominal significance was achieved for the high-dose arm; overall, results were consistent with those observed in the rest of the world and, given that objective data can be measured for NT1, the pathophysiology of the illness is likely to be consistent across global populations, as are the drug’s effects. Nonetheless, the limited representation of U.S. patients warrants consideration. Representation by race and ethnicity also remains a concern. For example, Black Americans were minimally represented across the entire development program, with only seven participants enrolled. While narcolepsy is known to affect all ethnic groups, relatively little is understood regarding phenotypic expression and prevalence of the disorder across the diverse ethnic populations of the United States. The generalizability of these findings to underrepresented groups therefore cannot be fully established. Finally, the age subgroup of patients older than 65 years was not adequately investigated, as nearly all participants enrolled in the studies were between 18 and 65 years of age. The safety and efficacy of the drug in older adults therefore remains an open question and a residual area of uncertainty.

Notwithstanding the aforementioned limitations, taken together, the efficacy data from Studies TAK-861-3001 and TAK-861-3002 constitute substantial evidence of effectiveness for oveporexton as a treatment for NT1. The results are highly consistent across two independent, adequate and well-controlled trials, with comparable or numerically larger effect sizes in Study TAK-861-3002 relative to Study TAK-861-3001, and provide compelling evidence of a treatment effect across all five components of the NT1 symptom pentad. The review team considers this evidence supportive of the Applicant's approach to the NT1 indication.



(b) (4)

APPEARS THIS WAY ON ORIGINAL

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The Applicant, Takeda Pharmaceuticals, has submitted NDA 220860 for the approval of TAK-861, also known as oveporexton, with the proposed trade name of Orzeyful, for the treatment of narcolepsy type 1 (NT1; narcolepsy with cataplexy, an orphan indication) in patients (b) (4). Oveporexton is a new molecular entity (NME) and a selective oral orexin receptor 2 (OX2R) agonist that would be the first in its pharmacological class approved for the treatment of narcolepsy.

The Applicant submitted data from two phase 3 randomized, double-blind, placebo-controlled, 12-week efficacy and safety studies, TAK-861-3001 (N=168) and TAK-861-3002 (N=105), conducted at multiple global sites. Against a placebo arm, Study 3001 tested two dosages (1 mg twice daily and 2 mg twice daily) and Study 3002 tested 2 mg twice daily in patients with NT1 in patients 16 to 65 years of age. On the primary efficacy endpoint of change from Baseline at Week 12 in mean sleep latency on the Maintenance of Wakefulness Test (MWT) on polysomnography (PSG), both study results were strongly statistically significant for the difference between drug versus placebo. These results were generally consistent across subgroups of region, race, and sex. (In particular, the regional consistency on an objective endpoint signifies likely mechanistic and pathophysiological consistency for the drug's effects on NT1, so that the overall study results should apply to the U.S. population.) Also, on the prespecified secondary and additional secondary endpoints, results were statistically or nominally significant. The review team analyzed all of these endpoints to determine their viability in representing clinically meaningful results for the pentad of symptoms known to contribute to NT1. We determined that the evidence supports the conclusion that oveporexton has demonstrated effectiveness and clinically meaningful benefit for the treatment of the whole syndrome of NT1. Additional support was provided by the adequate and well-controlled phase 2 Study TAK-861-2001, whose positive efficacy results were consistent with the phase 3 findings across both studies.

The safety profile of oveporexton was consistent across the two placebo-controlled studies as well as the entirety of the safety study database, including a long-term open-label extension (LTE) study. The most common adverse events (AEs) include insomnia (56%), pollakiuria (57%), micturition urgency (16%), and salivary hypersecretion (7%). These events are consistent with the expected on-target pharmacological effects of orexin receptor agonism, occurred predominantly within the first 2 days of treatment, and were generally mild-to-moderate and self-limited. Only one death occurred in the development program, during the LTE study, a myocardial infarction in a subject with pre-existing cardiovascular risks that were the likely primary contributing factors. Serious AEs were infrequent (1%) and were not clearly related to the study drug's effects. No clear trends with vital signs (including blood pressure and weight) or liver function or renal function tests (sometimes seen in other drugs in this class) or other safety factors were noted; no major psychiatric or suicidal ideation/behavior signals were observed. Some cases of elevated CPK on laboratory testing were observed, as well as mild mean increases in LDL cholesterol versus placebo in the 12-week studies and in the LTE study. The major detected AEs and safety issues will be addressed by

labeling, and the drug will remain under ongoing routine postmarket pharmacovigilance. Our Controlled Substances Staff Team did not detect any major abuse potential signals in the studies and recommends Schedule IV for oveporexton.

Overall, the benefits outweigh the risks for oveporexton for the proposed dosages and treatment paradigm for patients with NT1. The strongly positive efficacy results across the entire NT1 symptom pentad, the manageable and well-tolerated safety profile, and the novel mechanism of action with decreased abuse potential risks relative to some existing drugs for this condition provide an important new therapeutic option for this serious condition. Our review team recommends approval for oveporexton, as the first drug to be available in the United States for the treatment of the entire syndrome of NT1.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Narcolepsy type 1 (NT1) is a rare, chronic, and serious disease. The prevailing hypothesis is that NT1 is caused by a loss of orexin-producing neurons resulting in orexin deficiency. • Its prevalence is estimated at approximately 25 to 50 per 100,000 individuals, with no significant [redacted] predominance, though there is a strong association with the human leukocyte antigen (HLA)-DQB1*06:02 allele, which is present in approximately 90 to 95% of patients with cataplexy. • It is characterized by a classic pentad of symptoms that include excessive daytime sleepiness (EDS), cataplexy, sleep paralysis, hypnagogic and/or hypnopompic hallucinations, and disrupted nighttime sleep (DNS), with the latter three representing intrusions of rapid eye movement (REM) sleep phenomena into wakefulness or sleep-wake transitions. • The International Classification of Sleep Disorders–3 (ICSD-3) diagnostic criteria for NT1 require 1) symptoms of EDS for ≥3 months and 2) threshold findings on the multiple sleep latency test (MSLT) or a sleep onset REM periods (SOREMP) on nocturnal polysomnogram associated with the presence of cataplexy or/and 3) low (i.e., below threshold) cerebrospinal fluid (CSF) hypocretin-1 concentration.	NT1 is a serious and chronic condition characterized by EDS, cataplexy, and other symptoms that have a significant impact on patients' quality of life and ability to function in multiple spheres.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Symptoms typically start in adolescence, with a small second peak of onset at around age 35 years. In 10 to 15% of patients, narcolepsy starts before the age of 10 years. • The core symptoms of NT1 have a significant impact on patients' quality of life, increasing the risk of injury, accidents, and falls, and impacting in daily functioning.	
Current Treatment Options	• FDA approved treatments for excessive daytime sleepiness include amphetamines, methylphenidates, modafinil, armodafinil, and solriamfetol. These treatments carry risks of abuse and cardiovascular adverse events. Stevens-Johnson Syndrome, a life-threatening dermatologic condition, has been associated with modafinil and armodafinil. • Sodium oxybate is approved for the treatment of both EDS and cataplexy. Risks associated with sodium oxybate include respiratory depression, central nervous system depression, seizure, and abuse (Schedule III drug). Sodium oxybate is only available through a Risk Evaluation and Mitigation Strategy (REMS) program • Pitolisant is approved for the treatment of both EDS and cataplexy. Risk associated with pitolisant include QT interval prolongation.	Patients with NT1 would benefit from additional treatment options, particularly treatments that address the entire pentad of symptoms with low abuse potential and limited effects on the cardiovascular system.
Benefit	The application included the results of two pivotal 12-week studies to support approval of an indication for the treatment of NT1 as a whole: Studies TAK-861-3001 and TAK-861-3002. • The Applicant submitted the results of Study TAK-861-3001, a phase 3, randomized, double-blind, placebo-controlled, multicenter, efficacy and safety trial of oveporexton versus placebo in participants with NT1. Of the 168 randomized participants, participants were randomized to placebo (N=41), oveporexton 1 mg twice daily (N=61), or oveporexton 2 mg twice daily (N=66).	Two adequate and well-controlled clinical trials demonstrated oveporexton's effectiveness across the full spectrum of narcolepsy type 1 symptoms as defined by the NT1 pentad: excessive daytime sleepiness, cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	The study population had a median age of 28 years (range: 16 to 65 years), was predominantly female (58.3% in the oveporexton group), and was enrolled across sites in Europe (65.5%), North America (19.6%), and the Asia-Pacific region (14.9%). Only three adolescent participants (ages 16 to 17 years) and one participant aged ≥65 years were enrolled. • The Applicant also submitted the results of Study TAK-861-3002, a phase 3, randomized, double-blind, placebo-controlled, multicenter, efficacy and safety trial of oveporexton 2 mg twice daily versus placebo in adult participants with NT1. Of the 105 randomized participants, participants were randomized to placebo (N=35) or oveporexton 2 mg twice daily (N=70). The study population had a median age of 27 years (range: 18 to 62 years), with no adolescent or geriatric participants enrolled. The trial was conducted exclusively in Europe, Australia, and the Asia-Pacific region, with no North American sites. • In both studies, the primary endpoint was the change from Baseline to Week 12 in mean sleep latency on the Maintenance of Wakefulness Test (MWT). Key (prespecified) secondary endpoints included the Epworth Sleepiness Scale (ESS) total score, weekly cataplexy rate (WCR), Narcolepsy Symptom Severity Composite Tool (NSS-CT) total score, mean number of lapses on the Psychomotor Vigilance Task (PVT), Patient Global Impression of Change (PGI-C) responder status, the Functional Impact of Narcolepsy Index (FINI) across all six domains, and the SF-36 Mental and Physical Component Summaries. Secondary endpoints were tested using a prespecified hierarchical multiple testing procedure. • In Study TAK-861-3001, both dosages of oveporexton achieved highly statistically significant improvements in the primary endpoint. The LS mean difference versus placebo in MWT sleep latency was 13.83 minutes (95% CI: 10.23, 17.44; p<0.001) for the 1 mg twice daily dosage and 17.20 minutes (95% CI: 13.66, 20.73; p<0.001) for the 2 mg twice daily dosage. All secondary	disturbed/disrupted nighttime sleep. Both studies yielded statistically significant results on the primary endpoint of MWT sleep latency and on all secondary endpoints included in the pre-specified multiple testing procedure, with large and consistent effect sizes. The results were robust to missing data and modeling assumptions, and were generally consistent across subgroups of region, race, and sex. Exploratory analyses further supported a treatment effect across all five components of the NT1 pentad. There is substantial evidence to approve oveporexton for the treatment of narcolepsy type 1 in adult patients. Residual uncertainties remain regarding the generalizability of the findings to certain populations. The studies were conducted predominantly outside of the United States, and representation of U.S. patients was limited. Racial and ethnic minority groups, particularly Black Americans, were minimally represented across the development program. The geriatric population (≥65 years) was not adequately studied, as nearly all enrolled participants were

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	endpoints included in the multiple testing procedure were also statistically significant for both dosages, including robust reductions in WCR (incidence rate ratios of 0.34 and 0.38 for the 1 mg and 2 mg twice daily dosages, respectively, reflecting greater than 60% reductions relative to placebo), and large improvements in ESS, NSS-CT total score, PVT lapses, PGI-C responder status, all six FINI domains, and SF-36 Mental and Physical Component Summaries. The 2 mg twice daily dosage consistently yielded numerically greater improvements across the majority of endpoints, providing evidence of a dose-response relationship. • In Study TAK-861-3002, oveporexton 2 mg twice daily achieved a highly statistically significant improvement in the primary endpoint, with an LS mean difference versus placebo in MWT sleep latency of 20.09 minutes (95% CI: 16.57, 23.61; p<0.001). All secondary endpoints included in the multiple testing procedure were also statistically significant, including a 75% reduction in WCR (incidence rate ratio: 0.25; 95% CI: 0.15, 0.42; p<0.001). Results were consistent with and confirmatory of those from Study TAK-861-3001. • In both studies, the primary and secondary endpoint results were robust to missing data and modeling assumptions, as confirmed by multiple sensitivity analyses conducted by both the Applicant and the Statistical Reviewer, including a worst-case imputation analysis. Results were also generally consistent across subgroups of region, race, and sex, with treatment effects trending in favor of oveporexton across all subgroups. • To assess the effect of oveporexton on the full NT1 symptom pentad—encompassing EDS, cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and DNS—exploratory endpoints were also evaluated. Although not multiplicity protected, these analyses consistently supported a treatment effect across all five pentad components in both studies. Nominally significant reductions in the frequency and distress of hypnagogic and hypnopompic	between 18 and 65 years of age. These limitations are acknowledged; however, given the objective nature of the primary endpoint, the consistency of results across two independent trials and across geographic subgroups, and the well-established pathophysiology of NT1 as a disease of orexin deficiency that is not expected to vary meaningfully across populations, these uncertainties do not alter the overall conclusion that the evidence is sufficient to support approval.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	hallucinations and sleep paralysis were demonstrated in both the overall study populations and in symptomatic subgroups, with consistent and large effect sizes across studies. For the DNS domain, positive results were observed for NSS-CT item 15, nPSG-measured REM latency (with a highly consistent treatment effect of approximately 70 to 72 minutes versus placebo replicated across both studies), subjective sleep quality measures, and indirect quality-of-life measures including the SF-36 Vitality domain and the FINI Tiredness domain. A numerical increase in nPSG-measured nocturnal awakenings was observed with oveporexton relative to placebo in both studies, which is not unexpected given the drug's wake-promoting mechanism of action and should not be interpreted in isolation as evidence of a detrimental effect on nighttime sleep.	
Risk and Risk Management	• The safety database for oveporexton included 770 unique participants exposed to oveporexton across the clinical development program. At the time of the 90-day safety update, 358 participants had been exposed for at least 6 months and 148 for at least 1 year, meeting ICH E1 recommendations for both durations. The safety review focused on the pivotal trial pool (Studies TAK-861-3001 and TAK-861-3002), which included only the to-be-marketed doses and a placebo comparator. • No deaths occurred in the placebo-controlled studies. One death (cardiac arrest) occurred in the long-term extension study in a participant with multiple pre-existing cardiovascular risk factors; a causal relationship with oveporexton cannot be definitively established or excluded, though the background cardiovascular risk factors may have been the primary contributors. • Serious adverse events were uncommon in the development program. In the pivotal trial pool, the SAE incidence was 1.0% in the oveporexton group versus 0% in placebo, with observed events having clear alternative etiologies	Although the placebo-controlled trials were limited to 12 weeks in duration, the long-term extension study (TAK-861-2003) and the 90-day safety update have not identified unexpected safety signals with extended exposure. ICH E1 recommendations for 6-month and 12-month exposure have been met at the time of the 90-day safety update. Additional studies to evaluate the effects on pregnancy and lactation will be required, given that oveporexton is likely to be used by women of childbearing potential. A study to evaluate the pharmacokinetics (PK) and safety of oveporexton in participants

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	unrelated to the drug. SAEs observed in the long-term extension study similarly had identifiable alternative etiologies in most cases. • The most commonly reported adverse events associated with oveporexton compared to placebo were insomnia (56% vs. 1%), pollakiuria (57% vs. 5%), micturition urgency (16% vs. 1%), and salivary hypersecretion (7% vs. 0%). These events are consistent with the expected on-target pharmacological effects of orexin receptor agonism and were generally self-limiting, occurring predominantly within the first two days of treatment. Their frequency decreased during long-term exposure in the extension study, suggesting potential tolerance over time. • Discontinuations due to adverse events were low and numerically higher in the oveporexton group (2.6%) compared to placebo (1.3%). Events leading to discontinuation included urinary symptoms (pollakiuria and urinary incontinence), which represent on-target pharmacological effects, and laboratory findings (elevated liver enzymes and CPK elevations associated with intense physical activity), which had identifiable alternative etiologies in most cases. • Laboratory findings were generally unremarkable. CPK elevations above 5× ULN occurred at a numerically higher rate in the oveporexton group (10.7%) compared to placebo (5.3%), and three cases were labeled as rhabdomyolysis, all with confounding factors (intense physical exercise, Gilbert's syndrome). No cases met the clinical criteria for true rhabdomyolysis (muscle symptoms, myoglobinuria, and renal impairment). A modest, reproducible increase in LDL cholesterol (approximately 8 to 12 mg/dL) was observed in the oveporexton groups compared to placebo, though the magnitude was small, as well as during the LTE study. No cases met Hy's Law criteria for drug-induced liver injury. • Cardiovascular assessments revealed minimal and transient increases in blood pressure and heart rate on Day 1 (mean increases of 7 mm Hg SBP, 5 mm Hg	with severe hepatic impairment (Child-Pugh Class C) will also be required, as the impact of severe hepatic impairment on the PK of oveporexton is not known. The safety and efficacy of oveporexton in patients older than 65 years of age have not been adequately characterized, and this issue remains a residual uncertainty. Product labeling will describe the treatment-emergent AEs that occurred most frequently in placebo-controlled trials, including insomnia, pollakiuria, micturition urgency, and salivary hypersecretion, as well as the observed CPK elevations and modest LDL cholesterol increases. Labeling will also include a warning and precaution to address the risk of exercise-associated CPK elevations. Additionally, labeling will include a warning and precaution stating that oveporexton may cause increased urinary frequency and urinary urgency, that patients should be informed about these potential urological symptoms prior to treatment initiation, and that

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	DBP, and 5 bpm HR), which returned to near baseline by Week 12. Oveporexton does not prolong the QTcF interval, as confirmed by a phase 1 QTc assessment study accepted as a substitute for a thorough QT study per ICH E14 Q&A 5.1. • No signal for suicidal ideation or behavior was identified based on C-SSRS assessment across the development program. • Potential hypersensitivity-related events (rash, urticaria, pruritus, eczema) occurred at a numerically higher rate in the oveporexton group compared to placebo (4.6% vs. 0%), exclusively in the 2 mg twice daily arm. Upon review of individual narratives, plausible alternative explanations were identified for the majority of cases. None of the events were serious or led to treatment discontinuation. The rate was consistent in the long-term extension study, providing reassurance that the rate does not increase with longer exposure. This signal warrants continued monitoring through routine post-marketing surveillance. • Visual disturbances (vision blurred and dry eye) occurred exclusively in the oveporexton group at low rates (1.5% and 1.0%, respectively). All events were mild-to-moderate, nonserious, self-limited, and resolved during continued treatment. This assessment was conducted post hoc following reports of visual safety signals with another molecule in the same pharmacological class; the pivotal trials did not include dedicated ophthalmologic monitoring, and the incidence may be underestimated. Routine post-marketing surveillance is sufficient to monitor this signal. • Limited data are available in the geriatric population (≥65 years), as only one participant aged 65 or older was enrolled across the pivotal studies. The safety profile of oveporexton in older adults therefore cannot be adequately characterized from the available data. • Limited data are available regarding the effects of oveporexton on pregnancy and lactation. Given the age distribution of the NT1 population, oveporexton	caution is advised in patients with pre-existing lower urinary tract conditions, such as men with benign prostatic hyperplasia or lower urinary tract symptoms. Labeling will also include a warning and precaution stating that oveporexton may cause insomnia, including difficulty falling asleep and difficulty staying asleep, that patients should be informed about these potential effects prior to treatment initiation, and counseled on appropriate dosing (including timing of dose) and sleep hygiene practices.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	is likely to be used by women of childbearing potential. • The safety profile was generally consistent across demographic subgroups of sex, race, and geographic region, though these analyses are exploratory and limited by small and unbalanced subgroup sizes. Additional favorable safety characteristics of oveporexton: • No evidence of QTc prolongation was seen at recommended dosages in the studies, as confirmed by the Cardiac Safety-IRT. • No signal of abuse, misuse, dependence, or withdrawal were identified in the clinical development program. Schedule IV is recommended for this drug. (The approved oxybate class drugs for narcolepsy treatment are Schedule III.) • No pattern of clinically significant cardiovascular adverse events were seen at recommended dosages in the studies, with only transient and minimal blood pressure and heart rate changes observed on Day 1.	

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1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		
		☒	Patient reported outcome (PRO)	See Section 8.1.1.1, Study Endpoints
		☒	Observer reported outcome (ObsRO)	"
		☒	Clinician reported outcome (ClinRO)	"
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☒	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☒	Input informed from participation in meetings with patient stakeholders		See Section 8.1.1.1, Study Endpoints and Statistical Analysis Plan discussions of ESS and EDS
	☒	Patient-focused drug development or other stakeholder meeting summary reports		"
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Narcolepsy is a chronic sleep disorder characterized by excessive daytime sleepiness (EDS) that interferes with functioning and is typically accompanied by at least some associated symptoms including cataplexy, sleep paralysis, hypnogogic or hypnopompic hallucinations, and disturbed/disrupted nighttime sleep (DNS). Cataplexy, sudden loss of voluntary muscle tone with a preserved state of consciousness, can be triggered by strong positive or negative emotions, occurs in most patients with narcolepsy, and is frequently debilitating. Classic or typical narcolepsy, now termed narcolepsy type 1 (NT1), is characterized by the presence of cataplexy, and orexin deficiency, i.e., loss of hypocretin (orexin)-producing neurons in the hypothalamus, leading to dysregulation of sleep-wake cycles. By contrast, narcolepsy without either cataplexy or orexin deficiency—now termed narcolepsy type 2 (NT2)—remains poorly understood and represents a distinct clinical entity with likely different pathophysiology.

This application focuses on the treatment of NT1. NT1 is a rare, lifelong disease without an identified cure. The classic pentad of NT1 symptoms includes EDS, cataplexy, sleep paralysis, hypnagogic/hypnopompic hallucinations, and DNS, with the latter three representing intrusions of rapid eye movement (REM) sleep phenomena into wakefulness or sleep-wake transitions.

EDS is usually the initial and often the most disabling symptom, experienced as repeated daily episodes of an irrepressible need to sleep or lapses into sleep. "Sleep attacks" can occur in unusual situations such as eating or walking, often on a background of overall sleepiness. EDS can manifest as lapses in vigilance or inattentiveness. Young children may also manifest sleepiness as excessively long night sleep or resumption of previously discontinued naps (AASM 2014). According to the 2014 report from a September 24, 2013, FDA Patient-Focused Drug Development Voice of the Patient meeting to hear perspectives from people living with narcolepsy about their disease, treatment, and impact on their daily life, patients “stressed that the effects of EDS go far beyond feeling tired or falling asleep during the day. Because of EDS, they constantly battle 'brain fog' and other cognitive impairments, automatic behaviors [performing actions such as walking, eating, or driving, in a semiconscious way without awareness], and chronic sleeping deprivation.” (The Voice of the Patient, Patient-Focused Drug Development Public Meeting: September 24, 2013, Center for Drug Evaluation and Research, FDA 2014)

Cataplexy, defined as >1 episode of generally brief (a matter of seconds to <2 minutes) sudden loss of muscle tone with retained consciousness, is usually bilaterally symmetrical and can be precipitated by strong emotions (usually positive). Cataplexy usually occurs within 1 year of onset but can rarely be the initial or a long-delayed symptom. The presentation and frequency are variable (from subtle partial attacks to complete attacks, from <1/month to >20/day). Presentation may include manifestations such as neck weakness with head drop, facial weakness with dysarthria, peripheral weakness with collapse, and phenomena such as

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muscle twitching or small jerks. According to the 2014 Voice of the Patient report, "for those who experience cataplexy, hallucinations or sleep paralysis, the uncontrollable and often unpredictable loss of control can be terrifying." One web participant described cataplexy "as feeling like a puppet where all the puppet strings have been released, without warning" (Voice of Patient Report, Center for Drug Evaluation and Research, FDA 2014).

Associated features may include disrupted nocturnal sleep, hypnagogic or hypnopompic hallucinations (vivid, often frightening dreamlike experiences when falling asleep or awakening, respectively), and sleep paralysis (temporary inability to move voluntary muscles when falling asleep or awakening).

Additional associated features include automatic behaviors (performing routine tasks without conscious awareness during microsleep episodes), cognitive difficulties including problems with attention and memory. Common comorbidities include obesity, depression, anxiety disorders, obstructive sleep apnea (OSA), and cardiovascular disease, with some studies suggesting increased rates of type 2 diabetes.

According to the *International Classification of Sleep Disorders, Third Edition* (ICSD-3), the diagnostic criteria for NT1 require daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months, plus the presence of either cataplexy and a mean sleep latency of ≤8 minutes with two or more sleep-onset REM periods (SOREMPs) on multiple sleep latency testing (MSLT), or cerebrospinal fluid (CSF) orexin/hypocretin-1 concentration ≤110 pg/mL or less than one-third of mean values in normal participants. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria are similar, requiring a period of at least 3 months with daily episodes of an irrepressible need to sleep, along with the presence of cataplexy occurring at least a few times per month, plus either orexin/hypocretin deficiency (as measured by CSF levels ≤110 pg/mL or <1/3 of normal control values) or positive MSLT findings showing a mean sleep latency ≤8 minutes and ≥2 SOREMPs (with one SOREMP potentially occurring during the preceding nocturnal polysomnography).

NT1 usually starts in adolescence, and a small second peak of onset occurs at around age 35 years. In 10 to 15% of patients, narcolepsy starts before the age of 10 years. However, NT1 in children was only rarely systematically studied before the current century. NT1 can have an acute course, in which symptoms develop within a few days or weeks after a triggering event, such as vaccination, stress or head trauma; a chronic course, in which the onset of symptoms is difficult to determine; or a progressive course, in which the onset of different symptoms is separated by years or even decades. In a series of 1,099 patients with narcolepsy, cataplexy most often developed at the same time as EDS in 49% of the cohort and developed after EDS in another 43%. Cataplexy preceded EDS in only 8% of the patients. The interval between onset of EDS and onset of cataplexy is usually <2 to 3 years but can exceed 40 to 50 years. Narcolepsy with cataplexy typically does not remit (remission of this presentation has been reported only once, in a patient who received immunotherapy soon after disease onset). In addition, narcoleptic symptoms often improve over time; the severity of EDS and cataplexy typically decreases with age, possibly as a result of coping mechanisms (reviewed in Bassetti CLA, et al., 2019).

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The prevalence of NT1 is estimated at approximately 25 to 50 per 100,000 individuals, with no significant [redacted] predominance, though there is a strong association with the human leukocyte antigen (HLA)-DQB1*06:02 allele, which is present in approximately 90 to 95% of patients with cataplexy (Bassetti CLA, et al., 2019). However, because of the uncertainties concerning the narcoleptic diagnoses (particularly NT2, as previously mentioned), the exact incidence of NT1 remains unknown. A recent study, based on a large representative sample of the U.S. general population, reports a current prevalence of NT1 at 12.6/100,000 individuals, with prevalence similar between men and women, and not significant difference between age groups, although it was slightly higher in individuals younger than 35 years old (Ohayon MM et al., 2023).

The impact on quality of life (QOL) is substantial and multifaceted, affecting academic and occupational performance, social relationships, driving safety, and overall psychological well-being, with many patients experiencing stigmatization, reduced employment opportunities, and increased risk of accidents due to sudden sleep attacks or cataplexy episodes. According to the 2022 FDA Patient-Led Listening Session summary report, a patient whose NT1 symptoms began at age 12 (preceding his diagnosis by 13 years) stated that he "fears walking down stairs due to his cataplexy. He has broken ribs, his leg, and incurred concussions from falling." The mother of a child with NT1 reported that "if the school feels he is at risk of injury, they will want him to have a homebound placement, which means he would be excluded from the social interaction school provides" (Project Sleep 2022).

In summary, NT1 is a serious and chronic condition characterized by EDS, cataplexy, and other symptoms that have a significant impact on patients' quality of life and ability to function in multiple spheres.

2.2. Analysis of Current Treatment Options

To date, there is no approved treatment specifically indicated for NT1. Available treatments focus on managing individual symptoms associated with narcolepsy broadly, such as excessive daytime sleepiness or cataplexy, without distinction between NT1 and NT2. Importantly, none of the currently available therapies address the underlying pathophysiology of NT1, namely the loss of hypocretin (orexin)-producing neurons in the hypothalamus and the resulting orexin deficiency. Instead, existing treatments which provide only symptomatic relief of one or two symptoms.

Drug treatments approved to treat both EDS and cataplexy associated with narcolepsy include: sodium oxybate (Xyrem) and its extended-release formulation (Lumryz), mixed salts of oxybate (Xywav), and pitolisant (Wakix). Drug treatments approved to treat EDS only include: modafinil (Provigil), armodafinil (Nuvigil), and solriamfetol (Sunosi). Older drugs that have an approved indication for the treatment of patients with narcolepsy broadly, without distinction between NT1 or NT2, include: amphetamine, dextroamphetamine, and methylphenidate (Ritalin, Methylin). Treatment effect data are not labeled for these stimulant drugs, but they are expected to be effective only for EDS and not for cataplexy.

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Antidepressants, such as selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and tricyclic antidepressants, are used off-label for the treatment of cataplexy. Non-pharmacologic interventions that are used to manage narcolepsy symptoms include brief regularly scheduled naps, consistent sleep schedule, avoidance of caffeine, alcohol, and heavy meals before bedtime, relaxation before bedtime, regular exercise, and taking safety precautions while driving or operating heavy machinery.

The currently available options for treating EDS or cataplexy in narcolepsy have several significant limitations. Stimulants such as amphetamines and methylphenidate have wake-promoting effects, but patients often develop tolerance to these effects over time. Amphetamines and methylphenidate have high abuse potential and are Schedule II controlled substances. Sodium oxybate is the sodium salt of gamma-hydroxybutyric acid (GHB), which, because of its effects, has been misused to commit drug-facilitated sexual assault. It is a Schedule III controlled substance because of its abuse potential, but illicit use is subject to Schedule I penalties. It is available in the United States only through a risk evaluation and mitigation strategy (REMS) program. Modafinil and armodafinil have lower abuse potential and are Schedule IV controlled substances. However, for many patients they do not adequately promote wakefulness throughout the day. In addition, modafinil and armodafinil are substrates, inducers, and inhibitors of CYP450 isoenzymes, raising the possibility of interactions with medications that patients may be prescribed for other illnesses. The labeling for modafinil and armodafinil both include warnings for Stevens-Johnson Syndrome, angioedema, anaphylactoid reactions, and multi-organ hypersensitivity reactions. Aside from pitolisant (a histamine-3 [H3] receptor antagonist/inverse agonist), drugs approved to treat narcolepsy are classified as Schedule II, III, or IV due to their abuse potential. Pitolisant, while not a controlled substance, carries warnings and precautions for increases in QT interval.

The significant impact of NT1 on patients' lives, combined with the limitations of available treatments, underscores the critical need for additional therapeutic options. Most importantly, there is currently no drug that addresses the associated underlying pathophysiology of NT1 by restoring orexin function or replacing the lost orexin/hypocretin-producing neurons in the hypothalamus. A therapy that directly targets this fundamental deficit represents a new target in the treatment landscape for NT1.

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3 Regulatory Background

3.1. U.S. and International Regulatory Actions and Marketing History

Oveporexton was approved in China on July 22, 2026, and Japan on August 3, 2026, as the first drug in its class. It but has not yet been approved or marketed anywhere else in the world.

3.2. Summary of Presubmission/Submission Regulatory Activity

On July 16, 2021, the Applicant, Takeda Pharmaceuticals USA, Inc., submitted a new investigational new drug (IND) application and fast track designation request for oveporexton for the treatment of narcolepsy. IND 154232 was allowed to proceed on August 25, 2021. On August 25, 2021, oveporexton was also granted fast track designation for the treatment of narcolepsy based on its proposed mechanism of action which may restore OX2R signaling at the postsynaptic receptors addressing the loss of orexin peptide found in narcolepsy.

On January 20, 2022, the Applicant submitted a request for a special protocol assessment (SPA) for a 24-month carcinogenicity study in rats. On March 3, 2022, the executive Carcinogenicity Assessment Committee (eCAC) reached agreement on the SPA and recommended doses of 0, 1, 20, and 100 mg/kg/day for male and female rats. On May 3, 2022, the Applicant submitted a second request for a SPA for a 6-month oral gavage carcinogenicity study in TG-RASH2 mice. On June 16, 2022, the eCAC reached agreement on the SPA and recommended doses of 0, 3, 30, and 300 mg/kg/day in female mice. For male mice, the eCAC recommended doses of 20, 60, and 600 mg/kg/day.

On April 24, 2023, the Applicant submitted a breakthrough therapy designation request (BTDR) for the treatment of excessive daytime sleepiness in NT1. On June 23, 2023, the Division denied the initial BTDR because the preliminary clinical evidence submitted did not indicate that oveporexton may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. The Division determined that the exploratory efficacy data from the phase 1 study submitted in the request suggested an improvement over available therapies, but comparisons were difficult due to limited interpretability from the small number of participants and unexplained missing data. (b) (4) The Division recommended that the Applicant resubmit their BTDR with efficacy and safety data from at least one phase 2 study.

On September 28, 2023, the Applicant submitted a Type C meeting request to discuss Study TAK-861-3001. On December 7, 2023, the Division issued preliminary comments and noted that the protocol for Study TAK-861-3001 appeared reasonable, but the Applicant should request a clinical outcome assessment (COA)-focused meeting to discuss whether sustained attention is significant enough to patients to be measured during the study. The Division agreed with the inclusion of participants 16 to <18 years of age and stated that this

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population may need additional or differing safety monitoring and inclusion/exclusion criteria due to hormonal influences and lifestyle factors. The Applicant cancelled the meeting upon receipt of the preliminary comments.

On February 29, 2024, the Applicant submitted a second BTDR and included efficacy and safety data from their positive phase 2 study TAK-861-2002. On April 26, 2024, breakthrough therapy designation was granted for the treatment of excessive daytime sleepiness in NT1.

On May 30, 2024, an iPSP was submitted (b) (4)



In June 12, 2024, a Type B End-of-Phase 2 (EOP2) meeting was held to discuss the Applicant's phase 3 development plans. The Division informed the Applicant that their proposal to use the results of Studies TAK-861-3001 and TAK-861-3002, supported by TAK-861-2003, as substantial evidence of effectiveness would be a matter of review upon submission of an NDA. The Division recommended change in mean sleep latency (minutes) from Baseline to Week 12 as a primary endpoint and reminded the Applicant that if they plan to pursue an NT1 indication their study results should demonstrate a clinically meaningful effect on cataplexy. The Division also recommended that the Applicant select secondary outcomes that measure distinct constructs of NT1. The Division informed the Applicant that a dedicated human abuse potential study would be required to determine drug scheduling. Additionally, the Division clarified that a scientific bridge should be established between the previously studied formulation and the phase 3 clinical trial formulation, and that a food effect study should be conducted with the to-be-marketed formulation. Meeting minutes were issued on July 12, 2024.

On July 25, 2024, the Applicant submitted a waiver request for a thorough QT study report. On December 18, 2024, the Division informed the Applicant that because QT prolongation was not found in their phase 1 study TAK-861-1001, a dedicated thorough QT study is not necessary. The Division stated that the data from the QTc assessment in study TAK-861-1001 could be used as a substitute for a thorough QT study.

On September 16, 2024, the Applicant requested a dedicated COA Type C meeting to discuss the psychomotor vigilance test (PVT) and Functional Impact of Narcolepsy Instrument (FINI). Written responses were issued on November 27, 2024, asking for additional information on those assessments and noting remaining major conceptual anchoring, validation, and scoring concerns, especially with the FINI, even if some of these assessments' aspects were aligned with relevant concepts of the condition.

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A Type B CMC EOP2 meeting was requested on December 6, 2024. Written responses were issued on February 12, 2025. OPQ agreed with the Applicant's proposed starting materials for the TAK-861 drug substance but requested that supportive data be submitted with their NDA. OPQ also provided feedback on the Applicant's dissolution method and comparability studies.

On January 17, 2025, a Type D meeting was requested to discuss the statistical analysis plan for the integrated summary of safety (ISS) and for the integrated summary of efficacy (ISE). Written responses were issued on March 5, 2025; the Division informed the Applicant that their ISS and ISE pooling strategies appear reasonable, but additional analyses and/or pooling strategies may be requested during the NDA review.

On February 7, 2025, the Applicant submitted a request for a proposed proprietary name review. The proprietary name, Orzeyful, was conditionally approved on April 21, 2025.

On March 24, 2025, an Agreed iPSP was submitted (b) (4)

On May 14, 2025, the Applicant submitted a Type B Pre-NDA meeting request. In the preliminary comments, the Division informed the Applicant that the proposed nonclinical and clinical data described in the briefing document appear adequate to support the filing and review of an NDA. The Division agreed that both studies TAK-861-3001 and TAK-861-3002 appear to be adequate and well-controlled trials, but whether their results demonstrate substantial evidence of effectiveness will be a matter of NDA review. In addition, the Division commented on quality data to include in the Applicant's NDA and agreed that their proposal to add new manufacturing and testing sites appeared reasonable. The Applicant cancelled the meeting upon receipt of the October 3, 2025, preliminary comments.

On July 14, 2025, the Applicant submitted a Type D meeting request to discuss the adequacy of the proposed safety database for an NDA. Written responses were issued on August 26, 2025, informing the Applicant that their proposal seemed reasonable, but the final determination of adequacy was a matter of NDA review.

A rolling review request was submitted on October 7, 2025, and rolling review was granted on October 24, 2025. On March 2, 2026, oveporexton received orphan-drug designation for the treatment of NT1 (which meant that the prior agreed iPSP was now optional). (b) (4)

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4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

See the Clinical Inspection Summary from Dr. Jing Zhang et al. dated July 2, 2026, for more details. OSI personnel inspected four clinical trial sites, the Applicant, and a contract research organization (b) (4). OSI personnel found no unacceptable study conduct or data quality issues during their inspections related to this NDA.

4.2. Product Quality

Based on our evaluation of the available information, the Applicant provided sufficient information to support an approval recommendation from the product quality perspective. The Applicant provided adequate information to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. See the Office of Pharmaceutical Quality (OPQ) integrated quality assessment (IQA) for additional information.

4.3. Clinical Microbiology

Not applicable to this product.

4.4. Devices and Companion Diagnostic Issues

Not applicable to this product.

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5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Oveporexton is an orally available, brain-penetrant OX2R agonist developed for the treatment of NT1. Orexins are neuropeptides that play a role in maintaining wakefulness and sleep (Abad and Guilleminault, 2017). A precursor peptide is cleaved to form two neuropeptide neurotransmitters, orexin-A and orexin-B, that bind to two different subtypes of G-protein coupled receptors, orexin type-1 receptor (OX1R) and OX2R. Both subtypes of orexin receptors are reported to contribute to the regulation of arousal; OX2R plays a role in the maintenance of wakefulness, whereas both OX1R and OX2R are involved in the inhibition of REM sleep. An association between the development of NT1 and loss of orexin-producing neurons in the brain has been reported in published literature (Tsujino and Sakurai, 2013).

In vivo pharmacology data demonstrated significant wake-promoting effects through OX2R activity and improvements in cataplexy-like symptoms in a NT1 mouse model. Although oveporexton showed off-target binding to cannabinoid receptor type 1 (CB-1) and progesterone receptor B (PR-B) receptors, with functional antagonism at the CB-1 receptor (functional activity was not assessed for the PR-B receptor), these effects are not expected to result in clinically significant off-target effects in humans at the maximum recommended human dosage (MRHD) of 4 mg/day (2 mg twice daily). Results from GLP-compliant safety pharmacology studies indicated that oveporexton can affect the CNS (increased body temperature at 20 and 100 mg/kg, decreased body temperature at 1000 mg/kg, and hyperactivity at ≥20 mg/kg in rats), the cardiovascular system (increased blood pressure and left ventricular pressure at ≥3 mg/kg in monkeys), and the respiratory system (non-dose-dependent increased respiratory rate at 20 and 100 mg/kg and minute volume at 100 mg/kg in rats). However, these effects are not expected to constitute a significant clinical risk, given the large exposure margins (>100-fold) compared to clinical exposures at the MRHD.

The pharmacokinetic profile of oveporexton was studied in vitro and in vivo in mice, rats, rabbits, and monkeys. Oveporexton was rapidly absorbed after a single oral dose in rats and monkeys; absorption was non-dose proportional in rats but approximately dose proportional in monkeys. The major circulating component in all animal species was unchanged [^{14}C]oveporexton, which accounted for 95.6% (mice), 92.5% (rats), and 75.5% (monkeys) of the total radioactivity. [^{14}C]oveporexton was widely distributed into tissues of pigmented and albino rats with the greatest exposure observed in the adrenal cortex, adrenal gland, and liver, with no evidence of binding to melanin-containing tissues. Oveporexton can be transferred into the fetus via the placenta during gestation and is also secreted into milk in lactating rats. Oveporexton is highly bound to plasma proteins in vitro in rat, monkey, and human hepatocytes. The unbound fraction of oveporexton in plasma is similar in rats, monkeys and humans (4.5%, 2.8%, and 3.8%, respectively). Oveporexton is metabolized via multiple metabolic pathways in animals, including oxidation, glucuronidation, sulfation and glutathione-related conjugation, resulting in both fluorinated and defluorinated metabolites. There are no human-specific metabolites. As a result of oveporexton metabolism and

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generation of defluorinated metabolites, free fluoride was detected in plasma of rats and monkeys (higher in rats than in monkeys). In human hepatocytes, CYP enzymes contributed 100% to oveporexton metabolism with CYP3A4 as the predominant contributor (97.3%) and CYP2C9 and 2D6 contributed much less (2.6 and 0.1%, respectively). The results from excretion studies indicate that [^{14}C]oveporexton-related substances are mainly excreted into the feces via bile with very little excretion in urine after single-dose oral administration to mice, rats, and monkeys.

Single-dose and repeat-dose general toxicity studies were performed in Sprague-Dawley rats (up to 26-weeks duration) and in cynomolgus monkeys (up to 39-weeks duration). In rats, the primary target organs of toxicity included incisors, kidneys, and liver. Drug-related effects on the incisors were characterized by whitening and fractures of the teeth with histopathology of degeneration of ameloblasts. This finding was indicative of tooth fluorosis caused by increased fluoride concentrations which disrupts enamel formation. The tooth fluorosis is considered a species-specific metabolism-related change for rodents. Oveporexton is a fluoride-containing molecule and upon metabolism free fluorine is released and was detected in plasma of both rats and monkeys, as measured in the 2-week and 4-week repeat-dose toxicity studies. However, no fluoride-related toxicity was observed in any of the repeat-dose toxicity studies in monkeys up to 39-weeks in duration. Additionally, no de-fluorinated metabolites were detected in human plasma (Report TKD-BCS-01618-R1); therefore, the tooth changes observed in rats are not considered clinically relevant to humans. Drug-related findings were also observed in the kidneys of rats which included dilatation of kidney proximal and distal tubules in females at doses ≥750 mg/kg/day which was associated with increased blood urea nitrogen (BUN), creatinine, and urine volume. Drug-related findings in the liver of rats included hypertrophy of centrilobular hepatocytes in both males and females at doses ≥100 mg/kg, which correlated with increased liver weights. Decreases in body weight that correlated with decreases in food consumption were also observed in longer duration repeat-dose toxicity studies in rats. The effects on the kidneys, liver, and body weight were all reversible upon drug cessation, while the effects observed in the incisors showed partial reversibility upon drug cessation. The no observed adverse effect level (NOAEL) in the 26-week general toxicity study in rats was 100 mg/kg/day for both males and females, which was associated with a mean C_{max} of 7,860 and 11,800 ng/mL, and a mean AUC_{24h} of 115,000 and 168,000 h*ng/mL in males and females, respectively taken from Week 26 values. Safety margins at the NOAEL compared to the MRHD are approximately 311- and 455-fold for males and females, respectively based on AUC.

In monkeys, no adverse toxicity findings were observed in any parameter across all repeat-dose toxicity studies at doses up to the highest tested dose of 300 mg/kg/day and up to 39-weeks in duration. Non-adverse drug-related findings were limited to vomiting, transient decreases in food consumption, increases in triglycerides, and microscopic findings of minimal hepatocyte hypertrophy; and all findings were reversible upon drug cessation. The NOAEL in the 39-week general toxicity study in monkeys was 300 mg/kg/day for both males and females, which was associated with a mean C_{max} of 14,500 and 15,500 ng/mL and a mean AUC_{24h} of 211,000 and 169,000 h*ng/mL in males and females, respectively on Day 273 of the

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study. Safety margins at the NOAEL in monkeys compared to the MRHD are approximately 571- and 457-fold for males and females, respectively based on AUC.

Measurement of hepatic drug-metabolizing enzymes was conducted in both the rat and monkey 4-week repeat-dose toxicity studies. In both rats and monkeys, oveporexton was associated with an induction of several hepatic drug-metabolizing enzymes. Therefore, the findings of hepatocyte hypertrophy in the livers of both rats and monkeys was considered to be caused by hepatic drug-metabolizing enzyme induction, an adaptive and non-adverse change.

A full battery of GLP developmental and reproductive toxicity studies were conducted with oveporexton. In the fertility and early embryonic development (FEED) study in rats, decreased number of corpora lutea associated with decreased numbers of implantations and live embryos were observed at 750 mg/kg (the highest dose tested) compared to control. There were no effects on male fertility at doses up to 750 mg/kg. The NOAEL for fertility and early embryonic development was 100 mg/kg in females and 750 mg/kg in males (approximately 455- and 747-fold the MRHD, respectively, based on AUC). In embryo-fetal development (EFD) studies in pregnant rats and rabbits, maternal toxicity (decreases in body weight and body weight gain) was noted in both species at the highest doses tested (750 mg/kg/day and 100 mg/kg/day, in rats and rabbits respectively). In rats, decreased fetal weights and decreased ossification of metatarsal bones were observed at 750 mg/kg/day compared to control, secondary to the low maternal body weight. There were no drug-related effects on the incidence of congenital malformations or embryo-fetal lethality in either rats or rabbits. The NOAELs for maternal toxicity were 100 mg/kg in rats and 20 mg/kg in rabbits, approximately 346- and 38-fold the MRHD, respectively, based on AUC; and the NOAELs for effects on EFD were 750 mg/kg and 100 mg/kg in rats and rabbits, respectively, approximately 1166- and 153-fold the MRHD, respectively, based on AUC. In the pre- and postnatal development (PPND) study in rats, there were no drug-related effects on maternal endpoints or reproductive function, or on offspring development (survival, growth, behavior, and reproductive function). The NOAEL for effects on PPND was the highest tested dose of 10 mg/kg/day, approximately 118-fold the MRHD based on AUC. Oveporexton did not show adverse effects in juvenile animal toxicity study (JAS) in rats dosed from the age of 28 days through sexual maturity. The NOAEL for juvenile toxicity was the highest tested dose of 50 mg/kg in the 6-week JAS rat study. Based on the totality of nonclinical reproductive and developmental toxicity data, oveporexton has a low risk of reproductive and developmental toxicity in humans.

Oveporexton was found to be negative in an Ames assay and in an in vivo micronucleus assay; however, it was found to be positive for induction of micronuclei in an in vitro micronucleus assay following 24-hours of continuous treatment. Overall oveporexton was determined to be non-genotoxic. Oveporexton was also found to be non-carcinogenic in a GLP 2-year rat and a GLP 6-month transgenic mouse carcinogenicity study.

Note: Safety exposure margins are based on human population pharmacokinetic $AUC_{24,ss}$ at the MRHD of 4 mg/day (2 mg BID) of 369.6 h*ng/mL in patients from clinical Study TAK-861-3001.

Reference ID: 5847402

5.2. Referenced NDAs, BLAs, DMFs

See the full nonclinical reviews archived under IND 154232.

5.3. Pharmacology

Primary Pharmacology

The primary pharmacology of oveporexton, was assessed in both in vitro and in vivo animal studies and NT1 models.

In Vitro Studies

In vitro, the selectivity of oveporexton was established in CHO-K1 cells stably expressing recombinant human OX1R or OX2R. Oveporexton showed agonist activity on human OX2R and OX1R in vitro with an EC_{50} of 0.0025 µmol/L and 7.5 µmol/L, respectively, indicating that it is a potent OX2R agonist with a 3000-fold selectivity for OX2R over OX1R. Receptor binding assays to determine binding affinities (Ki values) at OX1R and OX2R were not conducted.

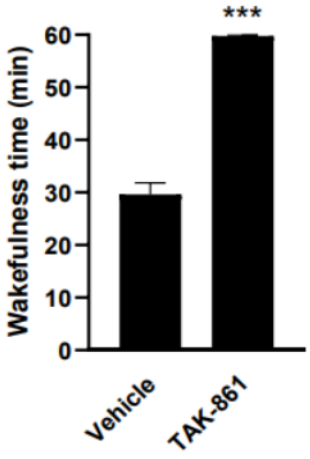
In Vivo Studies

The effect of oveporexton on wakefulness in animals was studied in wild type (WT) mice, orexin 2 receptor knockout (OX2R KO) mice, and in an NT1 mouse model (OX/ataxin-3 transgenic (TG) mice). Because mice are nocturnal animals with a polyphasic sleep/wake structure, studies were also conducted in cynomolgus monkeys which are diurnal and have a monophasic sleep/wake structure more analogous to humans.

Oveporexton at 10 mg/kg produced a statistically significant increase in wakefulness time during the sleep phase in both normal C56BL/6J mice (Study No. Neuroscience2024-KM-001) and in non-transgenic WT littermates of OX2R KO mice; however, the same dose did not affect wakefulness time in OX2R KO mice (Study No. Neuroscience2020-KM-005), demonstrating that oveporexton produces an arousal effect in mice through activation of the OX2R. The effect of oveporexton on wakefulness during the sleep phase was also demonstrated in OX/ataxin-3 transgenic mice (a NT1 mouse model in which the transgene selectively eliminates orexin producing neurons in the hypothalamus) and their non-transgenic WT littermates.

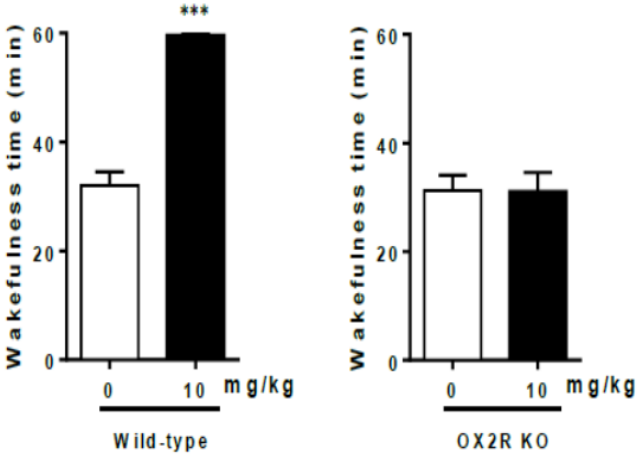
Reference ID: 5847402

Figure 1. Effect of Oveporexton on Wakefulness Time in C57BL/6J Mice in Sleep Phase



***: p<0.001: paired t test; compared to vehicle Data presented as mean +standard error of the mean (SEM). N=16/group
Source: Neuroscience2024-KM-001-Report, Pharmacology Written Summary, p. 9

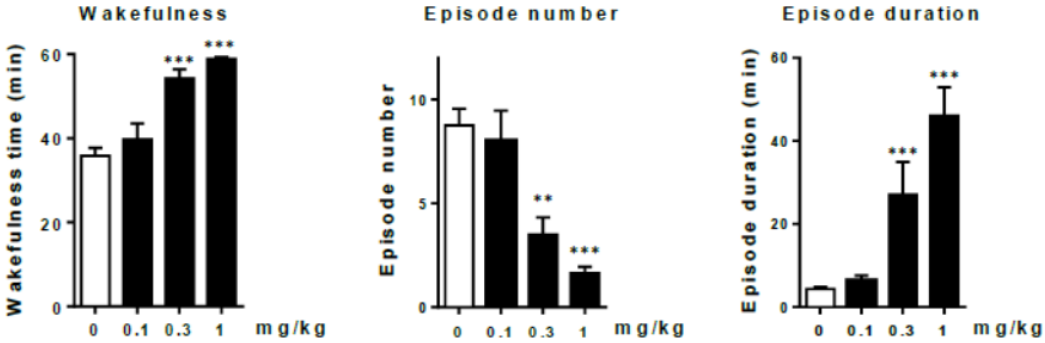
Figure 2. Effect of Oveporexton on Wakefulness Time in WT and OX2R KO Mice in Sleep Phase



***p<0.001: paired t test; compared to vehicle. Data presented as mean +standard error of the mean (SEM) (WT mice, n=7; OX2R KO mice, n=8). Oveporexton (10 mg/kg) or vehicle administered orally to WT or OX2R KO mice and wakefulness time during 1 h after administration was analyzed.
Source: Neuroscience2024-KM-005-Report, Pharmacology Written Summary, p. 11

In both the OX/ataxin-3 transgenic and non-transgenic mice, oveporexton dose-dependently and statistically significantly increased wakefulness times at 0.3 and 1 mg/kg (PO). However, the sensitivity of OX/ataxin-3 transgenic mice for oveporexton was approximately 30-fold higher compared to non-transgenic mice, based on the minimum effective doses of ≤0.03 and 1 mg/kg, respectively. In the OX/ataxin-3 transgenic mice, oveporexton at doses of 0.3 and 1.0 mg/kg also statistically significantly decreased the number of wakefulness episodes and increased the duration of wakefulness episodes (Study No. Neuroscience2020-KM-002 and Study No. Neuroscience2020-KM-003).

Figure 3. Effect of Oveporexton on Wakefulness Time, Episode Number and Duration in OX/Ataxin-3 TG Mice in the Active Phase

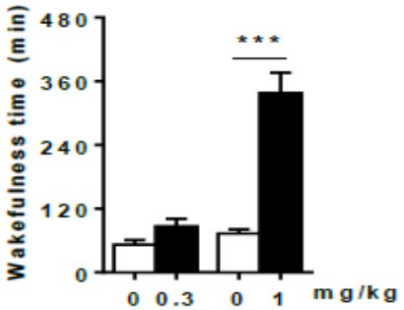


**p<0.01, ***p<0.001; compared with vehicle-treated mice (two-tailed Shirley-Williams' test). Data presented as mean +standard error of the mean (SEM) (n=8). Oveporexton (0.1, 0.3 or 1.0 mg/kg) or vehicle administered orally to orexin (OX)/ataxin-3 transgenic (TG) mice, and wakefulness time, and episode number and duration of wakefulness for 1 h after administration were calculated.
Source: Neuroscience2024-KM-003-Report, Pharmacology Written Summary, p. 13

In the same NT1 mouse model, oveporexton at 1 mg/kg (PO) also statistically significantly decreased the number of cataplexy-like episodes during the first 3 hours after drug administration (cataplexy-like episodes were induced by a chocolate stimulus; Study No. Neuroscience2020-KM-004). The arousal effect of oveporexton (1 mg/kg, PO) was persistent over a 14-day treatment period, indicating a low risk for OX2R desensitization after repeated administration (Study No. Neuroscience2020-KM-009).

In cynomolgus monkeys, oveporexton at 1 mg/kg (PO) produced a statistically significant increase in wakefulness times during the sleep phase (Study No. Neuroscience2020-KM-006) when the physiological orexin level is thought to be low (Narita et al., 2023). These results suggest that oveporexton shows arousal effects not only in nocturnal mice but also in diurnal non-human primates with normal orexin levels during their sleep phase.

Figure 4. Effect of Oveporexton on Wakefulness Time in Cynomolgus Monkeys in the Sleep Phase



***p<0.001, compared with vehicle (Paired t test); Data presented as mean +standard error of the mean (SEM) (n=8). Oveporexton (0.3 or 1 mg/kg) or vehicle administered orally to cynomolgus monkeys and wakefulness time analyzed over 8 h after administration.
Source: Neuroscience2024-KM-006-Report, Pharmacology Written Summary, p. 17

Overall, the primary pharmacology studies demonstrated that oveporexton acts as a OX2R agonist, with much greater selectively for OX2R versus OXR1, and is capable of producing wakefulness and ameliorating narcolepsy-like characteristics in relevant animal models.

Secondary Pharmacology

Secondary pharmacology studies included in vitro off-target assessments against a broad array of receptors, ion channels, and enzymes (102 targets in total, including opioid receptors, 5-HT and dopamine transporters and receptors, NMDA, GABA, nicotinic acetylcholine and cannabinoid receptors; Study No. Neuroscience2020-KM-001). Oveporexton at 10 µmol/L (5205 ng/mL) did not show significant activity (>50% inhibition or stimulation of radioligand binding) at any of the tested targets, except for cannabinoid receptor type 1 (CB1) and progesterone receptor B (PR-B), which showed 58% and 62% inhibition, respectively. The maximum recommended human dosage (MRHD) of oveporexton of 4 mg/day (2 mg twice daily) is associated with a total $C_{max,ss}$ of 26.4 ng/mL and an unbound $C_{max,ss,unbound}$ of 0.98 ng/mL (based on an unbound fraction of 0.037 in human plasma). The Applicant proposed that the concentration at which oveporexton may affect CB1 and PR-B receptors is approximately >5000-fold than the highest unbound C_{max} and approximately 200-fold the total $C_{max,ss}$ reached at the MRHD, and therefore significant CB1- and/or PR-B-related clinical effects are not expected in humans.

A second in vitro assessment was conducted to evaluate the potential off-target functional activity of oveporexton (Study No. US073-0004661-O_TAK-861) at various receptors, ion channels, and enzymes (47 targets in total but not including PR-B receptors). Oveporexton did not show significant activity (defined as 50% inhibitory concentration [IC_{50}] or EC_{50} ≤10 µmol/L) on any of the tested receptors, ion channels, or enzymes except for CB1, in which oveporexton showed antagonistic activity with an IC_{50} of 3.2 µmol/L (1666 ng/mL). Activity at CB-1 is approximately 1700-fold higher than the $C_{max,ss,unbound}$ (0.98 ng/mL) and approximately 63-fold the $C_{max,ss}$ (26.4 ng/mL) at the MRHD of 4 mg/day (2 mg twice daily), suggesting no significant CB-1-related off-target effects in humans.

Regarding the assessment of oveporexton functional activity at the progesterone B receptor, a nonclinical information request was sent to the Applicant on May 20, 2026, asking if any additional specific assays to assess functional activity at the progesterone B receptor were conducted. The Applicant responded that no further progesterone B receptor assays were performed (Response letter of May 22, 2026) and stated:in the first study, oveporexton showed 62% inhibition of ligand binding to the PR-B at a concentration of 10 µmol/L (5,205 ng/mL). Since a single concentration was tested in this assay and no concentration-response relationship was obtained, an IC_{50} value was not calculated. Under a conservative assumption that the IC_{50} would be one-tenth of the concentration producing 62% inhibition of ligand binding (i.e., 1 µmol/L (520.5 ng/mL)), this concentration is more than 500-fold higher than the human $C_{max,ss,unbound}$ (0.98 ng/mL) at the MRHD of 4 mg/day (2 mg twice daily). Given the low likelihood of clinically relevant off-target effects mediated by PR-B, no additional specific assays beyond those described above were conducted to assess functional activity on the PR-B.

Although there are no nonclinical data to determine if oveporexton has functional activity at the PR-B receptor, it appears that the clinical relevance of any potential adverse effects is minimal.

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A computational approach to evaluate the structural similarity between oveporexton and every controlled substance named in the U.S. Controlled Substances Act (CSA), inclusive of Schedule I through V (Study No. TKD-SDS-15870) indicated no structural similarity of oveporexton to substances specified in the CSA.

Because other orexin-2 agonist drugs developed by the Applicant caused urinary urgency and frequency in clinical trials, a urinary function study in C57BL/6J mice with oveporexton was conducted. The results of the study demonstrated that orally administered oveporexton at doses of 3 mg/kg and 10 mg/kg caused significant increases in void frequency without affecting total void volume or water intake (Study No. Neuroscience2023-AK-001).

Safety Pharmacology

The safety pharmacology of oveporexton was evaluated in a series of good laboratory practices (GLP)-compliant in vitro and in vivo studies to assess potential effects in the CNS, cardiovascular, and respiratory systems.

CNS

The effects of oveporexton on the CNS were evaluated in male Sprague-Dawley rats administered single doses of 0, 20, 100, and 1000 mg/kg/day by oral gavage (6 rats/group) (Study No. B200314). Modified Irwin's multiple observation method was used to examine the effects on general physical condition and behavior, and body temperature was also measured. Observations were conducted at pre-dose and at 1, 2, 4, 8, and 24h post-dose. Body temperature increased at 20 and 100 mg/kg (+1.0°C and+0.5°C, respectively compared to controls) and a decrease occurred at 1000 mg/kg (-0.7°C compared to controls). The changes in body temperature may be related to pharmacological action of oveporexton; based on literature data, orexin-A induces both hypothermia and hyperthermia, and orexin-B induces hyperthermia in rats (Szekely et al., 2002).

Restlessness was observed in all animals at 20 and 100 mg/kg and in 3 of 6 animals at 1000 mg/kg at 1 and 2 h post-dose, and slight increases in spontaneous activity were observed in 1 or 2 animals at 20 and 100 mg/kg at 1 h post-dose (Study No. B200314). These findings were also considered to be due to the pharmacological actions of oveporexton, as OX2R agonists have been reported to increase locomotor activity in rats (Samson et al., 2010). The lowest observed effect level (LOEL) for effects on the CNS in male rats was 20 mg/kg, which provides approximately a 127-fold exposure margin based on C_{max} at the LOEL of 3350 ng/ml (taken from Day 1 C_{max} value in male rats from the 4-week toxicity Study No. B-8713) compared to the total $C_{max,ss}$ of 26.4 ng/ml at the MRHD in humans.

The abuse potential of oveporexton was assessed in several in vivo studies in rats. See the Controlled Substance Staff review for a review of the nonclinical and clinical abuse potential studies.

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Cardiovascular

In in vitro cardiovascular assessments, oveporexton produced a minimal but statistically significant inhibitory effect on the hERG current at 3 µg/mL (the highest concentration tested) of 9.0% compared to the vehicle control when tested using HEK293 cells stably expressing hERG channels under physiological conditions and temperature. The IC_{50} value for hERG inhibition was >3 µg/mL, which provides an approximate safety margin of >3000-fold compared with the human $C_{max,ss,unbound}$ (0.98 ng/mL) at the MRHD (Study No.B240294). The potential effects of oveporexton on late Nav1.5 and Cav1.2 current amplitudes at physiologic temperatures were tested at 1, 3, 10, 100 µmol/L in HEK293 cells stably expressing Nav1.5 and Cav1.2 channels (Study No. TPI-24-01). Oveporexton did not block late Nav1.5 current but blocked the Cav1.2 current with an IC_{50} of 85.8 µM (step pulse) and 7.9 µM (ramp pulse). The IC_{50} of 7.9 µM oveporexton (4112 ng/mL) corresponds to an approximate exposure margin of >4000-fold compared with the human $C_{max,ss,unboud}$ of 0.98 ng/mL at the MRHD.

In vivo evaluation of cardiovascular function was performed in a GLP-compliant study in cynomolgus monkeys (4 males, 5 to 6 years of age) using a telemetry system after single oral gavage administration of oveporexton at doses of 0, 3, 30, and 300 mg/kg, administered in a Latin Square design with a washout period of 7 to 14 days between doses (Study No. SBL010-416). Systemic blood pressure (systolic (SBP), diastolic (DBP), and mean (MBP)), left ventricular pressure (LVSP, LVEDP, and LV dP/dt max), heart rate, and ECG parameters (PR interval, QRS duration, QT interval, and QTc interval) were measured at pre-dose and at 1, 2, 4, 8, 12, 18, and 24 h post-dose. TK analysis was conducted at 3 mg/kg after the telemetry data acquisition.

Increased systemic blood pressure and LVSP were noted between 1 and 4 h post-dose at all doses, with maximum increases compared to controls of +27, +19, and +23 mm Hg in SBP, DBP, and MBP, respectively, and +28 mm Hg in LVSP, observed 1 h post-dose at 300 mg/kg. At 300 mg/kg, significant increases in LV dP/dt max and heart rate were noted in one animal at 1h post-dose (+1618 mm Hg/sec and +42 beats/min, respectively). These increases may be attributed to the pharmacological action of oveporexton at OX2R in the CNS, because it has been reported that intracerebroventricular administration of orexin increases arterial blood pressure and heart rate in rats mainly via OX2R (Huang et al., 2010). These changes were non-adverse because the degree of change was small and/or the changes were transient. A decrease in LV dP/dt max was also noted at 300 mg/kg (-639 mm Hg/sec) from 8 to 18h. Although mechanisms for this change were not clear, there were no effects on other hemodynamic parameters (systemic blood pressure or HR) at the same time points. Therefore, the decreased LV dP/dt max was considered non-adverse. There were no reported adverse ECG findings.

In conclusion, a single oral administration of oveporexton to male monkeys induced increases in systemic blood pressure and LVSP at ≥3 mg/kg and a transient increase in LV dP/dt max and heart rate and then a decrease in LV dP/dt max at 300 mg/kg. Although a no observed effect level (NOEL) was not identified in this study, the C_{max} at the LOEL of 3 mg/kg (449 ng/mL) is 17-fold higher than the clinical $C_{max,ss}$ at the MRHD suggesting low clinical relevance.

Reference ID: 5847402

In vivo evaluation of cardiovascular function was also conducted as part of the 4-, 13-, and 39-week GLP-compliant repeat-dose toxicity studies in monkeys (Studies No. B-8714, B-8802, and B-8934, respectively). In the repeat-dose toxicity studies in male and female monkeys (n=3 to 4/sex/group), oveporexton was administered by oral gavage once daily at 30, 100, and 300 mg/kg/day. ECGs were measured pre-dose, and at the end of the dosing period. No drug-related changes in ECG parameters were noted in any of the studies. At the NOEL of 300 mg/kg/day for ECG effects in the 39-week study, the highest dose tested in monkeys, the sex-combined exposures provided an approximate 429-fold margin compared to the $C_{max,ss,unbound}$ and an approximate 568-fold margin compared to the total $C_{max,ss}$ at the MRHD.

Table 1. Oveporexton Safety Margins for Cardiovascular Assessments in GLP-Compliant Repeat-Dose Toxicology Studies in Monkeys

Study	NOEL for ECG parameters (mg/kg/day)	$C_{max,ss}$ (ng/mL) [a]	$C_{max,ss,unbound}$ (ng/mL) [b]	Safety Margin [c]	Report No.
4-Week repeat-dose toxicity	300	19,400	543	554	B-8714
13-Week repeat-dose toxicity	300	28,250	791	807	B-8802
39-Week repeat-dose toxicity	300	15,000	420	429	B-8934

Abbreviations: C_{max} = maximum observed concentration; $C_{max,ss}$ = maximum observed concentration at steady state; $C_{max,ss,unbound}$ = unbound maximum observed concentration at steady state
[a] Sex combined values of the last measured $C_{max,ss}$ values in the study.
[b] $C_{max,ss,unbound}$ = $C_{max,ss}$ multiplied by the unbound fraction (fu =0.028) in monkey plasma at 5 µg/mL [Report DDA-A41-006] c. Safety margin = $C_{max,ss,unbound}$ at the NOEL for ECGs in monkeys/$C_{max,ss,unbound}$ at 4 mg/day (2 mg twice daily) in humans (Human exposure is 0.98 ng/mL at the MRHD).
Source: Pharmacology Written Summary, Table 4.b, p. 32

Respiratory

The effects of oveporexton on the respiratory system were evaluated in male Sprague-Dawley rats administered single doses of 0, 20, 100, and 1000 mg/kg by oral gavage (8 animals/group) (Study No. B200362). Respiratory rate (RR), tidal volume (TV), and minute volume (MV) were measured using whole-body plethysmography at pre-dose and 1, 2, 4, 8, and 24 h post-dose. Statistically significant increases in RR at 8 h post-dose at 20 and 100 mg/kg and in MV at 8 h post-dose at 100 mg/kg were observed compared to the vehicle group. At 1000 mg/kg, there were no statistically significant changes for RR or MV. There were also no statistically significant changes in tidal volume at any dose level.

Reference ID: 5847402

Table 2. Respiratory Rate in Rat Respiratory Safety Pharmacology Study

Test article	Dose (mg/kg, p.o.)	Number of animals	Respiratory rate (breaths/min)					
			Before	Time after dosing (hour)				
				1	2	4	8	24
Vehicle [a]	---	8	123 ± 12	117 ± 14	113 ± 13	118 ± 12	117 ± 10	122 ± 6 [1)]
TAK-861	20	8	128 ± 12	- [2)]	- [2)]	- [2)]	133 ± 10 *[1)]	122 ± 13
	100	8	116 ± 6	- [2)]	- [2)]	- [2)]	140 ± 18 *[1)]	111 ± 10 [1)]
	1000	8	120 ± 11	- [2)]	- [2)]	- [2)]	120 ± 5	112 ± 11

Each value represents the mean ± S.D.
a: 0.5 w/v% Methylcellulose solution
1) n=7 : Since 1 value in each group was affected by body movement of the animal, the value was excluded from evaluation.
2) Since all data were affected by body movement of animals, they were excluded from evaluation.
*: Significantly different from the vehicle control value by Steel test, $p<0.05$.

Source: Study Report No. B200362, Table 1, p. 19

Table 3. Minute Volume in Rat Respiratory Safety Pharmacology Study

Test article	Dose (mg/kg, p.o.)	Number of animals	Minute volume (mL/min)					
			Before	Time after dosing (hour)				
				1	2	4	8	24
Vehicle [a]	---	8	104.5 ± 11.8	95.7 ± 8.7	90.3 ± 12.7	92.2 ± 9.5	104.1 ± 7.2	107.5 ± 8.0 [1)]
TAK-861	20	8	99.9 ± 9.6	- [2)]	- [2)]	- [2)]	115.0 ± 8.5 [1)]	103.5 ± 15.3
	100	8	103.7 ± 7.6	- [2)]	- [2)]	- [2)]	126.5 ± 13.5 #[1)]	104.0 ± 4.1 [1)]
	1000	8	100.1 ± 10.6	- [2)]	- [2)]	- [2)]	98.4 ± 5.3	107.4 ± 12.3

Each value represents the mean ± S.D.
a: 0.5 w/v% Methylcellulose solution
1) n=7 : Since 1 value in each group was affected by body movement of the animal, the value was excluded from evaluation.
2) Since all data were affected by body movement of animals, they were excluded from evaluation.
#: Significantly different from the vehicle control value by Dunnett's test, $p<0.05$.

Source: Study Report No. B200362, Table 3, p. 21

The non-dose dependent effect of oveporexton on respiratory function in rats correlates with the effects on the CNS observed in the rat safety pharmacology study (Study No. B200314) in which increased restlessness and spontaneous activity were more notable at 20 and 100 mg/kg than at 1000 mg/kg. Therefore, the increased activity might have contributed to the increased RR and MV observed in rats at 20 and 100 mg/kg as a secondary factor. The increase in RR and MV may also be attributed to the direct pharmacological action of oveporexton in the CNS as published literature data suggest orexin-A, which acts on both orexin receptor subtypes 1 and 2, elicits cardiovascular and respiratory excitation, and administration of orexin-A into the lateral ventricles of the brain of mice induces a rise in RR and tidal volume (Sakurai et al., 1998). The exposure margin for oveporexton effects on respiratory function is approximately 127-fold, which is based on the C_{max} at the LOEL of 20 mg/kg (C_{max} value taken from the 4-week toxicity study in male rats, dose 20 mg/kg, Day 1; Study No. B-8713), compared to the $C_{max,ss}$ at the MRHD.

Reference ID: 5847402

5.4. ADME/PK

Table 4. ADME/PK

Type of Study	Major Findings
Absorption	
Study title: Plasma concentration - time profiles of T-4060761 after single oral and intravenous administration of T-4060761 to rats. *Study No: DDA-A41-003*	Rapid absorption in rats after single oral (PO) doses of 10 and 30 mg/kg, with t_{max} 2 to 3 h post-dose and $t_{1/2}$ of 3 h AUC_{24h} increased in a greater than dose proportional manner from 10 to 30 mg/kg. The t_{max} and $t_{1/2}$ values after a PO [^{14}C]oveporexton dose of 100 mg/kg (Study No. 313N-2106) were 2 and 3.8 h, respectively, consistent with the results at 10 and 30 mg/kg. High oral bioavailability in rats (>100%) with much lower oral bioavailability observed in monkeys (32%) Rapid absorption in monkeys after single PO doses 1 or 3 mg/kg, with t_{max} 2 to 3 h post-dose and $t_{1/2}$ 4 to 5 h. AUC_{24h} increased dose proportionally from 1 to 3 mg/kg. The t_{max} and $t_{1/2}$ values after a PO [^{14}C]oveporexton dose of 100 mg/kg (Study No. 313N-2106) were 4.7 and 7.2 h, respectively, suggesting a slightly delayed absorption and prolonged elimination at the higher dose of 100 mg/kg compared to 1 and 3 mg/kg.
Study title: Plasma concentration—time profiles of T-4060761 after single oral and intravenous administration of T-4060761 to monkeys. *Study No. DDA-A41-004*	**Table 5. Pharmacokinetic Parameters of Oveporexton in Male Rats and Male Monkeys** Source: DDA-A41-003 and DDA-A41-004. -: not evaluated; AUC_{24}: area under the concentration-time curve from time 0 to 24 hours; CL: clearance; C_{max}: maximum observed concentration; F: absolute bioavailability, $(AUC_{24,po}/Dose_{po}) / (AUC_{24,iv}/Dose_{iv}) \times 100$; IV: intravenous(ly); PO: oral(ly); $t_{1/2}$: half-life; t_{max}: time of first occurrence of C_{max}; V_{ss}: volume of distribution at steady state. The mean value of 3 animals is presented. [a] The C_{max} after IV administration denotes the concentration at 0.083 hours postdose. [b] Because of the nonlinear PK in rats after PO administration, the absolute bioavailability in rats was considered to be overestimated. Source: Study reports DDA-A41-003 and DDA-A41-004.
Distribution	
Study title: Quantitative Whole Body Auto-radiography Tissue Distribution in Male Long-Evans and Sprague Dawley Rats Following a Single Oral Administration of [^{14}C] TAK-861 *Study No. 313N-2106*	After a single PO administration of 100 mg/kg [^{14}C]oveporexton to male pigmented and albino rats, [^{14}C]oveporexton was widely distributed in the tissues of pigmented rats with quantifiable levels in 30 of 43 sampled tissues through 24 h post-dose. The greatest exposure (AUC_{all} >3000 h*µg equiv/g) was observed in adrenal cortex, adrenal gland, and liver. Tissues with low exposure (AUC_{all} <100 h*µg equiv/g) included the spinal cord, brain, eye lens, and bone. At 336 h post-dose, the only tissues with quantifiable levels of radioactivity were adrenal gland (adrenal cortex and medulla), liver, and gastric mucosa. Albino rats showed a pattern of tissue distribution and exposure of [^{14}C]oveporexton similar to that observed in pigmented rats. There was no evidence of melanin binding in pigmented rats.

Species	Route	Dose (mg/kg)	AUC_{24} (h*ng/mL)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	V_{ss} (mL/kg)	CL (mL/h/kg)	F (%)
Rat	IV	1	481	596 [a]	-	0.7	1820	2100	-
	PO	10	15,400	1760	2.0	3.4	-	-	320.2 [b]
	PO	30	70,400	5290	3.3	3.2	-	-	-
Monkey	IV	0.3	1200	338 [a]	-	3.5	1140	253	-
	PO	1	1270	104	2.7	4.3	-	-	32.3
	PO	3	4080	379	2.0	5.4	-	-	-

Type of Study	Major Findings
Study title: Determination of Lacteal Secretion and Placental Transfer in Lactating and Pregnant Female Albino Sprague Dawley Rats Following a Single Oral Dose of [^{14}C]TAK-861. *Study No. 313N-2333*	Placental transfer of [^{14}C]oveporexton was studied in pregnant and lactating rats. In pregnant rats, after a single PO dose of 100 mg/kg, [^{14}C]oveporexton-related radioactivity was widely distributed in amnion, amnionic fluid, placenta, fetal blood, and fetal tissues indicating that [^{14}C]oveporexton- related materials were transferred into fetus via the placenta; it was also present in the milk of lactating rats. [^{14}C]Oveporexton was identified as the predominant compound in all plasma and milk samples from both lactating and pregnant rats. No metabolites were detected in the plasma or milk of lactating rats or in fetal plasma.
Study title: In vitro plasma protein binding of [^{3}H]T-4060761 in rats, monkeys and humans. *Study No. DDA-A41-006*	In vitro plasma protein bindings of [^{3}H]oveporexton (0.05 to 5 µg/mL) were 95.5 to 97.8% (rat), 97.2 to 97.5% (monkey), and 96.2 to 96.4% (human), and were concentration independent. The unbound fraction of oveporexton in plasma was similar in rats, monkeys, and humans (4.5%, 2.8%, and 3.8%, respectively).
Study title: In vitro distribution of [^{14}C]TAK-861 into blood cells in rats, monkeys and humans. *Study No. DDA-A41-0058*	In vitro distribution of [^{14}C]oveporexton into red blood cells was studied in rats, monkeys, and humans. [^{14}C]Oveporexton (0.05 to 5 µg/mL) was distributed into red blood cells at low levels, ranging from 12.4 to 24.9% (rats), 22.9 to 24% (monkeys), and 17.8 to 18% (humans). In vitro blood-to-plasma ratios of [^{14}C]oveporexton ranged from 0.698 to 0.802, suggesting that [^{14}C]oveporexton were not extensively distributed into blood cells of rats, monkeys, and humans.
Metabolism	
Study title: In Vitro Metabolism of [^{14}C]TAK-861 by Hepatocytes of Humans, Mice, Rats and Monkeys *Study No.* DDA-A41-028	The in vitro metabolite profile of [^{14}C]oveporexton in mouse, rat, monkey, and human hepatocytes showed numerous metabolites: M4, M5, M6, and M12 produced by monooxygenation; M11 by oxidative ring opening and monooxygenation; M13 by glucuronidation; M8 and M9 by monooxygenation and glucuronidation; M10 by monooxygenation and sulfation; and M1 and M7 by oxidative defluorination and glutathione conjugation.

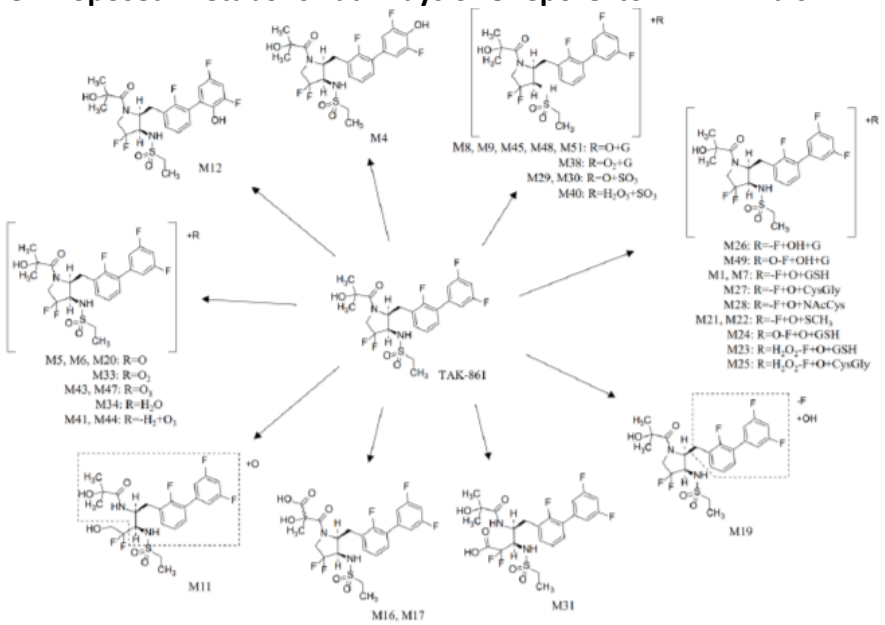
Reference ID: 5847402

Type of Study	Major Findings
Study title: Contribution of CYP Isoforms to In Vitro Metabolism of TAK-861.*Study No.* DDA-A41-011	Oxidative defluorination- and glutathione conjugation-related metabolites (M1 and M7) together accounted for 51.8%, 70.8%, 19.4%, and 14.9% of the sum of all identified metabolites in mice, rats, monkeys, and humans, respectively. M8 and M10 were the predominant metabolites formed in human hepatocytes. There were no human-specific metabolites.
Study title: In Vitro Metabolic Stability of [^{14}C]TAK-861 by Hepatocytes from Humans and Animals. *Study No.* DDA-A41-026	In vitro metabolism studies with CYP-expressing microsomes showed that [^{14}C]oveporexton was metabolized 97.3% by CYP3A4 with 2.6% and 0.1% metabolism by CYP2C9 and CYP2D6. The estimated relative contribution ratio of CYP to the in vitro metabolism of [^{14}C]oveporexton in human hepatocytes was 100%.
Study title: In vivo Metabolism of [^{14}C] TAK-861 after Single Administration to Mice, Rats, and Monkeys. *Study No.* DDA-A41-070	In vivo, the major circulating component in all animal species was unchanged [^{14}C]oveporexton which accounted for 95.6% (mice), 92.5% (rats), and 75.5% (monkeys) of the total radioactivity; 94.5%, 85.0, and 57.3% of the administered dose in mice (15 mg/kg), rats (100 mg/kg), and monkeys (100 mg/kg), respectively, were recovered as metabolites in feces, suggesting that oveporexton undergoes extensive biotransformation in all species tested. Forty four metabolites were detected in plasma, urine, feces, and bile after PO administration of [^{14}C]oveporexton to mice, rats, and monkeys. It was estimated that oveporexton was metabolized via multiple metabolic pathways including oxidation with and without defluorination, glucuronidation together with oxidation with and without defluorination; sulfation together with oxidation, and oxidative defluorination (or with further oxidation) followed by glutathione-related conjugation; and unidentified metabolism. The defluorination pathway and the unextracted fecal fractions were higher in mice and rats than in monkeys. The sum of urinary and fecal excretion of defluorinated metabolites (M19, M21, M22, and M26) was 21.2%, 15.0%, and 3.9% of the dose in mice, rats, and monkeys, respectively. The toxicokinetic profile of metabolite M4 (an oxidative metabolite) was measured proactively in several nonclinical studies based on a preliminary human metabolite profiling study, however, a subsequent definitive human ADME study (Report TKD-BCS-01618-R1) confirmed that all circulating metabolites were less than 10% total circulating radioactivity.

Reference ID: 5847402

Type of Study	Major Findings

Figure 5. Proposed Metabolic Pathways of Oveporexton in Animals



Source: DDA-A41-070
CysGly: Cysteinylglycine, G: Glucuronic acid, GSH: Glutathione, NAcCys: N-acetylcysteine
All structures of metabolites are presumed. Unknown metabolites, M32, M35, M36, M37, M39, M42, M46, and M50, were also detected.

Source: Study DDA-A41-070

Excretion	
Study title: - PK and mass balance studies of [^{14}C]TAK-861 following oral administration to mice, rats, monkeys. Study Nos. DDA-A41-041 DDA-A41-044 DDA-A41-03	[^{14}C]oveporexton was mainly excreted into the feces via bile. After single PO administration to mice, rats, and monkeys, the excretion ratios of [^{14}C]oveporexton-related substances to the dose were 1.0% and 95.9% in urine and feces, respectively, by 24 h post-dose in mice (Study No. DDA-A41-041); 0.5% and 98.7% respectively in rats by 72 h post-dose (Study No. DDA-A41-044); and 7.7% and 89.4% respectively in monkeys by 168 h post-dose (Study No. DDA-A41-038). These results indicated that oveporexton-related substances were well absorbed, mainly metabolized and excreted into the feces via bile after single PO administration in all tested animal species.

Reference ID: 5847402

Type of Study	Major Findings
TK Data From General Toxicology Studies	
Study title: 26-Week Oral Toxicity Study of TAK-861 in Rats with a 13-Week Recovery Period. *Study No.* B-8933	In the 26-week rat study, plasma TK of oveporexton and its metabolite M4 were determined. For oveporexton, the mean C_{max} and AUC_{24h} increased less than dose-proportionally, except between 10 and 100 mg/kg on Day 1, which increased in a dose-proportional manner. After repeated dosing, the mean C_{max} and AUC_{24h} on Day 1 and Week 26 were generally comparable. The mean C_{max} and AUC_{24h} at 750 mg/kg in in males were lower than those in females. Safety margins at the NOAEL of 100 mg/kg compared to the MRHD based on AUC: 311x and 455x for males and females, respectively. For metabolite M4, the mean C_{max} and AUC_{24h} in males increased in a dose-proportional manner between 10 and 100 mg/kg and in a less than dose-proportional manner between 100 and 750 mg/kg. The mean C_{max} and AUC_{24h} in females increased greater than dose-proportionally between 10 and 100 mg/kg and less than dose proportionally between 100 and 750 mg/kg. The mean C_{max} and AUC_{24h} of M4 were lower in males than in females at 100 and 750 mg/kg and were lower in males than in females at 10 mg/kg. *Note:* Metabolite M4 was proactively evaluated, based on observed levels in an exploratory human ADME clinical study. However, a definitive human ADME study (No. TAK-861-1003) found that there were no major metabolites in human plasma (Report TKD-BCS-01618-R1). As such, TK values for M4 are presented by the Sponsor for completeness. **Table 6. Mean Plasma Toxicokinetic Parameters of Oveporexton in the 26-Week Toxicity Study in Rats** Source: Study report B-8933

Dose (mg/kg)	Male				Female			
	C_{max} (ng/mL)		AUC_{24} (h*ng/mL)		C_{max} (ng/mL)		AUC_{24} (h*ng/mL)	
TAK-861	Day 1	Week 26	Day 1	Week 26	Day 1	Week 26	Day 1	Week 26
10	963	2250	12,200	25,100	1870	3430	20100	44300
100	9510	7860	142,000	115,000	10,300	11,800	142,000	168,000
750	20,400	17,200	406,000	276,000	23,000	35,400	422,000	554,000
M4	Day 1	Week 26	Day 1	Week 26	Day 1	Week 26	Day 1	Week 26
10	NE	3.10	NE	21.2	NE	3.04	NE	30.7
100	NE	20.8	NE	257	NE	66.9	NE	904
750	NE	53.4	NE	792	NE	104	NE	1740

AUC_{24}: area under the concentration-time curve from the time 0 to time 24 hours; C_{max}: maximum observed concentration; n=3 rats/sex, NE: Not examined

Reference ID: 5847402

Type of Study	Major Findings
Study title: 39-Week Oral Toxicity Study of TAK-861 in Monkeys. *Study No. B-8934*	In the 39-week monkey study, the mean oveporexton plasma exposure (C_{max} and AUC_{24h}) increased in an approximately dose-proportional manner between 100 and 300 mg/kg, but less than dose-proportionally between 30 and 100 mg/kg in both sexes. Following repeated dosing, the mean C_{max} and AUC_{24h} were similar between Days 1 and 273 except for the mean AUC_{24h} in males at 100 mg/kg and in females at 300 mg/kg, that was lower on Day 273 compared to Day 1. There were no apparent sex-related differences in the TK parameters. Safety margins at the NOAEL of 300 mg/kg compared to the MRHD based on AUC: 570x and 457x for males and females, respectively.

Table 7. Mean Plasma Toxicokinetic Parameters of Oveporexton in the 39-Week Toxicity Study in Monkeys

	Male (n=4)		Female (n=4)		Sex combined (n=8)	
Dose (mg/kg)	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)
Day 1						
30	4,860	62,400	3,900	38,800	4,380	50,600
100	9,550	131,000	8,150	113,000	8,850	122,000
300	18,800	313,000	19,700	337,000	19,200	325,000
Day 273						
30	3,800	42,100	3,340	30,600	3,570	36,300
100	5,940	61,700	6,960	64,100	6,450	62,900
300	14,500	211,000	15,500	169,000	15,000	190,000

AUC_{24}: area under the concentration-time curve from time 0 to time 24 hours, C_{max}: maximum observed concentration.

Source: Study report B-8934

TK Data From Reproductive/Developmental Toxicology Studies

Study title: Study of TAK-861 for Effects on Embryo-Fetal Development in Rats. *Study No. R-1276*

Rat

Exposure to oveporexton in dams (mean C_{max} and AUC_{24h}) increased in a less than dose-proportional manner between GDs 6 and 17. There was no evidence of drug accumulation upon repeated dosing. The individual t_{max} ranged from 1 to 24 h and 2 to 8 h on GDs 6 and 17, respectively. AUC: Maternal exposure to oveporexton (AUC_{24h} on GD 17) at the NOAEL for maternal toxicity (100 mg/kg) was 128,000 h*ng/mL; at the NOAEL for embryo-fetal toxicity (750 mg/kg) it was 431,000 h*ng/mL. Safety margins at NOAEL compared to the MRHD based on AUC: 346x and 1166x for maternal and embryo-fetal toxicity, respectively.

Table 8. Mean Plasma Toxicokinetic Parameters of Oveporexton in Pregnant Rats

Dose (mg/kg)	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)
GD 6		
10	2000	23,100
100	9760	165,000
750	21,300	426,000
GD 17		
10	3030	43,500
100	8580	128,000
750	24,900	431,000

Source: R-1276.

AUC_{24}: area under the concentration-time curve from time 0 to 24 hours; C_{max}: maximum observed concentration; GD: gestation day.

n = 4/group

Source: Study Report R-1276

Reference ID: 5847402

Type of Study	Major Findings
Study title: Study of TAK-861 for Effects on Embryo-Fetal Development in Rabbits. *Study No. R-1275*	Rabbit Oveporexton mean C_{max} and AUC_{24h} in pregnant females increased in an approximately dose-proportional manner between GDs 7 and 20. There was no evidence of drug accumulation upon repeated dosing. Maternal exposure to oveporexton (AUC_{24h} on GD 20) at the NOAEL for maternal toxicity (20 mg/kg) was 13,900 h*ng/mL; at the NOAEL for embryofetal toxicity (100 mg/kg) it was 56,600 h*ng/mL. Safety margins at NOAEL compared to the MRHD based on AUC: 38x and 153x for maternal and embryo-fetal toxicity, respectively.

Table 9. Mean Plasma Toxicokinetic Parameters of Oveporexton in Pregnant Rabbits

	GD7		GD20	
Dose (mg/kg)	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)
4	271	3410	353	4000
20	1130	16, 600	1500	13,900
100	5070	86,500	4770	56,600

Source: R-1275.
AUC_{24}: area under the concentration-time curve from time 0 to 24 hours; C_{max}: maximum observed concentration; GD: gestation day.
n = 5/group

Source: Study Report R-1275

Study title: A 6-Week Repeated Oral Gavage Juvenile Toxicity Study of TAK-861 in 28-day old Rats with a 4-Week Recovery Period. Study No. SBL010-561	In juvenile rats, oveporexton mean C_{max} in plasma increased in an approximately dose-proportional manner in both sexes, while the mean AUC_{24h} increased approximately dose-proportionally between 10 and 50 mg/kg, and greater than dose-proportionally between 2 and 10 mg/kg. Following repeated administration, the mean C_{max} and AUC_{24h} were comparable between Days 1 and 42 indicating no drug accumulation over time. There were no apparent sex-related differences in exposure. The t_{max} ranged from 1 to 4 h. The mean C_{max} for plasma fluoride ion increased less than dose-proportionally, while the mean AUC_{24h} generally increased with increasing dose. Following repeated administration, the mean fluoride C_{max} and AUC_{24h} did not increase, except at 50 mg/kg, where they were higher on Day 42 than on Day 1. Generally, there were no apparent sex differences, except for the mean AUC_{24h} at 10 and 50 mg/kg on Day 1 which was lower in males, and the mean AUC_{24h} at 2 mg/kg on Day 42, which was lower in females. The t_{max} was generally 1 h. Exposure to oveporexton (mean AUC_{24h}) at the NOAEL of 50 mg/kg was 70,800 and 82,000 h*ng/mL in males and females, respectively.

Table 10. Mean Plasma Toxicokinetic Parameters of Oveporexton in Juvenile Rats

	Male			Female		
Dose (mg/kg)	t_{max} (h)	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)	t_{max} (h)	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)
Day 1 of Dosing (PND28)						
2	2.0	222	1,190	1.0	238	3,130
10	2.0	1,520	17,900	2.0	1,680	17,200
50	4.0	6,750	90,600	4.0	6,750	85,900
Day 42 of Dosing (PND69)						
2	1.0	221	1,170	1.0	389	2,490
10	2.0	1,850	15,400	2.0	2,520	29,100
50	2.0	5,450	70,800	2.0	6,130	82,000

AUC_{24}: area under the concentration-time curve from 0 to 24 hours; C_{max}: maximum observed concentration; PND: postnatal day; t_{max}: time of first occurrence of maximum observed concentration.
n = 3 of each sex per timepoint.

Source: Study Report SBL010-561

Reference ID: 5847402

Type of Study **Major Findings**

Table 11. Mean Plasma Fluoride Ion Parameters in Juvenile Rats

Dose (mg/kg)	Male t_{max} (h)	Male C_{max} (ng/mL) (µmol/L)	Male AUC_{24} (h*ng/mL) (h*µmol/L)	Female t_{max} (h)	Female C_{max} (ng/mL) (µmol/L)	Female AUC_{24} (h*ng/mL) (h*µmol/L)
Day 1 of Dosing (PND28)						
2	8.0	56.6 3.0	1,043.6 54.9	1.0	70.3 3.7	1,141.2 60.0
10	1.0	63.3 3.3	649.9 34.2	1.0	92.3 4.9	1,083.1 57.0
50	1.0	89.4 4.7	424.8 22.4	1.0	117.5 6.2	1,674.4 88.1
Day 42 of Dosing (PND69)						
2	1.0	80.1 4.2	675.5 35.5	1.0	65.6 3.5	88.8 4.7
10	1.0	147.1 7.7	652.8 34.4	1.0	102.7 5.4	1,186.4 62.4
50	1.0	316.7 16.7	3,706.8 195.1	1.0	289.3 15.2	3,396.8 178.8

AUC_{24}: area under the concentration-time curve from 0 to 24 hours; C_{max}: maximum observed concentration; PND: postnatal day; t_{max}: time of first occurrence of maximum observed concentration.
n = 3 of each sex per timepoint.
Source: Study Report SBL010-561

TK Data From Carcinogenicity Studies: No tumor findings

Study title: 24- Month Oral Carcinogenicity Study of TAK-861 in Rats. *Study No. B-8962*

Oveporexton systemic exposure was dose related in both sexes. The mean C_{max} and AUC_{24h} in males increased in a greater than dose-proportional manner between 1 and 20 mg/kg and approximately dose-proportionally between 20 and 100 mg/kg. In females, the mean AUC_{24h} increased in a greater than dose-proportional manner between 1 and 20 mg/kg, while between 20 and 100 mg/kg, the C_{max} and AUC_{24h} increased less than dose-proportionally. With repeated dosing, the C_{max} and AUC_{24h} were comparable between Days 1 and 363, except for the C_{max} and AUC_{24h} at 1 mg/kg in both sexes on Day 363 that were higher compared to Day 1. The C_{max} and AUC_{24h} were lower in males than in females. T_{max} ranged from 1 to 8, and 1 to 4 hours on Days 1 and 363, respectively.

Table 12. Mean Plasma Toxicokinetic Parameters of Oveporexton in the 2-Year Carcinogenicity Study in Rats

Dose (mg/kg)	Male C_{max} (ng/mL)	Male AUC_{24} (h*ng/mL)	Female C_{max} (ng/mL)	Female AUC_{24} (h*ng/mL)
Day 1				
1	12.8	73.0	105	331
20	2430	32,500	3880	55,100
100	8860	127,000	9560	147,000
Day 363				
1	55.9	357	207	1100
20	2940	39,900	6490	89,000
100	8500	124,000	13,100	178,000

AUC_{24}: area under the concentration-time curve from the time 0 to time 24 hours; C_{max}: maximum observed concentration; n=3/sex
Source: Study Report No. B-8962

At the highest dose of 100 mg/kg/day, the mean AUC_{24h} values were 124,000 h*ng/mL for males, and 178,000 h*ng/mL for females, respectively, on Day 363, which is approximately 335x and 482x the MRHD based on AUC.

Reference ID: 5847402

5.5. Toxicology

5.5.1. General Toxicology

Single-dose toxicity studies and repeat-dose toxicity studies were performed in Sprague-Dawley rats (2-, 4-, 13- and 26-weeks duration) and in Cynomolgus monkeys (2-, 4-, 13- and 39-weeks duration). Exposure based safety margins were calculated based on a clinical population pharmacokinetic $AUC_{24,ss}$ value at the MRHD of 369.6 h*ng/mL in patients from Study TAK-861-3001.

Study Title/Number: Thirteen-Week Oral Gavage Toxicity Study of TAK-861 in Rats With a Recovery Period of 4-Weeks/B-8803

- Degeneration of ameloblasts in the incisors occurred at the high dose of 1500 mg/kg, with corresponding clinical observations of whitening and fractures. Whitening and fractures in the incisors were still noted during the recovery period due to time required for rat incisor renewal (40-50 days), however, the severity of ameloblast degeneration decreased by the end of recovery period.
- Dilatation of kidney proximal and distal tubules occurred in high dose females associated with increased plasma blood urea nitrogen (BUN) levels, increased urine volume, and increased kidney weights; findings were reversible; Decreased body weight for high dose males.
- NOAEL: 100 mg/kg for both sexes, associated with a mean C_{max} of 9090 and 12,400 ng/mL, and a mean AUC_{24h} of 128,000 and 164,000 h*ng/mL in males and females, respectively, in Week 13 of dosing. Safety margins at NOAEL compared to the MRHD are 346- and 444-fold for males and females, respectively, based on AUC.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 13. Methods, Study B-8803

Category	Details
Dose and frequency of dosing:	0, 20, 100, 1500 mg/kg, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% [w/v] Methylcellulose (MC) solution
Species/Strain:	Rat/Sprague-Dawley [Crl:CD(SD)]
Number/Sex/Group:	15 (main); 5 (recovery- Control and HD)
Age:	6 weeks
Satellite groups/ unique design:	TK: Additional 4/rats/sex/group
Deviation from study protocol affecting interpretation of results:	No

Table 14. Observations and Results: Changes From Control, Study B-8803

Parameters	Major Findings
Mortality	A single HD (1500 mg/kg/day) female was terminated early on Day 10 of dosing due to moribund condition. The animal presented with decreased movement, bradypnea, hypothermia, and emaciation prior to termination. A marked decrease in body weight from Day 4 to Day 10 (-34% from Day 1 values). Macroscopic findings of reduced organ size (likely due to weight loss) of the mesenteric lymph node, spleen, and thymus, and multiple dark red foci in the glandular stomach were noted. Minimal single cell necrosis and mild regeneration of the collecting ducts of the kidney were noted. There were changes in hematology and clinical pathology parameters that are likely due to deteriorating health condition. The underlying cause of moribundity was not determined; however, a drug related cause cannot be ruled out.
Clinical Signs	Whitening of incisors at HD of 1500 mg/kg with all animals affected by the end of the dosing period. Fracture of the incisors was also noted starting in weeks 11 and 12 of dosing. Incisor whitening was still present at the end of the recovery period; however, the incidence of incisor fractures was lower at the end of recovery indicating reversibility. This finding corresponded with histopathology of ameloblast degeneration, associated with fluorosis.
Body Weights	Significant reduction in mean body weight (-9%) compared to controls in HD males at the end of the dosing period. At the end of the recovery period, mean body weight remained lower (-11%) compared to controls while mean body weight gain was similar to control. In females, mean body weight and body weight gain were similar to controls during the dosing period however, during recovery, HD females lost weight and mean body weight was reduced (-8%) compared to controls.
Food consumption	Food consumption was transiently decreased at HD in both males and females during the first two weeks of the dosing period.
Ophthalmoscopy	No drug-related findings.
Hematology	Significant decreases (up to -6%) in RBC counts compared to controls in males at ≥20 mg/kg/day. At 1500 mg/kg/day, significant increases in PLT (+13%) in males; WBC (+36%) and MONO (+69%) in females; RDW (+12-21%) and Retic (+30-34%) in both and significant decreases in MCV (-4%) and MCH (-7%) in females; HGB (-7- 8%), HCT (-5%) and MCHC (-2-3%) in both sexes. All hematology changes were considered non-adverse due to the low magnitude of the changes and no correlated microscopic findings in any organs or tissue. At the end of the recovery period, significant decreases in MONO (males); and MCH and Retic (females) at 1500 mg/kg/day. The changes were generally within historical control ranges.
Clinical Chemistry	A significant increase (+55%) in ALT levels in males at 1500 mg/kg/day. A significant and dose-related increase in total cholesterol in males (up to +101%) at ≥100 mg/kg/day and in females (up to +174%) at ≥20 mg/kg/day. A significant increase in BUN (up to +58%) in females at 1500 mg/kg/day. At the end of the recovery period no significant differences compared to controls were noted.
Urinalysis	Significant increase in urine volume (122%) and water intake (23%) in HD females compared to controls. At the end of recovery period, no significant differences compared to controls were noted.
Gross Pathology	Enlarged liver at ≥100 mg/kg/day, whitening and fracture of the incisors at 1500 mg/kg/day in both males and females. In the kidney, focal white discoloration in a single HD female with no correlated microscopic finding. At the end of recovery period, macroscopic finding of incisor whitening was still present; however, the occurrence of incisor fracture was reduced (males) or completely resolved (females).

Reference ID: 5847402

Parameters	Major Findings
Organ Weights	Dose-related increase in liver weights at ≥20 mg/kg/day in males (up to +108%) and females (up to +189%) correlated with macroscopic and microscopic findings. Dose-related increase in kidney weights at ≥100 mg/kg/day in females (up to +20%) correlated with increased urine volume and microscopic findings in HD females. Increased adrenal gland weights in HD females (up to +20%). Increased testis weights in HD males (up to +22%). Decrease in pituitary gland weights (up to -27%) in HD females. At the end of recovery period, liver weights remained higher than controls (up to 34%) in HD females though the magnitude was diminished compared to end of the dosing phase. Adrenal weights were also significantly higher than controls in HD females the end of recovery period, however the values were close to the historical control range.
Histopathology Adequate battery: Yes	**Dental**: minimal to mild ameloblast degeneration of the lower jaw incisors in both males and females of the HD group. This finding correlated with whitening of the incisors and was related to increased plasma levels of fluoride. The severity of ameloblast degeneration decreased by the end of recovery period. **Kidney**: minimal to mild dilatation of the proximal and distal tubules in HD females correlated with a minimal increase in urine volume. These findings were resolved by the end of the recovery period. **Liver**: Dose-related minimal to moderate centrilobular hepatocellular hypertrophy in both males and females at ≥100 mg/kg/day, in correlation with larger liver size and increased liver weights and increased activities of hepatic drug metabolizing enzymes indicating a potential adaptive response. At the end of the recovery period, complete reversal of hepatocellular hypertrophy was noted, however, a finding of multinucleated hepatocytes was observed believed to be a result of cellular fusion and no abnormal cytokinesis due to the absence of nuclear atypia. **Thyroid and adrenal glands**: Minimal hypertrophy of follicular cells in the thyroid gland in both males and females at ≥100 mg/kg/day. Minimally increased diffuse vacuolation in the adrenal gland cortex in males at ≥100 mg/kg/day and in HD females. These findings were resolved by the end of the recovery period. **Ovary**: Dose-related increased incidence and severity of minimal to mild vacuolation of the interstitial cells in the ovary at ≥100 mg/kg/day, fully reversible at 100 mg/kg/day and partially reversible at 1500 mg/kg/day by the end of the recovery period.

LD = low dose; MD = mid dose; HD = high dose
-: indicates reduction in parameters compared to control; +: indicates increase in parameters compared to control.
Source: Study Report B-8803

Study Title/Number: Twenty-Six-Week Oral Gavage Toxicity Study of TAK-861 in Rats With a 13-Week Recovery Period/B-8933

- Degeneration of ameloblasts in the incisors occurred at 750 mg/kg, with corresponding clinical observations of whitening and fractures; findings were reversible. Decreased body weight occurred in females at ≥100 mg/kg and in males at 750 mg/kg/day which correlated

Reference ID: 5847402

with decreased food consumption. Effects on food consumption were fully reversible and effects on body weight were partially reversible.

- Dilatation of kidney proximal and distal tubules in females at 750 mg/kg/day which was associated with increased blood urea nitrogen (BUN), creatinine, and urine volume; findings were reversible. Dose-dependent hypertrophy of centrilobular hepatocytes in the liver of both males and females at ≥100 mg/kg, which correlated with increased liver weights; findings were reversible.
- NOAEL: 100 mg/kg for both sexes, associated with a mean C_{max} of 7860 and 11,800 ng/mL, and a mean AUC_{24h} of 115,000 and 168,000 h*ng/mL in males and females, respectively, in Week 26 of dosing. Safety margins at NOAEL compared to the MRHDare 311- and 455-fold for males and females, respectively, based on AUC.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 15. Methods, Study B-8933

Category	Details
Dose and frequency of dosing:	0, 10, 100, 750 mg/kg, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% [w/v] Methylcellulose (MC) solution
Species/Strain:	Rat/Sprague-Dawley [Crl:CD(SD)]
Number/Sex/Group:	15
Age:	6 weeks
Satellite groups/ unique design:	Additional 4/rats/sex/group were used to evaluate plasma TK of TAK-861 and its metabolite M4 (Week 26 only).
Deviation from study protocol affecting interpretation of results:	No

Table 16. Observations and Results: Changes From Control, Study B-8933

Parameters	Major Findings
Mortality	None
Clinical Signs	Whitening and fracture of incisors in all animals at 750 mg/kg by the end of the dosing period (starting in Week 10 of dosing in females and Week 11 in males), fully reversible at the end of the recovery period. This finding corresponded with histopathology of ameloblast degeneration, associated with fluorosis.
Body Weights	Statistically significant decreases in body weight at 100 mg/kg in females (-6% vs. control) and 750 mg/kg in males and females (-11% and -14% vs. control, respectively) at the end of the dosing period, associated with lower food consumption at ≥100 mg/kg throughout the dosing period. A decrease in body weight was also observed in males at 750 mg/kg throughout the recovery period (-11% compared to controls); however, the effect was no longer statistically significant after Day 42, indicating partial recovery. The effect on body weight in females was also partially reversible, as there was only a -6% (not statistically significant) decrease at 750 mg/kg compared to controls at the end of the recovery period.
Food consumption	Decreased food consumption compared to controls was observed at ≥100 mg/kg in both males and females throughout the dosing period.
Ophthalmoscopy	No drug-related findings

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Parameters	Major Findings
Hematology	Dose dependent decreases in hemoglobin, hematocrit, and mean corpuscular hemoglobin in females at ≥100 mg/kg (up to -10%, -7% and -9%, respectively), at 750 mg/kg compared to control; decreases in hemoglobin in males by -3% at 750 mg/kg; and increase in white blood cell count in females by 34% at 750 mg/kg compared to control.
Clinical Chemistry	Drug-related but non-adverse changes included increases in: inorganic phosphorus in males at ≥100 mg/kg and females at ≥10 mg/kg; in total cholesterol, calcium and total protein in both sexes at ≥100 mg/kg; in γ-glutamyl transpeptidase in females at ≥100 mg/kg and in males at 750 mg/kg, and increases in blood urea nitrogen in both sexes, creatinine in females, and potassium in males at 750 mg/kg. Decreases were found in: triglycerides in females at ≥10 mg/kg, in chloride and A/G ratio in females at ≥100 mg/kg, in glucose and total bilirubin in females at ≥100 mg/kg and in males at 750 mg/kg, as well as in glutamate dehydrogenase in both sexes, and in aspartate aminotransferase and alkaline phosphatase in males at 750 mg/kg. These changes were reversible.

Table 17. Summary of Drug-Related Clinical Chemistry Findings (Dosing Period)

Sex	Male				Female			
Dose (mg/kg)	0	10	100	750	0	10	100	750
No. of animals	14	15	14	14	15	15	15	15
AST (IU/L)	60	59 (−2%)	54 (−10%)	48*$ (−20%)	/	/	/	/
ALP (IU/L)	240	224 (−7%)	213 (−11%)	198*$ (−18%)	/	/	/	/
γ-GTP (IU/L)	0	0	1	8*$ (↑)	1	1	2*$ (+100%)	13*$ (+1200%)
T-CHO (mg/dL)	76	82 (+8%)	104*$ (+37%)	114*$ (+50%)	97	103 (+6%)	137*$ (+41%)	201*$ (+107%)
TG (mg/dL)	/	/	/	/	93	55*$ (−41%)	58*$ (−38%)	39*$ (−58%)
T-BIL (mg/dL)	0.1	0.1	0.1	0.0*$ (↓)	0.1	0.1	0.1*$ (↓)	0.0*$ (↓)
GLU (mg/dL)	136	135 (−1%)	130 (−4%)	121*$ (−11%)	121	121 (±0%)	109*$ (−10%)	99*$ (−18%)
BUN (mg/dL)	13	14 (+8%)	14 (+8%)	17*$ (+31%)	17	16 (−6%)	19 (+12%)	32*$ (+88%)
CRNN (mg/dL)	/	/	/	/	0.35	0.35 (±0%)	0.34 (−3%)	0.40*$ (+14%)
K (mmol/L)	3.7	3.8 (+3%)	3.8 (+3%)	3.8*$ (+3%)	/	/	/	/
Cl (mmol/L)	/	/	/	/	107	107 (±0%)	105*$ (−2%)	104*$ (−3%)
Ca (mg/dL)	10.6	10.8 (+2%)	11.1*$ (+5%)	11.2*$ (+6%)	10.8	10.8 (±0%)	11.3*$ (+5%)	11.5*$ (+6%)
P (mg/dL)	5.0	5.4 (+8%)	5.7*$ (+14%)	5.7*$ (+14%)	3.7	4.3*$ (+16%)	4.6*$ (+24%)	5.1*$ (+38%)
TP (g/dL)	6.6	6.6 (±0%)	6.9*$ (+5%)	7.5*$ (+14%)	7.2	7.1 (−1%)	7.7*$ (+7%)	8.4*$ (+17%)
ALB (g/dL)	3.2	3.3 (+3%)	3.5*$ (+9%)	3.6*$ (+13%)	/	/	/	/
A/G ratio	/	/	/	/	1.3	1.3 (±0%)	1.2*$ (−8%)	1.0*$ (−23%)
GLDH (IU/L)	17	18 (+6%)	15 (−12%)	4*$ (−76%)	90	25 (−72%)	14 (−84%)	8*$ (−91%)

Values in the table indicate group mean, and values in the parentheses indicate percentage of change from the control mean (+: increase, −: decrease).
*: p≤0.05 (statistically significant difference from the vehicle control group)
/: No effects of TAK-861
$: TAK-861-related

Source: Study Report B-8933, Text Table 23, p. 45

Reference ID: 5847402

Parameters	Major Findings
Urinalysis	Increase in urine volume (+59% compared to control) occurred in females at 750 mg/kg, which correlated with microscopic changes in the kidneys of dilatation of the proximal/distal tubules. The effects were fully reversible.
Gross Pathology	Whitening and fractures of the incisors in all animals at 750 mg/kg. Liver enlargement at 750 mg/kg in males (4 of 14), and at ≥100 mg/kg in females (3 of 15 and 14 of 15 animals at MD and HD, respectively).
Organ Weights	Dose-dependent increase in liver weights at ≥100 mg/kg in both sexes compared to controls (up to 40% and 96% at HD in males and females, respectively) correlating with microscopic findings. Increased ovary weights in females at 750 mg/kg (by 23%, compared to control) correlating with microscopic findings. All effects on organ weights were fully reversible during the recovery period.
Histopathology Adequate battery: Yes	**Dental**: Degeneration of ameloblasts with corresponding macroscopic whitening and fractures of incisors (10 of 20 males and 15 of 20 females at HD of 750 mg/kg). These changes were not observed at the end of the recovery period. **Kidney**: dilatation of the proximal/distal tubules in 4 of 20 females at 750 mg/kg, but microscopic findings suggesting tubular damage were not observed. **Liver**: hypertrophy of centrilobular hepatocytes in both males and females at ≥100 mg/kg, correlating with increased liver weights and macroscopic enlargement; considered a non-adverse change associated with induction of hepatic drug metabolizing enzymes. **Ovary**: vacuolation of interstitial cells at 750 mg/kg; considered non-adverse because there were no necrotic or inflammatory changes or other findings suggesting abnormalities in reproductive system. All findings from all tissues were fully reversible by the end of the recovery period.

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Parameters	Major Findings

Table 18. Summary of Drug-Related Microscopic Findings (Dosing Period)

Sex		Male				Female			
Dose (mg/kg)		0	10	100	750	0	10	100	750
No. of animals		14	15	14	14	15	15	15	15
Adrenal gland									
Vacuolation, cortex, increased, diffuse	(±)	0	0	4	6	0	0	4	5
Duodenum									
Erosion	(±)	0	NE	NE	0	0	0	0	3
Incisor									
Degeneration, ameloblast		0	0	0	10	0	0	0	15
	(±)	0	0	0	10	0	0	0	4
	(+)	0	0	0	0	0	0	0	11
Kidney									
Dilatation, proximal/distal tubule		0	NE	NE	0	0	0	0	4
	(±)	0	NE	NE	0	0	0	0	3
	(+)	0	NE	NE	0	0	0	0	1
Liver									
Hypertrophy, hepatocyte, centrilobular		0	0	9	14	0	0	14	15
	(±)	0	0	9	0	0	0	13	0
	(+)	0	0	0	10	0	0	1	10
	(++)	0	0	0	4	0	0	0	5
Ovary									
Vacuolation, interstitial cell		NA	NA	NA	NA	0	0	0	11
	(±)	NA	NA	NA	NA	0	0	0	6
	(+)	NA	NA	NA	NA	0	0	0	5
Pancreas									
Vacuolation, acinar cell	(±)	0	NE	NE	0	0	0	0	10
Stomach									
Dilatation, glands	(±)	2	0	2	3	1	0	1	5
Thyroid gland									
Hypertrophy, follicular cell	(±)	0	0	7	14	0	0	3	9

Values in the table indicate the number of animals with lesions.
±: Minimal, +: Mild, ++: Moderate, NA: Not applicable, NE: Not examination
Source: Study Report B-8933, Text Table 26, p. 50

LD = low dose; MD = mid dose; HD = high dose.
-: indicates reduction in parameters compared to control; +: indicates increase in parameters compared to control.
Source: Study Report B-8933

Study Title/Number: 13-Week Oral Gavage Toxicity Study of TAK-861 in Monkeys/B-8802

- Drug-related findings were limited to transient vomiting and decrease in food consumption, increases in triglycerides in males at ≥30 mg/kg and in females at ≥100 mg/kg.
- Minimal hepatocyte hypertrophy was observed at 300 mg/kg, which is considered an adaptive change related to induction of hepatic drug-metabolizing enzymes.
- NOAEL: 300 mg/kg for both sexes, associated with a mean C_{max} of 35,100 and 21,400 ng/mL, and a mean AUC_{24h} of 568,000 and 290,000 h*ng/mL for plasma oveporexton in males and females, respectively.
- Safety margins at NOAEL compared to the MRHD are 1535- and 785-fold for males and females, respectively based on AUC.

Reference ID: 5847402

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 19. Methods, Study B-8802

Category	Details
Dose and frequency of dosing:	0, 30, 100, and 300 mg/kg/ once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% [w/v] Methylcellulose (MC) solution
Species/Strain:	Monkey/Cynomolgus
Number/Sex/Group:	3
Age:	3 years
Satellite groups/ unique design:	No satellite groups/ Plasma concentration of TAK-861 was determined in all animals on Days 1 and 91 of dosing
Deviation from study protocol affecting interpretation of results:	No

Table 20. Observations and Results: Changes From Control, Study B-8802

Parameters	Major Findings
Mortality	None
Clinical Signs	Vomiting in two males and two females at 300 mg/kg (for the females on Day 2 only; for the males on Days 60 and 74 for one male and less than once a week for the other male).
Body Weights	No drug-related findings
Food consumption	A transient decrease in food consumption compared to control was observed in 1 female at 300 mg/kg at Weeks 1 and 6 of dosing; it was not associated with body weight changes.
Ophthalmoscopy	No drug-related findings
ECG	No drug-related findings
Hematology	There were no drug-related effects on hematology or coagulation at any dose. Statistically significant changes compared to vehicle control were noted for several parameters; however, they were not considered drug-related because they were not dose-dependent, or substantially different from the range of control values or individual pre-dose values, or they were within the range of historical control.
Clinical Chemistry	Drug-related increases in triglycerides (TG) in males at ≥30 mg/kg (up to 247% and 193% at MD and HD, respectively) and in females at ≥100 mg/kg (up to 30% and 60% at MD and HD, respectively) in Weeks 8 and 13 of dosing compared to controls. There were no corresponding microscopic findings.

Reference ID: 5847402

Parameters	Major Findings

Table 21. Summary of Drug-Related Clinical Chemistry Findings

		Male				Female			
Dose (mg/kg)		0	30	100	300	0	30	100	300
No. of animals		3	3	3	3	3	3	3	3
TG (mg/dL)	Week −1	23	23 (0%)	34 (+48%)	23 (0%)	32	17 (−47%)	28 (−13%)	25 (−22%)
	Week 1	29	41$ (+41%)	48$ (+66%)	34$ (+17%)	44	25 (−43%)	29 (−34%)	35 (−20%)
	Week 8	30	57$ (+90%)	104W$ (+247%)	88W$ (+193%)	38	37 (−3%)	45$ (+18%)	45$ (+18%)
	Week 13	21	48$ (+129%)	61$ (+190%)	50$ (+138%)	36	30 (−17%)	47$ (+31%)	58$ (+61%)

$: TAK-861-related changes, +: increase, −: decrease, W: statistically significant the control value (Williams, $p \leq 0.05$), The values in the table indicate the group mean values and the percentages in the parentheses indicate increases/decreases from the control values.

Source: Study Report B-8802, Text Table 12, p.31

Urinalysis	No drug-related findings
Gross Pathology	No drug-related findings
Organ Weights	No drug-related findings
Histopathology Adequate battery: Yes	Minimal hypertrophy of hepatocytes was observed in 3 of 3 males/group at ≥100 mg/kg and in 1 of 3 females at 300 mg/kg. The appearance of enlarged hepatocytes indicated proliferation of the smooth endoplasmic reticulum as a consequence of induction of P450-related enzymes.

Abbreviations: LD = low dose; MD = mid dose; HD = high dose.
-: indicates reduction in parameters compared to control; +: indicates increase in parameters compared to control.
Source: Study Report B-8802

Study Title/Number: 39-Week Oral Gavage Toxicity Study of TAK-861 in Monkeys/B-8934

- Drug-related findings were limited to vomiting, transient decreases in food consumption, increases in triglycerides in males at 300 mg/kg.
- Liver histopathology of minimal hepatocyte hypertrophy at 300 mg/kg, considered to be associated with induction of hepatic drug metabolizing enzymes.
- NOAEL: 300 mg/kg for both sexes, associated with mean plasma oveporexton C_{max} of 14,500 and 15, 500 ng/mL and a mean AUC_{24h} of 211,000 and 169,000 h*ng/mL in males and females, respectively, in week 39 of dosing. Safety margins at NOAEL compared to the MRHD are 571 and 457-fold for males and females, respectively, based on AUC.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 22. Methods, Study B-8934

Category	Details
Dose and frequency of dosing:	0, 30, 100, and 300 mg/kg/ once daily
Route of administration:	Oral gavage

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Category	Details
Formulation/Vehicle:	0.5% [w/v] Methylcellulose (MC) solution
Species/Strain:	Monkey/Cynomolgus
Number/Sex/Group:	4
Age:	3 years
Satellite groups/ unique design:	No
Deviation from study protocol affecting interpretation of results:	No

Table 23. Observations and Results: Changes From Control, Study B-8934

Parameters	Major Findings
Mortality	None
Clinical Signs	Vomiting was observed at 300 mg/kg (2 females on Day 2; 1 male on Days 60 and 74; and a second male once a week or less). The findings were not considered adverse because of low frequency and absence of abnormalities in general condition or associated imbalance of plasma electrolytes.
Body Weights	No drug-related findings
Food Consumption	A transient decrease in food consumption was noted in 1 female at 300 mg/kg on Day 2 through 4 of dosing.
Ophthalmoscopy	No drug-related findings
ECG	No drug-related findings
Hematology	There were no drug-related findings. Several statistically significant changes compared to vehicle control were noted; however, they were considered incidental because they were not substantially different from the pre-dose values, or they were not dose related.
Clinical Chemistry	Drug-related increases in triglycerides (TG) in males at 30 and 300 mg/kg (up to +66% and +57%, respectively) in week 13 compared to controls. This change was non-adverse because there were no related microscopic findings. Several statistically significant differences compared to the vehicle control group were noted; however, they were considered incidental because the values were not substantially different from the pre-dose values, or the changes were transient.

Table 24. Summary of Drug-Related Clinical Chemistry Findings

		Male			
Dose (mg/kg)		0	30	100	300
No. of animals		4	4	4	4
TG (mg/dL)	Week −1	35	32 (-9%)	22 (-37%)	25 (-29%)
	Week 1	40	46 (+15%)	40 (0%)	22 (−45%)
	Week 13	47	78$ (+66%)	56 (+19%)	74$ (+57%)
	Week 27	64	103$ (+61%)	52 (−19%)	81$ (+27%)
	Week 39	54	83$ (+54%)	52 (−4%)	68$ (+26%)

$: TAK-861-related changes, +: increase, −: decrease, The values in the table indicate the group mean values and the percentages in the parentheses indicate increases/decreases from the control values at respective study days.

Source: Study Report B-8934, Text Table 15, p.31

Urinalysis	No drug-related findings
Gross Pathology	No drug-related findings
Organ Weights	Statistically significant differences were observed in the absolute and relative-to body/brain weights for the thymus in females at 300 mg/kg, however this effect was not drug- related because the individual values were within the range of the historical control data.

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Parameters	Major Findings
Histopathology Adequate battery: Yes	Minimal hypertrophy of hepatocytes was observed in 2 of 4 males at 300 mg/kg. The appearance of enlarged hepatocytes indicated proliferation of the smooth endoplasmic reticulum as a consequence of induction of P450-related enzymes.

Abbreviations: LD = low dose; MD = mid dose; HD = high dose.
-: indicates reduction in parameters compared to control; +: indicates increase in parameters compared to control.
Source: Study Report B-8934

General Toxicology, Additional Studies

Single- and repeat-dose toxicity studies of 2- and 4-weeks duration were also conducted in rats and monkeys**.**

Rats

A single-dose non-GLP toxicity study was conducted in rats (Study No. 19-341/ac) assessing single doses of 0, (0.5% [w/v] methylcellulose (MC) solution), 100, 300, and 1000 mg/kg by oral gavage. All rats survived and no adverse clinical signs were noted; no other parameters were evaluated besides mortality and clinical signs.

Similar doses were used in an exploratory 2-week repeat-dose non-GLP-compliant toxicity study in rats (Study No. N-2315), in which oral gavage doses of 0, (0.5% [w/v] MC solution), 30, 100, and 1000 mg/kg were evaluated to inform dose selection for the definitive toxicology studies. There were no drug-related findings in survival and clinical signs. Body weight decrease occurred in males at 1000 mg/kg compared to control, and food consumption was decreased in both males and females at 1000 mg/kg compared to control. In clinical chemistry, the following changes were noted compared to control: increases in total cholesterol in males at 1000 mg/kg and in females at ≥30 mg/kg; higher γ-GTP at 1000 mg/kg in both sexes; higher ALT, glucose, calcium, and total protein and lower A/G ratio in females at 1000 mg/kg, and higher triglycerides in females at ≥30 mg/kg. Histopathology findings were noted in the liver, thyroid, adrenals and ovary. In the liver, hypertrophy of the centrilobular hepatocytes was observed at ≥100 mg/kg in association with increased liver weight and macroscopic liver enlargement at 1000 mg/kg. In the thyroid gland, follicular cell hypertrophy was observed at 1000 mg/kg. These findings were consistent with induction of hepatic drug-metabolizing enzymes and therefore, were considered adaptive and non-adverse. In the adrenal gland, increased diffuse vacuolation of adrenal cortex was found at 1000 mg/kg. In the ovary, vacuolation in interstitial cells of the ovary was observed at ≥100 mg/kg, and inflammation of the interstitial gland of the ovary at 1000 mg/kg. Inflammation of the interstitial gland of the ovary at 1000 mg/kg was considered adverse. However, vacuolation without cytotoxic changes observed in the adrenal gland at 1000 mg/kg and ovary at ≥100 mg/kg were considered non-adverse. The NOAEL for males was 1000 mg/kg/day, and the NOAEL for females was 100 mg/kg/day.

In the 4-week repeat-dose GLP-compliant toxicity study in rats (Study No. B-8713), doses of 0, (0.5% [w/v] MC solution), 20, 100, and 1000 mg/kg were evaluated, including determination of plasma fluoride concentrations. A similar toxicity profile was observed in the 4-week study in rats as compared to the subsequent 13- and 26-week studies. In the incisors, degeneration

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of ameloblasts was observed at 1000 mg/kg; however, no abnormalities were noted in clinical and macroscopic observation of the incisors. In the liver, hypertrophy of centrilobular hepatocytes was observed at ≥100 mg/kg, accompanied by liver enlargement at ≥100 mg/kg and increased liver weight in males at ≥100 mg/kg and females at ≥20 mg/kg. In this study, the determination of hepatic drug metabolizing enzyme activities revealed increases in aminopyrine N-demethylase and 7-ethoxyresorufin O-deethylase activity in males at ≥100 mg/kg (up to +154%) and females at ≥20 mg/kg (up to +234%) and in p-nitrophenol UDP-glucuronosyltransferase activity at ≥100 mg/kg (up to +293%). Therefore, findings in the liver were considered to be caused by hepatic drug-metabolizing enzyme induction, an adaptive and non-adverse change. In the adrenal gland, increased diffuse vacuolation in the cortex was observed in males at ≥100 mg/kg and females at 1000 mg/kg. In the ovary, interstitial cell vacuolation was noted at ≥100 mg/kg. The vacuolation in these organs was considered non-adverse because the changes were minimal, not cytotoxic, and were not accompanied by organ weight changes. Inflammation of the interstitial gland of the ovary (found in 1 animal at 1000 mg/kg/day in the preceding 2-week rat study and considered adverse) was not observed in the present study. Therefore, the NOAEL was 1000 mg/kg for both males and females.

Fluoride released from oveporexton via metabolism was detected in rat plasma. The mean plasma fluoride C_{max} and AUC_{24h} increased in a less than dose-proportional manner and were comparable between both sexes.

Table 25. Mean Plasma Fluoride Parameters Following 4-Week Oral Administration of Oveporexton to Rats

	Male		Female	
Dose (mg/kg)	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)
	Day 28			
0	NC [a]	NC [a]	22.2	11.1
20	116.7	1882.0	104.7	1652.2
100	417.3	5086.9	299.3	4439.4
1000	1793.3	30,953.7	1980.0	40,737.7

Source: B-8713.

AUC_{24}: area under the concentration-time curve from time 0 to 24 hours; C_{max}: maximum observed concentration; MC: methylcellulose; NC: not calculated; t_{max}: time of first occurrence of C_{max}.

n = 2/sex for 0 mg/kg and 3/sex for oveporexton groups. The vehicle was 0.5% (w/v) MC.

[a] Values were not calculated because the plasma fluoride was detected only at 1 timepoint for 1 male (predose).

Monkeys

A single-dose non-GLP toxicity study was conducted in monkeys (Study No. 19-340/ac) assessing single escalating doses of 0, (0.5% [w/v] methylcellulose (MC) solution), 100, 300, and 1000 mg/kg by oral gavage, to inform dose selection for repeat-dose toxicity studies. Based on the following findings at 1000 mg/kg, the high dose for the subsequent repeat dose was capped at 300 mg/kg: vomiting in all animals at 1000 mg/kg which could potentially impact animal health with repeated doses and delayed t_{max} at 24 h post-dose suggesting a potential increase in systemic exposure by repeated dosing. Together, these results indicated

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that administration of oveporexton at 1000 mg/kg in monkeys was not tolerable for repeat-dose toxicity studies.

In a 2-week repeat-dose non-GLP-compliant toxicity study in monkeys (Study No. N-2316) oral gavage doses of 0, (0.5% [w/v] MC solution), 30, 100, and 300 mg/kg were evaluated to assess the potential toxicity and toxicokinetic profile of oveporexton, including determination of plasma fluoride concentrations. Toxicity was limited to a single incidence of vomiting in one HD female on Day 1, and non-adverse increases in white blood cell, neutrophil and/or monocyte counts, and in triglycerides at 300 mg/kg without any related microscopic findings. Increased liver weights with minimal hypertrophy of hepatocytes and/or macroscopically enlarged liver were observed in 1 male at 100 mg/kg and in all animals at 300 mg/kg. The morphological characteristics of microscopic findings in the liver were compatible with hepatic drug-metabolizing enzyme induction and were considered adaptive and non-adverse.

In the 4-week repeat-dose GLP-compliant toxicity study in monkeys (Study No. B-8714), doses of 0, (0.5% [w/v] MC solution), 30, 100, and 300 mg/kg were evaluated, including determination of plasma fluoride concentrations. A similar toxicity profile was observed in the 4-week study as compared to the subsequent 13- and 26-week studies. The main findings included changes in hematology and/or clinical chemistry parameters at ≥30 mg/kg and microscopic findings in the liver. The observation of minimal hepatocyte hypertrophy in males at ≥100 mg/kg and in females at 300 mg/kg was determined to be associated with a hepatic drug-metabolizing enzyme induction: increases in 7-ethoxyresorufin O-deethylase at ≥30 mg/kg in males (up to +136% versus control), in aminopyrine N-demethylase at 300 mg/kg in males (+59% versus control) and at ≥100 mg/kg in females (+57% and +61% versus control) , and in p-nitrophenol UDP-glucuronosyltransferase activity at 300 mg/kg in males (+35%) and at ≥30 mg/kg in females (up to +30%). Therefore, similar to rats, the microscopic findings in the liver were considered to be non-adverse adaptive changes. The NOAEL for both the 2-week and 4-week monkey studies was the HD of 300 mg/kg/day for males and females.

Fluoride released from oveporexton via metabolism was detected in monkey plasma. The mean C_{max} and AUC_{24h} for plasma fluoride increased in a less than dose-proportional manner for both sexes. No clear sex-related differences in fluoride C_{max} or AUC_{24h} were observed at any dose.

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Table 26. Mean Plasma Fluoride Parameters Following 4-Week Oral Administration of Oveporexton to Monkeys

	Male		Female	
Dose (mg/kg)	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)	C_{max} (ng/mL)	AUC_{24} (h*ng/mL)
		Day 28		
0	54.0	113.2	NC [a]	NC [a]
30	227.5	2999.4	268.7	3499.3
100	358.0	4824.7	446.7	5554.7
300	443.3	6092.4	620.0	10,173.5

Source: B-8714.

AUC_{24}: area under the concentration-time curve from time 0 to 24 hours; C_{max}: maximum observed concentrati
MC: methylcellulose; NC: not calculated; t_{max}: time to first occurrence of C_{max}.

n = 3/sex/group. The vehicle was 0.5% (w/v) MC.

[a] Values were not calculated because the plasma fluoride was detected postdose only in 1 female.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study Title/Number: Bacterial Reversion Assay of TAK-861/T-3244

Key Study Findings

There was no increase in the mean number of revertant colonies for all tester strains and all drug concentrations, both with and without metabolic activation (S9), compared to the respective negative control. Therefore, the study was negative, and TAK-861 is considered non-mutagenic under the conditions of this assay.

GLP compliance: Yes

Test system: Bacterial strains *S. typhimurium* TA100, TA1535, TA98, TA1537, *E. coli* WP2 uvr A

Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study Title/Number: In Vitro Micronucleus Test of TAK-861 in TK6 Cells/T-G492

Key Study Findings

There was a statistically significant increase in the frequency of micronucleated cells at the highest concentration tested of 60.0 µg/mL compared to the negative control for the 24-hour continuous treatment. The mean percent frequency of 1.7% was within the historical control range of 0.45 to 1.85, but outside the average 95% confidence interval of 0.79%. The effect was also concentration dependent. Therefore, it was concluded that chromosomal aberration

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was induced with continuous treatment of 60.0 µg/mL TAK- 861 under the conditions of this assay.

GLP compliance: Yes

Test system: TK6 Cells

Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study Title/Number: Comet-Micronucleus Combination Assay With TAK-861 in Rat/M-1597

Key Study Findings

TAK-861 was negative for both DNA damaging potential (Comet Assay) and clastogenic potential (micronucleus assay) under the conditions of this combination assay. The overall weight of evidence indicates that TAK-861 has no genotoxic potential.

GLP compliance: Yes

Test system: Rat/Sprague-Dawley

Study is valid: Yes

Other Genetic Toxicity Studies

None

5.5.3. Carcinogenicity

Oveporexton was not carcinogenic in two adequately conducted GLP rodent carcinogenicity studies.

26-Week Oral Gavage Carcinogenicity Study in Tg RasH2 Mice (Study B-8968)

Oveporexton was administered once daily for 26 weeks by oral gavage to CByB6F1-Tg (HRAS)2Jic mice (Tg-rasH2 mice) (25/sex/group) at 0 (vehicle control 0.5% [w/v] methylcellulose solution), 6, 20, 60, and 600 mg/kg for males and 0, 3, 30, and 300 mg/kg for females. A positive control group (15/sex) was administered *N*-methyl-*N*-nitrosourea (75 mg/kg, IP). Additional satellite groups of nonTg-rasH2 mice (20 /sex/group) were used to evaluate TK parameters of oveporexton in plasma. The dose selection was based on approximately one-third of the respective lethal doses in a 1-week and 4-week toxicity study in nonTg-rasH2 mice for males and females, respectively (Study No. N-2552 and No. B-8817), in agreement with the recommendation of the Executive Carcinogenicity Assessment Committee (ECAC meeting minutes of June 16, 2022).

There was no drug-related, or statistically significant, increase in tumors in Tg-rasH2 mice at doses up to 600 and 300 mg/kg in males and females, respectively. The nonclinical statistical reviewer's (Dr. Hepei Chen) analysis confirmed that "no statistically significant dose response

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relationship or pairwise comparisons in any tested tumor were noted in either male or female mice. For both male and female mice, the pairwise comparisons between the positive control group and the vehicle control group showed p-values less than 0.05 for many tumors, confirming animal expressed oncogenes and responded to carcinogenic insult as expected."

The ECAC concluded that the mouse carcinogenicity study was adequate and that there was no evidence of drug-related neoplasms in male and female mice in the 6-month study (ECAC meeting minutes of June 2, 2026).

The highest tested doses of 600 and 300 mg/kg in males and females, respectively were associated with a mean C_{max} of 23,400 and 12,500 ng/mL, and a mean AUC_{24h} of 148,000 and 64,100 h*ng/mL, respectively, on Week 26, which is approximately 400-and 173-fold the MRHD, for males and females, respectively, based on AUC.

24-Month Oral Gavage Carcinogenicity Study of TAK-861 in Rats (Study B-8962)

Oveporexton was administered once daily for 24 months by oral gavage to Sprague Dawley rats (60/sex/group) at 0 (vehicle control 0.5% [w/v] methylcellulose solution), 1, 20, and 100 mg/kg for both males and females. Additional satellite groups (8/sex/group) were used to evaluate TK parameters of oveporexton in plasma. The basis for dose selection was AUC ratio with the high dose achieving an AUC ratio greater than 25-fold the clinical exposure, in agreement with the recommendations of the Executive Carcinogenicity Assessment Committee (ECAC meeting minutes of March 3, 2022).

There were no drug-related neoplastic or non-neoplastic changes at any dose level. The nonclinical statistical reviewer's (Dr. Hepei Chen) analysis concluded that a statistically significant increase (p-value=0.0477) was noted in the mid-dose group in the incidence of hepatocellular adenoma in liver of male rats, without a corresponding statistically significant dose response relationship. No other statistically significant dose response relationship or pairwise comparisons were observed in the tumor data for either male or female rats.

The ECAC concluded that the rat carcinogenicity study was adequate and that there was no evidence of drug-related neoplasms in male and female rats in the 2-year study (ECAC meeting minutes of June 2, 2026).

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study Title/Number: Study of TAK-861 for Effects on Fertility and Early Embryo-Fetal Development in Rats/R-1274

Key Study Findings

- Males: No drug-related effect on any fertility parameters. General toxicity at 750 mg/kg: Dental fractures and whitening, lower body weight and food consumption, and enlarged liver compared to control (attributable to induction of hepatic drug-metabolizing enzymes,

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and therefore non-adverse). NOAEL: 100 mg/kg for general toxicity and 750 mg/kg for fertility.

- Females: Lower number of corpora lutea at 750 mg/kg compared to control, in association with decreased numbers of implantations and live embryos. Non-adverse general toxicity findings at 750 mg/kg: slight decrease in body weights and food consumption and enlarged liver compared to control. NOAEL: 750 mg/kg for general toxicity and 100 mg/kg for fertility.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 27. Methods, Study R-1274

Category	Details
Dose and frequency of dosing:	0, 10, 100, 750 mg/kg, once daily (from 6 weeks and 10 weeks of age, in males and females, respectively)
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) Methylcellulose (MC) solution
Species/Strain:	Rat/ Sprague-Dawley
Number/Sex/Group:	20
Satellite groups:	No
Study design:	Dose selection was based on a 13-week oral gavage toxicity study of TAK-861 in rats (Study No. B-8803), at doses of 0, 20, 100, and 1500 mg/kg/day, where mortality (1 HD female) and fluorosis-related changes in the incisors (fractures, whitening, and degeneration of the ameloblasts) were observed in both males and females at 1500 mg/kg/day. In the current study, males were dosed once daily for 9 weeks prior to mating, for 28 days throughout the mating period and up to the day of necropsy, for a total duration of dosing of 91 days. The treated (dosed) males were mated with untreated females in Experiment 1. In Experiment 2, treated (dosed) females were mated with untreated males to evaluate drug effect on the female reproductive function. The dosing period for females was 2 weeks prior to mating, 1 to 14 days during the mating period, and during the gestation up to Gestation Day (GD) 6; for a total duration of dosing of 22 to 35 days. Females were necropsied on GD 14. The following parameters were evaluated: mortality, clinical signs, body weights, food consumption, macroscopic observations, reproductive organ weights (males only), estrous cycle (females), mating, and cesarean section. Toxicokinetics was not evaluated in this study; however similar doses were used in rat general toxicity studies with toxicokinetic evaluations.
Deviation from study protocol affecting interpretation of results:	No

Table 28. Observations and Results, Study R-1274

Parameters	Major Findings
Mortality	None
Clinical Signs	Males: Fracture and whitening of incisors at HD starting from Week 11 of dosing (Day 71) in 4 of 20 HD animals, with incidence increasing with duration of dosing (up to 17 of 20 HD animals by Day 85 and throughout the end of the study).

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Parameters	Major Findings
	Females: No clinical signs were observed. The lack of similar dental findings in females can be explained by the shorter duration of drug treatment in females compared to males.
Body Weights	Lower body weights accompanied by suppressed body weight gain and lower food consumption were observed at HD in both males and females. In HD males, statistically significant decrease in body weights (-8% compared to control) was observed at the end of dosing period. In HD females, the mean body weight on GD 7 (the day after the last dosing) and GD 14 (the day of cesarean section) was 7% and 6% lower compared to controls, respectively, and was statistically significant. There were no drug-related effects on body weights in either sex at MD or LD.
Necropsy findings [Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc]	Males: No drug-related effects occurred in any fertility parameters in drug-treated males. No drug-related effects were observed in any embryofetal development parameters in untreated females mated with drug-treated males. Females: In drug-treated females mated with untreated males, a statistically significant decrease in the number of corpora lutea (-14%) which was associated with decreased numbers of implantations (-19.5%) and live embryos (-21%) was found in the HD group compared to control.

Abbreviations: LD = low dose; MD = mid dose; HD = high dose
Source: Study Report R-1274

Embryo-Fetal Development

Study Title/Number: Study of TAK-861 for Effects on Embryo-Fetal Development in Rats/R-1276

Key Study Findings

- Decrease in maternal body weight at 750 mg/kg compared to control, associated with decreased food consumption. Trend to a decrease in fetal weight and ossification of fetal metatarsal bones at 750 mg/kg, finding was secondary to the lower maternal body weight and considered non-adverse.
- NOAEL for maternal toxicity: 100 mg/kg based on a decrease in maternal body weight at 750 mg/kg; NOAEL for embryo-fetal development: 750 mg/kg.
- Maternal exposure to oveporexton at the NOAEL for maternal toxicity (100 mg/kg): 8580 ng/mL for C_{max} and 128,000 for AUC_{24h}; and at the NOAEL for embryo-fetal toxicity (750 mg/kg):24,900 ng/mL for C_{max} and 431,000 h*ng/mL for AUC_{24h} on GD 17.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 29. Methods, Study R-1276

Category	Details
Dose and frequency of dosing:	0, 10, 100, and 750 mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) methylcellulose solution

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Category	Details
Species/Strain:	Rat/ Sprague Dawley
Number/Sex/Group:	20 pregnant females (18 in control)
Satellite groups:	TK satellite groups (additional 4 dams/group)
Study design:	Dose selection was based on a 13-week oral gavage toxicity study of TAK-861 in rats (Study No. B-8803, at doses of 0, 20, 100, and 1500 mg/kg/day), where mortality (1 HD female) and fluorosis-related dental fractures were observed at 1500 mg/kg/day, and on the preliminary embryofetal development study in rats (Study No.R-1267 at doses of 0, 10, 100, and 1000 mg/kg/day), where low body weights in dams, associated with decreased food consumption and fetal growth inhibition, were observed at 1000 mg/kg. Therefore, in the present study, the high dose was selected at 750 mg/kg/day, half of the lethal dose of 1500 mg/kg, and the mid and low doses were 100 and 10 mg/kg/day, respectively. The dams were dosed during the period of organogenesis from Gestation Day (GD) 6 to 17, then sacrificed and necropsied on GD 20. Note: Two females in the vehicle control group were found to be non-pregnant and were excluded from the evaluation. TK assessments (C_{max} and AUC_{24h}) were performed on GDs 6 and 17 in additional satellite animals.
Deviation from study protocol affecting interpretation of results:	No

Table 30. Observations and Results, Study R-1276

Parameters	Major Findings
Mortality	None
Clinical Signs	None observed
Body Weights	Statistically significant decrease in maternal body weight (up to -14%) and suppressed body weight gain accompanied by decreased food consumption was observed at HD compared to control from GD 8 to the end of the study (GD 20). At MD, decreased body weight compared to control was observed from GDs 8 to 14 secondary to decreased food consumption; at LD, suppressed body weight gain was observed only in the early phase of dosing (GD 6 to 8); however, these changes in mid- and low dose groups were non-adverse because they were transient and/or slight.
Necropsy findings	Maternal liver enlargement at HD in 9 of 20 dams (non-adverse adaptive change due to the induction of hepatic drug metabolizing enzymes).
Necropsy findings Cesarean Section Data Offspring	Fetal weights tended to decrease at HD compared to control, secondary to decreased maternal food consumption and lower maternal body weight. The changes did not reach statistical significance, and the group mean was slightly lower than the historical control data at the test facility, therefore the findings were considered non-adverse. Ossification of fetal metatarsal bones tended to decrease at HD, secondary to the decrease in maternal body weight at this dose, but the effect was minimal and considered non-adverse. An increased incidence of fetal umbilical artery transposition was noted at HD [7.2%, significantly higher than that in the control group (0%) as well as in the historical control (2.1%)]. The Applicant considered the finding to be non-adverse because this variation has been reported as spontaneously occurring in this strain of rats without affecting postnatal viability (Kuwagata et al., 2019) and no abnormalities were noted in any other blood vessels. The Applicant's conclusion that the finding is non-adverse is acceptable because there were no other correlating adverse toxicities observed in HD fetuses, but the finding is considered drug related.

Abbreviations: LD = low dose; MD = mid dose; HD = high dose
Source: Study Report R-1276

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Study Title/Number: Study of TAK-861 for Effects on Embryo-Fetal Development in Rabbits/ R-1275

Key Study Findings:

- Decrease in maternal body weight (-6%) and weight gain (-100%) at 100 mg/kg compared to control, associated with decreased food consumption (up to -67% compared to control). Lack of adverse embryo/fetal effects at any dose.
- NOAEL for maternal toxicity: 20 mg/kg based on a decrease in maternal body weight, weight gain and food consumption at 100 mg/kg; NOAEL for embryofetal development: 100 mg/kg.
- Maternal exposure to oveporexton at the NOAEL for maternal toxicity (20 mg/kg) was 1500 ng/mL for C_{max} and 13,900 h*ng/mL for AUC_{24h}; and at the NOAEL for embryofetal toxicity (100 mg/kg) it was 4770 ng/mL for C_{max} and 56,600 h*ng/mL for AUC_{24h} on GD 20.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 31. Methods, Study R-1275

Category	Details
Dose and frequency of dosing:	0, 4, 20, and 100 mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) methylcellulose solution
Species/Strain:	Rabbit/New Zealand White
Number/Sex/Group:	23 (in control and MD), 22 (in HD and LD)
Satellite groups:	TK satellite groups (additional 5 pregnant animals/group)
Study design:	Dose selection was based on a preliminary embryofetal development study in rabbits (Study No. R-1268), at oveporexton oral doses of 0, 10, 30, and 100 mg/kg/day from GDs 7 to 20, with a NOAEL of 30 mg/kg for does and 100 mg/kg for embryo-fetal development, based on decreased maternal body weights at HD and absence of adverse embryofetal findings at any dose level. In the current study, pregnant females were dosed during the period of organogenesis, from Gestation Day (GD) 7 to GD 20. TK assessments of plasma C_{max} and AUC_{24h} of TAK-861 and metabolite M4 were performed on GDs 7 and 20 in additional 5 TK animals /group. *Note*: While metabolite M4 was not a major human metabolite, its TK values were collected proactively by the Applicant and are submitted for completeness.
Deviation from study protocol affecting interpretation of results:	No

Table 32. Observations and Results, Study R-1275

Parameters	Major Findings
Mortality	None
Clinical Signs	None observed

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Parameters	Major Findings
Body Weights	Decrease in total weight gain at HD over the entire dosing period (-100% compared to control), associated with a decrease in food consumption (up to -67% compared to control). At LD and MD, maternal weight gain was transiently decreased in the early dosing period in association with reduced food consumption; however, these findings were non-adverse because they were minimal and/or transient, limited to the early phase of dosing, and fully reversible upon dosing cessation. Body weight gain increased compared to controls in all dose groups during GD 21 to 28 in correlating with an increase in food consumption.
Necropsy findings Cesarean Section Data	There were no drug-related changes in placental or uterine weights in any dose group compared to control. There were no drug-related effects on the number of resorptions, post-implantation loss, number of live fetuses, or sex ratio at any dose. *Note:* A statistically significant lower mean number of fetuses at HD compared to control was not drug related because it was due to the lower mean number of corpora lutea in this group which is not drug- related, because the number of corpora lutea is fixed at the time of ovulation, before the start of dosing.
Necropsy findings Offspring	There were no drug-related external, visceral or skeletal malformations in any group. At HD, increased incidences of a visceral variation (absent accessory lung lobe), and of a skeletal variation (27th presacral vertebra) were noted. These variations are commonly observed in rabbits and are considered non-adverse. There were no drug-related effects on skeletal ossification.

Abbreviations: LD = low dose; MD = mid dose; HD = high dose
Source: Study Report R-1275

Prenatal and Postnatal Development

Study Title/Number: Study of TAK-861 on Pre- and Postnatal Development, Including Maternal Function in Rats/R-1305

Key Study Findings

- Administration of oveporexton at oral doses of 0, 1, 3, and 10 mg/kg to female rats during gestation, parturition and lactation through weaning, did not result in drug-related adverse maternal effects, or effects on the conceptus and postnatal morphological, neurobehavioral, functional, and reproductive development of the generation.
- NOAEL was the high dose of 10 mg/kg for both maternal toxicity and for offspring pre- and postnatal development and reproductive function.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 33. Methods, Study R-1305

Category	Details
Dose and frequency of dosing:	0, 1, 3, and 10 mg/kg, once daily (from GD 6 to postnatal lactation Day 20)
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) methylcellulose solution

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Category	Details
Species/Strain:	Rat/ Sprague Dawley
Number/Sex/Group:	20
Satellite groups:	No
Study design:	Dose selection was based on the definitive embryo-fetal development study in rats (Study No. R-1276), at oveporexton oral doses of 0, 10, 100, and 750 mg/kg/day, with a NOAEL of 100 mg/kg/day for maternal toxicity (low body weight). In the present study, the high dose was set at 10 mg/kg, which the Applicant stated was expected to provide sufficient systemic exposure compared to the maximum anticipated clinical exposure. Pregnant F0 females were dosed from gestation day (GD) 7 through postnatal Lactation Day (LD) 20, corresponding to the period from implantation to weaning. Animals were allowed to rear their progeny until LD 21 and were euthanized on LD 21. Assessments of F1 generation pups included: viability, clinical signs, body weights, external anomalies, physical development, reflex function, behavior (open field and water T-maze tests), sexual maturation, reproductive function, and macroscopic evaluation of the next F2 generation. After the observations and measurements on Postnatal Day (PND) 4, F1 litter size was adjusted to 8 animals per litter (4 males and 4 females, where possible). On PND 21, 2 male and 2 female offspring were selected randomly from each litter for observation after weaning. The rest of the offspring were euthanized. F1 reproductive function tests were performed for 1 male and 1 female in each litter. At 11 to 12 weeks of age, F1 males and females in the same group were housed together on one-to- one basis avoiding sibling mating. For F1 females that had successful copulation, body weight gain (GD 0 to 14) was determined, and they were euthanized on GD 14. The major organs/tissues in the thoracic and abdominal cavities were assessed macroscopically, and the numbers of corpora lutea, implantations, live and dead F2 embryos, and external abnormalities were determined. Toxicokinetics was not evaluated in this study.
Deviation from study protocol affecting interpretation of results:	No

Table 34. Observations and Results, Study R-1305

Generation	Major Findings
F0 Dams	Increased food consumption (up to 9%) was observed during the lactation period at all doses; the changes were small, transient and had no effect on body weights. There were no drug-related clinical signs and no effects on maternal body weight, no macroscopic findings at necropsy, and no effects on reproductive function, including the gestation period duration, gestation index, birth index, number of implantations, live and dead newborns and sex ratio.
F1 Generation	Increased F1 body weights compared to controls were observed during the late lactation period at MD and HD (up to 7% and 8% in males and females, respectively), that correlated with the increase in maternal F0 food consumption during the lactation period; however, they were considered non-adverse because the changes were small and there were no effects on any other examination endpoints. At all dose levels, the vaginal opening indices on Postnatal Day (PND) 35 were lower than control (60 to 60.5% in all drug-treated groups vs. 84% in control). However, this delay was considered non-adverse since vaginal opening was 100% completed in all animals on PND 42 (which is generally considered the time of sexual maturation completion in rats), and there were no abnormalities in F1 reproductive function.

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Generation	Major Findings
	There were no drug-related mortalities, clinical signs, or external anomalies, nor adverse changes in physical development landmarks, reflex development, behavioral functional tests (open field test or multiple water T-maze test), or reproductive capacity tests (reproductive performance and cesarean section data of F1 animals during mid-gestation), and no gross macroscopic findings.

Juvenile Toxicity

Study Title/Number: A 6-Week Repeated Oral Gavage Toxicity Study of TAK-861 in 28-day old Rats with a 4-Week Recovery Period/SBL010-561

Key Study Findings

- Drug-related changes in clinical pathology at ≥10 mg/kg: decreases in erythrocyte count, hemoglobin, hematocrit, and mean corpuscular hemoglobin concentration in females at ≥10 mg/kg, decrease in total bilirubin in both sexes at ≥10 mg/kg, and increase in gamma-glutamyl transferase in females at 50 mg/kg. These changes were non-adverse because they were minimal, recovered following the 4-week recovery period and/or were not associated with histopathological findings.
- Drug-related microscopic findings in the liver in females at 50 mg/kg: slight hypertrophy of centrilobular hepatocytes at the end of dosing period, accompanied by increased liver weight in both sexes at 50 mg/kg. These findings recovered following the 4-week recovery period and were non-adverse as they were attributable to induction of hepatic drug-metabolizing enzymes and similar to findings in adult rats.
- NOAEL: 50 mg/kg for both sexes, associated with a mean C_{max} of 5,450 and 6,130 ng/mL and a mean AUC_{24h} of 70,800 and 82,000 h*ng/mL in males and females, respectively

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 35. Methods, Study SBL010-561

Category	Details
Dose and frequency of dosing:	0, 2, 10, and 50 mg/kg/ once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% [w/v] Methylcellulose (MC) solution
Species/Strain:	Rat/ Sprague-Dawley
Number/Sex/Group:	26 (10 terminal +16 recovery)
Age:	28 days
Period of development studied:	From weaning through sexual maturity (dosing from postnatal day (PND) 28 for a total of 6 weeks followed by a 4-week recovery period)
Satellite groups/ unique design:	TK satellite: 6 (control) and 12 (TAK-861) groups

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Category	Details
Study design	The dose selection was based on a preliminary 2-week oral gavage toxicity study of TAK-861 in juvenile 28-day old rats (Study No. SBL010-546) at dose levels of 10, 100, and 750 mg/kg, and a NOAEL of 750 mg/kg/day, with systemic plasma exposure equivalent to that of adult rats. In the present study, the high dose was set at 50 mg/kg, expected to provide sufficient systemic exposure compared to the maximum clinical exposure, and the mid- and low-dose levels were set at 10 and 2 mg/kg, respectively. *Note:* the current indication is for adults. Assessments included: mortality, clinical observations, body weight, food consumption, ophthalmology, auditory startle response, memory and learning, locomotor activity, morphological development of external genitalia, estrous cycle, clinical pathology, anatomic pathology (macroscopic and histopathology), organ weights, and bone length and density.
Deviation from study protocol affecting interpretation of results:	No

Table 36. Observations and Results: Changes From Control, Study SBL010-561

Parameters	Major Findings
Mortality	None
Body Weights	No drug-related findings
Food consumption	No drug-related findings
Ophthalmoscopy	No drug-related findings
Hematology	Drug-related decreases in erythrocyte count, hemoglobin, hematocrit, and mean corpuscular hemoglobin concentration (RBC, HGB, HCT, and MCHC) were found in females at ≥10 mg/kg at the end of the dosing period. Although these findings were drug-related, they were not adverse because the change was minimal compared to controls and effects were reversible following the 4-week recovery period.
Clinical Chemistry	Drug-related decrease in total bilirubin (T-Bil) in both sexes at ≥10 mg/kg and increased gamma glutamyl transferase (GGT) in females at 50 mg/kg occurred at the end of the dosing period. However, these changes were not adverse because they were not associated with any corresponding histopathological changes. Additionally, the effects on T-Bil were reversible following the 4-week recovery period. The increase in GGT for females was partially reversible at 50 mg/kg/day (GGT at the end of recovery period 2-fold lower compared to GGT value at the end of the dosing period, but still significantly higher compared to control).

Table 37. Drug-Related Hematology Changes (End of Dosing Period) JAS Study

Sex	Male				Female			
Dose (mg/kg)	0[a]	2	10	50	0[a]	2	10	50
No. of animals	10	10	10	10	10	10	10	10
RBC (10^6/μL)	/	/	/	/	8.029	7.843 (-2.3%)	7.666W$ (-4.5%)	7.550W$ (-6.0%)
HGB (g/dL)	/	/	/	/	15.88	15.51 (-2.3%)	15.15W$ (-4.6%)	14.83W$ (-6.6%)
HCT (%)	/	/	/	/	44.16	43.44 (-1.6%)	42.80W$ (-3.1%)	42.42W$ (-3.9%)
MCHC (g/dL)	/	/	/	/	35.96	35.70 (-0.7%)	35.39W$ (-1.6%)	34.96W$ (-2.8%)

Values in the table indicate group mean, and values in parentheses indicate the percentage of change against the control mean (+: high, −: low).
W: P≤0.05: Significantly different from the vehicle control by the Williams test.
$: TAK-861-related changes. /: No TAK-861-related changes.
[a] vehicle control: 0.5 w/v% MC solution.
Source: Study Report SBL010-561, Text table 25, p. 43

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Parameters	Major Findings

Table 38. Drug-Related Clinical Chemistry Changes (End of Dosing Period) JAS Study

Sex	Male				Female			
Dose (mg/kg)	0[a]	2	10	50	0[a]	2	10	50
No. of animals	10	10	10	10	10	10	10	10
T-Bil (mg/dL)	0.035	0.026 (-25.7%)	0.013W$ (-62.9%)	0.006W$ (-82.9%)	0.052	0.057 (+9.6%)	0.042W$ (-19.2%)	0.021W$ (-59.6%)
GGT (IU/L)	/	/	/	/	0.3	0.1 (-66.7%)	0.4 (+33.3%)	1.3W$ (+333%)

Values in the table indicate group mean, and values in parentheses indicate the percentage of change against the control mean (+: high, −: low).
W: P<0.05: Significantly different from the vehicle control by the Williams test.
$: TAK-861-related changes. /: No TAK-861-related changes.
[a] vehicle control: 0.5 w/v% MC solution.

Source: Study Report SBL010-561, Text table 26, p. 44

Urinalysis	Not performed
Sexual Maturation	No drug-related changes were noted in morphological development of external genitalia as assessed by the timing of cleavage of the balano-preputial gland in males and in vaginal opening in females. No changes in estrous cycle (as assessed by the frequency of estrus and number of days of estrous cycle) were found at any dose level during the dosing or recovery period.
Reproductive Capacity	Not assessed
CNS/ Neurobehavioral Assessment	No drug-related changes in reactivity (auditory startle response) and locomotor activity (during the dosing period (9 weeks after birth) and recovery period (13 weeks after birth), or learning and memory capacity [(Biel Water Maze test during the dosing period (8 weeks after birth) and recovery period (12 weeks after birth)] were found at any dose level during the dosing or recovery period. Note: A transient decrease in locomotor activity was noted at 9 weeks of age in males and females at 50 mg/kg compared to control and an increase in locomotor activity was noted in females at 10 mg/kg during the recovery period (13 weeks of age); however, these changes were either non-adverse or not drug related as they were temporary and/or not dose dependent.
Gross Pathology	No drug-related findings
Organ Weights	Drug-related increases in liver weights occurred in both sexes at 10 and 50 mg/kg (up to 10% and 22% higher than controls in males and females, respectively) at the end of the dosing period. These effects correlated with microscopic findings in the liver and were reversible following the 4-week recovery period.
Bone Evaluation	Bone Length There were no changes in bone length at the end of the dosing period. Bone Density At the end of the dosing period, statistically significant increases in bone density of the proximal femur at ≥10 mg/kg and distal femur at 50 mg/kg were found in males; however, these changes were not adverse because they were minimal and there were no statistically significant changes in bone mineral density of the total femur. At the end of the recovery period, statistically significant increase in bone mineral density of the total and proximal femur was found in females at 50 mg/kg; however, these changes were not adverse because the magnitude of effect was minimal, and individual values were within the control group range.
Histopathology Adequate battery: Yes	Slight hypertrophy of the centrilobular hepatocytes was observed in 2 of 10 females at 50 mg/kg at the end of the dosing period, correlating with increased liver weight (both reversible after recovery period). This finding has also been observed in adult rats, in the 4, 13-, and 26-week oral gavage toxicity studies (Studies No. B-8713, B-8803, and B-8933, respectively), as well as in the 2-week oral gavage dose range-finding toxicity study in juvenile rats (Study No. SBL010-546). Similar to

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Parameters	Major Findings
	adult rats, these effects are attributable to induction of drug-metabolizing enzymes in the liver and therefore considered non-adverse.

Abbreviations: LD = low dose; MD = mid dose; HD = high dose.
Source: Study Report SBL010-561

5.5.5. Other Toxicology Studies

Study Title/Number: UV-Visible Absorbance Measurement for Photosafety

Evaluation of TAK-861/ A-3186

Key Study Findings

- TAK-861 evaluation for UV-visible absorption (range between 290 and 700 nm) demonstrated that molar extinction coefficients of TAK-861 were 664 and 605 L/mol/com, below the threshold of 1000 L/mol/cm, for determining photochemical properties set in the guideline for photosafety evaluation of pharmaceuticals (ICH S10). Therefore, TAK-861 has no significant potential for direct phototoxicity.

GLP compliance: Yes

Several additional other toxicity studies were conducted as supplemental/supportive information but were not relied upon for regulatory decision making. See full reviews of those studies archived under IND 154232.

Safety Assessment of Non-Mutagenic Impurities

During the review, the CMC team requested nonclinical to conduct safety evaluations of four impurities, (b) (4) in the drug substance. The proposed specification limit is (b) (4) for (b) (4) respectively. The Applicant conducted in silico quantitative structure-activity relationship ((Q)SAR, Ultra Case and DEREK NEXUS) and concluded that all four impurities belong to (b) (4) has been tested negative in an adequate battery of genotoxicity assays. Therefore, the Applicant proposes that all of the above listed impurities are non-mutagenic. The Agency conducted an independent (Q)SAR analysis and agreed with the Applicant's conclusion that these impurities can be controlled as non-mutagenic impurities (see Table 39 below).

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Table 39. Summary (Q)SAR Bacterial Mutagenicity Predictions by the Applicant's and Agency's Independent Analyses

No.	Chemical Name	Applicant's Bacterial Mutagenicity Overall Prediction[1]	Agency's Bacterial Mutagenicity Expert Prediction[1]
1	(b) (4)	-	-
2		-	-
3		-	-
4		-	-

[1] - = negative.

For impurity (b) (4) the proposed specification limits do not exceed the qualification threshold per ICH Q3A. Therefore, no additional nonclinical studies or data are needed to qualify (b) (4) For impurities (b) (4) the Applicant proposed to rely on the nonclinical batches 28120J and 001121-028-10, which were used in the 13-week rat (Study no. B-8803) and 4-week monkey (Study no. B-8714) toxicology studies to qualify (b) (4) respectively. (b) (4) was present at the level of (b) (4) % in Batch 28210J and (b) (4) was present at the level of (b) (4) % in Batch 001121-028-10. At the NOAELs from the 13-week and 4-week toxicology studies, after adjustment with a 10-fold safety factor to account for difference in nonclinical study duration and the proposed chronic indication of oveporexton, the corresponding (b) (4) levels provide support for up to (b) (4) % in the drug substance at the maximum recommended human dose (MRHD) of 4 mg (as shown in Table 40 below). Therefore, existing nonclinical data provide adequate safety support for (b) (4) at the proposed specification limits and no additional nonclinical studies are needed.

(b) (4)

6 Clinical Pharmacology

6.1. Executive Summary

Takeda Pharmaceuticals U.S.A., Inc. (Takeda) is seeking approval of oveporexton immediate-release tablets for the treatment of NT1 in adults. The proposed tablet strengths are 0.5 mg, 1 mg, and 2 mg, with the recommended dosage of 1 mg or 2 mg orally twice daily (the first dose after awakening and second dose 3 to 5 hours later). The recommended maximum total daily dosage is 4 mg. Orexin 2 receptor agonism is thought to be the mechanism responsible for oveporexton-mediated wakefulness effects in patients with NT1.

The clinical pharmacology program in this submission included single and multiple ascending dose safety and pharmacokinetic (PK) studies, dedicated food effect study, mass-balance study, QT assessment report, drug-drug interaction (DDI) studies, and organ impairment studies (effects of mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment (HI), and severe renal impairment (RI; estimated glomerular filtration rate (eGFR) <30 mL/min) on the PK of oveporexton). A relative bioavailability study (rBA) was conducted to bridge two early phase formulations (T1 and T2 formulation) while the to-be-marketed formulation (T3 formulation) was bridged to T2 formulation via population pharmacokinetic (PK) model-based approach. T3 formulation was used in the two pivotal phase 3 safety and efficacy studies, confirmatory food effect study and organ impairment studies. Population PK and exposure-response (ER) analyses were conducted to characterize the relationship between systemic exposures and efficacy/safety response of oveporexton.

Following oral administration, oveporexton showed dose-proportional PK characteristics over the dose range of 1 to 75 mg. The rBA study and the popPK model-based bridging showed that the exposures following T1, T2, and T3 formulations are comparable. With twice daily (BID) dosing, steady state is achieved within approximately five days, with an accumulation ratio of approximately 1.6. High-fat meal did not appreciably affect the PK of oveporexton. Oveporexton is primarily metabolized by CYP3A4. The human mass balance study findings suggest that oveporexton was the major moiety in the circulation and it accounts for approximately 60% of total circulating moieties. The metabolites, M4 and M30, each account for approximately 5% of total moieties in the circulation. Of the administered dose, approximately 11% was recovered in urine (0.1% as unchanged oveporexton) and 80.5% excreted in feces. No clinically relevant QT prolongation effects were observed with concentration up to 16 times of the mean peak plasma concentration (C_{max}) at steady state for the maximum recommended dosage. Concomitant administration with strong CYP3A4 inhibitor increased oveporexton area under the plasma concentration-time curve (AUC_{∞}) by 7.4-fold. Therefore, concomitant use of oveporexton with strong CYP3A4 inhibitors is contraindicated. Concomitant administration with moderate CYP3A4 inhibitor increased oveporexton AUC_{∞} by 2.9-fold. Dosage reduction of oveporexton (i.e., 0.5 mg BID, with a maximum total daily dose of 1 mg) is recommended when concomitantly administered with moderate CYP3A4 inhibitors.

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The dedicated PK trials and population PK analysis showed that exposures to oveporexton were not appreciably increased in patients with mild (Child-Pugh Class A) and moderate (Child-Pugh B) HI or patients with severe RI (eGFR <30 mL/min) compared to participants with normal hepatic and renal function. Exposure-response analyses suggest that the probability of insomnia, urinary events, and micturition urgency increased with increasing exposures. However, the probabilities to have insomnia, urinary events, and micturition urgency in patients with HI (mild to moderate) or RI (moderate to severe) were largely within the range of those in patients with normal hepatic and renal function. As a result, the effect of HI and RI were not considered clinically significant, and no dosage adjustment is required for these conditions. A post-marketing requirement (PMR) study is recommended to evaluate the effect of severe HI (Child-Pugh C) on the PK of oveporexton.

The Office of Clinical Pharmacology (OCP) finds that the clinical pharmacology data are sufficient to support the safety and efficacy of oveporexton immediate-release tablets and recommends approval of oveporexton 0.5 mg, 1 mg, and 2 mg immediate-release tablets for the treatment of narcolepsy type 1 in adults.

6.2. Summary of Clinical Pharmacology Assessment

In the development program of oveporexton, three types of formulations were used. These include immediate-release (IR) formulations (T1 [phase 1 tablets], T2 [phase 2 tablets], and T3 [phase 3 tablets]). However, the to-be marketed formulation of oveporexton is different from the clinical trial formulations. T3 formulation was used in both pivotal safety and efficacy studies (TAK-861-3001 and TAK-861-3002), food effect study (TAK-861-1010), and hepatic and renal impairment studies (TAK-861-1004 and TAK-861-1005). Because the core tablet composition of the to-be-marketed is same as that of the T3 formulation, the Applicant demonstrated a bridge between the to-be-marketed formulation and T3 formulation using in vitro dissolution study. The results from the in vitro dissolution suggest that the bridge between the formulations is adequate (refer to the integrated Office of Product Quality review for additional information).

T2 formulation was used in the phase 2 dose ranging study (TAK-861-201) and clinical DDI study (TAK-861-1007) and the T1 formulation was used in the early phase PK and tolerability studies. A comparative bioavailability study (TAK-861-1007) was conducted to establish the PK bridge between T1 and T2 formulations, and a population PK (popPK) model-based approach was used to establish a PK bridge between T2 and T3 formulations along with the results of an in vitro dissolution study. Overall, although this is not pivotal (T3 was used in phase 3 trials), the PK bridging among T1, T2, and T3 formulations is deemed to be adequate.

The proposed dosage regimens (1 mg or 2 mg orally twice daily) are acceptable based on the demonstration of favorable efficacy compared to placebo and acceptable safety results from the two pivotal phase 3 trials (TAK-861-3001 and TAK-861-3002).

The effect of food on the PK of oveporexton was evaluated using T3 formulation at the highest strength (2 mg T3 tablet) in Study TAK-861-1010. Administration with high-fat meal delayed the time to reach peak plasma concentration (T_{max}) of oveporexton for 1.5 hours but

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did not appreciably change the exposures (C_{max}, AUC_{last}, and AUC_{inf}) of oveporexton when compared to administration under fasted conditions. Therefore, the product can be taken with or without food.

Oveporexton did not have any clinically significant effect on the QT interval with concentration up to 11 times of the peak plasma concentration at steady state ($C_{max,ss}$) for the maximum recommended dosage (2 mg BID). No thorough QT study was conducted as a waiver request for a thorough QT study was granted by the Agency based on the results of clinical QT assessment in Study TAK-861-1001. The results of concentration-QTc analysis suggest that the risk of QTc prolongation effects of oveporexton is low.

Positive exposure-safety relationships were identified for the most common adverse events (insomnia, urinary events, and micturition urgency) and the overall percentage of events are comparable between 1 mg BID and 2 mg BID based on the pooled data from the two pivotal phase 3 studies.

The effect of HI on oveporexton PK was evaluated in a dedicated study (TAK-861-1004) in patients with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) HI and population PK analysis. In participants with mild HI, total oveporexton AUC_{∞} was 28% higher and C_{max} was 17% higher compared to participants with normal hepatic function. In participants with moderate HI, AUC_{∞} was 23% higher and C_{max} was 15% lower compared to controls. The population PK analysis, which included 10 participants with moderate hepatic, showed that mild or moderate HI increased median $C_{avg,ss}$ by up to 43%. The effect of severe HI (Child-Pugh Class C) was not studied. Based on the exposure-response analysis for safety, these elevated exposures caused by mild and moderate HI are not expected to result in clinically meaningful risks (See Section 16.4.4 Pharmacometrics Assessment for additional information), and no dosage adjustment is required. A post-marketing requirement (PMR) to evaluate the effect of severe HI (Child-Pugh Class C) on oveporexton PK is recommended to determine whether there is a need to adjust the dosage for the safe use of oveporexton in patients with severe HI.

The effect of RI on the PK of oveporexton was evaluated in a reduced design study (TAK-861-1005) in patients with severe RI (estimated glomerular filtration rate [eGFR] ≥15 to <30 mL/min; not requiring dialysis) and through population PK analysis. In participants with severe RI, oveporexton AUC_{∞} was 45% higher, AUC_t was 35% higher, and C_{max} was 16% lower compared to matched participants with normal renal function (eGFR 90 mL/min or greater). The population PK analysis included participants across a broader range of renal function: 83 with mild RI, 4 with moderate RI, 10 with severe RI, and 397 with normal renal function. The results suggest that moderate to severe RI increased $C_{avg,ss}$ by up to 49%. The mild RI had no effect, and moderate-to-severe RI had minimal effects on the clearance of oveporexton. These findings are consistent with the minimal role of renal elimination in oveporexton clearance, as renal clearance accounts for only approximately 11% of total elimination, with less than 1% of the dose excreted as unchanged drug in urine. Based on the exposure-response analysis for safety, these elevated exposures caused by severe RI are not expected to result in clinically meaningful risks in patients with mild, moderate and severe RI (not requiring dialysis) (See Section 16.4.4 Pharmacometrics Assessment for additional

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information). As the PK of oveporexton in patients with severe RI on dialysis (eGFR <15 mL/min) has not been studied, the reviewer proposed an avoid use recommendation in patients with eGFR <15 mL/min on dialysis in the prescribing information.

The drug-drug interaction (DDI) potential of oveporexton was evaluated through in vitro studies, clinical DDI trials, and physiologically based pharmacokinetic (PBPK) modeling. Given the predominant role of CYP3A4 in oveporexton metabolism, the primary focus was on interactions with CYP3A inhibitors and inducers, both as an object and as a precipitant. When oveporexton is concomitantly administered with strong CYP3A inhibitors, it resulted in a 7.4-fold increase in AUC_{∞}, a 67% increase in C_{max}, and approximately a 5-fold increase in terminal half-life compared to oveporexton administered alone. Coadministration of fluconazole, a moderate CYP3A inhibitor, with oveporexton 10 mg resulted in a 2.86-fold increase in AUC_{∞}, a 50% increase in C_{max}, and approximately a 2-fold increase in terminal half-life compared to oveporexton alone. Based on these substantial increases in exposures and prolongation of half-life, concomitant use of oveporexton with strong CYP3A inhibitors is contraindicated and a dosage reduction is recommended (0.5 mg BID) when oveporexton is concomitantly used with moderate CYP3A inhibitors.

In the clinical DDI study, coadministration of phenytoin, a strong CYP3A inducer, with oveporexton 10 mg resulted in an 81% decrease in AUC_{∞} and a 56% decrease in C_{max} compared to oveporexton alone. The terminal half-life of oveporexton decreased from approximately 32 hours to 14 hours in the presence of phenytoin. Based on these substantial decreases in exposure, concomitant use of oveporexton with strong CYP3A inducers should be avoided. In addition, PBPK modeling suggested that coadministration with moderate CYP3A inducer will result in a 55% decrease in C_{max} and 72% decrease in AUC_{∞}. Therefore, concomitant use of oveporexton with moderate CYP3A inducers should also be avoided.

PBPK modeling suggested that coadministration with weak CYP3A inhibitors and weak CYP3A inducers will not have clinically significant effects on the PK of oveporexton. Therefore, dosage adjustment is not required when oveporexton is concomitantly administered with weak CYP3A inhibitors and weak CYP3A inducers.

6.2.1. Pharmacology and Clinical Pharmacokinetics

The mechanism of action of oveporexton for the treatment of NT1 is presumed to be through agonism of the orexin receptor 2 (OX2R). The orexin neuropeptide signaling system plays a role in wakefulness.

Oveporexton showed dose proportional increase in exposures (C_{max} and AUC0-t) at steady state over the dosage range of 1 mg twice daily to 2 mg twice daily. With two times daily administration, steady state was reached within 5 days, with an accumulation ratio of approximately 1.6 after an oveporexton dosage of 1 mg twice daily to 2 mg twice daily.

Absorption

Oveporexton median (min, max) time to maximum plasma concentration (T_{max}) is 1.5 hours (1 to 4 hours) at steady state.

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Effect of Food: No clinically significant differences in the pharmacokinetics of oveporexton were observed following administration with a high-fat high-calorie meal.

Distribution

The apparent steady state volume of distribution of oveporexton is approximately 325 L. Protein binding is high (>96%) and concentration-independent in human plasma. The whole blood to plasma concentration ratio ranged from 0.61 to 0.90.

Elimination

The mean terminal elimination half-life of oveporexton is approximately 23.2 hours.

Metabolism: oveporexton is primarily eliminated by hepatic metabolism. CYP3A4 is the predominant CYP enzyme involved in oveporexton metabolism with no major metabolites identified in circulation.

Excretion: After a single 25-mg radiolabeled oral dose of oveporexton, 80.5% of the total dose was recovered in feces and 11.0% was recovered in urine. Renal elimination of unchanged drug accounts for <1% of the total clearance of oveporexton.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dosage of oveporexton is 1 mg or 2 mg twice daily. The first dose should be taken after awakening and the second dose should be taken 3 to 5 hours later.

The maximum recommended total daily dosage is 4 mg orally.

Therapeutic Individualization

Patients With Hepatic Impairment

Avoid use of oveporexton in patients with severe HI (Child-Pugh C). No dosage adjustment is required when administering oveporexton to patients with mild or moderate HI (Child-Pugh A or B).

Concomitant Use of CYP3A Inducers

Avoid use of oveporexton in patients taking strong and moderate CYP3A inducers.

Concomitant Use of CYP3A Inhibitors

Avoid use of oveporexton in patients taking strong CYP3A inhibitors. If oveporexton is used concomitantly with moderate CYP3A inhibitors, reduce the oveporexton dosage to 0.5 mg twice daily.

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6.3. Comprehensive Clinical Pharmacology Review

6.3.1. Clinical Pharmacology Questions

Are the proposed dosage regimens acceptable for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimens (1 mg or 2 mg twice daily) of oveporexton are acceptable for the general patient population with narcolepsy type 1 (NT1). The proposed dosage regimens of oveporexton showed favorable efficacy and acceptable safety compared to placebo in the pivotal phase 3 efficacy and safety studies. Refer to Section 8 for additional details about efficacy of 1 mg BID and 2 mg BID dosage regimens.

The clinical development program evaluated different dosing frequencies (once-daily (QD) and twice-daily (BID)) to ensure sustained daytime wakefulness. Data from the phase 1b study (TAK-861-1001) established that, although QD dosing improved symptoms, a BID split-dosing regimen was necessary to maintain efficacy throughout the entire waking day. Pharmacodynamic (PD) measurements demonstrated that BID dosing yields significantly stronger improvements in the Maintenance of Wakefulness Test (MWT) compared to QD dosing. With the same total daily amount of oveporexton (4 mg/day), the 2 mg BID dosing regimen achieved higher reductions in terms of MWT (24.39 versus 14.74) at Week 4 compared to 4 mg QD dosing (Table 41). In addition, the magnitude of effect is comparable between the 2 mg BID and 4 mg BID cohorts, which suggests that by adopting a split-dosing regimen, similar efficacy can be achieved with a lower total daily dosage. The BID administration schedule provided sustained therapeutic plasma concentrations and symptom control throughout the patient's waking hours, which provided superior efficacy compared to a single-dose regimen with the same total daily dosage. Therefore, the BID dosing regimen was selected for phase 2 and phase 3 studies.

Table 41. Comparison of Improvements in the Maintenance of Wakefulness Test Following Single-Dose and Split-Dosing Regimen

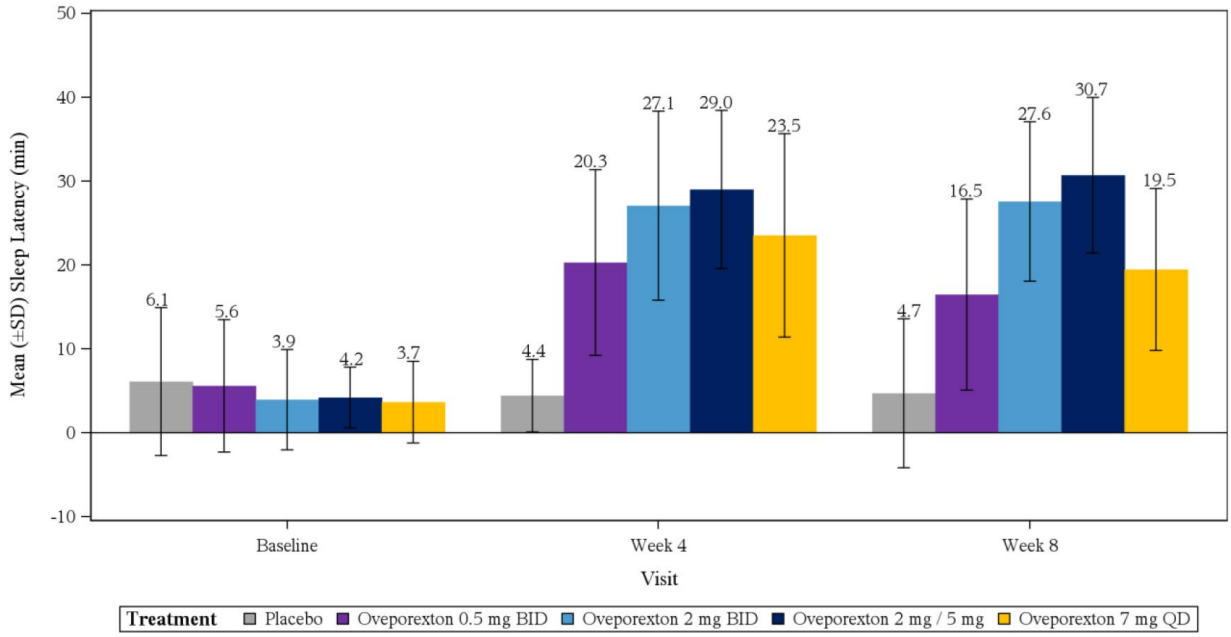
Parameters	Oveporexton 4 mg QD (N=3)	Oveporexton 2 mg BID (N=21)	Oveporexton 4 mg BID (N=3)
Week 2			
LS mean (SE)	14.21 (7.712)	No Measurement	24.75 (3.287)
Difference from placebo—LS Mean (SE)	11.65 (8.516)		22.20 (4.911)
p-value	0.184		0.0002
Week 4			
LS mean (SE)	13.58 (3.945)	23.00 (2.136)	26.83 (1.675)
Difference from placebo—LS mean (SE)	14.74 (4.315)	24.39 (3.028)	27.99 (2.601)
p-value	0.0021	<0.001	<0.0001
Week 8			
LS mean (SE)	No Measurement	23.50 (2.042)	No Measurement
Difference from placebo—LS mean (SE)		24.67 (2.921)	
p-value		<0.001	

Mean sleep latency = mean of the sleep latency from the 4 MWT sessions; LS Mean: least squares mean; SE: standard error.
Source: TAK-861-1001 Part D PD Set and Study TAK-861-2001

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The Applicant conducted a phase 2 dose-ranging study (TAK-861-2001) to support the 1-mg and 2-mg twice-daily dosages for the subsequent phase 3 pivotal trials. Four dosage levels were evaluated: 0.5 mg BID, 2 mg BID, 2 mg BID titrated to 5 mg BID (the 2 mg/5 mg group), and 7 mg QD. In this study, oveporexton demonstrated statistically significant and clinically meaningful improvements compared with placebo for the change from Baseline to Week 8 in mean sleep latency on the MWT ($p \leq 0.001$ for all dosages) at all tested dosages. However, 0.5 mg BID showed relatively lower mean sleep latency compared to other dosages, and comparable mean sleep latency (MSL) values were observed for the 2 mg BID group and the 2 mg/5 mg group. Increasing the dosage from 2 mg BID to 2 mg/5 mg per day yielded only an additional 1.91 minutes of sleep latency on the MWT. This marginal gain was not considered clinically significant. Administration of 7 mg QD resulted in relatively decreased change from Baseline to Week 8 in mean sleep latency (19.5 min versus 27.6min (2 mg BID); 19.5 min versus 30.7 min (2 mg/5 mg per day) compared to 2 mg BID and 2 mg/5 mg per day dosing.

Figure 6. Changes of Mean Sleep Latency From the Maintenance of Wakefulness Test Following Different Dosage Regimens



Mean sleep latency = mean of the sleep latency from the 4 MWT sessions.
Source: TAK-861 Additional Baseline Tables and Phase 2 Figures, Figure 15.2.1.1.

A similar pattern is observed for weekly cataplexy rate (WCR), which is derived post hoc from the sum of estimated daily counts over 2-week intervals divided by 2. For the four dosage regimens tested (0.5 mg BID, 2 mg BID, 2 mg/5 mg BID, 7 mg QD) in the phase 2 study (TAK-861-2001), only the 2 mg BID group and 2 mg/5 mg BID group showed statistically significant improvement at Week 8 in terms of incidence rate ratios (IRRs) of WCR when compared to the placebo group. Please see Section 8.1.2 for additional details. The results from this study supported selection of 1 mg BID and 2 mg BID for subsequent two pivotal phase 3 studies. These dosage regimens of oveporexton demonstrated favorable efficacy and acceptable

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safety compared to placebo in the phase 3 studies and are deemed to be appropriate for the general patient population with NT1.

Is there an alternative dosage regimen or management strategy required for subpopulations based on intrinsic patient factors (age, sex, race/ethnicity, body weight, hepatic impairment and renal impairment)?

No, the population PK analysis and dedicated PK studies suggest that the intrinsic factors (age, sex, race/ethnicity, body weight, HI (mild and moderate) and RI) did not appreciably affect the PK of oveporexton. Therefore, no dosage adjustment is recommended based on age, sex, race/ethnicity, body weight, HI, and RI in adult patients with NT1.

In Study TAK-861-1001 Part B and Part C, the Applicant compared the PK of oveporexton in healthy elderly Japanese participants (aged 65 years and older) and in healthy Japanese participants 18 to 55 years of age following 5 mg QD dosing for 14 days. The geometric mean ratios of PK parameters ($C_{max,ss}$ and AUC_{0-24h}) are similar between young adults and elderly subjects following the administration of oveporexton 5 mg QD (Table 42). These findings are consistent with the population PK analysis, where age was not a significant covariate in the final model for oveporexton PK (Section 16.4.3 Population PK Review). Therefore, dosage adjustment is not required in the elderly population for oveporexton.

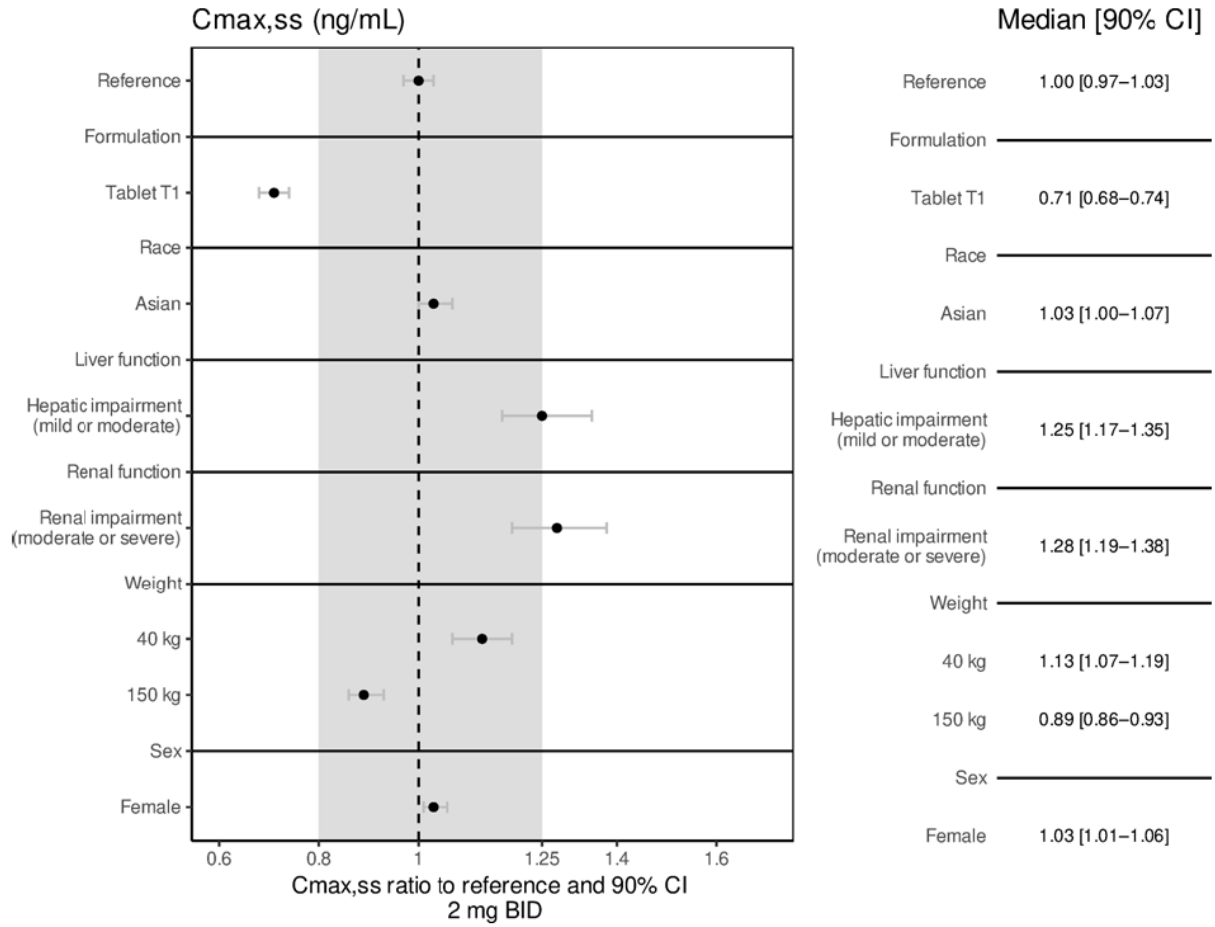
Table 42. PK Parameters of Oveporexton in Young and Elderly Subjects Following 5 mg QD at Steady State.

PK Parameter	Unit	Young Adults (Part B, n=6)	Elderly Adults (Part C, n=6)	GMR% [90% CI (Elderly/Young Adults)
AUC_{∞} [a]	h·ng/mL	624.5 (28.8%)	594.7 (48.0%)	94.99 [64.13 – 140.72
AUC_{0-24h} [a]	h·ng/mL	337.5 (18.0%)	308.6 (34.4%)	91.40 [69.13 – 120.84]
$C_{max,ss}$ [a]	ng/mL	31.66 (27.1%)	32.42 (33.3%)	102.4 [75.07 – 139.66]
T_{max} [b]	h	1.00 (1.00, 2.00)	1.00 (0.50, 1.00)	-

[a] Values are shown as geometric mean (geometric CV%).
[b] Values are shown as median (min, max).
Abbreviations: AUC_{∞} = area under the plasma concentration-time curve from time zero to infinity; AUC_{0-24h} = area under the plasma concentration-time curve from time zero to 24 hours; $C_{max,ss}$ = maximum observed plasma concentration at steady state; CV% = percent coefficient of variation; T_{max} = time to maximum observed plasma concentration; GMR = geometric mean ratio
Source: Reviewer's analysis and TAK-861-1001 Clinical Study Report.

Population PK analysis suggests that the PK parameters, C_{max} and AUC at steady state of oveporexton were similar across sex, race/ethnicity, and body weight subgroups (Figure 7 and Figure 8). Therefore, no dosage adjustment is required based on sex, race/ethnicity, and body weight.

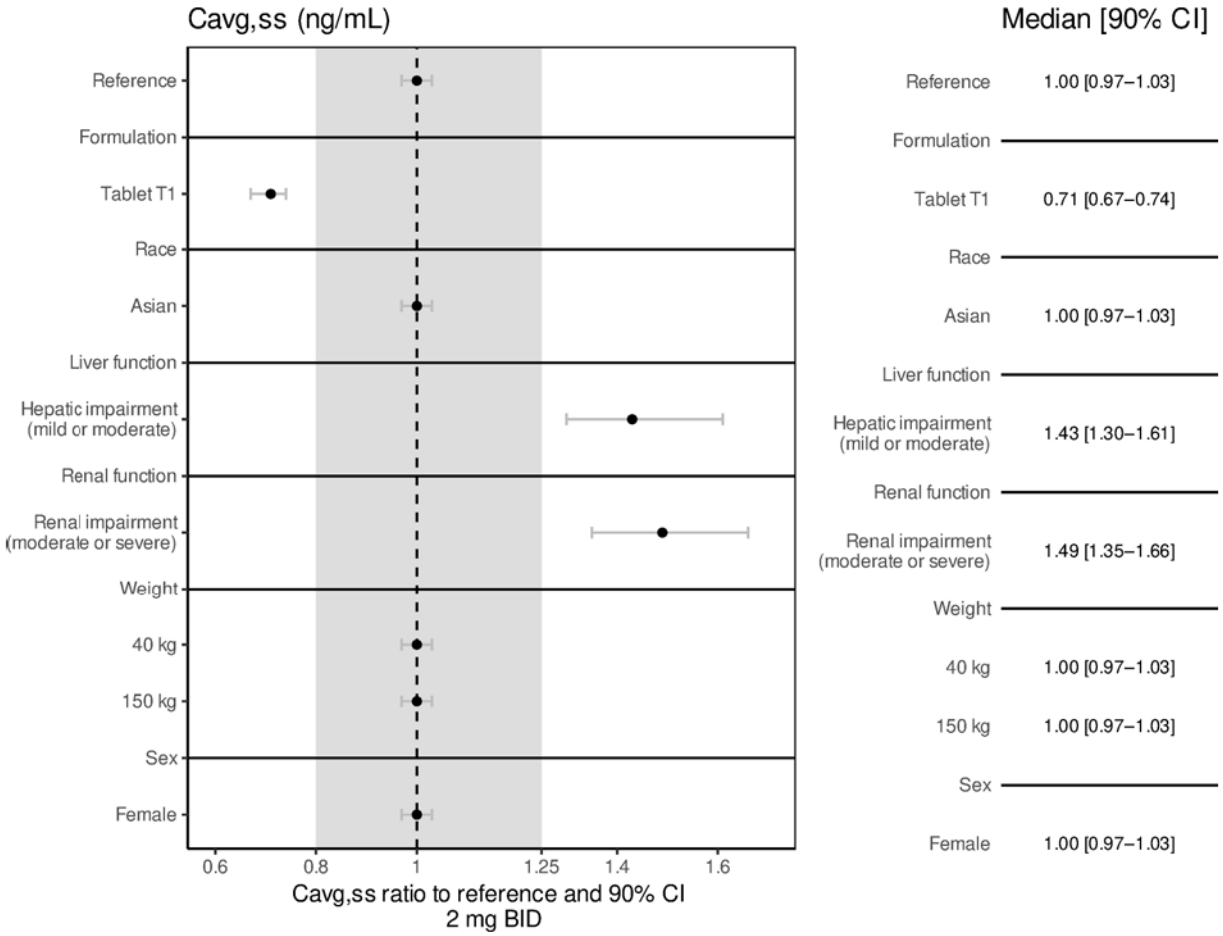
Figure 7. Impact of Covariates on Oveporexton C_{max} at Steady State



Reference simulation: male, body weight of 75.4 kg, not Asian, no hepatic impairment, no/mild renal impairment, T3 formulation, total daily dosage of 4 mg.
Source: Adapted from TAK-861 Population PK Study Report, Figure 1.

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Figure 8. Impact of Covariates on Oveporexton C_{avg} at Steady State



Reference simulation: male, body weight of 75.4 kg, not Asian, no hepatic impairment, no/mild renal impairment, T3 formulation, total daily dosage of 4 mg.
Source: Adapted from TAK-861 Population PK Study Report, Figure 2.

Effect of Hepatic and Renal Impairment

Two dedicated safety and PK studies were conducted to evaluate the effect of mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) HI (TAK-861-1004), and severe RI (eGFR 15 to <30 mL/min, not requiring dialysis; TAK-861-1005) on the PK of oveporexton along with additional population PK analysis. Given that oveporexton is mainly metabolized by CYP3A4, HI is expected to have a significant effect on its PK. However, the results from a dedicated HI study suggest that oveporexton's C_{max} and AUC_{∞} increased by 16% and 28%, respectively, in patients with mild HI, and 16% decrease in C_{max} and 23% increase in AUC_{∞} in patients with moderate HI, when compared to participants with normal hepatic function (Table 43). Exposure-safety analyses suggest that the probability of adverse events (e.g., insomnia, urinary events, and micturition urgency) in subjects with mild or moderate HI is generally comparable to patients with normal hepatic functions (See Section 16.4.4 Pharmacometrics Assessment for additional information). Therefore, the effect of HI (mild or moderate) on the PK of oveporexton is not considered to be clinically meaningful. No dosage adjustment is required for patients with mild or moderate HI.

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The effect of severe HI (Child-Pugh Class C) on the PK of oveporexton has not been studied. Therefore, the review team recommends avoiding the use of oveporexton in patients with severe HI given the potential risk of elevated systemic exposures and associated safety risks to patients with NT1 and severe HI. A post-marketing requirement study to evaluate the effects of severe HI (Child-Pugh Class C) on the PK of oveporexton will be issued.

Table 43. Summary of the PK Parameters of Oveporexton Following Oral Administration of Two Doses of 2 mg Oveporexton (Separated by 3 Hours Apart) in Subjects With Organ Impairments

Cohort	N	C_{max} [a] (ng/mL)	AUC_{last} [a] (h*ng/mL)	AUC_{∞} [a] (h*ng/mL)	C_{max} GMR% [90% CI]	AUC_{∞} GMR% [90% CI]
Mild Hepatic Impairment	10	23.35 (17.9%)	548.8 (35.9%)	574.3 (37.7%)	116.98 [97.09 – 140.96]	128.42 [100.02 – 164.88]
Moderate Hepatic Impairment	10	16.91 (30.8%)	530.3 (26.6%)	554.3 (31.1%)	84.72 [70.31 – 102.08]	123.51 [96.20 – 158.59]
Normal Hepatic Function	13	19.96 (16.73%)	440.53 (35.5%)	455.54 (37.51%)	—	—
Severe Renal Impairment	10	17.42 (29.72%)	502.07 (38.79%)	565.20 (52.68%)	83.55 [64.95 – 107.49]	145.77 [108.32 – 196.17]
Normal Renal Function	10	20.85 (36.68%)	371.65 (21.61%)	387.73 (22.24%)	—	—

[a] Values are shown as geometric mean (geometric CV%).
Abbreviations: AUC_{∞} = area under the concentration-time curve from time zero to infinity; AUC_{last} = area under the concentration-time curve from time zero to last measurable concentration; CI = confidence interval; C_{max} = maximum observed plasma concentration; CV% = percent coefficient of variation; GMR = geometric mean ratio (organ impairment/Normal organ function); HI = hepatic impairment; RI = renal impairment.
Source: Reviewer's analysis based on TAK-861-1004 Clinical Study Report and TAK-861-1005 Clinical Study Report.

In Study TAK-861-1005, subjects with severe RI (eGFR less than 30 mL/min, not on dialysis) showed 16% lower C_{max} and 45% higher AUC_{∞} compared to subjects with normal renal function. Exposure-safety analyses suggest that the probability of adverse events in subjects with severe RI is generally comparable to patients with normal renal functions (See Section 16.4.4 Pharmacometrics Assessment for additional information). Therefore, the effect of RI (mild, moderate, or severe) on the PK of oveporexton is not considered to be clinically meaningful, and dosage adjustment based on RI is not required for oveporexton.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No clinically relevant food effects on the PK of oveporexton were observed. However, clinically significant drug-drug interactions were observed with strong and moderate CYP3A4 inhibitors and strong and moderate CYP3A4 inducers.

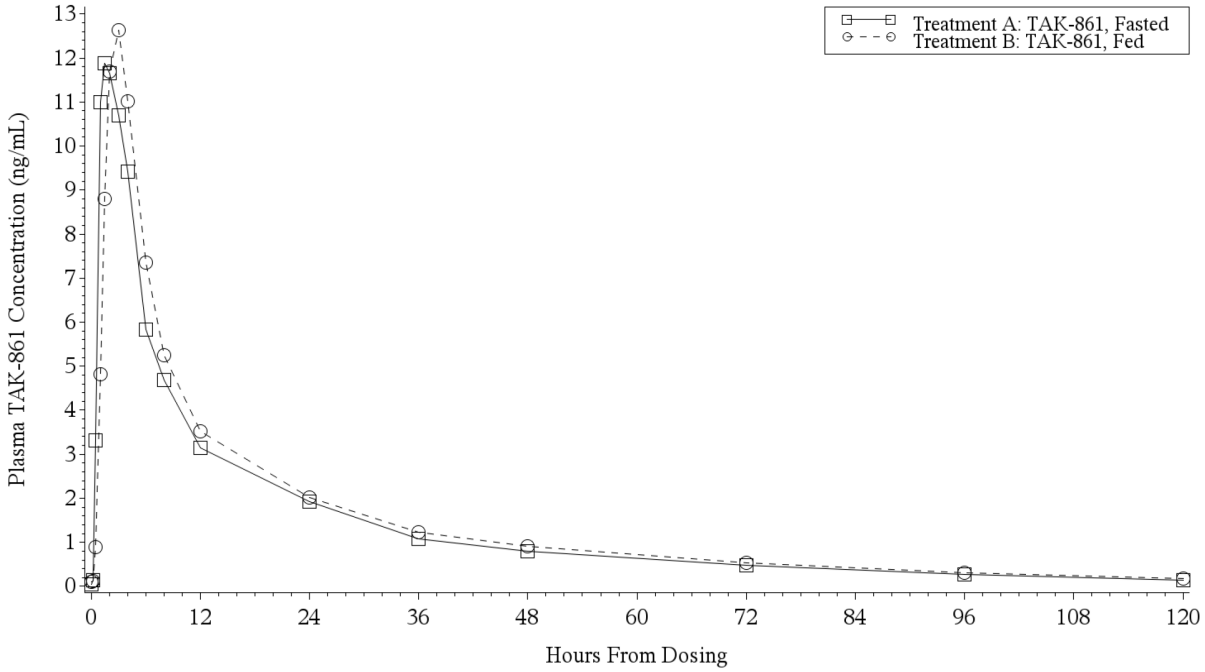
Food Effects

The effect of high-fat meal on the PK of oveporexton was evaluated with the highest strength (2 mg T3 tablet) of to-be-marketed formulation in Study TAK-861-1010. Twelve subjects

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received oveporexton either following an overnight fast or a high-fat, high-calorie breakfast (800 to 1000 calories and 50% or more fat) conditions. Similar PK characteristics were observed for oveporexton under fasted and fed conditions.

Figure 9. Mean Plasma Oveporexton Concentration Versus Time Profiles After a Single Oral Dose of 2 mg TAK-861 Under Fasted (Treatment a) and Fed (Treatment B) Conditions in Healthy Adult Participants



Source: TAK-861-1010 CSR, Figure 2.

The results showed that the plasma PK parameters of oveporexton, C_{max}, AUC_{last}, and AUC_{∞} were approximately 3% lower, 5% higher, and 6% higher, respectively, after TAK-861 dosing under fed conditions (Treatment B) compared to the fasted conditions (Treatment A). The 90% confidence intervals around the geometric mean ratios of PK parameters were within the regulatory limits of 80.00% to 125.00%. Therefore, the effect of food on the PK of oveporexton is deemed clinically not meaningful. Oveporexton can be administered with or without food.

Table 44. Effect of High-Fat Meal on the PK of Oveporexton

Condition	C_{max}* (ng/mL)	AUC_{∞}* (h*ng/mL)	AUC_{last}* (h*ng/mL)
Fed[a]	12.83 (19.6%)	172.2 (40.9%)	165.8 (37.7%)
Fasted[b]	13.24 (21.9%)	162.9 (32.9%)	158.2 (29.8%)
GMR% (90% CI)	96.93 (85.60 - 109.75)	105.69 (96.18 - 116.14)	104.79 (95.49 - 114.99)

* Values are shown as geometric mean (geometric CV%).
[a] 2 mg TAK-861 (1 × 2 mg TAK-861 T3 tablet) on Day 1 under fed conditions.
[b] 2 mg TAK-861 (1 × 2 mg TAK-861 T3 tablet) on Day 1 under fasted conditions.
Abbreviations: AUC_{∞} = area under the concentration–time curve from time zero to infinity; AUC_{last} = AUC to last measurable concentration; C_{max} = maximum observed plasma concentration; CI = confidence interval; GMR = geometric mean ratio.
Source: Reviewer's analysis based on TAK-861-1010 CSR, Tables 9.

Drug-Drug Interactions (DDIs)

Given that CYP3A4 is the predominant contributor (97.3%), with lesser contributions from CYP2C9 (0.1%) and CYP2D6 (2.6%), clinical DDI studies were conducted to evaluate the effects of strong and moderate CYP3A4 inhibitors and a strong CYP3A4 inducer on the PK of oveporexton (TAK-861-1007). PBPK simulations were also performed to evaluate the effects of weak inhibitor of CYP3A4 and moderate and weak inducers of CYP3A4.

Following coadministration of fluconazole (moderate CYP3A4 inhibitor) compared to oveporexton alone, C_{max}, AUC_{∞}, and AUC_{last} increased 50%, 2.8-fold, and 2.6-fold, respectively (Table 45). A dosage reduction to 0.5 mg BID is recommended when oveporexton is concomitantly administered with moderate CYP3A4 inhibitors. Coadministration of oveporexton with itraconazole (strong CYP3A4 inhibitor) resulted in 67%, 7.4-fold, and 7.4-fold increases in C_{max}, AUC_{∞}, and AUC_{last}, respectively (Table 45) compared to oveporexton administration alone. Therefore, avoiding the use of oveporexton with strong CYP3A4 inhibitors is recommended.

Table 45. Effect of Moderate and Strong CYP3A4 Inhibitors on the Plasma PK of Oveporexton

Condition	C_{max}* (ng/mL)	AUC_{∞}* (h*ng/mL)	AUC_{last}* (h*ng/mL)
Moderate CYP3A4 Inhibitor			
Oveporexton 10 mg alone [a]	53.42 (27.4%)	846.7 (35.1%)	804.8 (29.1%)
Oveporexton 10 mg + Fluconazole [b]	79.99 (27.0%)	2426 (29.5%)	2098 (34.0%)
GMR% (90% CI)	149.76 (130.75, 171.54)	286.52 (255.20, 321.69)	260.65 (230.38, 294.91)

Condition	C_{max}* (ng/mL)	AUC_{∞}* (h*ng/mL)	AUC_{last}* (h*ng/mL)
Strong CYP3A4 Inhibitor			
Oveporexton 1 mg alone [c]	7.698 (49.9%)	87.29 (62.1%)	81.27 (62.7%)
Oveporexton 1 mg + Itraconazole [d]	12.83 (34.6%)	648.6 (48.0%)	605.0 (49.4%)
GMR% (90% CI)	166.71 (103.65, 268.11)	743.09 (561.71, 983.03)	744.48 (538.51, 1029.22)

* Values are shown as geometric mean (geometric CV%).
[a] Single oral dose of 10 mg oveporexton on Day 1 (reference).
[b] Single oral dose of 400 mg fluconazole on Day 6 and 200 mg QD on Days 7–13, coadministered with a single oral dose of 10 mg oveporexton on Day 9.
[c] Single oral dose of 1 mg oveporexton on Day 1 (reference).
[d] Oral doses of 200 mg itraconazole oral solution on Days 6–22, coadministered with a single oral dose of 1 mg oveporexton on Day 9.
Abbreviations: AUC_{∞} = area under the concentration–time curve from time zero to infinity; AUC_{last} = AUC to last measurable concentration; C_{max} = maximum observed plasma concentration; CI = confidence interval; GMR = geometric mean ratio.
Source: Reviewer's analysis based on TAK-861-1007 CSR, Tables 11.m and 11.u.

Physiologically-based pharmacokinetic (PBPK) modeling was utilized to evaluate the effect of weak CYP3A4 inhibitor on the exposure of oveporexton. Coadministration of a weak CYP3A inhibitor is predicted to resulted in a 30% and 43% increase in C_{max} and AUC of oveporexton. Based on the exposure-safety relationship, no dosage adjustment is required when oveporexton is concomitantly administered with weak CYP3A4 inhibitors.

The effect of strong CYP3A4 inducer, phenytoin, on the PK of oveporexton was also evaluated in Study TAK-861-1007. Coadministration of phenytoin (strong CYP3A4 inducer) with oveporexton was associated with approximately 56%, 81%, and 80% lower C_{max}, AUC_{∞}, and AUC_{last} when compared to oveporexton alone (Table 46). Such lower systemic exposures are anticipated to cause substantial loss of efficacy of oveporexton for the treatment of NT1. Therefore, avoiding the use of oveporexton with strong CYP3A4 inducers is recommended.

Table 46. Effect of Strong CYP3A4 Inducer on the PK of Oveporexton

Condition	C_{max}* (ng/mL)	AUC_{∞}* (h*ng/mL)	AUC_{last}* (h*ng/mL)
Strong CYP3A4 Inducer			
Oveporexton 10 mg alone [a]	59.43 (22.6%)	1039 (18.4%)	976.9 (16.2%)
Oveporexton 10 mg + Phenytoin [b]	26.12 (23.6%)	194.1 (39.3%)	190.6 (40.1%)
GMR% (90% CI)	43.94 (37.31, 51.75)	18.72 (15.33, 22.88)	19.55 (16.08, 23.77)

* Values are shown as geometric mean (geometric CV%).
[a] Single oral dose of 10 mg oveporexton on Day 1 (reference).
[b] Multiple oral doses of 100 mg phenytoin TID on Days 6 to 23 coadministered with a single oral dose of 10 mg oveporexton on Day 19.
Abbreviations: AUC_{∞} = area under the concentration–time curve from time zero to infinity; AUC_{last} = AUC to last measurable concentration; C_{max} = maximum observed plasma concentration; CI = confidence interval; GMR = geometric mean ratio.
Source: Reviewer's analysis based on TAK-861-1007 CSR, Tables 11.q.

PBPK model suggest that coadministration of a weak CYP3A-family inducer is predicted to resulted in a 23% and 34% decrease in C_{max} and AUC of oveporexton. Based on the exposure-response relationship, no dosage adjustment is required when oveporexton is concomitantly administered with weak CYP3A4 inducer.

In addition, coadministration of a moderate CYP3A inducer is predicted to resulted in a 55% and 72% decrease in C_{max} and AUC of oveporexton (See Section 16.4.4 Pharmacometrics Assessment for additional information). Such lower systemic exposures are anticipated to cause substantial loss of efficacy of oveporexton for the treatment of NT1. Therefore, avoiding the use of oveporexton with moderate CYP3A4 inducers is recommended.

Oveporexton is not expected to directly induce or inhibit CYP enzymes at clinically relevant concentrations (unbound C_{max} at steady state of the maximum recommended dosage, 2 mg BID: 0.46 ng/mL) based on the in vitro DDI study. Furthermore, PBPK modeling also suggest that the risk of oveporexton to decrease or increase systemic exposures of CYP3A substrates via CYP3A induction or inhibition is considered very low. Therefore, oveporexton is not expected to affect the PK of other drugs when concomitantly administered.

Is the PK bridge between the to-be-marketed formulation and clinical trial formulations adequately established?

Yes, the PK bridge between the to-be-marked formulation and clinical trial formulations is adequately established.

In the development of oveporexton, three clinical trial formulations were administered to participants, including T1 tablet (phase 1 studies), T2 tablet (phase 2 dose ranging study and clinical drug-drug interaction studies), and T3 tablet (phase 3 studies, food effect study, and hepatic and renal impairment studies) formulations. The to-be-marketed formulation shares the same core tablet composition as the T3 formulation. However, the color coating and debossing of the to-be-marketed formulation is different from the T3 formulation. The Applicant demonstrated a bridge between the to-be-marketed formulation and T3 formulation based on the in vitro dissolution study. The results from the in vitro dissolution study suggest that the in vitro dissolution characteristics across all strengths (0.5 mg, 1 mg, and 2 mg) are similar between the to-be-marketed formulation and T3 formulation. This suggests that the bridge between the to-be-marketed formulation and T3 formulation is adequate. See the Integrated Review of Office of Pharmaceutical Quality archived on June 24, 2026, for additional information.

A comparative bioavailability study (TAK-861-1007) was conducted to establish a PK bridge between T1 and T2 formulations, and a population PK (popPK) model-based approach was used to establish a bridge between T2 and T3 formulations along with the results of an in vitro dissolution study.

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Table 47. Comparison of Plasma PK Parameters of Oveporexton Following 10 mg Oveporexton Given as 2x5 mg T1 and T2 Tablets

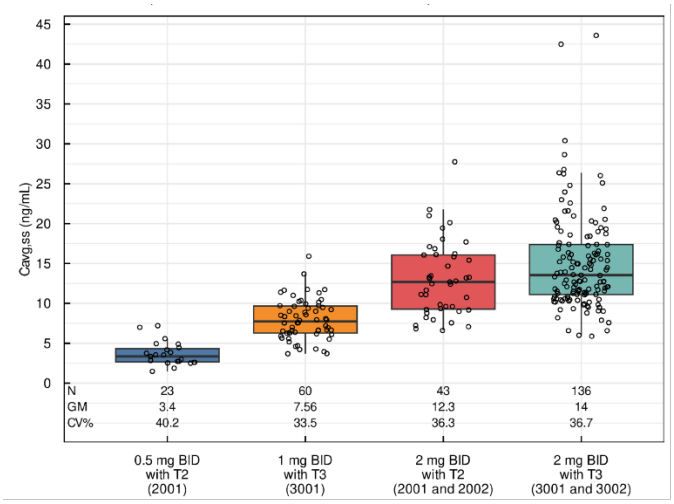
PK Parameter	N	T2 Geometric Mean	T1 Geometric Mean	GMR (T2/T1, %)	90% CI
C_{max}* (ng/mL)	12	59.88 (22.0)	50.93 (21.1)	117.59	107.83 - 128.23
AUC_{∞}* (ng•hr/mL)	12	858.4 (18.1)	785.3 (19.9)	109.31	104.21 - 114.65
AUC_{last}* (ng•hr/mL)	12	835.2 (17.0)	759.2 (18.4)	110.00	105.22 - 115.00

* Values are shown as geometric mean (geometric CV%).
Abbreviations: AUC_{∞} = area under the concentration–time curve from time zero to infinity; AUC_{last} = AUC to last measurable concentration; C_{max} = maximum observed plasma concentration; CI = confidence interval; GMR = geometric mean ratio.
Source: Reviewer's analysis based on TAK-861-1007 CSR, Tables 11.h.

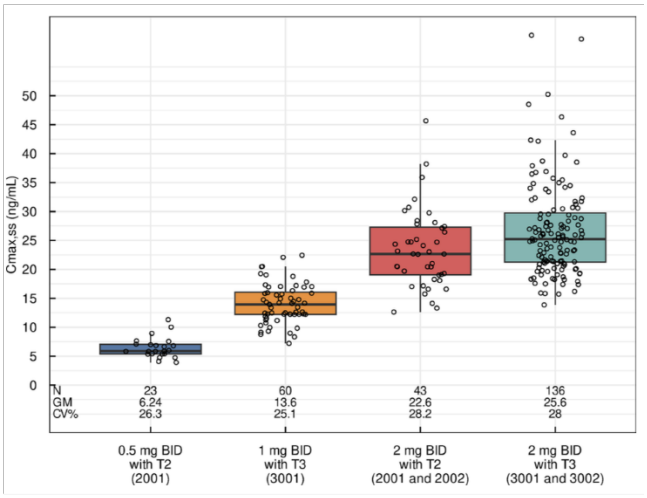
As shown in the table above, the exposures following administration of T1 and T2 formulations are comparable. The 90% confidence intervals of the GMRs of the PK parameters were generally within the 80% to 125% interval except for the upper limit of the 90% CI for C_{max}. However, such minor increase in upper 90% CI of C_{max} is not expected to be clinically significant. Therefore, the bridge between the T1 and T2 formulations is deemed to be adequate.

The T3 formulation is further bridged to T2 formulation via a population PK model-based approach. PK data from studies TAK-861-1007, TAK-861-1010, and TAK-861-1011 were used for the comparison of population PK model-simulated oveporexton concentration-time profiles with observed oveporexton concentration-time profiles. The results showed that the exposures ($C_{avg,ss}$ and $C_{max,ss}$) following the administration of T2 and T3 formulations are comparable. In addition, in vitro dissolution study showed that T3 and T2 formulation exhibit similar dissolution profiles, with f2 values ≥50 in three different pH dissolution media (refer to the Integrated Review of Office of Pharmaceutical Quality dated June 24, 2026). The findings support the bridge between T2 and T3 formulations.

Figure 10. Comparison of Simulated Oveporexton Exposures Following the Administration of T2 and T3 Tablets



Cavg,ss,24h



Cmax,ss

Source: PopPK Report, Figure 6 and Figure 80; note different scales.

Were there any QT prolongations observed at the highest therapeutic dosage (i.e., 2 mg BID) or supratherapeutic dosage (i.e., 75 mg QD)?

Oveporexton did not prolong the QT interval or affect the electrocardiogram (ECG) parameters at the maximum recommended therapeutic dosage, 2 mg BID.

No dedicated thorough QT study was conducted for oveporexton. The effect of oveporexton on QTc interval was evaluated in Study TAK-861-1001. The highest exposures evaluated was achieved with a 75-mg single oral dose and this dosage regimen provided an 11-fold coverage for the maximum proposed therapeutic dosage (2 mg BID) based on C_{max} values (See Interdisciplinary Review Team for Cardiac Safety Studies QT Study Review dated December 18, 2024, for additional information). These results provided adequate coverage over the highest exposure scenario in clinical settings.

Table 48. Predictions From Concentration-QTcF Model

Dosage Regimen	C_{max} (ng/ml)	ΔΔQTcF (msec)
TAK-861 2 mg BID	24.6	0.6
TAK-861 2 mg BID + Strong CYP3A4 inhibitors	41.0	0.6
TAK-861 75 mg	285.7	0.4

Source: Studies TAK-861-1001 and population PK report.

Additionally, in the concentration-QTc analysis, a linear model with a treatment effect-specific intercept was fitted for plasma concentrations. The estimated slope of TAK-861 plasma concentration in the concentration-QTc relationship was positive and not statistically significant: 0.00039 ms per ng/mL (90% CI: -0.014704 to 0.015479) with a very small, not statistically significant treatment effect-specific intercept of 0.036 ms. Therefore, the risk of

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oveporexton to cause QT prolongation is minimal. See the Cardiac Safety integrated review archived on January 16, 2026, for additional information.

Does oveporexton exert dose-proportional PK characteristics?

Yes. Following single-dose and multiple-dose (i.e., at steady-state) administration in healthy adults, oveporexton showed dose proportional increase plasma exposures (C_{max} and AUC) over the dose range of 1 to 75 mg.

Table 49. Dose Proportional PK Characteristics of Oveporexton Following Single Oral Dose Administration in Healthy Adults

Trial Part/ Formulation	Parameter (unit)	n	Intercept	90% CI of Intercept	Slope	90% CI of Slope
Part A: Suspension (Dose range 1 to 10 mg)	AUC_{∞} (h*ng/mL)	18	4.4031	4.2289, 4.5773	0.9835	0.8653, 1.1018
	AUC_{last} (h*ng/mL)	18	4.3464	4.1754, 4.5175	1.0023	0.8862, 1.1184
	AUC_{24} (h*ng/mL)	18	3.9583	3.8352, 4.0814	1.0009	0.9173, 1.0845
	C_{max} (ng/mL)	18	2.0417	1.8955, 2.1878	1.0229	0.9237, 1.1221
Part A: Tablet (Dose range 5 to 75 mg)	AUC_{∞} (h*ng/mL)	24	4.4525	4.1270, 4.7780	0.9376	0.8425, 1.0327
	AUC_{last} (h*ng/mL)	24	4.4185	4.1083, 4.7288	0.9415	0.8509, 1.0321
	AUC_{24} (h*ng/mL)	24	3.9667	3.7524, 4.1811	0.9382	0.8756, 1.0008
	C_{max} (ng/mL)	24	1.7192	1.4053, 2.0332	0.9054	0.8137, 0.9971
Part E: Tablet (Dose range 5 and 30 mg)	AUC_{∞} (h*ng/mL)	11	3.3060	2.6188, 3.9932	1.2576	1.0191, 1.4961
	AUC_{last} (h*ng/mL)	11	3.2959	2.6765, 3.9153	1.2453	1.0304, 1.4603
	AUC_{24} (h*ng/mL)	11	3.0310	2.6578, 3.4042	1.1575	1.0280, 1.2870
	C_{max} (ng/mL)	12	1.1014	0.7711, 1.4317	0.9790	0.8609, 1.0970

Source: TAK-861-1001 CSR, Tables 11.g and 11 z

Analysis of dose proportionality in Part A of the trial included all fasted treatments administered.

A linear regression model (power model), ln(parameter) = intercept + slope*ln(dose), was fit to describe the relationship between each parameter and the corresponding dose levels.

Table 50. Dose Proportional PK Characteristics of Oveporexton Following Multiple Oral Dose Administration

Trial Part/ Formulation	Parameter (unit)	n	Intercept	90% CI of Intercept	Slope	90% CI of Slope
Part B: Tablet (Dose range 5 to 30 mg QD), Day 14	AUC_{τ} (h*ng/mL)	17	4.4395	4.1475, 4.7316	0.8584	0.7517, 0.9652
	$C_{max,ss}$ (ng/mL)	17	1.9766	1.5964, 2.3568	0.9085	0.7695, 1.0475
Part E: Tablet (Dose range 5 and 30 mg QD), Day 19	AUC_{τ} (h*ng/mL)	10	3.3581	2.6991, 4.0170	1.1969	0.9636, 1.4302
	$C_{max,ss}$ (ng/mL)	10	1.1026	0.6613, 1.5439	1.1257	0.9694, 1.2819

Source: TAK-861-1001 CSR, Tables 11.l and 11.aa

A linear regression model (power model), ln(parameter) = intercept + slope*ln(dose), was fit to describe the relationship between each parameter and the corresponding dose levels.

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Clinical trial efficacy and safety data for the treatment of NT1 in adults are provided by two phase 3, randomized, double-blind, placebo-controlled studies TAK-861-3001 and TAK-861-3002, and the long-term extension phase 2/3 study TAK-861-2003. Additional supportive data are provided by the phase 2 Study TAK-861-2001. Safety data from the phase 2 study TAK-861-2002 in patients with NT2, as well as safety data from phase 1 studies, are included in the integrated summary of safety to provide a comprehensive assessment of the safety profile of TAK-861 across the clinical development program. See Table 51 for a listing of all clinical trial sources of safety and efficacy data.

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Table 51. Listing of Clinical Trials Relevant to This NDA/BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
TAK-861-3001	NCT06470828	Randomized, DB, PC, multicenter, parallel group	OVE: 1 mg BID at least 3 hours apart; 2 mg BID at least 3 hours apart; Matching PBO; Oral	Primary: Change from baseline to Week 12 in MWT	12 weeks	OVE: 126 PBO: 41	NT1; F, M; 16 to 65 years of age	41 sites: JP, CH, DE, ES, FR, UK, IT, NL, NO, CA, US
TAK-861-3002	NCT06505031	Randomized, DB, PC, multicenter, parallel group	OVE: 2 mg BID at least 3 hours apart; Matching PBO; Oral	Primary: Change from baseline to Week 12 in MWT	12 weeks	OVE: 70; PBO: 35	NT1; F, M; 18 to 62 years of age	28 sites: CN, KR, AT, AU, BE, ES, FI, FR, IT, PL, SE
TAK-861-2001		Randomized, DB, PC, multicenter, parallel group	OVE: 0.5 mg BID approximately 3 hours apart; 2 mg BID approximately 3 hours apart; 2 mg +5 mg approximately 3 hours apart; 7 mg QD; Matching PBO; Oral	Primary: Change from baseline to Week 8 in MWT	8 weeks +4 weeks optional	OVE: 90; PBO: 22	NT1; F, M; 18 to 59 years of age	33 sites: AU, JP, CH, DE, ES, FI, FR, IT, NL, NO, SE, US
Studies to Support Safety								
TAK-861-2003		LTE, dose-blind, multicenter	OVE: 0.5 mg BID approximately 3 hours apart; 1 mg BID approximately 3 hours apart; 2 mg BID approximately 3 hours apart; 2 mg/5 mg approximately 3 hours apart; 7 mg QD	Primary: Long-term safety and tolerability (TEAEs)	Up to approximately 5 years	OVE: 356	NT1; F, M; 17 to 65 years of age	93 sites: AU, CN, JP, KR, AT, BE, CH, DE, ES, FI, FR, IT, NL, NO, PL, SE, CA, US
TAK-861-2002		Randomized, DB, PC, multicenter, parallel group	OVE: 2 mg BID at least 3 hours apart; 2 mg +5 mg at least 3 hours apart; Matching PBO; Oral	Primary: Change from baseline to Week 8 in mean sleep latency from the MWT	8 weeks	OVE: 47; PBO: 24	NT2; F, M; 21 to 69 years of age	28 sites: JP, ES, FR, IT, US

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Trial Identity NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Other Studies Pertinent to the Review of Efficacy or Safety (e.g., Clinical Pharmacological Studies)							
TAK-861-1001 (Parts A-F)	Randomized, DB, PC, SRD, MRD, and MD	Various dosages ranging from 1 mg to 75 mg single dose; 5 mg to 30 mg QD; 10 mg BID; 7 mg TID; Matching PBO; Oral	Primary: Safety and tolerability of OVE (TEAEs; MAV for laboratory assessments, vital signs, and ECGs)	1 to 28 days (depending on part)	OVE: 103; PBO: 30	HP (Parts A, B, E, F), Elderly HP (Part C), NT1 (Part D); F, M; 18 to 72 years of age	20 sites: US, JP
TAK-861-1001 Part G	Randomized, DB, PC, MD, multicenter	OVE: 4 mg BID approximately 3 hours apart; Matching PBO; Oral	Primary: Safety and tolerability of OVE (TEAEs, MAV for laboratory assessments, vital signs, and ECGs)	28 days	OVE: 9; PBO: 4	NT1; F, M; 19 to 59 years of age	4 sites: CN
TAK-861-1002	Randomized, DB, PC, 3-period crossover	OVE HD: 40 mg (30 mg at 11 PM +10 mg at 3 AM); OVE LD: 15 mg (10 mg at 11 PM +5 mg at 3 AM); PBO: 2 single doses; Oral	Primary: Safety and tolerability of OVE during an acute sleep phase delay paradigm (TEAEs); Effect of OVE on sleepiness as measured by the MWT (mean sleep latency on the MWT)	3 days (with a 7-day washout between each treatment day)	11	HP; M; 23 to 40 years of age	1 site: US
TAK-861-1003	Open-label, single dose	[^{14}C]OVE 25 mg; Oral	Primary: Mass balance of [^{14}C]OVE in urine and feces (Cum%Dose)	1 day	6	HP; M; 29 to 55 years of age	1 site: US
TAK-861-1004	Open-label, parallel group	OVE: 2 doses of 2 mg administered at least 3 hours apart; Oral	Primary: PK of OVE in participants with mild or moderate HI compared to participants with normal hepatic	1 day	Cohort 1 (mild HI): 10; Cohort 2 (moderate HI): 10; Cohort 3 (HP): 13	Participants with mild or moderate HI and HP; F, M; 43 to 73 years of age	2 sites: US

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Trial Identity NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
			function (C_{max}, AUC_{last}, AUC_{∞})				
TAK-861-1005	Open-label, parallel group	OVE: 2 doses of 2 mg administered at least 3 hours apart; Oral	Primary: PK of OVE in participants with severe RI compared to participants with normal renal function (C_{max}, AUC_{last}, AUC_{∞})	1 day	Cohort 1 (severe RI): 10; Cohort 2 (HP): 10	Participants with severe RI and HP; F, M; 38 to 78 years of age	3 sites: US
TAK-861-1007	Group 1: Randomized, open-label, 2-period crossover; Group 2: Open-label, fixed-sequence DDI with fluconazole; Group 3: Open-label, fixed-sequence DDI with phenytoin; Group 4: Open-label, fixed-sequence DDI with itraconazole	Group 1: OVE single dose T1 IR 10 mg or T2 IR 10 mg; Oral; Group 2: OVE T2 IR 10 mg single dose + Fluconazole tablet QD (400 mg on Day 6; 200 mg on Days 7-13); Oral; Group 3: OVE T2 IR 10 mg single dose + Phenytoin capsule 100 mg TID on Days 6-23; Oral; Group 4: OVE T2 IR 1 mg single dose + Itraconazole solution 200 mg QD on Days 6-22; Oral	Primary: Group 1: Relative bioavailability of T1 and T2 IR tablet (C_{max}, AUC_{∞} or $AUC_{\infty}obs$, AUC_{last}); Groups 2-4: DDI (C_{max}, AUC_{∞} or $AUC_{\infty}obs$, AUC_{last})	Group 1: 2 days (with a 5-day washout between each treatment day); Groups 2-4: 2 days	Group 1: 12; Group 2: 12; Group 3: 12; Group 4: 3	HP; F, M; 25 to 56 years of age	1 site: US
TAK-861-1009	Randomized, DB, double-dummy, active-and placebo-controlled, 5-way crossover	OVE single dose: 6 mg, 18 mg, 30 mg; Phentermine 75 mg single dose; Matching PBO; Oral	Primary: Relative abuse potential of OVE as measured by VAS for Drug Liking (E_{max} "at this moment")	5 days (with at least 7-day washout between each treatment period)	50	Healthy adult nondependent recreational drug users with CNS stimulant experience; F, M; 23 to 46 years of age	1 site: US
TAK-861-1010	Randomized, open-label, 2-way crossover	OVE single dose: 2 mg, fasted, oral OR 2 mg, fed, oral	Primary: Food effect (C_{max}, AUC_{∞}, AUC_{last})	2 days (with a 5-day washout between treatments)	12	HP; M; 21 to 46 years of age	1 site: US

Reference ID: 5847402

Trial Identity NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
TAK-861-1011	Randomized, open-label, 3-way crossover	OVE 2 mg single dose, fasted: T3 Tablet with d50=21 µm (Reference); T3 Tablet with d50=14 µm (Test 1); T3 Tablet with d50=26 µm (Test 2); Oral	Primary: Effect of PSD of OVE DS on bioavailability of 2 mg OVE administered as T3 tablet (C_{max}, AUC_{∞}, AUC_{last})	3 days (with a 5-day washout between treatments)	36	HP; F, M; 24 to 55 years of age	1 site: US

Abbreviations: AT = Austria; AU = Australia; AUC_{∞} or AUC_{∞}_obs = Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration; AUC_{last} = Area under the concentration-time curve from time 0 to the last quantifiable concentration; BE = Belgium; BID = Twice daily; CA = Canada; CH = Switzerland; C_{max} = Maximum observed concentration; CN = China; CNS = Central nervous system; Cum%Dose = Cumulative percentage of the dose eliminated (recovered); DB = Double-blind; DDI = Drug-drug interaction; DE = Germany; DS = Drug substance; ECG = Electrocardiogram; E_{max} = Maximum effect; ES = Spain; ESS = Epworth Sleepiness Scale; F = Female; FI = Finland; FR = France; HD = High dose; HI = Hepatic impairment; HP = Healthy participants; IR = Immediate release; IT = Italy; JP = Japan; KR = Korea; LD = Low dose; LTE = Long-term extension; M = Male; MAV = Markedly abnormal value; MD = Multiple dose; MRD = Multiple-rising dose; MWT = Maintenance of Wakefulness Test; NL = The Netherlands; NO = Norway; NT1 = Narcolepsy type 1; NT2 = Narcolepsy type 2; OVE = Oveporexton; PBO = Placebo; PC = Placebo-controlled; PK = Pharmacokinetic; PL = Poland; PSD = Particle size distribution; QD = Once daily; RI = Renal impairment; SE = Sweden; SRD = Single-rising dose; TEAE = Treatment-emergent adverse event; TID = Three times a day; UK = United Kingdom; US = United States; VAS = Visual analogue scale.
Source: Clinical reviewer-created from Applicant's documents Synopses of Individual Studies, Integrated Summary of Safety, individual Clinical Study Reports.

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7.2. Review Strategy

The efficacy review focuses on Study TAK-861-3001 and Study TAK-861-3002, the phase 3 randomized, double-blind, placebo-controlled, multicenter trials of oveporexton in patients 16 years of age and older with NT1; the Applicant also references these phase 3 studies in draft labeling. The Applicant has submitted studies TAK-861-3001 and TAK-861-3002 as substantial evidence of effectiveness of oveporexton for the treatment of NT1 in patients (b) (4) Additional supportive clinical efficacy data for NT1 are provided by the phase 2 Study TAK-861-2001. The biometrics reviewer for this application has conducted the primary efficacy analysis review and also reviewed the Applicant's statistical analyses. The review Division consulted the Division of Clinical Outcome Assessment (DCOA) for review of the clinical outcome assessments used in the efficacy trials.

The safety review includes detailed safety analyses of the two aforementioned phase 3 efficacy studies, TAK-861-3001 and TAK-861-3002, given their placebo-controlled data. The clinical reviewer also performed a detailed review of phase 2/3 study TAK-861-2003, which provides information about long-term safety. For each of these studies, the clinical reviewer reviewed the study reports, adverse event (AE) database, laboratory database, electrocardiogram (ECG) database, vital sign database, and participants' scores on the Columbia Suicide Severity Rating Scale (C-SSRS). In addition, the clinical reviewer reviewed the Applicant's integrated summary of safety (ISS) database, which includes data from additional narcolepsy trials as well as trials of oveporexton in healthy volunteers, for serious adverse events (SAEs). The clinical reviewer also considered the Applicant's draft label, and the most recent Periodic Benefit Risk Evaluation Report (PBER).

The Division consulted the Drug-Induced Liver Injury (DILI) team in the Division of Hepatology and Nutrition (DHN) and the Division of Urology, Obstetrics, and Gynecology (DUOG) for expert review of hepatic and urological treatment-emergent adverse events (TEAEs). The Division consulted the Interdisciplinary Review Team for QT Studies (QT/IRT) for expert review of the drug effect on QT interval based on data from the development program. FDA Controlled Substance Staff (CSS) were consulted for review of data related to human abuse liability potential. The Division of Pediatric and Maternal Health (DPMH) were consulted on issues related to use in pregnancy and lactation and provided language for labeling consistent with the Pregnancy and Lactation Labeling Rule (PLLR).

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8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study TAK-861-3001

8.1.1.1. Study Design

Overview and Objective

Study Title

"A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TAK-861 for the Treatment of Narcolepsy with Cataplexy (Narcolepsy Type 1)"

Primary Objectives

The study's primary objective was to assess the efficacy of oveporexton compared to placebo with regard to EDS as measured by the MWT.

Secondary Objectives

Secondary objectives included assessment of between-group difference in:

- Changes in EDS as measured by the Epworth Sleepiness Scale (ESS) total score
- Changes in cataplexy episodes as measured by the weekly cataplexy rate (WCR)
- Changes in sustained attention as measured by the psychomotor vigilance test (PVT)
- Changes in overall narcolepsy symptoms measured by the Patient Global Impression of Change (PGI-C) scale
- Changes in overall severity of narcolepsy symptoms measured by the Narcolepsy Severity Scale for Clinical Trials (NSS-CT)
- Changes in functional impacts of narcolepsy as assessed by the Functional Impacts of Narcolepsy Instrument (FINI)
- Changes in quality of life of participants, as assessed by the Short Form-36 Survey (SF-36).

Trial Design

Study Design Overview

Study TAK-861-3001 was a phase 3, randomized, double-blind, placebo-controlled, 12-week parallel-group trial to assess the safety and efficacy of two oral dosages of oveporexton for the treatment of NT1.

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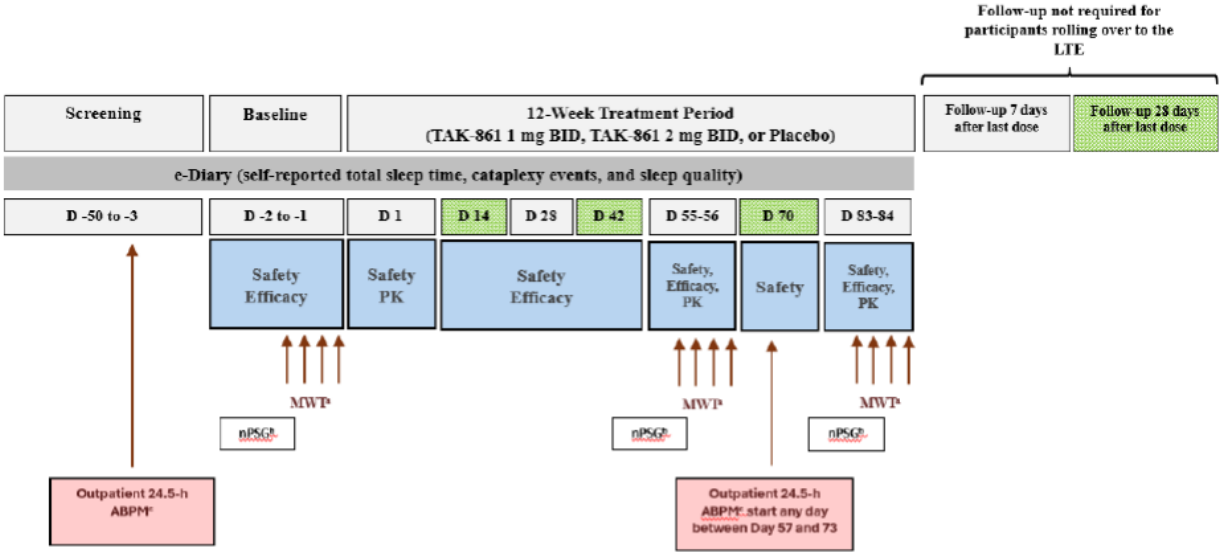
The study began with a screening period of up to 50 days, which could be extended on a case-by-case basis with Sponsor approval. During screening, participants were required to discontinue their narcolepsy medications, including antidepressants and sodium or multisalt oxybate. Starting no later than Day -16, participants completed an electronic diary to track cataplexy episodes. To be eligible, participants had to complete the diary for at least 11 of the 14 days between Day -16 and Day -3 and had to experience at least four partial and/or complete cataplexy episodes per week during this period.

Throughout the study, participants were required to stay overnight at the study site on three occasions: Days -2 to 1 (with one mandatory overnight at Day -2 and one optional overnight at Day -1), Days 55 to 56, and Days 83 to 84. After completing the 12-week treatment period, participants had the option to enroll in a long-term extension study under a separate protocol (Study TAK-861-2003). Those who chose not to participate in the extension study completed two follow-up visits at approximately 7 and 28 days after their final dose of study drug and could restart their restricted medications (except those associated with liver function test elevations) 7 days after the last dose. Participants who terminated the trial early were required to complete an early termination visit as soon as possible and a follow-up visit approximately 28 days after the last dose of trial intervention.

For a schematic of the study design, see Figure 11.

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Figure 11. Study Design – TAK-861-3001



Abbreviations: ABPM = ambulatory blood pressure monitoring; BID = twice daily; D = Day; e-Diary = electronic diary; h = hour; LTE = long-term extension; MWT = Maintenance of Wakefulness Test; nPSG = nocturnal polysomnography; PK = pharmacokinetic(s).
Note: Green shading indicated the visit consisted of a blood chemistry assessment and could be in-clinic or remote; the sample could be analyzed in a local laboratory.
[a] Confinement started on the evening of Days -2, 55, and 83 with MWT done on Days -1, 56, and 84.
[b] nPSG was done on the nights of Days -2, 55, and 83.
[c] ABPM recordings were obtained over at least 24.5 hours and participants were not confined to the clinical site during most of the 24.5-hour recording period. ABPM could be repeated as long as the recording ended no later than 1 day before check-in for the next nPSG/MWT.
Source: Clinical Study Report (CSR) of Study TAK-861-3001, Figure 1, page 24.

Trial Location

This multi-center study was conducted at 41 sites: 20 trial sites in Europe, 12 trial sites in North America, and 9 trial sites in Asia Pacific.

Diagnostic Criteria

The diagnosis of NT1 for participant screening was based on criteria from either the *International Classification of Sleep Disorders, Third Edition* (ICSD-3) or its revised version (ICSD-3-Text-Revised, ICSD-3-TR). According to ICSD-3 or ICSD-3-TR, both Criteria A and B must be met for a diagnosis of NT1. Criterion A required that participants experience daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months. Criterion B required the presence of one or both of the following: (1) cataplexy with a mean sleep latency of ≤8 minutes and two or more SOREMPs on an MSLT performed according to standard techniques (a SOREMP within 15 minutes of sleep onset on the preceding nocturnal polysomnogram could replace one of the SOREMPs on the MSLT), or (2) CSF hypocretin-1 concentration measured by immunoreactivity of either ≤110 pg/mL or less than one-third of mean values obtained in normal subjects with the same standardized assay.

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Key Eligibility Criteria

Key **inclusion** criteria were:

Besides having an ICSD-3 or ICSD-3-TR diagnosis of NT1 as previously described, for enrollment participants must have had the following:

- Age 18 to 70 years (inclusive). Participants aged 16 and 17 years could be included in some countries/trial sites (United States, Japan).
- Participants were required to have an ESS score of ≥11 at screening. If a participant had an ESS score of <11 at screening but was taking medication to treat NT1 symptoms, the ESS could be repeated after discontinuation or tapering of medications, prior to the Day -2 visit. The ESS is an 8-question self-report measure that asks patients to rate the likelihood that they would fall asleep while doing common daily activities, including sitting and reading, watching television, sitting in a public place, riding in a car or on public transport, lying down to rest in the afternoon, sitting and talking to someone, sitting quietly after lunch, and sitting in a stopped car. Each item on the ESS is rated from 0 (would never doze) to 3 (high chance of dozing), with a maximum total score of 24. An ESS score higher than 10 suggests that the subject is experiencing higher than average, or mild-to-moderate, sleepiness during daily activities.
- Participants had ≥4 partial or complete episodes of cataplexy per week, calculated as the weekly average over the 14-day period from Days -16 to -3 of the screening period. Participants must have completed self-reported cataplexy questions in the e-diary for at least 11 of 14 days during Days -16 to -3 to be considered compliant.
- Participant positive for the HLA genotype HLA-DQB1*06:02 (positive results for either homozygous or heterozygous alleles were considered "positive" and acceptable) or results from radioimmunoassay indicated the participant's CSF orexin/hypocretin-1 concentration was ≤110 pg/mL (or less than one-third of the mean values obtained in normal participants within the same standardized assay).

Key **exclusion** criteria were:

- The participant had a current medical disorder, other than narcolepsy with cataplexy, associated with EDS (e.g., restless leg syndrome) or apnea-hypopnea index (AHI) ≥15 on Day -2 nocturnal polysomnography (nPSG). Of note, participants with moderate-to-severe obstructive sleep apnea could be eligible if they were compliant with treatment and had an AHI <15 on treatment. The AHI measures the average number of apnea (complete breathing pauses) and hypopnea (partial obstruction) events per hour of sleep, used to diagnose and grade OSA. A normal range for adults is less than 5 events per hour, with 5 to 15 classified as mild.
- The participant: (a) had a history of myocardial infarction; (b) had a history of clinically significant hepatic disease, thyroid disease, coronary artery disease, cardiac rhythm abnormality or heart failure; or (c) had any medical condition (such as unstable cardiovascular, pulmonary, renal or gastrointestinal disease, or an ongoing condition

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causing bladder outlet obstruction or urinary retention [e.g., benign prostatic hyperplasia or pelvic organ prolapse with obstructive voiding symptoms, neurogenic bladder, or urethral stricture]) that would preclude enrollment in the view of the investigator.

- The participant had a clinically significant history of head injury or head trauma.
- The participant had a history of epilepsy, seizure, or convulsion (except for a single febrile seizure in childhood).
- The participant had a history of cerebral ischemia, transient ischemic attack (<5 years from screening), intracranial aneurysm, or arteriovenous malformation.
- Participants were excluded if they had one or more of the following psychiatric disorders: a current or past history of manic or hypomanic episodes, schizophrenia, any other psychotic disorder, obsessive compulsive disorder, intellectual disability, organic mental disorders, or mental disorders due to a general medical condition as defined in the DSM-5; a current diagnosis or history of substance use disorder as defined in the DSM-5 (though participants with a history of substance use disorder more than 12 months before baseline could be enrolled after consultation with the Sponsor); a current active major depressive episode or an active major depressive episode in the past 6 months; or any current unstable psychiatric disorder. Neurodevelopmental disorders such as attention deficit hyperactivity disorder were not excluded unless their severity prevented termination of prohibited medications.
- The participant was unable to refrain from or anticipated using excluded food products, beginning by Day -7 and continuing until 7 days after the last dose, or prohibited medications (including known cytochrome P450 type 3A inducers and moderate and strong inhibitors).
- Blood pressure >140 mm Hg (systolic) or >90 mm Hg (diastolic) during screening
- Resting heart rate <40 or >100 beats per minute during screening
- QTcF >450 milliseconds (genetically male) or >470 milliseconds (genetically female) on screening ECG
- Positive test for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus antibody, or HIV antibody/antigen
- Renal creatinine clearance ≤30 mL/min
- ALT or AST values >1.5 times the upper limit of normal or GGT >3 times the upper limit of normal
- Positive pregnancy test at screening or Day -2
- Breastfeeding
- Positive urine screen for drugs of abuse and/or positive alcohol test (with exceptions for prescribed medications and CBD products)
- Excessive caffeine consumption (>600 mg per day)

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- Alcohol consumption exceeding 2 standard drinks per day on average
- Nicotine dependence likely to affect sleep or unwillingness to refrain from smoking during confinement
- Considered at imminent risk of suicide or injury to self/others, attempted suicide within past year, or positive answers on Columbia-Suicide Severity Rating Scale (C-SSRS) Items 4 or 5 within past year
- Study site employee or immediate family member/dependent of study site employee
- Unwillingness to refrain from driving/operating dangerous machinery during sleepiness or medication changes
- Usual bedtime later than midnight, nighttime/variable shift work within past 6 months, or recent/planned travel with significant jet lag
- Unlikely to comply with protocol or unsuitable per investigator opinion
- Considered vulnerable as defined by local regulations.

Overall, the inclusion and exclusion criteria are acceptable. The Agency agreed to the inclusion of participants 16 to 17 years of age at the Type C meeting held on December 13, 2023. The adequacy of the small number of pediatric subjects 16 to 17 years enrolled to support generalization of the results to the pediatric population 16 to 17 years is one focus of this review. The ESS score threshold of ≥11 and the WCR requirement of ≥4 episodes per week are acceptable, as these criteria ensured enrollment of participants with at least mild NT1. The use of ICSD-3 diagnostic criteria is appropriate given that these criteria require objective evaluation of NT1 through either polysomnography or CSF orexin level measurement. The allowance for mild hypopnea (AHI 5 to 15) is acceptable. The liver function assessment requirements, including the thresholds for ALT, AST, and GGT values, are in accordance with recommendations from the DILI team, which was consulted during the development program. For additional details regarding hepatic safety monitoring, see the dedicated DILI team review.

Study Treatments, Dosage Selection, and Compliance

At the beginning of the 12-week-treatment period, on Day 1 participants were randomized in a 2:3:3 randomization ratio to receive:

- Matching placebo tablet, 1 placebo tablet BID, at least 3 hours apart
- Oveporexton tablet, 1 mg tablet BID, at least 3 hours apart
- Oveporexton tablet, 2 mg tablet BID, at least 3 hours apart

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Starting on the morning of Day 1, the study drug was administered at approximately the same time each day for 12 weeks, with the following schedules:

- For all days during the treatment period except clinic MWT days, participants were instructed to take the first dose no later than 10 am and the second dose at least 3 hours after the first morning dose, but no later than 1 pm.
- On clinic MWT days (Days 1, 56, and 84), the drug was administered as close to 8 am and 11 am as possible, respectively.

Investigators assessed compliance based on tablet dispensation and return for participants in the safety set. Compliance percentage was calculated as:

Equation 1. Compliance Percentage

$$\frac{\textbf{Total number of tablets dispensed} - \textbf{Total number of tablets returned}}{\textbf{2} \times (\textbf{date of last dose} - \textbf{date of first dose} + \textbf{1})} \times \textbf{100}\%$$

The denominator represents the expected total number of tablets (2 tablets per day × number of treatment days) based on the prescribed BID regimen.

In addition, the number and percentage of participants in the following compliance categories were summarized: <70%, 70 to 100%, and >100% by treatment group.

Concomitant Medications

Any medication or supplement used for the treatment of NT1 was required to be discontinued. Drugs associated with a risk of causing severe HI were prohibited. Known inducers and moderate or strong cytochrome P450 type 3A inhibitors were also excluded.

The medication taper plan took into consideration the medication pharmacokinetics (e.g., half-life), as illustrated in Table 52.

Table 52. Prohibited Concomitant Medications and Therapies

Prohibited Drug Category	Beginning of Restriction Period
Any investigational drug (restriction does not apply to TAK-861 administration described in this protocol or any approved drugs)	From 60 days (or 6 months if participant received an investigational biologic product) before the screening visit
Oxybate (multisalt or sodium)	Excluded from Day -16
Antidepressants with anticataplexy effect including tricyclic antidepressants, SSRIs, SNRIs, MAOIs	Excluded from Day -16 except for the following: Venlafaxine >150 mg/d: Day -23; Fluoxetine: Day -23
Psychostimulants including methylphenidate hydrochloride, modafinil, armodafinil, all amphetamine products, and solriamfetol	Excluded from Day -7
Pitolisant	Excluded from Day -7
Antipsychotic drugs	Excluded from 7 days or 5 half-lives (whichever is longer) before Day 1

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Prohibited Drug Category	Beginning of Restriction Period
Antianxiety medications/tranquilizers/sleeping medications including benzodiazepines, nonbenzodiazepine drugs, melatonergic agonists, and Yokukansan, Yokukansankachinpihange used for insomnia	Excluded from 7 days or 5 half-lives (whichever is longer) before Day 1
Varenicline (Chantix)	Excluded from 7 days or 5 half-lives (whichever is longer) before Day 1
St. John's wort, health foods containing melatonin	Excluded from 7 days or 5 half-lives (whichever is longer) before Day 1
Herbal medicine (topical use is not restricted)	Excluded from 7 days or 5 half-lives (whichever is longer) before Day 1
Mood stabilizers (such as lithium or valproic acid or other antipsychotic drugs)	Excluded from 7 days or 5 half-lives (whichever is longer) before Day 1
Anticonvulsants (including gabapentin)	Excluded from 7 days or 5 half-lives (whichever is longer) before Day 1
Anti-Parkinson disease drugs including amantadine	Excluded from 7 days or 5 half-lives (whichever is longer) before Day 1
Adrenocorticosteroids (excluded except for inhaled and topical; systemic administration would only occur during the study to treat an AE)	Excluded from 7 days or 5 half-lives (whichever is longer) before Day 1
Interferon, interleukin-formulation	Excluded from 7 days or 5 half-lives (whichever is longer) before Day 1
Muscle-relaxant drug (e.g., baclofen)	Excluded from 7 days or 5 half-lives (whichever is longer) before Day 1
Prescribed cannabis products containing THC (Non-prescribed cannabis products containing THC are prohibited throughout the study. Products containing CBD, but not THC, are allowed throughout the study; at the discretion of the investigator.)	Excluded from 7 days or 5 half-lives (whichever is longer) before Day 1
Centrally-acting antihistamines including OTC drugs and pharmaceutic adjuvants	Excluded from 7 days or 5 half-lives (whichever is longer) before Day 1
Antitussives with CNS action including theophylline	Excluded from 7 days or 5 half-lives (whichever is longer) before Day 1
Antiemetics with CNS action	Excluded from 7 days or 5 half-lives (whichever is longer) before Day 1
Opioid analgesics	Excluded from 7 days or 5 half-lives (whichever is longer) before Day 1
Nonopioid analgesics, other than occasional use of ibuprofen, naproxen, or aspirin (paracetamol and acetaminophen are prohibited)	Excluded from 7 days or 5 half-lives (whichever is longer) before Day 1
Medications associated with liver enzyme elevations including pemoline and atorvastatin (see more examples listed in Appendix 2; this category of medications cannot be restarted during the study)	Excluded from 7 days or 5 half-lives (whichever is longer) before Day 1
Known inducers and moderate or strong CYP3A inhibitors (Appendix 1)	Excluded from 7 days or 5 half-lives (whichever is longer) before Day 1

Abbreviations: AE = adverse event; CBD = cannabidiol; CNS = central nervous system; CYP = cytochrome P450; d = day; MAOI = monoamine oxidase inhibitors; OTC = over the counter; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; THC = tetrahydrocannabinol.
Note: If these medications are required to treat an AE, certain medications, including supplements, may be allowed after discussion and agreement between the Sponsor or designee and investigator, unless the investigator or investigator's designee considers immediate administration necessary. If tapering of any restricted medication is required, this tapering should be started early in the screening period, so the participant is no longer taking the medication by study day specified in this table.
Source: Applicant's CSR Study TAK-861-3001, Table 6.b, pages 69-71.

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Meals and Dietary Restrictions/Activity

Grapefruit and Seville oranges (including juices) were prohibited from Day -7 until 7 days after the last dose; alcohol was restricted 3 days before check-ins/visits and limited to ≤2 drinks per day at other times (or per local guidelines if more conservative); caffeine was prohibited on nPSG/MWT days and limited to ≤600 mg/day otherwise; and nicotine smoking was allowed outside the center but prohibited during confinement periods, with all restrictions subject to local legal age requirements. Participants abstained from strenuous exercise for 72 hours before check-in until checkout for all study visits, could engage in usual activities at other times except driving or operating hazardous machinery during periods of heightened sleepiness/fatigue or medication weaning/changes, and were required to follow local regulations and investigator guidance on driving restrictions.

Subject Completion, Dose Discontinuation, and Withdrawal

Subjects were considered to have completed the double-blind portion of the study if they completed Week 12.

Dosage adjustment was not allowed in the study. Discontinuation of participants from treatment or the study could occur for the following reasons: voluntary withdrawal of consent, loss to follow-up, pregnancy, major protocol deviations, appearance of an AE that would impose an unacceptable risk to the participant's health if participation continued (such as clinically significant LFT abnormalities, suicidal ideation/behavior as indicated by C-SSRS item 4 or 5 "yes" response or per investigator's judgment, or BP and HR increases, such as SBP >160 mm Hg, DBP >100 mm Hg, or HR >100 bpm, or the participant was unwilling to continue because of the AE.

Participants who discontinued study drug were asked to remain in the study for all protocol-specified visits (especially Week 12), were required to have blood chemistry performed at approximately 2 weeks and 28 days after the last dose and did not need follow-up visits if they completed the Week 12 visit and had discontinued study drug more than 28 days prior.

Schedule of Assessments

All participants checked into the clinic in the afternoon on Days -2, 55, and 83. Discharge occurred after the last study assessment of the last day was performed.

See Table 53 and Table 54 for the Study TAK-861-3001 schedule of assessment and procedures.

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Table 53. Schedule of Assessment Study TAK-861-3001

	Screening/ Baseline [a]			12-Week Treatment Period									Follow-up [b]	
				1									7 Days After Last Dose [d]/ ET [e]	28 Days After Last Dose
Day	**-50 to -3**	**-2**	**-1**	**Pre**	**Post**	**14 [c]**	**28**	**42 [c]**	**55**	**56**	**70 [c]**	**83**	**84**	**91**	**112 [c]**
Week	**NA**	**NA**		**NA**		**2 [c]**	**4**	**6 [c]**	**8**		**10 [c]**	**12**		**13**	**16 [c]**
Visit Window (days) [f]	**NA**	**-3**		**NA**		**±3**	**±3**	**±3**	**±3**		**±3**	**±3**		**±3**	**±3**
Visit Number	**1**	**2**		**3**		**4 [c]**	**5**	**6 [c]**	**7**		**8 [c]**	**9**		**10/11 [g]**	**12 [c]**
Administrative Procedures															
Informed consent	X														
Inclusion/exclusion criteria	X	X	X	X											
Demographics, medical history, medication history	X														
Concomitant medications/ procedures	*From signing the informed consent through the last visit on the study*														
Pregnancy avoidance counseling	*From signing the informed consent through the last visit on the study*														
Clinical Procedures and Assessments															
TAK-861/ placebo administration [h]				*Throughout the 12-week treatment period*											
AE assessment	*From signing the informed consent through the last visit on the study*														
BP (sitting) and HR (sitting) [i,j]	X	X	X	X	X		X		X	X		X	X	X	

	Screening/ Baseline [a]			12-Week Treatment Period									Follow-up [b]	
				1									7 Days After Last Dose [d]/ ET [e]	28 Days After Last Dose
Day	**-50 to -3**	**-2**	**-1**	**Pre**	**Post**	**14 [c]**	**28**	**42 [c]**	**55**	**56**	**70 [c]**	**83**	**84**	**91**	**112 [c]**
Week	**NA**	**NA**		**NA**		**2 [c]**	**4**	**6 [c]**	**8**		**10 [c]**	**12**		**13**	**16 [c]**
Visit Window (days) [f]	**NA**	**-3**		**NA**		**±3**	**±3**	**±3**	**±3**		**±3**	**±3**		**±3**	**±3**
Visit Number	**1**	**2**		**3**		**4 [c]**	**5**	**6 [c]**	**7**		**8 [c]**	**9**		**10/11 [g]**	**12 [c]**
Respiratory rate and temperature	X	X	X	X	X		X		X	X		X	X	X	
ABPM (start before time of first morning dose) [i,k]	X										X				
ECG [i]	X			X			X		X			X		X	
Height	X												X		
Body weight	X		X				X			X			X	X	
Physical examination [l]	X		X				X			X			X	X	
CSSRS	X		X				X			X			X	X	
PSG/MSLT (if needed to confirm eligibility)	X														
Fundoscopic examination and coagulation tests (required only for participants opting to undergo CSF sample collection)	X														
CSF sample for OX assessment [w]	X														
PAP compliance check (if applicable) [m]	X		X				X			X			X		
Clinical Laboratory Procedures and Assessments															
Serology (hBsAg, anti-HBc, anti-HCV, HIV)	X														

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	Screening/ Baseline [a]			12-Week Treatment Period									Follow-up [b]	
				1									7 Days After Last Dose [d]/ ET [e]	28 Days After Last Dose
Day	-50 to -3	-2	-1	Pre	Post	14 [c]	28	42 [c]	55	56	70 [c]	83	84	91	112 [c]
Week	NA	NA		NA		2 [c]	4	6 [c]	8		10 [c]	12		13	16 [c]
Visit Window (days) [f]	NA	-3		NA		±3	±3	±3	±3		±3	±3		±3	±3
Visit Number	1	2		3		4 [c]	5	6 [c]	7		8 [c]	9		10/11 [g]	12 [c]
Pregnancy test [n]	X	X					X		X			X		X	
FSH assessment (required for postmenopausal women only)	X														
Hematology [i]	X	X					X			X			X	X	
Blood chemistry [i]	X [o]	X		X [p]	X	X	X	X		X	X		X	X	X
Urinalysis	X	X		X [p]			X		X			X		X	
Urine drug screening [q]	X	X		X [p]			X		X			X			
Alcohol screening [r]	X	X		X [p]			X		X			X			
Blood samples for HLA genotyping [s]	X														
Blood sample for DNA analysis [t, w]	X														
Efficacy Assessments															
e-diary [u]	*Throughout the study, starting no later than Day -16 and continuing up to the Week 12 Visit is completed or rollover into LTE*														
nPSG [i, v]		X							X			X			
MWT [i]			X							X			X		
KSS	X		X							X			X		
Cognitive assessments (PVT, CPAL, ONB, iDSST-s) [i]	X		X							X			X		

	Screening/ Baseline [a]			12-Week Treatment Period									Follow-up [b]	
				1									7 Days After Last Dose [d]/ ET [e]	28 Days After Last Dose
Day	-50 to -3	-2	-1	Pre	Post	14 [c]	28	42 [c]	55	56	70 [c]	83	84	91	112 [c]
Week	NA	NA		NA		2 [c]	4	6 [c]	8		10 [c]	12		13	16 [c]
Visit Window (days) [f]	NA	-3		NA		±3	±3	±3	±3		±3	±3		±3	±3
Visit Number	1	2		3		4 [c]	5	6 [c]	7		8 [c]	9		10/11 [g]	12 [c]
ESS [i]	X		X				X			X			X		
CGI-S/PGI-S [i]	X		X				X			X			X		
CGI-C/PGI-C [i]							X			X			X		
NSS-CT [i]	X		X				X			X			X		
FINI [i]	X		X							X			X		
BC-CCI-E [i]	X		X							X			X		
TSQM [i]										X			X		
EQ-5D-5L [i]	X		X							X			X		
SF-36 [i]	X		X							X			X		
PK Evaluation															
Plasma sample for TAK-861 PK [i]				X	X				X	X		X	X		

Dark grey highlights indicate the visit requires overnight confinement; overnight stay on Day -1 at the clinic is optional. Light grey highlights indicate the visit consists of a blood chemistry assessment and may be in-clinic or remote; the sample can be collected and analyzed in a local laboratory.

Abbreviations: ABPM = ambulatory blood pressure monitoring; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BC-CCI-E = British Columbia Cognitive Complaints Inventory– Extended; BP = blood pressure; CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; CPAL = continuous paired associate learning; CSF = cerebrospinal fluid; CSSRS = Columbia Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eCRF = electronic case report form; e-diary = daily electronic patient-reported diary; EQ-5D-5L = EuroQol-5 Dimensions 5-Levels; ESS = Epworth Sleepiness Scale; ET = early termination; FINI = Functional Impacts of Narcolepsy Instrument; FSH = follicle stimulating hormone; GGT = gamma glutamyl transferase; hBsAg = Hepatitis B surface antigen; HBc = Hepatitis B core antigen; hCG = human chorionic gonadotropin; HCV = Hepatitis C virus; HIV = human immunodeficiency virus; HLA = human leukocytic antigen; HR = heart rate; iDSST-s = international Digit Symbol Substitution Test-symbols; IEC = independent ethics committee; IRB = institutional review board; KSS = Karolinska Sleepiness Scale; LFT = liver function test; LTE = long-term extension; MSLT = Multiple Sleep Latency Test; MWT = Maintenance of Wakefulness Test; NA = not applicable; nPSG = nocturnal polysomnography; NSS-CT = Narcolepsy Severity Scale for Clinical Trials; NT1 = narcolepsy type 1; ONB = One Back test; OX = orexin; PAP = positive airway pressure; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic(s); PSG = polysomnography; PVT = psychomotor vigilance test; SF-36 = Short Form-36 Survey; TSQM = Treatment Satisfaction Questionnaire for Medication

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[a] The screening window may be extended on a case-by-case basis after consultation with and approval from the Sponsor or designee for a reason such as an unexpected schedule change, or to perform a diagnostic PSG/MSLT or other assessments to confirm eligibility.
[b] Two follow-up visits are planned approximately 7 and 28 days after the final study drug intake (corresponding to Days 91 and 112 for participants whose final study drug intake is on Day 84). The follow-up visit 7 days after the final study drug intake is an in-clinic visit; the follow-up visit 28 days after the last dose may be in-clinic or remote (i.e., visit to an off-site laboratory to draw blood). After the Week 12 visit, participants who remained on study treatment throughout the treatment period will have the option to participate in an LTE study. Participants who immediately enroll in the LTE study will not have follow-up visits in this study.
[c] Visits 4, 6, 8, and 12 (i.e., Weeks 2, 6, 10, and 16, respectively) may be in-clinic or remote (i.e., visit to an off-site laboratory to draw blood).
[d] Discontinued medication (except medications associated with LFT elevations) can be restarted 7 days after the last administration of study drug.
[e] For all participants who withdraw early from the study, except those who refuse further contact, every effort should be deployed to have them attend an ET visit as soon as possible. If the ET visit coincides with another scheduled visit and the participant has not yet discontinued study drug, participants should be encouraged to complete all scheduled assessments. Participants who withdraw early will be encouraged to continue completing their daily e-diary until the ET visit. Further, every effort should be deployed to have these participant complete the follow-up visit 28 days after the last dose (the follow-up visit 7 days after the last dose is not needed in addition to the ET visit).
[f] If the date of a participant visit does not conform to the study plan, the timing of subsequent visits should be planned so that the visit schedule relative to the first study drug intake (Day 1) is maintained. For the Week 12 visit, every effort should be deployed to have participants come in as close to Day 84 as possible.
[g] Visit 10 for 7-day follow-up visit; Visit 11 for ET.
[h] On Day 1 and MWT days (Days 56 and 84), the first dose of TAK-861 or matched placebo will be administered in the morning by mouth (as close to 8 AM as possible). Participants will take the second dose at least 3 hours after the first morning dose (as close to 11 AM as possible). At home, the first dose should be taken in the morning, no later than 10 AM and the second dose should be taken at least 3 hours later, but no later than 1 PM.
[i] Refer to Table 54 for time requirements.
[j] BP will be checked (single measurement) with the participant resting for a minimum of 5 minutes and sitting with back supported. If systolic BP measurement is >160 mm Hg or diastolic BP measurement >100 mm Hg, BP measurement must be repeated in approximately 15 minutes to assess study drug discontinuation criteria, as described in Section 8.1.1.1. For screening BP assessment, if the BP is slightly elevated, the measurement may be repeated 3 times, and the median of the 3 recordings used to assess eligibility.
[k] The ABPM device will be applied on-site. ABPM should begin just before the first morning dose of study drug (or 8:00 AM ±2 hours for ABPM during screening period) and continue for at least 24.5 hours. If necessary, participants may delay their first morning dose (8 AM ±2 hours) so that it is taken right after the ABPM device begins recording. For convenience, site staff may offer to confine participants the evening before ABPM begins. The participants should not be confined to a clinical site for the majority of the 24.5-hour recording period, as real-world data collection while wearing the device is critical. ABPM should not be started the day before or during overnight confinement for a nPSG/MWT. If recording quality is not satisfactory, ABPM should be repeated. During screening the ABPM timing should account for potential repeat of the recording. ABPM recording during the treatment period will start any day between Days 57 and 73, inclusive, but must not start before the Day 56 Visit is completed. If this treatment period ABPM recording quality is not satisfactory, ABPM may be repeated as long as the recording ends no later than 1 day before check-in for the Week 12 visit.
[l] Full physical examination will be performed at screening and at the first follow-up visit (or ET visit). On all other time points, an abbreviated physical examination may be performed.
[m] Compliance with PAP is defined as having at least 4 hours of PAP use per night on at least 70% of nights for approximately 1 month (assessed by machine tracking time if possible).
[n] Pregnancy test is required for women of childbearing potential only. Serum pregnancy test will be done at screening. At all other time points, urine hCG testing may be done. Pregnancy testing can be repeated at any time at the investigator's discretion.
[o] An additional blood sample may be required during screening to ensure there is at least one AST, ALT and GGT result available from ≤16 days before randomization (fasting not required). This may be done in-clinic or remotely (i.e., visit to an off-site laboratory to draw blood).
[p] The pre 8 AM dose on Day 1 assessments of blood chemistry, urinalysis, urine drug screening, and alcohol screening are only required if the participant opted not to stay overnight at the clinic on Day -1.
[q] Urine drug screening may be performed using a dipstick and may be repeated any time at the investigator's discretion. Confirmatory urine drug tests will be performed in regions where available at the investigator's discretion.
[r] At the screening visit, alcohol screening will be done initially with a breathalyzer, and, if positive, a serum ethanol level will be obtained. For other time points, a breathalyzer will be done at check-in.
[s] Previous HLA results are acceptable if available for review by the investigator and provided for inclusion in the eCRF.
[t] One blood sample for DNA analysis may be collected at any visit before the initiation of study drug administration. Country-level participation to be determined by local regulations and IRB/IEC approval.
[u] e-diary measures, including self-reported assessments of sleep and cataplexy, will be obtained starting after the successful initial screening visit, no later than Day -16, and continuing until the Week 12 Visit entry is completed or until rollover into the LTE. In cases where the e-diary becomes unavailable, the site may use alternative methods to collect these data with approval from the Sponsor or designee. In case a participant did not complete cataplexy questions 11 of 14 days (i.e., is not compliant) during Days -16 to -3, the screening period can be extended at the discretion of the investigator to allow the participant to improve compliance.
[v] nPSG consisting of 8-hour nighttime PSG will be obtained. In the rare event that PSG exclusion criteria cannot be assessed by Day -1, dosing may be delayed until the issue is resolved. Site investigator may opt to repeat baseline nPSG/MWT before randomization. The Sponsor or designee should be consulted for any such situation.
Note: Per the inclusion criteria, if there is a potential participant with NT1 for whom a diagnostic PSG/MSLT was performed more than 15 years from screening or is not available, a diagnostic PSG/MSLT may be performed before Day -2.
[w] Assessment is optional.
Source: Applicant's CSR Study TAK-861-3001, Table 1.a, pages 29-32.

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Table 54. Efficacy, Safety and PK Assessment With Time Requirement—Study TAK-861-3001

	Screening/ Baseline [a]			12-Week Treatment Period									Follow-up [b]	
				1									7 Days After Last Dose [d]/ ET [e]	28 Days After Last Dose
Day	-50 to -3	-2	-1	Pre	Post	14 [c]	28	42 [c]	55	56	70 [c]	83	84	91	112 [c]
Week	NA	NA		NA		2 [c]	4	6 [c]	8		10 [c]	12		13	16 [c]
Visit Window (days) [f]	NA	-3		NA		±3	±3	±3	±3		±3	±3		±3	±3
Visit Number	1	2		3		4 [c]	5	6 [c]	7		8 [c]	9		10/11 [g]	12 [c]
Primary Specimens															
Hematology	Fasted	X					X			Fasted pre 8 AM dose			Fasted pre 8 AM dose	X	
Blood chemistry	Fasted [h]	X		Fasted pre 8 AM dose [i]	11 AM	X	X	X		Fasted pre 8 AM dose	X		Fasted pre 8 AM dose	X	X
Plasma sample for TAK-861 PK				Pre 8 AM dose	9:30 AM 11 AM (11 AM sample before second dose)				Anytime between after dinner and 1 h before nPSG start	Pre 8 AM dose 9:30 AM 11:30 AM 1:30 PM 3:30 PM		Anytime between after dinner and 1 h before nPSG start	Pre 8 AM dose 9:30 AM 11:30 AM 1:30 PM 3:30 PM		

	Screening/ Baseline [a]			12-Week Treatment Period									Follow-up [b]	
				1									7 Days After Last Dose [d]/ ET [e]	28 Days After Last Dose
Day	-50 to -3	-2	-1	Pre	Post	14 [c]	28	42 [c]	55	56	70 [c]	83	84	91	112 [c]
Week	NA	NA		NA		2 [c]	4	6 [c]	8		10 [c]	12		13	16 [c]
Visit Window (days) [f]	NA	-3		NA		±3	±3	±3	±3		±3	±3		±3	±3
Visit Number	1	2		3		4 [c]	5	6 [c]	7		8 [c]	9		10/11 [g]	12 [c]
Vital Signs and ECG															
BP (sitting) and HR (sitting)	X [l]	Anytime between after dinner and 1 h before nPSG start	Pre 8 AM 9:30 AM 11:30 AM 1:30 PM 3:30 PM	Pre 8 AM dose	9:30 AM 11:30 AM		X		Anytime between after dinner and 1 h before nPSG start	Pre 8 AM dose 9:30 AM 11:30 AM 1:30 PM 3:30 PM		Anytime between after dinner and 1 h before nPSG start	Pre 8 AM dose 9:30 AM 11:30 AM 1:30 PM 3:30 PM	X	
ABPM [j]	Start 24.5-h recording 8 AM ± 2 h										Start 24.5-h recording pre 8 AM dose				
ECG	X [l]			Pre 8 AM dose			X		X			X		X	
Efficacy Assessment															
nPSG		Overnight							Overnight			Overnight			
MWT (4 wake trials)			10 AM 12 PM 2 PM 4 PM							10 AM 12 PM 2 PM 4 PM			10 AM 12 PM 2 PM 4 PM		
KSS	Shortly before PVT		Shortly before each PVT							Shortly before each PVT			Shortly before each PVT		

	Screening/ Baseline [a]			12-Week Treatment Period									Follow-up [b]	
Day	-50 to -3	-2	-1	1 Pre	1 Post	14 [c]	28	42 [c]	55	56	70 [c]	83	84	7 Days After Last Dose [d]/ ET [e]	28 Days After Last Dose
														91	112 [c]
Week	NA	NA		NA		2 [c]	4	6 [c]	8		10 [c]	12		13	16 [c]
Visit Window (days) [f]	NA	-3		NA		±3	±3	±3	±3		±3	±3		±3	±3
Visit Number	1	2		3		4 [c]	5	6 [c]	7		8 [c]	9		10/11 [g]	12 [c]
PVT	X [l]		9 AM 3 PM							9 AM 3 PM			9 AM 3 PM		
CPAL, ONB, iDSST-s	X [l]		9 AM							9 AM			9 AM		
ESS	X [l]		After 1st MWT wake trial [k]				X			After 1st MWT wake trial [k]			After 1st MWT wake trial [k]		
CGI-S, PGI-S	X [l]		After 1st MWT wake trial [k]				X			After 1st MWT wake trial [k]			After 1st MWT wake trial [k]		
CGI-C, PGI-C							X			After 1st MWT wake trial [k]			After 1st MWT wake trial [k]		
TSQM										After 1st MWT wake trial [k]			After 1st MWT wake trial [k]		
BC-CCI-E, FINI, NSS-CT, SF-36, EQ-5D-5L	X [l]		After 1st MWT wake trial [k]				X (NSS-CT only)			After 1st MWT wake trial [k]			After 1st MWT wake trial [k]		

Dark grey highlights indicate the visit requires overnight confinement; overnight stay on Day -1 at the clinic is optional.
Light grey highlights indicate the visit consists of a blood chemistry assessment and may be in-clinic or remote; the sample can be collected and analyzed in a local laboratory.
Abbreviations: ABPM = ambulatory blood pressure monitoring; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BC-CCI-E = British Columbia Cognitive Complaints Inventory – Extended; BP = blood pressure; CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; CPAL = continuous paired associate learning; ECG = electrocardiogram; ediary = electronic patient-reported diary; EQ-5D-5L = EuroQol-5 Dimensions 5-Levels; ESS = Epworth Sleepiness Scale; ET = early termination; FINI = Functional Impacts of Narcolepsy Instrument; GGT = gamma glutamyl transferase; h = hour; HR = heart rate; iDSST-s = international Digit Symbol Substitution Test-symbols; LTE = long-term extension; MSLT = Multiple Sleep Latency Test; MWT = Maintenance of Wakefulness Test; NA = not applicable; nPSG = nocturnal polysomnography; NSS-CT = Narcolepsy Severity Scale for Clinical Trials; ONB = One Back test; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic(s); pre = pre-8am-dose; PSG = polysomnography; PVT = psychomotor vigilance test; SF-36 = Short Form-36 Survey; TSQM = Treatment Satisfaction Questionnaire for Medication
[a] The screening window may be extended on a case-by-case basis after consultation with and approval from the Sponsor or designee for a reason such as an unexpected schedule change, or to perform a diagnostic PSG/ MSLT or other assessments to confirm eligibility.
[b] Two follow-up visits are planned approximately 7 and 28 days after the final study drug intake (corresponding to Days 91 and 112 for participants whose final study drug intake is on Day 84). The follow-up visit 7 days after the final study drug intake is an in-clinic visit; the follow-up visit 28 days after the last dose may be in-clinic or remote (i.e., visit to an off-site laboratory to draw blood). After the Week 12 visit, participants who remained on study treatment throughout the treatment period will have the option to participate in an LTE study. Participants who immediately enroll in the LTE study will not have follow-up visits in this study.
[c] Visits 4, 6, 8, and 12 (i.e., Weeks 2, 6, 10, and 16, respectively) may be in-clinic or remote (i.e., visit to an off-site laboratory to draw blood).
[d] Discontinued medication (except medications associated with LFT elevations) can be restarted 7 days after the last administration of study drug.
[e] For all participants who withdraw early from the study, except those who refuse further contact, every effort should be deployed to have them attend an ET visit as soon as possible. If the ET visit coincides with another scheduled visit and the participant has not yet discontinued study drug, participants should be encouraged to complete all scheduled assessments. Participants who withdraw early will be encouraged to continue completing their daily e-diary until the ET visit. Further, every effort should be deployed to have these participants complete the follow-up visit
28 days after the last dose (the follow-up visit 7 days after the last dose is not needed in addition to the ET visit).
[f] If the date of a participant visit does not conform to the study plan, the timing of subsequent visits should be planned so that the visit schedule relative to the first study drug intake (Day 1) is maintained. For the Week 12 visit, every effort should be deployed to have participants come in as close to Day 84 as possible.
[g] Visit 10 for 7-day follow-up visit; Visit 11 for ET.
[h] An additional blood sample may be required during screening to ensure there is at least one AST, ALT, and GGT result available from ≤16 days before randomization (fasting not required). This may be done in-clinic or remotely (i.e., visit to an off-site laboratory to draw blood).
[i] Blood chemistry test only to be performed in case the participant opted not to stay overnight at the clinic on Day -1.
[j] The ABPM device will be applied on-site. ABPM should begin just before the first morning dose of study drug (or 8:00 AM ±2 hours for ABPM during screening period) and continue for at least 24.5 hours. If necessary, participants may delay their first morning dose (8 AM ±2 hours) so that it is taken right after the ABPM device begins recording. For convenience, site staff may offer to confine participants the evening before ABPM begins. The participants should not be confined to a clinical site for the majority of the 24.5-hour recording period, as real-world data collection while wearing the device is critical. ABPM should not be started the day before or during overnight confinement for an nPSG/MWT. If recording quality is not satisfactory, ABPM should be repeated. During screening the ABPM timing should account for potential repeat of the recording. ABPM recording during the treatment period will start any day between Days 57 and 73, inclusive, but must not start before the Day

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56 Visit is completed. If this treatment period ABPM recording quality is not satisfactory, ABPM may be repeated as long as the recording ends no later than 1 day before check-in for the Week 12 visit.
[k] Should begin after first MWT wake trial concludes but can continue when convenient during the remainder of the day. Additional details are provided in the study manual.
[l] At first visit, no specific time.
Source: Applicant's CSR Study TAK-861-3001, Table 1.b, pages 35-37.

Administrative Structure

According to the Applicant, an oveporexton program-level external Data Monitoring Committee (DMC) reviewed unblinded safety data quarterly and had access to data from the trial for safety assessment.

Per Applicant's report, a Liver Safety Evaluation Committee (LSEC), independent from the DMC, reviewed any cases in which there was concern for possible DILI, trial intervention discontinuations due to liver-related AEs, and liver-related SAEs.

Trial sites were monitored by (b) (4) Monitoring visits were conducted as directed by the site monitoring plan, and documentation of the visits was completed and filed. Monitors were provided access to participant and site records to review adherence to the protocol; compliance with GCP; and the completeness, accuracy, and consistency of the data.

A Sponsor representative trained the investigators to comply with GCP and to conduct the trial in accordance with the trial protocol.

The investigator or designee was to maintain 100% accountability for all trial interventions during his or her entire participation in the trial.

Each clinical trial site was responsible for performing internal quality management of trial conduct, data, and biological specimen collection, documentation, and completion. Quality control procedures and a risk assessment plan were to be developed and followed.

Accredited central laboratories were used to ensure consistency of analyses and reporting of results for clinical laboratory tests. Where local laboratories were used, their participation in internal and external quality control, quality assurance, and accreditation schemes were evaluated by the trial monitors.

Audits of the investigator trial sites and other facilities used during the trial were included as part of the independent Takeda quality assessment performed by Takeda or designees.

A designated vendor generated the randomization schedule using the permuted block method with the stratification factors (region and prior use of medication for NT1) and randomization ratio for the IRT system.

Summary

In general, the trial appears adequately planned. During the development program, the Applicant explored several dosages in the NT1 population and selected the dosages for the current study based on efficacy and safety/tolerability measures from the phase 2 trial (TAK-861-2001). At the EOP2 meeting held on June 12, 2024, the Applicant explained that the

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0.5 mg BID dosage in the phase 2 study showed an effect on the endpoint measuring cataplexy rate but did not survive multiplicity correction. Therefore, they planned to conduct the phase 3 studies with a 1 mg BID dosage arm of TAK-861 (instead of 0.5 mg BID), anticipating a positive result on both measures of EDS and cataplexy rate. On the other hand, they did not plan to include an arm with the highest dosage used in phase 2 (2 mg + 5 mg 3 hours apart) because, although it showed positive results on both EDS and cataplexy endpoints, it increased AEs by more than 20% with minimal improvement in endpoints compared to the lower dosages. The dosage selection appears adequate, and the Applicant's dosage strategy appears reasonable.

The randomization ratio of 2:3:3 (placebo: oveporexton 1 mg BID: oveporexton 2 mg BID) appears acceptable. Per Biometrics, this allocation provides adequate sample sizes for both dosage groups while maintaining a placebo control group (which is reasonable given that NT1 is a rare disease)—maximizing the number of participants receiving active treatment (helping optimize the safety information gained from the limited patient population) and minimizing the number of participants receiving placebo.

The procedures for maintaining the blind appear adequate, with all participants, irrespective of dosage level, receiving the same number of tablets and bottles.

Excluding all other medications that could have affected EDS or cataplexy appears adequate to isolate oveporexton's effect. The exclusion of medications associated with causing severe HI was appropriate during the development program, considering the cases of DILI observed with a drug of similar chemical structure (firazorexton).

The establishment of an independent DMC for quarterly review of unblinded safety data and a LSEC to review potential DILI cases and liver-related adverse events was appropriate and strengthened the safety oversight of this program, particularly given the hepatotoxicity concerns from the structurally related compound firazorexton.

Study Endpoints

Primary Endpoint

The primary endpoint was the change from Baseline to Week 12 in mean sleep latency during four Maintenance of Wakefulness Test (MWT) trials.

MWT is an objective measure used to assess a person's ability to remain awake during soporific (sleep-inducing) conditions. In the context of NT1, the MWT is used to evaluate the severity of EDS and the effectiveness of treatments aimed at promoting wakefulness. The test consists of four trials conducted throughout the day at 2-hour intervals (see Table 54). During each trial, the participant is connected to polysomnography (PSG) electrodes that continuously monitor brain waves, eye movements, breathing, heart rate, and muscle tone to objectively detect sleep onset. The participant sits in a comfortable, semi-reclined position in a quiet, dimly lit room and is instructed to try to stay awake for up to 40 minutes. The trial ends either when the participant falls asleep (defined by specific PSG criteria showing sleep onset as recorded by the electrodes) or when the maximum time is reached if the participant

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remains awake. The primary outcome is the mean sleep latency across all trials—that is, the average time it takes for the participant to fall asleep as objectively determined by the PSG recordings. Longer sleep latencies indicate a greater ability to maintain wakefulness, suggesting better control of EDS. In NT1 patients, baseline MWT sleep latencies are typically very short, reflecting their severe difficulty staying awake. Effective treatments should increase these latencies, demonstrating improved wakefulness.

Secondary Endpoints

The multiplicity protected secondary endpoints were:

- Weekly Cataplexy Rate (WCR): Irregular Sleep-Wake Rhythm Rate (IRR) of WCR at Week 12 (i.e., treatment effect of oveporexton compared to placebo on cataplexy as measured by the WCR at Week 12).
  - WCR was derived from the partial and full episodes of cataplexy reported by participants in the eDiary daily throughout the trial, averaged over 2-week periods. Specifically, participants completed a daily electronic patient-reported outcome (ePRO) diary to record the cataplexy episodes (both partial and full) that they experienced the previous day, and the day before the previous day if the diary from the previous day was not completed. WCR at baseline was derived as the average number of cataplexy episodes over a consecutive 2-week period prior to the Day 1 visit, adjusting for non-missing diary days. WCR was calculated every 2 weeks (Baseline, Week 2, Week 4, Week 6, Week 8, Week 10, and Week 12) as:

    (Total number of cataplexy episodes over the non-missing diary days for a given 2 weeks / number of non-missing diary days in these 2 weeks) × 7

  - Cataplexy episodes attributed to any day after end-of-study (EOS) day were not included in WCR calculation. In the event that a participant completed their Week 12 visit but the visit did not fall exactly on Day 84, the last two-week period for WCR calculation was the period from Day 71 to the earliest of Day 84 and their EOS day. If a diary attributed to a given day reported 0 or more episodes of cataplexy, the day was counted as a non-missing diary day. If a given day did not have any diary entry attributed to it, then it was counted as a missing diary day.
- The Epworth Sleepiness Scale (ESS): Change from Baseline to Week 12 in ESS total score.
  - ESS is a validated, self-administered questionnaire used to measure subjective daytime sleepiness. The ESS asks participants to rate their likelihood of dozing off or falling asleep in eight different everyday situations, such as sitting and reading, watching television, sitting inactive in a public place, or as a passenger in a car. Each situation is rated on a 4-point scale from 0 (would never doze) to 3 (high chance of dozing). The total ESS score ranges from 0 to 24, with higher scores indicating greater subjective sleepiness. In NT1 patients, baseline ESS scores are typically elevated, reflecting their severe EDS. A reduction in ESS score following treatment indicates improvement in subjective daytime sleepiness. In this study, the ESS was administered to assess sleep propensity on selected days indicated in the Schedule of Assessment

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Table 53. Participants was asked to evaluate their subjective sleepiness based on recalling their most recent daily life experiences.

- Patient Global Impression of Change (PGI-C): PGI-C score at Week 12.
  - The PGI-C is a patient-reported assessment that captured the overall change in a participant's narcolepsy symptoms as perceived by the participant compared to baseline. The Patient Global Impression rating scales are designed to capture the global effect of treatment on daytime sleepiness and overall narcolepsy symptoms from the patient's perspective. The PGI-C measured change due to treatment relative to Baseline using a 7-point scale ranging from "very much improved" to "very much worse." Per the Applicant's report, instructions were provided to participants to help ensure consistency in the assessments.
- Narcolepsy Severity Scale for Clinical Trials (NSS-CT): Change from Baseline to Week 12 in NSS-CT total score.
  - The NSS-CT is a 15-item self-administered questionnaire that assessed the severity and consequences of the five major narcolepsy symptoms: daytime sleepiness, cataplexy, hallucinations, sleep paralysis, and disrupted nighttime sleep (DNS). The total score ranged from 0 to 57, with higher scores indicating greater symptom severity. In a validation study by Dauvilliers et al., the mean symptom number, NSS-CT total score, and number of narcolepsy symptoms were statistically significantly different between treated and untreated patients, and the symptom number was associated with diagnosis delay, age at onset, and ESS and Beck Depression Inventory scores (Dauvilliers et al. 2020). This patient-reported outcome measure may provide a comprehensive assessment of the full spectrum of narcolepsy symptoms and their impact on patients.
- The Functional Impacts of Narcolepsy Instrument (FINI): Change from Baseline to Week 12 in all six FINI domain scores (Tiredness, Cognitive Functioning, Cataplexy, Social Activities, Everyday Activities, and Everyday Responsibilities).
  - FINI is a 28-item instrument developed by the Applicant to measure the functional impacts of narcolepsy across six domains that the Applicant reports are meaningful to narcolepsy patients: Tiredness (items 1 to 7), Cognitive Functioning (items 8 to 12), Cataplexy (items 13 to 17), Social Activities (items 18 to 21), Everyday Activities (items 22 to 25), and Everyday Responsibilities (items 26 to 28). Each item asked participants about the impact that narcolepsy had on their daily functioning during the past 7 days and was scored from 0 to 4, where 0 indicated the best health and 4 the worst. There was no total score; for each participant, an average score was calculated for each domain if at least half the items in the domain had been answered by summing the responses in the domain and dividing by the number of completed items. The average domain score was then standardized to a 0 to 100 scale, where 0 indicated the best health and 100 the worst health, calculated as (average score/4) × 100. A decrease from Baseline indicated improved health.

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- Short Form-36 Survey (SF-36): Change from Baseline to Week 12 in SF-36 mental and physical component summary scores.
  - The SF-36 is a 36-item, participant-reported survey that assessed participant health across eight scaled domains: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. Each scale was directly transformed into a 0 to 100 scale, where higher scores indicated less disability and better health (0 = maximum disability; 100 = no disability). When scores for all eight scales were available, two summary component scores were derived: the Physical Health Component Score and the Mental Health Component Score, both positively scored so that higher scores represented better health-related quality of life. This generic health status measure provided a broad assessment of the impact of the disorder and its treatment on overall physical and mental well-being.
- Psychomotor Vigilance Test (PVT): Change from Baseline to Week 12 in mean number of lapses on the PVT.
  - The PVT is a simple reaction performance task that aims to measure sustained attention with no learning effects over repeated administration. According to the Applicant, the PVT is sensitive to the effects of total sleep loss, partial sleep restriction, naps, and circadian variation in the healthy population. The duration of the test is 10 minutes.

<u>Exploratory Endpoints:</u>

- NSS-CT individual question scores: change from Baseline to Week 12 was analyzed separately for EDS, cataplexy, hallucinations, sleep paralysis, and DNS.
- Nocturnal Polysomnography (nPSG): The nPSG is a standardized procedure used to assess various sleep parameters, including sleep latency and sleep architecture. In this study, nPSG was used to evaluate the effects of oveporexton on sleep latency and nighttime sleep architecture. Participants with narcolepsy have disrupted nighttime sleep, with frequent awakenings and shorter REM latency that is associated with sleep paralysis and hypnagogic/hypnopompic hallucinations. In this study, there was an exploratory evaluation for changes in nighttime sleep metrics after oveporexton multiple dosing. The raw electroencephalogram data obtained in this study could be used for an exploratory evaluation of pharmacodynamic effects. Participants who used continuous PAP regularly at home were instructed to use continuous PAP during the nPSG.
- Clinical Global Impression Scale-Change (CGI-C) and Clinical Global Impression Scale-Severity (CGI-S): The CGI provides an overall clinician-determined summary measure of a participant's treatment experience that takes into account all available information, including knowledge of the participant's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the participant's ability to function. The CGI-C

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and CGI-S serve as global clinician-reported assessments of symptom severity and change of symptoms (relative to baseline), respectively.

- The CGI-S assesses the severity of overall narcolepsy symptoms using a 7-point Likert-type scale ranging from "normal, not at all ill" to "among the most extremely ill."
- The CGI-C is a clinician-rated assessment that evaluates the overall change in a participant's narcolepsy symptoms compared to Baseline. The CGI-C uses a 7-point Likert-type scale ranging from "very much improved" to "very much worse" to rate the extent to which participants' current overall narcolepsy symptoms had changed since Baseline.

The Applicant stated that clinicians were trained on what aspects to take into consideration when rating the CGI-C to ensure consistency of responses. These global assessments complemented objective and patient-reported measures by incorporating the clinician's comprehensive evaluation of treatment response across all aspects of the participant's condition.

- Patient Global Impression-Severity (PGI-S) and Patient Global Impression-Change (PGI-C): The PGI-S requires the participant to rate his/her disease severity at the time of assessment on a 5-point scale ranging from “none” to “very severe.” The PGI-C measures change due to treatment relative to baseline on a 7-point scale ranging from “very much improved” to “very much worse”.
- Daily e-Diary: Participants completed a daily e-diary to record self-reported total sleep time, cataplexy events, and sleep quality. In cases where the e-diary became unavailable, a site could use alternative methods to collect these data with approval from the Sponsor or designee.
- Cogstate Battery—Continuous Paired Associate Learning (CPAL), One Back Test (ONB), and International Digit Symbol Substitution Test-Symbols (iDSST-s): These cognitive tests measured visual associate memory (CPAL), working memory (ONB), and processing speed (iDSST-s) to assess the impact of narcolepsy and treatment on cognitive functioning.
- EuroQol 5-Dimension, 5-Level (EQ-5D-5L): The EQ-5D-5L is a standardized, generic (non-disease-specific), participant-reported measure of health-related quality of life. The descriptive system comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each rated on a five-level severity scale, from which dimension scores can be presented as a health profile or converted to a single summary utility index. Participants also self-rate their overall health on a visual analog scale (VAS) ranging from 0 to 100 (where 100 is the best imaginable health state).
- Treatment Satisfaction Questionnaire for Medication (TSQM) is a generic patient-reported outcome assessment that measured satisfaction with treatment across four dimensions: effectiveness, side effects, convenience, and global satisfaction, with scores ranging from 0 to 100 where higher scores indicated better treatment satisfaction.
- The British Columbia Cognitive Complaints Inventory-Extended (BC-CCI-E) is a 9-item scale that assessed perceived cognitive difficulties and their functional and quality of life impacts,

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with total scores ranging from 0 to 18 where higher scores indicated greater impact of cognitive difficulties.

- The Karolinska Sleepiness Scale (KSS) is a 10-point, self-rating scale that measured subjective sleepiness at a particular moment, with higher scores indicating greater sleepiness; it was administered prior to the PVT to assess the participant's arousal state at the time of assessment.

Statistical Analysis Plan

The primary endpoint of MWT was derived from four MWT sessions (10 am, 12 pm, 2 pm, and 4 pm) recorded on Day -1, Week 8 (Day 56), and Week 12 (Day 84) for each subject using the mean of the sleep latency (SL). If there were two or more missing values, the mean was assigned as missing for that day. The change from Baseline for the mean of the four MWT session was derived for each subject at each post-dose visit.

The primary estimand was defined by the Applicant as:

- Treatment: TAK-861 (two dosage levels: 1 mg BID or 2 mg BID) or placebo.
- Population: Targeted patient population as defined through the inclusion/exclusion criteria.
- Endpoint: Change from Baseline to Week 12 in mean sleep latency from the MWT.
- Population level summary: The mean of the endpoint was estimated for each treatment group and comparison to placebo was based on the difference in means between treatment groups.
- Strategy for Addressing Intercurrent Events: The treatment policy strategy was used to address all intercurrent events. The anticipated intercurrent events included premature discontinuation of study drug. Participants who discontinued study drug were asked to remain in the study and continue all protocol-specified visits and procedures.

The primary endpoint was analyzed using the linear mixed-effect model for repeated measures (MMRM), using change from Baseline in mean SL as the response. The model included visit, treatment, treatment-by-visit interaction, baseline mean SL, and electronic data capture (EDC)-derived indicator for prior use of medication for narcolepsy (requiring washout) as fixed effects.

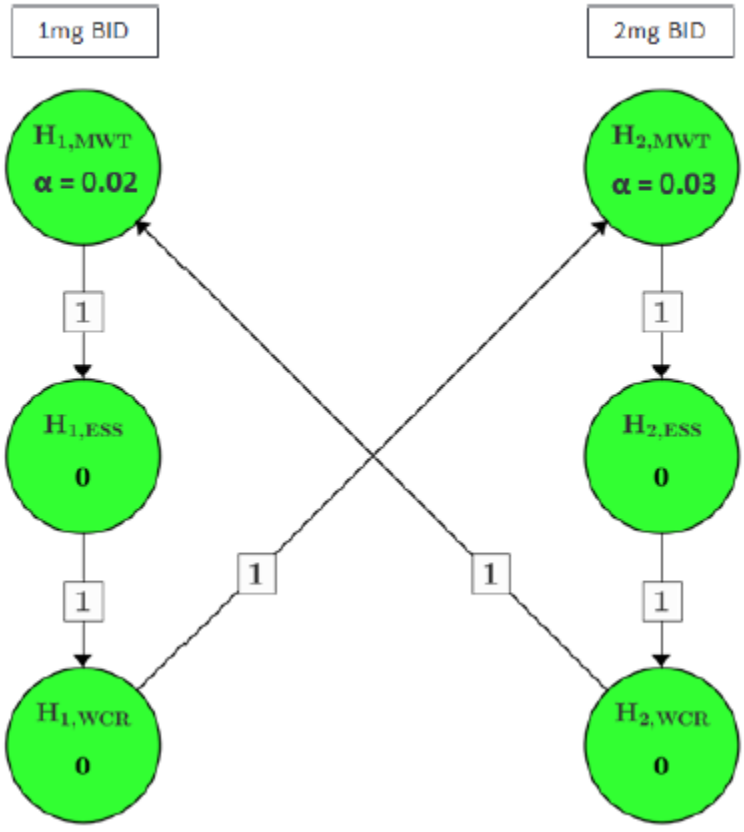
The following multiple imputation method was used to impute missing data: for subjects who did not complete the study, regardless of treatment group, all missing data were imputed under the assumption that the joint distribution of observed and missing outcomes is the same as that from the placebo group. For subjects that completed the study, but still have missing data, regardless of treatment group, all missing data were assumed to be missing at random (MAR) and were imputed under this assumption. Multiple imputation was used to account for uncertainty in the imputation process. Analysis results from all imputed datasets were combined using Rubin’s method. Estimated treatment difference along with the 95% CI and the corresponding p-value for the treatment effects at each visit were reported.

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All efficacy analyses were presented in the Full Analysis Set (FAS), defined as all participants who were randomized. All participants in the FAS were analyzed according to the treatment group to which they were randomized.

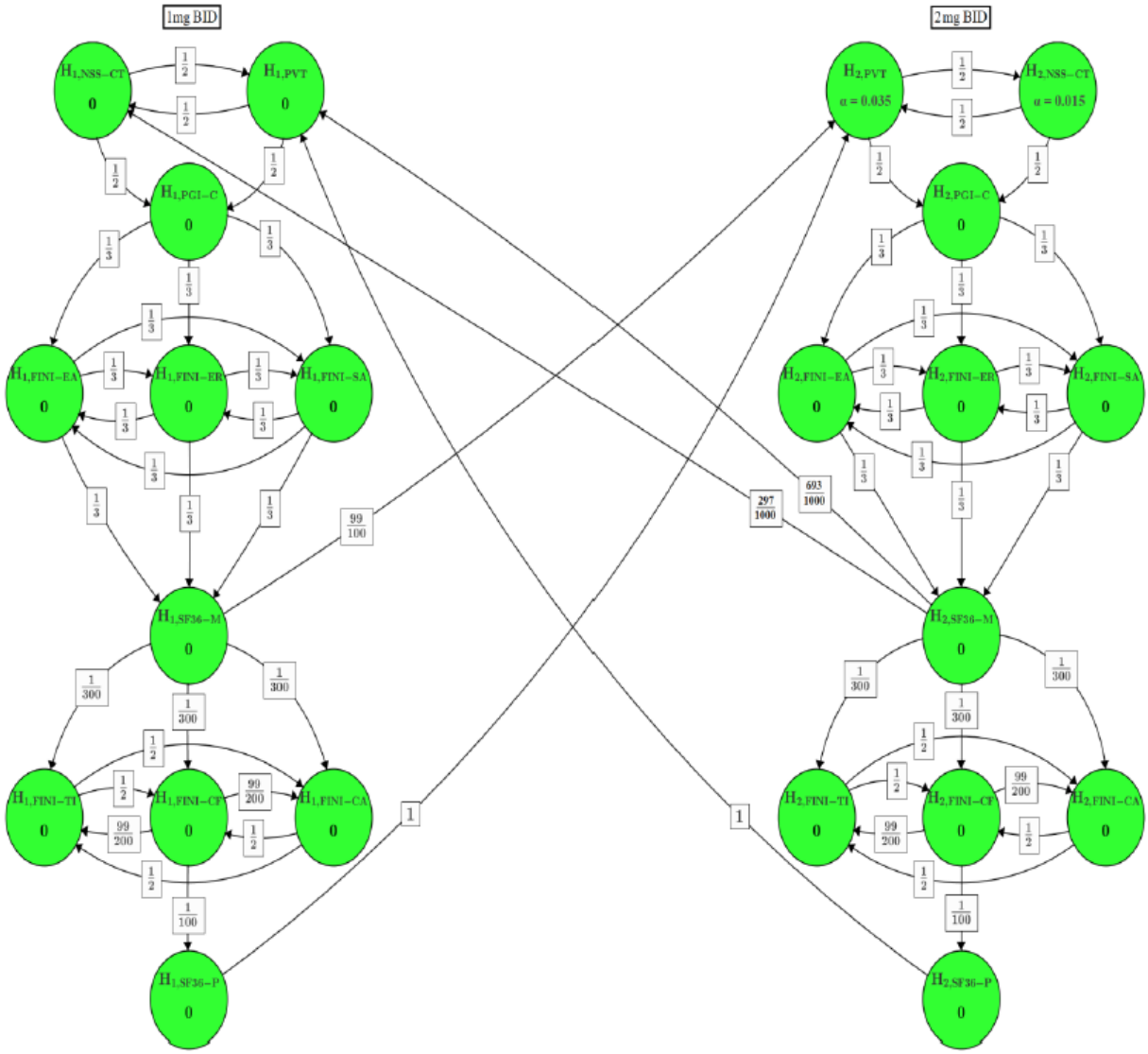
The hierarchical multiple testing procedure employed a graphical testing approach. The primary and secondary efficacy endpoints were grouped into two families, where family 1 included hypotheses associated with change from Baseline to Week 12 in mean sleep latency on the MWT, change from Baseline to Week 12 in ESS total score, and WCR at Week 12. Family 2 included hypotheses associated with the remaining secondary efficacy endpoints (change from Baseline to Week 12 in mean number of lapses on the PVT, PGI-C score at Week 12, change from Baseline to Week 12 in NSS-CT total score, change from Baseline to Week 12 in six FINI domain scores, and change from Baseline to Week 12 in SF-36 mental and physical component summary scores). The multiple testing approach for each family is presented in Figure 12 and Figure 13, respectively.

Figure 12. Multiple Testing Procedure, Family 1 (Study TAK-861-3001)



Source: Statistical Analysis Plan v2.0, page 19

Figure 13. Multiple Testing Procedure, Family 2 (Study TAK-861-3001)



Source: Statistical Analysis Plan v2.0, page 20

Sensitivity analyses provided by the Applicant included using Tobit model to account for ceiling effect in MWT and exploring alternative missing data handling approaches.

For the secondary endpoints, the estimand was defined similarly to the primary estimand. The continuous secondary endpoints of ESS, NSS-CT, FINI, and SF-36 were analyzed using an MMRM model similar to the primary analysis method. WCR was analyzed using a generalized estimating equations (GEE) model featuring a negative binomial distribution and a log link function. The response variable was the total number of cataplexy attacks within a given 2-week period, and the log of (the number of nonmissing diary days over the given 2-week period/7) was included as offset in the model to estimate the weekly cataplexy rate. The model included visit, treatment, and treatment-by-visit interaction, baseline WCR, and EDC-derived indicator for prior use of medication for narcolepsy (requiring washout) as

explanatory variables. An unstructured working correlation matrix was used initially in the model. If there were convergence issues with the model, an exchangeable working correlation matrix was used, followed by an independent working correlation matrix, until convergence was reached. The estimated incidence rate of weekly cataplexy for each treatment group and the associated 95% CIs were extracted from the model, along with the incidence rate ratio (IRR) of weekly cataplexy (TAK-861/placebo) for all TAK-861 treatment groups, and the associated 95% CIs and two-sided p-values. PVT was analyzed using a constrained longitudinal data analysis (cLDA) model after a square root transformation, and PGI-C responder status was analyzed by GEE featuring a binomial distribution and a logit link function. The responder indicator was used as the response variable in the model. The model included visit, treatment, and treatment-by-visit interaction, baseline PGI-S (as a continuous variable), and EDC-derived indicator for prior use of medication for narcolepsy (requiring washout) as explanatory variables.

The statistical analysis plan was aligned with the Agency a priori, with the exception of several minor technical comments. Most notably, there was a concern about the model chosen for the secondary endpoint of PVT, which utilized a non-traditional cLDA model and relied on delta method approximations. For this reason, when analyzing PVT, the Agency also explored a more standard MMRM approach consistent with the primary analysis model. In general, the analyses proposed by the Applicant were suitable for the analysis of the endpoints of interest. The same applies to the statistical analysis of TAK-861-3002.

Given that the Applicant is seeking an indication for NT1 as a whole rather than for individual symptoms, the endpoint selection strategy must reflect the multidimensional complexity of the disorder. NT1 is characterized by a well-described pentad of symptoms (excessive daytime sleepiness, cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and disrupted nocturnal sleep, as reviewed in Bassetti et al., 2019, and described in ICSD-3, and no single endpoint is sufficient to capture the breadth of the disease burden or the full scope of a treatment's effect on NT1. Accordingly, the endpoint hierarchy was structured with two guiding principles: (1) ensuring coverage of the NT1 symptom pentad across the primary and secondary endpoints, and (2) balancing objective, performance-based measures with patient-centered, patient-reported outcomes (PROs) to mitigate ascertainment bias while preserving clinical meaningfulness from the patient's perspective.

- Objectivity and Clinical Meaningfulness of the Primary Endpoint: The MWT was selected as the primary endpoint because it provides an objective, PSG-confirmed measure of a patient's ability to sustain wakefulness under standardized soporific conditions—a core functional deficit in NT1. As an instrumented, observer-independent measure of sleep onset latency, the MWT minimizes the potential for response bias inherent in self-reported assessments of sleepiness. Furthermore, improvement in MWT latency represents a clinically meaningful outcome, as the inability to maintain wakefulness is central to the disease definition, carries significant safety implications (e.g., driving, occupational functioning), and is a common treatment target in the NT1 patient community. The Agency considered the MWT to be an appropriate outcome measure for the primary analysis given

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its established use in narcolepsy clinical trials and its capacity to objectively quantify the severity of EDS and treatment response.

- Endpoint Coverage of the NT1 Symptom Pentad and Disease Specificity: Among the multiplicity-protected secondary endpoints, the WCR was prioritized as the first secondary endpoint because cataplexy is the pathognomonic feature of NT1, distinguishing it from other central disorders of hypersomnolence, including NT2 and idiopathic hypersomnia. The inclusion of WCR as a co-primary or high-priority secondary endpoint therefore ensures that a therapeutic claim for NT1 is directly supported by evidence of efficacy specific to the condition. Cataplexy is directly attributable to orexin deficiency—the presumed underlying pathophysiology of NT1—and the symptom's reduction constitutes a meaningful clinical benefit independent of improvements in EDS.
- Patient-Centered Endpoints and Alignment with Patient Perspective: Consistent with the Agency's patient-focused drug development (PFDD) framework, the endpoint hierarchy was also designed to incorporate the patient's perspective on treatment benefit. The Epworth Sleepiness Scale (ESS), although not without problems (e.g., requiring patients to imagine how they would react in hypothetical situations), was included as a multiplicity-protected secondary endpoint because it captures subjective daytime sleepiness—a dimension of disease burden that patients consistently identify as among the most disabling features of NT1 (Voice of Patient Report, Public Meeting: September 24, 2013, Report Date: June 2014, CDER 2014)—and because it has been widely used as a PRO in narcolepsy clinical programs. Its inclusion alongside the MWT allows for a concordance assessment between objective wakefulness capacity and the patient's subjective experience of sleepiness, which are related but distinct constructs.
- The Narcolepsy Severity Scale for Clinical Trials (NSS-CT) was further included as a protected secondary endpoint because, as a validated, disease-specific, 15-item patient-reported instrument, it comprehensively addresses all five components of the NT1 symptom pentad (daytime sleepiness, cataplexy, hallucinations, sleep paralysis, and DNS). This breadth of coverage is particularly important in the context of an indication claim for NT1 as a whole, as it ensures that the secondary endpoint set captures the full disease profile rather than a subset of symptoms.
- Exploratory Objective Endpoints: Biological Plausibility and Mechanistic Evidence: Although classified as exploratory, the nPSG assessment—with particular attention to REM sleep latency—was considered an important additional dimension of the trial's evidentiary framework. Given that NT1 is defined by orexin-mediated dysregulation of REM sleep, and that abbreviated or abnormal REM sleep latency is one of the objective biological hallmarks of the disease, changes in nPSG-derived REM latency following oveporexton treatment would provide corroborating mechanistic and pharmacodynamic evidence of the drug's effect on the core neuropathological substrate of NT1. As an objective, PSG-confirmed measure, nPSG REM latency findings—if directionally consistent with the primary and secondary endpoints—support the biological plausibility of the observed clinical effects and strengthen the overall characterization of the drug's benefit-risk profile.

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Protocol Amendments

The initial protocol was amended once locally for the EU (July 15, 2024) and once globally (October 23, 2024). The first participant was enrolled on August 21, 2024, under the original protocol.

Noteworthy Changes

Initial Protocol EU Version 1 (July 15, 2024):

- Changed the primary endpoint for EDS assessment from MWT to ESS total score exclusively in the EU/EEA (MWT became a secondary endpoint in EU/EEA only).
- Clarified that pregnant participants were to be withdrawn from treatment but preferably not from the trial.
- Clarified analysis set definitions: safety set analyzed according to treatment received; full analysis set (FAS) analyzed according to randomized treatment assignment.
- Moved the PVT number of lapses endpoint from Family 1 to Family 2.
- Added missing data handling section specifying placebo-based multiple imputation for intercurrent events (ICEs).

Global Protocol Amendment 1 (October 23, 2024):

- Incorporated the EU-specific changes regarding ESS as primary endpoint in EU/EEA.
- Specified that primary and secondary endpoints (MWT, ESS, NSS-CT, FINI, PVT lapses, SF-36) were measured as change from Baseline at Week 12.
- Changed PVT assessment from single 3 pm session to mean of two intraday sessions.
- Allowed ESS retesting after medication discontinuation/tapering if screening ESS was <11 in participants taking NT1 medications.
- Clarified that pregnant participants were to be withdrawn from treatment but preferably not from the trial.
- Clarified that all participants in the safety set were to be analyzed according to the treatment they received.
- Clarified that the FAS consisted of all participants who were randomized and all participants in the FAS were to be analyzed according to the treatment group to which they were randomized.
- The endpoint of number of lapses on the PVT was moved from Family 1 to Family 2.
- Added a section on missing data handling. Clarified that placebo-based multiple imputation would be used to handle missing data due to ICEs in the primary analysis.

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The protocol amendments do not appear to have substantially affected the conduct or integrity of the trial. The first participant was enrolled on August 21, 2024, under the original protocol, and the amendments were implemented relatively early in the trial timeline.

The Global Protocol Amendment 1 was implemented primarily in response to FDA feedback. Notably, during the development program, the Agency informed the Applicant that the ESS was not considered an adequate primary endpoint because it is a subjective measure and recommended the MWT as the preferred primary endpoint due to its objective nature. The EU-specific amendment, which designated ESS as the primary endpoint exclusively in the EU/EEA, reflects regional regulatory differences but does not impact the U.S. regulatory assessment, where MWT remains the primary endpoint.

Additionally, at the EOP2 meeting, the Agency recommended that the Applicant change their MWT endpoint from assessment at Week 12 to change from Baseline at Week 12, as the trajectory of change over time provides important information for labeling to inform healthcare providers about the expected treatment response pattern. The Applicant incorporated this recommendation into Global Protocol Amendment 1, which specified that primary and secondary endpoints were to be measured as change from Baseline at Week 12.

The other amendments primarily consisted of clarifications to analysis set definitions, missing data handling procedures, and minor adjustments to assessment timing (e.g., PVT measurement from two intraday sessions rather than a single session), none of which appear to compromise the trial's scientific validity or interpretability.

8.1.1.2. Study Results

Compliance With Good Clinical Practices

The Applicant states that “This trial was conducted with the highest respect for the individual participants in accordance with the protocol and ethical principles that have their origins in the Declaration of Helsinki and in compliance with IRB regulations stated in Title 21 of the US Code of Federal Regulations Part 56, ICH Harmonised Tripartite Guideline for GCP E6, IECs and EU Clinical Trials Regulation No 536/2014, and all applicable industry regulations and applicable national and local laws and regulations,“ and “The clinical trial protocol, protocol amendments, the investigator’s brochure, a sample ICF, and other trial-related documents were reviewed and approved by the local or central IRBs/IECs of all trial sites.”

The Applicant has provided attestation that Study TAK-861-3001 was conducted in accordance with Good Clinical Practice (GCP).

Financial Disclosure

The Applicant has adequately disclosed financial interests and arrangements with clinical investigators. The Applicant did not disclose any interests or arrangements that raised questions about the integrity of the study data.

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Patient Disposition

A total of 234 individuals were screened for the trial, from whom 168 participants were enrolled across 41 sites in Japan, Europe, and North America. Of the 66 screen failures, 57 participants did not meet the inclusion/exclusion criteria, six withdrew consent, one experienced an adverse event, and two were classified as "other" (no additional information available). All 168 enrolled participants were randomized to one of three groups: placebo (n=41), oveporexton 1 mg BID (n=61), or oveporexton 2 mg BID (n=66). In total, 167 participants received at least one dose of the trial intervention. One participant in the oveporexton 1 mg BID group was randomized but not treated, did not complete the pre-dose pharmacokinetic (PK) collection, and was subsequently lost to follow-up.

Of the 167 treated participants, 10 (6.0%) discontinued the trial. The reasons for discontinuation are summarized by treatment group in Table 55 below.

Table 55. Participant Discontinuations by Treatment Group – Safety Set (Study TAK-861-3001)

Reason for Discontinuation	Placebo (N=41) n (%)	Overall Oveporexton (N=126) n (%)	Total (N=167) n (%)
Total Discontinuations	5 (12.2%)	5 (4.0%)	10 (6.0%)
Adverse Event	1 (2.4%)	3 (2.4%)	4 (2.4%)
Protocol Deviation	2 (4.9%)	1 (0.8%)	3 (1.8%)
Withdrawal of Consent	2 (4.9%)	1 (0.8%)	3 (1.8%)

Note: The "Overall Oveporexton" group combines the 1 mg BID (n=60 treated) and 2 mg BID (n=66 treated) groups. Percentages are calculated using the number of treated participants in each group as the denominator.
Source: Clinical reviewer-created from Study TAK861-3001 CSR, Table 5 and Figure 2

In total, 157 participants completed the trial, representing 87.8% (36/41) of the placebo group and 96.0% (121/126) of the overall oveporexton group. Of these completers, 150 (95.5%) entered the long-term extension (LTE) trial. A full summary of participant disposition, including the number of participants (n) for each category, is provided in Table 56.

Table 56. Participant Disposition (All Randomized Subjects, Study TAK-861-3001)

Participant Disposition	Placebo (N=41) n (%)	OVE 1 mg BID (N=61) n (%)	OVE 2 mg BID (N=66) n (%)	OVE Overall (N=127) n (%)	Total (N=168) n (%)
Randomized	41 (100)	61 (100)	66 (100)	127 (100)	168 (100)
Randomized and treated	41 (100)	60 (98.4)	66 (100)	126 (99.2)	167 (99.4)
Completed trial	36 (87.8)	57 (93.4)	64 (97.0)	121 (95.3)	157 (93.5)
Discontinued trial	5 (12.2)	4 (6.6)	2 (3.0)	6 (4.7)	11 (6.5)
Randomized but not treated	0	1 (1.6)	0	1 (<1)	1 (<1)
Treated	5 (12.2)	3 (4.9)	2 (3.0)	5 (3.9)	10 (6.0)
Completed trial intervention	36 (87.8)	57 (93.4)	64 (97.0)	121 (95.3)	157 (93.5)
Discontinued trial intervention	5 (12.2)	3 (4.9)	2 (3.0)	5 (3.9)	10 (6.0)
Continuing to LTE trial	34 (82.9)	57 (93.4)	59 (89.4)	116 (91.3)	150 (89.3)
Reason for discontinuation of trial for randomized but not treated participants					
Lost to follow-up	0	1 (1.6)	0	1 (<1)	1 (<1)

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Participant Disposition	Placebo (N=41) n (%)	OVE 1 mg BID (N=61) n (%)	OVE 2 mg BID (N=66) n (%)	OVE Overall (N=127) n (%)	Total (N=168) n (%)
Reason for discontinuation of trial for treated participants					
AE	1 (2.4)	3 (4.9)	0	3 (2.4)	4 (2.4)
Protocol deviation	2 (4.9)	0	1 (1.5)	1 (<1)	3 (1.8)
Withdrawal by participant	2 (4.9)	0	1 (1.5)	1 (<1)	3 (1.8)
Reason for discontinuation of trial intervention					
AE	1 (2.4)	3 (4.9)	0	3 (2.4)	4 (2.4)
Protocol deviation	2 (4.9)	0	1 (1.5)	1 (<1)	3 (1.8)
Withdrawal by participant	2 (4.9)	0	1 (1.5)	1 (<1)	3 (1.8)

Source: Applicant's CSR Study TAK861-3001, Table 5, page 39

The screen failure rate was 28.2% (66/234), which is reasonable for a trial with specific eligibility criteria in a rare disease population. The majority of screen failures (86.4%; 57/66) were due to not meeting inclusion/exclusion criteria, which does not raise concerns about the representativeness of the enrolled population.

Few participants discontinued the overall program. The discontinuation rate was slightly higher in the placebo group (12.2%; 5/41) compared to the overall oveporexton group (4.0%; 5/126).

The specific adverse events (AEs) and protocol deviations that led to these discontinuations are described in detail in the paragraphs that follow.

Protocol Violations/Deviations

Participant-Level Deviations

Significant protocol deviations affected 52 of 168 participants (31.0%) in the randomized sample. The overall proportion of participants with at least one deviation was similar between the placebo (29.3%) and overall oveporexton (31.5%) groups.

Key Deviation Categories by Treatment Group:

- Good Clinical Practice (GCP) Deviations (12.5% of all participants): This was the most frequent category and was balanced between the placebo (12.2%) and overall oveporexton (12.6%) groups. The majority of these (n=14) were administrative issues and were described as "site staff recorded participant credentials used to access the Signant Health TrialMax systems." Seven cases involved breaches of participant confidentiality.
- Informed Consent Deviations (8.9% of all participants): These were more frequent in the overall oveporexton group (9.4%) than the placebo group (7.3%). The deviation for a "consenting process was missed" occurred in six participants, total. This deviation was heavily concentrated in the oveporexton 2 mg BID group, affecting five participants (7.6% of that group), compared to only one participant (2.4%) in the placebo group.

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- Eligibility Criteria Deviations (5.4% of all participants): Nine participants were randomized despite not meeting the study's eligibility criteria. This deviation was more frequent in the placebo group (7.3%) compared to the overall oveporexton group (4.7%).
  - Placebo group:
    - One participant was randomized with an Epworth Sleepiness Scale (ESS) score below 11, failing to meet inclusion criterion 6.
    - One participant was randomized based on a diagnostic PSG/MSLT conducted more than 15 years prior without a repeat assessment before Day -2, failing to meet inclusion criterion 5.
    - One participant was randomized with an Apnea-Hypopnea Index (AHI) at or greater than 15, meeting exclusion criterion 1. This participant was subsequently discontinued from the study.
  - Oveporexton group:
    - One participant was randomized despite having a current medical disorder associated with Excessive Daytime Sleepiness (EDS), meeting exclusion criterion 1.
    - Three participants were randomized with a Weekly Cataplexy Rate (WCR) score of 3 or less, failing to meet inclusion criterion 7.
    - One participant was randomized despite being at imminent risk of suicide or having attempted suicide within the year prior to screening, meeting exclusion criterion 22.
    - One participant was randomized with a Body Mass Index (BMI) outside the required range of 18 to 40 kg/m^2, failing to meet inclusion criterion 4.
- Safety Deviations (3.6% of all participants): These were substantially more frequent in the placebo group (7.3%) than the overall oveporexton group (2.4%). This was driven by the use of prohibited concomitant medications, which was reported in two placebo participants (4.9%) and two oveporexton participants (1.6%).
- Missing Endpoint Assessments (1.2% of all participants): Both instances of this deviation occurred in the overall oveporexton group (1.6%), with none reported in the placebo group.
- Discontinuations Due to Protocol Deviations (n=3): Two occurred in the placebo group (one for enrolling an ineligible participant who met an exclusion criterion for Apnea-Hypopnea Index (discussed previously), one for prohibited substance use, i.e., cocaine and marijuana) and one occurred in the oveporexton 2 mg BID group (for prohibited medication use, i.e., amphetamine/dextroamphetamine).

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Trial-Level Deviations

At the trial level, eight trial sites reported at least one significant site-level deviation. These included:

- Protocol Implementation (four sites): Issues included lack of staff training, non-compliance with IRB/IEC requirements, insufficient resources.
- Informed Consent (three sites): All deviations in this category were for a "consenting process was missed."
- Safety (two sites): Deviations involved safety assessments being performed by non-authorized staff.
- GCP (one site): The deviation was for inadequate PI oversight.

Additionally, the Applicant identified a few additional protocol deviations after the database lock (DBL) and submitted an amendment detailing these findings.

- Participant-Level Deviations: Four deviations were reclassified from non-significant to significant. The Applicant stated that the treatment assignments for these four participants would remain blinded, justifying that while the deviations were reclassified as significant, they were not considered substantial enough to warrant unblinding. The reclassified deviations included:
  - One instance of failure to perform a protocol-required repeat ECG.
  - One missed C-SSRS assessment.
  - Two critical informed consent process failures: one case of a missed consent form for the optional DNA process and another involving an improperly timed signature.
- Site-Level Deviation: One additional significant deviation was reported for a site that failed to maintain Investigational Product (IP) accountability logs as required by the pharmacy manual.

An analysis of protocol deviations revealed numerical imbalances between the treatment arms in several key categories. For instance, the rate of certain safety-related deviations (e.g., prohibited medication use) appeared higher in the placebo group. However, a particularly noteworthy imbalance in eligibility criteria occurred in the oveporexton group, where three participants were randomized with a WCR of 3 or less, compared to zero such participants in the placebo group. Additionally, the few instances of missing endpoint assessments occurred exclusively in the oveporexton arm.

The potential impact of these imbalances on the overall trial results is likely minimal, and in the case of the WCR discrepancy, would have biased the results against the observed treatment effect. Specifically, by including participants with a lower cataplexy burden at Baseline, the potential magnitude of improvement in the oveporexton group was limited, which may have masked the true treatment effect on this endpoint. For the other deviations, the observed differences are based on very small absolute numbers of events. When dealing with such low counts, even a minor difference of one or two participants can create a large

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percentage difference that is not statistically robust and is likely attributable to random chance.

Therefore, while these specific imbalances are noted for completeness in this review, it is unlikely that they meaningfully affected the interpretation of the trial's primary efficacy and safety outcomes. Given that the most significant numerical imbalance would have biased the results in the opposite direction of what was observed, and other differences are driven by a small number of events, there is no evidence of a systematic bias that would invalidate the study's overall findings.

Demographic Characteristics

Demographic characteristics were generally similar across the treatment groups (Table 57). Of the 168 randomized participants, 35% were White and 4% were Black. For another 35% of participants, race was categorized as unknown, as these data were not collected due to local regulations.

The study population was predominantly female, accounting for 58.3% of the overall oveporexton group and 58.5% of the placebo group. The median age of participants was 28 years, with a range of 16 to 65 years. The study enrolled only three adolescent participants (1.8%) 16 and 17 years of age across three trial sites (two in the United States, one in Japan), one in each of the three study arms. These participants were distributed among the treatment arms: one in the placebo group, one in the oveporexton 1 mg BID group, and one in the oveporexton 2 mg BID group. There was only one participant aged ≥65 years.

Table 57. Demographic Characteristics of the Full Analysis Set (Randomized Sample) (TAK-861-3001)

		Oveporexton Group			
Demographic Parameters	**Placebo Group (N=41) n (%)**	**Oveporexton 1 mg BID (N=61) n (%)**	**Oveporexton 2 mg BID (N=66) n (%)**	**Oveporexton overall (N=127) N (5)**	**Total (N=168) n (%)**
Sex					
Male	17 (41.5)	33 (54.1)	20 (30.3)	53 (41.7)	70 (41.7)
Female	24 (58.5)	28 (45.9)	46 (69.7)	74 (58.3)	98 (58.3)
Age					
Mean years (SD)	30.9 (12.71)	33.5 (11.82)	29.7 (9.64)	31.5 (10.87)	31.4 (11.31)
Median (years)	27.0	32.0	26.0	28.0	28.0
Min, max (years)	16, 61	16, 65	17, 52	16,6 5	16, 65
Age Group					
<18	1 (2.4)	1 (1.6)	1 (1.5)	2 (1.6)	3 (1.8)
≥18	40 (97.6)	60 (98.4)	65 (98.5)	125 (98.4)	165 (98.2)
<65 years	41 (100)	60 (98.4)	66 (100)	126 (99.2)	167 (99.4)
≥65 years	0	1 (1.6)	0	1 (<1)	1 (<1)

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		Oveporexton Group			
Demographic Parameters	**Placebo Group (N=41) n (%)**	**Oveporexton 1 mg BID (N=61) n (%)**	**Oveporexton 2 mg BID (N=66) n (%)**	**Oveporexton overall (N=127) N (5)**	**Total (N=168) n (%)**
Race					
White	15 (36.6)	17 (27.9)	27 (40.9)	44 (34.6)	59 (35.1)
Black or African American	4 (9.8)	3 (4.9)	0	3 (2.4)	7 (4.2)
Asian	6 (14.6)	10 (16.4)	10 (15.2)	20 (15.7)	26 (15.5)
American Indian or Alaska Native	0	0	1 (1.5)	1 (<1)	1 (<1)
Multiracial	1 (2.4)	0	0	0	1 (<1)
Not reported	5 (12.2)	3 (4.9)	7 (10.6)	10 (7.9)	15 (8.9)
Unknown[1]	10 (24.4)	28 (45.9)	21 (31.8)	49 (38.6)	59 (35.1)
Ethnicity					
Hispanic or Latino	3 (7.3)	6 (9.8)	5 (7.6)	11 (8.7)	14 (8.3)
Not Hispanic or Latino	22 (53.7)	23 (37.7)	30 (45.5)	53 (41.7)	75 (44.6)
Not reported	5 (12.2)	4 (6.6)	8 (12.1)	12 (9.4)	17 (10.1)
Unknown	11 (26.8)	28 (45.9)	23 (34.8)	51 (40.2)	62 (36.9)
Region (optional)					
Asia-Pacific	6 (14.6)	9 (14.8)	10 (15.2)	19 (15.0)	25 (14.9)
Europe	27 (65.9)	40 (65.6)	43 (65.2)	83 (65.4)	110 (65.5)
North America	8 (19.5)	12 (19.7)	13 (19.7)	25 (19.7)	33 (19.6)

[1] Data on race and/or ethnicity were not collected in some countries because of local regulations.
Source: Clinical reviewer, Study TAK-861-3001, randomized sample.

The demographic and baseline characteristics, including age [redacted], were well-balanced across the placebo and oveporexton treatment groups. A notable limitation is the lack of data in the older adult population; although the protocol allowed for enrollment up to age 70, only one participant aged 65 was included. Therefore, the effects of oveporexton in this population cannot be characterized from this study.

Although the trial's multinational enrollment means the overall population may not be directly representative of the United States, certain factors support the generalizability of the findings. The [redacted] distribution aligns with recent U.S.-based epidemiological data on NT1 (Ohayon et al., 2023). Given that the underlying pathophysiology of NT1 does not differ across populations, and the standard of care for diagnosis and treatment is similar in the E.U. and U.S., the large proportion of European participants does not present a concern for generalizability. To address the geographic diversity, a subgroup analysis of the North American cohort was performed to confirm that the efficacy results in this specific population are consistent with those of the overall study group; see the discussion of study demographics under Study 3002 (Section 8.1.2.2).

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Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

The baseline disease characteristics of the participants were generally well-balanced across the placebo and oveporexton treatment arms:

- Disease History and Severity of Sleepiness: The treatment groups were highly comparable in terms of disease history. The median age at symptom onset (approximately 15 years) and the median age at NT1 diagnosis (approximately 21 years) were consistent across all arms. Furthermore, the key baseline measures for EDS were severe and well-matched. The mean MWT sleep latency was extremely low (around 5.0 minutes), and the mean ESS total score was very high (around 18.5), indicating a population with a significant disease burden at study entry.
- Baseline Cataplexy Rate: A numerical imbalance was noted in the baseline WCR. The mean WCR was higher in the placebo group (48.9) compared to the overall oveporexton group (40.0). However, the median values were more closely aligned (28.5 versus 26.0, respectively), and the standard deviations were very large in all groups. This suggests that the difference in means is likely driven by a few participants with extremely high cataplexy rates and may not represent a clinically significant systematic imbalance in cataplexy severity across the groups.
- Diagnostic Confirmation and Prior Treatment: All participants had confirmed diagnoses of NT1 through PSG/MSLT and HLA positivity or documented historical CSF orexin levels ≤110 pg/mL per trial inclusion criteria. The proportion of participants that were HLA positive (95.8%) or had documented low CSF orexin levels (44.5% combining participants with CSF reported in numeric or categorical values) were similar across groups. The high rate of prior use of NT1 medications requiring washout (approximately 80%) was also consistent across all groups, indicating that the trial enrolled a predominantly treatment-experienced population.
- Lifestyle Factors: Baseline lifestyle characteristics such as caffeine and tobacco use were similar across groups. A slightly higher percentage of current alcohol users was noted in the placebo group (63.4%) compared to the overall oveporexton group (53.5%), though this small difference is unlikely to be clinically meaningful.
- PAP Ventilation Use: The rate of Positive Airway Pressure (PAP) use for comorbid obstructive sleep apnea (OSA) in the overall oveporexton group (7.1%; 9/126) was nearly three times that of the placebo group (2.4%; 1/41).

In conclusion, although the treatment groups were highly comparable for most key parameters, minor numerical imbalances were noted for baseline cataplexy rates, current alcohol use, and the rate of PAP ventilation use. A careful consideration of each is warranted.

The numerical imbalance in current alcohol users is highly unlikely to have influenced the primary efficacy results. The protocol not only prohibited alcohol consumption on the days of key assessments, such as the MWT, but also required participants to be admitted to the clinical unit the day prior to the MWT. This confinement provides a robust layer of control, ensuring compliance with the alcohol restriction and effectively mitigating any potential for

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acute alcohol effects to confound these critical measurements. Similarly, the imbalance in PAP use, while noted, is based on a very small number of participants, and its clinical significance is likely limited.

The higher mean baseline WCR in the placebo group would likely lead to more conservative treatment effects (i.e., it could artificially inflate the placebo response and, in turn, diminish the observed treatment difference between oveporexton and placebo), and as such is not of great concern.

Therefore, despite these minor imbalances, their potential impact on the study's conclusions is likely minimal due to mitigating factors in the trial's conduct and statistical plan (i.e., baseline WCR is included as a covariate in the primary analysis model). The treatment groups remained highly comparable with respect to disease history, severity of sleepiness, and diagnostic confirmation, providing a solid basis for evaluating the treatment effects of oveporexton.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Overall treatment compliance was very high in both groups, with a median compliance rate of 99.7% in the overall oveporexton group and 98.8% in the placebo group. A difference was observed in the rate of low compliance; while no participants in the oveporexton group had a compliance rate below 70%, two participants (4.9%) in the placebo group fell below this threshold. A slightly higher proportion of participants in the oveporexton groups (28.6%, 36/126) had a compliance rate over 100% compared to the placebo group (17.1%, 7/41), suggesting some instances of taking more than the prescribed dosage.

An information request (IR) was issued to the Applicant seeking clarification on this finding. In response, the Applicant attributed the above-threshold compliance rates to reconciliation discrepancies during tablet accountability, such as tablets being dropped or lost, or participants failing to return tablets that had been stored in a secondary container, rather than to actual excess dosing. All cases of compliance exceeding 100% were reviewed for potential overdose and associated adverse events and were further assessed for possible protocol deviations. Where an overdose was confirmed, a special situation form was completed, and a significant protocol deviation was filed accordingly. In Study TAK-861-3001, one participant (subject ID # 63015-406) was identified as having unintentionally taken one extra pill, which was documented as a significant protocol deviation. These issues likely had no significant impact on efficacy results.

Comorbidity

Concurrent medical conditions were frequently reported, affecting approximately 58% of participants, and were generally balanced between the placebo (61%) and overall oveporexton (57%) groups. Among the most common conditions, nervous system disorders were reported in 12.6% of participants and were well-balanced across treatment arms. This

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category was followed by metabolism and nutrition disorders, where a numerical imbalance was observed, with a higher frequency in the overall oveporexton group (14.3%) compared to the placebo group (7.3%). Seasonal allergy was also common at 12% and was balanced across groups.

Two comorbidities of particular relevance to this trial, sleep apnea and psychiatric disorders, were also examined. A notable imbalance was observed for sleep apnea syndrome, which was reported in 4% of participants in the oveporexton group but in zero participants in the placebo group. In contrast, the prevalence of psychiatric disorders was found to be well-balanced, affecting 9.8% of participants in the placebo arm and 7.9% in the overall oveporexton arm.

Past and Concomitant Medications

The trial enrolled a heavily treatment-experienced population, with a high rate of prior medication use for NT1 that was generally comparable between groups. Approximately 92% of participants in the overall oveporexton group and 88% in the placebo group had a lifetime history of using at least one NT1 therapy.

Although the use of common prior therapies such as modafinil (52.7% of total participants) and methylphenidate (27.5% of total participants) was well-balanced, numerical imbalances were noted for other specific agents. Lifetime use of sodium oxybate was more frequent in the overall oveporexton group (42.9%) compared to the placebo group (29.3%). A similar trend was observed for venlafaxine hydrochloride, which was reported by 15.9% of participants in the oveporexton group versus 9.8% in the placebo group. The high level of active treatment prior to the study was further evidenced by the large and well-balanced proportion of participants—approximately 80% in both the oveporexton and placebo arms—who required washout from their existing NT1 medications.

Regarding medication use during the trial, the rate of concomitant medication was also high and balanced, reported in approximately 58% of participants across all groups. The most frequently reported therapeutic class was anti-inflammatory products, where a slight imbalance was observed, with use being somewhat lower in the overall oveporexton group (20.6%) compared to the placebo group (29.3%).

Importantly, a review of the concomitant medication list revealed that a few participants were on prohibited medications during the study. One participant each was reported as taking atomoxetine, venlafaxine, milnacipran, amphetamine aspartate, or dexamphetamine. Most of these instances were appropriately identified and recorded as significant protocol deviations. However, the use of sertraline by one participant was not recorded as a deviation, which prompted an IR to be sent to the Applicant for clarification of this oversight. In response, the Applicant clarified that sertraline was a prior medication that had been discontinued before randomization, and that its erroneous inclusion in the concomitant medication dataset resulted from a date imputation error in the electronic data capture system.

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Rescue Medication Use

No rescue medications were specified in the protocol.

Summary

A thorough review of baseline characteristics, comorbidities, and medication history confirms that the treatment groups were generally well-balanced; any minor differences are based on small absolute numbers of participants and are unlikely to have a clinically meaningful impact on the interpretation of the efficacy and safety results.

The use of prohibited concomitant medications by a few participants was noted as a trial conduct issue, and an IR was issued to the Applicant for clarification. The Applicant responded adequately, and no further issues were identified; this matter is therefore not considered to affect the overall baseline comparability of the randomized groups.

With respect to treatment compliance, the higher proportion of participants in the oveporexton groups with compliance rates exceeding 100% is acknowledged; however, following the Applicant's clarification, this finding appears attributable to tablet accountability reconciliation discrepancies rather than systematic excess dosing and is therefore not considered to meaningfully affect the reliability of the exposure data. Therefore, despite these minor observations, the study arms are considered highly comparable, providing a solid foundation for the evaluation of oveporexton's treatment effects.

Efficacy Results–Primary Endpoint

Both dosages of oveporexton achieved highly statistically significant improvements in the change from Baseline to Week 12 in mean sleep latency on the MWT. The Least Square (LS) mean changes and treatment differences in sleep latency on the MWT are displayed in Table 58. The change from Baseline to Week 12 in mean sleep latency on the MWT was significantly higher in oveporexton 2 mg BID group than placebo (LS mean difference [95% CI] =17.20 [13.66, 20.73]; p<0.0001). Similarly, the change from Baseline to Week 12 in mean sleep latency on the MWT was significantly higher in oveporexton 1 mg BID group than placebo (LS mean difference [95% CI] =13.83 [10.23, 17.44]; p<0.0001).

Table 58. Primary Analysis: Sleep Latency on the MWT Change From Baseline to Week 12 in the Full Analysis Set (TAK-861-3001)

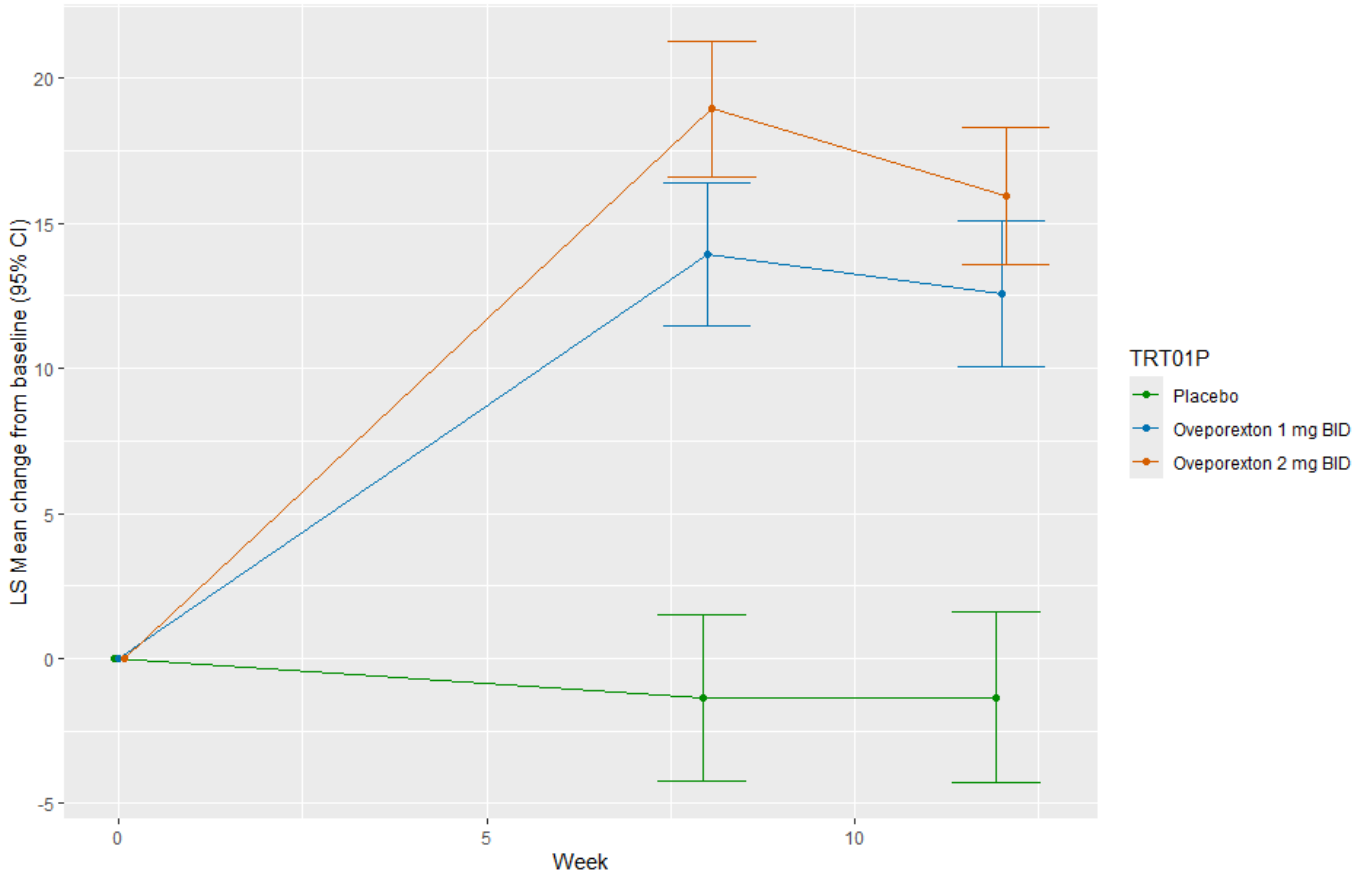
Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	41	-1.32 (1.502)	(-4.27, 1.62)	NA	NA	NA
OVE 1 mg BID	61	12.51 (1.284)	(9.99, 15.02)	13.83 (1.840)	(10.23, 17.44)	<0.001
OVE 2 mg BID	66	15.87 (1.205)	(13.51, 18.24)	17.20 (1.804)	(13.66, 20.73)	<0.001

Source: CSR Table 9 on page 57, confirmed by statistical reviewer

The adjusted mean change from Baseline in sleep latency on the MWT over the entire study period is presented in Figure 14. There is a clear separation starting at Week 8.

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Figure 14. Primary Analysis: Sleep Latency on the MWT Change From Baseline by Visit in the Full Analysis Set (TAK-861-3001)



Source: Statistical reviewer

The Applicant conducted sensitivity analyses of the primary efficacy endpoint to explore sensitivity of the results to different modeling approaches or missing data assumptions. The results of the sensitivity analyses were consistently similar to the primary analysis results, likely due to a robust treatment effect observed. The results are omitted here for the sake of brevity.

The Statistical Reviewer also conducted a sensitivity analysis that makes the most conservative assumption around missing data. For any post-baseline missing data, the worst possible score was imputed. The results of this sensitivity analysis are below; the study remains highly significant.

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Table 59. Sensitivity Analysis: Sleep Latency on the MWT Change From Baseline to Week 12 in the Full Analysis Set, Assuming Worst Score for All Missing Data (TAK-861-3001)

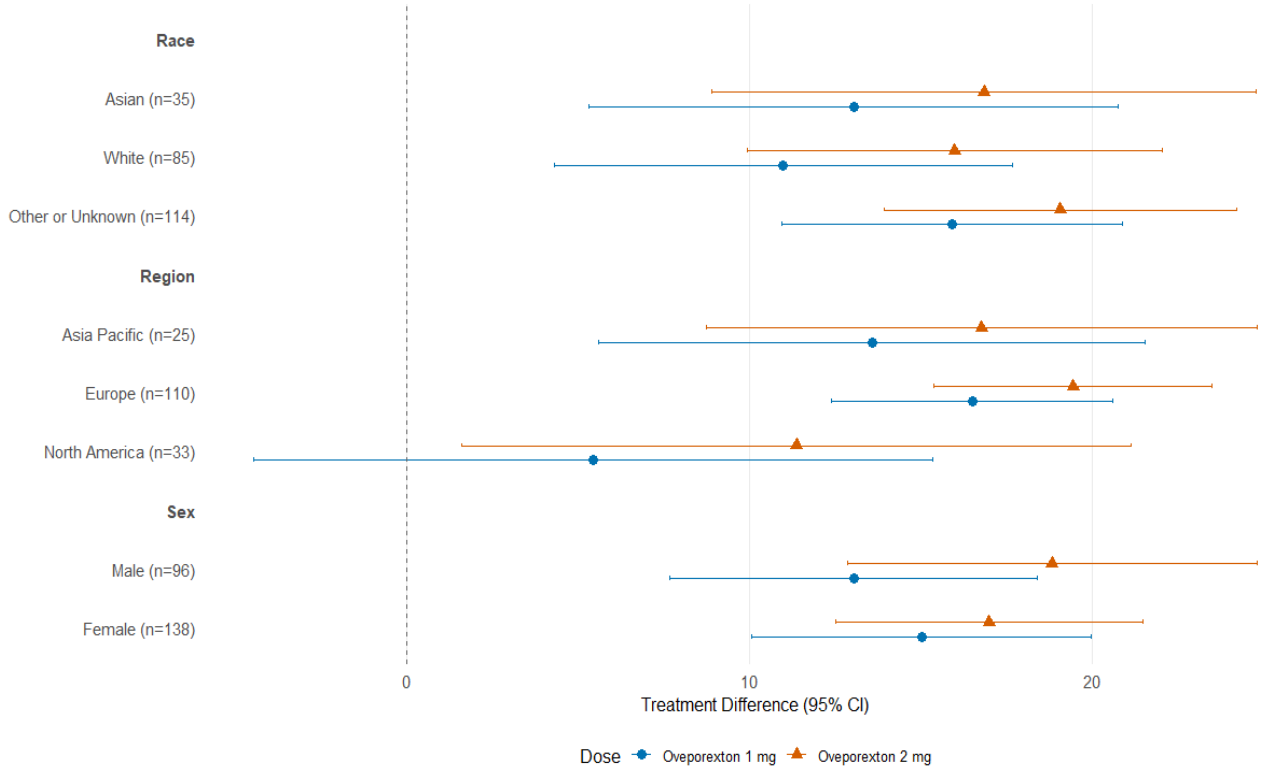
Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	41	-1.42 (1.690)	(-4.76, 1.92)	NA	NA	NA
OVE 1 mg BID	61	12.70 (1.440)	(9.86, 15.54)	14.12 (2.094)	(9.98, 18.26)	<0.001
OVE 2 mg BID	66	15.60 (1.330)	(12.98, 18.23)	17.02 (2.040)	(12.99, 21.05)	<0.001

Source: Statistical reviewer

Lastly, the primary endpoint results were generally consistent across subgroups of region, race, and sex (Figure 15). Although the study was not designed or powered to demonstrate efficacy within subgroups, observed treatment effects across subgroups trended in the same direction in favor of oveporexton and most subgroups reached nominal statistical significance. One notable exception was the subgroup of North America, which consisted of 33 participants from the United States and Canada—the results were directionally consistent with the rest of the world, but did not reach nominal significance. The age subgroup was not investigated, as almost all participants in the studies were between 18 and 65 years of age.

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Figure 15. Subgroup Analysis: Sleep Latency on the MWT Change From Baseline vs. Placebo in the Full Analysis Set (TAK-861-3001)



Source: Statistical reviewer, using the same method as pre-specified by the Applicant, results consistent with Applicant's

Data Quality and Integrity

There were no data quality or integrity issues noted during the review.

Efficacy Results–Secondary and Other Relevant Endpoints

All secondary endpoints included in the multiple testing procedure were statistically significant. The results of the secondary endpoint analyses were supportive of the primary endpoint analysis and also yielded a very robust treatment effect. None of the results were sensitive to missing data or modeling assumptions.

Both dosages of oveporexton achieved a highly statistically significant improvements in the change from Baseline to Week 12 in ESS total score, WCR, NSS-CT total score, mean number of lapses in PVT, PGI-C Responder status at Week 12, FINI (all six domains of tiredness, cognitive functioning, cataplexy, social activities, everyday activities, everyday responsibilities), and SF-36. The results for all of these multiplicity protected endpoints are presented in Table 60.

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Table 60. Primary Analysis: All Multiplicity Protected Secondary Endpoints: ESS Total Score, WCR, NSS-CT Total Score, Mean Number of Lapses in PVT, PGI-C Responder Status, FINI, SF-36 in the Full Analysis Set (TAK-861-3001)

ESS Total Score

Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	41	-1.42 (0.794)	(-2.97, 0.14)	NA	NA	NA
OVE 1 mg BID	61	-9.42 (0.679)	(-10.75, -8.08)	-8.00 (0.954)	(-9.87, -6.13)	<0.001
OVE 2 mg BID	66	-11.17 (0.618)	(-12.38, -9.95)	-9.75 (0.941)	(-11.59, -7.90)	<0.001

WCR

Treatment Group	n	Incidence Rate	95% CI	IRR vs. Placebo Estimate	IRR vs. Placebo 95% CI	p-value
Placebo	41	34.04	(22.70, 51.06)	NA	NA	NA
OVE 1 mg BID	61	11.50	(7.33, 18.03)	0.34	(0.20, 0.57)	<0.001
OVE 2 mg BID	66	12.80	(9.24, 17.71)	0.38	(0.23, 0.61)	<0.001

NSS-CT Total Score

Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	41	-2.99 (1.446)	(-5.82, -0.15)	NA	NA	NA
OVE 1 mg BID	61	-17.36 (1.224)	(-19.75, -14.96)	-14.37 (1.754)	(-17.81, -10.93)	<0.001
OVE 2 mg BID	66	-19.87 (1.106)	(-22.04, -17.70)	-16.88 (1.713)	(-20.24, -13.52)	<0.001

Mean Number of Lapses in PVT

Treatment Group	n	Estimate (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	41	2.09 (1.862)	(-1.57, 5.74)	NA	NA	NA
OVE 1 mg BID	61	-7.60 (1.159)	(-9.87, -5.32)	-9.68 (2.005)	(-13.61, -5.75)	<0.001
OVE 2 mg BID	66	-8.43 (1.114)	(-10.61, -6.25)	-10.51 (1.986)	(-14.41, -6.62)	<0.001

PGI-C Responders

Treatment Group	n	Response Rate	95% CI	Odd Ratio vs. Placebo Estimate (SE)	Odds Ratio vs. Placebo 95% CI	p-value
Placebo	41	0.21	(0.07, 0.35)	NA	NA	NA
OVE 1 mg BID	61	0.69	(0.55, 0.83)	8.44	(3.22, 22.12)	<0.001
OVE 2 mg BID	66	0.94	(0.88, 1.01)	62.17	(16.40, 235.60)	<0.001

FINI: Tiredness

Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	41	2.09 (1.862)	(-1.57, 5.74)	NA	NA	NA
OVE 1 mg BID	61	-7.60 (1.159)	(-9.87, -5.32)	-9.68 (2.005)	(-13.61, -5.75)	<0.001
OVE 2 mg BID	66	-8.43 (1.114)	(-10.61, -6.25)	-10.51 (1.986)	(-14.41, -6.62)	<0.001

FINI: Cognitive Functioning

Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	41	3.20 (3.572)	(-3.81, 10.20)	NA	NA	NA
OVE 1 mg BID	61	-27.50 (3.080)	(-33.53, -21.46)	-30.70 (4.342)	(-39.21, -22.19)	<0.001
OVE 2 mg BID	66	-34.72 (2.747)	(-40.10, -29.34)	-37.92 (4.212)	(-46.17, -29.66)	<0.001

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FINI: Cataplexy						
Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	41	-1.35 (3.301)	(-7.82, 5.12)	NA	NA	NA
OVE 1 mg BID	61	-19.52 (2.744)	(-24.90, -14.15)	-18.18 (3.998)	(-26.01, -10.34)	<0.001
OVE 2 mg BID	66	-23.78 (2.513)	(-28.71, -18.86)	-22.43 (3.908)	(-30.09, -14.77)	<0.001
FINI: Social Activities						
Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	41	-3.12 (3.858)	(-10.68, 4.44)	NA	NA	NA
OVE 1 mg BID	61	-28.32 (3.248)	(-34.68, -21.95)	-25.20 (4.638)	(-34.29, -16.11)	<0.001
OVE 2 mg BID	66	-34.27 (2.979)	(-40.10, -28.43)	-31.14 (4.555)	(-40.07, -22.22)	<0.001
FINI: Everyday Activities						
Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	41	-5.70 (3.564)	(-12.68, 1.29)	NA	NA	NA
OVE 1 mg BID	61	-37.78 (3.016)	(-43.69, -31.87)	-32.09 (4.350)	(-40.61, -23.56)	<0.001
OVE 2 mg BID	66	-49.00 (2.778)	(-54.44, -43.55)	-43.30 (4.247)	(-51.62, -34.97)	<0.001
FINI: Everyday Responsibilities						
Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	41	-8.71 (4.310)	(-17.16, -0.26)	NA	NA	NA
OVE 1 mg BID	61	-35.62 (3.639)	(-42.75, -28.48)	-26.90 (5.247)	(-37.19, -16.62)	<0.001
OVE 2 mg BID	66	-43.05 (3.336)	(-49.59, -36.51)	-34.34 (5.137)	(-44.41, -24.27)	<0.001
SF-36: Mental Component Summary						
Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	41	-1.74 (1.548)	(-4.78, 1.29)	NA	NA	NA
OVE 1 mg BID	61	5.04 (1.292)	(2.51, 7.57)	6.79 (1.907)	(3.05, 10.53)	<0.001
OVE 2 mg BID	66	8.36 (1.162)	(6.08, 10.64)	10.11 (1.842)	(6.50, 13.72)	<0.001
SF-36: Physical Component Summary						
Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	41	0.37 (0.908)	(-1.41, 2.15)	NA	NA	NA
OVE 1 mg BID	61	5.90 (0.761)	(4.41, 7.39)	5.54 (1.091)	(3.40, 7.67)	<0.001
OVE 2 mg BID	66	6.63 (0.702)	(5.25, 8.00)	6.26 (1.066)	(4.17, 8.35)	<0.001

Abbreviations: IRR = incidence rate ratio; OVE = oveporexton; N/A = not applicable.
Source: CSR Tables 11, 13, 15, 16, 17, 18, 19 on pages 61, 66, 72, 74, 76, 78, 82 confirmed by statistical reviewer

Dose/Dose Response

The efficacy results across the primary and secondary endpoints suggest a dose-response relationship between oveporexton and improvement in narcolepsy symptoms.

Oveporexton demonstrated robust and statistically significant efficacy at both the 1-mg and 2-mg BID dosages across the primary and key secondary endpoints. Both dosages produced

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meaningful improvements in sleep latency, excessive daytime sleepiness, cataplexy rate, and patient-reported outcomes relative to placebo. The 2-mg BID dosage consistently yielded numerically greater improvements across the majority of evaluated endpoints, providing evidence of a dose-response relationship. The weekly cataplexy rate results did not follow this same pattern—both dosages produced robust reductions relative to placebo, with overlapping confidence intervals suggesting the numerical difference between dosages is unlikely to be clinically meaningful. Taken together, the efficacy data support the clinical benefit of oveporexton in patients with NT1.

Durability of Response

This study compared MWT scores at baseline and at the end of treatment and did not assess the durability of response. However, a separation between oveporexton and placebo was observed as early as Week 8 (Figure 14).

There are no placebo-controlled data beyond 12 weeks. Overall, efficacy after 12 weeks of dosing indicates reasonable durability of effect over time for NT1. An additional randomized withdrawal study for maintenance treatment was not felt to be necessary given this duration of effectiveness.

Persistence of Effect

The persistence of effect is the effect of the drug over time after treatment is stopped or withheld.

The Applicant did not report on persistence of effect; however, oveporexton and its PK profile are intended for chronic daily dosing, and there is no expectation for a meaningful persistence of effect after stopping oveporexton.

Efficacy Results–Additional or Exploratory COA (PRO) Endpoints

The NT1 pentad comprises five core clinical features: EDS, cataplexy, hypnagogic/ hypnopompic hallucinations, sleep paralysis, and disturbed/disrupted nighttime sleep (DNS). Although the primary and secondary endpoints adequately captured the effect of oveporexton on EDS (via MWT and ESS) and cataplexy (via weekly cataplexy rate), a comprehensive assessment of the drug's effect on the complete NT1 pentad requires evaluation of the remaining three symptoms. These symptoms—hypnagogic/hypnopompic hallucinations, sleep paralysis, and DNS—are critical components of the disease burden experienced by patients with NT1. Hypnagogic/hypnopompic hallucinations and sleep paralysis are REM-related phenomena that occur at sleep-wake transitions; DNS encompasses both sleep architecture abnormalities and sleep instabilities.

To assess oveporexton's effect on these symptoms, we reviewed secondary and exploratory endpoints that the Applicant included to determine whether oveporexton demonstrates efficacy across the full spectrum of NT1 pentad symptoms. Although these analyses were not multiplicity protected, and as such, need to be interpreted with caution, they are informative when assessing the overall impact of oveporexton on the NT1 pentad.

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The endpoints included were:

For Disturbed/Disrupted Nighttime Sleep (DNS):

1. NSS-CT item 15
2. nPSG parameters that measure REM sleep regulation and sleep architecture. These parameters provide objective evidence of oveporexton's effect on REM regulation, which is mechanistically linked to the pathophysiology of hallucinations and sleep paralysis in NT1. Exploratory nPSG endpoints include:
    a. REM Latency
    b. Sleep onset latency
    c. Total Sleep time
    d. Wake after sleep onset
    e. Nocturnal awakenings
3. Sleep Diary
    a. Subjective improvement in good/excellent sleep nights (sleep efficiency %)
    b. Number of nights per week of good or excellent sleep quality
    c. FINI tiredness domain (assessed above as part of the multiplicity protected endpoints)
    d. SF-36 Vitality Domain

For hypnagogic/hypnopompic hallucinations:

1. NSS-CT domain score items 11 and 12 provide both frequency and bother ratings for hallucinations and sleep paralysis
    a. Items 11 and 12
    b. Hallucinations in those with at least one episode per week at baseline

For sleep paralysis:

1. NSS-CT domain score items 13 and 14 provide both frequency and bother ratings for sleep paralysis
    a. Items 13 and 14
    b. Sleep paralysis in those with at least one episode per week at baseline

The results for all the above exploratory endpoints covering the remaining pentad symptoms are presented in Table 61.

Table 61. Exploratory Analysis: Endpoints Regarding DNS, Hallucinations, and Sleep Paralysis Symptoms of the NT1 Pentad in the Full Analysis Set (TAK-861-3001)

Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
NSS-CT item 15 score (Disturbed/Disrupted Nighttime Sleep Domain)						
Placebo	36	-0.29 (0.149)	(-0.58, 0.01)	NA	NA	NA
OVE 1 mg BID	57	-0.45 (0.126)	(-0.70, -0.20)	-0.17 (0.184)	(-0.53, 0.20)	0.366
OVE 2 mg BID	64	-0.77 (0.116)	(-1.00, -0.54)	-0.48 (0.179)	(-0.84, -0.13)	0.008

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Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
nPSG - REM Latency (min)						
Placebo	36	-5.50 (16.232)	(-37.56, 26.55)	NA	NA	NA
OVE 1 mg BID	56	66.28 (13.593)	(39.44, 93.11)	71.78 (20.023)	(32.22, 111.34)	<0.001
OVE 2 mg BID	63	64.80 (12.581)	(39.95, 89.64)	70.30 (19.591)	(31.59, 109.01)	<0.001
nPSG - Sleep Onset Latency (min)						
Placebo	36	-1.53 (1.827)	(-5.14, 2.09)	NA	NA	NA
OVE 1 mg BID	57	-0.97 (1.487)	(-3.90, 1.97)	0.56 (2.293)	(-3.98, 5.09)	0.808
OVE 2 mg BID	64	1.19 (1.390)	(-1.56, 3.93)	2.71 (2.245)	(-1.73, 7.15)	0.229
nPSG - Total Sleep Time (min)						
Placebo	36	4.18 (7.291)	(-10.22, 18.58)	NA	NA	NA
OVE 1 mg BID	57	-11.32 (6.160)	(-23.48, 0.85)	-15.50 (8.882)	(-33.04, 2.05)	0.083
OVE 2 mg BID	64	-6.55 (5.687)	(-17.78, 4.68)	-10.73 (8.674)	(-27.87, 6.41)	0.218
nPSG - Wake After Sleep Onset (min)						
Placebo	36	-7.88 (7.185)	(-22.07, 6.31)	NA	NA	NA
OVE 1 mg BID	57	13.92 (6.052)	(1.96, 25.87)	21.79 (8.780)	(4.45, 39.14)	0.014
OVE 2 mg BID	64	-1.81 (5.591)	(-12.85, 9.23)	6.07 (8.582)	(-10.88, 23.02)	0.481
nPSG - Number of Sleep Awakenings						
Placebo	36	-3.16 (2.451)	(-8.00, 1.68)	NA	NA	NA
OVE 1 mg BID	57	6.02 (2.043)	(1.98, 10.05)	9.18 (3.021)	(3.21, 15.15)	0.003
OVE 2 mg BID	64	2.50 (1.894)	(-1.24, 6.23)	5.66 (2.954)	(-0.18, 11.49)	0.057
Sleep Diary: Sleep Efficiency %						
Placebo	36	0.52 (1.616)	(-2.67, 3.71)	NA	NA	NA
OVE 1 mg BID	57	1.97 (1.351)	(-0.69, 4.64)	1.45 (1.990)	(-3.02, 5.93)	0.682
OVE 2 mg BID	64	1.37 (1.261)	(-1.12, 3.86)	0.85 (1.95)	(-3.53, 5.22)	0.859
Sleep Diary: Number of Nights per Week of Good or Excellent Sleep Quality						
Placebo	36	0.51 (0.316)	(-0.11, 1.14)	NA	NA	NA
OVE 1 mg BID	57	1.30 (0.263)	(0.79, 1.82)	0.79 (0.389)	(-0.29, 1.66)	0.082
OVE 2 mg BID	64	1.25 (0.245)	(0.77, 1.74)	0.74 (0.382)	(-0.12, 1.59)	0.103
SF-36 Vitality Domain						
Placebo	36	1.42 (3.239)	(-4.98, 7.82)	NA	NA	NA
OVE 1 mg BID	57	23.18 (2.747)	(17.76, 28.61)	21.76 (3.932)	(13.99, 29.53)	<0.001
OVE 2 mg BID	64	28.82 (2.513)	(23.85, 33.78)	27.39 (3.862)	(19.76, 35.02)	<0.001
NSS-CT Items 11-12 score (Hallucination Domain)						
Placebo	36	-0.48 (0.218)	(-0.91, -0.04)	NA	NA	NA
OVE 1 mg BID	57	-1.92 (0.185)	(-2.29, -1.56)	-1.45 (0.267)	(-1.97, -0.92)	<0.001
OVE 2 mg BID	64	-2.00 (0.172)	(-2.34, -1.66)	-1.52 (0.261)	(-2.04, -1.01)	<0.001
NSS-CT Items 11-12 Score in Those with at Least 1 Hallucination Episode at Baseline (Hallucination Domain)						
Placebo	22	-0.91 (0.346)	(-1.60, -0.23)	NA	NA	NA
OVE 1 mg BID	36	-3.10 (0.278)	(-3.65, -2.54)	-2.18 (0.399)	(-2.98, -1.39)	<0.001
OVE 2 mg BID	39	-3.27 (0.275)	(-3.82, -2.73)	-2.36 (0.396)	(-3.15, -1.57)	<0.001
NSS-CT Items 13-14 score (Sleep Paralysis Domain)						
Placebo	36	-0.29 (0.211)	(-0.71, 0.12)	NA	NA	NA
OVE 1 mg BID	57	-1.24 (0.176)	(-1.59, -0.90)	-0.95 (0.262)	(-1.47, -0.43)	<0.001
OVE 2 mg BID	64	-1.41 (0.165)	(-1.73, -1.08)	-1.12 (0.257)	(-1.62, -0.61)	<0.001
NSS-CT Items 13-14 score in Those with at Least 1 Paralysis Episode at Baseline (Sleep Paralysis Domain)						
Placebo	18	-0.99 (0.425)	(-1.84, -0.15)	NA	NA	NA
OVE 1 mg BID	27	-2.63 (0.359)	(-3.34, -1.91)	-1.63 (0.512)	(-2.65, -0.61)	0.002
OVE 2 mg BID	29	-3.06 (0.364)	(-3.78, -2.33)	-2.06 (0.512)	(-3.08, -1.04)	<0.001

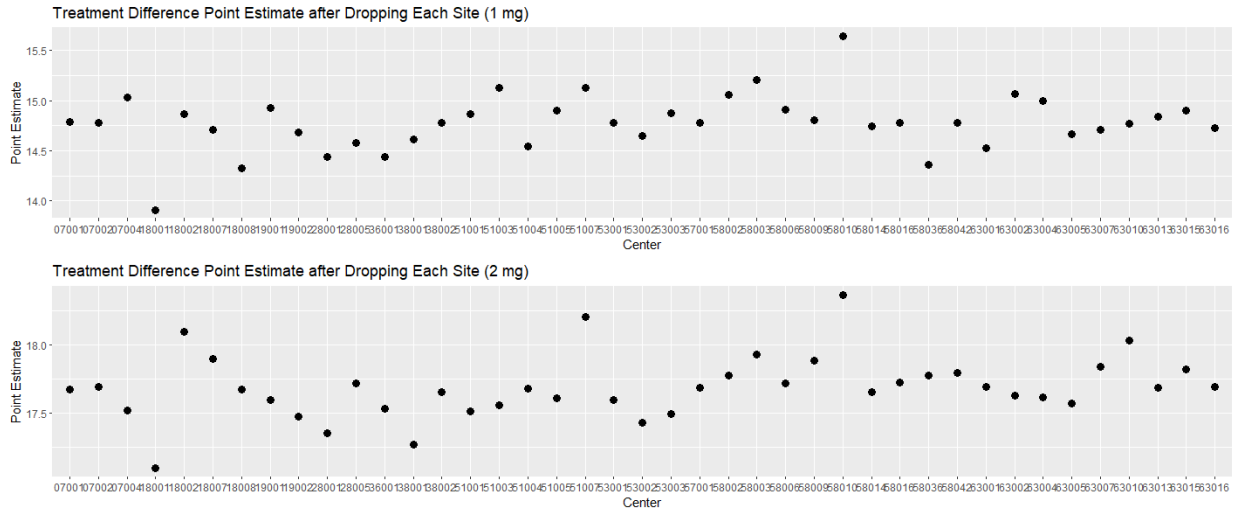
Source: CSR Tables 15.2.6.7, 15.2.14.2, 15.2.9.4, except for sleep efficiency and number of nocturnal awakenings, which were only provided as summary statistics by Applicant. Model-adjusted results yielded by statistical reviewer.

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Additional Analyses Conducted on the Individual Trial

In addition to the sensitivity analyses above, the Statistical Reviewer also conducted an analysis focusing on study sites, to explore whether any one study site yielded results strongly different from the rest of the study, or whether the efficacy results were primarily driven by a single site. The results are presented in Figure 16, where the primary analysis is repeated, leaving out one site at a time, with the results plotted against the site being left out. The results were highly consistent and not dependent on any one site.

Figure 16. Sensitivity Analysis: Impact of Each Site on the Sleep Latency on the MWT Change From Baseline Treatment Effect vs. Placebo at Week 12 in the Full Analysis Set (TAK-861-3001)



Source: Statistical reviewer

Integrated Review of Effectiveness

Overall, for the Study TAK-861-3001, a randomized, double-blind, placebo-controlled trial of oveporexton 1 mg and 2 mg, the review team confirms the Applicant's primary finding that both dosages of oveporexton are shown to be superior compared with placebo for the primary endpoint of change from Baseline to Week 16 in mean sleep latency on the MWT. The study yielded highly statistically significant results on the primary endpoint and all secondary endpoints included in the multiple testing procedure. The results were robust to missing data or modeling choices due to large magnitude of effect and low amount of missing data. As such, any reasonable sensitivity analysis did not have a notable effect on the results. In addition, exploratory endpoints that evaluate other aspects of the NT1 symptom pentad compared to the endpoints included in the multiple testing procedure also generally supported the finding that oveporexton yielded an effect on all of the symptoms in the pentad.

The Applicant is seeking an indication for NT1 as a whole, rather than a symptom-specific indication such as EDS or cataplexy, which have historically been the focus of approved

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narcolepsy therapies. This approach represents a novel regulatory paradigm for NT1 and, to be supported, requires demonstration of a meaningful treatment effect across all core components of the disease. For NT1, these core components are defined by the NT1 pentad: EDS, cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and DNS. The efficacy results from Study TAK-861-3001 are reviewed below through the lens of each pentad symptom.

- Excessive Daytime Sleepiness (EDS): The evidence supporting an effect of oveporexton on EDS is robust. Both dosages achieved highly statistically significant improvements on the MWT (the primary endpoint) and the ESS, two well-established objective and subjective measures of EDS, respectively. Additionally, NSS-CT items 1 through 7, which capture the frequency and burden of EDS symptoms, were also nominally significant for both dosages, further corroborating the effect of oveporexton on this domain (data not shown).
- Cataplexy: Both dosages of oveporexton demonstrated a robust and statistically significant reduction in WCR, with incidence rate ratios of 0.34 and 0.38 for the 1-mg and 2-mg BID dosages, respectively, reflecting a greater than 60% reduction in cataplexy episodes relative to placebo. NSS-CT items 8 through 10, which assess the frequency and bother of cataplexy symptoms, were also nominally significant for both dosages, providing additional subjective corroboration of the effect on this domain.
- Hypnagogic/Hypnopompic Hallucinations: Both dosages of oveporexton showed nominally significant reductions in hallucination frequency and bother as measured by NSS-CT items 11 and 12, both in the overall population and in the subgroup of participants with at least one hallucination episode per week at baseline. The magnitude of effect was large and consistent across dosages, supporting a meaningful treatment effect on this pentad symptom.
- Sleep Paralysis: Similarly, both dosages showed nominally significant reductions in sleep paralysis as measured by NSS-CT items 13 and 14, both in the overall population and in the subgroup of participants with at least one sleep paralysis episode per week at baseline. These results provide clear evidence of an effect on this pentad symptom.
- Disturbed/Disrupted Nighttime Sleep (DNS): The DNS domain presents a more complex picture than the other pentad symptoms, in part due to the wake-promoting mechanism of action of oveporexton. Positive results were observed for NSS-CT item 15 (nominally significant for the 2-mg BID dosage), nPSG-measured REM latency (nominally significant for both dosages), number of nights per week of good or excellent sleep quality (nominally significant for the 1-mg BID dosage), and indirect measures of sleep-related quality of life including the SF-36 Vitality domain and the FINI Tiredness domain (nominally and statistically significant, respectively, for both dosages). However, nocturnal awakenings as measured by nPSG appeared numerically increased with oveporexton relative to placebo, which is not unexpected given the drug's wake-promoting properties. The clinical review team notes that DNS is a multidimensional domain that extends beyond the number of nocturnal awakenings; it encompasses the subjective perception of sleep quality and broadly captures poor sleep experiences, including low sleep quality, nightmares, and

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parasomnias—many of which are REM-related phenomena. Given that oveporexton restores REM sleep regulation, as evidenced by the nominally significant improvement in REM latency, the clinical review team considers it biologically plausible and clinically reasonable to conclude that oveporexton improves the DNS domain as a whole, notwithstanding the absence of a significant effect on nPSG-measured nocturnal awakenings.

Taken together, the efficacy data from Study TAK-861-3001 provide evidence of a treatment effect across all five components of the NT1 pentad. The team considers the evidence from Study TAK-861-3001 supportive of the Applicant's approach to the NT1 indication.

8.1.2. Study TAK-861-3002

8.1.2.1. Study Design

Overview and Objective

Study Title:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TAK-861 for the Treatment of Narcolepsy with Cataplexy (Narcolepsy Type 1)

Primary Objectives:

The study's primary objective was to assess the efficacy of oveporexton compared to placebo with regard to EDS as measured by the MWT.

Secondary Objectives:

Secondary objectives included assessment of between-group difference in:

- Changes in EDS as measured by the ESS total score
- Changes in cataplexy episodes as measured by the WCR
- Changes in sustained attention as measured by the PVT
- Changes in overall narcolepsy symptoms measured by the PGI-C scale
- Changes in overall severity of narcolepsy symptoms measured by the NSS-CT
- Changes in functional impacts of narcolepsy as assessed by the FINI
- Changes in quality of life of participants, as assessed by the SF-36.

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Trial Design

Study Design Overview:

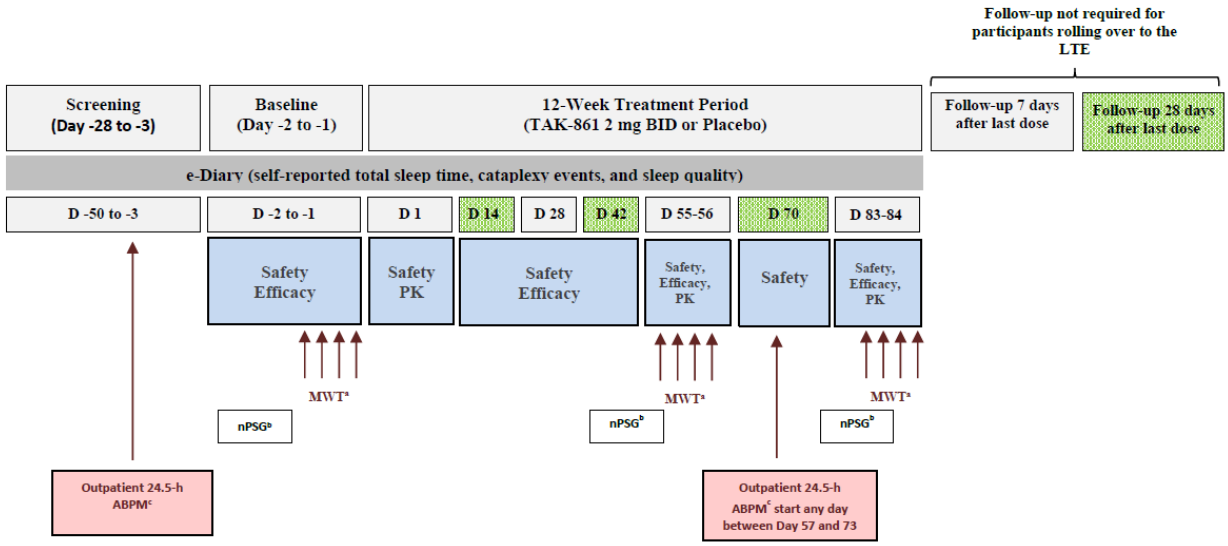
Study TAK-861-3002 was a phase 3, randomized, double-blind, placebo-controlled, 12-week parallel-group trial to assess the safety and efficacy of one oral dosage of oveporexton for the treatment of NT1.

As with Study TAK-861-3001, the study began with a screening period of up to 50 days, which could be extended on a case-by-case basis with Sponsor approval. During Screening, participants were required to discontinue their narcolepsy medications, including antidepressants and sodium or multisalt oxybate. Starting no later than Day -16, participants completed an electronic diary to track cataplexy episodes. To be eligible, participants had to complete the diary for at least 11 of the 14 days between Day -16 and Day -3 and had to experience at least 4 partial and/or complete cataplexy episodes per week during this period.

Throughout the study, participants were required to stay overnight at the study site on three occasions: Days -2 to 1 (with one mandatory overnight at Day -2 and one optional overnight at Day -1), Days 55 to 56, and Days 83 to 84. After completing the 12-week treatment period, participants had the option to enroll in a long-term extension study under a separate protocol (Study TAK-861-2003). Those who chose not to participate in the extension study completed two follow-up visits at approximately 7 and 28 days after their final dose of study drug and could restart their restricted medications (except those associated with liver function test elevations) 7 days after the last dose. Participants who terminated the trial early were required to complete an early termination visit as soon as possible and a follow-up visit approximately 28 days after the last dose of trial intervention. For a schematic of the study design, see Figure 17.

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Figure 17. Study Design – TAK-861-3002



Abbreviations: ABPM = ambulatory blood pressure monitoring; BID = twice daily; D = Day; e-Diary = electronic diary; h = hour; LTE = long-term extension; MWT = Maintenance of Wakefulness Test; nPSG = nocturnal polysomnography; PK = pharmacokinetic(s)
Note: Green shading indicated the visit consisted of a blood chemistry assessment and could be in-clinic or remote; the sample could be analyzed in a local laboratory.
[a] Confinement started on the evening of Days -2, 55, and 83 with MWT done on Days -1, 56, and 84.
[b] nPSG was done on the nights of Days -2, 55, and 83.
[c] ABPM recordings were obtained over at least 24.5 hours and participants were not confined to the clinical site during most of the 24.5-hour recording period. ABPM could be repeated as long as the recording ended no later than 1 day before check-in for the next nPSG/MWT.
Source: Clinical Study Report (CSR) of Study TAK-861-3002, Figure 1, page 23

Trial Location

This multi-center study was conducted at 28 sites: 20 trial sites in Europe, 7 trial sites in Asian Pacific, and 20 trial sites in Australia. Notably, no sites in North America recruited for this trial.

Diagnostic Criteria

The key diagnostic criteria for enrollment into Study TAK-861-3002 were identical to those of the registrational Study TAK-861-3001. For a detailed description of these criteria, see the corresponding section of the review for Study TAK-861-3001.

Key Eligibility Criteria

The key eligibility criteria for enrollment into Study TAK-861-3002 were identical to those of the registrational study, TAK-861-3001. For a detailed description of these criteria, see the corresponding section of the review for Study TAK-861-3001.

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Study Treatments, Dosage Selection, and Compliance

At the beginning of the 12-week-treatment period, on Day 1 participants were randomized in a 1:2 randomization ratio to receive:

- Matching placebo tablet, 1 placebo tablet BID, at least 3 hours apart
- Oveporexton tablet, 2 mg tablet BID, at least 3 hours apart

Starting on the morning of Day 1, the study drug was administered at approximately the same time each day for 12 weeks, with the following schedules:

- For all days during the treatment period except clinic MWT days, participants were instructed to take the first dose no later than 10 am and the second dose at least 3 hours after the first morning dose, but no later than 1 pm.
- On clinic MWT days (Days 1, 56, and 84), the drug was administered as close to 8 am and 11 am as possible, respectively.

Compliance, Prohibited Concomitant Medications, Meals and Dietary Restrictions/Activity, Subject Completion, Dose Discontinuation, and Withdrawal

Several key aspects of trial conduct in Study TAK-861-3002 were identical to those of the registrational Study TAK-861-3001. This includes compliance assessment, prohibited concomitant medications, definition of study completion, reasons for dosage discontinuation, as well as meals and dietary restrictions or allowed activity. For a detailed description of these characteristics, see the corresponding section of the review for Study TAK-861-3001.

Schedule of Assessments

As for Study TAK-861-3001, all participants checked into the clinic in the afternoon on Days -2, 55, and 83. Discharge occurred after the last study assessment of the last day was performed.

See Table 62 and Table 63 for the Study TAK-861-3002 schedule of assessment and procedures.

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Table 62. Schedule of Assessment Study TAK-861-3002

	Screening/ Baseline [a]			12-Week Treatment Period									Follow-up [b]	
Day	-50 to -3	-2	-1	1 Pre	1 Post	14 [c]	28	42 [c]	55	56	70 [c]	83	84	7 Days After Last Dose [d]/ ET [e] 91	28 Days After Last Dose 112 [c]
Week	NA	NA		NA		2 [c]	4	6 [c]	8		10 [c]	12		13	16 [c]
Visit Window (days) [f]	NA	-3		NA		±3	±3	±3	±3		±3	±3		±3	±3
Visit Number	1	2		3		4 [c]	5	6 [c]	7		8 [c]	9		10/11 [g]	12 [c]
Administrative Procedures															
Informed consent	X														
Inclusion/exclusion criteria	X	X	X	X											
Demographics, medical history, medication history	X														
Concomitant medications/ procedures	*From signing the informed consent through the last visit on the study*														
Pregnancy avoidance counseling	*From signing the informed consent through the last visit on the study*														
Clinical Procedures and Assessments															
TAK-861/ placebo administration [h]				*Throughout the 12-week treatment period*											
AE assessment	*From signing the informed consent through the last visit on the study*														
BP (sitting) and HR (sitting) [i,j]	X	X	X	X	X		X		X	X		X	X	X	

	Screening/ Baseline [a]			12-Week Treatment Period									Follow-up [b]	
Day	-50 to -3	-2	-1	1 Pre	1 Post	14 [c]	28	42 [c]	55	56	70 [c]	83	84	7 Days After Last Dose [d]/ ET [e] 91	28 Days After Last Dose 112 [c]
Week	NA	NA		NA		2 [c]	4	6 [c]	8		10 [c]	12		13	16 [c]
Visit Window (days) [f]	NA	-3		NA		±3	±3	±3	±3		±3	±3		±3	±3
Visit Number	1	2		3		4 [c]	5	6 [c]	7		8 [c]	9		10/11 [g]	12 [c]
Respiratory rate and temperature	X	X	X	X	X		X		X	X		X	X	X	
ABPM (start before time of first morning dose) [i,k]	X										X				
ECG [i]	X			X			X		X			X		X	
Height	X												X		
Body weight	X		X				X			X			X	X	
Physical examination [l]	X		X				X			X			X	X	
CSSRS	X		X				X			X			X	X	
PSG/MSLT (if needed to confirm eligibility)	X														
Fundoscopic examination and coagulation tests (required only for participants opting to undergo CSF sample collection)	X														
CSF sample for OX assessment [w]	X														
PAP compliance check (if applicable) [m]	X		X				X			X			X		
Clinical Laboratory Procedures and Assessments															
Serology (hBsAg, anti-HBc, anti-HCV, HIV)	X														

	Screening/ Baseline [a]			12-Week Treatment Period									Follow-up [b]	
				1									7 Days After Last Dose [d]/ ET [e]	28 Days After Last Dose
Day	-50 to -3	-2	-1	Pre	Post	14 [c]	28	42 [c]	55	56	70 [c]	83	84	91	112 [c]
Week	NA	NA		NA		2 [c]	4	6 [c]	8		10 [c]	12		13	16 [c]
Visit Window (days) [f]	NA	-3		NA		±3	±3	±3	±3		±3	±3		±3	±3
Visit Number	1	2		3		4 [c]	5	6 [c]	7		8 [c]	9		10/11 [g]	12 [c]
Pregnancy test [n]	X	X					X		X			X		X	
FSH assessment (required for postmenopausal women only)	X														
Hematology [i]	X	X					X			X			X	X	
Blood chemistry [i]	X [o]	X		X [p]	X	X	X	X		X	X		X	X	X
Urinalysis	X	X		X [p]			X		X			X		X	
Urine drug screening [q]	X	X		X [p]			X		X			X			
Alcohol screening [r]	X	X		X [p]			X		X			X			
Blood samples for HLA genotyping [s]	X														
Blood sample for DNA analysis [t, w]	X														
Efficacy Assessments															
e-diary [u]	*Throughout the study, starting no later than Day -16 and continuing up to the Week 12 Visit is completed or rollover into LTE*														
nPSG [i, v]		X							X			X			
MWT [i]			X							X			X		
KSS	X		X							X			X		
Cognitive assessments (PVT, CPAL, ONB, iDSST-s) [i]	X		X							X			X		

	Screening/ Baseline [a]			12-Week Treatment Period									Follow-up [b]	
				1									7 Days After Last Dose [d]/ ET [e]	28 Days After Last Dose
Day	-50 to -3	-2	-1	Pre	Post	14 [c]	28	42 [c]	55	56	70 [c]	83	84	91	112 [c]
Week	NA	NA		NA		2 [c]	4	6 [c]	8		10 [c]	12		13	16 [c]
Visit Window (days) [f]	NA	-3		NA		±3	±3	±3	±3		±3	±3		±3	±3
Visit Number	1	2		3		4 [c]	5	6 [c]	7		8 [c]	9		10/11 [g]	12 [c]
ESS [i]	X		X				X			X			X		
CGI-S/PGI-S [i]	X		X				X			X			X		
CGI-C/PGI-C [i]							X			X			X		
NSS-CT [i]	X		X				X			X			X		
FINI [i]	X		X							X			X		
BC-CCI-E [i]	X		X							X			X		
TSQM [i]										X			X		
EQ-5D-5L [i]	X		X							X			X		
SF-36 [i]	X		X							X			X		
WPAI:SHP	X		X							X			X		
PK Evaluation															
Plasma sample for TAK-861 PK [i]				X	X				X	X		X	X		

Dark grey highlights indicate the visit requires overnight confinement; overnight stay on Day -1 at the clinic is optional.
Light grey highlights indicate the visit consists of a blood chemistry assessment and may be in-clinic or remote; the sample can be collected and analyzed in a local laboratory.

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Abbreviations: ABPM = ambulatory blood pressure monitoring; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BC-CCI-E = British Columbia Cognitive Complaints Inventory– Extended; BP = blood pressure; CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; CPAL = continuous paired associate learning; CSF = cerebrospinal fluid; CSSRS = Columbia Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eCRF = electronic case report form; e-diary = daily electronic patient-reported diary; EQ-5D-5L = EuroQol-5 Dimensions 5-Levels; ESS = Epworth Sleepiness Scale; ET = early termination; FINI = Functional Impacts of Narcolepsy Instrument; FSH = follicle stimulating hormone; GGT = gamma glutamyl transferase; hBsAg = Hepatitis B surface antigen; HBc = Hepatitis B core antigen; hCG = human chorionic gonadotropin; HCV = Hepatitis C virus; HIV = human immunodeficiency virus; HLA = human leukocytic antigen; HR = heart rate; iDSST-s = international Digit Symbol Substitution Test-symbols; IEC = independent ethics committee; IRB = institutional review board; KSS = Karolinska Sleepiness Scale; LFT = liver function test; LTE = long-term extension; MSLT = Multiple Sleep Latency Test; MWT = Maintenance of Wakefulness Test; NA = not applicable; nPSG = nocturnal polysomnography; NSS-CT = Narcolepsy Severity Scale for Clinical Trials; NT1 = narcolepsy type 1; ONB = One Back test; OX = orexin; PAP = positive airway pressure; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic(s); PSG = polysomnography; PVT = psychomotor vigilance test; SF-36 = Short Form-36 Survey; TSQM = Treatment Satisfaction Questionnaire for Medication; WPAI:SHP = Work Productivity and Activity Impairment – Specific Health Problems questionnaire

[a] The screening window may be extended on a case-by-case basis after consultation with and approval from the Sponsor or designee for a reason such as an unexpected schedule change, or to perform a diagnostic PSG/MSLT or other assessments to confirm eligibility.

[b] Two follow-up visits are planned approximately 7 and 28 days after the final study drug intake (corresponding to Days 91 and 112 for participants whose final study drug intake is on Day 84). The follow-up visit 7 days after the final study drug intake is an in-clinic visit; the follow-up visit 28 days after the last dose may be in-clinic or remote (i.e., visit to an off-site laboratory to draw blood). After the Week 12 visit, participants who remained on study treatment throughout the treatment period will have the option to participate in an LTE study. Participants who immediately enroll in the LTE study will not have follow-up visits in this study.

[c] Visits 4, 6, 8, and 12 (i.e., Weeks 2, 6, 10, and 16, respectively) may be in-clinic or remote (i.e., visit to an off-site laboratory to draw blood).

[d] Discontinued medication (except medications associated with LFT elevations) can be restarted 7 days after the last administration of study drug.

[e] For all participants who withdraw early from the study, except those who refuse further contact, every effort should be deployed to have them attend an ET visit as soon as possible. If the ET visit coincides with another scheduled visit and the participant has not yet discontinued study drug, participants should be encouraged to complete all scheduled assessments. Participants who withdraw early will be encouraged to continue completing their daily e-diary until the ET visit. Further, every effort should be deployed to have these participant complete the follow-up visit 28 days after the last dose (the follow-up visit 7 days after the last dose is not needed in addition to the ET visit).

[f] If the date of a participant visit does not conform to the study plan, the timing of subsequent visits should be planned so that the visit schedule relative to the first study drug intake (Day 1) is maintained. For the Week 12 visit, every effort should be deployed to have participants come in as close to Day 84 as possible.

[g] Visit 10 for 7-day follow-up visit; Visit 11 for ET.

[h] On Day 1 and MWT days (Days 56 and 84), the first dose of TAK-861 or matched placebo will be administered in the morning by mouth (as close to 8 AM as possible). Participants will take the second dose at least 3 hours after the first morning dose (as close to 11 AM as possible). At home, the first dose should be taken in the morning, no later than 10 AM and the second dose should be taken at least 3 hours later, but no later than 1 PM.

i Refer to Table 63 for time requirements.

[j] BP will be checked (single measurement) with the participant resting for a minimum of 5 minutes and sitting with back supported. If systolic BP measurement is >160 mm Hg or diastolic BP measurement >100 mm Hg, BP measurement must be repeated in approximately 15 minutes to assess study drug discontinuation criteria, as described in Section 8.1.1.1. For screening BP assessment, if the BP is slightly elevated, the measurement may be repeated 3 times, and the median of the 3 recordings used to assess eligibility.

[k] The ABPM device will be applied on-site. ABPM should begin just before the first morning dose of study drug (or 8:00 AM ±2 hours for ABPM during screening period) and continue for at least 24.5 hours. If necessary, participants may delay their first morning dose (8 AM ±2 hours) so that it is taken right after the ABPM device begins recording. For convenience, site staff may offer to confine participants the evening before ABPM begins. The participants should not be confined to a clinical site for the majority of the 24.5-hour recording period, as real-world data collection while wearing the device is critical. ABPM should not be started the day before or during overnight confinement for a nPSG/MWT. If recording quality is not satisfactory, ABPM should be repeated. During screening the ABPM timing should account for potential repeat of the recording. ABPM recording during the treatment period will start any day between Days 57 and 73, inclusive, but must not start before the Day 56 Visit is completed. If this treatment period ABPM recording quality is not satisfactory, ABPM may be repeated as long as the recording ends no later than 1 day before check-in for the Week 12 visit.

[l] Full physical examination will be performed at screening and at the first follow-up visit (or ET visit). On all other time points, an abbreviated physical examination may be performed.

[m] Compliance with PAP is defined as having at least 4 hours of PAP use per night on at least 70% of nights for approximately 1 month (assessed by machine tracking time if possible).

[n] Pregnancy test is required for women of childbearing potential only. Serum pregnancy test will be done at screening. At all other time points, urine hCG testing may be done. Pregnancy testing can be repeated at any time at the investigator's discretion.

[o] An additional blood sample may be required during screening to ensure there is at least one AST, ALT and GGT result available from ≤16 days before randomization (fasting not required). This may be done in-clinic or remotely (i.e., visit to an off-site laboratory to draw blood).

[p] The pre 8 AM dose on Day 1 assessments of blood chemistry, urinalysis, urine drug screening, and alcohol screening are only required if the participant opted not to stay overnight at the clinic on Day -1.

[q] Urine drug screening may be performed using a dipstick and may be repeated any time at the investigator's discretion. Confirmatory urine drug tests will be performed in regions where available at the investigator's discretion.

[r] At the screening visit, alcohol screening will be done initially with a breathalyzer, and, if positive, a serum ethanol level will be obtained. For other time points, a breathalyzer will be done at check-in.

[s] Previous HLA results are acceptable if available for review by the investigator and provided for inclusion in the eCRF.

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[t] One blood sample for DNA analysis may be collected at any visit before the initiation of study drug administration. Country-level participation to be determined by local regulations and IRB/IEC approval.
[u] e-diary measures, including self-reported assessments of sleep and cataplexy, will be obtained starting after the successful initial screening visit, no later than Day -16, and continuing until the Week 12 Visit entry is completed or until rollover into the LTE. In cases where the e-diary becomes unavailable, the site may use alternative methods to collect these data with approval from the Sponsor or designee. In case a participant did not complete cataplexy questions 11 of 14 days (i.e., is not compliant) during Days -16 to -3, the screening period can be extended at the discretion of the investigator to allow the participant to improve compliance.
[v] nPSG consisting of 8-hour nighttime PSG will be obtained. In the rare event that PSG exclusion criteria cannot be assessed by Day -1, dosing may be delayed until the issue is resolved. Site investigator may opt to repeat baseline nPSG/MWT before randomization. The Sponsor or designee should be consulted for any such situation.
Note: Per the inclusion criteria, if there is a potential participant with NT1 for whom a diagnostic PSG/MSLT was performed more than 15 years from screening or is not available, a diagnostic PSG/MSLT may be performed before Day -2.
[w] Assessment is optional
Source: Applicant's protocol amendment 1, Study TAK-861-3002, Table 1.a, pages 29-32

Table 63. Efficacy, Safety and PK Assessment With Time Requirement—Study TAK-861-3002

	Screening/ Baseline [a]			12-Week Treatment Period										Follow-up [b]	
Day	-50 to -3	-2	-1	1 Pre	1 Post	14 [c]	28	42 [c]	55	56	70 [c]	83	84	7 Days After Last Dose [d]/ ET [e]	28 Days After Last Dose
Week	NA	NA		NA		2 [c]	4	6 [c]	8		10 [c]	12		13	16 [c]
Visit Window (days) [f]	NA	-3		NA		±3	±3	±3	±3		±3	±3		±3	±3
Visit Number	1	2		3		4 [c]	5	6 [c]	7		8 [c]	9		10/11 [g]	12 [c]
Primary Specimens															
Hematology	Fasted	X					X			Fasted pre 8 AM dose			Fasted pre 8 AM dose	X	
Blood chemistry	Fasted [h]	X		Fasted pre 8 AM dose [i]	11 AM	X	X	X		Fasted pre 8 AM dose	X		Fasted pre 8 AM dose	X	X
Plasma sample for TAK-861 PK				Pre 8 AM dose	9:30 AM 11 AM (11 AM sample before second dose)				Anytime between after dinner and 1 h before nPSG start	Pre 8 AM dose 9:30 AM 11:30 AM 1:30 PM 3:30 PM		Anytime between after dinner and 1 h before nPSG start	Pre 8 AM dose 9:30 AM 11:30 AM 1:30 PM 3:30 PM		

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	Screening/ Baseline [a]			12-Week Treatment Period									Follow-up [b]	
Day	-50 to -3	-2	-1	1 Pre	1 Post	14 [c]	28	42 [c]	55	56	70 [c]	83	84	7 Days After Last Dose [d]/ ET [e] 91	28 Days After Last Dose 112 [c]
Week	NA	NA		NA		2 [c]	4	6 [c]	8		10 [c]	12		13	16 [c]
Visit Window (days) [f]	NA	-3		NA		±3	±3	±3	±3		±3	±3		±3	±3
Visit Number	1	2		3		4 [c]	5	6 [c]	7		8 [c]	9		10/11 [g]	12 [c]
Vital Signs and ECG															
BP (sitting) and HR (sitting)	X [1]	Anytime between after dinner and 1 h before nPSG start	Pre 8 AM 9:30 AM 11:30 AM 1:30 PM 3:30 PM	Pre 8 AM dose	9:30 AM 11:30 AM		X		Anytime between after dinner and 1 h before nPSG start	Pre 8 AM dose 9:30 AM 11:30 AM 1:30 PM 3:30 PM		Anytime between after dinner and 1 h before nPSG start	Pre 8 AM dose 9:30 AM 11:30 AM 1:30 PM 3:30 PM	X	
ABPM [j]	Start 24.5-h recording 8 AM ± 2 h										Start 24.5-h recording pre 8 AM dose				
ECG	X [1]			Pre 8 AM dose			X		X			X		X	
Efficacy Assessment															
nPSG		Overnight							Overnight			Overnight			
MWT (4 wake trials)			10 AM 12 PM 2 PM 4 PM							10 AM 12 PM 2 PM 4 PM			10 AM 12 PM 2 PM 4 PM		
KSS	Shortly before PVT		Shortly before each PVT							Shortly before each PVT			Shortly before each PVT		

	Screening/ Baseline [a]			12-Week Treatment Period									Follow-up [b]	
Day	-50 to -3	-2	-1	1 Pre	1 Post	14 [c]	28	42 [c]	55	56	70 [c]	83	84	7 Days After Last Dose [d]/ ET [e] 91	28 Days After Last Dose 112 [c]
Week	NA	NA		NA		2 [c]	4	6 [c]	8		10 [c]	12		13	16 [c]
Visit Window (days) [f]	NA	-3		NA		±3	±3	±3	±3		±3	±3		±3	±3
Visit Number	1	2		3		4 [c]	5	6 [c]	7		8 [c]	9		10/11 [g]	12 [c]
PVT	X [1]		9 AM 3 PM							9 AM 3 PM			9 AM 3 PM		
CPAL, ONB, iDSST-s	X [1]		9 AM							9 AM			9 AM		
ESS	X [1]		After 1st MWT wake trial [k]				X			After 1st MWT wake trial [k]			After 1st MWT wake trial [k]		
CGI-S, PGI-S	X [1]		After 1st MWT wake trial [k]				X			After 1st MWT wake trial [k]			After 1st MWT wake trial [k]		
CGI-C, PGI-C							X			After 1st MWT wake trial [k]			After 1st MWT wake trial [k]		
TSQM										After 1st MWT wake trial [k]			After 1st MWT wake trial [k]		
BC-CCI-E, FINI, NSS-CT, SF-36, EQ-5D-5L, WPAI:SHP	X [1]		After 1st MWT wake trial [k]				X (NSS-CT only)			After 1st MWT wake trial [k]			After 1st MWT wake trial [k]		

Dark grey highlights indicate the visit requires overnight confinement; overnight stay on Day -1 at the clinic is optional.
Light grey highlights indicate the visit consists of a blood chemistry assessment and may be in-clinic or remote; the sample can be collected and analyzed in a local laboratory.

Abbreviations: ABPM = ambulatory blood pressure monitoring; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BC-CCI-E = British Columbia Cognitive Complaints Inventory – Extended; BP = blood pressure; CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; CPAL = continuous paired associate learning; ECG = electrocardiogram; eDiary = electronic patient-reported diary; EQ-5D-5L = EuroQol-5 Dimensions 5-Levels; ESS = Epworth Sleepiness Scale; ET = early termination; FINI = Functional Impacts of Narcolepsy Instrument; GGT = gamma glutamyl transferase; h = hour; HR = heart rate; iDSST-s = international Digit Symbol Substitution Test-symbols; LTE = long-term extension; MSLT = Multiple Sleep Latency Test; MWT = Maintenance of Wakefulness Test; NA = not applicable; nPSG = nocturnal polysomnography; NSS-CT = Narcolepsy Severity Scale for Clinical Trials; ONB = One Back test; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic(s); pre = pre-8am-dose; PSG = polysomnography; PVT = psychomotor vigilance test; SF-36 = Short Form-36 Survey; TSQM = Treatment Satisfaction Questionnaire for Medication; WPAI:SHP = Work Productivity and Activity Impairment – Specific Health Problems questionnaire

[a] The screening window may be extended on a case-by-case basis after consultation with and approval from the Sponsor or designee for a reason such as an unexpected schedule change, or to perform a diagnostic PSG/ MSLT or other assessments to confirm eligibility.

[b] Two follow-up visits are planned approximately 7 and 28 days after the final study drug intake (corresponding to Days 91 and 112 for participants whose final study drug intake is on Day 84). The follow-up visit 7 days after the final study drug intake is an in-clinic visit; the follow-up visit 28 days after the last dose may be in-clinic or remote (i.e., visit to an off-site laboratory to draw blood). After the Week 12 visit, participants who remained on study treatment throughout the treatment period will have the option to participate in an LTE study. Participants who immediately enroll in the LTE study will not have follow-up visits in this study.

[c] Visits 4, 6, 8, and 12 (i.e., Weeks 2, 6, 10, and 16, respectively) may be in-clinic or remote (i.e., visit to an off-site laboratory to draw blood).

[d] Discontinued medication (except medications associated with LFT elevations) can be restarted 7 days after the last administration of study drug.

[e] For all participants who withdraw early from the study, except those who refuse further contact, every effort should be deployed to have them attend an ET visit as soon as possible. If the ET visit coincides with another scheduled visit and the participant has not yet discontinued study drug, participants should be encouraged to complete all scheduled assessments. Participants who withdraw early will be encouraged to continue completing their daily e-diary until the ET visit. Further, every effort should be deployed to have these participants complete the follow-up visit
28 days after the last dose (the follow-up visit 7 days after the last dose is not needed in addition to the ET visit).

[f] If the date of a participant visit does not conform to the study plan, the timing of subsequent visits should be planned so that the visit schedule relative to the first study drug intake (Day 1) is maintained. For the Week 12 visit, every effort should be deployed to have participants come in as close to Day 84 as possible.

[g] Visit 10 for 7-day follow-up visit; Visit 11 for ET.

[h] An additional blood sample may be required during screening to ensure there is at least one AST, ALT, and GGT result available from ≤16 days before randomization (fasting not required). This may be done in-clinic or remotely (i.e., visit to an off-site laboratory to draw blood).

[i] Blood chemistry test only to be performed in case the participant opted not to stay overnight at the clinic on Day -1.

[j] The ABPM device will be applied on-site. ABPM should begin just before the first morning dose of study drug (or 8:00 AM ±2 hours for ABPM during screening period) and continue for at least 24.5 hours. If necessary, participants may delay their first morning dose (8 AM ±2 hours) so that it is taken right after the ABPM device begins recording. For convenience, site staff may offer to confine participants the evening before ABPM begins. The participants should not be confined to a clinical site for the majority of the 24.5-hour recording period, as real-world data collection while wearing the device is critical. ABPM should not be started the day before or during overnight confinement for an nPSG/MWT. If recording quality is not satisfactory, ABPM should be repeated. During screening the ABPM timing should account for potential repeat of the recording. ABPM recording during the treatment period will start any day between Days 57 and 73, inclusive, but must not start before the Day 56 Visit is completed. If this treatment period ABPM recording quality is not satisfactory, ABPM may be repeated as long as the recording ends no later than 1 day before check-in for the Week 12 visit.

[k] Should begin after first MWT wake trial concludes but can continue when convenient during the remainder of the day. Additional details are provided in the study manual.

[l] At first visit, no specific time.

Source: Applicant's protocol amendment 1, Study TAK-861-3002, Table 1.b, pages 35-37

Administrative Structure

As already described for Study TAK-861-3001, Study TAK-861-3002 also had:

- DMC: An oveporexton program-level external DMC reviewed unblinded safety data quarterly and had access to trial data for safety assessment
- LSEC: Independent from the DMC, reviewed cases of possible DILI, trial intervention discontinuations due to liver-related adverse events, and liver-related serious adverse events
- Trial Monitoring: Sites were monitored by (b) (4) with visits conducted per the site monitoring plan to review protocol adherence, GCP compliance, and data completeness, accuracy, and consistency

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- Investigator Training: A Sponsor representative trained investigators on GCP compliance and trial protocol conduct
- Trial Intervention Accountability: The investigator or designee maintained 100% accountability for all trial interventions during participation
- Quality Management: Each clinical trial site was responsible for internal quality management of trial conduct, data, and biological specimen collection, documentation, and completion
- Central Laboratories: Accredited central laboratories ensured consistency of analyses and reporting for clinical laboratory tests
- Audits: Audits of investigator trial sites and other facilities were included as part of independent Takeda quality assessment
- Randomization: A designated vendor generated the randomization schedule using the permuted block method with stratification factors (region and prior use of medication for NT1).

The trial design for TAK-861-3002 was generally adequate and consistent with the overall development program. The selection of the 2-mg BID dosage was based on the efficacy and safety/tolerability profile observed in the phase 2 trial (TAK-861-2001), which is appropriate. Of note, Study 3002 is identical to Study 3001 with the exception of the dosages tested (only the higher dosage of 2 mg BID is tested in 3002), the number of arms (just two), and the regions where the studies were conducted (none in the United States).

The randomization ratio of 1:2 (placebo: oveporexton 2 mg BID) was acceptable and aligned with the goal of maximizing enrollment to the active treatment group while maintaining a placebo control. This allocation strategy is reasonable for a rare disease like NT1, as it allows for greater safety data collection on the active treatment while minimizing the number of participants receiving placebo.

Blinding procedures were adequate, with all participants receiving the same number of tablets and bottles regardless of treatment assignment.

The exclusion of medications that could affect EDS or cataplexy was appropriate to isolate the treatment effect of oveporexton. The exclusion of medications associated with severe HI remained appropriate given the ongoing hepatotoxicity concerns related to the structurally similar compound firazorexton.

As with Study TAK-861-3001, the program-level DMC and LSEC provided appropriate safety oversight throughout the trial, which was particularly important given the hepatotoxicity signal from firazorexton.

Study Endpoints

The endpoint structure for Study TAK-861-3002 was nearly identical to that of Study TAK-861-3001, as previously described.

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Primary Endpoint

As in Study TAK-861-3001, the primary endpoint was:

- Change from Baseline to Week 12 in mean sleep latency from four MWT wakefulness trials

The key difference from Study TAK-861-3001 is that TAK-861-3002 evaluated only the 2-mg BID dosage compared to placebo, whereas Study TAK-861-3001 evaluated both the 1-mg BID and 2-mg BID dosages.

Secondary Endpoints

The secondary endpoints were the same as in Study TAK-861-3001, grouped into Family 1 and Family 2 for multiplicity control:

- Family 1: Change from Baseline to Week 12 in ESS total score and weekly cataplexy rate (WCR) at Week 12
- Family 2: Change from Baseline to Week 12 in mean number of lapses on PVT, PGI-C score at Week 12, change from Baseline to Week 12 in NSS-CT total score, change from Baseline to Week 12 in all six FINI domain scores (Tiredness, Cognitive Functioning, Cataplexy, Social Activities, Everyday Activities, and Everyday Responsibilities), and change from Baseline to Week 12 in SF-36 mental and physical component summary scores.

Exploratory Endpoints

The exploratory endpoints were consistent with those in Study TAK-861-3001, with one notable addition: Study TAK-861-3002 included the Work Productivity and Activity Impairment:Narcolepsy questionnaire, which was not included in Study TAK-861-3001.

The WPAI:Narcolepsy is a participant-reported 6-item questionnaire that measures work time missed and work and activity impairment due to narcolepsy during the past 7 days. The instrument yields four scores: absenteeism, presenteeism, work productivity loss, and activity impairment due to NT1. Work impairment was evaluated among employed participants and activity impairment outside of work was assessed among all participants. For each score, the corresponding WPAI:Narcolepsy outcome is expressed as a percentage, with higher numbers indicating greater impairment and less productivity. This additional endpoint provided information on the impact of oveporexton on work productivity and activity impairment in employed participants.

All other exploratory endpoints (CGI-C/CGI-S/PGI-S, NSS-CT individual questions, nPSG, eDiary, cognitive tests, KSS, BC-CCI-E, TSQM, EQ-5D-5L, and SF-36 domain scores) were the same as in Study TAK-861-3001.

Statistical Analysis Plan

The estimand definitions, derivations, and analysis methods were generally the same as for Study TAK-861-3001, described previously. The only exception is the multiple testing

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approach, which was simpler due to the fact that the Study TAK-861-3001 only contained one active arm. Except for the difference in number of active arms, the general multiple testing approach and order of endpoints remained the same, with the same two families. The hierarchical multiple testing procedure employed a graphical testing approach.

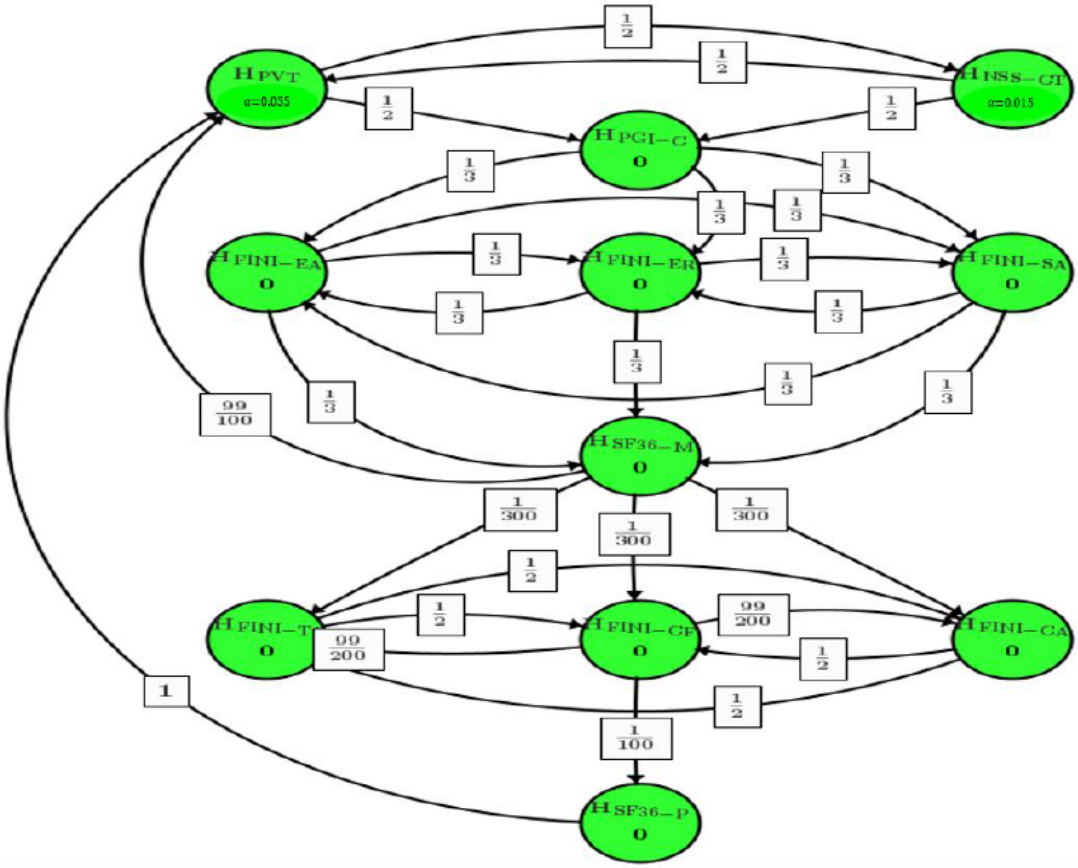
The primary and secondary efficacy endpoints were grouped into two families, where family 1 included hypotheses associated with change from Baseline to Week 12 in mean sleep latency on the MWT, change from Baseline to Week 12 in ESS total score, and WCR at Week 12. Family 2 included hypotheses associated with the remaining secondary efficacy endpoints (change from Baseline to Week 12 in mean number of lapses on the PVT, PGI-C score at Week 12, change from Baseline to Week 12 in NSS-CT total score, change from Baseline to Week 12 in six FINI domain scores, and change from Baseline to Week 12 in SF-36 mental and physical component summary scores). The multiple testing approach for each family is presented in Figure 18 and Figure 19, respectively.

Figure 18. Multiple Testing Procedure, Family 1 (Study TAK-861-3002)



Source: Statistical Analysis Plan v1.0 (Page 19)

Figure 19. Multiple Testing Procedure, Family 2 (Study TAK-861-3002)



Source: Statistical Analysis Plan v1.0 (Page 20)

See the review of Study TAK-861-3001; the consistent endpoint selection across both pivotal studies allowed for direct comparison of results.

Protocol Amendments

The initial protocol was amended once locally for the EU (September 6, 2024) and once globally (October 29, 2024). The first participant was enrolled on November 7, 2024, under the original protocol.

Noteworthy changes included:

Initial Protocol EU Version 1 (September 6, 2024):

- Changed the primary endpoint for EDS assessment from MWT to ESS total score exclusively in the EU/EEA (MWT became a secondary endpoint in EU/EEA only).
- Clarified the exploratory objective as "To assess the effect of oveporexton on quantity and quality of sleep" (instead of only nocturnal sleep) and updated the corresponding endpoint to include daytime and nocturnal sleep quantity and quality questions from the eDiary.
- Clarified that pregnant participants were to be withdrawn from treatment but preferably not from the trial.

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- Clarified analysis set definitions: safety set analyzed according to treatment received; full analysis set (FAS) analyzed according to randomized treatment assignment.
- Moved the PVT number of lapses endpoint from Family 1 to Family 2.
- Added a section on missing data handling

Global Protocol Amendment 1 (October 29, 2024):

- Incorporated the EU-specific changes regarding ESS as primary endpoint in EU/EEA.
- Specified that primary and secondary endpoints (MWT, ESS, NSS-CT, FINI, SF-36) were measured as change from Baseline at Week 12, as per Agency's recommendation.
- Changed PVT assessment from single 3 PM session to mean of 2 intraday sessions.
- Specified components of the eye examination within the physical examination to be performed at Baseline and at subsequent visits.
- Allowed ESS retesting after medication discontinuation/tapering if screening ESS was <11 in participants taking NT1 medications.
- Clarified that pregnant participants were to be withdrawn from treatment but preferably not from the trial.
- Clarified that all participants in the safety set were to be analyzed according to the treatment they received.
- Clarified that the FAS consisted of all participants who were randomized and all participants in the FAS were to be analyzed according to the treatment group to which they were randomized.
- The endpoint of number of lapses on the PVT was moved from Family 1 to Family 2.
- Added a section on missing data handling. Clarified that placebo-based multiple imputation would be used to handle missing data due to ICEs in the primary analysis.

The protocol amendments do not appear to have substantially affected the conduct or integrity of the trial. The first participant was enrolled on November 7, 2024, under the original protocol, and the amendments were implemented relatively early in the trial timeline.

The Applicant implemented Global Protocol Amendment 1 primarily in response to FDA feedback. Notably, during the development program, the Agency informed the Applicant that the ESS was not considered an optimal primary endpoint because it is a subjective measure, and recommended the MWT as the preferred primary endpoint due to its objective nature. The EU-specific amendment, which designated ESS as the primary endpoint exclusively in the EU/EEA, reflects regional regulatory differences but does not impact the U.S. regulatory assessment, where MWT remains the primary endpoint.

Additionally, at the EOP2 meeting, the Agency recommended that the Applicant change their MWT endpoint from assessment at Week 12 to change from Baseline at Week 12, as the trajectory of change over time provides important information for labeling to inform

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healthcare providers about the expected treatment response pattern. This recommendation was incorporated into Global Protocol Amendment 1, which specified that primary and secondary endpoints were to be measured as change from Baseline at Week 12.

The other amendments primarily consisted of clarifications to analysis set definitions, missing data handling procedures, specification of eye examination components, and minor adjustments to assessment timing (e.g., PVT measurement from two intraday sessions rather than a single session), none of which appear to compromise the trial's scientific validity or interpretability.

8.1.2.2. Study Results

Compliance With Good Clinical Practices

The Applicant states that "This trial was conducted with the highest respect for the individual participants in accordance with the protocol and ethical principles that have their origins in the Declaration of Helsinki and in compliance with IRB regulations stated in Title 21 of the US Code of Federal Regulations Part 56, ICH Harmonised Tripartite Guideline for GCP E6, IECs and EU Clinical Trials Regulation (CTR) No 536/2014, and all applicable industry regulations and applicable national and local laws and regulations," and "The clinical trial protocol, protocol amendments, the investigator's brochure, a sample ICF, and other trial-related documents were reviewed and approved by the local or central IRBs/IECs of all trial sites."

The Applicant has provided attestation that Study TAK-861-3002 was conducted in accordance with GCP.

Financial Disclosure

The Applicant has adequately disclosed financial interests and arrangements with clinical investigators. The Applicant did not disclose any interests or arrangements that raised questions about the integrity of the study data.

Patient Disposition

A total of 140 individuals were screened for the trial, from whom 105 participants were enrolled across 28 sites in Asia-Pacific, Australia, and Europe. Of the 35 screen failures, 32 participants did not meet the inclusion/exclusion criteria and three withdrew consent. All 105 enrolled participants were randomized to one of two groups: placebo (n=35) or oveporexton 2 mg BID (n=70). All enrolled participants received at least one dose of the trial intervention.

Of the 105 treated participants, 5 (4.8%) discontinued the trial. The reasons for discontinuation are summarized by treatment group in the table below.

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Table 64. Participant Discontinuations by Treatment Group – Safety Set (Study TAK-861-3002)

Reason for Discontinuation	Placebo (N=35) n (%)	Oveporexton 2 mg BID (N=70) n (%)	Total (N=105) n (%)
Total Discontinuations	1 (2.9%)	4 (5.7%)	5 (4.8%)
Adverse Event	0	2 (2.9%)	2 (1.9%)
Withdrawal of Consent	1 (2.9%)	1 (1.4%)	2 (1.9%)
Other[a]	0	1 (1.4%)	1 (1.0%)

[a] Participant completed trial intervention and elected not to enter the LTE trial, but did not attend the follow-up visits.
Source: Clinical reviewer-created from Study TAK861-3002 CSR, Table 5 and Figure 2

A total of 101 participants completed trial intervention, 96 (95%) entered the long-term extension (LTE) trial immediately. Four additional participants (two in the oveporexton group, two in the placebo group) entered the LTE trial with a dosing gap and were not captured in the TAK-861-3002 electronic database. The total number entering the LTE trial was 100 of 101 (99%) participants who completed trial intervention. One participant completed trial intervention and elected not to enter the LTE trial but did not attend the follow-up visits, so he/she did not complete the trial.

In total, 100 participants completed the trial, representing 97.1% (34/35) of the placebo group and 94.3% (66/70) of the oveporexton 2 mg BID group. A full summary of participant disposition, including the number of participants (n) for each category, is provided in Table 65.

Table 65. Participant Disposition (All Randomized Subjects) (Study TAK-861-3002)

Participant Disposition	Placebo (N=35) n (%)	OVE 2 mg BID (N=70) n (%)	Total (N=105) n (%)
Randomized	35 (100)	70 (100)	105 (100)
Randomized and treated	35 (100)	70 (100)	105 (100)
Completed trial	34 (97.1)	66 (94.3)	100 (95.2)
Discontinued trial	1 (2.9)	4 (5.7)	5 (4.8)
Randomized but not treated	0	0	0
Treated	1 (2.9)	4 (5.7)	5 (4.8)
Completed trial intervention	34 (97.1)	67[b] (95.7)	101 (96.2)
Discontinued trial intervention	1 (2.9)	3 (4.3)	4 (3.8)
Continuing to LTE trial[a]	32 (91.4)	64 (91.4)	96 (91.4)
Reason for discontinuation of trial for treated participants			
AE	0	2 (2.9)	2 (1.9)
Withdrawal by participant	1 (2.9)	1 (1.4)	2 (1.9)
Other[b]	0	1 (1.4)	1 (1.0)

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Participant Disposition	Placebo (N=35) n (%)	OVE 2 mg BID (N=70) n (%)	Total (N=105) n (%)
Reason for discontinuation of trial intervention			
AE	0	2 (2.9)	2 (1.9)
Withdrawal by participant	1 (2.9)	1 (1.4)	2 (1.9)

[a] Four additional participants (2 in the oveporexton group, 2 in the placebo group) continued to the LTE trial with a dosing gap, and were not captured in the TAK-861-3002 electronic database. Of the 101 participants who completed the trial intervention, 100 (99.0%) entered the LTE trial (data on file).
[b] One participant completed trial intervention and elected not to enter the LTE trial, but did not attend the follow-up visits.
Source: Applicant's CSR Study TAK-861-3002, Table 5, page 38

The screen failure rate was 25.0% (35/140), which is reasonable for a trial with specific eligibility criteria in a rare disease population. The majority of screen failures (91.4%; 32/35) were due to not meeting inclusion/exclusion criteria, which does not raise concerns about the representativeness of the enrolled population.

Few participants discontinued the overall program. A numerical imbalance in discontinuations was observed between the treatment arms. The discontinuation rate was higher in the oveporexton 2 mg BID group (5.7%; 4/70) compared to the placebo group (2.9%; 1/35).

This finding should be interpreted with caution. The interpretation of group difference is limited by the small absolute number of discontinuation events in each group (n=1 in placebo, n=4 in oveporexton). With such small event counts, a large difference in percentages can arise due to random chance, and the analysis lacks the statistical power to support definitive conclusions. Therefore, it is difficult to attribute clinical significance to this observed imbalance based on the current data.

The specific AEs that led to these discontinuations are described in detail in the paragraphs that follow.

Protocol Violations/Deviations

Participant-Level Deviations

Significant protocol deviations affected 61 of 105 participants (58.1%) in the randomized sample. The overall proportion of participants with at least one deviation was higher in the oveporexton group (61.4%) compared to the placebo group (51.4%).

Key Deviation Categories by Treatment Group:

- Good Clinical Practice (GCP) Deviations (45.7% of all participants): This was the most frequent category and was similar between the placebo (42.9%) and oveporexton (47.1%) groups. The majority of these (n=46) involved breaches of participant confidentiality, specifically "date of birth visible in ambulatory blood pressure monitoring (ABPM) report due to system issue." Two participants had deviations in the subcategory of other GCP

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deviations (prior medication washout period started before the informed consent document was signed).

- Protocol Implementation Deviations (9.5% of all participants): These were more frequent in the oveporexton group (11.4%) than the placebo group (5.7%). The most common subcategory was "other (protocol implementation)" affecting 7 participants (6.7% overall). Example of Other included: “Cataplexy e-Diary not completed for more than 7 days in a 2-week period (except for Week 10 Week 12),” “Participant was not discontinued after they met discontinuation criteria for elevated diastolic blood pressure,” and “Site gave dose past D84 on EOT.”
- Informed Consent Deviations (8.6% of all participants): These were balanced between the placebo (8.6%) and oveporexton (8.6%) groups. The deviation for "consenting process was missed" occurred in 6 participants total, with a higher concentration in the oveporexton group (5 participants, 7.1%) compared to the placebo group (1 participant, 2.9%).
- Eligibility Criteria Deviations (4.8% of all participants): Five participants were randomized despite not meeting the study's eligibility criteria. All of these deviations occurred in the oveporexton group (7.1%), with none reported in the placebo group.
  - Oveporexton group: Two participants did not have an ESS score ≥11 at screening, one participant had cataplexy eDiary compliance not met during screening period, one participant had lack of PAP compliance prior to enrollment, and one participant did not show to have a routine bedtime in the sleep diary.
- Safety Deviations (2.9% of all participants): These occurred exclusively in the oveporexton group (4.3%), with none reported in the placebo group. All three deviations involved assessments (C-SSRS and CGI-S) performed by non-authorized staff.
- Clinical Trial Material Deviations (1.0% of all participants): One participant in the oveporexton group accidentally received an overdose of trial intervention.
- Discontinuations Due to Protocol Deviations: No participants discontinued trial intervention because of a protocol deviation.

At the trial level, five trial sites reported at least one significant site-level deviation. These included:

- GCP Deviations (three sites): Issues included participant identifier communicated to Sponsor, CRO, vendor, and other vendor stipend deficiencies.
- Protocol Implementation (two sites): Deviations involved failure to comply with IRB/IEC requirements and lack of principal investigator’s oversight on trial.

Additionally, the Applicant identified additional protocol deviations after the database lock (DBL) and submitted an erratum detailing these findings as follows:

<u>Participant-Level Deviations</u>

New Deviations Identified:

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Five new significant participant-level deviations were identified: three in the category of safety deviations (non-qualified rater performed C-SSRS), and one each in the categories of eligibility criteria (participant met exclusion criterion for elevated blood pressure) and informed consent (optional DNA sample taken without obtaining consent).

In addition, five protocol deviations were reclassified following the database lock (DBL):

- Three deviations were reclassified from nonsignificant to significant. All three deviations were in the informed consent category and occurred because an optional DNA sample was collected from a participant who had not signed the corresponding Informed Consent Form (ICF).
- Two deviations were reclassified from significant to nonsignificant. Both deviations were in the protocol implementation category. One involved a missed visit at Early Termination, and the other pertained to missing endpoint assessments at the Day 84 visit.

Site-Level Deviations

- One new significant site-level deviation was identified in the category of protocol implementation.

An analysis of protocol deviations revealed numerical imbalances between the treatment arms in several key categories. Most notably, all eligibility criteria deviations occurred exclusively in the oveporexton group. Prior to database lock, five such deviations were identified, with an additional deviation found post-DBL, bringing the total to six participants (8.6% of the oveporexton group) compared to zero in the placebo group.

An assessment of these six deviations shows they were heterogeneous in nature. While two participants were enrolled who did not meet the ESS severity threshold, the other four deviations were distinct, involving a lack of PAP compliance, failure to meet cataplexy eDiary compliance, an irregular bedtime in the sleep diary, and meeting an exclusion criterion for elevated blood pressure. This lack of a consistent pattern suggests isolated enrollment errors rather than a systematic flaw that consistently skewed the study population toward being more or less severe.

Additionally, all three safety deviations (assessments performed by non-authorized staff) occurred in the oveporexton group. The GCP deviations, although the most frequent category overall, were relatively balanced between groups (42.9% placebo versus 47.1% oveporexton) and were primarily administrative in nature.

Given the varied nature of the eligibility deviations, it is unlikely they introduced a systematic bias into the efficacy analysis. If these deviations had any collective impact, it would likely be to underestimate the true treatment effect rather than artificially inflate it (i.e., recruitment of less severe participants in the oveporexton group). Importantly, no participants discontinued the trial intervention because of a protocol deviation, suggesting these issues did not substantially impact participant conduct.

Ultimately, the observed differences are based on a very small number of participants. Therefore, although these specific imbalances are noted for completeness, the varied nature

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and low frequency of these deviations make it improbable that they meaningfully altered the interpretation of the trial's primary efficacy and safety outcomes. The Applicant's conclusion that "participant-level protocol deviations did not affect the use and interpretation of the trial data" appears reasonable.

Demographic Characteristics

Demographic characteristics were generally similar across the treatment groups (Table 66). Of the 105 randomized participants, 45% were White and 20% were Asian. No Black participants were enrolled. For 35% of participants, race was categorized as unknown, as these data were not collected due to local regulations.

There was an imbalance in sex distribution between the groups. The placebo group was predominantly male (62.9%), whereas the oveporexton group had a higher proportion of females (52.9%). The median age of participants was 27.0 years, with a range of 18 to 62 years. No adolescent (<18 years) or older adult (≥65 years) participants were enrolled in the study.

The study was conducted in Europe, Australia, and the Asia-Pacific region, with 80% of participants enrolled in the Europe/Australia region.

Table 66. Demographic Characteristics of the Full Analysis Set (Randomized Sample) (Study TAK-861-3002)

Demographic Parameters	Placebo (N=35) n (%)	Oveporexton 2 mg BID (N=70) n (%)	Total (N=105) n (%)
Sex			
Male	22 (62.9)	33 (47.1)	55 (52.4)
Female	13 (37.1)	37 (52.9)	50 (47.6)
Age			
Mean years (SD)	34.0 (13.14)	29.1 (9.62)	30.7 (11.10)
Median (years)	30.0	26.5	27.0
Min, max (years)	18, 58	18, 62	18, 62
Age Group			
<18	0	0	0
≥18 and <65 years	35 (100)	70 (100)	105 (100)
≥65 years	0	0	0
Race			
White	19 (54.3)	28 (40.0)	47 (44.8)
Asian	7 (20.0)	14 (20.0)	21 (20.0)
Unknown[1]	9 (25.7)	28 (40.0)	37 (35.2)
Ethnicity			
Not Hispanic or Latino	26 (74.3)	42 (60.0)	68 (64.8)
Missing[1]	9 (25.7)	28 (40.0)	37 (35.2)
Region			
Europe/Australia	28 (80.0)	56 (80.0)	84 (80.0)
Asia-Pacific	7 (20.0)	14 (20.0)	21 (20.0)

[1] Data on race and/or ethnicity were not collected in some countries because of local regulations.
Source: Clinical reviewer, Study TAK-861-3002, randomized sample

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The demographic and baseline characteristics were generally similar across the placebo and oveporexton treatment groups, though an imbalance in sex distribution was noted. There are significant limitations regarding the age distribution, as the study population completely lacks adolescent (<18) and older adult (≥65) participants. Therefore, the efficacy and safety of oveporexton in these populations cannot be characterized from this study.

The generalizability of the findings to the United States population warrants consideration, as the trial was conducted exclusively in Europe, Australia, and Asia, with no North American sites. The complete absence of U.S. participants and the limited racial diversity are notable. However, given that the underlying pathophysiology of NT1 does not differ across populations, and given that the standard of care for diagnosis and treatment is similar in the E.U., Australia, and the U.S., the concerns around generalizability are somewhat mitigated. Additional reassurance is provided by data from TAK-861-3001, which enrolled 26 U.S. participants, whose baseline demographics and NT1 disease severity were broadly comparable to the non-U.S. population.

Furthermore, the Applicant conducted sensitivity analyses using a Bayesian hierarchical model—implemented to address the limitation of small regional sample sizes—which showed that treatment effects on MWT, ESS, and WCR in the North America subgroup were consistent with the overall study population. Consistent with this finding, our own exploratory subgroup analyses also showed a positive treatment effect in the U.S. population, although only for the 2-mg BID dosage, as previously described in the TAK-861-3001 efficacy results, although these analyses are of limited interpretability due to small sample size and lack of prespecification.

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

The baseline disease characteristics of the participants were generally well-balanced across the placebo and oveporexton treatment arms:

- Disease History and Severity of Sleepiness: The treatment groups were highly comparable in terms of disease history. The median age at symptom onset (15.0 years) and the median age at NT1 diagnosis (21.6 years) were consistent across both arms. Furthermore, the key baseline measures for EDS were severe and well-matched. The mean MWT sleep latency was very low (around 4.5 minutes), and the mean ESS total score was very high (around 18), indicating a population with a significant disease burden at study entry.
- Baseline Cataplexy Rate: A numerical imbalance was noted in the baseline WCR. The mean WCR was higher in the placebo group (45.8) compared to the oveporexton group (33.2). However, the median values were more closely aligned (27 versus 22, respectively), and the standard deviations were very large in both groups (around 40). This result suggests that the difference in means is likely driven by a few participants with extremely high cataplexy rates and may not represent a clinically significant systematic imbalance.
- Diagnostic Confirmation and Prior Treatment: All participants had confirmed diagnoses of NT1 through PSG/MSLT and either HLA positivity or documented historical CSF orexin levels ≤110 pg/mL, per the trial inclusion criteria. The proportion of participants who were HLA

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positive (approximately 98%) and had documented low CSF orexin levels (approximately 45%, combining participants with CSF reported in numeric or categorical values) were similar across groups. The high rate of prior use of NT1 medications requiring washout (approximately 87%) was also consistent across groups, indicating that the trial enrolled a predominantly treatment-experienced population.

- Lifestyle Factors: Baseline lifestyle characteristics such as alcohol and tobacco use were similar across groups. A numerical imbalance was noted in caffeine consumption, with a higher percentage of current users in the placebo group (68.6%) compared to the oveporexton group (52.9%).
- PAP Ventilation Use: The rate of PAP use for comorbid OSA was similar between groups (5.7% in the placebo group versus 8.6% in the oveporexton group).

In conclusion, the treatment groups were highly comparable for most key parameters, with minor numerical imbalances noted for baseline cataplexy rates and current caffeine use. A careful consideration of each is warranted.

The higher rate of caffeine use in the placebo group could theoretically bias the results against finding a significant effect for oveporexton, as caffeine could potentially improve alertness and mask underlying sleepiness in the placebo arm. However, the protocol required participants to be admitted to the clinical unit the day prior to key assessments like the MWT. This controlled environment, which includes restrictions on substances like caffeine, provides a robust layer of control that effectively mitigates any potential for acute caffeine effects to confound these critical measurements.

The higher mean baseline WCR in the placebo group is a more complex issue. It is noteworthy that a similar numerical imbalance in baseline WCR, with a higher mean in the placebo group, was also observed in the pivotal Study TAK-861-3001. The recurrence of this imbalance across two independent trials is likely a product of random chance combined with the high variability of the WCR endpoint, rather than an indication of a systematic issue in trial conduct. Theoretically, this imbalance could bias the results against finding a significant effect for oveporexton. A group starting with a more extreme (higher) value has a greater potential to show a large reduction, even by chance (i.e., regression to the mean). This difference could artificially inflate the placebo response and, in turn, diminish the observed treatment difference between oveporexton and placebo.

Therefore, despite these minor imbalances, their potential impact on the study's conclusions is likely minimal due to mitigating factors in the trial's conduct. The treatment groups remained highly comparable with respect to disease history, severity of sleepiness, and diagnostic confirmation, again providing a solid basis for evaluating the treatment effects of oveporexton.

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Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Overall treatment compliance was very high and comparable between groups, with a median compliance rate of 99.4% in the oveporexton group and 98.8% in the placebo group. No participants in either group had a compliance rate below 70%. A moderately higher proportion of participants in the oveporexton group (20.0%, 14/70) had a compliance rate over 100% compared to the placebo group (14.3%, 5/35), which may suggest some instances of taking more than the prescribed dosage. An IR was issued to the Applicant for clarification. As described for Study TAK-861-3001, the Applicant clarified that the above-threshold compliance rates were attributable to reconciliation discrepancies during tablet accountability, such as tablets being dropped or lost, or participants failing to return tablets stored in a secondary container, rather than to actual excess dosing. No cases of confirmed overdose were identified in Study TAK-861-3002.

Comorbidity

Concurrent medical conditions were frequently reported, affecting approximately 53% of all participants, with a higher incidence in the placebo group (62.9%) than in the oveporexton group (48.6%). Among the most common conditions, a higher rate in the placebo group was noted for both Metabolism and nutrition disorders (17.1% versus 7.1% in the oveporexton group) and Musculoskeletal and connective tissue disorders (14.3% versus 5.7%).

Two comorbidities of particular relevance to this trial, sleep apnea and psychiatric disorders, were also examined. A slight numerical imbalance was observed for sleep apnea syndrome, which was reported in 7.1% (5/70) of participants in the oveporexton group compared to 2.9% (1/35) in the placebo group. In contrast, the prevalence of psychiatric disorders was found to higher in the placebo group, affecting 11.4% (4/35) of participants in the placebo group versus 4.3% (3/70) in the oveporexton group.

Past and Concomitant Medications

The trial enrolled a heavily treatment-experienced population, with a high rate of prior medication use for NT1 that was highly comparable between groups. Approximately 90% of participants in the oveporexton group and 83% in the placebo group had a lifetime history of using at least one NT1 therapy. A slight numerical imbalance was noted for lifetime use of psychostimulants, which was reported in 78.6% of participants in the oveporexton group versus 65.7% in the placebo group. Lifetime use of antidepressants, oxybate sodium, and pitolisant was similar between groups.

The high level of active treatment prior to the study was further evidenced by the large proportion of participants—approximately 81%—who required washout from their existing NT1 medications (84% in the oveporexton group and 74% in the placebo group).

Regarding medication use during the trial, the rate of concomitant medication was approximately 48% of participants across both groups (52.9% in the oveporexton group and

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37.1% in the placebo group). The most frequently reported therapeutic classes were Anti-inflammatory and Antirheumatic Products, Non-Steroids, which were used at a similar rate in the placebo (20%) and oveporexton (16%) groups.

The use of several prohibited medications was noted during the trial: modafinil, sodium oxybate, and vortioxetine were each used by one participant in the oveporexton group, and caffeine citrate was used by one participant in the placebo group. None of these cases were reported as protocol deviations. An IR was issued to the Applicant for clarification. The Applicant responded adequately, clarifying that modafinil and sodium oxybate were prior medications incorrectly classified as concomitant due to date imputation and data entry errors, respectively; that vortioxetine was approved by the Takeda medical monitor for treatment of a depression adverse event and was not considered to have anticataleptic properties; and that caffeine citrate use remained within the protocol-allowed limits and did not overlap with key assessment days. Based on the Applicant's clarifications, none of these cases constitute protocol deviations, and their potential impact on the trial results is considered negligible.

Rescue Medication Use

No rescue medications were specified in the protocol.

A thorough review of baseline characteristics, comorbidities, and medication history confirms that the treatment groups were generally well-balanced. Several minor numerical imbalances were identified; however, these differences are based on small absolute numbers of participants and are unlikely to have a clinically meaningful impact on the interpretation of the efficacy and safety results.

Two trial conduct issues were identified and IRs were issued to the Applicant: the use of prohibited concomitant medications by a small number of participants, and a higher proportion of participants in the oveporexton group with compliance rates exceeding 100%. The Applicant responded adequately to both IRs. The prohibited medication cases were attributable to data entry and date imputation errors or were otherwise approved per protocol procedures, and none constituted actual protocol deviations. The above-threshold compliance rates were similarly explained by tablet accountability reconciliation discrepancies rather than actual excess dosing. These matters are therefore considered resolved and are not expected to have a meaningful impact on the interpretation of the efficacy and safety results.

Overall, the initial randomization appears to have been successful, and the study arms are considered highly comparable at baseline, providing a solid foundation for the evaluation of oveporexton's treatment effect.

Efficacy Results–Primary Endpoint

Oveporexton 2 mg BID achieved a highly statistically significant improvement in the change from Baseline to Week 12 in mean sleep latency on the MWT. The Least Square (LS) mean changes and treatment differences in sleep latency on the MWT are displayed in Table 67.

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The change from Baseline to Week 12 in mean sleep latency on the MWT was significantly higher in oveporexton 2 mg group than placebo (LS mean difference [95% CI] =20.09 [16.57, 23.61]; p<0.0001).

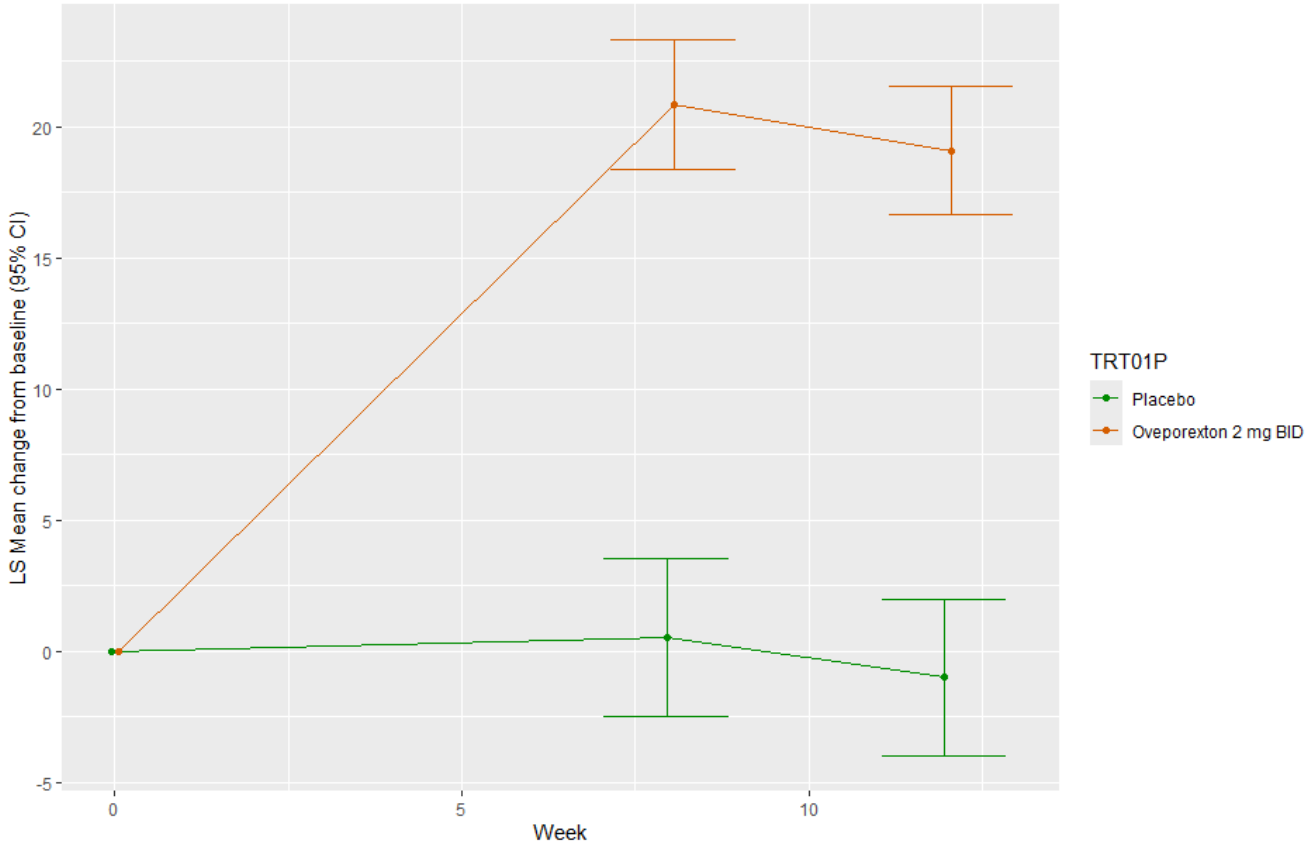
Table 67. Primary Analysis: Sleep Latency on the MWT Change From Baseline to Week 12 in the Full Analysis Set (TAK-861-3002)

Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	35	-1.01 (1.529)	(-4.00, 1.99)	NA	NA	NA
OVE 2 mg BID	70	19.09 (1.254)	(16.63, 21.54)	20.09 (1.796)	(16.57, 23.61)	<0.001

Source: CSR Table 9 on page 51, confirmed by statistical reviewer

The adjusted mean change from Baseline in sleep latency on the MWT over the entire study period is presented in Figure 20. There is again a separation starting on Week 8.

Figure 20. Primary Analysis: Sleep Latency on the MWT Change From Baseline by Visit in the Full Analysis Set (TAK-861-3002)



Source: Statistical reviewer

The Applicant conducted sensitivity analyses of the primary efficacy endpoint to explore sensitivity of the results to different modeling approaches or missing data assumptions. The results of the sensitivity analyses were consistently similar to the primary analysis results, likely due to a robust treatment effect observed. The results are omitted here for the sake of brevity.

The statistical reviewer also conducted a sensitivity analysis that makes the most conservative assumption around missing data. For any post-baseline missing data, the worst possible score was imputed. The results of this sensitivity analysis are in Table 68, the study remains highly significant.

Table 68. Sensitivity Analysis: Sleep Latency on the MWT Change From Baseline to Week 12 in the Full Analysis Set, Assuming Worst Score for All Missing Data (TAK-861-3002)

Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	35	-1.09 (1.560)	(-4.19, 2.01)	NA	NA	NA
OVE 2 mg BID	70	18.97 (1.260)	(16.46, 21.48)	20.06 (1.843)	(16.41, 23.72)	<0.001

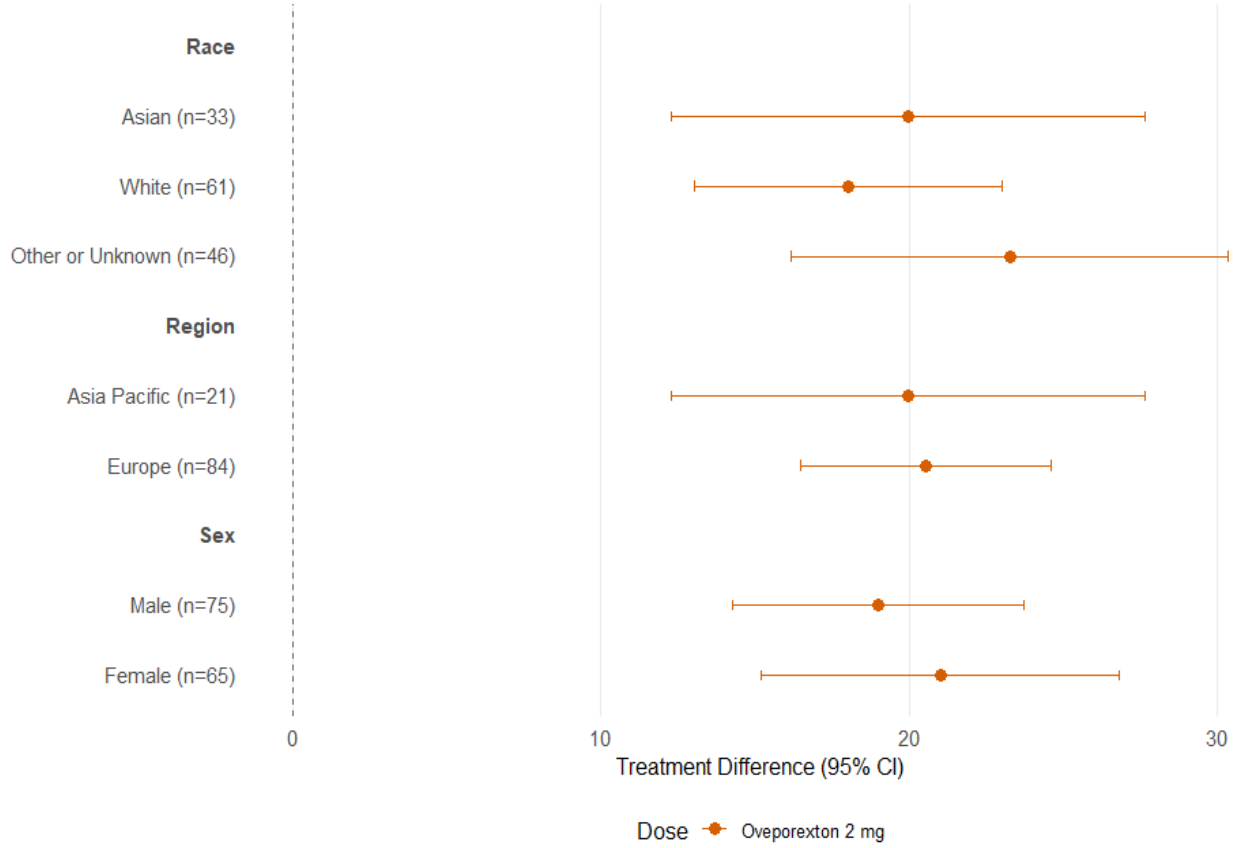
Source: Statistical reviewer

Lastly, the primary endpoint results were generally consistent across subgroups of region, race, and sex (Figure 21). Although the study was not designed or powered to demonstrate efficacy within subgroups, observed treatment effects across all subgroups trended in the same direction in favor of oveporexton and all subgroups reached nominal statistical

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significance. The age subgroup was not investigated, as almost all participants were between 18 and 65 years of age.

Figure 21. Subgroup Analysis: Sleep Latency on the MWT Change From Baseline vs. Placebo in the Full Analysis Set (TAK-861-3002)



Source: Statistical reviewer

Data Quality and Integrity

There were no data quality or integrity issues noted during the review.

Efficacy Results–Secondary and Other Relevant Endpoints

All secondary endpoints included in the multiple testing procedure were statistically significant, yielding a very robust treatment effect. None of the results were sensitive to missing data or modeling assumptions.

Oveporexton achieved a highly statistically significant improvements in the change from Baseline to Week 12 in ESS total score, WCR, NSS-CT total score, mean number of lapses in PVT, PGI-C Responder status at Week 12, FINI (all 6 domains of tiredness, cognitive functioning, cataplexy, social activities, everyday activities, everyday responsibilities), and SF-36. The results for all of these multiplicity protected endpoints are presented in Table 69.

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Table 69. Primary Analysis: All Multiplicity Protected Secondary Endpoints: ESS Total Score, WCR, NSS-CT Total Score, Mean Number of Lapses in PVT, PGI-C Responder Status, FINI, SF-36 in the Full Analysis Set (TAK-861-3002)

ESS Total Score						
Treatment Group	**n**	**LS Mean (SE)**	**95% CI**	**Difference vs. Placebo Estimate (SE)**	**Difference vs. Placebo 95% CI**	**p-value**
Placebo	35	-1.57 (0.676)	(-2.89, -0.24)	NA	NA	NA
OVE 2 mg BID	70	-11.10 (0.550)	(-12.18, -10.02)	-9.53 (0.799)	(-11.10, -7.97)	<0.001
WCR						
Treatment Group	**n**	**Incidence Rate**	**95% CI**	**IRR vs. Placebo Estimate**	**IRR vs. Placebo 95% CI**	**p-value**
Placebo	35	24.43	(16.83, 35.46)	NA	NA	NA
OVE 2 mg BID	70	6.12	(4.44, 8.42)	0.25	(0.15, 0.42)	<0.001
NSS-CT Total Score						
Treatment Group	**n**	**LS Mean (SE)**	**95% CI**	**Difference vs. Placebo Estimate (SE)**	**Difference vs. Placebo 95% CI**	**p-value**
Placebo	35	-3.04 (1.367)	(-5.72, -0.36)	NA	NA	NA
OVE 2 mg BID	70	-21.15 (1.090)	(-23.28, -19.01)	-18.11 (1.605)	(-21.25, -14.96)	<0.001
Mean Number of Lapses in PVT						
Treatment Group	**n**	**Estimate (SE)**	**95% CI**	**Difference vs. Placebo Estimate (SE)**	**Difference vs. Placebo 95% CI**	**p-value**
Placebo	35	3.36 (1.800)	(-0.17, 6.89)	NA	NA	NA
OVE 2 mg BID	70	-5.46 (1.018)	(-7.45, -3.46)	-8.82 (1.980)	(-12.70, -4.94)	<0.001
PGI-C Responders						
Treatment Group	**n**	**Response Rate**	**95% CI**	**Odd Ratio vs. Placebo Estimate (SE)**	**Odds Ratio vs. Placebo 95% CI**	**p-value**
Placebo	35	0.15	(0.02, 0.27)	NA	NA	NA
OVE 2 mg BID	70	0.90	(0.82, 0.97)	51.21	(14.14, 185.42)	<0.001
FINI: Tiredness						
Treatment Group	**n**	**LS Mean (SE)**	**95% CI**	**Difference vs. Placebo Estimate (SE)**	**Difference vs. Placebo 95% CI**	**p-value**
Placebo	35	-4.32 (3.410)	(-11.00, 2.37)	NA	NA	NA
OVE 2 mg BID	70	-45.09 (2.822)	(-50.62, -39.56)	-40.77 (3.996)	(-48.60, -32.94)	<0.001
FINI: Cognitive Functioning						
Treatment Group	**n**	**LS Mean (SE)**	**95% CI**	**Difference vs. Placebo Estimate (SE)**	**Difference vs. Placebo 95% CI**	**p-value**
Placebo	35	-3.56 (3.586)	(-10.59, 3.46)	NA	NA	NA
OVE 2 mg BID	70	-33.74 (2.835)	(-39.29, -28.18)	-30.17 (4.250)	(-38.50, -21.84)	<0.001

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FINI: Cataplexy						
Treatment Group	**n**	**LS Mean (SE)**	**95% CI**	**Difference vs. Placebo Estimate (SE)**	**Difference vs. Placebo 95% CI**	**p-value**
Placebo	35	-5.53 (3.028)	(-11.46, 0.41)	NA	NA	NA
OVE 2 mg BID	70	-24.63 (2.484)	(-29.50, -19.76)	-19.10 (3.552)	(-26.06, -12.14)	<0.001
FINI: Social Activities						
Treatment Group	**n**	**LS Mean (SE)**	**95% CI**	**Difference vs. Placebo Estimate (SE)**	**Difference vs. Placebo 95% CI**	**p-value**
Placebo	35	0.05 (3.769)	(-7.34, 7.43)	NA	NA	NA
OVE 2 mg BID	70	-36.06 (3.009)	(-41.96, -30.16)	-36.11 (4.451)	(-44.83, -27.38)	<0.001
FINI: Everyday Activities						
Treatment Group	**n**	**LS Mean (SE)**	**95% CI**	**Difference vs. Placebo Estimate (SE)**	**Difference vs. Placebo 95% CI**	**p-value**
Placebo	35	-6.66 (3.476)	(-13.47, 0.15)	NA	NA	NA
OVE 2 mg BID	70	-47.84 (2.814)	(-53.35, -42.32)	-41.17 (4.098)	(-49.21, -33.14)	<0.001
FINI: Everyday Responsibilities						
Treatment Group	**n**	**LS Mean (SE)**	**95% CI**	**Difference vs. Placebo Estimate (SE)**	**Difference vs. Placebo 95% CI**	**p-value**
Placebo	35	-2.98 (4.145)	(-11.10, 5.14)	NA	NA	NA
OVE 2 mg BID	70	-42.20 (3.363)	(-48.79, -35.61)	-39.22 (4.899)	(-48.82, -29.62)	<0.001
SF-36: Mental Component Summary						
Treatment Group	**n**	**LS Mean (SE)**	**95% CI**	**Difference vs. Placebo Estimate (SE)**	**Difference vs. Placebo 95% CI**	**p-value**
Placebo	35	-0.86 (1.431)	(-3.67, 1.94)	NA	NA	NA
OVE 2 mg BID	70	8.45 (1.165)	(6.17, 10.74)	9.32 (1.694)	(6.00, 12.64)	<0.001
SF-36: Physical Component Summary						
Treatment Group	**n**	**LS Mean (SE)**	**95% CI**	**Difference vs. Placebo Estimate (SE)**	**Difference vs. Placebo 95% CI**	**p-value**
Placebo	35	-0.30 (1.049)	(-2.35, 1.76)	NA	NA	NA
OVE 2 mg BID	70	4.71 (0.854)	(3.03, 6.38)	5.01 (1.251)	(2.55, 7.46)	<0.001

Abbreviation: IRR = incidence rate ratio
Source: CSR Tables 10, 11, 12, 13, 14, 15, 16 on pages 55, 58, 62, 64, 66, 68, 71 confirmed by statistical reviewer

Dose/Dose Response

Only one dosage was investigated in this study.

Durability of Response

As noted with Study 3001, effectiveness at 12 weeks likely indicates reasonable durability of effect for oveporexton.

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Persistence of Effect

The Applicant did not report on persistence of effect; however, oveporexton and its PK profile are intended for chronic daily dosing, and there is no expectation for a meaningful persistence of effect after stopping oveporexton.

Efficacy Results–Additional or Exploratory COA (PRO) Endpoints

To investigate the effect of oveporexton on the entirety of the NT1 pentad (EDS, cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and disturbed/disrupted nighttime sleep), exploratory endpoints may be used to examine the features not covered by the multiplicity protected endpoints. Same as for Study TAK-861-3001, results for the pentad symptoms of hypnagogic/hypnopompic hallucinations, sleep paralysis, and DNS are examined using exploratory endpoints. Again, these analyses were not controlled for multiplicity, and as such, need to be interpreted with caution. However, oveporexton appears to demonstrate a treatment benefit for all of the NT1 pentad symptoms (Table 70).

Table 70. Exploratory Analysis: Endpoints Regarding DNS, Hallucinations and Sleep Paralysis Symptoms of the NT1 Pentad in the Full Analysis Set (TAK-861-3002)

NSS-CT item 15 score (Disturbed/Disrupted Nighttime Sleep Domain)						
Treatment Group	**n**	**LS Mean (SE)**	**95% CI**	**Difference vs. Placebo Estimate (SE)**	**Difference vs. Placebo 95% CI**	**p-value**
Placebo	34	-0.20 (0.153)	(-0.50, 0.11)	NA	NA	NA
OVE 2 mg BID	67	-0.60 (0.123)	(-0.84, -0.36)	-0.40 (0.181)	(-0.76, -0.05)	0.028
nPSG - REM Latency (min)						
Treatment Group	**n**	**LS Mean (SE)**	**95% CI**	**Difference vs. Placebo Estimate (SE)**	**Difference vs. Placebo 95% CI**	**p-value**
Placebo	34	-10.74 (16.381)	(-43.23, 21.76)	NA	NA	NA
OVE 2 mg BID	67	60.77 (13.219)	(34.58, 86.97)	71.51 (19.359)	(33.09, 109.93)	<0.001
nPSG - Sleep Onset Latency (min)						
Treatment Group	**n**	**LS Mean (SE)**	**95% CI**	**Difference vs. Placebo Estimate (SE)**	**Difference vs. Placebo 95% CI**	**p-value**
Placebo	34	-1.44 (2.124)	(-5.65, 2.78)	NA	NA	NA
OVE 2 mg BID	67	-0.32 (1.741)	(-3.77, 3.13)	1.12 (2.472)	(-3.79, 6.02)	0.652
nPSG - Total Sleep Time (min)						
Treatment Group	**n**	**LS Mean (SE)**	**95% CI**	**Difference vs. Placebo Estimate (SE)**	**Difference vs. Placebo 95% CI**	**p-value**
Placebo	34	-1.02 (9.142)	(-19.15, 17.11)	NA	NA	NA
OVE 2 mg BID	67	-18.43 (7.164)	(-32.62, -4.24)	-17.41 (10.864)	(-38.97, 4.14)	0.112

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nPSG - Wake After Sleep Onset (min)

Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	34	-5.13 (7.881)	(-20.76, 10.50)	NA	NA	NA
OVE 2 mg BID	67	12.39 (6.227)	(0.05, 24.72)	17.51 (9.402)	(-1.13, 36.16)	0.065

nPSG - Number of Sleep Awakenings

Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	34	1.50 (2.303)	(-3.07, 6.07)	NA	NA	NA
OVE 2 mg BID	67	5.49 (1.799)	(1.93, 9.06)	4.00 (2.756)	(-1.47, 9.46)	0.150

Sleep Diary: sleep efficiency %

Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	34	0.27 (1.718)	(-3.14, 3.68)	NA	NA	NA
OVE 2 mg BID	67	0.41 (1.371)	(-2.31, 3.13)	0.14 (2.020)	(-3.86, 4.14)	0.946

Sleep Diary: Number of Nights per Week of Good or Excellent Sleep Quality

Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	34	-0.09 (0.320)	(-0.72, 0.55)	NA	NA	NA
OVE 2 mg BID	67	0.70 (0.249)	(0.20, 1.19)	0.79 (0.382)	(0.03, 1.54)	0.041

SF-36 Vitality Domain

Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	34	-3.32 (2.588)	(-8.45, 1.81)	NA	NA	NA
OVE 2 mg BID	67	26.21 (2.124)	(22.00, 30.42)	29.53 (3.064)	(23.45, 35.61)	<0.001

NSS-CT Items 11-12 score (Hallucination Domain)

Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	34	-0.30 (0.219)	(-0.74, 0.13)	NA	NA	NA
OVE 2 mg BID	67	-2.29 (0.177)	(-2.64, -1.94)	-1.99 (0.261)	(-2.51, -1.47)	<0.001

NSS-CT Items 11-12 score in those with at least 1 hallucination episode at baseline (Hallucination Domain)

Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	26	-0.90 (0.289)	(-1.47, -0.32)	NA	NA	NA
OVE 2 mg BID	40	-3.68 (0.278)	(-4.24, -3.13)	-2.79 (0.331)	(-3.45, -2.12)	<0.001

NSS-CT Items 13-14 score (Sleep Paralysis Domain)

Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	34	-0.30 (0.210)	(-0.72, 0.12)	NA	NA	NA
OVE 2 mg BID	67	-1.79 (0.165)	(-2.12, -1.46)	-1.49 (0.250)	(-1.99, -0.99)	<0.001

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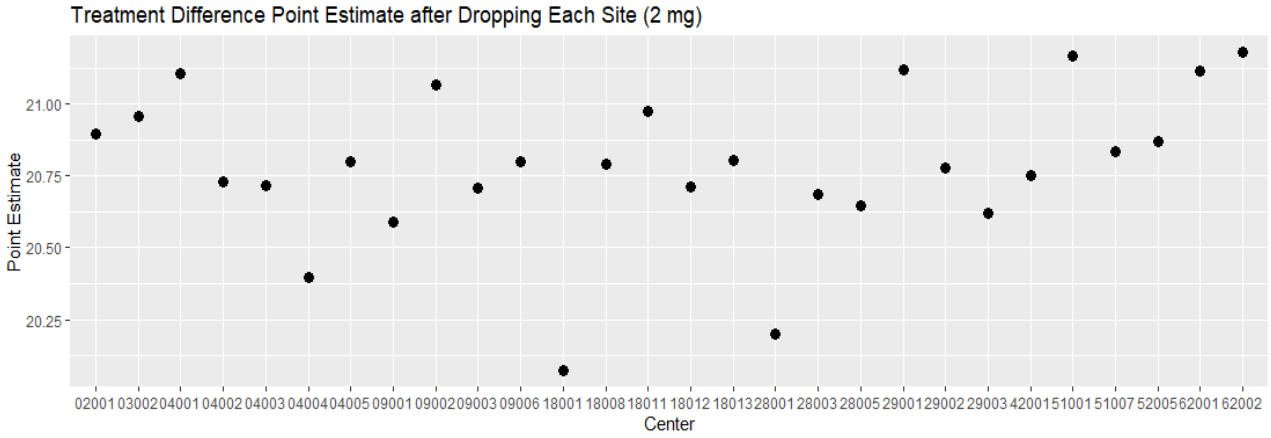
NSS-CT Items 13-14 score in those with at least 1 paralysis episode at baseline (Sleep Paralysis Domain)						
Treatment Group	n	LS Mean (SE)	95% CI	Difference vs. Placebo Estimate (SE)	Difference vs. Placebo 95% CI	p-value
Placebo	19	-1.18 (0.329)	(-1.84, -0.52)	NA	NA	NA
OVE 2 mg BID	31	-3.51 (0.283)	(-4.07, -2.94)	-2.33 (0.391)	(-3.11, -1.54)	<0.001

Source: CSR Tables 15.2.6.7, 15.2.14.2, 15.2.9.4, except for sleep efficiency and number of nocturnal awakenings, which were only provided as summary statistics by Applicant. Model-adjusted results yielded by statistical reviewer.

Additional Analyses Conducted on the Individual Trial

In addition to the sensitivity analyses above, the Statistical Reviewer also conducted an analysis focusing on study sites, to explore whether any one study site yielded results strongly different from the rest of the study, or whether the efficacy results were primarily driven by a single site. The results are presented in Figure 22, where the primary analysis is repeated, leaving out one site at a time, with the results plotted against the site being left out. The results were highly consistent and not dependent on any one site.

Figure 22. Sensitivity Analysis: Impact of Each Site on the Sleep Latency on the MWT Change From Baseline Treatment Effect vs. Placebo at Week 12 in the Full Analysis Set (Study TAK-861-3002)



Source: Statistical Reviewer

Integrated Review of Effectiveness

Similar to the conclusion for Study TAK-861-3001, for Study TAK-861-3002 the review team confirms the Applicant's primary finding that the 2-mg BID dosage of oveporexton is superior compared with placebo for the primary endpoint of change from Baseline to Week 12 in mean sleep latency on the MWT. The study yielded highly statistically significant results on the primary endpoint and all secondary endpoints included in the multiple testing procedure. The results were robust to missing data or modeling choices due to large magnitude of effect and low amount of missing data. In addition, exploratory endpoints that evaluate other aspects of the NT1 symptom pentad compared to the endpoints included in the multiple testing procedure also generally supported the finding that oveporexton yielded an effect on all of the symptoms in the pentad.

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As with Study TAK-861-3001, the Applicant is seeking an indication for NT1 as a whole, requiring demonstration of a meaningful treatment effect across all five core components of the NT1 pentad (EDS, cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and DNS). The efficacy results from Study TAK-861-3002, which evaluated oveporexton 2 mg BID only, are reviewed below through the lens of each pentad symptom.

- Excessive Daytime Sleepiness (EDS): The evidence supporting an effect of oveporexton 2 mg BID on EDS is robust and consistent with Study TAK-861-3001. Oveporexton 2 mg BID achieved a highly statistically significant improvement on the MWT, with a magnitude of effect numerically larger than that observed in Study TAK-861-3001. A highly statistically significant improvement was similarly observed on the ESS, confirming concordance between objective and subjective measures of EDS.
- Cataplexy: Oveporexton 2 mg BID demonstrated a robust and statistically significant reduction in weekly cataplexy rate relative to placebo—a numerically greater effect than observed in Study TAK-861-3001. This result provides strong and consistent evidence of a clinically meaningful treatment effect on cataplexy, the pathognomonic feature of NT1.
- Hypnagogic/Hypnopompic Hallucinations: Oveporexton 2 mg BID showed nominally significant reductions in hallucination frequency and bother, both in the overall population and in the subgroup of participants with at least one hallucination episode per week at baseline. The magnitude of effect in the symptomatic subgroup was numerically larger than that observed in Study TAK-861-3001, further supporting a meaningful treatment effect on this pentad symptom.
- Sleep Paralysis: Oveporexton 2 mg BID showed nominally significant reductions in sleep paralysis, both in the overall population and in the subgroup of participants with at least one sleep paralysis episode per week at Baseline. These results are consistent with and confirmatory of the findings from Study TAK-861-3001.
- Disturbed/Disrupted Nighttime Sleep (DNS): As in Study TAK-861-3001, the DNS domain presents a nuanced picture. Positive and nominally significant results were observed for multiple DNS-related measures, including subjective sleep quality items, nPSG-measured REM latency, nights per week of good or excellent sleep quality, and the SF-36 Vitality domain. As observed in Study TAK-861-3001, nPSG-measured nocturnal awakenings showed a numerical increase with oveporexton relative to placebo, though this did not reach nominal significance in Study TAK-861-3002. The clinical review team reiterates the interpretation offered in the context of Study TAK-861-3001: the increase in objectively measured nocturnal awakenings is not unexpected given the wake-promoting mechanism of action of oveporexton and should not be interpreted in isolation as evidence of a detrimental effect on nighttime sleep. The nominally significant improvement in nPSG-measured REM latency—replicated across both pivotal studies with a highly consistent magnitude of effect—provides compelling objective evidence that oveporexton restores REM sleep regulation, which is the core biological abnormality underlying DNS, hallucinations, and sleep paralysis in NT1. Taken together with the nominally significant

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improvements in subjective sleep quality measures, the clinical review team considers the DNS-related evidence supportive of a treatment benefit on this pentad domain.

Taken together, the efficacy data from Study TAK-861-3002 provide consistent and confirmatory evidence of a treatment effect across all five components of the NT1 pentad. The results are highly concordant with those from Study TAK-861-3001, with comparable or numerically larger effect sizes across all evaluated endpoints. This clinical reviewer considers the evidence from Study TAK-861-3002 further supportive of the Applicant's approach to the NT1 indication.

8.1.3. Study TAK-861-2001

8.1.3.1. Study Design

Study TAK-861-2001 was a phase 2 dose-ranging study designed to inform dosage selection and further development of TAK-861 as a potential treatment for NT1. The study was a randomized, double-blind, placebo-controlled, multicenter trial designed to evaluate the efficacy, safety, and tolerability of different dosages of TAK-861 in adults with NT1. Participants were randomized across 33 sites in the United States, Europe, Australia, and Japan to one of the following five treatment arms over an 8-week treatment period:

- TAK-861 Dose Regimen 1: 0.5 mg twice daily approximately 3 hours apart
- TAK-861 Dose Regimen 2: 2 mg twice daily approximately 3 hours apart
- TAK-861 Dose Regimen 3: 2 mg followed by 5 mg approximately 3 hours apart
- TAK-861 Dose Regimen 4: 7 mg once daily (QD)
- Matching placebo

After the Week 8 visit, participants had the option to participate in the LTE TAK-861-2003, similar to the phase 3 studies previously described.

Participants were adults with an ICSD-3 diagnosis of NT1 confirmed by PSG or MSLT, and ≥4 partial and/or complete episodes of cataplexy per week, with inclusion criteria similar to those of the phase 3 studies.

The primary endpoint was change from Baseline to Week 8 in mean sleep latency on the MWT, with secondary endpoints including change from Baseline to Week 8 in ESS total score and WCR at Week 8. Exploratory endpoints included, among others, change from Baseline in NSS-CT and change from Baseline in various nPSG measures.

Based on the results of this study, the Applicant designed and selected the dosages for the phase 3 pivotal studies previously described.

8.1.3.2. Study Results

A total of 112 participants were randomized, of which 22% (n=25) were from the United States. The Full Analysis Set included all participants who were randomized, received at least one dose of study drug, and had at least one postdose efficacy measurement (N=112).

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Demographics and disease baseline characteristics were similar across treatment groups (Table 71).

Table 71. Demographic Characteristics of the Full Analysis Set (Randomized Sample) (Study TAK-861-2001)

		TAK-861					
Characteristic	Placebo (N=22)	0.5 mg BID (N=23)	2 mg BID (N=21)	2 mg/5 mg (N=23)	7 mg QD (N=23)	Overall (N=90)	Total (N=112)
Demographics							
Age (years)							
Mean (SD)	37.5 (11.86)	32.7 (11.06)	31.7 (11.31)	34.7 (11.48)	33.3 (11.94)	33.1 (11.31)	34.0 (11.50)
Median	38.0	33.0	32.0	35.0	32.0	33.5	34.0
Min, max	19, 58	18, 59	18, 53	18, 58	18, 57	18, 59	18, 59
Sex, n (%)							
Male	8 (36.4)	12 (52.2)	12 (57.1)	9 (39.1)	13 (56.5)	46 (51.1)	54 (48.2)
Female	14 (63.6)	11 (47.8)	9 (42.9)	14 (60.9)	10 (43.5)	44 (48.9)	58 (51.8)
Ethnicity, n (%)							
Hispanic or Latino	3 (13.6)	2 (8.7)	1 (4.8)	0	2 (8.7)	5 (5.6)	8 (7.1)
Not Hispanic or Latino	19 (86.4)	21 (91.3)	20 (95.2)	23 (100.0)	20 (87.0)	84 (93.3)	103 (92.0)
Unknown	0	0	0	0	1 (4.3)	1 (1.1)	1 (0.9)
Race, n (%)							
Asian	1 (4.5)	2 (8.7)	0	3 (13.0)	2 (8.7)	7 (7.8)	8 (7.1)
Japanese	1 (4.5)	0	0	3 (13.0)	2 (8.7)	5 (5.6)	6 (5.4)
Korean	0	2 (8.7)	0	0	0	2 (2.2)	2 (1.8)
Black or African American	2 (9.1)	1 (4.3)	2 (9.5)	0	1 (4.3)	4 (4.4)	6 (5.4)
White	19 (86.4)	19 (82.6)	19 (90.5)	19 (82.6)	20 (87.0)	77 (85.6)	96 (85.7)
European	16 (72.7)	15 (65.2)	16 (76.2)	17 (73.9)	16 (69.6)	64 (71.1)	80 (71.4)
Not reported	3 (13.6)	4 (17.4)	3 (14.3)	2 (8.7)	4 (17.4)	13 (14.4)	16 (14.3)
Multiple	0	1 (4.3)	0	1 (4.3)	0	2 (2.2)	2 (1.8)
Baseline Disease Characteristics							
Mean sleep latency from MWT							
n	22	23	21	22	23	89	111
Mean (SD)	6.1 (8.82)	5.6 (7.89)	3.9 (5.98)	4.2 (3.63)	3.6 (4.87)	4.4 (5.78)	4.7 (6.48)
Median	2.0	2.3	1.8	2.8	2.5	2.5	2.5
Min, max	0.5, 32.0	0.5, 29.0	0.3, 26.4	0.1, 14.6	0.1, 19.6	0.1, 29.0	0.1, 32.0
ESS total score							
n	22	23	21	23	23	90	112
Mean (SD)	18.6 (2.68)	18.3 (3.35)	19.0 (3.07)	18.6 (2.97)	18.0 (3.01)	18.5 (3.07)	18.5 (2.99)
Median	19.0	19.0	19.0	19.0	18.0	19.0	19.0
Min, max	12.0, 23.0	11.0, 24.0	14.0, 24.0	14.0, 23.0	12.0, 24.0	11.0, 24.0	11.0, 24.0
WCR							
n	22	23	21	23	23	90	112
Mean (SD)	23.1 (25.68)	18.6 (16.86)	21.0 (30.00)	15.7 (13.53)	31.1 (29.11)	21.6 (23.71)	21.9 (23.99)
Median	13.3	11.0	11.3	9.5	20.0	12.0	12.0
Min, max	5.0, 100.9	2.7, 71.0	1.2, 130.5	4.0, 53.5	7.0, 107.5	1.2, 130.5	1.2, 130.5

Abbreviations: BID = twice daily; BMI = body mass index; ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; QD = once daily; WCR = weekly cataplexy rate
Source: modified from Applicant's CSR Study TAK-861-2001, Table 11.a and Table 11.b

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All four TAK-861 dosage regimens demonstrated statistically significant and clinically meaningful improvements in excessive daytime sleepiness compared to placebo (adjusted p≤0.001 on MWT), as illustrated in Table 72.

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Table 72. Statistical Analysis of Change From Baseline in Mean Sleep Latency From MWT Using a Linear Mixed Effects Model (Full Analysis Set) (Study TAK-861-2001)

					LS Mean Difference From Placebo			
Visit	Treatment Group	n	LS Mean (SE)	95% CI	Estimate (SE)	95% CI	P-value	Adjusted P-value
Week 4	Placebo	22	-1.39 (2.119)	(-5.59, 2.81)				
	TAK-861 0.5 mg BID	21	16.40 (2.147)	(12.14, 20.65)	17.79 (3.042)	(11.75, 23.82)	<0.001	
	TAK-861 2 mg BID	21	23.00 (2.136)	(18.76, 27.24)	24.39 (3.028)	(18.39, 30.40)	<0.001	
	TAK-861 2 mg / 5 mg	21	24.35 (2.125)	(20.14, 28.57)	25.74 (2.991)	(19.81, 31.67)	<0.001	
	TAK-861 7 mg QD	23	19.03 (2.042)	(14.98, 23.08)	20.42 (2.945)	(14.58, 26.26)	<0.001	
Week 8	Placebo	21	-1.16 (2.061)	(-5.25, 2.93)				
	TAK-861 0.5 mg BID	19	12.49 (2.128)	(8.27, 16.71)	13.65 (2.983)	(7.74, 19.57)	<0.001	0.001
	TAK-861 2 mg BID	21	23.50 (2.042)	(19.45, 27.56)	24.67 (2.921)	(18.87, 30.46)	<0.001	<0.001
	TAK-861 2 mg / 5 mg	20	25.42 (2.071)	(21.31, 29.52)	26.58 (2.910)	(20.81, 32.35)	<0.001	<0.001
	TAK-861 7 mg QD	23	14.96 (1.953)	(11.09, 18.84)	16.13 (2.842)	(10.49, 21.76)	<0.001	<0.001

Abbreviations: BID = twice daily; MWT = Maintenance of Wakefulness Test; QD = once daily
Mean sleep latency: mean of the sleep latency from the 4 MWT sessions. If there were 2 or more missing values, the mean was assigned as missing for that visit.
The analysis used a linear mixed effects model for repeated measures with fixed effects for baseline, age, prior use of narcolepsy medications, treatment, visit, and treatment-by-visit interaction.
Adjusted p-value: the minimum significance level, alpha, at which the hypothesis would be rejected with adjustment for multiplicity.
No imputation for missing data was applied.
Source: Applicant's CSR Study TAK-861-2001, Table 11.c

Only two of the four regimens (2 mg BID and 2 mg/5 mg) significantly reduced WCR (adjusted p<0.05; Table 73). At Week 8, the estimated incidence rate of weekly cataplexy episodes was 8.76 (95% CI: 5.68, 13.51) in the placebo group, compared to 4.24, 3.14, 2.48, and 5.89 in the TAK-861 0.5 mg BID, 2 mg BID, 2 mg/5 mg, and 7 mg QD groups, respectively. After adjustment for multiplicity, statistically significant reductions in WCR compared to placebo were observed in the TAK-861 2 mg BID (IRR 0.36, 95% CI: 0.16, 0.79; adjusted p =0.034) and 2 mg/5 mg (IRR 0.28, 95% CI: 0.13, 0.60; adjusted p =0.003) groups. The reductions observed in the TAK-861 0.5 mg BID (IRR 0.48, 95% CI: 0.25, 0.93; adjusted p =0.250) and 7 mg QD (IRR 0.67, 95% CI: 0.35, 1.29; adjusted p =0.250) groups did not reach statistical significance after multiplicity adjustment.

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Table 73. Statistical Analysis of WCR Using GEE (Negative Binomial) (Full Analysis Set) (Study TAK-861-2001)

			Incidence Rate		IRR (TAK-861 vs. Placebo)			
Visit	Treatment Group	n	Estimate	95% CI	Estimate (SE)	95% CI	P-value	Adjusted p-value
Week 8	Placebo	20	8.76	(5.68, 13.51)				
	TAK-861 0.5 mg BID	21	4.24	(2.60, 6.92)	0.48 (0.25, 0.93)	(0.25, 0.93)	0.030	0.250
	TAK-861 2 mg BID	21	3.14	(1.65, 5.98)	0.36 (0.16, 0.79)	(0.16, 0.79)	0.011	0.034
	TAK-861 2 mg / 5 mg	22	2.48	(1.30, 4.73)	0.28 (0.13, 0.60)	(0.13, 0.60)	0.001	0.003
	TAK-861 7 mg QD	23	5.89	(3.64, 9.53)	0.67 (0.35, 1.29)	(0.35, 1.29)	0.235	0.250

Abbreviations: BID = twice daily; GEE = generalized estimating equations; IRR = incidence rate ratio; QD = once daily; WCR = weekly cataplexy rate
Weekly episodes: (Total number of episodes over a given period / number of non-missing diary days in the given period) × 7.
If a diary for a given day reported ≥0 cataplexy episodes, the day was counted as non-missing diary day.
The analysis used a GEE model featuring a negative binomial distribution. The model included fixed effects for visit, treatment, treatment-by-visit interaction, baseline WCR, age, and prior use of narcolepsy medications. The incidence rates are the exponential estimates of the LS means and the IRRs are the exponential estimates of the LS mean differences from the model.
An IRR <1 indicates a lower WCR with TAK-861 compared to placebo.
Adjusted p-value: the minimum significance level, alpha, at which the hypothesis would be rejected with adjustment for multiplicity.
Source: modified from Applicant's CSR Study TAK-861-2001 Table 11.f

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At Week 8, all four TAK-861 dosage regimens reduced ESS total scores from baseline compared to placebo (adjusted p =0.004 for the 0.5 mg BID group; adjusted p<0.001 for all other groups). The LS mean change from Baseline in the placebo group was -2.50 (SE 1.109), compared to -8.92 (SE 1.085), -13.79 (SE 1.115), -12.81 (SE 1.073), and -11.29 (SE 1.064) in the TAK-861 0.5 mg BID, 2 mg BID, 2 mg/5 mg, and 7 mg QD groups, respectively. The corresponding LS mean differences from placebo ranged from -6.42 (95% CI: -9.53, -3.32) for the 0.5 mg BID group to -11.30 (95% CI: -14.44, -8.16) for the 2 mg BID group, with the two higher BID regimens showing the largest reductions.

At Week 8, all four TAK-861 dosage regimens reduced NSS-CT total scores from baseline compared to placebo (p<0.001 for all groups). The LS mean change from Baseline in the placebo group was -3.50 (SE 1.787), compared to -18.24 (SE 1.767), -21.03 (SE 1.812), -21.14 (SE 1.748), and -17.23 (SE 1.745) in the TAK-861 0.5 mg BID, 2 mg BID, 2 mg/5 mg, and 7 mg QD groups, respectively. The corresponding LS mean differences from placebo ranged from -13.73 (95% CI: -18.65, -8.81) for the 7 mg QD group to -17.64 (95% CI: -22.62, -12.66) for the 2 mg/5 mg group, with broadly similar reductions observed across the three higher-dosage regimens.

Taken together, the results of Study TAK-861-2001 suggest that TAK-861 reduced excessive daytime sleepiness, cataplexy frequency, and narcolepsy symptom severity across all dosage regimens tested, providing early evidence of efficacy across the core symptoms of NT1. However, the pattern of results across dosages was not straightforward: while all four regimens showed statistically significant improvements in EDS (MWT and ESS) and narcolepsy symptom severity (NSS-CT), only the two intermediate BID regimens (2 mg BID and 2 mg/5 mg) achieved statistically significant reductions in WCR after multiplicity adjustment. The lowest dosage (0.5 mg BID) and the once-daily regimen (7 mg QD) did not demonstrate significant cataplexy reduction, suggesting that dose level and regimen may differentially affect NT1 symptom domains. These findings informed the Applicant's decision to evaluate dosages of 1 mg BID and 2 mg BID in the phase 3 pivotal studies, with the aim of identifying a dosage range that balances efficacy across different endpoints with an acceptable safety and tolerability profile.

8.1.4. Assessment of Efficacy Across Trials: Integrated Assessment of Effectiveness

The substantial evidence of effectiveness for this NDA is based on the phase 3 Studies TAK-861-3001 and TAK-861-3002. The phase 2 Study TAK-861-2001 was also an adequate and well-controlled study that provided additional support for the phase 3 findings; however, it was not required for a determination of substantial evidence of effectiveness and was, therefore, not subject to independent reanalysis. Its results are summarized in this review for completeness. The positive efficacy results reported by the Applicant for TAK-861-2001 are consistent with the findings from TAK-861-3001 and TAK-861-3002. Note that efficacy results were not pooled.

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8.2. Review of Safety

8.2.1. Safety Review Approach

This safety review focused primarily on the two phase 3 safety and efficacy studies in the NT1 population that compared oveporexton to placebo at the to-be-marketed doses—TAK-861-3001 and TAK-861-3002, pooled together, as they were of similar dosing, design, and length. These studies were also used for the efficacy analysis. See Section 8.1 for a detailed description of the study designs and characteristics.

The clinical reviewer assessed study reports, AE database, laboratory database, electrocardiogram database, vital sign database, and participants' scores on the C-SSRS for each study separately and pooled together. Based on the mechanism of action and previous AEs associated with drugs in the same class, elevated liver function tests (LFTs), urinary events, blood pressure (BP) and heart rate (HR) increases, and insomnia were considered adverse events of special interest (AESI). Finally, given psychiatric comorbidities that often accompany narcolepsy and the product's effects on the central nervous system (CNS), psychiatric AEs were also examined closely, especially the risk for suicidal ideation and behavior (SI/B).

The clinical reviewer also conducted a review of AEs in the long-term safety study TAK-861-2003, including the updated 90-day safety report.

In addition, the clinical reviewer reviewed the Applicant's integrated summary of safety (ISS) database, which includes data from additional narcolepsy trials as well as trials of oveporexton in healthy volunteers, for serious AEs. The most recent Periodic Benefit Risk Evaluation Report was also reviewed.

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8.2.2. Review of the Safety Database

Overall Exposure

Table 74. Safety Population, Size and Denominators, Pool Safety Analysis Set (Data Cutoff for TAK-861-2003: August 29, 2025)

Clinical Trial Groups	Oveporexton (n=770)	Placebo (n=221)
Controlled trials conducted for this indication[1] (Includes trials TAK-861-3001 and TAK-861-3002)	196	76
All other than controlled trials conducted for this indication[2] (Includes trials TAK-861-1001, TAK-861-1002, TAK-861-1003, TAK-861-1004, TAK-861-1005, TAK-861-1007, TAK-861-1009, TAK-861-1010, TAK-861-1011, TAK-861-2001, and TAK-861-2003 [NT1 only])	689	121
Controlled trials conducted for other indications[3] (TAK-861-2002 [NT2] only)	47	24

Safety Database for Oveporexton - Individuals exposed to the study drug in this development program for the indication under review: N=823 (N is the sum of all available numbers from the columns above.)
Abbreviations: NT1 = narcolepsy type 1; NT2 = narcolepsy type 2.
Data cutoff date: November 30, 2025
Note: Participants may be included in more than one row when they contribute to different parts of the safety database (for example, a controlled trial and a long-term extension).
1 to be used in product's labeling
2 if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm
3 Participants who entered TAK-861-2003 (long-term extension) from TAK-861-1001 and TAK-861-2001 are only counted once.
Source: Applicant's Response to Information Request, ad hoc table

According to the ICH E1 Guidance, the safety database should include at least 1500 individuals who have had exposure to the investigational product in short-term trials, 300 to 600 individuals with at least 6 months of exposure, and 100 individuals with at least 1 year of exposure.

At the time of the original NDA submission, 770 unique participants had been exposed to oveporexton in clinical trials. A total of 312 participants had been exposed to oveporexton for at least 6 months, and 90 participants had been exposed for at least 1 year (Table 75).

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Table 75. Investigational Product Exposure by Treatment Group All Participants Pool Safety Analysis Set (Data Cutoff for TAK-861-2003: August 29, 2025)

Treatment Group	Placebo (N=221)	Oveporexton (N=770)	Total (N=823)
Duration of Exposure [n (%)]			
Any duration (at least 1 dose)	221 (100)	770 (100)	823 (100)
1-7 days	74 (33.5)	225 (29.2)	237 (28.8)
>7-14 days	14 (6.3)	62 (8.1)	75 (9.1)
>14-28 days	18 (8.1)	48 (6.2)	66 (8.0)
>28 days-3 months	115 (52.0)	35 (4.5)	37 (4.5)
>3 and <6 months	0	88 (11.4)	54 (6.6)
>=6 months	0	312 (40.5)	354 (43.0)
>=12 months	0	90 (11.7)	93 (11.3)
>=18 months	0	86 (11.2)	86 (10.4)
>=24 months	0	54 (7.0)	59 (7.2)
Duration of Exposure [days]			
n	221	770	823
Mean (SD)	41.2 (35.46)	181.2 (233.69)	180.6 (233.15)
Median	55.0	113.5	84.0
Q1, Q3	1.0, 83.0	3.0, 253.0	4.0, 262.0
Min, Max	1, 91	1, 934	1, 934

Abbreviations: Q1 = First Quartile; Q3 = Third Quartile; SD = Standard Deviation
Includes studies TAK-861-1001, TAK-861-1002, TAK-861-1003, TAK-861-1004, TAK-861-1005, TAK-861-1007, TAK-861-1009, TAK-861-1010, TAK-861-1011, TAK-861-2001, TAK-861-2002 (NT2), TAK-861-2003 (NT1 and NT2), TAK-861-3001 and TAK-861-3002.
Qualification phase and the phentermine period of the treatment phase in study TAK-861-1009 are not included in this pool.
Duration of exposure (in days) is defined as (date of last dose of study treatment - date of first dose of study treatment)+1.
Data Cutoff for TAK-861-2003: August 29, 2025.
Source: Applicant's document TAK-861-iss-safety-tables.pdf, Table 2.7.1

With the updated data provided at the 90-day safety update (data cutoff: November 30, 2025), 358 participants have been exposed for at least 6 months and 148 for at least 1 year (Table 76). When focused on the Applicant's recommended dosages for NT1 (i.e., 1 mg BID and 2 mg BID), 113 participants received 1 mg BID and 411 were exposed to 2 mg BID (Table 76). Of these, 315 (37+14 = 51 participants in the 1 mg BID group, and 159+105=264 participants in 2 mg BID group) were exposed for more than 6 months (Table 76). Note that Table 75 and Table 76 represent the same cohort of 770 participants at two different data cutoff timepoints (August 29, 2025 and November 30, 2025, respectively).

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Table 76. Duration of Exposure to Oveporexton in All Participants Pool Safety Set (Data Cutoff for TAK-861-2003: November 30, 2025)

	Number of Patients Exposed to Oveporexton in Narcolepsy Clinical Trials					
Dosage	<1 Month	1 to <3 Months	3 to <6 Months	6 Months to <1 Year	≥1 Year	Total
0.5 mg QD	5	0	0	0	0	5
0.5 mg BID	3	5	13	3	7	31
1 mg QD	9	0	0	0	0	9
1 mg BID	5	20	37	37	14	113
2 mg QD	48	0	0	0	0	48
3 mg QD	6	0	0	0	0	6
2 mg BID	69	30	48	159	105	411
4 mg QD	3	0	0	0	0	3
5 mg QD	33	0	0	0	0	33
6 mg QD	49	0	0	0	0	49
2 mg / 5 mg	5	20	27	28	7	87
7 mg QD	10	4	11	18	4	47
4 mg BID	13	1	0	0	0	14
10 mg QD	42	0	0	0	0	42
10 mg / 5 mg	10	0	0	0	0	10
18 mg QD	50	0	0	0	0	50
10 mg BID	6	0	0	0	0	6
20 mg QD	6	0	0	0	0	6
7 mg TID	6	0	0	0	0	6
25 mg QD	12	0	0	0	0	12
30 mg QD	61	0	0	0	0	61
30 mg / 10 mg	11	0	0	0	0	11
50 mg QD	6	0	0	0	0	6
75 mg QD	6	0	0	0	0	6
Total	337	35	40	210	148	770

Includes trials TAK-861-1001, TAK-861-1002, TAK-861-1003, TAK-861-1004, TAK-861-1005, TAK-861-1007, TAK-861-1009, TAK-861-1010, TAK-861-1011, TAK-861-2001, TAK-861-2002 (NT2), TAK-861-2003 (NT1 and NT2), TAK-861-3001 and TAK-861-3002.
Note: The qualification phase and the phentermine period of the treatment phase in trial TAK-861-1009 are not included in this pool.
Data cutoff for TAK-861-2003: November 30, 2025
Source: Applicant's Response to Information Request, dated May 8, 2026, Table 1.

Adequacy of the Safety Database

The safety population included all participants who received at least one dose of study medication.

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The Applicant presented safety data grouping studies in different ways:

- All participants pool includes all participants from all trials (see Table 51 for a list of all studies; dosages 0.5 mg/day to 75 mg/day)
- Healthy participant (HP) pool includes HP from phase 1 trials (TAK-861-1001 (parts A, B, C, E, F), TAK-861-1002, TAK-861-1003, TAK-861-1004, TAK-861-1005, TAK-861-1007, TAK-861-1010, TAK-861-1011; dosages 1 mg/day to 75 mg/day)
- NT1 Long Term Extension (LTE) Pool includes participants with NT1 from LTE trial including their phase 2 and 3 parent trial data (TAK-861-2001, TAK-861-2003, TAK-861-3001, TAK-861-3002; dosages 0.5 mg/day to 8 mg/day)
- NT1 Placebo-Controlled (PC) Pool includes participants with NT1 from phase 1, phase 2, and phase 3 double-blind placebo-controlled trials (TAK-861-1001 (parts D, G), TAK-861-2001, TAK-861-3001, TAK-861-3002; dosages 0.5 mg/day to 8 mg/day)
- Pivotal Trial Pool includes participants with NT1 from phase 3 registrational trials (TAK-861-3001 and TAK-861-3002; dosages 2 mg/day to 4 mg/day)

The heterogeneity of study designs, populations, and narcolepsy disease type (i.e., NT1 and NT2) limited the use of the Applicant's full ISS database (i.e., All participant pool) for analysis of safety signals for the narcolepsy indication. However, the Applicant's full ISS database was reviewed for deaths and serious adverse events.

This safety review focused on pooled data from the Pivotal Trial Pool (i.e., the two registrational studies) given the similarity in designs and populations and given that these two studies are the only placebo-controlled trials to include the to-be-marketed doses. The demographic and other baseline characteristics for participants in Study TAK-861-3001 and TAK-861-3002 were previously discussed (see relevant Sections 8.1.1.1 and 8.1.2.1).

Regarding exposure, the Agency may consider regulatory discretion in applying ICH E1 exposure guidelines because of oveporexton's Orphan Drug Designation for NT1, given the inherent challenges in achieving the recommended exposure numbers in rare disease populations. The 90-day safety update demonstrates that exposure totals meet ICH E1 requirements for both of the longer-term 6-month and 12-month durations (i.e., at least 300 participants with 6-month exposure and 100 participants with 12-month exposure).

For short-term exposure, although 823 subjects exposed is lower than the ICH-recommended 1500—given the unmet medical need for NT1 (and given the overall benefit-risk profile characterized in this review), we consider these exposure numbers acceptable to adequately characterize the safety of the drug to support an initial approval.

Furthermore, exposure to the maximum to-be-marketed dose (4 mg) is adequate, with 311 participants exposed to dosages ≥4 mg total daily dosage, representing approximately 40% of the total exposed population (311 out of 770 unique participants exposed to oveporexton).

Regarding baseline characteristics, the demographic results from the registrational studies are sufficiently generalizable for safety assessment purposes, consistent with previous comments on demographic characteristics and the use of foreign data.

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8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

This submission contains all required components of the eCTD. The overall quality and integrity of the datasets appear acceptable.

Categorization of Adverse Events

The Applicant categorized adverse events using Medical Dictionary for Regulatory Activities (MedDRA) version 28.0. The Applicant used standard methods for severity coding and definitions of serious adverse events (SAEs) and AEs leading to discontinuation. A TEAE was defined as "any event emerging or manifesting at or after the initiation of treatment with a study intervention or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the study intervention or medicinal product." The terms "AE" and "TEAE" are used interchangeably throughout this document and should be understood to refer to TEAEs as defined above.

AEs of special interest (AESIs) were events of scientific and medical concern specific to oveporexton that required ongoing monitoring and rapid communication, based on nonclinical data, clinical data from compounds with similar mechanisms of action, and literature on OX2R agonism effects. All AESIs were recorded in the eCRF and followed until resolution, with specific monitoring protocols established for blood pressure/heart rate and liver function tests throughout the studies. The four AESI categories identified for the oveporexton studies were:

- Urinary Events, including pollakiuria, micturition urgency, enuresis, dysuria, bladder discomfort, urinary incontinence, nocturia, urinary hesitation, and urine flow decreased
- Insomnia, including insomnia, initial insomnia, and middle insomnia
- Elevated Liver Function Tests, including alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, hepatic steatosis, hepatic function abnormal, liver function test abnormal, liver function test increased, metabolic dysfunction-associated steatohepatitis, and transaminases increased
- BP and HR Increases, including palpitations, blood pressure increased, heart rate increased, blood pressure diastolic increased, and hypertension

The NDA contained narratives for deaths and SAEs that occurred in the overall oveporexton clinical development program. The Applicant submitted case narratives for AEs leading to discontinuations and of serious AESIs in response to an Agency's IRs during the NDA review cycle.

The Applicant's SAE, AE severity, and TEAE definitions appear reasonable. On examination of TEAEs, no further AESI grouping appeared necessary to capture relevant AE concepts. Upon review of the AE databases for the two registrational studies, it appears that AEs were coded

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appropriately, and the Applicant's mapping of verbatim and preferred terms (PTs) was acceptable. The AE assessment strategies employed in the clinical development program were adequate and appropriate.

Routine Clinical Tests

See Table 53 and Table 62 for detailed schedules of assessments for studies TAK-861-3001 and TAK-861-3002.

Safety and tolerability were evaluated using reported AEs, clinical laboratory evaluations (including creatine kinase and liver function tests), pregnancy testing, vital signs, ECGs, ABPM, physical examination findings, and SI/B assessment. (See study protocols for more specific details.)

The C-SSRS was used to assess events of suicidal ideation and behavior at all visits. C-SSRS is a standard questionnaire (Screening/Baseline and Since Last Visit) used to assess treatment-emergent suicidal ideation and behavior in clinical studies. A “Yes” answer at any time to any one of the five suicidal ideation and associated behavioral questions on the C-SSRS Since Last Visit, was indicative of possible suicidal risk. The event was recorded as an AE. The Investigator ensured that any suicidal ideation or behavior was medically addressed, including assessment and treatment by qualified medical personnel. In addition, if the subject answered “yes” to question 4 or 5, the study drug should have been discontinued. If the subject answered “yes” to question 1 or 2 or 3, the mental health professional should have determined whether the study drug should have been discontinued or not. The C-SSRS was administered at least every 4 weeks, and during the first follow-up visit in the registrational studies.

Specific to the long-term extension study (TAK-861-2003), there was the modified International Prostate Symptom Score (mIPSS), an IPSS version without the quality of life (QoL) question. This scale is used to characterize the frequency and severity of lower urinary tract symptoms. It consists of seven questions to self-assess urinary symptoms of 1) incomplete emptying, 2) frequency, 3) intermittency, 4) urgency, 5) weak stream, 6) straining, and 7) nocturia. Total scores of 0 to 7, 8 to 19, and 20 to 35 are graded as mild, moderate, and severe lower urinary tract symptoms, respectively. The mIPSS with 7-day recall in the long-term extension study was administered to all participants at Day 1 (Baseline) and Weeks 2, 4, 12, 26, 38, 52, and 104.

To summarize, the clinical laboratory assessments, additional safety assessments, and collection schedule for laboratory assessments, vital signs, ECGs, and other assessments were generally reasonable. Follow-up at 7 and 28 days after the last dose appears an adequate timeframe to collect AEs that may arise after drug discontinuation. Blood chemistry assessments at 28 days after dose discontinuation also allowed for an adequate assessment of abnormal levels in laboratory parameters, including liver function tests. Threshold Levels 1, 2, and 3 are defined by the Standard Safety Tables & Figures Integrated Guide (Abnormality Level Criteria).

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The inclusion of the C-SSRS administered at least every 4 weeks and during the first follow-up visit was appropriate for monitoring suicidal ideation and behavior risk in this population. Additionally, the use of accredited central laboratories ensured consistency of analyses and reporting of results for clinical laboratory tests. The incorporation of the mIPSS in the long-term extension study (TAK-861-2003) was a reasonable approach to systematically monitor lower urinary tract symptoms given the known pharmacological effects of oveporexton on urinary function.

The DILI and DUOG teams were consulted during protocol review. An LSEC (Liver Safety Evaluation Committee), independent of the oveporexton clinical program and DMC, "reviewed any cases in which there was concern for possible DILI, including all cases of alkaline phosphatase elevations >2×ULN, trial intervention discontinuations due to liver-related AEs, and liver-related SAEs." For detailed assessment of hepatic safety issues, refer to the DILI team review. For evaluation of urological safety concerns, including urinary adverse events and mIPSS findings, refer to the DUOG review.

Long-Term Extension Safety Study TAK-861-2003

Study Title

Study TAK-861-2003 is titled "A Long-term Extension Study to Evaluate the Safety and Tolerability of TAK-861 in Participants With Selected Central Hypersomnia Conditions."

Objectives

The study's primary objective was to evaluate the long-term safety and tolerability of oveporexton, as measured by the occurrence of at least one treatment-emergent adverse event (TEAE). Secondary objectives included assessment of the effect of oveporexton on:

- Changes in EDS as measured by the mean sleep latency from the MWT
- Changes in EDS as measured by the ESS total score
- Changes in cataplexy episodes as measured by the WCR.

Study Design Overview

Study TAK-861-2003 is an ongoing phase 2/3, multicenter, dose-blind, long-term extension (LTE) trial designed to evaluate the long-term safety and tolerability of oveporexton in participants with NT1 who completed a parent trial. The planned trial period was approximately 5 years, or until the trial is stopped at the Sponsor's discretion, or until the product is approved and launched. This interim Clinical Study Report (CSR) contains data as of the data cutoff date of August 29, 2025. A 90-day safety report contains data as of the data cutoff date of November 30, 2025.

Participants who rolled over directly into the LTE from a parent trial with a dosing gap of ≤7 days had their eligibility assessed during the final visit of the parent trial. Participants entering the LTE with a dosing gap of >7 days from the end date of their parent trial underwent a

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screening period of up to 4 weeks, during which they completed washout of narcolepsy medications and other restricted medications.

Day 1 dosing for all participants occurred in-clinic with PK and safety assessments. Clinic visits after Week 4 were scheduled monthly up to Week 12, then approximately every 3 months until the end of the trial. The higher in-clinic visit frequency during the first 12 weeks ensured appropriate safety monitoring for participants who were previously on placebo and/or had a dosing gap. Additional visits could be conducted through a remote visit, such as completing a local/nearby medical laboratory draw or conducting a home visit.

Laboratory tests for safety were obtained biweekly up until Week 12, followed by monthly until Month 12, and then approximately every 3 months thereafter, as well as 4 weeks after the last dose. Participants who underwent nPSG and an MWT during the final assessment of their parent trial had the option of staying overnight in the clinic on Day -1 of the LTE. Participants stayed overnight at the clinic on Day 181 and were discharged on Day 182.

Trial Location

This multi-center study was conducted at 93 sites across three geographic regions: Asia-Pacific, Europe, and North America. The parent trials that rolled over into the LTE included TAK-861-2001, TAK-861-3001, TAK-861-3002, and TAK-861-1001 Part G. Participants from TAK-861-2002 (only NT2) also rolled over into this LTE; however, because TAK-861-2002 did not demonstrate clinical benefit, these participants were subsequently discontinued. The interim CSR submitted by the Applicant to the NDA did not include data on this participant population.

Diagnostic Criteria

Participants enrolled in Study TAK-861-2003 were required to have completed a controlled trial with oveporexton and to have a diagnosis of NT1 (or NT2 for participants from TAK-861-2002, who were subsequently discontinued from the LTE following the demonstration of lack of efficacy in the parent trial). The diagnostic criteria for NT1 were those applied in the respective parent trials, based on ICSD-3 or ICSD-3-TR criteria, as described in Section 8.1.1 (Study TAK-861-3001). The interim CSR submitted by the Applicant to the NDA included data only for participants with NT1.

Key Eligibility Criteria

Key **inclusion** criteria include that participants must have completed a controlled trial with oveporexton and have no clinical objection from the investigator to enrollment into the LTE.

- A dosing gap of up to 3 months was allowed between the parent trial and the screening for the LTE. Additionally, participants from TAK-861-1001 Part G could be enrolled regardless of the length of the dosing gap.
- Participants entering the LTE with a dosing gap of ≤7 days after the end of the parent trial followed the same rules as participants entering the trial without a dosing gap.

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Key **exclusion** criteria include:

- Any participant in a parent trial with an AE related to trial intervention that remained severe at the time of rollover was excluded from the LTE.
- Participants with a dosing gap >7 days were excluded if they had screening ALT or AST values >1.5 times the upper limit of normal (ULN) or GGT >3 times the ULN, and were required to have at least one AST and ALT result available from ≤16 days before the first dose.
- Participants with urinary conditions that would preclude enrollment, per the investigator's judgment.
- Participants unable to refrain from prohibited medications, including known moderate or strong cytochrome P450 type 3A inhibitors or inducers, and drugs used for the treatment of narcolepsy.

Subject Completion, Dose Discontinuation, and Withdrawal

The trial is ongoing. Participants can discontinue from the trial for the following reasons: voluntary withdrawal of consent, loss to follow-up, pregnancy, major protocol deviations, or appearance of an AE that would impose an unacceptable risk to the participant's health if participation continued. Participants who discontinued study drug were asked to remain in the study for all protocol-specified visits. Blood chemistry was required at approximately 4 weeks after the last dose.

8.2.4. Safety Results

Deaths

The Applicant submitted narrative summaries for all deaths that occurred in the clinical development program in the NDA and submitted an update in the 90-day safety report.

Pivotal Trial Pool

There were no deaths in Study TAK-861-3001 and Study TAK-861-3002.

Other Integrated Summary of Safety Studies

One death occurred in the oveporexton development program, in the LTE Study TAK-861-2003:

Participant (b) (6): A 52-year-old male participant receiving oveporexton 2 mg BID experienced a fatal AE of **cardiac arrest**. The participant had a medical history of hypertension, hyperlipidemia, class 2 obesity, and OSA. The cardiac arrest occurred on Day 480, approximately 18 months after treatment initiation, including exposure during the parent trial. There were no reported symptoms or signs of distress or foul play. The event was assessed by the investigator as not related to the trial intervention.

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Although this patient had comorbid health conditions (OSA, hyperlipidemia, untreated hypertension) that could have contributed to his risk of death, the data are insufficient to conclude whether the death was related to oveporexton. The presence of multiple cardiovascular risk factors in this participant raised important questions regarding baseline cardiovascular risk stratification and whether the Applicant appropriately followed the protocol's exclusion criteria. Specifically, the protocol defined exclusion criteria included "apnea-hypopnea index at or greater than 15 on Day -2 nPSG" and participants with pre-existing hypertension were defined as those with "baseline SBP >=130 mm Hg, baseline DBP >=80 mm Hg, or medical history of hypertension."

Notably, while the summary of clinical safety report indicated that the participant had a "medical history of untreated hypertension," this critical information was not included in the individual patient narrative provided in TAK-861-2003 CSR, Section 15.3.3.1.3, or other critical information necessary for a complete assessment of this fatal event, such as whether the participant met all eligibility criteria.

The Applicant responded to an Information Request (IR) with a detailed account of the participant's eligibility at enrollment. Regarding blood pressure, the borderline elevated BP recorded at the initial screening visit (143/89 mm Hg) was attributed by the investigator to concomitant use of solriamfetol and situational stress. A confirmatory Day -2 measurement of 123/86 mm Hg was below the protocol exclusion threshold, and BP remained generally stable throughout both trials, with no values meeting pre-specified discontinuation criteria. AHI values at all relevant time points were below the exclusionary threshold, and no evidence of clinically significant coronary artery disease, cardiac rhythm abnormality, or heart failure was present at baseline. The Applicant further clarified that the characterization of "untreated hypertension" in the Summary of Clinical Safety report was based on BP elevations observed during the trial, not on a documented diagnosis at enrollment.

Based on the above, the participant appears to have met all protocol-defined eligibility criteria, and the investigator's judgment regarding the borderline screening BP appears adequately justified. The final determination as to the death event’s association with the drug remains uncertain, although the aforementioned background cardiovascular risk factors may have contributed.

Serious Adverse Events

The Applicant submitted narrative summaries for all SAEs that occurred in the clinical development program in the NDA and submitted an update in the 90-day safety report.

Pivotal Trial Pool

In the pivotal trial pool, treatment-emergent SAEs occurred only in the overall oveporexton group (2/196 participants [1.0%] compared to 0/76 participants in the placebo group). Both SAEs occurred in Study TAK-861-3001:

- Participant (b) (6): A 23-year-old male receiving oveporexton 1 mg BID experienced an SAE of **ureterolithiasis** (kidney stone in the left ureter) on Day 79. The event required

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hospitalization for 2 days and led to temporary interruption of study drug for 2 days. The kidney stone resolved after spontaneous passage on Day 107. The event was assessed by investigators as not related to study drug because it was unrelated to bladder dysfunction or urinary retention.

- Participant (b) (6): A 39-year-old male with moderate-to-severe OSA (compliant with CPAP) receiving oveporexton 2 mg BID experienced an SAE of **nonspecific chest pain** with "minimal" troponin elevation (peak 67 ng/L; ULN not reported) on Day 68 following unaccustomed strenuous physical activity (first exercise in over a year: sprinting and lifting a 10 kg rock). The event required hospitalization for 3 days; coronary catheterization showed no lesions, and echocardiography revealed preserved LVEF (65%) with no significant structural heart disease. The event resolved on the same day of onset (Day 68), study drug was temporarily interrupted during hospitalization, and the event was assessed by investigators as not related to study drug; the participant restarted study drug on Day 72 and completed the trial.

Both SAEs in the pivotal trial pool appear unrelated to oveporexton based on the clinical presentations and available data. The ureterolithiasis case (Participant (b) (6)) had a clear alternative etiology (kidney stone). The chest pain case (Participant (b) (6)) occurred in the context of unaccustomed strenuous physical activity in a participant who had not exercised in over a year, with comprehensive cardiac workup revealing no coronary or structural abnormalities. Given the low overall SAE incidence (1.0%) and lack of apparent pattern or signal, no additional safety concerns are identified at this time.

Other Integrated Summary of Safety Studies

In the LTE trial (TAK-861-2003), in addition to the fatal SAE described previously, there were four additional non-fatal SAEs:

- Participant (b) (6): A 34-year-old female receiving oveporexton 1 mg BID experienced an SAE of **optic neuritis** (seriousness criterion: medically significant) 4 months and 23 days after starting oveporexton. Brain MRI showed demyelinating lesions. Oveporexton dosage was not changed. The SAE started on Day 144 and was considered ongoing at the time of data cutoff. The event was assessed by investigators as not related to study drug. Post-data cutoff note: The participant received a confirmed diagnosis of multiple sclerosis, with the occurrence of optic neuritis considered a manifestation secondary to this underlying condition.
- Participant (b) (6): A 53-year-old female with a history of being overweight, dyslipidemia, current tobacco use (1 pack/day), and post-menopausal status experienced an SAE of **myocardial infarction** 13 hours after starting oveporexton 1 mg BID. An ECG taken 3 days before was within normal limits. The participant was hospitalized for 1 week, and the trial intervention was discontinued on Day 1. During hospitalization, the subject had coronary angiography that showed diffuse and early coronary atheroma, thrombosis of the proximal right coronary artery revascularized by stenting, a second stenting over a long stenosis of the middle right coronary artery, and marginal occlusion of the right edge

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recovered by active balloon alone. Electrocardiogram showed ST-segment elevation myocardial infarction. The SAE resolved on Day 8. The event was assessed by investigators as not related to study drug. An alternative etiology was provided as concurrent illness (dyslipidemia) and other factors—smoking and sedentary lifestyle.

- Participant (b) (6): A 43-year-old female with a history of obesity, osteoarthritis, hypertension, edema of the knees, and tendon rupture experienced an SAE of joint injury (**left knee injury**) (seriousness criterion: medically significant) caused by jumping, 2 months and 14 days after starting oveporexton. The dosage of oveporexton was not changed. The investigator assessed the event as not related to the study drug and likely an acute injury due to jumping.
- Participant (b) (6): A 31-year-old male experienced an SAE of tendon rupture (**ruptured Achilles tendon**) during soccer practice, 2 months and 2 days after starting oveporexton. The participant was hospitalized for 1 day. The dosage of oveporexton was not changed. The investigator assessed the event as not related to the double-blind study drug and likely an acute injury due to soccer practice.

In the other studies with a placebo arm, there was one SAE that occurred in Study TAK-861-2001 in the oveporexton group and one SAE in the placebo group (TAK-861-1001, part G):

- Participant (b) (6) (TAK-861-2001): A 32-year-old female receiving oveporexton 2 mg, experienced an SAE of **right ankle fracture** on Day 12 following a fall while rollerblading, which was unrelated to cataplexy, sleepiness, or study drug. The event required hospitalization for 3 days and surgical intervention (osteosynthesis with external and internal fixation) on Day 13. Study drug was interrupted on Day 13 due to the surgery. At the time of follow-up on Day 59, the participant was recovering from the event. The event was assessed by investigators as not related to study drug, with the fall during rollerblading identified as the alternative etiology.
- Participant (b) (6) (TAK-861-1001): A 25-year-old male experienced an SAE of **muscle injury** on Day 14, while on placebo. The event was considered moderate in severity. The participant was hospitalized for observation as suggested by the investigator. The trial intervention was discontinued on Day 19 due to the SAE, and the event resolved on Day 25.

The SAEs observed in the LTE trial and other integrated safety studies demonstrate a consistent pattern of events with clear alternative etiologies that appear unrelated to oveporexton. The cardiovascular event (myocardial infarction in Participant (b) (6)) occurred in a participant with multiple established cardiovascular risk factors (dyslipidemia, smoking, sedentary lifestyle, post-menopausal status) within 13 hours of first dose in the LTE study. While the presence of multiple pre-existing risk factors suggests these factors were the primary contributors to the event, the close temporal association with drug administration cannot exclude the possibility that oveporexton may have exacerbated the underlying cardiovascular risk (although the mechanism would be unclear).

The musculoskeletal injuries (joint injury, tendon rupture, ankle fracture) all appear to have been associated with physical trauma or sports activities, that do not appear related to acute cataplexy or sleep attacks.

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The optic neuritis case was subsequently confirmed to be a manifestation of underlying multiple sclerosis, and unlikely related to the study drug.

The overall SAE profile across the development program does not suggest any drug-related safety signal.

90-Day Safety Update

This 90-day safety update presents updated data from the only ongoing trial (LTE trial TAK-861-2003) and lists all participants who experienced an SAE between August 29, 2025, and November 30, 2025.

There were two additional SAEs in the 90-day safety update:

- Participant (b) (6): A 23-year-old male receiving oveporexton experienced an SAE of severe **acute myeloid leukemia** (seriousness criterion: hospitalization) 5 months and 10 days after starting oveporexton. The study drug was interrupted, and the subject withdrew from the study. The investigator assessed the event as not related to the blinded study drug. There is very limited information available.
- Participant (b) (6): A 25-year-old female receiving oveporexton experienced an SAE of **multiple fractures** (right ankle and right navicular) after falling from an electric bicycle (which, per the report, was not caused by narcolepsy) 6 months and 9 days after starting oveporexton and required hospitalization. The drug was continued. The investigator assessed the event as not related to the study drug.

The two SAEs reported in the 90-day safety update are consistent with the overall safety profile observed in the oveporexton development program. The acute myeloid leukemia case (Participant (b) (6)) occurred after 5 months of exposure with very limited information available; given the very limited information available, a causal relationship with oveporexton cannot be definitively established or excluded at this time, but it is unlikely given there is no known mechanistic association between orexin receptor agonism and hematologic malignancies. This was discussed with the non-clinical team, the Division of Epidemiology, and the Division of Oncology. (See Section 8.2.8.1 Subsection Human Carcinogenicity or Tumor Development for more details.)

The multiple fractures case (Participant (b) (6)) resulted from a clear traumatic etiology (fall from electric bicycle) that was explicitly denied to be related to narcolepsy symptoms, and occurred in the placebo arm, raising no safety concerns.

In summary, across the oveporexton development program, the incidence of SAEs was low in placebo-controlled studies (pivotal trial pool: 1.0% oveporexton versus 0% placebo) and in the long-term extension (2.2% overall in the NT1 LTE pool). All reported SAEs appeared unrelated to study drug, with clear alternative etiologies identified in each case. Notably, the majority of musculoskeletal injury-related SAEs (joint injury, tendon rupture, ankle fracture, and multiple fractures) occurred in the LTE trial, where participants were not receiving placebo, making direct comparison with a placebo-control group not feasible. While these events had clear traumatic etiologies associated with physical activities or sports, it is

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theoretically possible that participants treated with oveporexton, experiencing improved wakefulness and reduced excessive daytime sleepiness, may have engaged in more physical activity and thus had increased exposure to situations where musculoskeletal injuries could occur. However, this remains a hypothesis, and the absence of a concurrent placebo control in the LTE trial limits the ability to establish any causal relationship with the drug. The SAE profile does not reveal any drug-related safety signal or pattern of concern.

Dropouts and/or Discontinuations due to Adverse Effects

In response to an Agency's IR, the Applicant submitted narrative summaries for participants with TEAEs that led to study and/or treatment discontinuation that occurred in the clinical development program, and submitted an update in the 90-day safety report.

Pivotal Trial Pool

In general, very few participants (n=15, 8%) discontinued the study for any reasons (Table 77). Five participants (2.6%) in the oveporexton group and one participant (1.3%) in the placebo group discontinued the study due to TEAEs (Table 77).

Table 77. Discontinuation of Treatment or Trial Participation, Safety Population, Trials TAK-861-3001 and TAK-861-3002

Reasons for Discontinuation	Oveporexton 1 mg N=60 n (%)	Oveporexton 2 mg N=136 n (%)	Oveporexton 1 to 2 mg N=196 n (%)	Placebo N=76 n (%)
Discontinued treatment	3 (5.0)	5 (3.7)	8 (4.1)	6 (7.9)
Adverse event	3 (5.0)	2 (1.5)	5 (2.6)	1 (1.3)
Protocol deviation	0 (0)	1 (0.7)	1 (0.5)	2 (2.6)
Withdrawal by subject	0 (0)	2 (1.5)	2 (1.0)	3 (3.9)
Discontinued study	3 (5.0)	6 (4.4)	9 (4.6)	6 (7.9)
Adverse event	3 (5.0)	2 (1.5)	5 (2.6)	1 (1.3)
Protocol deviation	0 (0)	1 (0.7)	1 (0.5)	0 (0)
Withdrawal by subject	0 (0)	1 (0.7)	1 (0.5)	2 (2.6)
Other	0 (0)	2 (1.5)	2 (1.0)	3 (3.9)

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
The confidence interval of risk difference is estimated by the Miettinen and Nurminen method.
Abbreviations: CI = confidence interval; N = number of participants in treatment arm; n = number of participants in specified subset of the treatment arm
Source: Clinical Data Scientist team, adsl.xpt and/or ds.xpt; Software: R

In the oveporexton group, two participants discontinued due to PT “rhabdomyolysis” (both cases associated with elevated LFTs and intense physical activity), one participant discontinued due to increased LFTs, one participant discontinued due to urinary incontinence, and one participant discontinued due to pollakiuria. In contrast, the placebo group had only one participant who discontinued treatment, which was due to increased LFTs.

Details for each participant are provided below:

Oveporexton group:

- Participant (b) (6) (TAK-861-3001): A 48-year-old female receiving oveporexton 1 mg BID, experienced **LFT increase** (ALT 20x ULN, AST 8x ULN, ALP 1.2x ULN, and GGT 2.3x ULN, but bilirubin WNL) on Day 42, with no signs or symptoms associated. Trial intervention was discontinued on Day 44, per protocol. On Day 45, the participant underwent an abdominal ultrasound, which showed normal results. Repeat laboratory results showed a decrease in ALT, AST, GGT, and ALP levels; however, the values remained above the ULN. She also presented with neck lymphadenopathy. The serology laboratory results showed positive IgG for Epstein-Barr Virus and CMV. The investigator suspected infectious mononucleosis given the presence of cervical lymphadenitis and also assessed liver enzyme elevations as not related to oveporexton.
- Participant (b) (6) (TAK-861-3002): A 20-year-old male receiving oveporexton (2 mg BID), experienced **LFT increase** on Day 42 (**CPK 17.8x ULN**; ALT 1.3x ULN, AST 2.8x ULN, GGT 1.1x ULN, and lactate dehydrogenase (LDH) 2.0x ULN). A corresponding AE of **rhabdomyolysis** related to elevation in CPK and LFTs was reported. The participant reported engaging in intensive exercise and experiencing aching limbs from his workout. Although the investigator considered it safe for the subject to continue the trial, the subject was discontinued from treatment due to meeting protocol defined discontinuation criteria. The event was assessed as mild and not related to oveporexton, and resolved within 2 weeks.
- Participant (b) (6) (TAK-861-3002): A 20-year-old male with a medical history of hyperbilirubinemia ongoing since July 2016, receiving oveporexton 2 mg BID, experienced **LFT increase** on Day 28 (ALT 3.7x ULN, AST 11.9x ULN, and bilirubin 2.2x ULN; elevations were also observed for **CPK >79.7x ULN**, direct bilirubin 1.7x ULN, indirect bilirubin 1.6x ULN, LDH 2.3x ULN, and creatinine clearance 1.4x ULN), 2 days after he went for a run, which was typical activity for the subject. On Day 33, the subject received his last dose of oveporexton and was discontinued from treatment due to meeting protocol defined discontinuation criteria. These elevations were reported as an AE of **rhabdomyolysis** due to the combination of intense sport and trial intervention, which was assessed moderate and related to oveporexton. A hepatologist reported that given the subject's history of elevated bilirubin, Gilbert's syndrome is the most probable cause and that there is no suspicion of underlying liver disease. The principal investigator (PI) confirmed the elevations are most likely multifactorial due to intense sport with drug intake likely amplifying muscle stress.
- Participant (b) (6) (TAK-861-3001): A 47-year-old female receiving oveporexton 1 mg BID, experienced a non-serious moderate event of **pollakiuria** starting on Day 1 and continuing during the study (urinary frequency increased from 4 times at baseline to 8 times during the day, and from 1 time to 6 times during the night). The investigational treatment was discontinued on Day 66 due to the event of pollakiuria, and the participant withdrew from the trial on Day 68. The event of pollakiuria was considered not resolved at that time of discontinuation from the trial.
- Participant (b) (6) (TAK-861-3001): A 40-year-old female receiving oveporexton 1 mg BID, experienced a nonserious, moderate adverse event of **urinary incontinence** on Day 19,

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assessed as related to oveporexton. The trial intervention was discontinued as of Day 29 due to urinary incontinence, and the participant was withdrawn from the trial on the same day.

Placebo group:

- Participant (b) (6) (TAK-861-3001): A 31-year-old female receiving placebo, experienced **LFT increase** ((ALT 3.4x ULN, AST 1.5x ULN, ALP 1x ULN; all other LFTs WNL) on Day 14. On Day 19, treatment with placebo was discontinued per protocol. Narrative states that "The subject reported attending a party on this same day where she had 3 glasses of champagne." Event was assessed as severe and not related to placebo.

The discontinuation rate due to adverse events appeared numerically higher in the oveporexton group (2.6%) compared to placebo (1.3%) in the pivotal trials; however, the absolute number of events was limited, making the clinical significance of this difference unclear.

Two cases of PT "rhabdomyolysis" occurred in participants receiving oveporexton 2 mg BID, both associated with intense physical exercise. These cases were characterized primarily by laboratory findings (elevated CK, AST, and ALT meeting protocol discontinuation criteria) rather than clinical symptoms. Notably, neither case presented with the classic triad of rhabdomyolysis—there was no dark (tea- or cola-colored) urine, no myalgia, and no muscle weakness—and therefore, despite meeting the PT definition by laboratory criteria, these cases may not represent true clinical rhabdomyolysis. Both participants were asymptomatic or minimally symptomatic, neither developed RI, and no medical intervention was required. One case was assessed as related to the combination of intense sport and trial intervention (Gilbert's syndrome was suspected per hepatologist assessment), while the other was considered unrelated and attributed solely to exercise, resolving within 2 weeks. These findings suggest exercise-induced rhabdomyolysis potentially amplified by oveporexton—a manageable risk with appropriate patient counseling.

The two cases of rhabdomyolysis due to excessive exercise included elevated liver function tests (LFTs). A third case of LFT elevation had an alternative etiology: suspected infectious mononucleosis (positive EBV/CMV serology with lymphadenitis). No cases met Hy's Law criteria, and the overall incidence of elevated LFTs leading to discontinuation remained low and comparable between groups (1.5% oveporexton versus 1.3% placebo).

Two urinary event discontinuations (pollakiuria and urinary incontinence) occurred in the oveporexton 1 mg BID group and related to treatment. These represent on-target pharmacological effects. Discontinuations were rare (1.0%), and most events were mild-to-moderate, starting within 2 days and resolving by trial end.

Product labeling should address increased CPK risk with recommendations for patients to report unexplained muscle symptoms.

Patient counseling about expected urinary effects and their transient nature may reduce discontinuations.

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Other Integrated Summary of Safety Studies

The following discontinuations for TEAEs were reported for the following other ISS studies (with most during LTE study), with clinical comment for discontinuations for TEAEs of interest:

LTE Trial (TAK-861-2003)

Table 78 reports the frequency of treatment and study discontinuation in the LTE. A percentage of 11% of participants (n=40) in the long-term extension study discontinued treatment and study for any reasons. Of these, 42% percent (17/40) discontinued due to a TEAE.

Table 78. Discontinuation of Treatment or Trial Participation, Safety Population, Trial TAK-861-2003

Reasons for Discontinuation	Oveporexton 0.5 mg N=25 n (%)	Oveporexton 1 mg N=92 n (%)	Oveporexton 2 mg N=185 n (%)	Oveporexton 2/5 mg N=26 n (%)	Oveporexton 7 mg N=28 n (%)	Overall Oveporexton N=356 n (%)
Discontinued treatment and study	7 (25.0)	10 (9.2)	27 (8.9)	7 (17.9)	7 (17.5)	40 (11.2)
Adverse event	3 (10.7)	4 (3.7)	10 (3.3)	3 (7.7)	4 (10.0)	17 (4.8)
Death	0 (0)	0 (0)	1 (0.3)	1 (2.6)	0 (0)	1 (0.3)
Lost to follow-up	0 (0)	0 (0)	1 (0.3)	0 (0)	1 (2.5)	1 (0.3)
Protocol deviation	1 (3.6)	0 (0)	1 (0.3)	0 (0)	0 (0)	1 (0.3)
Withdrawal by subject	1 (3.6)	5 (4.6)	10 (3.3)	2 (5.1)	1 (2.5)	13 (3.7)
Other	2 (7.1)	1 (0.9)	4 (1.3)	1 (2.6)	1 (2.5)	7 (2.0)

N under each dosage group is the total number of participants who have been exposed to that dosage level at the time of enrollment.
Abbreviations: N = number of participants in treatment arm; n = number of participants in specified subset of the treatment arm
Source: Clinical Data Scientist team, adsl.xpt and/or ds.xpt; Software: R

As illustrated in Table 79, the most common TEAEs leading to discontinuation in the LTE study, ranked by number of events, were:

Liver enzyme elevations (n=6): Six participants met protocol defined discontinuation criteria due to liver enzyme elevations, including one participant with concurrent infectious mononucleosis.

Most cases had alternative etiologies that could explain the LFT abnormalities, including infectious mononucleosis, intense physical exercise with concurrent rhabdomyolysis, underlying hepatic steatosis, and weight gain. For a detailed review of hepatotoxicity assessment and causality determination, the reader should refer to the clinical review conducted by the DILI team.

Insomnia (n=4): Five participants discontinued due to insomnia events, including one participant with concurrent pollakiuria; all of which were mild-to-moderate in severity and considered related to the trial intervention.

These events represent an expected on-target pharmacological effect of oveporexton and are consistent with the known safety profile established in the pivotal trials.

Breast cancer (n=2): Two participants discontinued due to breast cancer. The two breast cancer cases occurred in women aged 42 and 48 years during regular follow-up. The events occurred 523 and 608 days after treatment initiation, respectively. We discussed the two breast cancer cases with the nonclinical team, the Division of Epidemiology, and the Division of Oncology. Given that these cases occurred at 523 and 608 days after treatment initiation in relatively young women (aged 42 and 48 years), we considered whether the timing could be consistent with a causal relationship with the drug. The nonclinical team confirmed that there was no drug-related increase in mammary gland tumors in the 2-year carcinogenicity study in rats. Considering the high background prevalence of breast cancer in the general population and the absence of nonclinical signals, these cases are likely attributable to background incidence and are not considered related to oveporexton treatment. The Division of Epidemiology and the Division of Oncology agreed with this conclusion. (See Section 8.2.8.1 Subsection Human Carcinogenicity or Tumor Development for more details.)

Other individual events (n=1 each): The remaining TEAEs leading to trial intervention discontinuation included **blood pressure increased, dysgeusia, myocardial infarction, pollakiuria, and weight increased**, each occurring in one participant.

The single case of blood pressure increased leading to discontinuation occurred in a participant with inconsistent compliance, raising concern that the participant may have been taking higher dosages than recommended. This confounding factor limits the interpretability of this event as a treatment-related safety signal.

Table 79. TEAEs Leading to Discontinuation of Treatment or Trial Participation, Safety Population, Trial TAK-861-2003

TEAEs Leading To Discontinuation	Overall Oveporexton N=356 n (%)
Liver function test increased	6[1]
Insomnia	5
Breast cancer	2
Infectious mononucleosis	1[1]
Blood pressure increased	1
Weight increased	1
Pollakiuria	1
Dysgeusia	1

[1] One participant had infectious mononucleosis and liver function test increased and was counted twice in the table.
Source: Clinical Reviewer's created based on Applicant's response to Agency's Information Request (Applicant's document: Efficacy-Information-Amendment-Safety-Narrative.pdf)

Other Trials

In Study TAK-861-1001, there were two cases of **insomnia**, one case **of SARS-CoV-2 test positive**, and one case of **blood pressure diastolic increased** leading to discontinuation.

The insomnia cases are likely related to oveporexton and represent an expected on-target pharmacological effect consistent with the drug's profile. The case of SARS-CoV-2 test positive

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is not related to trial intervention. The case of diastolic blood pressure increase occurred in a participant receiving a supratherapeutic dose of 30 mg oveporexton (15 times the maximum recommended dose), and a causal relationship with oveporexton cannot be excluded.

90-Day Safety Updates

Since the original data cut-off date, two participants discontinued the study due to TEAEs:

- A participant with an SAE of acute myeloid leukemia that was diagnosed on Day 245
- A participant with a severe TEAE of cataplexy that began on Day 117

The acute myeloid leukemia case has been discussed previously under the SAE–90 days updates subsection. For the second case of cataplexy, cataplexy is a sign and symptom of the underlying disorder and is unlikely related to the treatment.

In summary, no new safety concerns emerged with extended treatment duration. The majority of discontinuations do not appear to be related to trial intervention, and the pattern of events is consistent with the known safety profile established in the pivotal trials. Routine postmarketing surveillance and regular postmarketing safety updates from the Applicant will allow FDA to continue to monitor the safety of oveporexton in the postmarket setting.

Significant Adverse Events

Pivotal Trial Pool

A total of eight participants experienced a severe TEAE during the pivotal trial pool, with equal distribution between the oveporexton and placebo groups (6/196 [3.1%] versus 2/76 [2.6%], respectively).

In the oveporexton group, three participants experienced **severe insomnia**. These events occurred on Day 1 and resolved within 3 to 4 days without requiring changes to study medication (two participants on oveporexton 2 mg BID, one on 1 mg BID). Two participants on oveporexton 2 mg BID experienced **severe pollakiuria** beginning on Day 1 or 2, which resolved after 2 days in one case and after 21 days in the second case, both without treatment modifications.

There was one case of **severe ureterolithiasis** in the oveporexton group that required treatment discontinuation and has been described in the treatment discontinuation paragraph. One of the participants who experienced insomnia also experienced **severe erythema** on Day 63, which resolved after 12 days.

In the placebo group, one participant experienced a **severe molar infection** on Day 67 and continued treatment. Another participant experienced **severe increases of AST/ALT** that required treatment discontinuation, as per protocol, and has been described in the treatment discontinuation subsection.

The incidence of severe TEAEs was low and comparable between oveporexton and placebo groups. The majority of severe events in the oveporexton group were insomnia and

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pollakiuria, which are consistent with the known pharmacologic effects of orexin receptor agonism. These events were generally self-limiting and did not require treatment discontinuation.

Other Integrated Summary of Safety Studies

Study TAK-861-2003

In the LTE study, excluding the fatal TEAE of cardiac arrest previously described, 16 participants (4.5% of 356 total participants) experienced 17 severe TEAEs.

One severe TEAE (blood pressure increase) required treatment discontinuation and has been previously described. Three severe TEAEs—one case of optic neuritis, one case of Achilles tendon rupture, and one case of myocardial infarction—were also coded as SAEs and have been previously described. See the appropriate subsections in this review for these cases.

The remaining 13 severe TEAEs are described below.

The majority of severe TEAEs were related to urinary symptoms and sleep disturbances, which are recognized on-target pharmacological effects of orexin receptor agonism. Six cases of **severe insomnia** were reported across treatment groups: three cases occurred in participants receiving 1 mg BID, two cases in the 2 mg BID group, and one case in the 7 mg QD group. Additionally, one case of **severe pollakiuria** (increased urinary frequency) and one case of **severe micturition urgency** were reported in participants receiving 2 mg BID.

Two severe events related to musculoskeletal injuries were reported in participants receiving 2 mg BID: one **severe limb injury** (puncture wound to the hand) and one **severe foot fracture**. These events were assessed as unrelated to trial intervention.

Three additional severe events were reported, each occurring in a single participant: **severe COVID-19, severe diarrhea, and severe tooth pain**. These events were assessed as unrelated to trial intervention.

The severe TEAEs observed in this long-term extension study are consistent with the known safety profile of orexin receptor agonists as a class. The predominance of insomnia and urinary events (pollakiuria and micturition urgency) among the severe TEAEs reflects the expected on-target pharmacological effects of OX2R agonism. These events are well-characterized for this drug class and do not represent unexpected safety signals. The musculoskeletal injuries and other likely unrelated events (COVID-19, diarrhea, tooth pain) are consistent with background rates expected in this patient population during long-term follow-up and do not raise concerns regarding the safety profile of oveporexton.

Study TAK-861-2001

Seven participants in Study TAK-861-2001 experienced severe AEs during the trial. Some participants experienced more than one severe AEs:

- The most common severe AE was **insomnia**, which affected four participants. Three cases occurred on Day 1, and one case occurred on Day 2. None of these participants required

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specific treatment for insomnia, and all continued taking the study medication without any dosage changes.

- Two participants experienced **severe cataplexy** episodes. Neither participant stopped taking the medication.
- Two participants experienced **severe headaches**. Both cases occurred on Day 2 of treatment and were considered related to oveporexton. One headache resolved the same day it started. The other resolved within 2 days, though a milder headache came back briefly on Day 3 and was treated with a single dose of paracetamol (acetaminophen).
- One participant experienced severe **mood swings** and vomiting on Day 2. Both events resolved within 2 days.
- One participant experienced **severe COVID-19-related** adverse events (cough, fever, muscle pain, and nasal congestion) on Day 83, which occurred during the follow-up period after completing the study medication.
- One participant experienced a **severe ankle fracture**. This case was coded as serious and has been described in the section related to serious adverse events (SAEs).

Severe AEs observed in Study TAK-861-2001 were generally consistent with the known safety profile of oveporexton. The most frequently reported severe adverse event was insomnia, which is an expected effect of this medication given its mechanism of action as a wake-promoting agent for the treatment of NT1. The severe cataplexy episodes reported in two participants are of particular interest, as cataplexy is a core symptom of NT1 that oveporexton is intended to treat. One case involved worsening of cataplexy that persisted throughout the trial, while the other was a transient episode that resolved the same day. These events may reflect either inadequate symptom control or natural fluctuation in disease severity rather than a drug-induced effect.

The severe headaches, mood swings, vomiting, and COVID-19 infection were isolated events that either resolved quickly or were likely unrelated to study medication (in the case of COVID-19). The ankle fracture, described separately as a serious adverse event, represents a traumatic injury and it is unlikely related to drug exposure.

<u>90-Day Safety Update</u>

The overall severity of TEAEs in the 90-day safety update was consistent with that reported in the original submission. The only change was in the overall total number of severe adverse events, which decreased by one from the original submission (the original total included one severe TEAE that was subsequently downgraded to moderate).

In summary, the incidence of severe TEAEs across the clinical development program was low and consistent with the known pharmacologic profile of orexin receptor agonism. The majority of severe events in oveporexton-treated participants were insomnia and urinary symptoms (pollakiuria and micturition urgency), which are expected on-target effects of OX2R agonism. These events were generally self-limiting, occurred early in treatment, and rarely required treatment discontinuation.

Reference ID: 5847402

Treatment Emergent Adverse Events and Adverse Reactions

Pivotal Trial Pool

Overall, the percentage of participants who experienced TEAEs in the oveporexton group was nearly double of that in the placebo group (87% versus 48.7%, respectively). See Table 80 for a summary of TEAEs that occurred at ≥2% frequency, and Figure 23 for a visual representation of TEAEs in each oveporexton dosage group compared to placebo.

Reference ID: 5847402

Table 80. Subjects With Common Adverse Events Occurring at ≥2% Frequency by Preferred Term, Safety Population, Trials TAK-861-3001 and TAK-861-3002

Preferred Term	Oveporexton 1 mg N=60 n (%)	Oveporexton 2 mg N=136 n (%)	Oveporexton 1 to 2 mg N=196 n (%)	Placebo N=76 n (%)
Any AE	52 (86.7)	119 (87.5)	171 (87.2)	37 (48.7)
Insomnia	32 (53.3)	78 (57.4)	110 (56.1)	1 (1.3)
Pollakiuria	32 (53.3)	79 (58.1)	111 (56.6)	4 (5.3)
Micturition urgency	9 (15.0)	22 (16.2)	31 (15.8)	1 (1.3)
Salivary hypersecretion	5 (8.3)	9 (6.6)	14 (7.1)	0
Influenza	3 (5.0)	4 (2.9)	7 (3.6)	1 (1.3)
Abdominal pain upper	2 (3.3)	2 (1.5)	4 (2.0)	0
Oropharyngeal pain	2 (3.3)	2 (1.5)	4 (2.0)	0
Paraesthesia	1 (1.7)	3 (2.2)	4 (2.0)	0
Rash	0	4 (2.9)	4 (2.0)	0
Sinusitis	3 (5.0)	3 (2.2)	6 (3.1)	1 (1.3)
Constipation	0	3 (2.2)	3 (1.5)	0
Influenza like illness	0	3 (2.2)	3 (1.5)	0
Middle insomnia	0	3 (2.2)	3 (1.5)	0
Vision blurred	0	3 (2.2)	3 (1.5)	0
Nasopharyngitis	6 (10.0)	12 (8.8)	18 (9.2)	6 (7.9)
Urinary incontinence	2 (3.3)	0	2 (1.0)	0
Urinary tract infection	2 (3.3)	0	2 (1.0)	0
Back pain	2 (3.3)	2 (1.5)	4 (2.0)	1 (1.3)
Cataplexy	0	4 (2.9)	4 (2.0)	1 (1.3)
Nausea	1 (1.7)	3 (2.2)	4 (2.0)	1 (1.3)
Weight increased	2 (3.3)	7 (5.1)	9 (4.6)	3 (3.9)
Alanine aminotransferase increased	2 (3.3)	1 (0.7)	3 (1.5)	1 (1.3)
Gastroenteritis viral	0	3 (2.2)	3 (1.5)	1 (1.3)

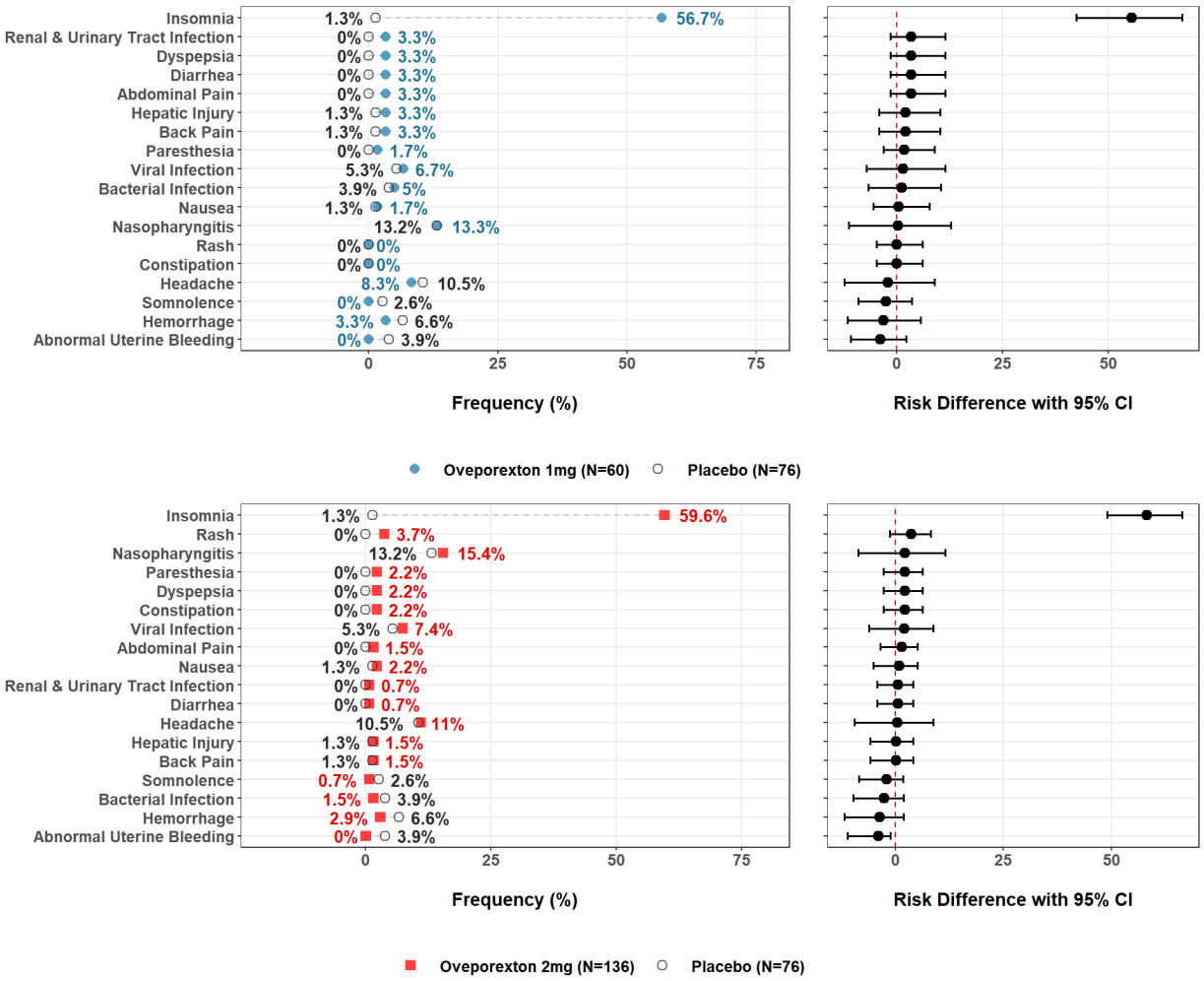
Reference ID: 5847402

Preferred Term	Oveporexton 1 mg N=60 n (%)	Oveporexton 2 mg N=136 n (%)	Oveporexton 1 to 2 mg N=196 n (%)	Placebo N=76 n (%)
Increased appetite	3 (5.0)	2 (1.5)	5 (2.6)	2 (2.6)
Headache	4 (6.7)	13 (9.6)	17 (8.7)	7 (9.2)
Gastroenteritis	0	2 (1.5)	2 (1.0)	2 (2.6)
Upper respiratory tract infection	2 (3.3)	5 (3.7)	7 (3.6)	4 (5.3)
Blood creatine phosphokinase increased	3 (5.0)	1 (0.7)	4 (2.0)	3 (3.9)
Contusion	1 (1.7)	0	1 (0.5)	2 (2.6)
Hypersomnia	0	0	0	2 (2.6)
Migraine	0	1 (0.7)	1 (0.5)	3 (3.9)

Abbreviations: AE = adverse event; CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants in treatment arm; n = number of participants with adverse event
Treatment-emergent AE defined as an AE that worsened or newly started on or after the date of first dose of study drug up to the study follow-up period.
MedDRA version 28.0.
Duration is 12 weeks.
Coded as MedDRA preferred terms.
Source: Clinical Data Scientist's team; adae.xpt; Software: R

Reference ID: 5847402

Figure 23. Subjects With Adverse Events ≥2% in Any Treatment Arm by OND Custom Medical Query (Narrow), Safety Population, Trials TAK-861-3001 and TAK-861-3002



Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants in treatment arm
Treatment-emergent AE defined as an AE that worsened or newly started on or after the date of first dose of study drug up to the study follow-up period. MedDRA version 28.0. Duration is 12 weeks. Risk difference (with 95% confidence interval) is shown between total treatment and comparator. The confidence interval of risk difference is estimated by the Miettinen and Nurminen method.
Source: Clinical Data Scientist' team; adae.xpt; Software: R

The most common TEAEs in the oveporexton group at a rate greater than placebo were insomnia (56% versus 1%), pollakiuria (57% versus 5%), micturition urgency (16% versus 1%), and salivary hypersecretion (7% versus 0%).

These results were confirmed when events were clustered by system organ class or OND broad and narrow queries (data not shown).

The nearly two-fold increase in overall TEAE incidence with oveporexton compared to placebo (87% versus 49%) is driven primarily by expected on-target pharmacologic effects of orexin receptor agonism. The most common TEAEs—insomnia (56% versus 1%), pollakiuria (57% versus 5%), micturition urgency (16% versus 1%), and salivary hypersecretion (7% versus

0%)—are consistent with the known effects of increased wakefulness and orexinergic signaling on sleep architecture, bladder function, and autonomic regulation.

The high incidence of insomnia is notable but expected given the wake-promoting mechanism of action. This finding underscores the importance of appropriate dose timing and patient counseling regarding sleep hygiene. Similarly, the urinary symptoms (pollakiuria and micturition urgency) reflect orexin's known role in bladder control and are consistent with the class effects observed with other orexin-acting drugs. Salivary hypersecretion has also been reported with other orexin receptor agonists, consistent with a class effect of orexinergic stimulation.

The remaining TEAEs occurred at low frequencies and were generally balanced between treatment groups or consistent with background rates in this population. Importantly, hypersomnia occurred less frequently in the oveporexton group compared to placebo, which may reflect therapeutic benefit.

Of note, the generally low incidence of CPK increase as a TEAE, even lower in the oveporexton group compared to the placebo group, does not align with the incidence of blood level measurements of CPK observed to be >5× ULN (see below data on chemistry results). See the discussion following Table 86.

The TEAE profile is acceptable and manageable for the treatment of NT1, provided that appropriate labeling addresses the common on-target effects.

Reference ID: 5847402

Other Integrated Summary of Safety Studies

LTE Trial (TAK-861-2003)

Table 81 illustrates TEAEs occurring at ≥2% Frequency in the LTE study.

Table 81. Subjects With Common Adverse Events Occurring at ≥2% Frequency by Preferred Term, Safety Population, LTE Trial TAK-861-2003

Preferred Term	Oveporexton 0.5 mg N=28 n (%)	Oveporexton 1 mg N=109 n (%)	Oveporexton 2 mg N=304 n (%)	Oveporexton 2/5 mg N=39 n (%)	Oveporexton 7 mg N=40 n (%)	Overall Oveporexton N=356 n (%)
Any AE	12 (42.9)	63 (57.8)	183 (60.2)	23 (59.0)	29 (72.5)	252 (70.8)
Pollakiuria	3 (10.7)	15 (13.8)	30 (9.9)	2 (5.1)	3 (7.5)	53 (14.9)
Insomnia	2 (7.1)	12 (11.0)	28 (9.2)	4 (10.3)	4 (10.0)	50 (14.0)
Micturition urgency	2 (7.1)	10 (9.2)	18 (5.9)	1 (2.6)	5 (12.5)	35 (9.8)
Influenza	0	5 (4.6)	17 (5.6)	5 (12.8)	2 (5.0)	28 (7.9)
Headache	1 (3.6)	3 (2.8)	19 (6.2)	1 (2.6)	4 (10.0)	27 (7.6)
Nasopharyngitis	1 (3.6)	3 (2.8)	21 (6.9)	3 (7.7)	5 (12.5)	26 (7.3)
Upper respiratory tract infection	1 (3.6)	7 (6.4)	13 (4.3)	0	0	21 (5.9)
Back pain	0	5 (4.6)	8 (2.6)	1 (2.6)	0	14 (3.9)
Weight increased	0	0	10 (3.3)	1 (2.6)	2 (5.0)	13 (3.7)
Blood creatine phosphokinase increased	0	3 (2.8)	7 (2.3)	1 (2.6)	2 (5.0)	12 (3.4)
Cataplexy	0	3 (2.8)	8 (2.6)	1 (2.6)	1 (2.5)	12 (3.4)
Initial insomnia	1 (3.6)	5 (4.6)	5 (1.6)	0	0	11 (3.1)
Arthralgia	0	1 (0.9)	9 (3.0)	0	1 (2.5)	10 (2.8)
Salivary hypersecretion	0	2 (1.8)	7 (2.3)	0	1 (2.5)	10 (2.8)
Dizziness	1 (3.6)	2 (1.8)	3 (1.0)	1 (2.6)	1 (2.5)	8 (2.2)
Dysmenorrhoea	0	2 (1.8)	6 (2.0)	0	0	8 (2.2)
Gastroenteritis	0	2 (1.8)	6 (2.0)	0	0	8 (2.2)
Middle insomnia	0	1 (0.9)	4 (1.3)	1 (2.6)	2 (5.0)	8 (2.2)
Oropharyngeal pain	1 (3.6)	0	4 (1.3)	1 (2.6)	2 (5.0)	8 (2.2)
COVID-19	0	1 (0.9)	3 (1.0)	2 (5.1)	1 (2.5)	7 (2.0)
Fall	0	1 (0.9)	6 (2.0)	0	1 (2.5)	7 (2.0)
Nausea	0	0	6 (2.0)	0	1 (2.5)	7 (2.0)
Anxiety	1 (3.6)	0	5 (1.6)	0	0	6 (1.7)

Reference ID: 5847402

Preferred Term	Oveporexton 0.5 mg N=28 n (%)	Oveporexton 1 mg N=109 n (%)	Oveporexton 2 mg N=304 n (%)	Oveporexton 2/5 mg N=39 n (%)	Oveporexton 7 mg N=40 n (%)	Overall Oveporexton N=356 n (%)
Diarrhoea	1 (3.6)	2 (1.8)	3 (1.0)	0	0	6 (1.7)
Pyrexia	2 (7.1)	0	2 (0.7)	2 (5.1)	0	6 (1.7)
Rash	1 (3.6)	3 (2.8)	3 (1.0)	0	0	6 (1.7)
Hypersomnia	0	0	4 (1.3)	0	1 (2.5)	5 (1.4)
Paraesthesia	0	1 (0.9)	1 (0.3)	2 (5.1)	1 (2.5)	5 (1.4)
Acne	0	1 (0.9)	2 (0.7)	0	1 (2.5)	4 (1.1)
Alanine aminotransferase increased	0	0	3 (1.0)	0	1 (2.5)	4 (1.1)
Aspartate aminotransferase increased	0	0	3 (1.0)	0	1 (2.5)	4 (1.1)
Limb injury	0	3 (2.8)	1 (0.3)	0	0	4 (1.1)
Sinusitis	1 (3.6)	0	2 (0.7)	0	1 (2.5)	4 (1.1)
Urticaria	0	0	1 (0.3)	1 (2.6)	2 (5.0)	4 (1.1)
Decreased appetite	1 (3.6)	0	0	0	2 (5.0)	3 (0.8)
Dry eye	1 (3.6)	0	2 (0.7)	0	0	3 (0.8)
Dry mouth	0	0	2 (0.7)	0	1 (2.5)	3 (0.8)
Dysuria	0	1 (0.9)	1 (0.3)	0	1 (2.5)	3 (0.8)
Enuresis	0	1 (0.9)	0	1 (2.6)	1 (2.5)	3 (0.8)
Alopecia	1 (3.6)	0	1 (0.3)	0	0	2 (0.6)
Blood pressure increased	1 (3.6)	0	1 (0.3)	0	0	2 (0.6)
Blood urine present	0	0	1 (0.3)	0	1 (2.5)	2 (0.6)
Brain fog	0	0	0	1 (2.6)	1 (2.5)	2 (0.6)
Chest discomfort	1 (3.6)	0	1 (0.3)	0	0	2 (0.6)
Dysentery	0	0	0	2 (5.1)	0	2 (0.6)
Gastrooesophageal reflux disease	0	0	1 (0.3)	0	1 (2.5)	2 (0.6)
Joint injury	1 (3.6)	0	1 (0.3)	0	0	2 (0.6)
Meniscus injury	0	0	1 (0.3)	1 (2.6)	0	2 (0.6)
Pruritus	1 (3.6)	0	1 (0.3)	0	0	2 (0.6)
SARS-CoV-2 test positive	0	0	0	1 (2.6)	1 (2.5)	2 (0.6)
Somnolence	0	1 (0.9)	0	1 (2.6)	0	2 (0.6)
Tension headache	0	1 (0.9)	0	1 (2.6)	0	2 (0.6)
Tonsillitis	0	0	1 (0.3)	1 (2.6)	0	2 (0.6)
Abnormal dreams	1 (3.6)	0	0	0	0	1 (0.3)
Beta haemolytic streptococcal infection	1 (3.6)	0	0	0	0	1 (0.3)
Blood creatinine decreased	0	0	0	0	1 (2.5)	1 (0.3)
Bursitis	0	0	0	0	1 (2.5)	1 (0.3)

Reference ID: 5847402

Preferred Term	Oveporexton 0.5 mg N=28 n (%)	Oveporexton 1 mg N=109 n (%)	Oveporexton 2 mg N=304 n (%)	Oveporexton 2/5 mg N=39 n (%)	Oveporexton 7 mg N=40 n (%)	Overall Oveporexton N=356 n (%)
Cervicobrachial syndrome	0	0	0	1 (2.6)	0	1 (0.3)
Conjunctivitis allergic	0	0	0	0	1 (2.5)	1 (0.3)
Dysphagia	0	0	0	0	1 (2.5)	1 (0.3)
Eczema	0	0	0	0	1 (2.5)	1 (0.3)
Energy increased	1 (3.6)	0	0	0	0	1 (0.3)
Foot fracture	0	0	1 (0.3)	0	1 (2.5)	1 (0.3)
Hand dermatitis	1 (3.6)	0	0	0	0	1 (0.3)
Hand fracture	0	0	0	1 (2.6)	0	1 (0.3)
Heat stroke	0	0	0	0	1 (2.5)	1 (0.3)
Infectious mononucleosis	1 (3.6)	0	0	0	0	1 (0.3)
Major depression	0	0	0	0	1 (2.5)	1 (0.3)
Meniere's disease	0	0	0	0	1 (2.5)	1 (0.3)
Menopausal symptoms	1 (3.6)	0	0	0	0	1 (0.3)
Muscle contracture	0	0	0	0	1 (2.5)	1 (0.3)
Muscle spasms	0	0	0	1 (2.6)	0	1 (0.3)
Myoclonus	0	0	0	1 (2.6)	0	1 (0.3)
Nocturia	0	0	0	1 (2.6)	0	1 (0.3)
Odynophagia	1 (3.6)	0	0	0	0	1 (0.3)
Otitis media acute	0	0	0	0	1 (2.5)	1 (0.3)
Peripheral swelling	1 (3.6)	0	0	0	0	1 (0.3)
Poor quality sleep	1 (3.6)	0	0	0	0	1 (0.3)
Post procedural inflammation	0	0	0	1 (2.6)	0	1 (0.3)
Rotator cuff syndrome	0	0	0	0	1 (2.5)	1 (0.3)
Self-destructive behaviour	0	0	0	1 (2.6)	0	1 (0.3)
Sleep talking	1 (3.6)	0	0	0	0	1 (0.3)
Stress	0	0	0	1 (2.6)	0	1 (0.3)
Tibia fracture	0	0	0	0	1 (2.5)	1 (0.3)
Transaminases increased	0	0	0	1 (2.6)	0	1 (0.3)
Umbilical hernia	0	0	0	1 (2.6)	0	1 (0.3)
Urinary incontinence	1 (3.6)	0	0	0	0	1 (0.3)
Vaginal haemorrhage	1 (3.6)	0	0	0	0	1 (0.3)
Vaginal infection	0	0	0	0	1 (2.5)	1 (0.3)
Viral upper respiratory tract infection	0	0	0	1 (2.6)	0	1 (0.3)
Vitreous floaters	0	0	0	0	1 (2.5)	1 (0.3)

Reference ID: 5847402

Preferred Term	Oveporexton 0.5 mg N=28 n (%)	Oveporexton 1 mg N=109 n (%)	Oveporexton 2 mg N=304 n (%)	Oveporexton 2/5 mg N=39 n (%)	Oveporexton 7 mg N=40 n (%)	Overall Oveporexton N=356 n (%)
Weight decreased	0	0	0	0	1 (2.5)	1 (0.3)
Wheezing	0	0	0	0	1 (2.5)	1 (0.3)

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants in treatment arm; n, number of participants with adverse event; SARS, severe acute respiratory syndrome

Treatment-emergent AE defined as an AE whose date of onset occurs on or after the first dose of study drug.

Data are summarized based on the Oveporexton dosage level at the time of onset of the AE.

N under each dosage group is the total number of participants who have been exposed to that dosage level during the trial.

MedDRA version 28.0.

Duration is 26.4 (0.1, 125.4) weeks.

Coded as MedDRA preferred terms.

Source: Clinical Data Scientist's team; adae.xpt; Software: R

Reference ID: 5847402

Pollakiuria, insomnia, and micturition urgency continue to represent the most common TEAEs, although with a lower frequency than the one reported in the pivotal trials. All of these events appear to be dose-dependent and are consistent with the known pharmacological effect of oveporexton on orexin receptor-2.

Nasopharyngitis, headache, and influenza were also among the most frequently reported TEAEs (>10%).

The LTE lacks a placebo comparator; however, TEAEs may inform the safety profile associated with long-term administration. The types of common TEAEs observed during long-term treatment are consistent with those seen in the short-term studies (i.e., pollakiuria, insomnia, and micturition urgency), although occurring at lower frequencies. This may suggest a decrease in TEAE incidence over time with continued exposure to oveporexton, given that most participants rolled over from the controlled studies to the LTE.

Nasopharyngitis, headache, and influenza were common as well across exposure intervals, with incidence comparable to background rates seen in real-world populations (https://www.who.int/, https://www.informedhealth.org/) and unlikely related to trial intervention.

Of note, musculoskeletal injuries were reported during the LTE study, including fractures (total n=3, 0.8%; foot fracture, hand fracture, and tibia fracture) and other injuries (total n=11, 3.1%; limb injury in four participants, joint injury in two participants, meniscus injury in two participants, and severe Achilles tendon rupture in one participant; the latter has been described in detail in the SAE section). Additionally, seven participants (2.0%) experienced falls during the study.

Given the relatively high number of fractures and joint injuries observed in the LTE, as well as the occurrence of falls, we conducted a retrospective analysis of these events in the pivotal trial pool. This analysis revealed no difference in the incidence of musculoskeletal injuries or falls between the placebo and oveporexton groups; the incidence was slightly higher in the placebo group (n=2, 1.0% in the oveporexton overall group versus n=2, 2.6% in the placebo group, both joint injury and contusion, no cases of fracture or fall in the pivotal trial pool). In addition, review of the available narratives did not suggest a consistent pattern or mechanism linking these events to oveporexton exposure. Based on these findings, we have no safety concern at this time and conclude that the observed events represent background incidences. Per the Applicant's report, the falls were not related to NT1 symptoms. Routine post-marketing surveillance is sufficient to collect additional data on this potential safety signal, although the current data do not suggest a rate different from background incidence.

90-Day Safety Update

The overall severity of TEAEs in the 90-day safety update was consistent with that reported in the original submission. The only changes were in the overall total number of back pain, blood creatine phosphokinase increased, and cataplexy, which increased by 2, 3, and 1 event, respectively, resulting in the proportion of these events exceeding 5%.

Reference ID: 5847402

The event of cataplexy was severe and required trial discontinuation. This case has been described in the section addressing discontinuations in the 90-day safety update.

In summary, the TEAE profile of oveporexton is characterized predominantly by expected on-target pharmacologic effects related to orexin receptor agonism, including insomnia, pollakiuria, micturition urgency, and salivary hypersecretion. These events occurred at higher incidences in the oveporexton group compared to placebo in the pivotal trials but decreased in frequency during long-term exposure in the LTE study, suggesting potential tolerance or adaptation over time. The musculoskeletal injuries and falls observed in the LTE do not appear to be treatment-related based on retrospective analysis of the pivotal trial pool, where rates were comparable to or lower than placebo. The overall safety profile is acceptable and manageable for the treatment of NT1, provided that appropriate labeling addresses the common on-target effects and patients receive counseling regarding dosing timing and sleep hygiene.

Laboratory Findings

Overall, laboratory results in the pivotal trial pool and in the LTE study did not show any majorly concerning clinical or toxicity-related issues, and no cases meeting Hy's law. See the DILI team consult for a detailed assessment of potential DILI signals and liver enzyme elevations.

Pivotal Trial Pool

Hematology

As described in the Schedule of Assessments of Studies TAK-861-3001 and TAK-861-3002, hematology laboratory tests were assessed at Screening, Baseline (Day -2), Week 4 (Day 28), Week 8 (Day 56), Week 12, (Day 84), and at Follow-up 7 days after last dose.

The clinical reviewer's examination of hematological parameter measures of central tendency (e.g., mean, median) found no clinically significant changes of note over the treatment period and results were generally balanced across arms (Table 82).

Table 82. Mean Change From Baseline for Hematology Data Over Time by Treatment Arm, Safety Population, Trials TAK-861-3001 and TAK-861-3002

Parameter Study Visit	Oveporexton 1 to 2 mg Mean (95% CI) N=196	Oveporexton 1 to 2 mg Mean Change from Baseline (95% CI)	Placebo Mean (95% CI) N=76	Placebo Mean Change from Baseline (95% CI)
Complete Blood Count				
Leukocytes (10^3 cells/µL)				
Baseline	7.4 (7.1, 7.6)	NA	7.6 (7.2, 8.1)	NA
Week 12	6.6 (6.3, 6.8)	-0.8 (-1.1, -0.6)	6.7 (6.3, 7.0)	-1.0 (-1.4, -0.6)
Hemoglobin (g/dL)				
Baseline	14.1 (13.9, 14.2)	NA	14.2 (13.9, 14.5)	NA
Week 12	14.1 (13.9, 14.3)	0.0 (-0.1, 0.1)	14.6 (14.2, 14.9)	0.2 (0.1, 0.4)

Reference ID: 5847402

Parameter Study Visit	Oveporexton 1 to 2 mg Mean (95% CI) N=196	Oveporexton 1 to 2 mg Mean Change from Baseline (95% CI)	Placebo Mean (95% CI) N=76	Placebo Mean Change from Baseline (95% CI)
Platelets (10^3 cells/µL)				
Baseline	284.4 (275.0, 293.8)	NA	280.7 (264.4, 297.0)	NA
Week 12	274.1 (264.6, 283.6)	-9.1 (-14.6, -3.6)	269.0 (254.9, 283.0)	-8.6 (-17.2, 0.1)
WBC differential				
Eosinophils (10^3 cells/µL)				
Baseline	0.2 (0.2, 0.2)	NA	0.2 (0.2, 0.3)	NA
Week 12	0.2 (0.2, 0.2)	0.0 (0.0, 0.0)	0.2 (0.2, 0.3)	-0.0 (-0.0, 0.0)
Lymphocytes (10^3 cells/µL)				
Baseline	2.3 (2.2, 2.4)	NA	2.4 (2.2, 2.5)	NA
Week 12	2.2 (2.1, 2.3)	-0.1 (-0.2, -0.1)	2.2 (2.1, 2.4)	-0.1 (-0.3, 0.1)
Neutrophils (10^3 cells/µL)				
Baseline	4.3 (4.1, 4.5)	NA	4.4 (4.0, 4.8)	NA
Week 12	3.6 (3.4, 3.8)	-0.7 (-0.9, -0.5)	3.6 (3.3, 3.9)	-0.8 (-1.2, -0.5)

Abbreviation: NA = not applicable
Source: Clinical Reviewer's Created.

The clinical reviewer's examination of shifts from normal baseline to abnormal results at any timepoint found generally low numbers of such shifts across parameters, and generally balanced numbers across arms (Table 83). A small numerical difference in the proportion of participants with Level 1 low hemoglobin was observed in the oveporexton 2 mg BID arm (5.1%) compared to placebo (0%); however, no participants met the Level 2 or Level 3 thresholds in any active treatment arm, and no dose-dependent pattern was observed. Similarly, a small difference in Level 1 low lymphocytes was noted, although the placebo arm showed a higher proportion of participants with low lymphocytes than either active treatment arm (6.6% versus 3.7% and 0%, respectively). Neither finding is considered to reflect a drug-related effect, and both are likely attributable to chance and of no clinical significance.

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Table 83. Subjects With Hematology Analyte Values Exceeding Specified Levels, Safety Population, Trials TAK-861-3001 and TAK-861-3002

Laboratory Parameter	Oveporexton 1 mg N=60 n/Nw (%)	Oveporexton 2 mg N=136 n/Nw (%)	Oveporexton 1 to 2 mg N=196 n/Nw (%)	Placebo N=76 n/Nw (%)
Complete blood count				
WBC, low (10^3 cells/µL)				
Level 1 (<3.5)	4/59 (6.8)	2/136 (1.5)	6/195 (3.1)	3/76 (3.9)
Level 2 (<3)	0/59 (0)	0/136 (0)	0/195 (0)	2/76 (2.6)
Level 3 (<1)	0/59 (0)	0/136 (0)	0/195 (0)	0/76 (0)
WBC, high (10^3 cells/µL)				
Level 1 (>10.8)	3/59 (5.1)	3/136 (2.2)	6/195 (3.1)	6/76 (7.9)
Level 2 (>13)	0/59 (0)	1/136 (0.7)	1/195 (0.5)	1/76 (1.3)
Level 3 (>15)	0/59 (0)	0/136 (0)	0/195 (0)	1/76 (1.3)
Hemoglobin, low (g/dL)				
Level 2 (>1.5 g/dL dec. from baseline)	0/59 (0)	7/136 (5.1)	7/195 (3.6)	0/76 (0)
Level 3 (>2 g/dL dec. from baseline)	0/59 (0)	0/136 (0)	0/195 (0)	0/76 (0)
Hemoglobin, high (g/dL)				
Level 2 (>2 g/dL inc. from baseline)	0/59 (0)	2/136 (1.5)	2/195 (1.0)	1/76 (1.3)
Level 3 (>3 g/dL inc. from baseline)	0/59 (0)	0/136 (0)	0/195 (0)	1/76 (1.3)
Platelets, low (10^3 cells/µL)				
Level 1 (<140)	1/59 (1.7)	1/136 (0.7)	2/195 (1.0)	1/76 (1.3)
Level 2 (<125)	0/59 (0)	1/136 (0.7)	1/195 (0.5)	0/76 (0)
Level 3 (<100)	0/59 (0)	0/136 (0)	0/195 (0)	0/76 (0)
WBC differential				
Lymphocytes, low (10^3 cells/µL)				
Level 1 (<1)	0/59 (0)	5/136 (3.7)	5/195 (2.6)	5/76 (6.6)
Level 2 (<0.75)	0/59 (0)	2/136 (1.5)	2/195 (1.0)	0/76 (0)
Level 3 (<0.5)	0/59 (0)	1/136 (0.7)	1/195 (0.5)	0/76 (0)
Lymphocytes, high (10^3 cells/µL)				
Level 1 (>4)	1/59 (1.7)	1/136 (0.7)	2/195 (1.0)	2/76 (2.6)
Level 2 (>10)	0/59 (0)	0/136 (0)	0/195 (0)	1/76 (1.3)
Level 3 (>20)	0/59 (0)	0/136 (0)	0/195 (0)	0/76 (0)

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Neutrophils, low (10^3 cells/µL)				
Level 1 (<2)	11/59 (18.6)	14/136 (10.3)	25/195 (12.8)	7/76 (9.2)
Level 2 (<1)	0/59 (0)	1/136 (0.7)	1/195 (0.5)	1/76 (1.3)
Level 3 (<0.5)	0/59 (0)	0/136 (0)	0/195 (0)	0/76 (0)
Eosinophils, high (10^3 cells/µL)				
Level 1 (>0.65)	4/59 (6.8)	9/136 (6.6)	13/195 (6.7)	4/75 (5.3)
Level 2 (>1.5)	0/59 (0)	0/136 (0)	0/195 (0)	0/75 (0)
Level 3 (>5)	0/59 (0)	0/136 (0)	0/195 (0)	0/75 (0)

Abbreviations: CI, confidence interval; dec., decrease; inc., increase; N, number of participants in treatment arm; n, number of participants meeting the specified laboratory criteria; NA, not applicable; N_w, total number of participants with data available for the laboratory test of interest; PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood cells
Threshold Levels 1, 2, and 3 as defined by the *Standard Safety Tables & Figures Integrated Guide* (Abnormality Level Criteria).
Duration is 12 weeks.
Subject counts are cumulative for each abnormality threshold.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Source: Clinical data scientist's team; adlb.xpt; Software: R

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Serum Chemistry

As described in the Schedule of Assessments of Studies TAK-861-3001 and TAK-861-3002, chemistry laboratory tests were assessed more frequently that hematology laboratory tests, specifically at Screening, Baseline (Day -2), Week 1 (Day 1), Week 2 (Day 14), Week 4 (Day 28), Week 8 (Day 56), Week 12, (Day 84), and at follow-up 7 and 28 days after last dose.

The clinical reviewer's examination of laboratory parameter measures of central tendency (e.g., mean, median) found no clinically significant changes of note over the treatment period and results were generally balanced across arms (Table 84).

Table 84. Mean Change From Baseline for General Chemistry Data Over Time by Treatment Arm, Safety Population, Trials TAK-861-3001 and TAK-861-3002

Parameter Study Visit	Oveporexton 1 to 2 mg Mean	Oveporexton 1 to 2 mg Mean Change from Baseline	Placebo Mean	Placebo Mean Change from Baseline
Sodium (mEq/L)				
Baseline	139.6	NA	139.7	NA
Week 12	139.1	-0.5	139.7	0.1
Potassium (mEq/L)				
Baseline	4.3	NA	4.3	NA
Week 12	4.4	0.0	4.3	0.1
Chloride (mEq/L)				
Baseline	102.1	NA	102.1	NA
Week 12	103.0	0.9	103.3	1.2
Bicarbonate (mEq/L)				
Baseline	23.5	NA	23.4	NA
Week 12	22.8	-0.7	22.9	-0.4
Glucose (mg/dL)				
Baseline	90.8	NA	90.5	NA
Week 12	91.2	0.5	92.0	1.0
Calcium (mg/dL)				
Baseline	9.5	NA	9.4	NA
Week 12	9.4	-0.1	9.4	-0.0
Protein (g/dL)				
Baseline	7.1	NA	6.9	NA
Week 12	6.9	-0.2	6.9	0.0
Albumin (g/dL)				
Baseline	4.6	NA	4.5	NA
Week 12	4.5	-0.1	4.5	-0.1
Creatine Kinase (IU/L)				
Baseline	127.6	NA	114.6	NA
Week 12	135.7	9.1	131.2	19.6
Blood Urea Nitrogen (mg/dL)				
Baseline	12.8	NA	13.2	NA
Week 12	12.4	-0.3	12.8	-0.2

Abbreviations: NA = not applicable.
Source: Clinical Reviewer's Created.

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The clinical reviewer's examination of shifts from normal baseline to abnormal results at any time points found generally low numbers of such shifts across parameters, generally balanced across arms, except for bicarbonate, with higher percentage of lower Level 2 (<18 mEq/L) in the oveporexton groups compared to placebo (16/196, 8.2% versus 1/76, 1.3% respectively). The clinical meaning of this change is likely negligible, given that there were not TEAEs related to this chemistry change reported in the adae.xpt dataset, such as fatigue, nausea, and hyperventilation.

Although not statistically significant, CPK values were higher in the oveporexton groups compared to placebo at all levels. For example, Level 2 (markedly abnormal value (MAV); >5× ULN) occurred in 21 participants (10%) in the oveporexton groups and 4 participants (5%) in the placebo group (Table 86). However, of the 21 cases of increased CPK observed in the oveporexton group, only 19% (n=4/21) were reported as TEAEs in the adae.xpt dataset, whereas of the four cases of increased CPK in the placebo group, the majority, 75% (n=3/4), were reported as TEAEs in the adae.xpt dataset (Table 80).

Table 85. Subjects With General Chemistry Analyte Values Exceeding Specified Levels, Safety Population, Trials TAK-861-3001 and TAK-861-3002

Laboratory Parameter	Oveporexton 1 mg N=60 n/Nw (%)	Oveporexton 2 mg N=136 n/Nw (%)	Oveporexton 1 to 2 mg N=196 n/Nw (%)	Placebo N=76 n/Nw (%)
Sodium, low (mEq/L)				
Level 1 (<132)	0/60 (0)	0/136 (0)	0/196 (0)	2/76 (2.6)
Level 2 (<130)	0/60 (0)	0/136 (0)	0/196 (0)	1/76 (1.3)
Level 3 (<125)	0/60 (0)	0/136 (0)	0/196 (0)	0/76 (0)
Sodium, high (mEq/L)				
Level 1 (>150)	0/60 (0)	1/136 (0.7)	1/196 (0.5)	0/76 (0)
Level 2 (>155)	0/60 (0)	0/136 (0)	0/196 (0)	0/76 (0)
Level 3 (>160)	0/60 (0)	0/136 (0)	0/196 (0)	0/76 (0)
Potassium, low (mEq/L)				
Level 1 (<3.6)	1/60 (1.7)	6/136 (4.4)	7/196 (3.6)	1/76 (1.3)
Level 2 (<3.4)	0/60 (0)	1/136 (0.7)	1/196 (0.5)	0/76 (0)
Level 3 (<3)	0/60 (0)	0/136 (0)	0/196 (0)	0/76 (0)
Potassium, high (mEq/L)				
Level 1 (>5.5)	0/60 (0)	5/136 (3.7)	5/196 (2.6)	1/76 (1.3)
Level 2 (>6)	0/60 (0)	0/136 (0)	0/196 (0)	0/76 (0)
Level 3 (>6.5)	0/60 (0)	0/136 (0)	0/196 (0)	0/76 (0)
Chloride, low (mEq/L)				
Level 1 (<95)	0/60 (0)	0/136 (0)	0/196 (0)	1/76 (1.3)
Level 2 (<88)	0/60 (0)	0/136 (0)	0/196 (0)	0/76 (0)
Level 3 (<80)	0/60 (0)	0/136 (0)	0/196 (0)	0/76 (0)
Chloride, high (mEq/L)				
Level 1 (>108)	3/60 (5.0)	3/136 (2.2)	6/196 (3.1)	3/76 (3.9)
Level 2 (>112)	0/60 (0)	0/136 (0)	0/196 (0)	0/76 (0)
Level 3 (>115)	0/60 (0)	0/136 (0)	0/196 (0)	0/76 (0)
Bicarbonate, low (mEq/L)				
Level 1 (<20)	20/60 (33.3)	36/136 (26.5)	56/196 (28.6)	19/76 (25.0)
Level 2 (<18)	3/60 (5.0)	13/136 (9.6)	16/196 (8.2)	1/76 (1.3)
Level 3 (<15)	0/60 (0)	1/136 (0.7)	1/196 (0.5)	0/76 (0)

Laboratory Parameter	Oveporexton 1 mg N=60 n/Nw (%)	Oveporexton 2 mg N=136 n/Nw (%)	Oveporexton 1 to 2 mg N=196 n/Nw (%)	Placebo N=76 n/Nw (%)
Bicarbonate, high (mEq/L)				
Level 3 (>30)	1/60 (1.7)	6/136 (4.4)	7/196 (3.6)	6/76 (7.9)
Glucose, low (mg/dL)				
Level 1 (<70)	7/60 (11.7)	36/136 (26.5)	43/196 (21.9)	18/76 (23.7)
Level 2 (<54)	2/60 (3.3)	1/136 (0.7)	3/196 (1.5)	2/76 (2.6)
Level 3 (<40)	0/60 (0)	0/136 (0)	0/196 (0)	0/76 (0)
Glucose, random, high (mg/dL)				
Level 2 (≥200)	1/60 (1.7)	0/136 (0)	1/196 (0.5)	1/76 (1.3)
Level 3 (>250)	1/60 (1.7)	0/136 (0)	1/196 (0.5)	1/76 (1.3)
Calcium, low (mg/dL)				
Level 1 (<8.4)	1/60 (1.7)	1/136 (0.7)	2/196 (1.0)	2/76 (2.6)
Level 2 (<8)	0/60 (0)	0/136 (0)	0/196 (0)	2/76 (2.6)
Level 3 (<7.5)	0/60 (0)	0/136 (0)	0/196 (0)	1/76 (1.3)
Calcium, high (mg/dL)				
Level 1 (>10.5)	1/60 (1.7)	7/136 (5.1)	8/196 (4.1)	1/76 (1.3)
Level 2 (>11)	0/60 (0)	1/136 (0.7)	1/196 (0.5)	0/76 (0)
Level 3 (>12)	0/60 (0)	0/136 (0)	0/196 (0)	0/76 (0)
Protein, total, low (g/dL)				
Level 1 (<6)	2/60 (3.3)	6/136 (4.4)	8/196 (4.1)	4/76 (5.3)
Level 2 (<5.4)	0/60 (0)	0/136 (0)	0/196 (0)	0/76 (0)
Level 3 (<5)	0/60 (0)	0/136 (0)	0/196 (0)	0/76 (0)
Albumin, low (g/dL)				
Level 1 (<3.1)	0/60 (0)	0/136 (0)	0/196 (0)	0/76 (0)
Level 2 (<2.5)	0/60 (0)	0/136 (0)	0/196 (0)	0/76 (0)
Level 3 (<2)	0/60 (0)	0/136 (0)	0/196 (0)	0/76 (0)
CPK, high (U/L)				
Level 1 (>3X ULN)	9/60 (15.0)	19/136 (14.0)	28/196 (14.3)	6/76 (7.9)
Level 2 (>5X ULN)	6/60 (10.0)	15/136 (11.0)	21/196 (10.7)	4/76 (5.3)
Level 3 (>10X ULN)	3/60 (5.0)	5/136 (3.7)	8/196 (4.1)	1/76 (1.3)
Blood urea nitrogen, high (mg/dL)				
Level 1 (>23)	3/60 (5.0)	2/136 (1.5)	5/196 (2.6)	5/76 (6.6)
Level 2 (>27)	0/60 (0)	0/136 (0)	0/196 (0)	4/76 (5.3)
Level 3 (>31)	0/60 (0)	0/136 (0)	0/196 (0)	2/76 (2.6)

Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of participants in treatment arm; n, number of participants meeting the specified laboratory criteria; NA, not applicable; Nw, total number of participants with data available for the laboratory test of interest; ULN, upper limit of normal
Threshold Levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (Abnormality Level Criteria).
Duration is 12 weeks.
Subject counts are cumulative for each abnormality threshold.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications
Source: Clinical Data Scientist's team; adlb.xpt; Software: R

An IR was sent to the Applicant to clarify the specific criteria used to determine whether an elevated CK/CPK value was coded as a TEAE, and to explain why some cases were coded as TEAEs while others were not. The Applicant responded that "no specific criteria or numeric thresholds were used to determine whether an elevated CK value was coded as a TEAE. Instead, per the protocol, abnormal laboratory tests were considered AEs when judged

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clinically significant by the investigator." Thus, variability in whether elevated CK values were coded as TEAEs reflects differences in investigator reporting rather than the application of specific laboratory thresholds or clinical criteria. Therefore, the comparison of TEAEs for increased CPK between treatment groups is not reliable. We requested narratives for each participant with increased blood CPK to review.

The comprehensive review of CK elevation cases (narratives) from both TAK-861-3001 and TAK-861-3002 studies reveals a pattern of transient, asymptomatic CK elevations that resolve spontaneously without intervention and are consistently attributed to alternative causes such as physical activity. Among all participants who experienced CK elevations above the upper limit of normal, 22 were receiving oveporexton and six were receiving placebo. Of the 22 cases in the oveporexton group, 14 (63.6%) were attributed to physical activity, with the remaining eight cases explained by other identifiable causes such as intercurrent illness (e.g., influenza; 2 cases) or unknown etiology. Of the six cases in the placebo group, three (50%) were associated with physical activity, with the remaining three attributable to other causes. CK elevations >5×ULN occurred in 21/196 (10.7%) participants in the oveporexton group compared to 4/76 (5.3%) participants in the placebo group. Some cases reached markedly elevated levels (>16,500 U/L; 10,402 U/L; 6,297 U/L). All cases were asymptomatic, none demonstrated myoglobinuria or renal impairment, and all resolved without specific intervention. In two cases, the drug was discontinued due to concomitant increases in liver enzymes per protocol-defined discontinuation criteria (refer to subsection related to discontinuation in the pivotal trials pool).

CPK values and the differences observed across treatment groups will be described in the Warnings and Precautions section of the product labeling.

Lipids

There was a higher percentage of participants with cholesterol and LDL levels exceeding level 2 and level 3 at any timepoint post-baseline in the oveporexton groups compared to placebo (43% versus 28% respectively for Level 3). However, a modest, consistent difference in LDL cholesterol was observed between the oveporexton and placebo groups in the 12-week pivotal trials (Figure 24). The mean change from Baseline at Week 12 was approximately +14 mg/dL higher in the oveporexton groups compared to placebo. This difference was consistent across both pivotal studies (TAK-861-3001 and TAK-861-3002) and across multiple timepoints; while the magnitude of change is small and unlikely to be markedly clinically meaningful, it was a consistent trend.

Total cholesterol showed a similar pattern, with a mean change of approximately +12 mg/dL in oveporexton groups versus essentially no change in placebo at Week 12. HDL cholesterol showed minimal changes in both treatment groups (approximately -3.7 mg/dL in the oveporexton groups compared to -1.7 mg/dL in placebo), and triglycerides actually decreased slightly in both groups (approximately -314.6 mg/dL in the oveporexton groups compared to -11.7 mg/dL in placebo) (Table 87 and Figure 24).

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Table 86. Subjects With Lipids Analyte Values Exceeding Specified Levels, Safety Population, Trials TAK-861-3001 and TAK-861-3002

Laboratory Parameter	Oveporexton 1 mg N=60 n/Nw (%)	Oveporexton 2 mg N=136 n/Nw (%)	Oveporexton 1 to 2 mg N=196 n/Nw (%)	Placebo N=76 n/Nw (%)
Cholesterol, total, high (mg/dL)				
Level 1 (>200)	43/60 (71.7)	83/136 (61.0)	126/196 (64.3)	42/76 (55.3)
Level 2 (>210)	39/60 (65.0)	74/136 (54.4)	113/196 (57.7)	31/76 (40.8)
Level 3 (>225)	29/60 (48.3)	56/136 (41.2)	85/196 (43.4)	21/76 (27.6)
HDL, males, low (mg/dL)				
Level 1 (<40)	15/33 (45.5)	33/53 (62.3)	48/86 (55.8)	18/39 (46.2)
Level 2 (<30)	2/33 (6.1)	8/53 (15.1)	10/86 (11.6)	4/39 (10.3)
Level 3 (<20)	0/33 (0)	0/53 (0)	0/86 (0)	0/39 (0)
HDL, females, low (mg/dL)				
Level 1 (<50)	11/27 (40.7)	42/83 (50.6)	53/110 (48.2)	22/37 (59.5)
Level 2 (<40)	4/27 (14.8)	19/83 (22.9)	23/110 (20.9)	8/37 (21.6)
Level 3 (<20)	0/27 (0)	0/83 (0)	0/110 (0)	0/37 (0)
LDL, high (mg/dL)				
Level 1 (>130)	39/60 (65.0)	75/136 (55.1)	114/196 (58.2)	33/76 (43.4)
Level 2 (>160)	22/60 (36.7)	40/136 (29.4)	62/196 (31.6)	15/76 (19.7)
Level 3 (>190)	10/60 (16.7)	13/136 (9.6)	23/196 (11.7)	3/76 (3.9)
Triglycerides, high (mg/dL)				
Level 1 (>150)	32/60 (53.3)	64/136 (47.1)	96/196 (49.0)	34/76 (44.7)
Level 2 (>300)	5/60 (8.3)	15/136 (11.0)	20/196 (10.2)	12/76 (15.8)
Level 3 (>500)	1/60 (1.7)	2/136 (1.5)	3/196 (1.5)	1/76 (1.3)

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, number of participants in treatment arm; n, number of participants meeting the specified laboratory criteria; N_w, total number of participants with data available for the laboratory test of interest
Threshold Levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (Abnormality Level Criteria).
Duration is 12 weeks.
Subject counts are cumulative for each abnormality threshold.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Source: Clinical Data Scientist's team; adlb.xpt; Software: R

Mean lipid values and their changes from baseline in the pivotal pool studies are presented in Table 87 and Figure 24.

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Table 87. Mean Change From Baseline for Lipid Data Over Time by Treatment Arm (Safety Population—Trials TAK-861-3001 and TAK-861-3002)

Lipid Parameter	Study Visit	Statistics	Oveporexton 1 mg N=60	Oveporexton 2 mg N=136	Oveporexton 1 to 2 mg N=196	Placebo N=76
Total Cholesterol (mg/dL)	Baseline	n	60	136	196	76
		Mean (SD)	200.3 (43.92)	185.0 (37.99)	189.6 (40.41)	184.8 (37.42)
	Day 1	n	59	133	192	74
		Mean (SD)	204.1 (45.66)	192.7 (39.32)	196.2 (41.58)	184.6 (38.95)
		Mean CFB (SD)	4.3 (13.24)	8.5 (12.03)	7.2 (12.53)	-0.3 (11.48)
	Week 2	n	56	127	183	69
		Mean (SD)	205.6 (43.54)	193.1 (37.39)	196.9 (39.68)	190.8 (30.54)
		Mean CFB (SD)	5.6 (25.32)	8.1 (22.36)	7.4 (23.26)	7.4 (18.70)
	Week 4	n	59	135	194	72
		Mean (SD)	205.2 (46.93)	198.3 (38.01)	200.4 (40.92)	188.3 (35.73)
		Mean CFB (SD)	5.2 (27.96)	13.5 (24.78)	10.9 (26.00)	2.4 (19.73)
	Week 8	n	58	134	192	71
		Mean (SD)	206.7 (45.26)	196.3 (41.67)	199.5 (42.93)	184.3 (37.95)
		Mean CFB (SD)	6.9 (28.83)	11.1 (24.24)	9.9 (25.71)	-1.9 (26.09)
	Week 12	n	56	130	186	70
		Mean (SD)	209.7 (51.04)	195.3 (39.36)	199.6 (43.58)	187.2 (35.84)
		Mean CFB (SD)	11.1 (30.05)	11.1 (24.69)	11.1 (26.33)	0.4 (21.33)

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Lipid Parameter	Study Visit	Statistics	Oveporexton 1 mg N=60	Oveporexton 2 mg N=136	Oveporexton 1 to 2 mg N=196	Placebo N=76
LDL Cholesterol (mg/dL)	Baseline	n	60	136	196	76
		Mean (SD)	118.0 (36.97)	106.1 (33.22)	109.8 (34.75)	110.3 (31.83)
	Day 1	n	59	132	191	74
		Mean (SD)	117.3 (40.78)	109.4 (34.96)	111.9 (36.93)	107.4 (33.91)
		Mean CFB (SD)	-0.5 (13.00)	3.8 (11.10)	2.4 (11.85)	-3.4 (11.70)
	Week 2	n	56	126	182	69
		Mean (SD)	126.1 (38.75)	116.7 (33.39)	119.6 (35.28)	113.8 (24.75)
		Mean CFB (SD)	7.6 (23.15)	11.1 (20.95)	10.0 (21.65)	4.7 (16.61)
	Week 4	n	58	135	193	72
		Mean (SD)	129.4 (42.29)	121.0 (34.71)	123.5 (37.24)	115.7 (32.22)
		Mean CFB (SD)	10.9 (22.70)	15.2 (22.55)	13.9 (22.62)	4.3 (17.55)
	Week 8	n	58	134	192	71
		Mean (SD)	132.4 (40.59)	122.2 (36.63)	125.3 (38.06)	112.8 (32.29)
		Mean CFB (SD)	14.2 (23.77)	16.1 (21.16)	15.5 (21.93)	1.2 (22.05)
	Week 12	n	56	129	185	70
		Mean (SD)	135.4 (46.49)	122.6 (36.73)	126.5 (40.24)	116.4 (30.95)
		Mean CFB (SD)	17.7 (24.68)	17.5 (20.66)	17.6 (21.88)	4.4 (17.50)
HDL Cholesterol (mg/dL)	Baseline	n	60	136	196	76
		Mean (SD)	56.4 (15.28)	54.9 (14.28)	55.3 (14.57)	51.0 (12.01)
	Day 1	n	59	132	191	74
		Mean (SD)	54.9 (15.41)	56.8 (15.88)	56.2 (15.72)	49.4 (12.05)
		Mean CFB (SD)	-1.4 (5.77)	1.9 (4.67)	0.9 (5.24)	-1.0 (4.37)
	Week 2	n	56	126	182	69
		Mean (SD)	54.0 (14.58)	55.3 (14.69)	54.9 (14.63)	54.4 (14.53)
		Mean CFB (SD)	-1.2 (7.29)	-0.1 (7.10)	-0.4 (7.16)	3.8 (6.58)
	Week 4	n	58	135	193	72
		Mean (SD)	53.4 (14.67)	54.5 (14.72)	54.2 (14.67)	51.5 (13.09)
		Mean CFB (SD)	-3.0 (7.05)	-0.5 (8.11)	-1.2 (7.87)	1.1 (6.15)
	Week 8	n	58	134	192	71
		Mean (SD)	50.7 (13.81)	52.0 (14.05)	51.6 (13.95)	48.4 (12.27)
		Mean CFB (SD)	-4.9 (7.81)	-3.1 (8.21)	-3.7 (8.11)	-1.9 (7.44)
	Week 12	n	56	130	186	70
		Mean (SD)	51.6 (13.70)	51.4 (13.90)	51.5 (13.81)	48.6 (10.27)
		Mean CFB (SD)	-4.1 (8.09)	-3.6 (8.48)	-3.7 (8.34)	-1.7 (9.73)

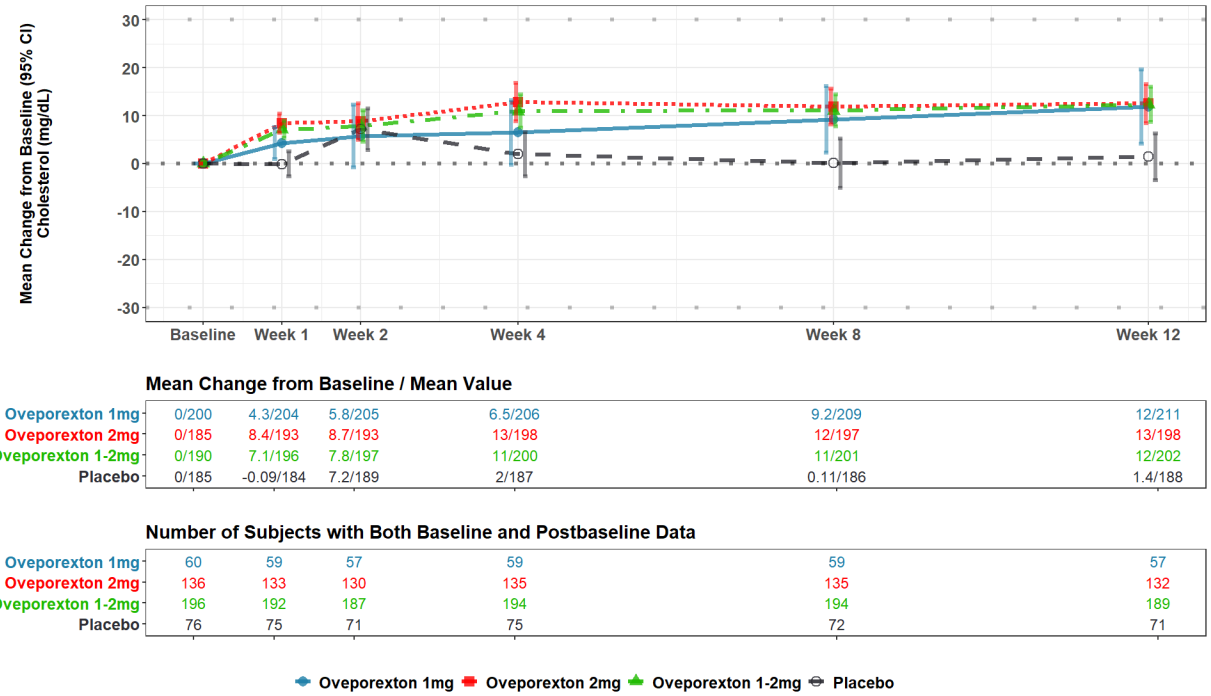
Reference ID: 5847402

Lipid Parameter	Study Visit	Statistics	Oveporexton 1 mg N=60	Oveporexton 2 mg N=136	Oveporexton 1 to 2 mg N=196	Placebo N=76
Triglycerides (mg/dL)	Baseline	n	60	136	196	76
		Mean (SD)	130.1 (80.50)	123.4 (110.22)	125.4 (101.89)	117.8 (68.59)
	Day 1	n	59	132	191	74
		Mean (SD)	158.6 (92.58)	137.6 (96.05)	144.1 (95.25)	138.7 (76.74)
		Mean CFB (SD)	29.5 (62.50)	14.7 (72.86)	19.3 (70.00)	20.3 (49.95)
	Week 2	n	56	127	183	69
		Mean (SD)	126.6 (78.31)	108.5 (66.19)	114.1 (70.40)	117.3 (79.24)
		Mean CFB (SD)	-5.2 (71.78)	-16.0 (98.93)	-12.7 (91.42)	-2.0 (66.96)
	Week 4	n	58	135	193	72
		Mean (SD)	109.6 (57.48)	114.3 (74.61)	112.9 (69.79)	108.5 (74.68)
		Mean CFB (SD)	-19.8 (65.08)	-8.9 (99.49)	-12.2 (90.50)	-12.5 (64.25)
	Week 8	n	58	134	192	71
		Mean (SD)	117.6 (68.96)	111.0 (63.26)	113.0 (64.93)	114.8 (62.88)
		Mean CFB (SD)	-12.6 (60.25)	-12.5 (89.92)	-12.6 (81.94)	-7.3 (53.43)
	Week 12	n	56	130	186	70
		Mean (SD)	115.9 (61.82)	107.5 (64.95)	110.0 (63.98)	110.7 (62.48)
		Mean CFB (SD)	-11.1 (63.86)	-16.1 (87.55)	-14.6 (81.01)	-11.7 (48.59)

Abbreviations: N, total number of participants who have been exposed to that dosage level during the study; n, number of safety set participants with a non-missing result for a given parameter at that timepoint; SD, Standard Deviation; CFB, Change from Baseline.
Source: Applicant's response dated June 22, 2026, to Agency.'IR. Data replicated by Clinical Data Scientist Team

Reference ID: 5847402

Figure 24. Mean Lipids Data Change From Baseline Over Time by Treatment Arm, Safety Population, Trials TAK-861-3001 and TAK-861-3002



Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein
Duration is 12 weeks.
The vertical bars shown on the plotted lines indicate the 95% confidence interval of the mean change at the corresponding time points.
Participants with both baseline and postbaseline data available are included in the mean change from baseline calculations at each visit. The number of participants reflects only those included in the mean change from baseline calculations, rather than the total number of participants.
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups as the results would not be considered a reliable indicator of the true mean.
Only central laboratory data are included in the analysis. equation.
Source: Clinical Data Scientist's team; adlb.xpt; Software: R

Although a higher proportion of participants in the oveporexton arms met threshold criteria for elevated total cholesterol and LDL levels compared to placebo, and both oveporexton dosage groups showed modest, broadly comparable decreases in HDL cholesterol from baseline without a discernible dose-response relationship, this review team does not consider these findings to represent a clinically meaningful safety concern at this time. It is worth noting that total cholesterol is mathematically derived from its components, including LDL, and therefore the two findings are not independent. Additionally, no dose-dependent effect was observed for LDL cholesterol, as elevations were broadly similar across both dosage groups, further limiting the inferential weight of this finding. More importantly, the broader metabolic picture does not support a pattern consistent with a drug-induced metabolic syndrome or increased cardiovascular risk: triglycerides were similar to placebo, and there were no TEAEs related to metabolic syndrome or cardiovascular risk observed at a higher rate in the oveporexton arms relative to placebo.

In the absence of a concerning metabolic profile and given the small magnitude of the LDL changes, the modestly higher proportion of participants with elevated LDL in the oveporexton groups is not considered clinically significant to the extent that a labeling warning is required.

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Interpretation of these findings is further limited by the small sample sizes across treatment arms, which reduce the reliability of between-group comparisons and preclude definitive conclusions. However, due to the consistent trends in the studies (including the LTE study to be discussed below), the laboratory data will be described in Section 6 of labeling.

Other Integrated Summary of Safety Studies

LTE Trial (TAK-861-2003)

As observed in the pivotal trial pool, the increase in CPK that met MAV criteria (>5× ULN) continued in the LTE (n=36, 10%). Of these cases, n=12 were reported as TEAEs of blood CPK increased in the TEAE adae.xpt dataset. However, all cases were asymptomatic, and the Applicant reported no cases of rhabdomyolysis. These cases were confounded by other potential etiologies, including exercise (n=29) and viral infections (n=3).

No other abnormal laboratory values were reported.

Notwithstanding the inherent limitations of direct comparisons between label extension studies and placebo-controlled pivotal trials, including high dropout rates, differences in patient populations, variable exposure durations, and other confounding factors, an IR was sent to the Applicant to further characterize the trend of LDL increases observed in the LTE study, with the specific aim of excluding any major or unusual shifts. As illustrated in Table 88, no such shifts were identified; the proportions of participants with LDL values exceeding specified thresholds in the LTE study were consistent with those observed in the Pivotal Trial Pool, providing some additional reassurance regarding the long-term lipid profile of oveporexton.

Table 88. Participants With Lipids Analyte Values Exceeding Specified Levels, TAK-861-2003 (Safety Analysis Set)

Laboratory Parameter	Oveporexton 0.5 mg BID N=28 n/Nw (%)	Oveporexton 1 mg BID N=109 n/Nw (%)	Oveporexton 2 mg BID N=304 n/Nw (%)	Oveporexton 2/5 mg N=39 n/Nw (%)	Oveporexton 7 mg QD N=40 n/Nw (%)	Overall Oveporexton N=356 n/Nw (%)
Cholesterol, total, high (mg/dL)						
Level 1 (>200)	17/27 (63.0)	68/107 (63.6)	208/300 (69.3)	25/38 (65.8)	21/39 (53.8)	251/356 (70.5)
Level 2 (>210)	11/27 (40.7)	62/107 (57.9)	173/300 (57.7)	23/38 (60.5)	16/39 (41.0)	212/356 (59.6)
Level 3 (>225)	9/27 (33.3)	48/107 (44.9)	143/300 (47.7)	20/38 (52.6)	13/39 (33.3)	173/356 (48.6)
HDL, males, low (mg/dL)						
Level 1 (<40)	5/11 (45.5)	27/57 (47.4)	72/146 (49.3)	8/18 (44.4)	12/23 (52.2)	94/169 (55.6)
Level 2 (<30)	1/11 (9.1)	4/57 (7.0)	22/146 (15.1)	2/18 (11.1)	2/23 (8.7)	26/169 (15.4)
Level 3 (<20)	0/11 (0.0)	0/57 (0.0)	1/146 (<1)	0/18 (0.0)	0/23 (0.0)	1/169 (<1)
HDL, females, low (mg/dL)						
Level 1 (<50)	9/16 (56.3)	23/50 (46.0)	75/154 (48.7)	7/20 (35.0)	7/16 (43.8)	98/187 (52.4)
Level 2 (<40)	3/16 (18.8)	10/50 (20.0)	28/154 (18.2)	5/20 (25.0)	1/16 (6.3)	41/187 (21.9)
Level 3 (<20)	0/16 (0.0)	1/50 (2.0)	0/154 (0.0)	0/20 (0.0)	0/16 (0.0)	1/187 (<1)

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Laboratory Parameter	Oveporexton 0.5 mg BID N=28 n/Nw (%)	Oveporexton 1 mg BID N=109 n/Nw (%)	Oveporexton 2 mg BID N=304 n/Nw (%)	Oveporexton 2/5 mg N=39 n/Nw (%)	Oveporexton 7 mg QD N=40 n/Nw (%)	Overall Oveporexton N=356 n/Nw (%)
LDL, high (mg/dL)						
Level 1 (>130)	12/27 (44.4)	61/107 (57.0)	191/300 (63.7))	25/38 (65.8)	22/39 (56.4)	228/356 (64.0)
Level 2 (>160)	7/27 (25.9)	41/107 (38.3)	103/300 (34.3)	16/38 (42.1)	12/39 (30.8)	130/356 (36.5)
Level 3 (>190)	4/27 (14.8)	18/107 (16.8)	42/300 (14.0)	9/38 (23.7)	7/39 (17.9)	61/356 (17.1)
Triglycerides, high (mg/dL)						
Level 1 (>150)	10/27 (37.0)	48/107 (44.9)	137/300 (45.7)	14/38 (36.8)	14/39 (35.9)	171/356 (48.0)
Level 2 (>300)	1/27 (3.7)	15/107 (14.0)	33/300 (11.0)	4/38 (10.5)	1/39 (2.6)	47/356 (13.2)
Level 3 (>500)	0/27 (0.0)	6/107 (5.6)	4/300 (1.3)	1/38 (2.6)	1/39 (2.6)	12/356 (3.4)

Abbreviations: N, number of participants who have been exposed to that dosage level during the trial; n, number of participants meeting the specified laboratory criteria; Nw, total number of participants with data available for the laboratory test of interest.
n and Nw are based on assessments completed while the participant was exposed to that dosage level during the trial. Data cutoff date: August 29, 2025.
Threshold Levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (Abnormality Level Criteria).
Source: Applicant's response to Agency's IR, TAK861_ Table 2, dated May 11, 2026

Mean lipid values in the LTE study are presented in Table 89, Table 90, Table 91, and Table 92. At the LTE baseline, mean total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were within or near normal limits and were broadly consistent with values observed at the end of the parent studies.

Small, stable increases in mean total cholesterol and LDL cholesterol from LTE baseline were observed across all timepoints and dosage groups. Mean HDL cholesterol showed small numerical decreases from baseline across all timepoints, without evidence of a progressive or dose-dependent trend. Mean triglycerides were similarly stable, with small numerical decreases from baseline at most timepoints; a small numerical increase observed at Week 104 is likely attributable to the substantially reduced sample size at that visit rather than a treatment effect.

Table 89. Actual Values and Change From Baseline in Total Cholesterol (mg/Dl) (Long-Term Extension Study TAK-861-2003, NT1 Safety Set, Data Cutoff: August 29, 2025)[a]

Visit	Statistic	Oveporexton 0.5 mg BID	Oveporexton 1 mg BID	Oveporexton 2 mg BID	Oveporexton 2 mg / 5 mg	Oveporexton 7 mg QD	Oveporexton Overall
Parent Baseline	n	25	92	185	26	28	356
	Mean (SD)	193.5 (44.94)	193.2 (42.57)	187.3 (39.00)	204.1 (39.90)	185.5 (38.77)	190.4 (40.49)
LTE Baseline	n	25	92	185	26	28	356
	Mean (SD)	194.1 (37.16)	201.7 (47.20)	194.3 (38.96)	216.0 (48.42)	201.3 (42.33)	198.3 (42.30)
Week 12 (Day 84)	n	12	50	218	28	27	335
	Mean (SD)	199.2 (36.47)	206.0 (47.33)	200.3 (42.97)	226.4 (56.27)	205.4 (42.42)	203.7 (44.96)
	Mean CFB (SD)	4.9 (17.10)	15.7 (33.65)	12.4 (29.96)	17.2 (38.78)	19.2 (22.66)	13.6 (30.47)
Week 38 (Day 266)	n	7	2	57	17	14	97
	Mean (SD)	210.3 (58.58)	211.3 (11.21)	212.4 (49.78)	209.5 (42.21)	199.0 (42.78)	209.8 (47.19)
	Mean CFB (SD)	15.0 (17.64)	29.6 (29.26)	9.3 (34.53)	12.1 (20.50)	17.9 (32.52)	11.9 (30.88)
Week 52 (Day 364)	n	9	NA	66	7	6	88
	Mean (SD)	202.4 (54.14)	NA	207.6 (43.44)	192.3 (27.62)	190.4 (32.32)	204.6 (42.73)
	Mean CFB (SD)	13.0 (22.31)	NA	7.1 (35.26)	5.1 (35.88)	14.1 (26.05)	8.0 (33.30)

Visit	Statistic	Oveporexton 0.5 mg BID	Oveporexton 1 mg BID	Oveporexton 2 mg BID	Oveporexton 2 mg / 5 mg	Oveporexton 7 mg QD	Oveporexton Overall
Week 78 (Day 546)	n	2	7	71	NA	NA	80
	Mean (SD)	215.4 (96.25)	225.7 (33.86)	211.8 (42.75)	NA	NA	213.1 (42.89)
	Mean CFB (SD)	22.0 (7.11)	23.9 (22.80)	13.8 (32.54)	NA	NA	14.9 (31.43)
Week 104 (Day 728)	n	NA	5	31	NA	NA	36
	Mean (SD)	NA	237.7 (55.60)	200.0 (39.18)	NA	NA	205.3 (42.93)
	Mean CFB (SD)	NA	34.7 (21.42)	13.5 (27.73)	NA	NA	16.5 (27.69)

[a] Participant counts within individual dose groups may exceed baseline enrollment figures because, in the long-term extension study, doses could be adjusted after initial enrollment. Additionally, participants originally assigned to lower doses were transitioned to higher doses as the development program advanced and demonstrated that 1 mg twice a day (BID) and 2 mg BID provided the optimal balance of efficacy and safety.

CFB = Change from Baseline. Baseline = last non-missing value prior to first LTE dose.

Values converted from mmol/L to mg/dL (×38.67 for cholesterol/HDL/LDL; ×88.57 for triglycerides). Data summarized by TAK-861 dosage level at time of assessment. NT1 Safety Set; ANL01FL = Y. NA = not available. Note: sample sizes decrease at later timepoints; results at Week 78 and Week 104 should be interpreted with caution.

Source: Applicant's response dated June 22, 2026, to Agency IR; data replicated by Clinical Data Scientist Team

Reference ID: 5847402

Table 90. Actual Values and Change From Baseline in HDL Cholesterol (mg/Dl) (Long-Term Extension Study TAK-861-2003, NT1 Safety Set, Data Cutoff: August 29, 2025)

Visit	Statistic	Oveporexton 0.5 mg BID	Oveporexton 1 mg BID	Oveporexton 2 mg BID	Oveporexton 2 mg / 5 mg	Oveporexton 7 mg QD	Oveporexton Overall
Parent Baseline	n	25	92	185	26	28	356
	Mean (SD)	54.4 (12.00)	53.2 (14.44)	54.2 (13.93)	54.2 (16.52)	55.9 (16.00)	54.1 (14.25)
LTE Baseline	n	25	92	185	26	28	356
	Mean (SD)	51.4 (12.90)	50.0 (12.37)	50.9 (13.47)	52.0 (15.61)	50.9 (13.97)	50.8 (13.30)
Week 12 (Day 84)	n	12	50	218	28	27	335
	Mean (SD)	50.9 (10.93)	51.7 (15.36)	52.1 (13.46)	50.3 (16.58)	51.1 (15.75)	51.8 (14.07)
	Mean CFB (SD)	-1.6 (4.50)	-2.0 (8.90)	-2.1 (9.43)	-2.7 (11.04)	-3.9 (6.92)	-2.2 (9.16)
Week 38 (Day 266)	n	7	2	57	17	14	97
	Mean (SD)	53.6 (12.83)	59.7 (10.66)	50.8 (13.95)	49.0 (11.28)	52.5 (14.63)	51.1 (13.35)
	Mean CFB (SD)	1.1 (5.80)	8.7 (0.82)	-6.4 (8.59)	-2.1 (7.09)	-4.1 (7.42)	-4.5 (8.37)
Week 52 (Day 364)	n	9	NA	66	7	6	88
	Mean (SD)	52.8 (14.15)	NA	51.1 (14.60)	49.6 (9.66)	54.1 (19.96)	51.3 (14.42)
	Mean CFB (SD)	0.9 (7.06)	NA	-4.8 (9.80)	-0.6 (5.19)	1.2 (6.03)	-3.5 (9.26)
Week 78 (Day 546)	n	2	7	71	NA	NA	80
	Mean (SD)	52.6 (13.67)	55.5 (21.66)	52.7 (15.03)	NA	NA	52.9 (15.45)
	Mean CFB (SD)	-4.4 (0.82)	1.6 (13.83)	-3.2 (8.47)	NA	NA	-2.8 (8.95)
Week 104 (Day 728)	n	NA	5	31	NA	NA	36
	Mean (SD)	NA	55.7 (7.66)	49.3 (12.88)	NA	NA	50.2 (12.40)
	Mean CFB (SD)	NA	3.6 (2.36)	-4.0 (10.15)	NA	NA	-2.9 (9.80)

CFB = Change from Baseline. Baseline = last non-missing value prior to first LTE dose. Values converted from mmol/L to mg/dL (×38.67 for cholesterol/HDL/LDL; ×88.57 for triglycerides). Data summarized by TAK-861 dosage level at time of assessment. NT1 Safety Set; ANL01FL = Y. NA = not available. Note: sample sizes decrease at later timepoints; results at Week 78 and Week 104 should be interpreted with caution.
Source: Applicant's response dated June 22, 2026, to Agency IR; data replicated by Clinical Data Scientist Team

Reference ID: 5847402

Table 91. Actual Values and Change From Baseline in LDL Cholesterol (mg/Dl) (Long-Term Extension Study TAK-861-2003, NT1 Safety Set , Data Cutoff: August 29, 2025)

Visit	Statistic	Oveporexton 0.5 mg BID	Oveporexton 1 mg BID	Oveporexton 2 mg BID	Oveporexton 2 mg / 5 mg	Oveporexton 7 mg QD	Oveporexton Overall
Parent Baseline	n	25	92	185	26	28	356
	Mean (SD)	118.1 (37.60)	115.4 (35.01)	109.2 (34.79)	116.7 (38.28)	107.3 (38.16)	111.8 (35.56)
LTE Baseline	n	25	92	185	26	28	356
	Mean (SD)	121.8 (34.17)	128.8 (42.26)	122.4 (35.64)	137.9 (40.75)	124.2 (44.58)	125.3 (38.51)
Week 12 (Day 84)	n	12	50	218	28	27	335
	Mean (SD)	125.2 (29.83)	132.1 (43.31)	125.2 (39.49)	150.4 (51.00)	130.6 (38.62)	128.8 (41.16)
	Mean CFB (SD)	7.3 (15.33)	18.6 (30.73)	15.7 (26.07)	29.8 (43.61)	20.1 (20.03)	17.4 (28.15)
Week 38 (Day 266)	n	7	2	57	17	14	97
	Mean (SD)	135.5 (47.63)	135.2 (12.85)	137.2 (41.84)	133.1 (40.99)	126.9 (35.93)	134.8 (40.40)
	Mean CFB (SD)	14.7 (14.82)	40.6 (4.92)	18.3 (33.76)	14.3 (24.50)	21.7 (25.07)	18.3 (29.67)
Week 52 (Day 364)	n	9	NA	66	7	6	88
	Mean (SD)	126.9 (46.52)	NA	132.5 (39.14)	124.3 (27.26)	119.0 (22.18)	130.4 (37.94)
	Mean CFB (SD)	12.7 (17.16)	NA	14.6 (36.85)	7.2 (34.38)	11.4 (25.45)	13.6 (34.13)
Week 78 (Day 546)	n	2	7	71	NA	NA	80
	Mean (SD)	147.3 (72.19)	145.6 (34.71)	135.8 (37.74)	NA	NA	137.0 (37.81)
	Mean CFB (SD)	24.2 (1.37)	24.7 (17.68)	18.7 (34.36)	NA	NA	19.4 (32.76)
Week 104 (Day 728)	n	NA	5	31	NA	NA	36
	Mean (SD)	NA	155.4 (37.00)	126.9 (38.81)	NA	NA	130.8 (39.33)
	Mean CFB (SD)	NA	28.0 (22.62)	14.4 (27.95)	NA	NA	16.3 (27.40)

CFB = Change from Baseline. Baseline = last non-missing value prior to first LTE dose. Values converted from mmol/L to mg/dL (×38.67 for cholesterol/HDL/LDL; ×88.57 for triglycerides). Data summarized by TAK-861 dosage level at time of assessment. NT1 Safety Set; ANL01FL = Y. NA = not available. Note: sample sizes decrease at later timepoints; results at Week 78 and Week 104 should be interpreted with caution.
Source: Applicant's response dated June 22, 2026, to Agency IR; data replicated by Clinical Data Scientist Team

Reference ID: 5847402

Table 92. Actual Values and Change From Baseline in Triglycerides (mg/Dl) (Long-Term Extension Study TAK-861-2003, NT1 Safety Set, Data Cutoff: August 29, 2025)

Visit	Statistic	Oveporexton 0.5 mg BID	Oveporexton 1 mg BID	Oveporexton 2 mg BID	Oveporexton 2 mg / 5 mg	Oveporexton 7 mg QD	Oveporexton Overall
Parent Baseline	n	25	92	185	26	28	356
	Mean (SD)	105.5 (54.00)	124.0 (76.32)	120.4 (73.85)	139.4 (97.08)	123.9 (101.81)	122.0 (77.54)
LTE Baseline	n	25	92	185	26	28	356
	Mean (SD)	104.6 (49.16)	116.7 (64.80)	106.1 (57.87)	130.7 (72.27)	136.8 (93.65)	113.0 (64.12)
Week 12 (Day 84)	n	12	50	218	28	27	335
	Mean (SD)	115.7 (57.43)	110.5 (59.34)	114.9 (66.56)	128.3 (74.63)	118.9 (64.47)	115.7 (65.54)
	Mean CFB (SD)	-3.9 (36.40)	-6.3 (64.31)	-6.5 (65.12)	-36.0 (76.24)	9.7 (83.10)	-7.6 (67.13)
Week 38 (Day 266)	n	7	2	57	17	14	97
	Mean (SD)	106.9 (64.03)	82.8 (44.47)	122.0 (74.60)	137.2 (100.82)	97.5 (50.45)	119.2 (75.71)
	Mean CFB (SD)	-3.5 (39.86)	-97.9 (127.14)	-7.5 (88.21)	0.2 (55.50)	-3.7 (51.30)	-7.2 (76.55)
Week 52 (Day 364)	n	9	NA	66	7	6	88
	Mean (SD)	112.3 (70.35)	NA	120.0 (69.51)	92.2 (22.26)	87.2 (37.74)	114.8 (65.54)
	Mean CFB (SD)	-3.6 (62.47)	NA	-8.3 (69.40)	-7.6 (25.44)	-2.5 (14.33)	-7.4 (63.38)
Week 78 (Day 546)	n	2	7	71	NA	NA	80
	Mean (SD)	77.9 (53.86)	122.6 (73.90)	117.4 (68.71)	NA	NA	116.9 (68.38)
	Mean CFB (SD)	12.4 (23.80)	-12.1 (24.49)	-4.1 (61.29)	NA	NA	-4.4 (58.25)
Week 104 (Day 728)	n	NA	5	31	NA	NA	36
	Mean (SD)	NA	132.1 (120.53)	119.3 (66.29)	NA	NA	121.1 (73.81)
	Mean CFB (SD)	NA	14.9 (46.31)	14.5 (47.99)	NA	NA	14.5 (47.11)

CFB = Change from Baseline. Baseline = last non-missing value prior to first LTE dose. Values converted from mmol/L to mg/dL (×38.67 for cholesterol/HDL/LDL; ×88.57 for triglycerides). Data summarized by TAK-861 dosage level at time of assessment. NT1 Safety Set; ANL01FL = Y. NA = not available. Note: sample sizes decrease at later timepoints; results at Week 78 and Week 104 should be interpreted with caution.
Source: Applicant's response dated June 22, 2026, to Agency IR; data replicated by Clinical Data Scientist Team

Overall, the LTE lipid data do not suggest a clinically meaningful effect of long-term oveporexton treatment on lipid metabolism but still show a slight trend towards mild elevation that plateaus. Direct comparison across timepoints and dosage groups is limited by the absence of a concurrent placebo arm, time-varying exposure due to dosage adjustments, and declining sample sizes at later visits. Nevertheless, product labeling should reflect the observed LDL increases.

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90-Day Safety Update

An additional eight participants experienced CPK elevation that met MAV criteria (>5× ULN). Two of these cases were reported as TEAEs:

- One participant experienced a TEAE of PT “rhabdomyolysis” (participant also had an increase in AST), which was mild and resolved while on treatment.
- One participant experienced a TEAE of blood CPK increase ("investigations"), severe, that resolved within 3 days. No clinical symptoms were associated.

No other abnormal laboratory values were reported.

The presence of confounding factors (exercise, viral infections) in the majority of cases of CPK elevations in the LTE study and its 90-day safety update, combined with the asymptomatic nature of most elevations and spontaneous resolution, suggests these events are likely multifactorial rather than directly drug-related. However, a trend of higher CPK elevations was also observed in the pivotal trial pool, with higher levels in the oveporexton group compared to placebo. Although there was not a higher incidence of TEAEs in the oveporexton group compared to placebo, there were two cases of PT “rhabdomyolysis” (but without dark urine, myalgia, or renal impairment) leading to discontinuation in the oveporexton group compared to zero cases in the placebo group, plus an additional case in the LTE 90-day safety update. Although there were confounding factors (excessive exercise in one case, routine exercise associated with Gilbert's syndrome in another case, and no apparent cofactor in the third mild case), we cannot exclude a causal relationship with the study drug.

In summary, while the majority of evidence suggests CPK elevations are likely multifactorial and primarily related to alternative causes (particularly physical activity), a causal relationship with oveporexton cannot be definitively excluded. The higher incidence in oveporexton-treated participants compared to placebo, the persistence of this pattern across the pivotal trials and LTE study, and the occurrence of three cases labeled as "rhabdomyolysis" (albeit with confounding factors and not meeting clinical criteria) warrant inclusion of comprehensive information about CPK elevations in product labeling.

An important consideration in causality assessment is the therapeutic context. Patients with narcolepsy often experience significant functional impairment and reduced physical activity due to excessive daytime sleepiness. Effective treatment may lead to increased energy levels and return to physical activities, which could independently contribute to CPK elevations. This creates a challenge in distinguishing between a direct drug effect and an indirect effect mediated through improved function and increased activity.

The absence of true rhabdomyolysis (defined by the triad of muscle symptoms, myoglobinuria, and renal impairment), the uniformly benign clinical course, and the consistent presence of confounding factors provide reassurance that oveporexton does not appear to cause clinically significant muscle toxicity. However, transparency regarding the observed laboratory findings is essential for informed prescribing and appropriate patient monitoring, particularly in patients who may be at higher risk (e.g., those taking concomitant

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statins or other myotoxic medications, those with underlying muscle disorders, or those engaging in strenuous physical activity).

The modest increases in LDL and total cholesterol, while consistently trending higher on drug versus placebo and also in the LTE study (and corresponding mild decrease in HDL), are of minimal clinical significance given their small magnitude and the absence of any cardiovascular or lipid-related adverse events. Standard lipid monitoring as part of routine clinical care would be appropriate, but these findings do not warrant specific warnings or precautions in labeling beyond inclusion of the lab value trends in the adverse reactions section with appropriate context.

Vital Signs

Pivotal Trial Pool

As described, vital signs including blood pressure, heart rate, body weight, respiratory rate, and temperature were measured at Screening, Baseline, Week 4 (Day 28), Week 8 (Day 56), Week 12 (Day 84), and 7 days after last dose (Day 91). Per protocol, height was measured at Screening and Week 12 only.

Blood Pressure and Heart Rate

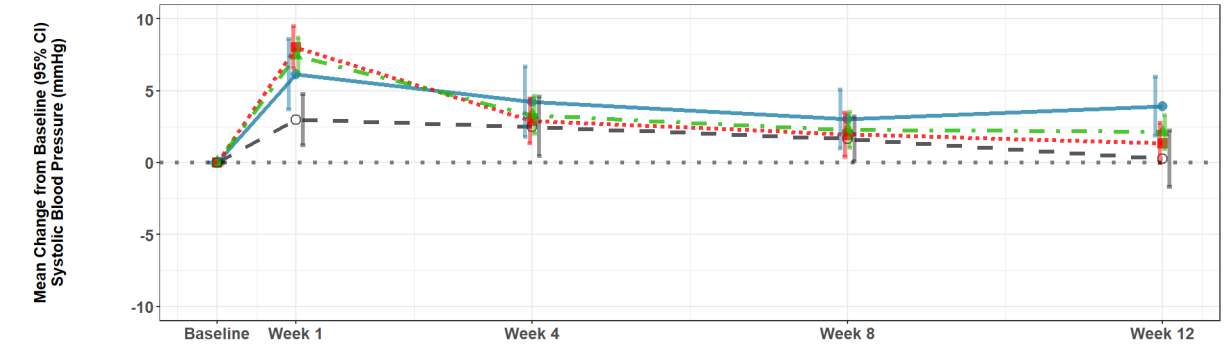
First, we examined the adae.xpt dataset to identify any TEAEs related to the cardiovascular system organ class. There was one case of clinically significant blood pressure increase and one case of palpitations in the oveporexton group (one in the 1 mg BID group and one in the 2 mg BID group), compared to no cases in the placebo group. There was one case of hypotension in the placebo group.

In addition, two cases in the oveporexton group reported chest pain, one of which was serious and has been described previously. Comprehensive cardiac workup of the SAE revealed no coronary or structural abnormalities.

The clinical reviewer's examination of vital signs parameter measures of SBP, DBP, and HR found no changes of note over time, with a mild increase in mean BP and HR observed on Day 1 in the overall oveporexton group, as illustrated in Figure 25, Figure 26, Figure 27 and Table 96. However, the changes were minimal (SBP mean increase of 7 mm Hg, DBP mean increase of 5 mm Hg, and HR mean increase of 5 bpm) and returned to near baseline values by Week 12 (see also Table 93, Table 94, Table 95, and Table 96).

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Figure 25. Mean Systolic Blood Pressure Data Change From Baseline Over Time by Treatment Arm, Safety Population, Trials TAK-861-3001 and TAK-861-3002



Mean Change from Baseline / Mean Value

	Baseline	Week 1	Week 4	Week 8	Week 12
Oveporexton 1mg	0/116	6.2/122	4.2/120	3/119	3.9/120
Oveporexton 2mg	0/114	8/122	2.9/117	1.9/116	1.3/115
Oveporexton 1-2mg	0/114	7.4/122	3.3/118	2.3/117	2.1/117
Placebo	0/117	3/120	2.5/119	1.6/118	0.25/117

Number of Subjects with Both Baseline and Postbaseline Data

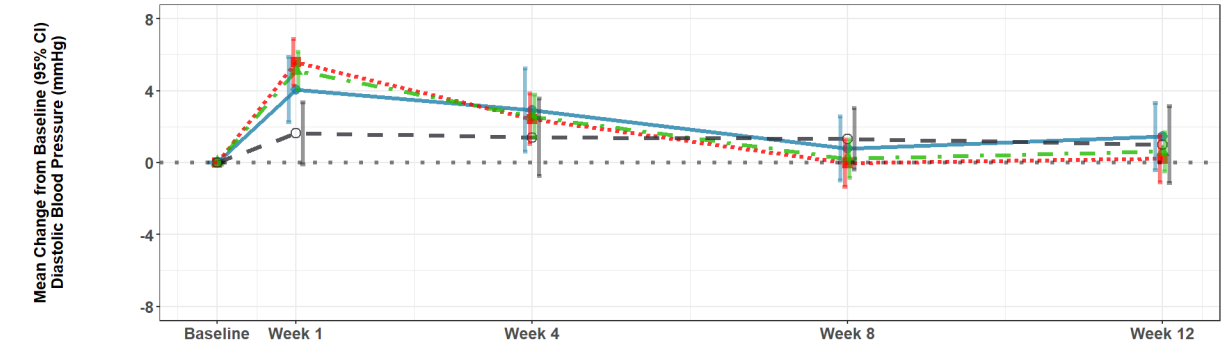
	Baseline	Week 1	Week 4	Week 8	Week 12
Oveporexton 1mg	60	60	59	58	57
Oveporexton 2mg	136	135	134	134	133
Oveporexton 1-2mg	196	195	193	192	190
Placebo	76	76	74	71	71

Oveporexton 1mg Oveporexton 2mg Oveporexton 1-2mg Placebo

Abbreviations: CI, confidence interval
Duration is 12 weeks.
Participants with both baseline and postbaseline data available are included in the mean change from baseline calculations at each visit. The number of subjects reflects only those included in the mean change from baseline calculations, rather than the total number of subjects.
The vertical bars shown on the plotted lines indicate the 95% confidence interval of probability of incidence at the corresponding time points.
Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups as the results would not be considered a reliable indicator of the true mean.
Source: Clinical Reviewer and Clinical Data Scientist's team; advs.xpt; Software: R

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Figure 26. Mean Diastolic Blood Pressure Data Change From Baseline Over Time by Treatment Arm, Safety Population, Trials TAK-861-3001 and TAK-861-3002



Mean Change from Baseline / Mean Value

	Baseline	Week 1	Week 4	Week 8	Week 12
Oveporexton 1mg	0/73	4.1/77	2.9/75	0.78/73	1.4/74
Oveporexton 2mg	0/72	5.6/77	2.4/74	-0.02/72	0.23/72
Oveporexton 1-2mg	0/72	5.1/77	2.6/74	0.22/72	0.59/72
Placebo	0/73	1.6/75	1.4/74	1.3/74	0.99/74

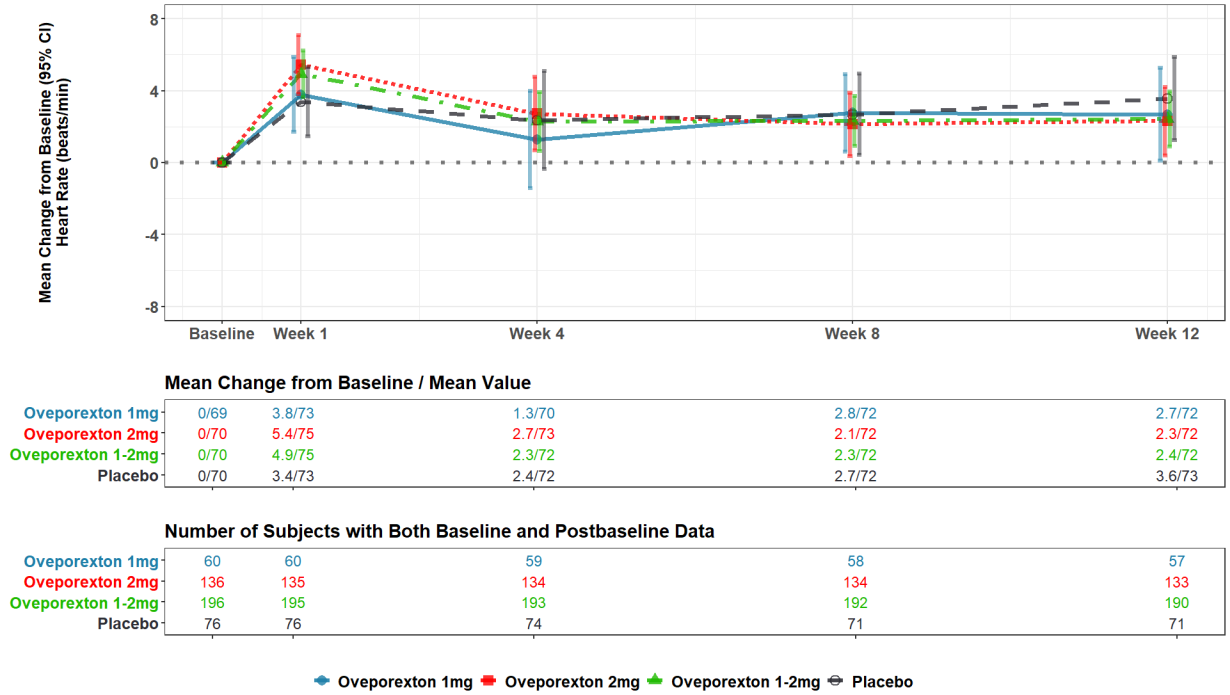
Number of Subjects with Both Baseline and Postbaseline Data

	Baseline	Week 1	Week 4	Week 8	Week 12
Oveporexton 1mg	60	60	59	58	57
Oveporexton 2mg	136	135	134	134	133
Oveporexton 1-2mg	196	195	193	192	190
Placebo	76	76	74	71	71

Oveporexton 1mg Oveporexton 2mg Oveporexton 1-2mg Placebo

Abbreviations: CI, confidence interval
Duration is 12 weeks.
Subjects with both baseline and postbaseline data available are included in the mean change from baseline calculations at each visit. The number of subjects reflects only those included in the mean change from baseline calculations, rather than the total number of subjects.
The vertical bars shown on the plotted lines indicate the 95% confidence interval of probability of incidence at the corresponding time points.
Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups as the results would not be considered a reliable indicator of the true mean.
Source: Clinical Reviewer and Clinical Data Scientist's team; advs.xpt; Software: R

Figure 27. Mean Heart Rate Data Change From Baseline Over Time by Treatment Arm, Safety Population, Trials TAK-861-3001 and TAK-861-3002



Mean Change from Baseline / Mean Value

	Baseline	Week 1	Week 4	Week 8	Week 12
Oveporexton 1mg	0/69	3.8/73	1.3/70	2.8/72	2.7/72
Oveporexton 2mg	0/70	5.4/75	2.7/73	2.1/72	2.3/72
Oveporexton 1-2mg	0/70	4.9/75	2.3/72	2.3/72	2.4/72
Placebo	0/70	3.4/73	2.4/72	2.7/72	3.6/73

Number of Subjects with Both Baseline and Postbaseline Data

	Baseline	Week 1	Week 4	Week 8	Week 12
Oveporexton 1mg	60	60	59	58	57
Oveporexton 2mg	136	135	134	134	133
Oveporexton 1-2mg	196	195	193	192	190
Placebo	76	76	74	71	71

Oveporexton 1mg Oveporexton 2mg Oveporexton 1-2mg Placebo

Abbreviations: CI, confidence interval
Duration is 12 weeks.
Subjects with both baseline and postbaseline data available are included in the mean change from baseline calculations at each visit. The number of subjects reflects only those included in the mean change from baseline calculations, rather than the total number of subjects.
The vertical bars shown on the plotted lines indicate the 95% confidence interval of probability of incidence at the corresponding time points.
Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups as the results would not be considered a reliable indicator of the true mean.
Source: Clinical Reviewer and Clinical Data Scientist's team; advs.xpt; Software: R

Table 93. Systolic Blood Pressure by Treatment Arm (at 3.5 Hours After Drug Administration), Safety Population, Trials TAK-861-3001 and TAK-861-3002

Visit	Statistic	Placebo	OVE 1 mg BID	OVE 2 mg BID
Baseline	n	75	60	136
	Mean (SD)	117.3 (13.24)	118.2 (10.43)	114.3 (11.41)
	Median	117.0	119.0	114.0
	Min, Max	94, 151	96, 142	90, 146
Day 1	n (actual)	76	60	135
	Mean (SD)	120.1 (12.97)	121.3 (14.97)	121.3 (13.00)
	Median	122.0	121.5	122.0
	Min, Max	86, 145	89, 159	88, 156
	n (CFB)	75	60	135
	CFB Mean (SD)	3.0 (9.86)	3.1 (10.24)	7.1 (10.35)
	CFB Median	2.0	3.0	6.0
	CFB Min, Max	-19, 25	-18, 34	-18, 38

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Visit	Statistic	Placebo	OVE 1 mg BID	OVE 2 mg BID
Week 8	n (actual)	71	58	134
	Mean (SD)	117.4 (13.96)	119.6 (12.47)	115.7 (11.27)
	Median	117.0	119.5	115.5
	Min, Max	87, 153	89, 150	88, 145
	n (CFB)	70	58	134
	CFB Mean (SD)	0.3 (12.09)	1.3 (10.26)	1.2 (10.85)
	CFB Median	1.0	2.0	1.0
	CFB Min, Max	-26, 35	-27, 21	-29, 32
Week 12	n (actual)	70	57	131
	Mean (SD)	114.6 (14.05)	119.4 (13.53)	115.0 (11.83)
	Median	115.0	119.0	115.0
	Min, Max	87, 147	89, 156	78, 147
	n (CFB)	69	57	131
	CFB Mean (SD)	-2.3 (9.98)	1.2 (10.98)	0.5 (10.75)
	CFB Median	-3.0	1.0	2.0
	CFB Min, Max	-39, 18	-32, 24	-29, 28

CFB = Change from Baseline. BID = Twice Daily. SD = Standard Deviation. N = number of subjects in safety analysis set; n = number with non-missing value at timepoint.
Participants with NT1 from studies TAK-861-3001 and TAK-861-3002. Baseline is defined as the last non-missing value prior to the first dose time-matched with each postdose timepoint within each visit.
Source: tak-861-iss-safety-tables-figures.pdf, Table 2.4.1.5.

Table 94. Diastolic Blood Pressure by Treatment Arm (at 3.5 Hours After Drug Administration), Safety Population, Trials TAK-861-3001 and TAK-861-3002

Diastolic Blood Pressure	Statistic	Placebo (N=76)	OVE 1 mg BID (N=60)	OVE 2 mg BID (N=136)
Baseline	n (actual)	75	60	136
	Mean (SD)	73.5 (8.87)	73.5 (8.24)	71.7 (8.48)
	Median	75.0	74.5	72.0
	Min, Max	51, 92	54, 89	53, 95
Day 1	n (actual)	76	60	135
	Mean (SD)	75.3 (9.88)	77.1 (10.27)	77.1 (9.12)
	Median	74.5	77.0	77.0
	Min, Max	53, 98	50, 98	57, 99
	n (CFB)	75	60	135
	CFB Mean (SD)	2.0 (7.85)	3.5 (7.96)	5.4 (8.47)
	CFB Median	2.0	4.0	5.0
	CFB Min, Max	-22, 21	-16, 20	-17, 30
Week 8	n (actual)	71	58	134
	Mean (SD)	72.9 (9.72)	74.3 (8.63)	72.1 (9.03)
	Median	71.0	75.0	73.0
	Min, Max	49, 94	46, 94	38, 98
	n (CFB)	70	58	134
	CFB Mean (SD)	-0.7 (9.79)	0.7 (6.73)	0.4 (7.89)
	CFB Median	-1.5	1.0	0.0
	CFB Min, Max	-18, 32	-22, 13	-21, 23

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Diastolic Blood Pressure	Statistic	Placebo (N=76)	OVE 1 mg BID (N=60)	OVE 2 mg BID (N=136)
Week 12	n (actual)	70	57	131
	Mean (SD)	72.8 (10.59)	73.5 (10.25)	72.5 (9.84)
	Median	73.5	74.0	72.0
	Min, Max	46, 97	50, 95	43, 108
	n (CFB)	69	57	131
	CFB Mean (SD)	-0.9 (9.46)	0.2 (9.60)	0.8 (9.82)
	CFB Median	0.0	0.0	0.0
	CFB Min, Max	-21, 24	-21, 25	-22, 36

CFB = Change from Baseline. BID = Twice Daily. SD = Standard Deviation. N = number of subjects in safety analysis set; n = number with non-missing value at timepoint.
Participants with NT1 from studies TAK-861-3001 and TAK-861-3002. Baseline is defined as the last non-missing value prior to the first dose time-matched with each postdose timepoint within each visit.
Source: tak-861-iss-safety-tables-figures.pdf, Table 2.4.1.5.

The clinical reviewer's examination of abnormal outliers in BP and HR found the numbers of participants with postbaseline outlier values (individual subject minimums and individual subject maximums for all postdose visits) were similar across groups, with no difference compared to placebo (Table 95).

Table 95. Subjects With Maximum and Minimum Postbaseline Systolic and Diastolic Blood Safety Population, Trials TAK-861-3001 and TAK-861-3002

Blood Pressure	Oveporexton 1 mg BID N=60 n/N_w (%)	Oveporexton 2 mg BID N=136 n/N_w (%)	Oveporexton 1 to 2 mg BID N=196 n/N_w (%)	Placebo N=76 n/N_w (%)
*Postbaseline Systolic Blood Pressure Categories (mm Hg)**				
<90	0/60 (0)	0/136 (0)	0/196 (0)	0/76 (0)
≥90	60/60 (100)	136/136 (100)	196/196 (100)	76/76 (100)
≥120	53/60 (88.3)	117/136 (86.0)	170/196 (86.7)	63/76 (82.9)
≥140	14/60 (23.3)	23/136 (16.9)	37/196 (18.9)	15/76 (19.7)
≥160	1/60 (1.7)	0/136 (0)	1/196 (0.5)	1/76 (1.3)
≥180	0/60 (0)	0/136 (0)	0/196 (0)	0/76 (0)
*Postbaseline Diastolic Blood Pressure Categories (mm Hg)**				
<60	1/60 (1.7)	0/136 (0)	1/196 (0.5)	0/76 (0)
≥60	59/60 (98.3)	136/136 (100)	195/196 (99.5)	76/76 (100)
≥80	48/60 (80.0)	99/136 (72.8)	147/196 (75.0)	51/76 (67.1)
≥90	14/60 (23.3)	29/136 (21.3)	43/196 (21.9)	18/76 (23.7)
≥110	0/60 (0)	0/136 (0)	0/196 (0)	0/76 (0)
≥120	0/60 (0)	0/136 (0)	0/196 (0)	0/76 (0)
>20 change from baseline	13/60 (21.7)	35/136 (25.7)	48/196 (24.5)	16/76 (21.1)
>30 change from baseline	1/60 (1.7)	4/136 (2.9)	5/196 (2.6)	2/76 (2.6)

Abbreviations: BID = twice daily; n, number of subjects meeting the specified criteria; Nw, number of subjects in treatment arm with available blood pressure data.
* Postbaseline Blood Pressure: Refers to the highest or lowest numerical value of SBP or DBP recorded across all postbaseline timepoints for a subject.
Duration is 12 weeks.
Subject counts are cumulative for each abnormality threshold.
Source: Clinical Reviewer and Clinical Data Scientist's team, advs.xpt; Software: R

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Table 96. Vital Signs: Clinically Notable Increases at Day 1—Safety Population, Trials TAK-861-3001 and TAK-861-3002

Parameter (Increase at Day 1)	Oveporexton 1 to 2 mg BID N=196 n/N (%)	Placebo N=76 n/N (%)
Systolic Blood Pressure (increase ≥20 mm Hg)	43/196 (21.9%)	10/76 (13.2%)
Diastolic Blood Pressure (increase ≥20 mm Hg)	18/196 (9.2%)	5/76 (6.6%)
Heart Rate (increase ≥15 bpm)	58/196 (29.6%)	17/76 (22.4%)

Abbreviations: BID = twice daily; bpm = beats per minute; N = number of patients in treatment group; n = number of patients with notable increase.
Source: Safety Review team, advs.xpt; Software: R.

Body Weight—Respiratory Rate—Temperature

Based on the TEAE adae.xpt dataset, a total of 4.5% (9/196) of participants experienced weight increase in the oveporexton group compared to 3.9% (3/76) in the placebo group. The clinical reviewer's examination of weight changes from baseline during the 12-week treatment found a higher percentage of participants with ≥5% weight gain in the placebo group compared to the oveporexton groups (28% [21/76] versus 20% [39/196], respectively).

Mean body weight increased modestly from baseline across all treatment groups over the 12-week double-blind period. At Week 12, patients receiving oveporexton 1 mg (n=57) gained a mean of 1.6 kg from baseline, while those receiving oveporexton 2 mg (n=133) gained 0.9 kg; the combined oveporexton 1 to 2 mg group (n=190) gained a mean of 1.1 kg. In comparison, placebo-treated patients (n=70) gained a mean of 2.3 kg over the same period. The difference in mean change from baseline between the combined oveporexton group and placebo was −1.2 kg, indicating that patients on oveporexton gained approximately 1.2 kg less than those on placebo over 12 weeks.

There were no TEAEs related to increased or decreased respiratory rate and temperature in the adae.xpt dataset. The clinical reviewer's examination of respiratory rate and temperature changes from baseline during the 12-week treatment did not find a notable difference between groups as measured by central tendency (mean, median).

In summary, the evaluation of vital signs in the pivotal trial pool revealed no major clinically significant safety concerns with oveporexton treatment. Cardiovascular assessments showed minimal and transient increases in blood pressure and heart rate on Day 1 (mean increases of 7 mm Hg SBP, 5 mm Hg DBP, and 5 bpm HR), which returned to near baseline values by Week 12. The incidence of post-baseline outlier values for blood pressure and heart rate was similar between oveporexton and placebo groups. While two cases of chest pain were reported in the oveporexton group (including one serious adverse event), comprehensive cardiac workup revealed no coronary or structural abnormalities.

Body weight changes were comparable between groups, with a slightly lower percentage of participants experiencing ≥5% weight gain in the oveporexton groups compared to placebo

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(19.9% versus 27.6%, respectively). Mean weight change from baseline was also numerically smaller in the combined oveporexton group compared to placebo at Week 12. Overall, these findings do not suggest any clear effect of oveporexton on body weight.

Respiratory rate and temperature measurements showed no notable differences between treatment groups. Overall, no clinically significant adverse trends were observed in the evaluation of vital signs parameters during the 12-week treatment period.

Other Integrated Summary of Safety Studies

LTE Trial (TAK-861-2003)

Blood Pressure and Heart Rate

First, we examined the adae.xpt dataset to identify any TEAEs related to the cardiovascular system organ class. There were seven participants (2.0%) that experienced a TEAEs related to BP or HR (three palpitations, two BP increased, one diastolic BP increased, one HR increased, and one hypertension), all mild to moderate, except for the participant who experienced a severe BP increase that resulted in trial intervention discontinuation and already described in the paragraph related to treatment discontinuation in the LTE TAK-861-2003 Study (the participant had inconsistent compliance, raising concern that the participant may have been taking higher dosages than recommended).

This clinical reviewer's examination of vital signs parameter measures of SBP, DBP, and HR found the mean change from Baseline to Month 6 of treatment for BP (both SBP and DBP) was <5 mm Hg, and HR was not changed meaningfully compared with baseline values at all time points.

The MAV analysis revealed that SBP values ≥160 mm Hg were observed in two participants (0.6%), and DBP values ≥100 mm Hg were observed in six participants (1.7%). All participants with SBP values >160 mm Hg had isolated single visit elevations. Only one participant had DBP >100 mm Hg at three visits; however, their SBP values remained within normal limits and no TEAEs of BP increased were reported.

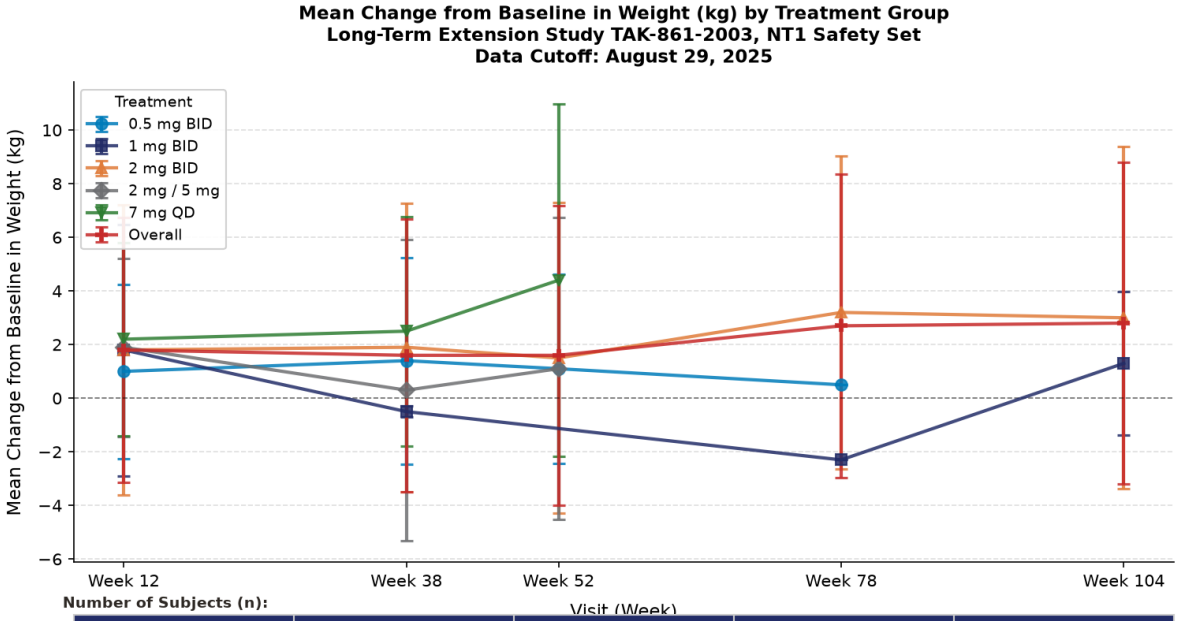
Body Weight—Respiratory Rate—Temperature

Based on the TEAE adae.xpt dataset, a total of 3.7% (13/356) of participants experienced weight increase in the oveporexton group in the LTE study. Body weight increase AEs did not appear to be dose-related (1-mg BID group = 0, 2-mg BID group = 3.3%, 2-mg/5-mg group = 2.6%, 7-mg group = 5%). There was one case of weight decrease in the LTE study as well.

Mean changes in weight in the LTE study are presented in Figure 28.

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Figure 28. Mean Change From Baseline in Weight (kg) (Long-Term Extension Study TAK-861-2003, NT1 Safety Set, Data Cutoff: August 29, 2025)



Number of Subjects (n):

	Week 12	Week 38	Week 52	Week 78	Week 104
0.5 mg BID	12	8	9	1	—
1 mg BID	50	2	—	1	5
2 mg BID	218	55	66	15	31
2 mg / 5 mg	28	17	7	—	—
7 mg QD	27	14	5	—	—
Overall	335	96	87	17	36

Error bars represent ±1 SD. "—" indicates no subjects at that visit for the treatment group.

Source: Clinical reviewer created, from data in Applicant's CSR Study TAK-861-2003, Table 15.3.5.3.1

The LTE baseline is defined as the last non-missing weight value prior to the first LTE dose (overall mean: 80.9 kg). Briefly, small and stable increases in mean weight from LTE baseline were observed across all dosage groups and timepoints, ranging from approximately +1.6 to +1.8 kg through Week 52, with a modest numerical increase at Weeks 78 and 104 that is likely attributable to the substantially smaller sample sizes at those visits rather than a progressive drug effect. Across all timepoints and dosage groups, weight changes were small in absolute terms and did not suggest a clinically meaningful effect of long-term oveporexton treatment on body weight. The magnitude of weight change observed in the LTE is broadly consistent with that seen in the oveporexton-treated arms of the pivotal studies (placebo-treated patients gained a mean of 2.3 kg over the 12-week period in the pivotal studies), though direct comparison and interpretation is limited by the absence of a placebo arm in the LTE and the declining sample sizes at later visits.

MAVs for respiratory rate and temperature vital signs were consistent with those in the pivotal trials pool.

Although the absence of a placebo-controlled arm in the LTE study limits the ability to definitively attribute these vital sign findings to background rates versus drug effect, the overall data are consistent with the pivotal trial placebo-controlled studies and do not reveal any new or unexpected safety signals. The low incidence of cardiovascular-related adverse

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events, minimal mean changes in blood pressure and heart rate, infrequent occurrence of markedly abnormal blood pressure values, and absence of dose-related patterns for weight increase over several months provide reassurance regarding the cardiovascular and general vital sign safety profile of oveporexton during long-term treatment.

90-Day Safety Update

Blood Pressure and Heart Rate

Since the original submission, TEAEs of palpitations, hypertension, and metabolic syndrome were reported in one participant each. These TEAEs were mild and did not require dosage changes.

Body Weight—Respiratory Rate—Temperature

No changes were observed in the 90-day safety update related to body weight, respiratory rate, or temperature.

Electrocardiograms

Pivotal Trial Pool

As described, standard 12-lead ECGs were collected and reviewed locally (per the protocol), including heart rate, sinus rhythm PR, QRS, and QTcF, with QTc analysis. QTcF values were flagged for a post-dose QTcF >450 msec in male or >470 msec in female, ΔQTcF ≥60 msec, and QT ≥500 msec. ECG was measured at Day 1, Week 4 (Day 28), Week 8 (Day 55) and Week 12 (Day 83) in both studies TAK861-3001 and TAK-861-3002.

As shown in Table 97, at Week 12, ECG parameters were generally similar across treatment groups. Mean changes from baseline in ECG heart rate, PR interval, QRS duration, and QTcF interval were small and comparable between the oveporexton 1-mg BID, 2-mg BID, and placebo groups.

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Table 97. Actual Values and Change From Baseline in ECG Parameters – Week 12 Pivotal Studies Pool (Safety Analysis Set)

	Placebo (N=76)		Oveporexton 1 mg BID (N=60)		Oveporexton 2 mg BID (N=136)		Oveporexton Overall (N=196)	
ECG Parameter/Statistic	Actual Value	Change From Baseline	Actual Value	Change From Baseline	Actual Value	Change From Baseline	Actual Value	Change From Baseline
ECG Heart Rate (beats/min)								
n	69	69	57	57	130	130	187	187
Mean (SD)	69.3 (12.7)	5.7 (11.0)	69.2 (12.7)	5.4 (13.0)	69.4 (11.7)	4.2 (12.8)	69.3 (12.0)	4.6 (12.8)
Median	69.0	5.0	69.0	4.0	68.0	5.0	68.0	5.0
Min, Max	42, 94	-22, 32	44, 101	-33, 53	44, 109	-39, 52	44, 109	-39, 53
PR Interval (ms)								
n	69	69	57	57	130	130	187	187
Mean (SD)	154.1	-5.3 (13.6)	160.3	-2.8 (11.8)	152.4	-3.4 (13.8)	154.8	-3.2 (13.2)
Median	153.0	-4.0	159.0	-2.0	149.0	-4.0	153.0	-3.0
Min, Max	106, 199	-54, 25	124, 205	-25, 30	115, 278	-61, 37	115, 278	-61, 37
QRS Duration (ms)								
n	69	69	57	57	130	130	187	187
Mean (SD)	92.2 (8.7)	-0.7 (7.4)	91.9 (8.3)	0.4 (7.0)	90.5 (7.7)	-1.4 (6.7)	90.9 (7.9)	-0.8 (6.8)
Median	93.0	0.0	93.0	1.0	89.0	-1.0	91.0	0.0
Min, Max	66, 107	-16, 22	73, 107	-19, 22	77, 115	-17, 14	73, 115	-19, 22
QTcF Interval (ms)								
n	69	69	57	57	130	130	187	187
Mean (SD)	395.5 (14.0)	0.9 (15.5)	393.9 (20.9)	-0.9 (16.0)	393.7 (19.0)	-1.0 (15.5)	393.7 (19.5)	-0.9 (15.6)
Median	394.0	1.0	393.0	-1.0	393.0	-1.5	393.0	-1.0
Min, Max	361, 428	-37, 33	343, 438	-39, 39	348, 434	-53, 60	343, 438	-53, 60

Source: Clinical Reviewer's created, modified from Applicant's "TAK-861-iss-safety-tables" document, Table 2.5.1.5.

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We then explored MAVs in ECG results at all postdose visits:

- PR interval: More subjects in the oveporexton group (4.6%, 9/195) had PR interval ≥200 msec compared to 1.3% (1/76) in the placebo group, and this did not appear to be dose-related (there was a higher percentage in the 1 mg BID group compared to the 2-mg BID group, 6.8% versus 3.7%, respectively). Per the Applicant's report, none were assessed as clinically significant.
- QRS duration: A slightly higher percentage of participants in the oveporexton group, 16.9% (33/195, equally distributed between 1-mg BID and 2-mg BID subgroups), had a QRS interval ≤80 msec versus 13.2% (10/76) in the placebo group. None were assessed as clinically significant.
- QTcF interval: One subject in the oveporexton group (in the 2-mg BID subgroup) had a QTcF interval change from baseline ≥60 msec, compared to no participants in the placebo group. This was not assessed as clinically significant.

Regarding ECG interpretation, the percentage of participants with "abnormal" ECG readings was similar across groups (Baseline: 6.6% placebo versus 10.2% oveporexton; Week 4: 11.1% placebo versus 10.4% oveporexton) or slightly higher in the placebo group compared to the oveporexton group (Week 8: 10% placebo versus 6.3% oveporexton; Week 12: 13% placebo versus 4.8% oveporexton).

However, there was one participant (Participant ID (b) (6)) receiving oveporexton 1 mg BID whose abnormal ECG was considered clinically significant: this participant had clinically significantly abnormal ECG results at Baseline and through Week 8 of the trial which were not considered a TEAE. Given that the participant had a clinically significant abnormal ECG at Baseline, it is unlikely this was related to study drug. An IR was sent to the Applicant to clarify why this participant was enrolled in the study despite having a clinically significant abnormal ECG at Baseline. The Applicant responded clarifying that the participant was appropriately enrolled, as the observed finding—a T wave inversion at the baseline visit—did not meet any protocol-defined exclusion criteria. Specifically, the only ECG-related exclusion criterion in the TAK-861-3001 protocol pertained to QTcF prolongation, and there were no exclusion criteria specific to T wave inversion. The Applicant further noted that the participant had no relevant cardiac medical history that would have precluded enrollment. Importantly, the finding resolved by the end of the study, with the Week 12 ECG reported as normal, and the participant successfully completed the trial. This clinical reviewer considers the Applicant's response satisfactory.

Of note, when each pivotal trial was assessed separately, no trends were observed. For example, the slightly higher percentage of longer PR intervals and shorter QRS durations in the oveporexton group was due to a few subjects in Study 3001. Study 3002 had percentages comparable to placebo.

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Other Integrated Summary of Safety Studies

TAK-861-2003

In TAK-861-2003, no clinically significant ECG abnormalities were reported.

90-Day Safety Update

Two clinically significant ECG abnormalities were reported since the original submission:

- A 46-year-old female participant had ECGs on trial Days 14 and 28 showing first-degree atrioventricular (AV) block, which were assessed as abnormal and clinically significant. However, the participant had a documented medical history of first-degree AV heart block dating to (b) (6).

The ECG findings observed during the trial are consistent with her preexisting condition and do not represent a new or treatment-emergent abnormality.

- A 37-year-old male participant had a markedly abnormal PR interval (>200 msec) on trial Day 182, with a recorded value of 203 msec, which was assessed as abnormal and clinically significant. The participant's medical history included gastroesophageal reflux disease, pharyngitis, obesity, Achilles tendinitis, obstructive sleep apnea syndrome, lumbar spondylolisthesis, and seasonal allergies. The ECG was interpreted as first-degree AV block, and a corresponding adverse event was reported and assessed as mild and related to trial intervention.

We cannot exclude whether this TEAE was related to the drug. However, the finding represents a nonserious, asymptomatic, isolated ECG abnormality with no evidence of progression to higher-grade AV block, and does not raise further concerns.

Cardiac Safety-Interdisciplinary Review Team (IRT) Consult

Per the Cardiac Safety-Interdisciplinary Review Team (IRT) consult review dated December 18, 2024, of the cardiac safety report for Study TAK-861-1001 (QT evaluation report):

- "TAK-861 did not prolong the QTcF interval in this clinical QTc assessment based on a Phase 1 study (TAK-861-1001) – see Table 1 for overall results. The data from the QTc assessment can be used as a substitute for a thorough QT study (ICH E14 Q&A 5.1)."
- "We agree that TAK-861 does not have a QTc prolonging effect. Therefore, a dedicated TQT study is not necessary, and routine ECG monitoring as clinically indicated is acceptable for clinical studies."

In summary, the ECG safety profile of oveporexton in the pivotal trial pool appears acceptable. Mean changes from baseline in ECG parameters at Week 12 were small and comparable across treatment groups.

Although slightly higher percentages of oveporexton-treated subjects had markedly abnormal PR intervals and shorter QRS durations compared to placebo, none were assessed as clinically

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significant. These findings were not dose-related and were driven by a few subjects in Study 3001; Study 3002 showed percentages comparable to placebo.

One participant with a preexisting clinically significant abnormal ECG at baseline was enrolled and maintained abnormal findings through Week 8. An IR has been sent to clarify the rationale for this enrollment. Given the preexisting condition, these findings are unlikely related to study drug.

The Cardiac Safety-IRT concluded that oveporexton does not prolong the QTcF interval based on the Phase 1 QTc assessment study, which can substitute for a thorough QT study per ICH E14 Q&A 5.1.

In conclusion, overall, the ECG data do not raise significant safety concerns for oveporexton.

Immunogenicity/Hypersensitivity

Pivotal Trial Pool

Overall, the rates of potential hypersensitivity-related AEs were higher in the oveporexton group than placebo, with a dose-dependent trend: 4.6% versus 0% oveporexton overall group versus placebo, all events occurred in the 2-mg BID group (four participants reported rash, one participant reported macular rash, one reported eczema, one reported erythema, and two reported hot flush). None of these events were serious, and none required treatment discontinuation.

An IR was sent to the Applicant requesting individual narratives for all participants who experienced potential hypersensitivity-related AEs, to better characterize the nature and clinical context of these events. Upon review of the narratives provided (summarized in Table 98), the clinical reviewer notes that in the majority of cases, a plausible alternative explanation was identified.

Specifically:

- Macular rash in Participant (b) (6), although assessed as related by the investigator, occurred in the context of a longstanding history of seasonal allergies and ongoing antihistamine use
- Eczema in Participant (b) (6) had a late onset (Trial Day 64)
- Erythema in Participant (b) (6), although severe, occurred after 9 weeks of stable dosing and in close temporal proximity to metronidazole use, a medication with a known association with localized erythema, and resolved with corticosteroid treatment
- Hot flushes in Participants (b) (6) were most plausibly attributable to menopause-related vasomotor symptoms and concomitant hormone therapy, respectively, rather than to mast cell release of histamine in response to a hypersensitivity reaction
- Rash in Participant (b) (6) appeared to be associated with alcohol consumption rather than study drug

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- Rash in Participant (b) (6) had a delayed onset (Trial Day 53) and resolved with antihistamine treatment without dosage modification
- Rash in Participant (b) (6), although assessed as related by the investigator, occurred in a participant with a known history of mild allergic reactions and contact dermatitis, suggesting underlying allergic sensitivity as a more likely etiology

Notably, in the cases where rash occurred early in the course of treatment—which would be more temporally consistent with a drug hypersensitivity reaction—alternative explanations were also present, except for the rash in Participant (b) (6), for which a possible association to the study drug cannot be excluded, although its clinical characteristics (localized, non-progressive, no systemic symptoms) make a drug-related etiology unlikely.

Across all cases, none of the events were serious or severe (with the exception of the erythema in Participant (b) (6), which was severe but, as noted above, attributed to concomitant metronidazole use), and none required treatment discontinuation or dosage modification.

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Table 98. Summary of Events Assessed for Potential Hypersensitivity in Participants Treated with Oveporexton—Pivotal Studies Pool (Safety Analysis Set)

Participant ID	Age/ Sex	Treatment Group (Oveporexton)	Reported Term/ Preferred Term	Severity	Relationship to Trial Intervention	Event Outcome	Action Taken	Trial Day	Event Duration	Reasons Why Not Related (Alternative Explanation/Late Onset)
TAK-861-3001										
(b) (6)	48 F	2 mg BID	Macular rash/ Rash macular	Mild	Not related	Resolved	Dosage not changed	6	3 days	Longstanding history of seasonal allergies and ongoing antihistamine use
	20 F	2 mg BID	Eczema face/ Eczema	Mild	Not related	Not Resolved	Dosage not changed	64	Ongoing	Late onset
	21 F	2 mg BID	Facial redness/ Erythema	Severe	Not related	Resolved	Dosage not changed	63	12 days	Recent metronidazole use, which has an established association with localized erythema/late onset
	45 F	2 mg BID	Hot flushes/ Hot flush	Mild	Not related	Resolved	Dosage not changed	8	70 days	Menopause-related vasomotor symptoms
	25 F	2 mg BID	Hot flush/ Hot flush	Mild	Not related	Resolved	Dosage not changed	1	55 days	Concomitant hormone therapy (estrogen and dydrogesterone) as plausible etiology for vasomotor symptoms

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Participant ID	Age/ Sex	Treatment Group (Oveporexton)	Reported Term/ Preferred Term	Severity	Relationship to Trial Intervention	Event Outcome	Action Taken	Trial Day	Event Duration	Reasons Why Not Related (Alternative Explanation/Late Onset)
TAK-861-3002										
(b) (6)	22 F	2 mg BID	Skin rash on the back/ Rash	Mild	Likely related	Resolved	Dosage not changed	14	71 days	Localized, not progressive
	23 M	2 mg BID	Facial rash when taking alcohol (10 to 20 g)/ Rash	Mild	Not related	Resolved	Dosage not changed	2	42 days	Rash associated with alcohol consumption
	27 F	2 mg BID	Rash on the inside of both thighs/ Rash	Mild	Not related	Resolved	Dosage not changed	53	21 days	Late onset
	29 F	2 mg BID	Mild rash in larger parts of body/ Rash	Mild	Not related	Resolved	Dosage not changed	8	21 days	History of mild allergic reactions and contact dermatitis suggesting underlying allergic sensitivity

Abbreviations: AE, adverse event; BID, twice daily; F, female; M, male; PT, preferred term.
Source: Clinical Reviewer's created, modified from Table 1.a in Applicant's response to Information Request (IR) dated April 27, 2026.

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Taken together, this clinical reviewer does not consider the reported events likely related to oveporexton. Although the numerically higher rate of potential hypersensitivity-related AEs in the oveporexton group compared to placebo (4.6% versus 0%) is noted and warrants attention, the small sample size precludes definitive conclusions at this time. Furthermore, the incidence of rash events in the LTE study was similar to that observed in the pivotal trials (see next paragraph), providing additional reassurance and suggesting that this finding does not raise a significant safety concern at this time. Rash will be captured in the label's adverse reactions table. Post-marketing experience may, over time, offer additional information on rash.

Other Integrated Summary of Safety Studies

TAK-861-2003

TEAEs of rash, urticaria, pruritus, and eczema were also reported in the long-term extension study (TAK-861-2003; Table 99) at rates similar to those observed in the Pivotal Trial Pool, which, despite the inherent limitations of cross-study comparisons as previously described, provides additional reassurance that the rate of potential hypersensitivity-related events does not appear to increase with longer duration of exposure.

Table 99. Adverse Events: Skin and Subcutaneous Tissue Disorders – LTE TAK-861-2003 Study

System Organ Class Preferred Term	OVE 0.5 mg N=28 n (%)	OVE 1 mg N=109 n (%)	OVE 2 mg N=304 n (%)	OVE 2/5 mg N=39 n (%)	OVE 7 mg N=40 n (%)	Overall OVE N=356 n (%)
Skin and subcutaneous tissue disorders (SOC)						
Rash	1 (3.6)	3 (2.8)	3 (1.0)	0	0	6 (1.7)
Urticaria	0	0	1 (0.3)	1 (2.6)	2 (5.0)	4 (1.1)
Pruritus	1 (3.6)	0	1 (0.3)	0	0	2 (0.6)
Eczema	0	0	0	0	1 (2.5)	1 (0.3)
Total (any of the above)*	2 (7.1)	3 (2.8)	5 (1.6)	1 (2.6)	3 (7.5)	13 (3.7)

* Total row represents the sum of individual event counts across Rash, Urticaria, Pruritus, and Eczema. Subjects experiencing more than one of these events may be counted more than once; the true number of unique subjects may be lower.
Abbreviations: SOC = System Organ Class. N = total number of subjects per treatment group; n = number of subjects with event; OVE = oveporexton
Source: Clinical Reviewer's created

90-Day Safety Update

A few additional cases of TEAEs potentially related to drug hypersensitivity were reported in the 90-day safety update (new cases PT: rash n=6, pruritus n=2, eczema n=1, macular rash n=1, pruritic rash n=2).

Overall, across the clinical development program, TEAEs potentially related to hypersensitivity were observed at a higher rate in the oveporexton group compared to placebo, and exclusively in the 2-mg BID arm, raising the question of whether these events could represent true hypersensitivity responses to oveporexton.

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However, upon review of the individual narratives provided by the Applicant in response to an IR, plausible alternative explanations were identified for the majority of cases, and this clinical reviewer does not consider the reported events likely related to oveporexton. Similar events were reported in the LTE study at rates consistent with those observed in the pivotal trials, which, despite the inherent limitations of cross-study comparisons in the absence of a placebo arm, provides additional reassurance that the rate of potential hypersensitivity-related events does not appear to increase with longer duration of exposure.

Across all cases in the clinical development program, none of the events were serious, none were severe with the exception of one case of erythema attributed to concomitant metronidazole use, and none led to treatment discontinuation or dosage modification. This clinical reviewer considers this finding to be of low concern at this time, though continued monitoring through post-marketing experience is warranted. Rash will be captured in labeling in the adverse reactions table.

C-SSRS

Pivotal Trial Pool

No participants reported at least one endorsement of Item 4 or 5 in the C-SSRS at any postdose visit.

Other Integrated Summary of Safety Studies

TAK-861-2003

No participants reported at least one endorsement of Item 4 or 5 in the C-SSRS at any postdose visit.

A 36-year-old female participating in the LTE trial experienced self-injurious behavior 12 days after the last dose of oveporexton, in association with a stressful traumatic life event. No associated suicidal ideation or behavior (C-SSRS items 4 or 5) was reported. The event was assessed as moderate in severity and resolved within 1 day. This participant had previously withdrawn from the trial due to increased cataplexy

The event is likely not related to the study drug, given that the participant had stopped treatment 12 days prior, and there is an alternative explanation (traumatic life event).

90-Day Safety Update

No new clinically significant adverse trends were observed in the evaluation of C-SSRS since the original TAK-861-2003 clinical study report submission.

Overall, across the oveporexton development program, there is no signal of suicidal ideation or behavior based on C-SSRS assessment. The single case of self-injurious behavior identified in the LTE trial is not considered drug-related, as discussed above. Overall, the available data do not raise concern for suicidality risk associated with oveporexton treatment.

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8.2.5. Analysis of Submission-Specific Safety Issues

Adverse Events of Special Interest

In part due to issues with other drugs in development in the same class, the Applicant identified adverse events of special interest (AESI) for oveporexton that included insomnia, hepatic function abnormalities, urinary symptoms, visual disturbances, and psychiatric disorders, including suicidal ideation and behavior. These AESIs were selected based on mechanistic, pharmacological class, and clinical safety considerations. Insomnia was identified as an AESI given the mechanism of action of oveporexton as an orexin receptor agonist, since dysregulation of the orexin system plays a central role in sleep-wake regulation. Hepatic function abnormalities were designated as an AESI because a prior investigational agent with a similar mechanism of action was associated with reported cases of drug-induced liver injury (DILI), leading to the interruption of its development. Urinary symptoms were included as an AESI due to a recognized class effect, as urinary frequency has been observed with other medications acting on the OX2 receptor, though the exact pathophysiologic mechanism of voiding dysfunction with OX2R antagonism remains unclear. Visual disturbances were included based on reports of such events with another agent in the same pharmacological class. Psychiatric disorders, including suicidal ideation and behavior, were included given that oveporexton is a new molecular entity acting on the central nervous system.

Hepatic function abnormalities and urinary symptoms are addressed separately by the Division of Hepatology (DILI team) and the Division of Urology and Gynecology (DUOG), respectively; the reader is referred to their corresponding consult reviews for a detailed discussion of these events. Briefly, the DILI team review found no clinically significant hepatotoxicity of concern in the phase 3 or long-term extension trials for oveporexton, no cases of DILI were identified, there were no substantial imbalances in liver-related adverse events or enzyme elevations versus placebo, and all elevated aminotransferase cases were attributed to non-DILI causes (primarily myopathy, acetaminophen use, or mononucleosis). The DUOG review found that urologically-relevant TEAEs were common across the clinical program, with urinary frequency (pollakiuria) occurring in approximately 57% and urinary urgency (micturition urgency) in 16% of oveporexton-treated patients in the pivotal trials versus 5% and 1% in placebo, respectively; these events were generally mild-to-moderate, onset was typically within 1 to 2 days of treatment initiation, and they are consistent with the drug's on-target pharmacological mechanism.

Insomnia and psychiatric TEAEs and visual disturbances are discussed in the sections that follow.

8.2.5.1. Insomnia

Pivotal Trial Pool

Insomnia was among the most frequently reported AESIs in the oveporexton treatment groups. As shown in Table 100, a notably high proportion of participants experienced at least one insomnia event during the study: 55.0% in the 1-mg BID group and 60.3% in the 2-mg BID

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group, yielding an overall rate of 58.7% across all oveporexton-treated participants, compared to only 1.3% in the placebo group. Although the rate appeared slightly higher in the 2-mg BID group relative to the 1-mg BID group, the difference between dosages is small and should be interpreted with caution, as it is unclear whether it represents a true dose-response relationship or reflects random variability.

Table 100. Insomnia – Pivotal Studies Pool Safety Analysis Set

AESI Category Preferred Term	Placebo (N=76) n (%)	Oveporexton 1 mg BID (N=60) n (%)	Oveporexton 2 mg BID (N=136) n (%)	Oveporexton Overall (N=196) n (%)
Insomnia	1 (1.3)	33 (55.0)	82 (60.3)	115 (58.7)
Insomnia	1 (1.3)	32 (53.3)	78 (57.4)	110 (56.1)
Middle insomnia	0	0	3 (2.2)	3 (1.5) 1.7
Initial insomnia	0	1 (1.7)	1 (0.7)	2 (1.0) 1.0

Abbreviations: AESI = adverse event of special interest; BID = twice daily; n = number of subjects with event; N = total number of subjects in treatment group; TEAE = treatment-emergent adverse event.
Note: Table displays insomnia-related AESI only.
Source: Clinical Reviewer's created, modified from Applicant's table 2.2.9.5 in TAK-861-iss-safety-tables.pdf document

Regarding the onset and duration of insomnia events (Table 101; data obtained from participants' diaries), the majority of events began within the first 2 days of treatment initiation, with approximately 90% of insomnia events in the oveporexton overall group starting within Days 1 and 2, and an additional ~4% starting between Days 2 and 7. This early onset pattern suggests that insomnia is likely a pharmacodynamic effect of the drug, consistent with its mechanism of action as an orexin receptor agonist. In terms of duration, most insomnia events were short-lived, with approximately 63% resolving within the first week of onset. A smaller proportion lasted between 1 and 8 weeks. Notably, however, approximately 17% of insomnia events were still ongoing at the time of study completion, indicating that for a subset of participants, insomnia persisted throughout the duration of the trial. Importantly, none of these insomnia events resulted in study discontinuation or were classified as serious adverse events.

Table 101. Start Day and Duration of Insomnia—Pivotal Studies Pool Safety Analysis Set

Start Day and Duration of Insomnia	Placebo (N=76) n (%)	Oveporexton 1 mg BID (N=60) n (%)	Oveporexton 2 mg BID (N=136) n (%)	Oveporexton Overall (N=196) n (%)
Number of insomnia events	1	33	86	119
1 – 2	0	31 (93.9)	77 (89.5)	108 (90.8)
>2 – 7	0	1 (3.0)	4 (4.7)	5 (4.2)
>14 – 28	0	0	3 (3.5)	3 (2.5)
>28 – 56	1 (100)	1 (3.0)	1 (1.2)	2 (1.7)
>56 – End of study	0	0	1 (1.2)	1 (0.8)
1 – 7	1 (100)	24 (72.7)	51 (59.3)	75 (63.0)
>7 – 14	0	1 (3.0)	9 (10.5)	10 (8.4)
>14 – 28	0	0	3 (3.5)	3 (2.5)
>28 – 56	0	1 (3.0)	4 (4.7)	5 (4.2)

Start Day and Duration of Insomnia	Placebo (N=76) n (%)	Oveporexton 1 mg BID (N=60) n (%)	Oveporexton 2 mg BID (N=136) n (%)	Oveporexton Overall (N=196) n (%)
>56 – Study completion	0	1 (3.0)	4 (4.7)	5 (4.2)
Ongoing	0	6 (18.2)	15 (17.4)	21 (17.6)

Abbreviations: BID = Twice Daily; m = Number of events
Participants with NT1 from the Studies TAK-861-3001 and TAK-861-3002.
Denominator is number of insomnia events.
Source: Applicant's table 2.2.12.5 in TAK-861-iss-safety-tables.pdf document

With respect to the nature of insomnia symptoms experienced (Table 102) (data obtained from participants' diaries), among participants who experienced at least one insomnia event, the most commonly reported symptoms were trouble falling asleep (83.5% in the oveporexton overall group) and trouble staying asleep (76.5%), with more than half of affected participants (59.1%) experiencing both simultaneously. Approximately 55% of participants also reported trouble falling back asleep after waking up. While 34.8% of participants reported feeling bothered by their insomnia, only 14.8% reported that their daytime activities were affected, suggesting that the functional impact of insomnia on daily life was limited for the majority of those affected.

Table 102. Insomnia Symptoms—Pivotal Studies Pool Safety Analysis Set

Insomnia Symptom	Placebo (N=76) n (%)	Oveporexton 1 mg BID (N=60) n (%)	Oveporexton 2 mg BID (N=136) n (%)	Oveporexton Overall (N=196) n (%)
Subjects who experienced insomnia	1 (1.3)	33 (55.0)	82 (60.3)	115 (58.7)
Trouble falling asleep	0	30 (90.9)	66 (80.5)	96 (83.5)
Trouble staying asleep	1 (100)	23 (69.7)	65 (79.3)	88 (76.5)
Trouble falling and staying asleep	0	20 (60.6)	48 (58.5)	68 (59.1)
Trouble falling back asleep after waking up	1 (100)	16 (48.5)	47 (57.3)	63 (54.8)
Daytime activities affected by the insomnia	0	7 (21.2)	10 (12.2)	17 (14.8)
Feels bothered by the insomnia	0	9 (27.3)	31 (37.8)	40 (34.8)

Abbreviation: BID = Twice Daily.
Participants with NT1 from the Studies TAK-861-3001 and TAK-861-3002.
n is the number of subjects who experienced insomnia symptoms at least once during the study.
Subjects are counted only once in each treatment column if they experienced the symptom at least once.
Symptoms are reported only for the subset of participants with at least one insomnia event.
Percentages for the subjects who experienced insomnia are based on all the subjects in the Safety Set within each column.
Percentages for the questionnaires are based on all subjects who experienced insomnia in the Safety Set within each column.
Subjects are counted in 'Trouble Falling and Staying Asleep' as long as they experienced each of these two symptoms at least once.
Source: Applicant's table 2.2.16.5 in TAK-861-iss-safety-tables.pdf document

Other Integrated Summary of Safety Studies

TAK-861-2003

In the LTE study (TAK-861-2003), new insomnia events were reported by a relatively small proportion of participants (68 [19.1%]). Of note, approximately half of these events occurred

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in participants who had been on placebo during the parent trials and were therefore being exposed to oveporexton for the first time in the LTE. Additionally, some events may be attributable to dosage adjustments during the extension period. Consistent with findings from the pivotal studies, the onset of new insomnia events in the LTE was typically within the first 1 to 2 days of initiating or modifying treatment, further supporting the early pharmacodynamic nature of this effect.

With regard to symptom burden, the functional impact of insomnia in the LTE appeared limited. The majority of participants who reported new insomnia events (71.1%) indicated that their daytime activities were not affected, and approximately half (46.7%) did not find the insomnia bothersome. Although a proportion of events resolved within the first 7 days, some were longer in duration. The interpretation of event duration in the LTE is subject to certain limitations, including the potential confounding effect of dosage changes, the overall lower number of new events reported, and differences in the timing of adverse event collection relative to the pivotal trials.

90-Day Safety Update

All new insomnia events (middle insomnia, initial insomnia) reported since the original submission were mild to moderate in intensity and resolved. No participants have discontinued trial intervention due to insomnia events since the original submission.

Overall, although insomnia was reported at a strikingly high frequency in oveporexton-treated participants (~58% versus 1.3% in placebo), the available data suggest that these events were predominantly short-lasting and of limited clinical impact. Most events resolved within the first week, and none resulted in study discontinuation or were classified as serious. Notably, despite more than one-third of affected participants reporting feeling bothered by their insomnia, fewer than 15% indicated that their daytime activities were meaningfully affected. Overall, both participants and principal investigators appear to have considered these events manageable and not sufficiently burdensome to warrant stopping treatment. Given the high frequency of insomnia relative to placebo, insomnia will be included in the Warnings and Precautions section of labeling to ensure that prescribers are informed of this risk and can counsel patients appropriately.

8.2.5.2. Psychiatric Disorders

Pivotal Trial Pool

Beyond insomnia, this reviewer conducted a detailed assessment of PTs related to, or potentially related to, psychiatric disorders. This evaluation included also PTs captured under other SOC domains that may nonetheless have psychiatric relevance—for example, psychomotor hyperactivity (coded under Musculoskeletal Disorders) and cataplexy (coded under Nervous System Disorders). In the pivotal trial pool, single cases of depressive symptoms, anhedonia, nervousness, restlessness, psychomotor hyperactivity, anxiety, and hypnagogic hallucination were reported in the oveporexton groups, with no such events observed in the placebo group. Cataplexy was reported in both treatment arms (n=4, 2% in

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the oveporexton group and n=1, 1.3% in the placebo group), which is not unexpected given the underlying narcolepsy diagnosis in this population. As anticipated, somnolence/ hypersomnia was reported exclusively in the placebo group (n=2, 2.6%), consistent with the expected pharmacological effect of oveporexton.

Other Integrated Summary of Safety Studies

TAK-861-2003

Beyond the self-injurious behavior already discussed in the C-SSRS and suicidal behavior section, six participants (1.7%) reported anxiety, and one participant each reported major depression (0.3%) and stress (0.3%).

90-Day Safety Update

Neither depression nor anxiety was mentioned in the 90-Day Safety Update.

In summary, the small sample sizes across treatment groups limit the ability to draw meaningful conclusions from these individual events. When considering PTs that may collectively reflect anxiety-related symptoms, using FDA query criteria, no difference in anxiety was noted. Overall, the available data do not suggest that oveporexton has a meaningful adverse effect on psychiatric domains beyond insomnia, which is discussed separately. Continued monitoring of psychiatric TEAEs in the post-marketing setting would nonetheless be prudent given that this is a new CNS-acting agent.

8.2.5.3. Visual Disturbance

Pivotal Trial Pool

The percentage of visual disorders was similar between placebo and oveporexton groups (2.6% in each group). However, examination of individual PTs reveals a potential signal for vision blurred, which occurred in three patients (1.5%) in the oveporexton group compared to 0 cases in the placebo group (Table 103). Additionally, dry eye was reported in two patients (1.0%) in the oveporexton group with no cases in placebo.

All these events were nonserious, mild to moderate, and did not result in trial intervention discontinuation. No consistent patterns in latency or duration were observed. All events resolved while participants were on trial treatment.

Table 103. Adverse Events: Vision-Related Symptoms

System Organ Class Preferred Term	Placebo N=76 n (%)	Oveporexton 1 mg N=60 n (%)	Oveporexton 2 mg N=136 n (%)	Oveporexton 1 to 2 mg N=196 n (%)
Eye disorders (SOC)	2 (2.6)	0	5 (3.7)	5 (2.6)
Vision blurred	0	0	3 (2.2)	3 (1.5)
Drye eye	0	0	2 (1.5)	2 (1.0)
Blepharitis	1	0	0	0

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System Organ Class Preferred Term	Placebo N=76 n (%)	Oveporexton 1 mg N=60 n (%)	Oveporexton 2 mg N=136 n (%)	Oveporexton 1 to 2 mg N=196 n (%)
Asthenopia	1	0	0	0

Source: Clinical Reviewer's created.

Other Integrated Summary of Safety Studies

TAK-861-2003

No safety concerns related to visual disturbance were identified with long-term oveporexton exposure.

90-Day Safety Update

No safety concerns related to visual disturbance were identified with long-term oveporexton exposure.

In summary, although vision blurred and dry eye occurred exclusively in the oveporexton group, the overall safety profile of these events is reassuring. All cases were mild-to-moderate in severity, nonserious, self-limited, and did not lead to treatment discontinuation. The absence of consistent temporal patterns and the resolution of all events during continued treatment further support a favorable benefit-risk assessment.

This focused assessment of visual disturbances was conducted post hoc, after study completion, following reports of visual safety signals with another molecule in the same class from a different commercial development program. Consequently, the pivotal trials for oveporexton did not include protocol-specified ophthalmologic assessments or systematic visual function evaluations. The reported incidence of visual disturbances may therefore be underestimated due to the reliance on spontaneous adverse event reporting without dedicated ophthalmologic monitoring.

Nonetheless, at this time, these findings do not raise significant safety concerns. The incidence and characteristics of visual disturbances can be monitored with routine post-marketing surveillance to ensure no emerging safety signals with broader exposure in real-world use, particularly given the limitations of the available clinical trial data in this domain.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

See Section 8.2.4. Safety Results–C-SSRS for discussion of results related to C-SSRS.

8.2.7. Safety Analyses by Demographic Subgroups

As shown in Table 104, the overall incidence TEAEs was generally consistent across demographic subgroups, with no evidence of meaningful heterogeneity in the safety profile of oveporexton across the populations examined. (As a word of general caution, these are

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post hoc safety analyses relying on limited sample size populations and are therefore of limited interpretability.)

With respect to sex, the incidence of any TEAE was broadly comparable between female (86% for oveporexton 1 to 2 mg BID combined versus 54% for placebo) and male participants (88% versus 44%), with risk differences of similar magnitude in both subgroups, suggesting no meaningful differential in the overall adverse event burden by sex.

With respect to race, a meaningful comparison is limited to the White and Asian subgroups, as all other racial categories (American Indian or Alaska Native, Black or African American, Multiple, and Unknown) had sample sizes too small to draw reliable conclusions. Among White participants, the incidence of any TEAE was 90% for oveporexton (1 to 2 mg BID combined) versus 59% for placebo, and among Asian participants, 85% versus 46%, indicating a broadly consistent pattern of adverse event incidence across these two racial subgroups.

Finally, the incidence of TEAEs was comparable between participants enrolled in the United States (88% for oveporexton versus 50% for placebo) and those enrolled outside the United States (87% versus 49%), suggesting that the safety profile of oveporexton is consistent across geographic regions and is not driven by any country-specific effect.

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Table 104. Overview of Adverse Events by Demographic Subgroups, Safety Population, Trials TAK-861-3001 and TAK-861-3002

Characteristic	Placebo N=76 n/Ns (%)	Oveporexton 1 mg N=60 n/Ns (%)	Oveporexton 2 mg N=136 n/Ns (%)	Oveporexton 1 to 2 mg N=196 n/Ns (%)
Any AE	37/76 (48.7)	52/60 (86.7)	119/136 (87.5)	171/196 (87.2)
Sex				
Female	20/37 (54.1)	22/27 (81.5)	73/83 (88.0)	95/110 (86.4)
Male	17/39 (43.6)	30/33 (90.9)	46/53 (86.8)	76/86 (88.4)
Race				
American Indian or Alaska Native	0/0 (NA)	0/0 (NA)	1/1 (100)	1/1 (100)
Asian	6/13 (46.2)	9/10 (90.0)	20/24 (83.3)	29/34 (85.3)
Black or African American	2/4 (50.0)	2/3 (66.7)	0/0 (NA)	2/3 (66.7)
White	20/34 (58.8)	14/16 (87.5)	50/55 (90.9)	64/71 (90.1)
Multiple	0/1 (0)	0/0 (NA)	0/0 (NA)	0/0 (NA)
Not reported	5/5 (100)	3/3 (100)	7/7 (100)	10/10 (100)
Unknown	4/19 (21.1)	24/28 (85.7)	41/49 (83.7)	65/77 (84.4)
Ethnicity				
Hispanic or Latino	1/3 (33.3)	4/5 (80.0)	4/5 (80.0)	8/10 (80.0)
Not Hispanic or Latino	26/48 (54.2)	20/23 (87.0)	64/72 (88.9)	84/95 (88.4)
Not reported	5/5 (100)	4/4 (100)	8/8 (100)	12/12 (100)
Unknown	4/11 (36.4)	24/28 (85.7)	19/23 (82.6)	43/51 (84.3)
Missing	1/9 (11.1)	0/0 (NA)	24/28 (85.7)	24/28 (85.7)
Location				
United States	4/8 (50.0)	6/7 (85.7)	9/10 (90.0)	15/17 (88.2)
Non-United States	33/68 (48.5)	46/53 (86.8)	110/126 (87.3)	156/179 (87.2)

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; NA, not applicable; N_s, total number of subjects for each specific subgroup
Duration is 12 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
The confidence interval of risk difference is estimated by the Miettinen and Nurminen method.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Source: Clinical Data Scientist's team; adae.xpt; Software: R

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These subgroup analyses are considered exploratory. The groups are severely unbalanced and underpowered for sex, race, and country subgroup comparisons. The Applicant has only one subject over age 65, which is one age group of interest (i.e., older adult subjects) from a differential safety perspective. As yet, we have no PK-related reason to expect any meaningful differences in AEs based on these subgroups.

8.2.8. Specific Safety Studies/Clinical Trials

8.2.8.1. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant did not provide human carcinogenicity data with this application.

During the review of the oveporexton clinical development program, two cases of breast cancer and one case of acute myeloid leukemia were identified in the LTE study TAK-861-2003, prompting an IR to the Applicant, asking them to report all cases of malignancy that occurred across the development program. In response, the Applicant clarified that a total of four malignancy cases had been identified (Table 105), all in the LTE study.

Table 105. Malignancy Cases in the Oveporexton Development Program

Participant ID/Age/Sex	MedDRA PT	Clinical Stage	Time to Onset	Investigator Causality Assessment
(b) (6) /48/Female	Breast Cancer	T2N1M0	579 days	Not related
/46/Female	Breast Cancer	cT2N0M0	607 days	Not related
/62/Female	Malignant Melanoma	Clinical Stage pT1a	126 days	Not related
/23/Male	Acute Myeloid Leukemia	Clinical stage not available pending follow up from the PI	245 days	Not related

Source: Applicant's response to Information Request (IR) dated May 15, 2026.

Cases were discussed with our experts in the Division of Oncology 1 (DO1) and the Division of Epidemiology 1 (DEPI1). Across all disciplines, including the nonclinical team, the consensus is that these cases are likely due to chance, for the following reasons:

- Negative nonclinical carcinogenicity studies: Oveporexton was not carcinogenic in the nonclinical studies.
- Biological plausibility is not established: The four cases span three histologically and etiologically distinct cancer types, all occurring within less than 2 years of drug exposure. There is currently no known mechanism by which selective orexin 2 receptor agonism would be expected to initiate or promote malignancy.
- Background malignancy risk in the narcolepsy population: A nationwide population-based cohort study by Tseng et al. (2015), reports a significantly elevated cancer risk in narcolepsy patients compared to the general population, independent of pharmacological treatment. This elevated background risk may account for the observed cases.

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An internal review of other premarketing studies evaluating drugs approved for patients with narcolepsy (i.e., sodium oxybate, mixed oxybate salts, and pitolisant) also noted similar frequencies of malignancy cases relative to this program, and no unusual post-marketing trends.

Based on the evidence to date, no additional regulatory action is warranted at this time. The Agency's conclusion is to continue routine postmarketing monitoring for malignancy as part of standard pharmacovigilance

Human Reproduction and Pregnancy

The studies conducted in this clinical development program excluded patients who were pregnant or who were unwilling to agree to use of contraception during study participation. Postmarketing studies related to the use of oveporexton during pregnancy and lactation will be required and are discussed in Section 13, Postmarketing Requirements and Commitment.

Pediatrics and Assessment of Effects on Growth

No clinical studies of oveporexton were conducted in the pediatric population. Three participants aged 16 to 17 were enrolled in the adult pivotal studies; however, their exposure to oveporexton and this sample was too limited to support any meaningful conclusions.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Controlled Substance Staff (CSS) team reviewed this application and did not note any major abuse potential signals in the studies. They have recommended Schedule IV for oveporexton based on the mechanism of action. See the CSS consult review for more details.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable as the drug is an NME and first-in-class (recently approved in China and Japan, not approved anywhere else globally) and not yet available for any indications.

Expectations on Safety in the Postmarket Setting

See Section 13, Postmarketing Requirements and Commitment. It is expected that use in the postmarket setting will include treatment of a broader range of patients than those enrolled in clinical trials (i.e., older patients and those with more medical comorbidities or concomitant medication use). In addition to assessing for safety findings in the broader general patient population, routine postmarketing pharmacovigilance will be important for assessing for adverse reactions too rare to be detected in the clinical development program.

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8.2.10. Integrated Assessment of Safety

Review of adverse events and laboratory, vital sign, and electrocardiogram data from the two placebo-controlled pivotal trials of oveporexton (TAK-861-3001 and TAK-861-3002), supplemented by data from the long-term extension study TAK-861-2003 and the broader integrated summary of safety database, reveals a safety profile that is largely consistent with the known pharmacological effects of OX2R agonism. The overall incidence of TEAEs was substantially higher in oveporexton-treated participants compared to placebo; however, this difference is driven predominantly by expected on-target pharmacodynamic effects rather than by unanticipated toxicities.

The most common adverse reactions for oveporexton were insomnia, pollakiuria, micturition urgency, and salivary hypersecretion, all occurring at substantially higher rates than placebo. These events are mechanistically consistent with OX2R agonism and its known effects on sleep-wake regulation, bladder function, and autonomic tone, and are therefore considered on-target pharmacological effects of the drug. Although insomnia events were predominantly of limited functional impact and urinary events were similarly manageable, their strikingly high frequency relative to placebo—and the potential for these effects to affect patients' quality of life and treatment adherence—warrants their inclusion in the Warnings and Precautions section of product labeling, to ensure that patients and prescribers are adequately informed prior to treatment initiation and can implement appropriate management strategies, including dosing timing optimization and sleep hygiene counseling for insomnia.

Discontinuations due to AEs were numerically slightly higher in the oveporexton group compared to placebo. The most clinically notable discontinuations involved cases of exercise-associated rhabdomyolysis in the oveporexton group, characterized primarily by laboratory findings—markedly elevated CPK and transaminases meeting protocol-defined discontinuation criteria—rather than clinical symptoms, with no renal impairment in any case. A broader pattern of CPK elevations above markedly abnormal value thresholds was observed at a numerically higher rate in oveporexton-treated participants compared to placebo across the pivotal trials, with a similar pattern persisting in the LTE study. Although the majority of CPK elevations were asymptomatic, transient, and attributable to physical activity—a confounder that is particularly relevant in this population given that effective treatment of narcolepsy may lead to increased physical activity and return to exercise—a causal contribution of oveporexton cannot be definitively excluded. Product labeling should address CPK elevations with appropriate guidance on patient counseling.

Hepatic enzyme elevations leading to discontinuation were observed at a low and comparable rate between oveporexton and placebo groups in the pivotal trials, with most cases having identifiable alternative etiologies. No cases met Hy's Law criteria across the development program, in contrast with similar products previously studied by the Applicant. The reader is referred to the DILI team review for a detailed assessment of hepatic safety. Similarly, urinary AEs are addressed in detail in the DUOG review.

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Laboratory findings were otherwise unremarkable. Beyond the CPK elevations noted above, a modest but detectable increase in LDL cholesterol and total cholesterol was observed in oveporexton-treated participants compared to placebo; however, the magnitude of these changes was small, triglycerides and HDL were largely unaffected, and no cardiovascular or lipid-related AEs were observed at a higher rate in the oveporexton arms. These findings are not considered clinically meaningful at this time so no warning is necessary; but the lab data will be briefly noted in Section 6 of labeling, and routine post-marketing pharmacovigilance monitoring is appropriate.

Vital sign assessments revealed transient increases in blood pressure and heart rate on the first day of treatment, which returned to near baseline by the end of the treatment period and no other trends were noticed on LTE study data as well. Product labeling should reflect the observed transient increases in blood pressure and heart rate.

In the LTE study, one death due to myocardial infarction and one non-fatal myocardial infarction were reported; the latter occurred approximately 13 hours after drug administration in the LTE, though the patient had already been exposed to oveporexton during the parent study. Both patients had significant pre-existing cardiovascular risk factors, including obesity and hypertension, and one was additionally a current smoker. Although these events warrant acknowledgment, a causal relationship to oveporexton is not established: no cardiovascular SAEs were observed in the placebo-controlled pivotal studies; QTc interval was unremarkable across the development program; and oveporexton did not demonstrate major exacerbation of cardiovascular risk factors—including blood pressure, heart rate, lipids, or glucose—beyond the transient first-day hemodynamic effects noted above or possible minor lipid increases over time.

A small number of malignancy cases were identified in the LTE study, spanning histologically and etiologically distinct cancer types. These cases are considered likely attributable to background incidence, given the absence of nonclinical carcinogenicity signals, the lack of biological plausibility for OX2R agonism-related oncogenesis, and the elevated background cancer risk reported in the narcolepsy population. Routine post-marketing pharmacovigilance for malignancy is appropriate.

The safety profile was generally consistent across demographic subgroups, though subgroup analyses are limited by small and unbalanced sample sizes. No meaningful pediatric safety data are available. Notably, the clinical development program enrolled virtually no participants aged 65 years and older, and the number of U.S.-enrolled participants was limited, leaving the safety profile in these groups not fully characterized. Post-marketing data will be essential to identify any safety signals specific to older patients, in whom age-related changes in pharmacokinetics, comorbidity burden, and polypharmacy may alter the risk profile, as well as any population-specific findings relevant to the broader U.S. patient population.

Overall, the safety profile of oveporexton is characterized predominantly by on-target pharmacological effects of OX2R agonism that are generally manageable and decrease in frequency with continued exposure. The absence of deaths or SAEs attributable to the drug in the placebo-controlled studies, the low discontinuation rate, the lack of QTc prolongation, the

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absence of clinically meaningful metabolic or hematologic toxicity, and the absence of suicidal ideation and behavior or any additional psychiatric signal are reassuring.

The key safety considerations that warrant attention in product labeling and post-marketing surveillance include insomnia, urinary symptoms, and salivary hypersecretion, as on-target or class-related effects, as well as CPK elevations. The overall safety profile is considered acceptable and manageable for the treatment of NT1, provided that appropriate labeling and routine post-marketing surveillance measures are implemented.

8.3. Statistical Issues

Potential for Functional Unblinding and Robustness of Efficacy Evidence

The relatively high incidence of TEAEs—notably insomnia and urinary symptoms, each occurring in approximately 50% of treated participants compared to near zero in the placebo group—raises the theoretical concern of functional unblinding, whereby participants and/or investigators may infer treatment assignment based on the presence or absence of these side effects. Of note, these potential adverse events were explicitly disclosed in the informed consent forms, meaning that participants were aware of their possibility prior to enrollment. This prior awareness may have further contributed to the potential for functional unblinding, as participants experiencing these symptoms could reasonably infer that they were receiving active treatment rather than placebo. If functional unblinding occurred, it could potentially inflate efficacy estimates through expectation bias, particularly for subjective outcome measures.

Nonetheless, both of these potential sources of functional unblinding—the high incidence of recognizable adverse events disclosed in the informed consent and the randomization ratio favoring active treatment—do not raise great concern in the context of this review. This is because the primary efficacy endpoints relied upon in this trial are objective and physiologically grounded, and therefore not meaningfully susceptible to expectation bias or conscious reporting tendencies. Efficacy was assessed using the MWT, a measure that quantifies a participant's physiological ability to remain awake under standardized conditions. Critically, efficacy was further corroborated by nocturnal polysomnography (nPSG), which demonstrated a normalization of sleep architecture, including a recovery of REM latency to approximately 60 minutes—a finding consistent with restoration of orexin-mediated sleep-wake regulation and strikingly distinct from the severely shortened REM latency (often just a few minutes) characteristic of NT1. These polysomnographic findings represent objective, physiologically grounded evidence of drug effect that cannot be attributed to participant or investigator expectation.

Taken together, the convergence of objective wakefulness measures and normalized sleep architecture on nPSG provides strong support for a genuine pharmacological effect of oveporexton, independent of any potential influence of functional unblinding arising from either the adverse event profile or the randomization design. The consistency of these objective findings across endpoints substantially strengthens confidence in the robustness of the efficacy conclusions.

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8.4. Conclusions and Recommendations

The evidence from the two pivotal phase 3 studies—TAK-861-3001 and TAK-861-3002—provides substantial evidence of the effectiveness of oveporexton for the treatment of NT1. The evidence is characterized by the following key features that collectively support a high degree of confidence in the robustness and clinical meaningfulness of the treatment effect:

- Large, highly statistically significant treatment effects on the primary endpoint (MWT) and all pre-specified secondary endpoints in Study TAK-861-3001, with independent replication in Study TAK-861-3002.
- Objective, physiologically grounded primary and secondary endpoints (MWT, nPSG-measured REM latency), which are not susceptible to expectation bias and provide strong evidence of a genuine pharmacological effect, independent of any potential influence of functional unblinding. As discussed in Section 8.3, the relatively high incidence of treatment-emergent adverse events—notably insomnia and urinary symptoms—disclosed in the informed consent forms, combined with a randomization ratio favoring active treatment, raised a theoretical concern for functional unblinding; however, this concern is substantially mitigated by the objective nature of the primary and secondary endpoints.
- Demonstrated dose-response relationship across the majority of endpoints, providing additional mechanistic support for the observed treatment effects and further reducing the likelihood that the efficacy findings are attributable to expectation bias alone.
- Broad coverage of the NT1 pentad, including EDS, cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and disturbed/disrupted nighttime sleep, supporting the Applicant's symptom-agnostic approach to the NT1 indication.
- Robust and consistent results across sensitivity analyses, subgroups, and study sites, with no evidence of dependence on any single site or patient subgroup.
- Meaningful improvements in patient-reported functional outcomes and quality of life, including the FINI, SF-36, and PGI-C, demonstrating that the objective treatment effects translate into clinically meaningful benefit from the patient's perspective (of note, FINI, SF-36 were not considered appropriate for labeling but support the general concept of clinically meaningful benefit).

The clinical review team concludes that the evidence from Studies TAK-861-3001 and TAK-861-3002 meets the statutory standard of substantial evidence of effectiveness for oveporexton in the treatment of NT1 and supports the Applicant's proposed symptom-agnostic indication.

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9 Advisory Committee Meeting and Other External Consultations

FDA did not hold an advisory committee (AC) meeting during this marketing application review. The team agreed that outside expertise was not necessary because there were no issues that would benefit from advisory committee discussion.

The safety profile did not raise significant safety issues that were unexpected or that required discussion with an AC; there were no significant efficacy issues, as both pivotal phase 3 studies yielded highly significant and robust results across the primary and all pre-specified secondary endpoints.

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10 Pediatrics

Oveporexton has been granted orphan drug designation in the United States for the treatment of NT1, the proposed indication; therefore, pediatric studies are not required under the Pediatric Research Equity Act (PREA) under section 505B(a)(3) of the Federal Food, Drug, and Cosmetic Act.

At the time the Applicant submitted the original NDA, orphan drug designation had not yet been granted. Accordingly, the Applicant submitted an agreed initial Pediatric Study Plan

(b) (4)

In light of the subsequently granted orphan drug designation, no further requirement to evaluate the safety and effectiveness of oveporexton in the pediatric population is applicable.

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11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

The table below summarizes high-level, significant changes to the proposed Prescribing Information made by FDA.

Table 106. Changes to Prescribing Information

Section	Changes From the Applicant's Original Proposed Labeling
1. Indications and Usage	• The safety and effectiveness of ORZEYFUL has not been established in pediatric patients; thus, the term "adults" was added to this section, (b) (4) • Removed the term (b) (4) " from the EPC text phrase in the I&U heading in Highlights because this term is ambiguous and for thousands of prescription drugs regulated in CDER and CBER we do not include this term in the EPC text phrase.
2. Dosage and Administration	• Added a statement recommending administering ORZEYFUL tablets at approximately the same time each day, and to split the 1-mg or 2-mg dosing into two separate dosages. • Removed the (b) (4) references in this section as there was no dosage adjustment recommendation in these situations. • Moved the missed dosing recommendations to a new subsection because missed dosing is a different concept than the recommended dosage.
3. Dosage Forms and Strengths	Agreed with the Applicant's proposed information in this section, made minor edits to reduce redundancy.
4. Contraindications	Removed (b) (4) We recommend avoiding use in patients with severe HI; that recommendation is in subsection 8.6.
5. Warnings and Precautions	• Added three warnings in the W&P section. Each of these items are clinically significant adverse reactions or risks: 5.1 Insomnia 5.2 Urinary Frequency and Urgency 5.3 Creatine Phosphokinase Elevations • Given that at this time we have not seen evidence of physical dependence (e.g., withdrawal adverse reactions after abrupt withdrawal of ORZEYFUL), we removed the (b) (4) from the W&P section.
6. Adverse Reactions	• Removed redundant information, and improved clarity of information (e.g., placing the frequency of the dosing in the table, removing the decimal from the text). • Removed negative findings (b) (4) s) because such findings were not convincingly demonstrated in a trial of adequate design and power. • Added Low-Density Lipoprotein Cholesterol elevations and associated safety data. • We removed (b) (4) and moved to W&P Section. • Included all adverse events that occurred at a meaningful rate (≥2% and greater than the placebo rate) in Table 1 (added terms: influenza, abdominal pain, oropharyngeal pain, rash, sinusitis). • Added description of insomnia events (time of onset, and duration)

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Section	Changes From the Applicant's Original Proposed Labeling
7. Drug Interactions	• Agreed with the Applicant's description and risk mitigation of clinically significant drug interactions. • Removed (b) (4) because the examples are not comprehensive and HCPs may incorrectly think that a list of drugs is comprehensive. Additionally, sometimes example drugs listed in the labeling are no longer available in the market. Finally, HCPs have access to databases that contain lists of drugs within many drug interacting classes. • Removed (b) (4).
8. Use in Specific Populations	• Agreed with the Applicant that the available data from clinical trials with ORZEYFUL use during pregnancy are insufficient to identify a drug associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. • Agreed with the Applicant that the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ORZEYFUL and any potential adverse effects on the breastfed infant from ORZEYFUL or from the underlying maternal condition. • Added the geriatric exposure data to the Geriatric Use subsection. • Removed (b) (4) recommended that use should be avoided in patients with severe HI.
9. Drug Abuse and Dependence	• Agreed with the Applicant that HCPs should carefully evaluate patients for a recent history of drug abuse, especially those with a history of CNS stimulant (e.g., methylphenidate, amphetamine, or cocaine) and follow such patients closely, observing them for signs of misuse or abuse of ORZEYFUL (e.g., incrementation of doses, drug seeking behavior). • Added information about the potential for misuse. • Deleted (b) (4) were not identified to date.
10. Overdosage	• Agreed with the Applicant to include a statement for the HCP to consider contacting the Poison Help line or medical toxicologist if an overdose occurs. • Removed (b) (4). • Removed the nonspecific statements " (b) (4) "
11. Description	Agreed with the Applicant's description of the drug product and drug substance and the listing of inactive ingredients.
12. Clinical Pharmacology	• Updated the mechanism of action description to focus on activity at orexin receptor. • Removed the term (b) (4) in the mechanism of action and in the EPC text phrase because we generally do not include ambiguous terminology in labeling. • Removed the statement (b) (4) in Section 12.2. • Added the values of the geometric mean ratio and 90% CI of PK parameters to the right of the forest plot in Figure 1, Section 12.3.
13. Nonclinical Toxicology	• Removed (b) (4) • Added information about the male and female fertility study.
14. Clinical Studies	• Removed regulatory information such as (b) (4) • Removed the description of the (b) (4) their results from the labeling because: (b) (4)

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Section	Changes From the Applicant's Original Proposed Labeling
	(b) (4) • Removed (b) (4) a secondary endpoint and we typically do not include figures showing results over time for secondary endpoints. • Modified Table 3, replacing (b) (4) e with two columns that better capture efficacy results: 1) mean weekly cataplexy rate during the baseline observation period 2) mean weekly cataplexy rate at Week 12.
16. How Supplied/ Storage and Handling	Agreed with the Applicant's proposal re: supply information and storage instructions of the supplied product.
17. Patient Counseling	Added information on Insomnia, Urinary Frequency and Urgency, and Creatine Phosphokinase Elevations to match the changes to the W&P section.
Medication Guide	The criteria for having a Medication Guide were not met as per 21 CFR 208.1(c). Thus, this drug will not have a Medication Guide.

Source: Team Labeling Discussions

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12 Risk Evaluation and Mitigation Strategies (REMS)

There were no safety signals identified that would require mitigation via a REMS program.

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13 Postmarketing Requirements and Commitment

Oveporexton (Orzeyful) is a first-in-class OX2R agonist approved for the chronic treatment of NT1 in adults. Because NT1 affects individuals of reproductive age and requires long-term pharmacotherapy, characterizing the safety of oveporexton in pregnancy, lactation, and special populations is essential to support safe use in the postmarket setting.

The clinical development program excluded pregnant and breastfeeding women; thus, no human data on pregnancy or infant outcomes, or on breast milk transfer was available. The nonclinical reproductive and developmental toxicology program identified findings at relevant exposures that cannot be directly extrapolated to humans without confirmatory postmarket data.

Additionally, the preapproval hepatic impairment study (TAK-861-1004) evaluated only mild and moderate hepatic impairment (Child-Pugh A and B); the effect of severe hepatic impairment (Child-Pugh C) on oveporexton pharmacokinetics was not studied, despite oveporexton being almost entirely cleared by hepatic CYP3A4-mediated metabolism (~91% fmCYP3A in vivo).

To address these gaps, the following postmarketing studies are required:

- **5020-1:** Conduct a retrospective pregnancy cohort study using claims or electronic health record data with medical chart validation that is adequately powered to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to oveporexton during pregnancy compared to appropriate comparator population(s).

- **5020-2:** Collect data from a prospective pregnancy exposure registry, preferably a disease-based multiproduct pregnancy registry, using a cohort analysis that compares the maternal, fetal, and infant outcomes of women exposed to drug name regardless of indication during pregnancy with unexposed comparator population(s) in a timely manner. Align the study protocol with protocol(s) outside the United States to reach the target sample size. The registry should identify and record pregnancy complications, major and minor congenital malformations, pregnancy complications, spontaneous abortion, stillbirths, elective pregnancy terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes described in the protocol 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.

- **5020-3:** Conduct a lactation study to measure concentrations of oveporexton and its major metabolites in breast milk using a validated assay. A mother-infant pair study is recommended. Assess the effects on the breastfed infant, if available, based on study population.

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- **5020-4:** Evaluate the effect of severe hepatic impairment on safety and pharmacokinetics of oveporexton.

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14 Division Director (DP) Comments

The content of this Unireview reflects the issues discussed in the marketing application assessment and regulatory decisions and actions taken. My feedback and edits have been incorporated above. I agree with the findings as documented by the primary review team.

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15 Office Deputy Director (Designated Signatory Authority) Comments

This review reflects my edits and feedback. I agree with the findings as described by the review team and concur with the approval recommendation.

Reference ID: 5847402

16 Appendices

16.1. References

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Reference ID: 5847402

16.2. Financial Disclosure

The submitted information including a list of clinical investigators are noted.

Table 107. Covered Clinical Study (Name and/or Number): Study TAK-861-3001, Study TAK-861-3002, Study TAK-861-2003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 75		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
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: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

16.3. Nonclinical Pharmacology/Toxicology

Refer to section 5.5.4 for a summary of the negative GLP-compliant carcinogenicity studies of oveporexton: a 26-week carcinogenicity study in transgenic hemizygous mice (Tg-rasH2 mice) and a 2-year carcinogenicity study in rats. Full reviews of the carcinogenicity studies are archived under IND 154232.

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16.4. Clinical Pharmacology

16.4.1. In Vitro Studies

Protein Binding

Study Method: The in vitro protein binding of [^{3}H]-oveporexton in rat, monkey, and human plasma, and the binding of [^{14}C]-oveporexton in human serum albumin (HSA) solution, α1-acid glycoprotein (AGP) solution, and human liver microsomes (HLM) were determined by equilibrium dialysis at 37°C for 8 hours. Total radioactivity (TRA) was measured by liquid scintillation counting (LSC).

Results: In vitro protein binding indicated that the binding of [^{3}H]-oveporexton to human plasma proteins is high (>96%) and concentration independent.

Table 108. Mean Oveporexton Protein Binding to HSA, AGP, and Human Liver Microsomes

	[^{14}C]Oveporexton Protein Binding Ratio (%)		
Matrix	**0.05 µg/mL**	**0.5 µg/mL**	**5 µg/mL**
4% HSA	89.4	89.8	89.2
0.18% AGP	83.2	82.3	77.3
4% HSA/0.18% AGP	95.8	96.0	95.5
0.2 mg protein/mL HLM	26.0	25.4	28.4
1 mg protein/mL HLM	68.6	67.9	66.8

Source: DDA-A41-059 and DDA-A41-059 Amendment 1.

AGP: α_1-acid glycoprotein; HLM: human liver microsomes; HSA: human serum albumin.
The mean value of 2 to 3 replicates is presented.
Source: Study report DDA-A41-059.

In Vitro Metabolism

Study Method: The in vitro metabolic stability of oveporexton was investigated using hepatocytes from rats, monkeys, and humans, including CYP reaction phenotyping using recombinant human CYP-expressing microsomes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4), hepatocyte incubations (mice, rats, monkeys, and humans), and human liver microsomes (HLM).

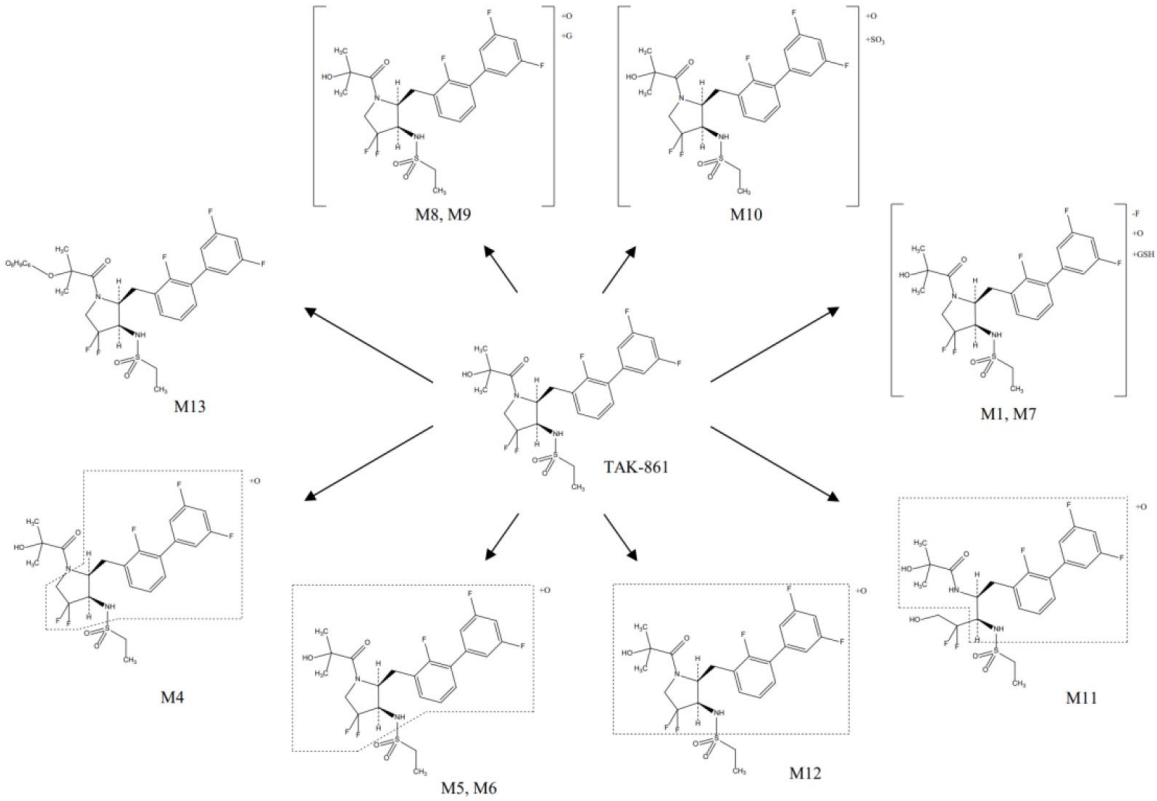
Results: Oveporexton (1 µmol/L) was metabolized by CYP2C9, 2D6, and 3A4 in the presence of a NADPH-generating system. The intrinsic clearance for CYP2C9, 2D6, and 3A4 was 0.0165, 0.0147, and 0.275 µL/min/pmol P450, respectively. Oveporexton was not metabolized by the other CYP-expressing microsomes (CYP1A2, 2B6, 2C8, or 2C19). The relative contribution ratios of CYP2C9, 2D6, and 3A4, calculated using the Relative Activity Factor (RAF) method, were 2.6%, 0.1%, and 97.3%, respectively.

Oveporexton was metabolized to 11 metabolites in hepatocytes derived from animals and humans. Unchanged oveporexton accounted for 95.6% of the total circulating radioactivity, with two metabolites (M5 and M6) each accounting for <3.5% of radioactivity. In urine, unchanged oveporexton was not detected, and 4 metabolites accounted for 0.4% of the

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administered dose. In feces, unchanged oveporexton accounted for 2.4% of the administered dose, and 9 metabolites were identified, with values ranging from 1.7% to 12.9% of the administered dose.

Figure 29. Metabolic Pathways of Oveporexton in Mice, Rat, Monkey, and Human



Source: Study report DDA-A41-028

Clinical Implications: Oveporexton is metabolized primarily by CYP3A4, and eliminated predominantly via fecal excretion of metabolites, with minimal renal involvement. No major circulating metabolites (>10%) were identified in plasma.

In Vitro Drug-Drug Interactions (DDIs)

CYP Inhibition

Study Method: The inhibitory effects of oveporexton (0.1, 0.3, 1, 3, 10, and 30 µmol/L) on the marker activities of 7 CYP isoforms (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5) were evaluated in human liver microsomes. In addition, time-dependent inhibition (TDI) effects of oveporexton on CYP activities were examined in human liver microsomes pre-incubated for 30 minutes with oveporexton in the presence of NADPH.

Results: Oveporexton inhibited CYP2C8, 2C9, 2C19, 2D6, and 3A4/5 activities with half-maximal inhibitory concentration (IC_{50}) values of 21, 18, 13, 4.6, and 18 µmol/L (midazolam

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1'-hydroxylation), respectively. Oveporexton did not inhibit CYP1A2, 2B6, or 3A4/5 (testosterone 6β-hydroxylation) activities (IC_{50} >30 µmol/L). In the pre-incubation study, oveporexton inhibited CYP2C8, 2C9, 2C19, 2D6, and 3A4/5 (midazolam 1'-hydroxylation and testosterone 6β-hydroxylation) activities with IC_{50} values of 29, 22, 16, 3.7, 4.0, and 4.7 µmol/L, respectively. Oveporexton did not inhibit CYP1A2 or 2B6 activity (IC_{50} >30 µmol/L). These results indicate that oveporexton has direct inhibitory effects in vitro on CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 activities.

Clinical Implications: Although oveporexton at high concentrations showed inhibition potential for CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5, the clinical unbound C_{max} following the proposed dosage regimen (2 mg BID) is low (~0.0015 µmol/L) and $C_{max,u}/IC_{50}$ ratios are well below the regulatory cutoff established in the guidance on M12 Drug Interaction Studies (0.02). Therefore, the risk of DDIs with oveporexton acting as an inhibitor is low.

CYP Induction

Study Method: The induction potential of oveporexton (0.1, 0.3, 1, 3, 10, and 30 µmol/L) on the gene expression of 5 CYP isoforms (CYP1A2, 2B6, 2C8, 2C9, and 3A4) was examined using cryopreserved human hepatocytes prepared from three donors.

Results: The mean fold change in gene expression of CYP1A2, 2B6, 2C8, 2C9, and 3A4 at an oveporexton concentration of 30 µmol/L was 2.55, 4.47, 4.42, 2.78, and 36.3, respectively. There were no significant differences among hepatocytes prepared from the three donors. The mean maximal induction (Emax) and concentration that exerts half-maximal induction (EC_{50}) for CYP1A2, 2B6, 2C8, 2C9, and 3A4 were 1.89 and 6.21 µmol/L, 4.38 and 2.87 µmol/L, 4.41 and 3.54 µmol/L, 4.62 and 50.1 µmol/L, and 44.1 and 2.75 µmol/L, respectively. These results indicate that oveporexton has induction potential in vitro for CYP1A2, 2B6, 2C8, 2C9, and 3A4.

Clinical Implications: Although oveporexton at high concentrations (30 µmol/L) showed induction potential for CYP1A2, 2B6, 2C8, 2C9, and 3A4, the clinical unbound C_{max} following the proposed dosage regimen (2 mg BID) is low (~0.0015 µmol/L) and $C_{max,u}/EC_{50}$ ratios are well below the regulatory cutoff established in the guidance on M12 Drug Interaction Studies (0.02). Therefore, the risk of DDIs with oveporexton acting as an inducer is low.

Transporter Interaction

Study Method: Multiple cell-based assays using transfected cell lines: MDCKII cells expressing P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) were used for evaluation of oveporexton as a substrate of P-gp and BCRP, and various cell lines (MDCK-MDR1, LLC-PK1, Caco-2, HEK293) for inhibition studies.

Transporters Tested: Efflux transporters: P-gp, BCRP and bile salt export pump (BSEP)

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Uptake transporters: Organic anion transporting polypeptide (OATP1B1 and OATP1B3), organic anion transporter (OAT1 and OAT3), organic cation transporter (OCT1 and OCT2), and multidrug and toxin extrusion protein (MATE1 and MATE2-K).

Results: Oveporexton did not inhibit P-gp-mediated digoxin transport or BCRP-mediated prazosin transport at concentrations up to 100 µmol/L. Oveporexton inhibited BSEP-mediated taurocholate transport with an IC_{50} value of 7.225 µmol/L. Oveporexton did not inhibit MATE1- or MATE2K-mediated metformin accumulation at concentrations up to 4.5 µmol/L. Oveporexton did not inhibit OAT1-mediated tenofovir, OAT3-mediated estrone 3-sulfate, OCT1-mediated sumatriptan, or OCT2-mediated metformin accumulation at concentrations up to 10 µmol/L. Oveporexton (0.3 to 100 µmol/L) inhibited the OATP1B1- and OATP1B3-mediated transport of typical substrates with IC_{50} values of 0.910 and 37.7 µmol/L, respectively.

Clinical Implications: Given that the estimated clinical unbound C_{max} following the proposed dosage regimen (2 mg BID) is low (~0.0015 µmol/L), the $C_{max,u}/IC_{50}$ ratios were well below thresholds of clinical concern (typically <0.1) for all transporters tested. Therefore, oveporexton is unlikely to cause clinically meaningful transporter-mediated drug interactions. The lack of P-gp and BCRP substrate activity suggests minimal risk for drug interactions involving these major efflux transporters.

16.4.2. Bioanalytical Methods

A liquid chromatography tandem mass spectrometry in negative ion mode (LC-MS/MS) method was developed and validated (validation reports: CB201176 and CB201177) by (b) (4) for the determination of TAK-861 in human plasma.

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Table 109. Overview of Bioanalytical Method Validation Results for Oveporexton

Analyte		TAK-861
Internal Standard (IS)		TAK-861-d6
Matrix		Human plasma (anticoagulant: EDTA-2K)
Incurred Sample Reproducibility (ISR)		ISR was performed on 207 subject samples (10.0% of the first 1,000 samples; 5.2% of samples exceeding 1,000). The assay variability (A.V.) was within ±20% for 207/207 samples (100.0%), meeting the acceptance criterion of ≥67%
Calibration	Range (ng/mL)	0.1 to 200 ng/mL
	#Conc. points	0.1, 0.2, 0.4, 2, 10, 50, 100 and 200 ng/mL
	% Coefficient of Variation (% CV; precision)	1.6 to 3.0%
	% Relative Error (RE; bias)	94.0–105.5%
Quality Control	Concentrations	LQC: 0.3 ng/mL; MQC: 8 ng/mL; HQC: 160 ng/mL
	%CV	2.7% (LQC), 2.1% (MQC), 1.9% (HQC)
	%Bias	99.7% (LQC), 101.1% (MQC), 98.1% (HQC)
Dilutional Integrity		DQC: 1000 ng/ml. Dilution factor: 10
	%CV	5.4%
	%Bias	112%
Carryover effect		No significant carryover was observed
Freeze-Thaw Stability		5 cycles at −30°C to −15°C/RT and −70°C or below/RT
Long-term Stability in plasma		366 days at −30°C to −15°C and at −70°C or below
Short-term Stability in plasma		15 hours at room temperature for all concentrations
Date Range of Bioanalytical Assays		May 6, 2021, to January 24, 2023 (41 analytical runs; 1 run [Run ID 20] rejected and re-analyzed)

DQC: Diluted Quality Control; LQC: Low quality control; MQC: Middle quality control; HQC: High quality control.
Source: Adapted from the bioanalytical report for Study TAK-861-1001 (Report No. CB210057).

The bioanalytical methods satisfied the criteria for method validation and "application to routine analysis" set by the guidance for industry, *Bioanalytical Method Development*, and is acceptable.

16.4.3. Summary of Individual Clinical Pharmacology Studies

Clinical Study Report TAK-861-1001

Title

A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Doses of TAK-861 in Healthy Adult and Elderly Subjects and Subjects with Narcolepsy Type 1.

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Primary Objectives:

- To investigate the safety and tolerability of TAK-861 when single and/or multiple oral doses are administered to healthy adults, healthy elderly subjects, and subjects with narcolepsy type 1 (NT1).

Secondary Objectives:

- To investigate the PK of TAK-861 following single and/or multiple oral doses of suspension and/or tablet formulation in healthy adults.
- To investigate the PK of TAK-861 following multiple oral doses of tablet formulation in healthy elderly subjects and subjects with NT1.
- To assess the effect of food on the PK of the TAK-861 tablet formulation.

Additional/Exploratory Objectives:

- To assess CYP3A4/5 inductive activity via the 4β-hydroxycholesterol/cholesterol ratio (Parts B–E).
- To assess OATP1B1/3 inhibition via coproporphyrin (CPI and CPIII) biomarkers (Parts B and E).
- To evaluate TAK-861 CNS penetration through cerebrospinal fluid (CSF) PK (Part F).
- To assess the PD effects of TAK-861 on NT1 symptoms including MWT, ESS, WCR, CGI, PGI, nPSG, and other measures (Part D).
- To evaluate orexin CSF levels following TAK-861 administration (Part F).

Study Design

A first-in-human (FIH), phase 1/1b, randomized, double-blind, placebo-controlled study of single- and multiple-rising oral doses of TAK-861 conducted across seven independent parts (Parts A through G; this report covers Parts A through F). The study was conducted at sites in Japan and the United States. Details of the study cohorts can be found in the table below.

Table 110. Summary of Cohorts Study Design, Study TAK-861-1001

Part	Population	Design	Dose Levels	Dosing Regimen
A	Healthy Japanese adults	SRD, fasted and fed	1, 3, 5, 10, 25, 50, 75 mg	Single dose
B	Healthy Japanese adults	MRD/MD	5, 20, 30 mg QD; 10 mg BID; 7 mg TID	14 days
C	Healthy elderly Japanese (≥65 yrs)	MD	5 mg QD	14 days
D	NT1 subjects (Japanese & non-Japanese*)	MRD	0.5 mg QD; 4 mg QD; 4 mg BID	28 days
E	Healthy non-Japanese adults	SRD/MRD QD	5 mg QD; 30 mg QD	Single dose +14 days

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Part	Population	Design	Dose Levels	Dosing Regimen
F	Healthy non-Japanese adults	MD + CSF sampling	5 mg QD	10 days

Abbreviations: SRD: single-rising dose; MRD: multiple-rising dose; MD: multiple dose; QD: once daily; BID: twice daily; TID: three times daily; CSF: cerebrospinal fluid.
*Non-Japanese subjects include Caucasian and African American subjects.
Source: Adapted from clinical study protocol for Study TAK-861-1001.

Randomization was 6:2 (active:placebo) for healthy subject cohorts and 6:3 for NT1 cohorts (Part D). All study drugs were administered orally, initially as a suspension (Cohorts A1, A2, A4) and subsequently as a film-coated tablet.

Pharmacokinetic Sampling

- Part A: Pre-dose and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 h post-dose (Days 1 and 6); fed cohort (A3) included a second period on Day 15.
- Parts B and C (QD): Pre-dose and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12 h post-dose on Day 1; pre-dose on Days 2 through 13; intensive sampling through 96 h after Day 14 dose.
- Part D: 1, 3, 5, 7, 9, 12, 14 h post-dose on Days 1, 14, and 28.
- Part E: Intensive sampling on Days 1 (single dose), 6 (first MRD dose), and 19 (Day 14 of MRD), including 96 h post-dose washout sampling.
- Part F: Intensive plasma and serial CSF sampling on Day 10 (0.25-24 h post-dose), with plasma trough collections on preceding days.

Results

Subject Disposition

Table 111. Subject Disposition, Study TAK-861-1001

Part	Population	Placebo Treated (n)	TAK-861 Treated (n)	Completed (TAK-861)
A	Healthy Japanese adults	14	42	42 (100%)
B	Healthy Japanese adults	10	30	29 (96.7%)
C	Healthy elderly Japanese	2	6	6 (100%)
D	NT1	5	13	10 (76.9%)
E	Healthy non-Japanese adults	4	13	11 (84.6%)
F	Healthy non-Japanese adults	0	9	9 (100%)

*Non-Japanese subjects include Caucasian and African American subjects.
Source: Adapted from clinical study protocol for Study TAK-861-1001, Tables 10.b and 10.c, Pages 124–125.

Table 112. Demographic for Subjects Included in the Dataset, Study TAK-861-1001

Demographic	Part A	Part B	Part C	Part D (NT1)	Part E	Part F
N (TAK-861)	42	30	6	13	13	9
Mean Age (yrs)	26.1	27.7	66.8	33.8	39.3	31.6
Sex (Male %)	100%	100%	50%	38.5%	92.3%	88.9%

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Demographic	Part A	Part B	Part C	Part D (NT1)	Part E	Part F
Race	Asian (100%)	Asian (100%)	Asian (100%)	White (46.2%), Asian (38.5%)	Black/White	Mixed
Median BMI (kg/m^2)	21.10	22.35	22.75	26.00	25.30	25.80

Source: Adapted from clinical study protocol for Study TAK-861-1001, Tables 11.b and 11.c, pages 130–134

PK Results

Part A – Single Dose (Healthy Japanese Adults, Fasted)

Following single oral administration, TAK-861 was absorbed with median t_{max} of 0.60 to 2.50 h. Geometric mean C_{max} and AUC_{∞} increased approximately dose proportionally over the dose range of 1- to 10-mg suspension and 5- to 75-mg tablet. Mean $t_{½z}$ ranged from 17.15 to 23.61 h; CL/F and V_z/F were generally stable across dose levels. Urinary excretion of unchanged TAK-861 was <1%.

Food effect (high-fat, high-calorie meal): A single 5-mg tablet co-administered with a high-fat meal increased C_{max} by ~46% and AUC_{∞} by ~37% versus fasted conditions; median t_{max} was unchanged (1.50 h).

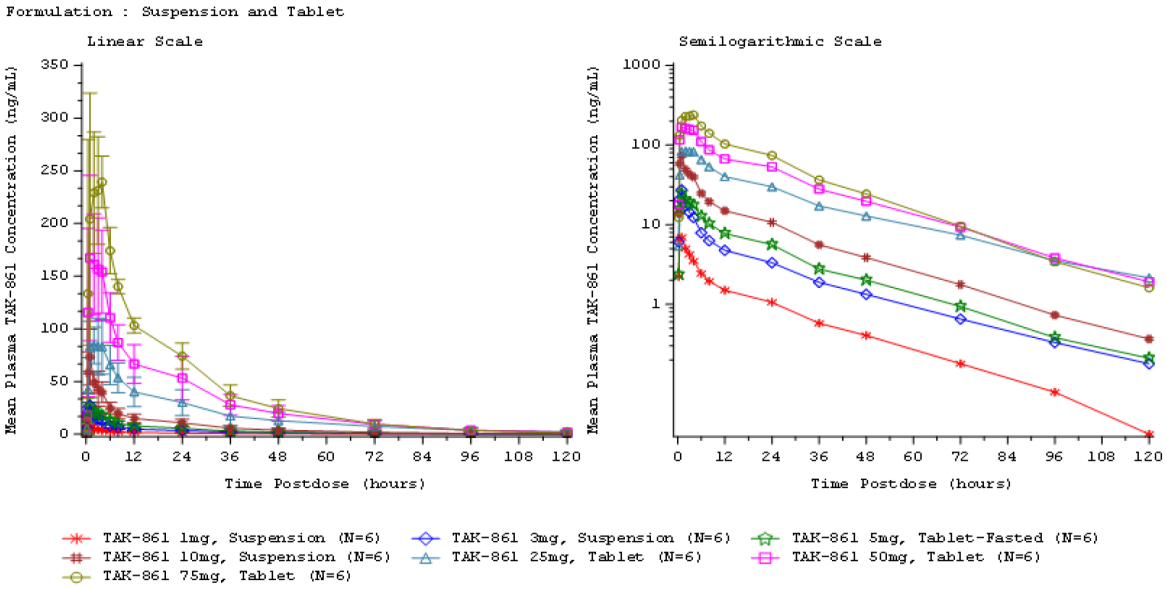
Table 113. Plasma PK Parameters (Geometric Mean and %CV) Following Single Oral Administration (Part a, PK Set), Study TAK-861-1001

Parameter (unit)	TAK-861 1 mg Fasted (A1) Suspension (N = 6)	TAK-861 3 mg Fasted (A2) Suspension (N = 6)	TAK-861 5 mg Fasted (A3) Tablet (N = 6)	TAK-861 5 mg Fed (A3) Tablet (N = 6)	TAK-861 10 mg Fasted (A4) Suspension (N = 6)	TAK-861 25 mg Fasted (A5) Tablet (N = 6)	TAK-861 50 mg Fasted (A6) Tablet (N = 6)	TAK-861 75 mg Fasted (A7) Tablet (N = 6)
n	6	6	6	6	6	6	6	6
t_{max} (h) [a]	0.60 (0.60, 1.08)	1.00 (1.00, 1.00)	1.50 (1.00, 6.00)	1.50 (1.00, 3.00)	1.00 (0.50, 3.00)	2.50 (1.00, 6.00)	1.50 (0.50, 6.00)	2.50 (0.50, 4.00)
C_{max} (ng/mL)	7.162 (19.0)	27.24 (10.5)	24.98 (33.8)	36.51 (13.6)	75.99 (29.4)	91.03 (28.6)	203.3 (24.6)	285.7 (23.1)
AUC_{24} (h*ng/mL)	50.53 (15.5)	168.4 (19.4)	236.3 (20.8)	317.7 (18.0)	508.0 (22.1)	1125 (26.3)	2017 (18.2)	3036 (7.0)
AUC_{last} (h*ng/mL)	73.72 (25.8)	253.6 (24.7)	363.1 (24.2)	493.8 (32.7)	744.1 (30.3)	1898 (44.1)	3275 (21.4)	4587 (13.1)
AUC_{∞} (h*ng/mL)	78.07 (25.6)	262.6 (25.7)	371.1 (24.5)	509.0 (34.4)	754.6 (31.2)	1968 (47.1)	3334 (21.7)	4628 (13.6)
$t_{1/2z}$ (h) [b]	19.92 (7.114)	22.49 (9.298)	18.89 (6.637)	20.64 (9.229)	19.37 (4.432)	23.61 (8.425)	20.73 (3.819)	17.15 (3.315)
CL/F (L/h) [c]	13.16 (25.9)	11.74 (25.9)	13.81 (24.6)	10.30 (33.8)	13.73 (27.1)	13.81 (44.9)	15.26 (18.4)	16.33 (13.8)
V_z/F (L) [c]	357.6 (24.2)	358.7 (31.6)	359.8 (30.0)	277.7 (28.4)	368.2 (19.9)	416.9 (20.1)	453.7 (24.9)	397.1 (13.7)

Source: Table 15.2.5.3.1.
%CV: percent coefficient of variation; AUC_{∞}: area under the concentration-time curve from time 0 to infinity; AUC_{24}: area under the concentration-time curve from time 0 to 24 hours; AUC_{last}: area under the concentration-time curve from time 0 to time of the last quantifiable concentration; CL/F: apparent clearance after extravascular administration; C_{max}: maximum observed concentration; PK: pharmacokinetic(s); $t_{1/2z}$: terminal disposition phase half-life; t_{max}: time of first occurrence of C_{max}; V_z/F: apparent volume of distribution during the terminal disposition phase after extravascular administration.
[a] Median (minimum, maximum).
[b] Mean (SD).
[c] Mean (%CV).
Source: Clinical Study Report TAK-861-1001, Table 11.f, page 146

Reference ID: 5847402

Figure 30. Mean (±Standard Deviation) Total Plasma TAK-861 Concentration vs. Time Profiles Following TAK-861 in Part a: Linear Scale (Left) and Semilogarithmic Scales (Right) (PK Set)



Source: Figure 15.2.5.1.1.1.
PK: pharmacokinetic(s).

Source: Clinical Study Report TAK-861-1001, Figure 11.a, page 143

Part B – Multiple Doses (Healthy Japanese Adults)

TAK-861 steady-state exposures increased approximately dose proportionally over the dose range of 5 to 30 mg QD following 14 days. Accumulation was consistent with the observed $t_{½z}$. CYP3A4/5 inductive activity (4β-hydroxycholesterol/cholesterol ratio) increased 21 to 41% after 14 days of repeat dosing. OATP1B1/3 inhibition potential was low (CPI and CPIII changes comparable to placebo).

Reference ID: 5847402

Table 114. Plasma PK Parameters (Geometric Mean and %CV) of Oveporexton at Steady State, Day 14 – QD Dosing (Part B, PK Set)

Parameter (unit)	TAK-861 5 mg Fasted (B1) (N = 6)	TAK-861 20 mg Fasted (B2) (N = 6)	TAK-861 30 mg Fasted (B3) (N = 6)
N	6	6	5
t_{max} (h) [a]	1.00 (1.00, 2.00)	1.00 (0.50, 4.00)	1.00 (1.00, 1.00)
$C_{max,ss}$ (ng/mL)	31.66 (27.1)	102.2 (30.3)	169.6 (15.7)
$C_{av,ss}$ (ng/mL)	14.06 (18.0)	46.10 (24.1)	65.58 (17.1)
AUC_{τ} (h*ng/mL)	337.5 (18.0)	1106 (24.1)	1574 (17.1)
AUC_{last} (h*ng/mL)	583.1 (24.9)	1832 (35.8)	2216 (21.3)
AUC_{∞} (h*ng/mL)	624.5 (28.8)	1932 (40.5)	2249 (21.8)
$t_{1/2z}$ (h) [b]	24.19 (7.197)	21.33 (7.020)	16.07 (1.508)
CL/F (L/h) [c]	15.02 (19.2)	18.49 (22.6)	19.28 (6.4)
V_z/F (L) [c]	521.5 (33.7)	544.4 (24.3)	444.4 (15.4)
$R_{ac(Cmax)}$ [Day 14/Day 1]	1.259 (24.6)	1.440 (13.1)	1.436 (17.9)
$R_{ac(AUC)}$ [Day 14/Day 1]	1.626 (12.1)	1.507 (17.7)	1.337 (6.2)

Source: Table 15.2.5.3.2.1.

%CV: percent coefficient of variation; AUC_{∞}: area under the concentration-time curve from time 0 to infinity; AUC_{τ}: area under the concentration-time curve during a dosing interval (steady-state), where τ is the length of the dosing interval; AUC_{last}: area under the concentration-time curve from time 0 to time of the last quantifiable concentration; $C_{av,ss}$: average plasma concentration during a dosing interval, at steady state; CL/F: apparent clearance after extravascular administration; $C_{max,ss}$: maximum observed concentration at steady state; PK: pharmacokinetic(s); QD: once daily; $R_{ac(AUC)}$: accumulation ratio based on AUC_{τ}; $R_{ac(Cmax)}$: accumulation ratio based on C_{max}; $t_{1/2z}$: terminal disposition phase half-life; t_{max}: time of first occurrence of C_{max}; V_z/F: apparent volume of distribution during the terminal disposition phase after extravascular administration.

[a] Median (minimum, maximum).

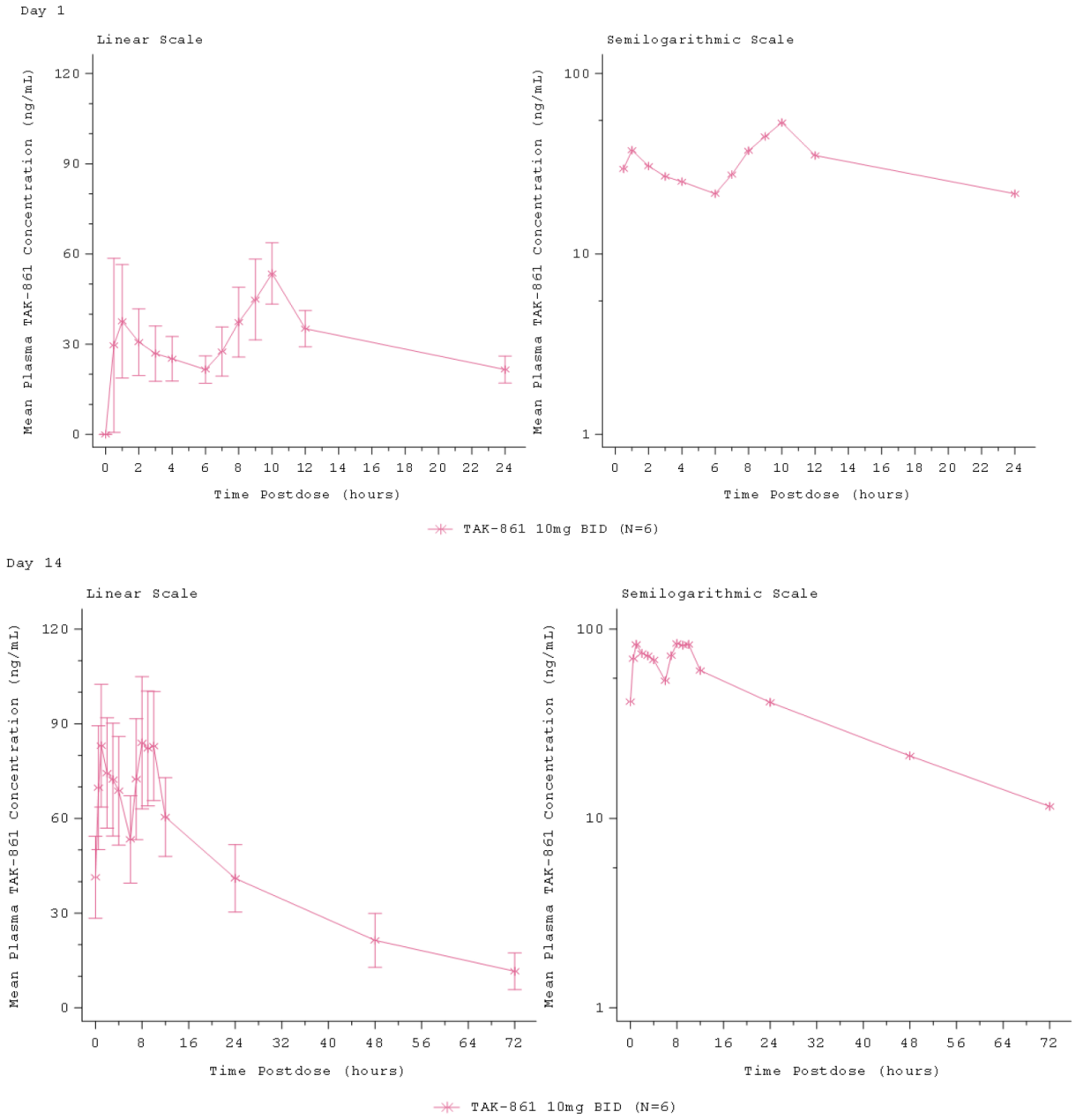
[b] Mean (SD).

[c] Mean (%CV).

Source: Clinical Study Report TAK-861-1001, Table 11.k, page 158

Reference ID: 5847402

Figure 31. Mean (±Standard Deviation) Total Plasma TAK-861 Concentration vs. Time Profiles Following TAK-861 in Part B: Linear Scale (Left) and Semilogarithmic Scales (Right) (PK Set)



Source: Figure 15.2.5.1.2.2.
BID: twice daily; PK: pharmacokinetic(s).

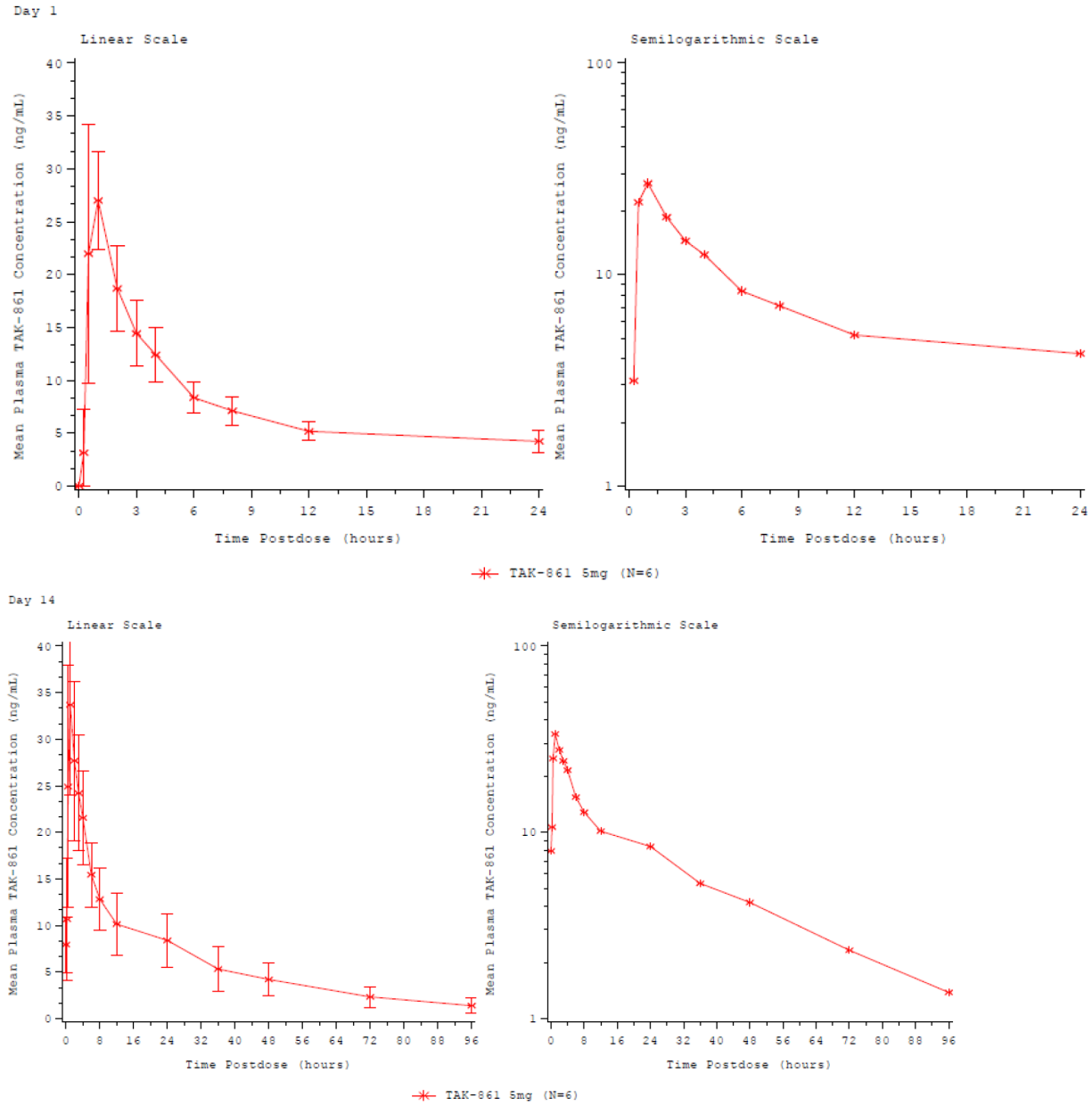
Source: Clinical Study Report TAK-861-1001, Figure 11.e, page 154

Systemic exposures (based on $C_{max,ss}$ and AUC_{τ}) in Japanese subjects and non-Japanese subjects (including Caucasian and African American subjects) are comparable following the administration of TAK-861 at the same dose level.

Part C – Multiple Doses (Healthy Elderly Japanese Subjects)

At steady state (Day 14, 5 mg QD), the geometric mean $C_{max,ss}$ and AUC_{τ} were 32.42 ng/mL and 308.6 h·ng/mL, respectively. The mean $t_{½z}$ of oveporexton was 28.57 h. The extent of accumulation based on AUC (Rac(AUC)) was 1.714. Exposures were comparable to those in younger Japanese adults at the same dose level, suggesting no clinically meaningful effect of age on TAK-861 PK.

Figure 32. Mean (±Standard Deviation) Total Plasma TAK-861 Concentration vs. Time Profiles Following TAK-861 in Part C: Linear Scale (Left) and Semilogarithmic Scales (Right) (PK Set)



Source: Clinical Study Report TAK-861-1001, Figure 11.k, page 183

Reference ID: 5847402

Table 115. Plasma PK Parameters (Geometric Mean and %CV) of TAK-861 at Day 1 and Day 14 – QD Dosing (Part C, PK Set)

Parameter (unit)	TAK-861 5 mg Fasted (Cohort C1) (N = 6)	
	Day 1	Day 14
n	6	6
t_{max} (h) [a]	1.00 (0.50, 1.00)	1.00 (0.50, 1.00)
C_{max} (ng/mL)	27.76 (24.9)	ND
$C_{max,ss}$ (ng/mL)	ND	32.42 (33.3)
$C_{av,ss}$ (ng/mL)	ND	12.86 (34.4)
AUC_{24} (h*ng/mL)	180.0 (20.3)	ND
AUC_{τ} (h*ng/mL)	ND	308.6 (34.4)
AUC_{∞} (h*ng/mL)	ND	594.7 (48.0)
$t_{1/2z}$ (h) [b]	ND	28.57 (6.697)
CL/F (L/h) [c]	ND	17.05 (38.2)
V_z/F (L) [c]	ND	671.5 (25.4)

Source: Clinical Study Report TAK-861-1001, Table 11.r, pages 185–186

Part D – Multiple Doses (Subjects with NT1)

Steady-state plasma exposures following 0.5 mg QD, 4 mg QD, and 4 mg BID in subjects with NT1, were generally consistent with those observed in healthy subjects, though interpretations are limited by small cohort sizes. At Day 28 (0.5 mg QD), geometric mean $C_{max,ss}$ and AUC_{τ} of oveporexton were 4.376 ng/mL and 48.65 h·ng/mL, respectively. For 4 mg BID at Day 28, geometric mean $C_{max,ss}$ (Dose 1 and Dose 2) were 26.02 and 37.77 ng/mL, respectively.

Reference ID: 5847402

Table 116. Plasma PK Parameters (Geometric Mean and %CV) of TAK-861 at Day 1, Day 14 and Day 28 (Part D, PK Set)

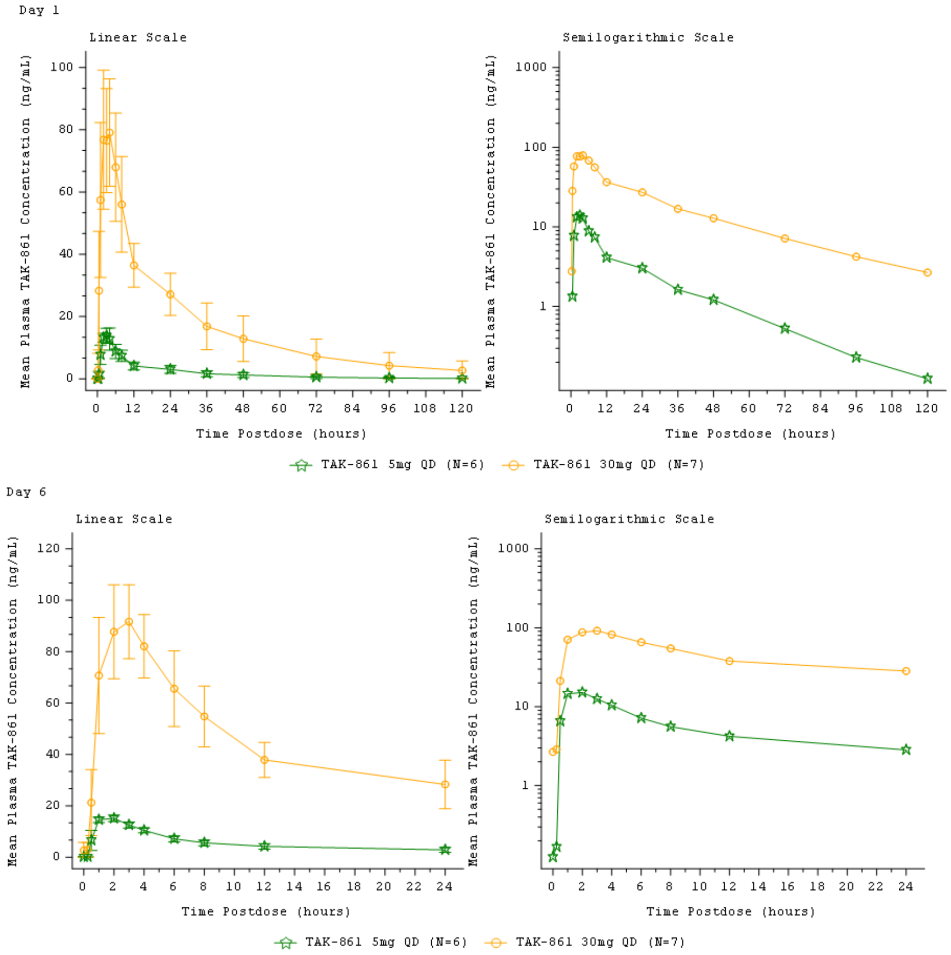
Parameter (unit)	TAK-861 4 mg QD (Cohort D1) (N = 3)	TAK-861 0.5 mg QD (Cohort D2) (N = 5)	TAK-861 4 mg BID (Cohort D3) (N = 5)
Day 1			
n	3	5	5
t_{max} (h) [a]	1.10 (1.00, 3.00)	1.17 (1.00, 3.00)	ND
t_{max} (Dose 1) (h) [a]	ND	ND	1.07 (1.00, 3.00)
t_{max} (Dose 2) (h) [a]	ND	ND	1.92 (0.00, 3.92)
C_{max} (ng/mL)	15.87 (16.0)	2.641 (26.6)	ND
C_{max} (Dose 1) (ng/mL)	ND	ND	10.42 (71.7)
C_{max} (Dose 2) (ng/mL)	ND	ND	14.51 (80.7)
AUC_{24} (h*ng/mL)	140, 155 [b]	23.29 (24.4)	175.7 (104.4)
Day 14			
n	2	5	4
t_{max} (h) [a]	1.02, 1.13 [b]	1.03 (1.00, 1.43)	ND
t_{max} (Dose 1) (h) [a]	ND	ND	1.08 (1.00, 3.00) [c]
t_{max} (Dose 2) (h) [a]	ND	ND	2.96 (1.62, 6.00)
$C_{max,ss}$ (ng/mL)	21.9, 25.1 [b]	4.450 (17.8)	ND
$C_{max,ss}$ (Dose 1) (ng/mL)	ND	ND	28.18 (64.4) [c]
$C_{max,ss}$ (Dose 2) (ng/mL)	ND	ND	35.69 (22.5)
Day 28			
n	2	5	3
t_{max} (h) [a]	1.00, 2.87 [b]	1.02 (1.00, 1.52)	ND
t_{max} (Dose 1) (h) [a]	ND	ND	3.00 (0.97, 3.00)
t_{max} (Dose 2) (h) [a]	ND	ND	3.92 (2.02, 4.00)
$C_{max,ss}$ (ng/mL)	17.1, 20.7 [b]	4.376 (21.5)	ND
$C_{max,ss}$ (Dose 1) (ng/mL)	ND	ND	26.02 (67.5)
$C_{max,ss}$ (Dose 2) (ng/mL)	ND	ND	37.77 (34.8)
$C_{av,ss}$ (ng/mL)	9.55, 11.9 [b]	2.021 (32.3)	ND
AUC_{τ} (h*ng/mL)	228, 286 [b]	48.65 (32.5)	ND
AUC_{24} (h*ng/mL)	ND	ND	535.9 (40.4)
$R_{ac(Cmax)}$ [Day 28/Day 1]	0.945, 1.25 [b]	1.657 (21.8)	ND
$R_{ac(Cmax)}$ (Dose 1) [Day 28/Day 1]	ND	ND	2.138 (55.8)
$R_{ac(Cmax)}$ (Dose 2) [Day 28/Day 1]	ND	ND	2.623 (84.7)

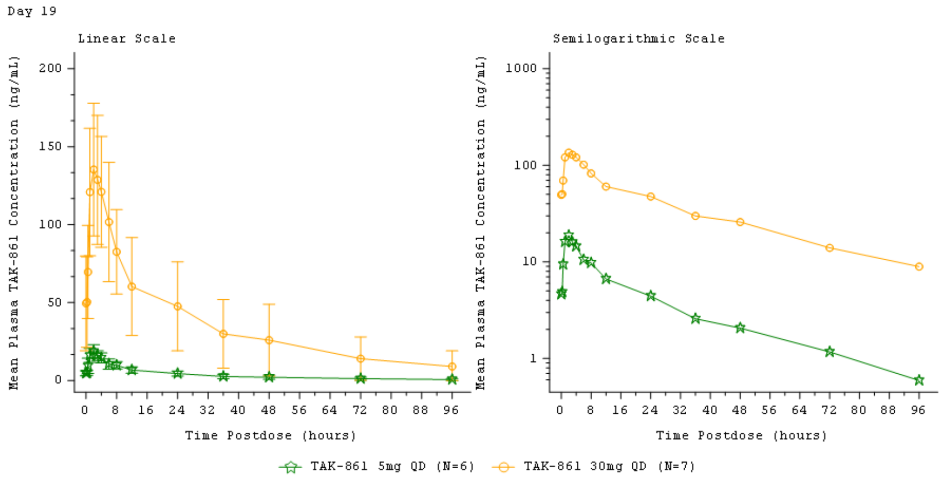
Source: Clinical Study Report TAK-861-1001, Table 11.u, pages 190-191

Part E – Single and Multiple Doses (Healthy Non-Japanese Adults)

TAK-861 exposures increased approximately dose proportionally after single ascending dose (5 to 30 mg) and at steady state (5 to 30 mg QD, 14 days). At steady state, mean $t_{½z}$ ranged from 25.28 to 28.08 h. Exposures at 30 mg QD were broadly consistent between Japanese (Part B) and non-Japanese (Part E) subjects. CYP3A4/5 inductive activity (4β-hydroxycholesterol/cholesterol ratio) increased approximately 58% at 30 mg QD; minimal effect was observed at 5 mg QD.

Figure 33. Mean (±Standard Deviation) Total Plasma TAK-861 Concentration vs. Time Profiles Following TAK-861 in Part D: Linear Scale (Left) and Semilogarithmic Scales (Right) (PK Set)





Source: Figure 15.2.5.1.3.1.
PK: pharmacokinetic(s); QD: once daily.
120 hours after Day 1 dose is also predose of Day 6.

Source: Clinical Study Report TAK-861-1001, Figure 11.l, pages 199–200

Table 117. Plasma PK (Geometric Mean and %CV) Parameters of Oveporexton at Steady State, Day 19 – QD Dosing (Part E, PK Set)

Parameter (unit)	TAK-861 5 mg Fasted (E1) (N = 6)	TAK-861 30 mg Fasted (E2) (N = 7)
n	4	6
t_{max} (h) [a]	2.09 (2.05, 2.15)	2.06 (1.02, 3.02)
$C_{max,ss}$ (ng/mL)	18.44 (20.8)	138.6 (25.2)
$C_{av,ss}$ (ng/mL)	8.196 (26.3)	69.73 (40.6)
AUC_{τ} (h*ng/mL)	197.2 (26.4)	1684 (40.8)
AUC_{last} (h*ng/mL)	308.5 (40.9)	2892 (61.2)
AUC_{∞} (h*ng/mL)	332.0 (45.5)	3163 (70.0)

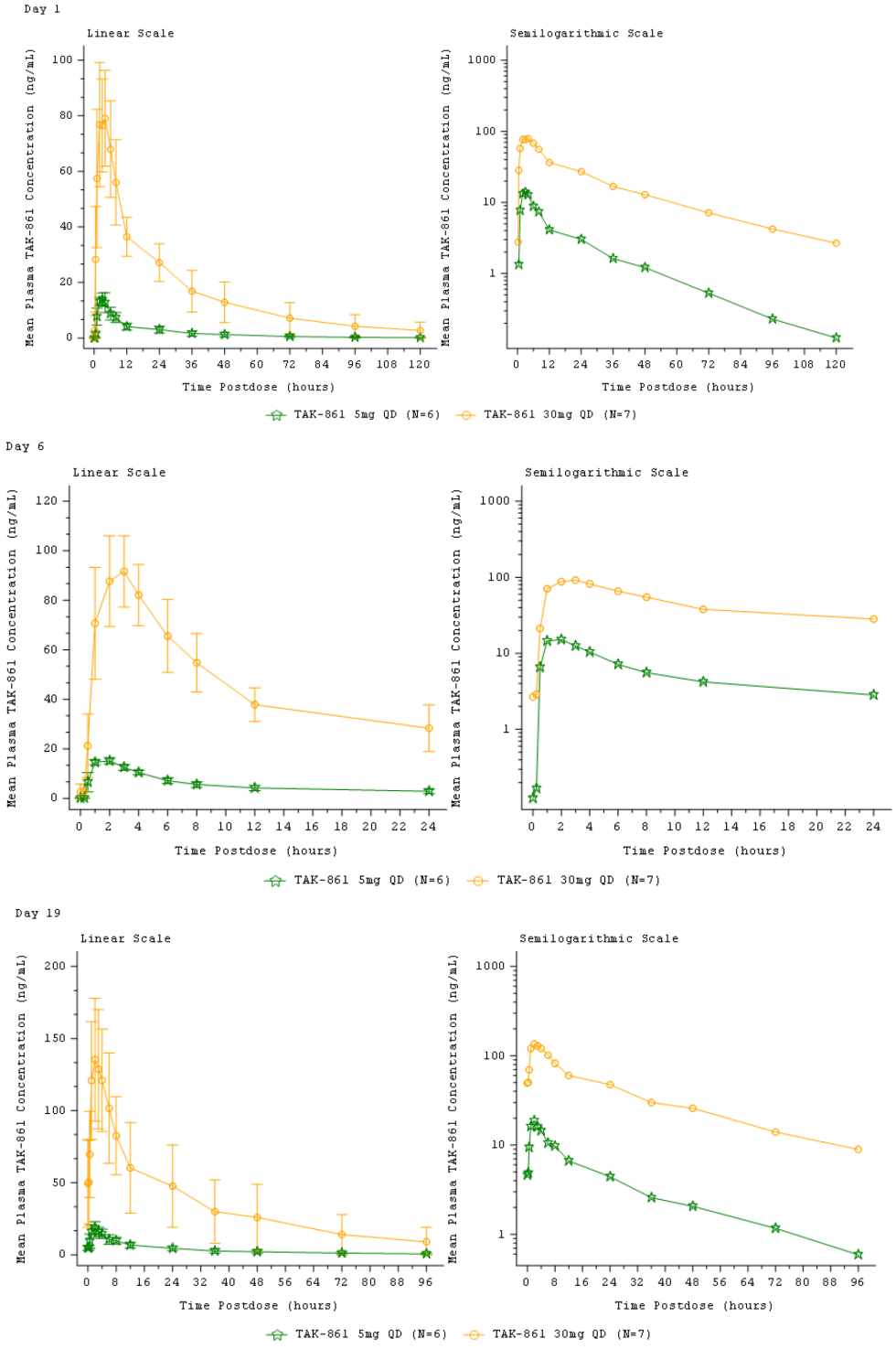
Source: Clinical Study Report TAK-861-1001, Table 11.y, pages 199–200

Part F – CSF PK (Healthy Non-Japanese Adults)

Following 5 mg QD for 10 days, geometric mean plasma and CSF $C_{max,ss}$ were 19.38 ng/mL and 0.6396 ng/mL, respectively. The median plasma and CSF t_{max} were 2.05 h and 4.00 h, respectively. Geometric mean AUC_{τ} ratio (CSF/plasma) was 0.04364, consistent with the unbound fraction of TAK-861 (Fu 2.2 to 3.8%).

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Figure 34. Mean (±Standard Deviation) Total Plasma TAK-861 Concentration vs. Time Profiles Following TAK-861 in Part F: Linear Scale (Left) and Semilogarithmic Scales (Right) (PK Set)



Source: Figure 15.2.5.1.3.1.
PK: pharmacokinetic(s); QD: once daily.
120 hours after Day 1 dose is also predose of Day 6.
Source: Clinical Study Report TAK-861-1001, Figure 11.p, pages 231

Reference ID: 5847402

Table 118. Plasma PK Parameters (Geometric Mean and %CV) of Oveporexton at Steady State, Day 19 – QD Dosing (Part F, PK Set)

Parameter (unit)	TAK-861 5 mg Fasted (E1) (N = 6)	TAK-861 30 mg Fasted (E2) (N = 7)
n	4	6
t_{max} (h) [a]	2.09 (2.05, 2.15)	2.06 (1.02, 3.02)
$C_{max,ss}$ (ng/mL)	18.44 (20.8)	138.6 (25.2)
$C_{av,ss}$ (ng/mL)	8.196 (26.3)	69.73 (40.6)
AUC_{τ} (h*ng/mL)	197.2 (26.4)	1684 (40.8)
AUC_{last} (h*ng/mL)	308.5 (40.9)	2892 (61.2)
AUC_{∞} (h*ng/mL)	332.0 (45.5)	3163 (70.0)

Source: Clinical Study Report TAK-861-1001, Table 11.y, pages 199–200

Clinical Study Report TAK-861-1003

Title

A Phase 1 Study to Characterize the Mass Balance, Pharmacokinetics, Absorption, Metabolism, and Excretion of [^{14}C]-TAK-861 in Healthy Adult Male Participants

Study Objectives

Primary Objective

- To evaluate the mass balance of [^{14}C]-TAK-861 in urine and feces following a single oral administration of 25 mg (~1 µCi) [^{14}C]-TAK-861.

Secondary Objectives

- Characterize the PK of TAK-861 in plasma and total radioactivity (TRA) concentration equivalents in plasma and whole blood following a single oral suspension dose of 25 mg [^{14}C]-TAK-861.
- Evaluate the safety and tolerability of TAK-861 and [^{14}C]-TAK-861.

Exploratory Objective

- Characterize the metabolite profile of TAK-861 in plasma, urine, and feces following a single oral administration of 25 mg [^{14}C]-TAK-861.

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Study Design

A phase 1, open-label, single-dose study in six healthy adult male participants. On Day 1, participants received a single oral dose of 25 mg (~1 µCi; 0.037 MBq) [^{14}C]-TAK-861 as an oral suspension after an overnight fast (≥10 h). Actual doses administered ranged from 26.1 to 26.2 mg (1.03 to 1.04 µCi). Participants were confined to the clinical research unit (CRU) until discharge criteria were met (≥90% TRA recovery in urine + feces, or TRA in both matrices ≤ lower limit of quantitation (LLOQ) for ≥2 consecutive 24-h intervals) or up to a maximum of 14 days postdose (Day 15).

Serial blood sampling (plasma and whole blood) was performed for TAK-861 PK, TRA determination, and metabolite profiling. Complete urine and fecal collections were made for TRA quantitation and metabolite profiling. A 30-day follow-up contact was performed. The estimated total radiation dose from ~1 µCi [^{14}C]-TAK-861 was below U.S. FDA and International Commission on Radiological Protection (ICRP) limits for radiation exposure in human subjects.

Table 119. Overview of Study Design

Parameter	Details
Dose	25 mg (~1 µCi) [^{14}C]-TAK-861 oral suspension
Route	Oral suspension, fasted (≥10 h overnight fast; fasted ≥4 h postdose)
Matrices analyzed	Plasma (TAK-861 PK + TRA + metabolites), Whole blood (TRA), Urine (TRA + metabolites), Feces (TRA + metabolites)
Blood PK sampling	Pre-dose, then at 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 240, and 336 h post-dose
Urine/feces collection	Pre-dose (baseline) and in 24-h intervals through up to 336 h post-dose

Source: Clinical Study Report TAK-861-1003, Sections 9.1 and 9.4, pages 17–25

All 6 enrolled participants received study drug and completed the study (100% completion). No protocol deviations of significant impact were observed.

Table 120. Demographic Summary (N=6)

Parameter	Value
Sex	Male, 100%
Race	White 67% (4/6); Black or African American 33% (2/6)
Ethnicity	Not Hispanic or Latino 83% (5/6); Hispanic or Latino 17% (1/6)
Mean Age (yrs)	41.5 (range: 29–55)
Mean BMI (kg/m^2)	26.74 (range: 25.1–29.1)
Mean Weight (kg)	85.6 (range: 78.1–94.9)

Source: Clinical Study Report TAK-861-1003, Table 11.a, pages 48–49

Bioanalytical Methods

The bioanalytical methods to determine the concentrations of TAK-861 in human plasma used in Study TAK-861-1003 are the same as those described in the bioanalytical report section (Section 16.4.2) of this Appendix ((b) (4) Study No. CB210057). In addition, the profiling of TAK-861 metabolites in plasma, urine, and feces was conducted by

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(b) (4) and the identification of TAK-861 metabolites in these matrices was performed by Takeda Development Center Americas, Inc. (TDCA).

Table 121. Overview of Bioanalytical Method Validation Results for Oveporexton in Plasma, Urine, and Feces

Parameter	Method 1: LC-MS/MS (Parent Drug)	Method 2: HPLC-AMS (Total Radioactivity (TRA) Profiling)	Method 3: LSC (TRA Excreta)
Detection technique	LC-MS/MS (liquid chromatography-tandem mass spectrometry)	HPLC fractionation + Accelerator Mass Spectrometry (AMS); HPLC-HRMS for identification	Liquid Scintillation Counting (LSC)
Matrix / Sample type	Plasma (individual time-point samples)	AUC-pooled plasma, whole blood (individual time points), pooled urine, pooled fecal homogenate extracts	Pooled urine and homogenized feces (individual 24-h collection intervals)
Purpose	Quantitation of unchanged TAK-861 in plasma for PK parameter estimation	Metabolite profiling and quantitation of TRA in plasma, whole blood, urine, and feces; generation of radiochromatograms	TRA quantitation in urine and fecal homogenate for mass balance
Analyte	Unchanged TAK-861	[^{14}C]-TRA, expressed as ng eq TAK-861/mL or g	[^{14}C]-TRA, expressed as ng eq TAK-861/g
Instrumentation	LC-MS/MS system (b) (4) validated platform)	Agilent 1290 HPLC + NEC SSAMS-250 AMS; AB SCIEX Triple TOF 6600 HRMS (for identification); β-RAM radiometric detector (TDCA)	PerkinElmer TriCarb 3180 TR/SL or 5110 TR LSC counter; PerkinElmer Model 307 Sample Oxidizer
Analytical range / LLOQ	0.100–200 ng/mL plasma	Plasma LLOQ: 1.02–1.17 ng eq TAK-861/mL Whole blood LLOQ: 2.89–3.21 ng eq TAK-861/mL Urine LLOQ: 36.2–37.5 ng eq TAK-861/g Feces LLOQ: 146–153 ng eq TAK-861/g	Urine LLOQ: 36.2–37.5 ng eq TAK-861/g Feces LLOQ: 146–153 ng eq TAK-861/g
Regulatory compliance	GLP-compliant validated assay	(b) (4) SOPs aligned with FDA GLP regs and ICH GCP; QA-audited (4 audits + report audit)	(b) (4) SOPs (non-GLP exploratory assay)

AMS = Accelerator Mass Spectrometry; HRMS = High-Resolution Mass Spectrometry; LSC = Liquid Scintillation Counting; pMC = Percent Modern Carbon; TRA = Total Radioactivity; LLOQ = Lower Limit of Quantification.
Sources: Analytical Report TKD-BCS-01618-R1, Sections 6.1–6.3, pages 8–11; (b) (4) 005/028, Sections 1–14, pages 12–28

Clinical Pharmacology Reviewer's Comments: The bioanalytical methods satisfied the criteria for method validation and "application to routine analysis" set by the guidance for industry, *Bioanalytical Method Development*, and is acceptable.

Pharmacokinetic Results

Plasma TAK-861 and Total Radioactivity (TRA) Concentrations

Plasma TAK-861 concentrations were quantifiable in all participants by 0.25 h post-dose and in the majority of participants through 168 h post-dose (2 participants through 240 h). Arithmetic mean peak plasma concentration (148.3 ng/mL) of TAK-861 reached at 2 h post-dose.

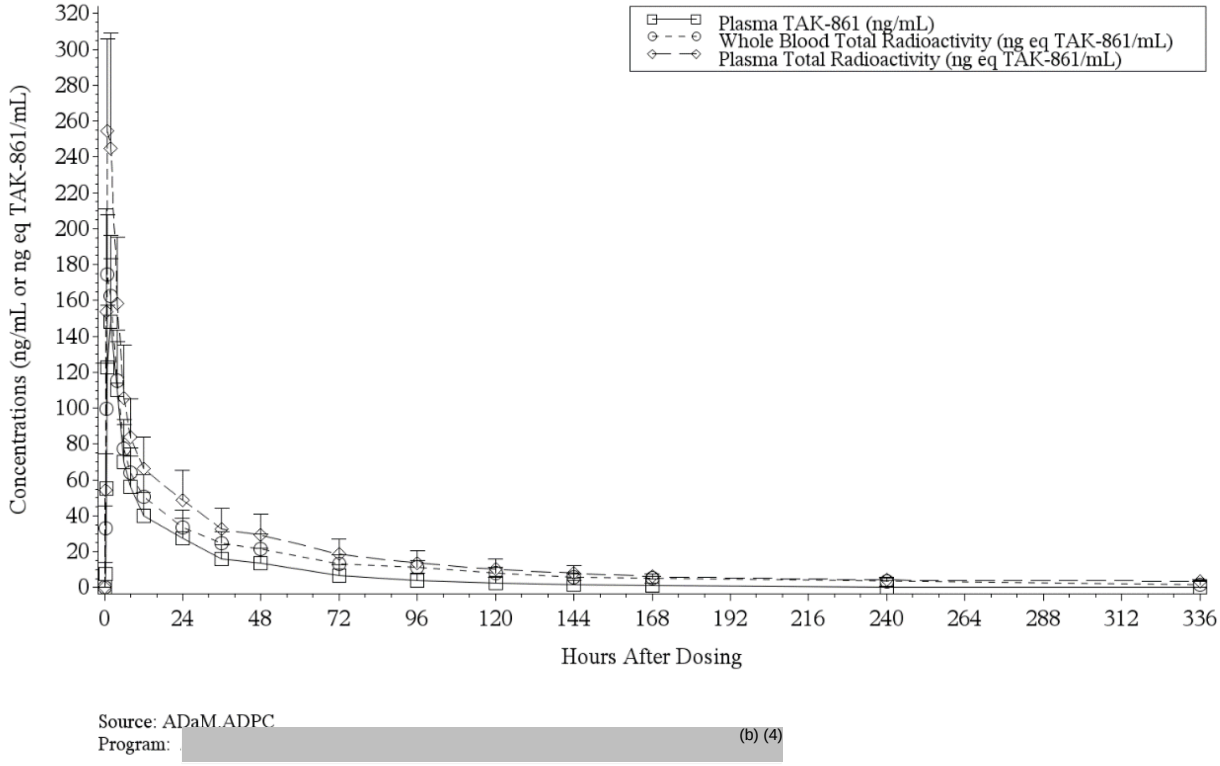
Whole blood TRA was quantifiable in all participants by 0.25 h and in the majority through 240 h (one participant through 336 h). Peak arithmetic mean was 174.5 ng eq TAK-861/mL at 1 h. Plasma TRA was quantifiable in all participants by 0.25 h and through 240 h in all participants (two through 336 h). Peak arithmetic mean was 254.5 ng eq TAK-861/mL at 1 h.

Unchanged oveporexton was the most abundant drug-related species in plasma (59.9%). No major metabolites (>10%) were observed in plasma. The two most abundant metabolites in plasma were M4 (5.12%) and M30 (4.92%); each of the other circulating metabolites accounted for <4% of the dose. Oveporexton was primarily eliminated through hepatic oxidation, approximately 80% of the dose recovered in feces was contributed by metabolites.

The higher TRA versus TAK-861 concentrations, longer TRA $t_{½z}$, and AUC_t Ratio of ~0.50 at 120 h indicate the presence of circulating radioactive metabolites (see metabolites profiling for additional information) in addition to parent drug. Whole blood: plasma TRA partitioning ratios ranged from 0.6054 to 0.8989, suggesting minimal extent of partitioning into the cellular fraction of whole blood.

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Figure 35. Arithmetic Mean (SD) Plasma TAK-861 Concentrations and Whole Blood and Plasma Total Radioactivity TAK-861 Concentration Equivalents vs. Time Following a Single Oral Dose of 25 mg (~1 µCi) [^{14}C]TAK-861 as an Oral Suspension in Healthy Male Participants (Linear Scale)



Source: Clinical Study Report TAK-861-1003, Figures 11.a

Table 122. Summary of Plasma TAK-861 and TRA PK Parameters

PK Parameter	Plasma TAK-861 (N=6)	Whole Blood TRA (N=6)	Plasma TRA (N=6)
T_{max} (h)[1]	2.027 (1.01, 2.04)	1.020 (1.00, 2.02)	1.241 (1.01, 2.03)
C_{max} (ng/mL or ng eq TAK-861/mL)[2]	147.6 (23.3%)	178.8 (14.8%)	263.1 (17.4%)
AUC_{last} (ng·h/mL)[2]	2110 (47.4%)	3698 (24.8%)	4970 (28.5%)
AUC_{∞} (ng·h/mL)[2]	2127 (48.1%)	4473 (23.6%)	5765 (26.3%)
$t_{½z}$ (h)[3]	26.551±11.929	135.326±64.964	137.255±37.289
B:P AUC_{∞} Ratio[2]	N/A	0.7760 (16.3%)	N/A
AUC_t Ratio (t =120 h)[2]	0.4954 (14.2%)	N/A	N/A

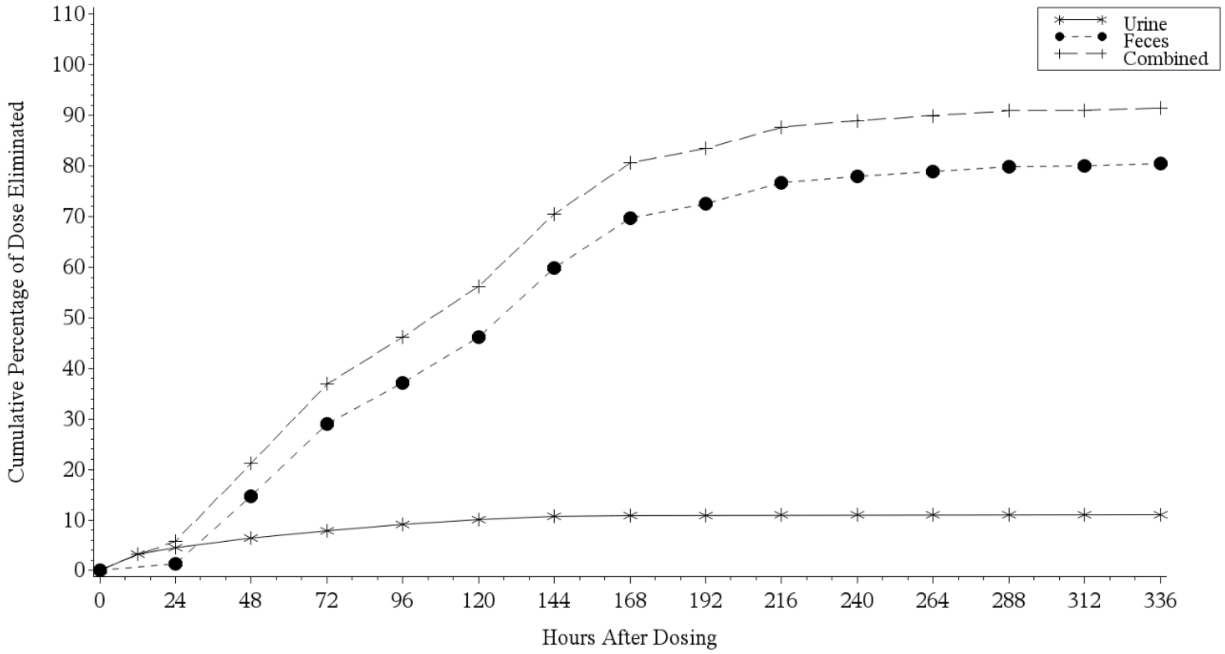
[1] Median (min, max). [2] Geometric mean (geometric %CV). [3] Arithmetic mean ± SD.
AUCt Ratio = plasma TAK-861 AUCt/plasma TRA AUCt (t =120 h post-dose).
B:P AUC_{∞} Ratio = whole blood TRA AUC_{∞}/plasma TRA AUC_{∞}.
Source: Clinical Study Report TAK-861-1003, Table 11.e, page 54

Mass Balance—Excretion of Total Radioactivity

Complete urine and fecal collections were obtained. Mean cumulative TRA recovery was 91.49% of the administered dose. Fecal excretion was the predominant route (80.47%), with urinary excretion playing a secondary role (11.02%). In urine, unchanged oveporexton

accounted for only 0.1% of the total dose. The most abundant metabolites were M8 and M9 (glucuronide conjugates of the oxidative metabolites M4 and M12), and M29 (sulfate conjugate); each of the other metabolites accounted for <1% of the dose. In feces, unchanged oveporexton contributed only 0.5% to the total dose. The most abundant metabolites (>4%) were M4 (oxidative metabolite), M16 (carboxylic acid derivative), M12 (oxidative metabolite), M19 (oxidative defluorinated derivative), and M17 (carboxylic acid derivative); each of the other metabolites accounted for <4% of the dose.

Figure 36. Arithmetic Mean Cumulative Percentage of the [^{14}C]-TAK-861 Dose Eliminated as Total Radioactivity in Urine, Feces, and Combined vs. Time Following a Single Oral Dose of 25 mg (~1 µCi) [^{14}C]-TAK-861 as an Oral Suspension in Healthy Male Participants (Linear Scale)



Source: Clinical Study Report TAK-861-1003,Figures 11.d

Metabolite Profiling

Primary Biotransformation Pathways

Aromatic oxidation (~39% of dose) → M4 and M12, subsequently conjugated to M8, M9, M29, M30. Aliphatic oxidation (~12%) → M16 and M17. Oxidative defluorination (~5%) → M19. M4 (from aromatic oxidation) was the major metabolite contributing ~28% of dose, predominantly excreted in feces. A mean 80% of dose in feces consisted of oxidative metabolites, confirming hepatic oxidation as the major clearance mechanism.

Reference ID: 5847402

Table 123. Overview of Metabolites Abundance by Matrix

Metabolite	Description	Plasma (% TRA)	Urine (% dose)	Feces (% dose)
TAK-861 (unchanged)	Parent drug	~59.9%	0.1%	0.5%
M4	Oxidative (aromatic)	5.12%	0.3%	27.3%
M12	Oxidative (aromatic)	3.78%	0.1%	5.0%
M8	Glucuronide of M4	2.61%	2.7%	—
M9	Glucuronide of M12	3.53%	2.0%	—
M29	Sulfate conjugate (oxidative)	2.12%	1.2%	—
M30	Sulfate conjugate (oxidative)	4.92%	0.2%	—
M16	Carboxylic acid (aliphatic oxidation)	<4%	0.5%	6.5%
M17	Carboxylic acid (aliphatic oxidation)	<4%	0.3%	4.2%
M19	Oxidative defluorinated derivative	—	—	4.5%

Plasma values are % of AUC-pooled TRA; urine and feces values are % of administered dose.
Source: Clinical Study Report TAK-861-1003, Sections 11.4.3 and 13.1, pages 57–66

Clinical Study TAK-861-1004

Title

A Phase 1, Open-Label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Oral Dosing of TAK-861 in Participants with or without Hepatic Impairment

Primary Objective

- To characterize the plasma PK of TAK-861 following oral dosing in participants with mild or moderate HI compared to participants with normal hepatic function. Primary PK endpoints: C_{max}, AUC_{last}, and AUC_{∞}.

Secondary Objective

- To evaluate the safety and tolerability of TAK-861 following oral dosing in participants with mild or moderate HI and in participants with normal hepatic function.

Exploratory Objectives

- Characterize unbound plasma TAK-861 PK ($C_{max,u}$, $AUC_{last,u}$, $AUC_{\infty,u}$, CL_u/F, $V_{z,u}/F$) in HI versus normal hepatic function participants.
- Characterize additional PK parameters (t_{max}, $t_{½z}$, CL/F, V_z/F) in HI versus normal hepatic function.
- Assess plasma protein binding (fraction unbound, fu) of TAK-861 across cohorts.

Study Design

A phase 1, open-label, parallel-group study conducted at two sites in the United States (Orlando, FL and Miami, FL). Participants with chronic, stable HI with features of cirrhosis were enrolled and classified by Child-Pugh score (mild (Class A): 5 and 6; moderate (Class B): 7 to 9). Each HI cohort was matched to a control group of healthy participants with normal hepatic function by body mass index (BMI; mean ±10%), age (mean ±10 years), and sex ratio

Reference ID: 5847402

(±2 per sex). All participants were confined to the clinical research unit from Day −1 through Day 10.

Table 124. Study Design Overview

Cohort	Population	N Dosed	Child-Pugh Score	Matched Controls
Cohort 1 (Mild HI)	Hepatically impaired	10	5–6 (Mean 5.6)	Matched to Cohort 3 (N=10)
Cohort 2 (Moderate HI)	Hepatically impaired	10	7–9 (Mean 7.4)	Matched to Cohort 3 (N=10)
Cohort 3 (Control)	Normal hepatic function	13	N/A	7 participants matched to both HI cohorts

Source: Clinical Study Report TAK-861-1004, Tables 4 and 10, pages 18 and 31

Treatment Administered

TAK-861 4-mg total dose (T3 tablet formulation), administered as two 2-mg oral tablets given at least 3 hours apart on Day 1. The first dose was administered under fasting conditions (≥10 h overnight fast), followed by a light meal (~400 to 500 cal, ~25% fat) approximately 1 hour after the first dose. The second dose was administered 3 hours after the first dose, followed by a second light meal approximately 1 hour later.

Pharmacokinetic Sampling

Blood samples for total and unbound plasma TAK-861 PK were collected at: pre-dose (Day 1), and at 0.25, 0.5, 1, 1.5, 2, 3, 3.25, 3.5, 4, 4.5, 5, 6, 8, and 12 hours post-first dose on Day 1; then at 24, 36, 48, 72, 96, 120, 168, and 216 hours post-first dose (Days 2 through 10). Samples for protein binding were collected at three selected postdose time points.

Results

Subject Disposition and Demographics

All 33 enrolled participants received trial intervention and completed the study. No participants withdrew or discontinued.

Table 125. Demographic Summary

Parameter	Mild HI (N=10)	Moderate HI (N=10)	NHF Matched to Mild HI (N=10)	NHF Matched to Mod HI (N=10)	NHF Pooled (N=13)	Overall (N=33)
Sex: Female (%)	40.0%	40.0%	40.0%	50.0%	46.2%	42.4%
Sex: Male (%)	60.0%	60.0%	60.0%	50.0%	53.8%	57.6%
Race: White (%)	80.0%	100.0%	90.0%	80.0%	76.9%	84.8%
Ethnicity: Hispanic/Latino (%)	50.0%	60.0%	70.0%	60.0%	61.5%	57.6%
Mean Age (yrs)	65.5	61.1	62.3	60.9	61.5	62.6
Mean BMI (kg/m²)	26.40	28.24	26.58	28.44	27.43	27.36
Mean Weight (kg)	76.91	77.54	75.85	79.02	77.42	77.30

Reference ID: 5847402

Parameter	Mild HI (N=10)	Moderate HI (N=10)	NHF Matched to Mild HI (N=10)	NHF Matched to Mod HI (N=10)	NHF Pooled (N=13)	Overall (N=33)
Child-Pugh Score (Mean)	5.6	7.4	N/A	N/A	N/A	—

Abbreviation: NHF = Normal Hepatic Function; HI = Hepatic Impairment
Source: Clinical Study Report TAK-861-1004, Table 11, pages 33–35

Bioanalytical Methods

The bioanalytical methods used in Study TAK-861-1004 are the same as those described in the bioanalytical report section (Section 16.4.2) of this Appendix (Report Nos. CB201176/CB201177; Study No. CB210057; [redacted](b) (4)). Total and unbound plasma TAK-861 concentrations were quantified by validated LC-MS/MS methods at [redacted](b) (4)

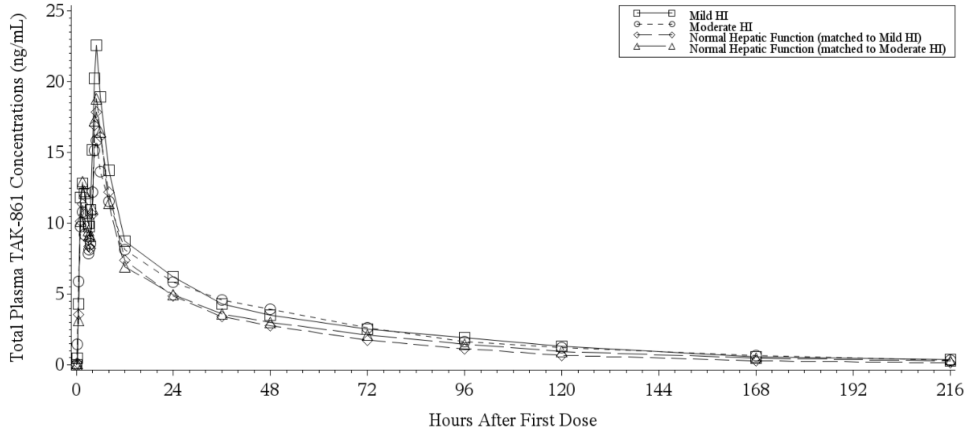
Pharmacokinetic Results

After oral administration of TAK-861 4 mg (2 mg BID, 3 hours apart), two plasma concentration peaks were observed reflecting the two doses. In participants with mild HI, arithmetic mean peak total plasma TAK-861 concentrations after Dose 1 (12.83 ng/mL) and Dose 2 (22.58 ng/mL) occur at approximately 1.5 hours and 5 hours (2 hours after Dose 2) post-initial dose, respectively. Concentrations were higher throughout the sampling period in participants with mild HI compared to matched healthy controls.

In participants with moderate HI, arithmetic mean concentrations after Dose 1 (10.80 ng/mL) and Dose 2 (15.84 ng/mL) occur at 1.5 hours and 5 hours post-initial dose, respectively. Concentrations tended to be slightly lower around the peaks but higher during the elimination phase compared to matched healthy controls, consistent with reduced hepatic clearance.

Reference ID: 5847402

Figure 37. Arithmetic Mean Total Plasma Concentration vs. Time Profiles of TAK-861 Following TAK-861 2 mg BID in Participants With Mild and Moderate Hepatic Impairment and Participants With Normal Hepatic Function (Linear Scale, PK Set)



Participants received a first dose of 2 mg TAK-861 under fasting conditions followed by a light meal approximately 1 hour after the first dosing, and a second dose of 2 mg TAK-861 at least 3 hours after the first dose.
Mild HI: Hepatically-impaired participants with a Child-Pugh score of 5 to 6
Moderate HI: Hepatically-impaired subject with a Child-Pugh score of 7 to 9
Normal Hepatic Function (matched to Mild HI): Healthy participants with normal hepatic function matched to the group mean of mild HI participants by BMI (±10%), age (±10 years), and sex (±2 per sex)
Normal Hepatic Function (matched to Moderate HI): Healthy participants with normal hepatic function matched to the group mean of Moderate HI participants by BMI (±10%), age (±10 years), and sex (±2 per sex)
HI = Hepatic impairment; BMI = Body mass index; BID = Two doses given at least 3 hours apart on Day 1
Program: (b) (4)

Source: ages 38

Table 126. Summary of Total Plasma Pharmacokinetic Parameters of TAK-861 Following TAK-861 2 mg BID in Participants With Mild and Moderate Hepatic Impairment and in Participants With Normal Hepatic Function

Pharmacokinetic Parameter	Mild HI (N=10)	Moderate HI (N=10)	Normal Hepatic Function (matched to Mild HI) (N=10)	Normal Hepatic Function (matched to Moderate HI) (N=10)
t_{max} (h)	5.000 (4.50, 6.00)	4.750 (0.50, 8.00)	5.000 (4.50, 8.00)	5.000 (1.50, 6.00)
C_{max} (ng/mL)	23.35 (19.5)	16.91 (40.7)	20.15 (16.1)	20.49 (16.9)
AUC_{last} (ng•h/mL)	548.8 (36.3)	530.3 (28.0)	409.7 (35.5)	464.0 (25.1)
AUC_{∞} (ng•h/mL)	574.3 (38.9)	554.3 (32.3)	416.0 (36.5)	483.0 (30.0)
$t_{1/2z}$ (h)	43.274 ± 17.1835	46.471 ± 18.2676	37.472 ± 6.3939	45.345 ± 18.3342
CL/F (L/h)	7.421 ± 2.7783	7.533 ± 2.2669	10.17 ± 3.6339	8.591 ± 2.3449
V_z/F (L)	412.4 ± 89.122	469.0 ± 118.56	524.5 ± 113.59	522.0 ± 92.753

Participants received a first dose of 2 mg TAK-861 under fasting conditions followed by a light meal approximately 1 hour after the first dosing, and a second dose of 2 mg TAK-861 at least 3 hours after the first dose.
Mild HI: Hepatically-impaired participants with a Child-Pugh score of 5 to 6
Moderate HI: Hepatically-impaired participants with a Child-Pugh score of 7 to 9
Normal Hepatic Function (matched to Mild HI): Healthy participants with normal hepatic function matched to the group mean of mild HI participants by BMI (±10%), age (±10 years), and sex (±2 per sex)
Normal Hepatic Function (matched to Moderate HI): Healthy participants with normal hepatic function matched to the group mean of moderate HI participants by BMI (±10%), age (±10 years), and sex (±2 per sex)
t_{max} is calculated relative to the first dose. t_{max} values are presented as median (minimum, maximum).
C_{max}, AUC_{last}, and AUC_{∞} values are presented as geometric mean (geometric percent coefficient of variation).
$t_{1/2z}$, CL/F, and V_z/F values are presented as arithmetic mean ± standard deviation.
HI = Hepatic Impairment; BMI = Body mass index; BID = Two doses given at least 3 hours apart on Day 1
Source: Table 15.2.1.13 through 15.2.1.16
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Source: Clinical Study Report TAK-861-1004, Table 13, pages 44

Reference ID: 5847402

The unbound plasma PK parameters were also measured in subjects with mild or moderate HI following oral administration of a single 4-mg dose of TAK-861, given as two 2-mg doses administered 3 hours apart. The results showed that HI did not alter the unbound fraction of oveporexton compared with subjects with normal hepatic function. The $C_{max,u}$, $AUC_{last,u}$, and $AUC_{\infty,u}$ of unbound plasma oveporexton were 11% lower, 23% higher, and 24% higher (GMRs of 88.89%, 123.09%, and 123.63%, respectively) in participants with moderate HI than in healthy matched participants with normal hepatic function, which is comparable to the changes observed in total plasma oveporexton PK in subjects with HI.

Table 127. Statistical Comparison of Total and Unbound Plasma Oveporexton PK Parameters Following in Participants With Mild and Moderate Hepatic Impairment

	Mild HI (Test)			Normal Hepatic Function (matched to Mild HI) (Reference)					
Pharmacokinetic Parameter	Geometric LSM	95% Confidence Interval	n	Geometric LSM	95% Confidence Interval	n	GMR (%)	90% Confidence Interval	Inter-participant CV%
C_{max} (ng/mL)	23.35	20.75 - 26.27	10	20.15	17.91 - 22.67	10	115.88	100.99 - 132.95	17.9
AUC_{last} (ng•h/mL)	548.8	435.5 - 691.5	10	409.7	325.1 - 516.2	10	133.96	102.28 - 175.45	35.9
AUC_{∞} (ng•h/mL)	574.3	450.7 - 731.7	10	416.0	326.5 - 530.1	10	138.04	104.03 - 183.16	37.7
$C_{max,u}$ (ng/mL)	0.5261	0.4663 - 0.5935	10	0.4272	0.3787 - 0.4820	10	123.14	106.97 - 141.75	18.3
$AUC_{last,u}$ (ng•h/mL)	12.37	9.886 - 15.47	10	8.687	6.945 - 10.87	10	142.36	109.62 - 184.87	34.7
$AUC_{\infty,u}$ (ng•h/mL)	12.94	10.21 - 16.40	10	8.821	6.962 - 11.18	10	146.69	111.27 - 193.39	36.8

	Moderate HI (Test)			Normal Hepatic Function (matched to Moderate HI) (Reference)					
Pharmacokinetic Parameter	Geometric LSM	95% Confidence Interval	n	Geometric LSM	95% Confidence Interval	n	GMR (%)	90% Confidence Interval	Inter-participant CV%
C_{max} (ng/mL)	16.91	13.84 - 20.65	10	20.49	16.77 - 25.03	10	82.53	65.34 - 104.24	30.8
AUC_{last} (ng•h/mL)	530.3	445.7 - 631.0	10	464.0	390.0 - 552.1	10	114.28	93.29 - 139.99	26.6
AUC_{∞} (ng•h/mL)	554.3	452.9 - 678.5	10	483.0	394.6 - 591.1	10	114.78	90.66 - 145.32	31.1
$C_{max,u}$ (ng/mL)	0.3981	0.3208 - 0.4941	10	0.4478	0.3608 - 0.5558	10	88.89	69.08 - 114.38	33.4
$AUC_{last,u}$ (ng•h/mL)	12.49	10.04 - 15.53	10	10.14	8.153 - 12.62	10	123.09	95.39 - 158.84	33.8
$AUC_{\infty,u}$ (ng•h/mL)	13.05	10.28 - 16.58	10	10.56	8.312 - 13.41	10	123.63	93.52 - 163.44	37.2

Participants received a first dose of 2 mg TAK-861 under fasting conditions followed by a light meal approximately 1 hour after the first dosing, and a second dose of 2 mg TAK-861 at least 3 hours after the first dose.
Mild HI: Hepatically-impaired participants with a Child-Pugh score of 5 to 6
Normal Hepatic Function (matched to Mild HI): Healthy participants with normal hepatic function matched to the group mean of mild HI participants by BMI (±10%), age (±10 years), and sex (±2 per sex)
The model includes hepatic function cohort as a fixed factor.
Parameters were natural log-transformed prior to analysis.
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the model.
Geometric LSM Ratio (GMR) (%) = 100 × (Test/Reference)
The 95% confidence intervals (CIs) for the geometric LSMs and the 90% CIs for GMRs are calculated by exponentiating the original CIs estimated from the model accordingly.
Inter-participant percent coefficient of variation (CV%) was calculated as 100 × (square root(exp[MSE] - 1)), where MSE = Residual variance from the model.
HI = Hepatic impairment; BMI = Body mass index; BID = Two doses given at least 3 hours apart on Day 1
Source: Clinical Study Report TAK-861-1004, Table 15 and Table 16, pages 48-49

Clinical Study TAK-861-1005

Title

A Phase 1, Open-Label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Oral Dosing of TAK-861 in Participants with or without Renal Impairment

Study Objectives

Primary Objective

- To characterize the plasma PK of TAK-861 following oral dosing in participants with severe RI (eGFR <30 mL/min, not on hemodialysis) compared to participants with normal renal function (eGFR ≥90 mL/min). Primary endpoints: C_{max}, AUC_{last}, AUC_{∞}.

Secondary Objective

- To evaluate the safety and tolerability of TAK-861 following oral dosing in participants with severe RI and in participants with normal renal function.

Exploratory Objectives

- Characterize unbound plasma TAK-861 PK ($C_{max,u}$, $AUC_{last,u}$, $AUC_{\infty,u}$, CLu/F, $V_{z,u}/F$) and additional PK parameters (t_{max}, $t_{½z}$, CL/F, V_z/F) in severe RI versus normal renal function; assess plasma protein binding (fraction unbound, fu).

Study Design

A phase 1, open-label, parallel-group study. Two cohorts: Cohort 1: participants with severe RI (eGFR <30 mL/min); Cohort 2: healthy participants with normal renal function (eGFR ≥90 mL/min) matched to Cohort 1 by BMI (±10%), age (±10 years), and sex (±2 per sex). eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula. Participants were confined to the CRU from Day −1 through Day 7.

Reference ID: 5847402

Treatments

TAK-861 4 mg (T3 tablet) as two 2-mg tablets given at least 3 hours apart on Day 1. First dose under fasting conditions (≥10 h), followed by a light meal (~400 to 500 cal, ~25% fat) ~1 h after each dose.

PK Sampling Schedule

Pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 3.25, 3.5, 4, 4.5, 5, 6, 8, 12 h post-first dose (Day 1), then at 24, 36, 48, 72, 96, 120, and 144 h post-first dose (Days 2–7). Protein binding samples collected at two postdose time points.

Subject Disposition and Demographics

All 20 enrolled participants received trial intervention and completed the study (100% completion). No participants withdrew or were discontinued.

Table 128. Demographic Summary

Parameter	Severe RI (N=10)	Normal RF (N=10)	Overall (N=20)
Sex: Female/Male	20% / 80%	20% / 80%	20% / 80%
Race: White	30%	70%	50%
Race: Black or African American	60%	30%	45%
Ethnicity: Hispanic or Latino	20%	60%	40%
Mean Age (yrs)	62.3	59.5	60.9
Mean BMI (kg/m²)	28.09	28.45	28.27
Mean Weight (kg)	82.4	84.1	83.3
Mean eGFR at Screening (mL/min)	19.71	118.36	—
Mean eGFR at Baseline (mL/min)	19.92	107.14	—

Abbreviations: RI = Renal Impairment
Source: Clinical Study Report TAK-861-1005, Table 10, pages 29–30

Bioanalytical Methods

The bioanalytical methods used in Study TAK-861-1005 are the same as those described in the bioanalytical report section (Section 16.4.2) of this Appendix ((b) (4) Study No. CB210057). Total and unbound plasma TAK-861 concentrations were quantified by validated LC-MS/MS methods at (b) (4)

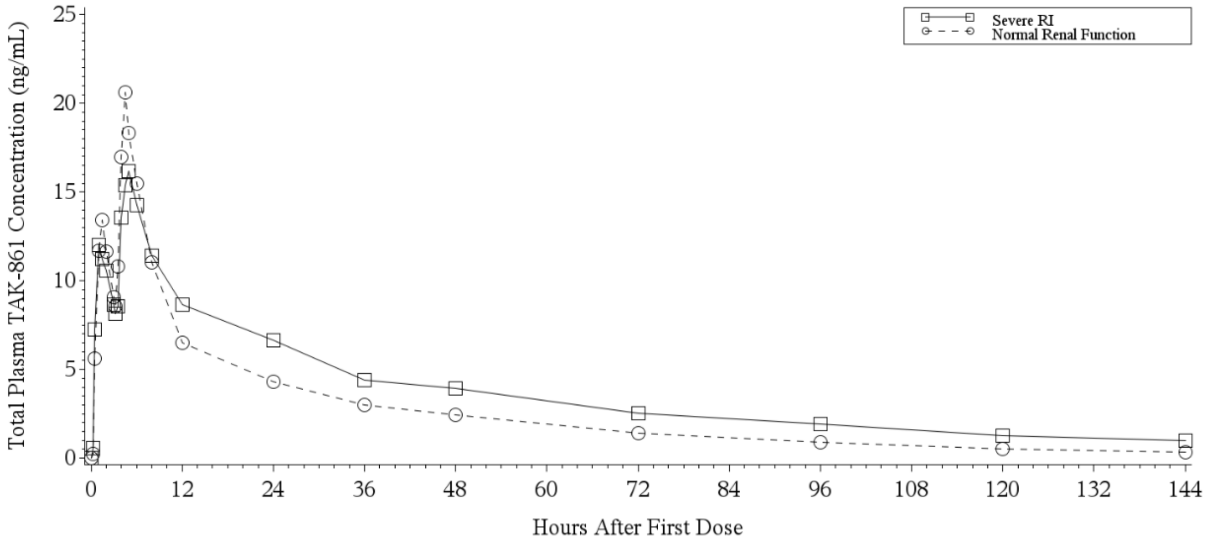
Pharmacokinetic Results

After TAK-861 4 mg (2 mg BID, 3 h apart), two plasma concentration peaks were observed. In severe RI subjects: mean peak 1 plasma concentration (12.02 ng/mL) reached at 1 hour after Dose 1, and mean peak 2 plasma concentration (16.17 ng/mL) reached at 5 h (2 hours after Dose 2) after the initial dose. In normal renal function: peaks (13.43 ng/mL (after Dose 1) and 20.63 ng/mL (after Dose 2)) reached at 1.5 h and 4.5 h after the initial dose. Peak

Reference ID: 5847402

concentrations were lower in severe RI; however, concentrations in the elimination phase remained higher in severe RI, consistent with reduced clearance.

Figure 38. Mean Plasma TAK-861 Concentration vs. Time Profiles Following TAK-861 2 mg BID in Participants With Severe Renal Impairment and in Participants With Normal Renal Function (Linear Scale)



Participants received a first dose of 2 mg TAK-861 under fasting conditions followed by a light meal approximately 1 hour after the first dosing, and a second dose of 2 mg TAK-861 at least 3 hours after the first dose.
Severe RI: Renally-impaired participants with an estimated glomerular filtration rate value <30 mL/min, not on hemodialysis
Normal Renal Function: Healthy participants with normal renal function (estimated glomerular filtration rate value ≥90 mL/min) matched to the group mean demographics of participants with severe RI by body mass index (mean ±10%), age (mean ±10 years), and sex ratio (±2 per sex)
RI = Renal impairment; BID = Two doses given at least 3 hours apart on Day 1
Source: ADaM.ADPC
Program: (b) (4)

Source: Clinical Study Report TAK-861-1005, Figure 1, page 33

Table 129. Summary of Plasma Pharmacokinetic Parameters of Oveporexton Following TAK-861 2 mg BID in Participants With Severe Renal Impairment and in Participants With Normal Renal Function

Pharmacokinetic Parameter	Severe RI (N=10)	Normal Renal Function (N=10)
t_{max} (h)	4.759 (1.00, 6.00)	4.500 (4.00, 5.83)
C_{max} (ng/mL)	17.42 (29.7)	20.85 (36.7)
AUC_{last} (ng•h/mL)	495.2 (39.3)	366.3 (21.7)
AUC_{∞} (ng•h/mL)	556.9 (52.3)	382.8 (22.3)
$t_{1/2z}$ (h)	44.363 ± 27.3090	32.670 ± 9.1202
CL/F (L/h)	7.897 ± 3.2091	10.68 ± 2.3506
V_z/F (L)	424.8 ± 136.38	497.1 ± 159.89

Participants received a first dose of 2 mg TAK-861 under fasting conditions followed by a light meal approximately 1 hour after the first dosing, and a second dose of 2 mg TAK-861 at least 3 hours after the first dose.
Severe RI: Renally-impaired participants with an estimated glomerular filtration rate value <30 mL/min, not on hemodialysis
Normal Renal Function: Healthy participants with normal renal function (estimated glomerular filtration rate value ≥90 mL/min) matched to the group mean demographics of participants with severe RI by body mass index (mean ±10%), age (mean ±10 years), and sex ratio (±2 per sex)
t_{max} is calculated relative to the first dose. t_{max} values are presented as median (minimum, maximum).
C_{max}, AUC_{last}, and AUC_{∞} values are presented as geometric mean (geometric percent coefficient of variation).
$t_{1/2z}$, CL/F, and V_z/F values are presented as arithmetic mean ± standard deviation.
RI = Renal impairment; BID = Two doses given at least 3 hours apart on Day 1
Source: Table 15.2.1.7 and Table 15.2.1.8
Program: (b) (4)

Source: Clinical Study Report TAK-861-1005, Table 12, page 36

Severe RI reduced plasma C_{max} of TAK-861 by 16% (GMR 83.56%, 90% CI: 64.95–107.49%) and increased AUC_{last} and AUC_{∞} by 35% and 45% (GMRs 135.21% and 145.48%), respectively, compared to subjects with normal renal function. Given the minor role of renal elimination (<1%) in TAK-861 disposition, the dosage adjustment is not necessary for patients with mild, moderate, and severe RI.

Unbound plasma oveporexton PK parameters following administration of 4 mg (split evenly as two 2-mg doses given at least 3 hours apart) in participants with severe RI were also evaluated. The geometric mean $C_{max,u}$ of unbound plasma TAK-861 in participants with severe RI (0.3667 ng/mL) was lower than that in healthy matched participants with normal renal function (0.4972 ng/mL). The geometric mean $AUC_{last,u}$ and $AUC_{\infty,u}$ of unbound plasma TAK-861 in participants with severe RI (10.43 ng·h/mL and 11.72 ng·h/mL, respectively) were slightly higher than those in healthy participants with normal renal function (8.736 ng·h/mL and 9.130 ng·h/mL, respectively).

Reference ID: 5847402

Table 130. Statistical Comparisons of Total and Unbound Plasma Oveporexton PK Parameters in Participants With Severe Renal Impairment vs. Participants With Normal Renal Function

	Severe RI (Test)			Normal Renal Function (Reference)					
Pharmacokinetic Parameter	Geometric LSM	95% Confidence Interval	n	Geometric LSM	95% Confidence Interval	n	GMR (%)	90% Confidence Interval	Inter-participant CV%
C_{max} (ng/mL)	17.42	14.04 - 21.62	10	20.85	16.80 - 25.87	10	83.56	64.95 - 107.49	33.4
AUC_{last} (ng•h/mL)	495.2	403.6 - 607.7	10	366.3	298.5 - 449.4	10	135.21	106.48 - 171.69	31.5
AUC_{∞} (ng•h/mL)	556.9	432.4 - 717.4	10	382.8	297.2 - 493.1	10	145.48	108.25 - 195.50	39.5
$C_{max,u}$ (ng/mL)	0.3667	0.2848 - 0.4722	10	0.4972	0.3862 - 0.6402	10	73.75	54.91 - 99.06	39.5
$AUC_{last,u}$ (ng•h/mL)	10.43	7.898 - 13.76	10	8.736	6.618 - 11.53	10	119.34	86.31 - 165.03	43.7
$AUC_{\infty,u}$ (ng•h/mL)	11.72	8.518 - 16.14	10	9.130	6.634 - 12.57	10	128.41	88.44 - 186.44	51.0

Participants received a first dose of 2 mg TAK-861 under fasting conditions followed by a light meal approximately 1 hour after the first dosing, and a second dose of 2 mg TAK-861 at least 3 hours after the first dose.
Severe RI: Renally-impaired participants with an estimated glomerular filtration rate value <30 mL/min, not on hemodialysis
Normal Renal Function: Healthy participants with normal renal function (estimated glomerular filtration rate value ≥90 mL/min) matched to the group mean demographics of participants with severe RI by body mass index (mean ±10%), age (mean ±10 years), and sex ratio (±2 per sex)
The model includes renal function cohort as a fixed factor.
Parameters were natural log-transformed prior to analysis.
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the model.
Geometric LSM Ratio (GMR) (%) = 100 × (Test/Reference)
The 95% confidence intervals (CIs) for the geometric LSMs and the 90% CIs for GMRs are calculated by exponentiating the original CIs estimated from the model accordingly.
Inter-participant percent coefficient of variation (CV%) was calculated as 100 × (square root (exp[MSE] - 1)), where MSE = Residual variance from the model.
RI = Renal impairment; BID = Two doses given at least 3 hours apart on Day 1
Source: Clinical Study Report TAK-861-1005, Table 14, page 38

Clinical Study TAK-861-1007

Title

A Phase 1, Open-Label Study to Evaluate the Relative Bioavailability of Immediate Release (IR) TAK-861 Tablets, and the Effects of CYP3A Inhibitors Fluconazole and Itraconazole, and CYP3A Inducer Phenytoin on the Single-Dose Pharmacokinetic Profile of TAK-861 in Healthy Adults

Study Objectives

Primary Objectives

- Group 1 (rBA): Evaluate the oral bioavailability (BA) of the T2 IR tablet relative to the T1 IR tablet formulation.
- Group 2 (Fluconazole Drug-Drug Interaction (DDI)): Evaluate the effect of multiple-dose fluconazole (moderate CYP3A inhibitor) on the PK of a single oral dose of TAK-861.
- Group 3 (Phenytoin DDI): Evaluate the effect of multiple-dose phenytoin (strong CYP3A inducer) on the PK of a single oral dose of TAK-861.
- Group 4 (Itraconazole DDI): Evaluate the effect of multiple-dose itraconazole (strong CYP3A inhibitor) on the PK of a single oral dose of TAK-861.

Secondary Objective

- Evaluate the safety and tolerability of TAK-861 following single oral dosing, with and without the interacting perpetrator drugs, in healthy adults.

Primary PK Endpoints

- C_{max}, AUC_{∞} (AUC_{∞}_obs), and AUC_{last} of plasma TAK-861.

Reference ID: 5847402

Study Design

A phase 1, open-label, four-group study in healthy adults aged 18 to 55 years (BMI 18 to 30 kg/m²). Groups 1 to 3 were conducted concurrently; Group 4 initiated after review of Groups 1 to 3 data. All participants were confined at the clinical research unit for the duration of each group period.

Table 131. Study Design Overview

Group	Purpose	TAK-861 Dose / Formulation	Precipitant Drug	Design	N Dosed
1 (rBA)	Relative bioavailability	10 mg T1 IR or T2 IR tablet, SD	None	2-way crossover (AB/BA)	12
2 (Fluconazole)	Moderate CYP3A inhibition DDI	10 mg T2 IR tablet, SD (Day 1 & Day 9)	Fluconazole 400 mg (Day 6) then 200 mg QD (Days 7–13)	Fixed-sequence	12
3 (Phenytoin)	Strong CYP3A induction DDI	10 mg T2 IR tablet, SD (Day 1 & Day 19)	Phenytoin 100 mg TID (Days 6–23)	Fixed-sequence	12
4 (Itraconazole)	Strong CYP3A inhibition DDI	1 mg T2 IR tablet, SD (Day 1 & Day 9)	Itraconazole 200 mg QD oral solution (Days 6–22)	Fixed-sequence	3

Abbreviations: SD = Single dose; rBA = Relative bioavailability; DDI = Drug-drug interaction; QD = Once daily; TID = Three times daily.
Group 4 was initiated with 3 sentinel participants; full enrollment was not conducted given conclusive results.
Source: Clinical Study Report TAK-861-1007, Sections 9.1, Tables 9.a–9.h, pages 23–30

PK Sampling Schedule

Groups 1 to 3: Pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 h post-dose. Follow-up samples at 432 h and 768 h (Groups 2 and 3 only).
Group 4: Pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 240, 288, and 336 h post-dose, with follow-up samples at 480, 648, and 984 h.

Subject Disposition and Demographics

All 12 participants in Groups 1 and 2 completed the study. In Group 3, 11 of 12 completed; 1 participant withdrew consent on Day 6 for personal reasons. All 3 sentinel participants in Group 4 completed the study. There were no deaths, serious adverse events (SAEs), or discontinuations due to AEs.

Table 132. Demographic Summary by Group

Parameter	Group 1 (N=12)	Group 2 (N=12)	Group 3 (N=12)	Group 4 (N=3)
Mean Age (yrs)	35.8	43.0	43.5	42.7
Sex: Male (%)	75%	58%	58%	67%
Race: White (%)	75%	75%	92%	100%
Ethnicity: Hispanic/Latino (%)	50%	67%	92%	100%
Mean BMI (kg/m²)	25.04	26.37	27.88	24.92
Mean Weight (kg)	74.6	77.5	79.0	70.6

Source: Clinical Study Report TAK-861-1007, Tables 11.a–11.d, pages 79–84

Reference ID: 5847402

Bioanalytical Methods

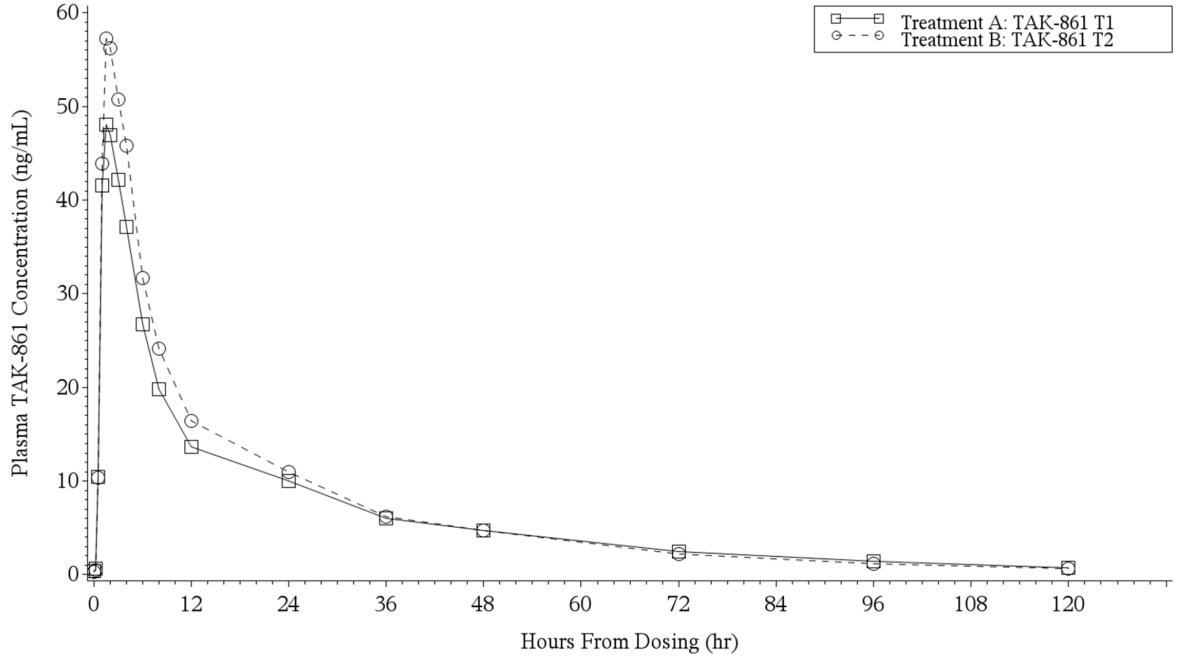
The bioanalytical methods used in Study TAK-861-1007 are the same as those described in the bioanalytical report section (Section 16.4.2) of this Appendix ((b) (4) Study No. CB210057).

Pharmacokinetic Results

Group 1—Relative Bioavailability (T2 vs. T1 IR Tablet, 10 mg)

Following a single oral 10 mg dose, the concentration-time profiles of both formulations were well characterized. Median t_{max} of T1 and T2 formulations was 1.5 h and 2.0 h, respectively, with individual values ranging from 1 to 4 h for both. Geometric mean C_{max} was higher for T2 (59.88 ng/mL) compared to T1 (50.93 ng/mL); AUC values were comparable. Mean $t_{½z}$ and CL/F were similar between formulations (~25 h and ~12 L/h).

Figure 39. Mean Plasma Concentrations vs. Time Profiles of TAK-861 Following a Single Oral Dose of 10 mg TAK-861 T1 IR Tablets and a Single Oral Dose of 10 mg TAK-861 T2 IR Tablets in Healthy Participants (Group 1) (Linear Scale)



Source: Clinical Study Report TAK-861-1007, Figure 11.a, page 88

Reference ID: 5847402

Table 133. Summary of Plasma Pharmacokinetic Parameters of TAK-861 Following a Single Oral Dose of 10 mg TAK-861 T1 IR Tablets and a Single Oral Dose of 10 mg TAK-861 T2 IR Tablets in Healthy Participants (Group 1)

Pharmacokinetic Parameters	Treatment A	Treatment B
t_{max} (hr)	1.541 (1.00, 4.03) [n=12]	2.000 (1.02, 4.01) [n=12]
C_{max} (ng/mL)	50.93 (21.1) [n=12]	59.88 (22.0) [n=12]
AUC_{∞} (ng•hr/mL)	785.3 (19.9) [n=12]	858.4 (18.1) [n=12]
AUC_{last} (ng•hr/mL)	759.2 (18.4) [n=12]	835.2 (17.0) [n=12]
$AUC_{extrap\%}$ (%)	3.289 ± 2.2302 [n=12]	2.686 ± 1.7963 [n=12]
$t_{½z}$ (hr)	25.238 ± 5.1734 [n=12]	24.353 ± 5.3121 [n=12]
CL/F (L/hr)	12.94 ± 2.2119 [n=12]	11.81 ± 1.9391 [n=12]
V_z/F (L)	462.8 ± 84.718 [n=12]	410.5 ± 91.061 [n=12]

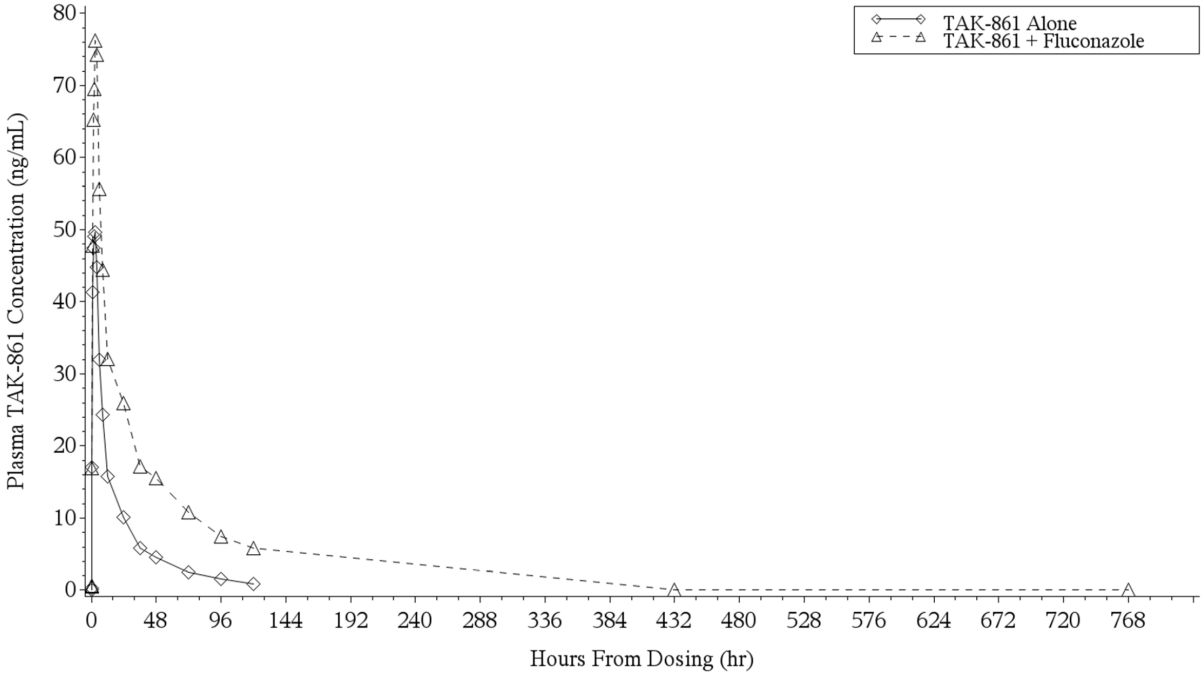
Treatment A: a single oral dose of 10 mg TAK-861 T1 IR tablets
Treatment B: a single oral dose of 10 mg TAK-861 T2 IR tablets
AUCs and C_{max} are presented as geometric mean and geometric CV%.
t_{max} values are presented as median (min, max).
All other parameters are presented as arithmetic mean (± SD).
Source: Clinical Study Report TAK-861-1007, Table 11.h, page 91

TAK-861 T2 IR tablets showed a modest (~18%) increase in C_{max} vs. T1 IR tablets, with the upper 90% CI for C_{max} slightly exceeding the 125% equivalence limit. AUC_{∞} and AUC_{last} were 9 to 10% higher for T2 but within equivalence limits, indicating comparable total exposure. The T2 formulation was selected for subsequent studies.

Group 2—DDI With Fluconazole (Moderate CYP3A Inhibitor)

In 12 participants, a single 10-mg TAK-861 dose was administered alone (Day 1) and in combination with fluconazole at steady state (Day 9: fluconazole 400 mg loading on Day 6, then 200 mg QD Days 7 to 13). TAK-861 + Fluconazole resulted in substantially higher concentrations throughout the sampling period. Median t_{max} was delayed (3.0 h versus 2.0 h) and mean $t_{½z}$ increased to ~48 h versus ~27 h.

Figure 40. Mean Plasma Concentrations vs. Time Profiles of TAK-861 Following a Single Oral Dose of 10 mg TAK-861 T2 IR Tablets on Day 1, and Following a Single Oral Dose of 400 mg Fluconazole on Day 6 and Oral Doses of 200 mg Fluconazole QD on Days 7 to 13 Coadministered With a Single Oral Dose of 10 mg TAK-861 T2 IR Tablets on Day 9 in Healthy Participants (Group 2) (Linear Scale)



Source: Clinical Study Report TAK-861-1007, Figure 11.f, page 97

Table 134. Summary of Plasma Pharmacokinetic Parameters of TAK-861 Following a Single Oral Dose of 10 mg TAK-861 T2 IR Tablets on Day 1, and Following a Single Oral Dose of 400 mg Fluconazole on Day 6 and Oral Doses of 200 mg Fluconazole QD on Days 7 to 13 Coadministered With a Single Oral Dose of 10 mg TAK-861 T2 IR Tablets on Day 9 in Healthy Participants (Group 2)

Pharmacokinetic Parameters	TAK-861 Alone	TAK-861 + Fluconazole
t_{max} (hr)	1.998 (0.51, 6.03) [n=12]	3.011 (2.00, 4.04) [n=12]
C_{max} (ng/mL)	53.42 (27.4) [n=12]	79.99 (27.0) [n=12]
AUC_{∞} (ng•hr/mL)	846.7 (35.1) [n=12]	2426 (29.5) [n=12]
AUC_{∞} (ng•hr/mL)	790.9 (26.2) [n=11*]	2403 (33.1) [n=9*]
AUC_{last} (ng•hr/mL)	804.8 (29.1) [n=12]	2098 (34.0) [n=12]
$AUC_{extrap\%}$ (%)	4.654 ± 7.3195 [n=12]	13.26 ± 7.1411 [n=12]
$AUC_{extrap\%}$ (%)	2.678 ± 2.7252 [n=11*]	10.44 ± 5.8088 [n=9*]
$t_{½z}$ (hr)	26.846 ± 15.1323 [n=12]	47.879 ± 12.5637 [n=12]
CL/F (L/hr)	12.39 ± 3.6453 [n=12]	4.266 ± 1.0574 [n=12]
V_z/F (L)	435.7 ± 126.19 [n=12]	291.0 ± 91.364 [n=12]

TAK-861 Alone: a single oral dose of 10 mg TAK-861 T2 IR tablets on Day 1
TAK-861 + Fluconazole: a single oral dose of 400 mg fluconazole on Day 6 and oral doses of 200 mg fluconazole QD on Days 7 to 13 coadministered with a single oral dose of 10 mg TAK-861 T2 IR tablets on Day 9
AUCs and C_{max} are presented as geometric mean and geometric CV%.
t_{max} values are presented as median (min, max).
All other parameters are presented as arithmetic mean (± SD).
* Excluding participants whose AUCextrap% is > 20%.

Source: Clinical Study Report TAK-861-1007, Table 11.l, page 100

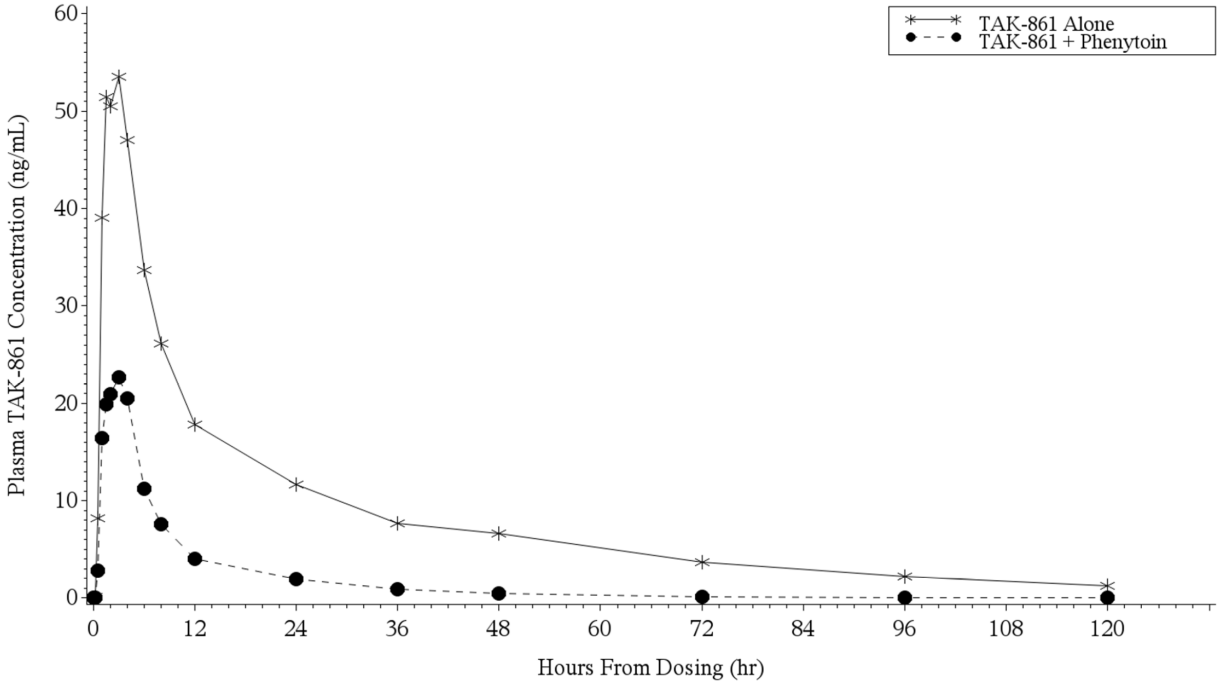
Co-administration with a moderate CYP3A inhibitor, fluconazole increased the C_{max} of TAK-861 by ~50% and AUC_{∞} by ~187%. These results confirm clinically meaningful CYP3A-mediated inhibition of TAK-861 metabolism by fluconazole. The review findings suggest that a dosage reduction (0.5 mg BID) is recommended when TAK-861 is concomitantly used with moderate CYP3A4 inhibitor.

Group 3—DDI With Phenytoin (Strong CYP3A Inducer)

In 11 evaluable participants (1 withdrew before phenytoin administration), a single 10-mg TAK-861 T2 dose was administered alone (Day 1) and co-administered with phenytoin at steady state (100 mg TID Days 6 to 23, with TAK-861 on Day 19). Mean concentrations were markedly lower with phenytoin co-administration compared to TAK-861 alone; only 18% of participants had quantifiable concentrations at 96 h post-dose when TAK-861 was concomitantly administered with phenytoin. However, all participants who received TAK-861 alone had quantifiable concentrations at 96 h post-dose. Mean $t_{½z}$ shortened to ~14 h vs. ~32 h.

Reference ID: 5847402

Figure 41. Mean Plasma Concentrations Versus Time Profiles of TAK-861 Following a Single Oral Dose of 10 mg TAK-861 T2 IR Tablets on Day 1, and Following Oral Doses of 100 mg Phenytoin TID on Days 6 to 23 Coadministered With a Single Oral Dose of 10 mg TAK-861 T2 IR Tablets on Day 19 in Healthy Participants (Group 3) (Linear Scale)



Source: ADaM.ADPC
Program: (b) (4)

Source: Clinical Study Report TAK-861-1007, Figure 11.k, page 107

Table 135. Summary of Plasma Pharmacokinetic Parameters of TAK-861 Following a Single Oral Dose of 10 mg TAK-861 T2 IR Tablets on Day 1, and Following Oral Doses of 100 mg Phenytoin TID on Days 6 to 23 Coadministered With a Single Oral Dose of 10 mg TAK-861 T2 IR Tablets on Day 19 in Healthy Participants (Group 3)

Pharmacokinetic Parameters	TAK-861 Alone	TAK-861 + Phenytoin
t_{max} (hr)	2.523 (1.00, 6.02) [n=12]	2.026 (1.00, 4.06) [n=11]
C_{max} (ng/mL)	59.43 (22.6) [n=12]	26.12 (23.6) [n=11]
AUC_{∞} (ng•hr/mL)	1039 (18.4) [n=12]	194.1 (39.3) [n=11]
AUC_{last} (ng•hr/mL)	976.9 (16.2) [n=12]	190.6 (40.1) [n=11]
$AUC_{extrap\%}$ (%)	5.980 ± 2.5789 [n=12]	1.829 ± 0.82887 [n=11]
$t_{½z}$ (hr)	31.648 ± 4.9808 [n=12]	14.208 ± 2.7437 [n=11]
CL/F (L/hr)	9.765 ± 1.7042 [n=12]	54.72 ± 18.752 [n=11]
V_z/F (L)	438.4 ± 63.426 [n=12]	1117 ± 454.67 [n=11]

TAK-861 Alone: a single oral dose of 10 mg TAK-861 T2 IR tablets on Day 1
TAK-861 + Phenytoin: multiple oral doses of 100 mg phenytoin TID on Days 6 to 23 coadministered with a single oral dose of 10 mg TAK-861 T2 IR tablets on Day 19
AUCs and C_{max} are presented as geometric mean and geometric CV%.
t_{max} values are presented as median (min, max).
All other parameters are presented as arithmetic mean (± SD).
Participant (b) (6) withdrew from the study prior to the 120-hour blood draw on Day 6 before receiving Phenytoin treatment.
Source: Clinical Study Report TAK-861-1007, Table 11.p, page 110

Co-administration with the strong CYP3A inducer phenytoin decreased TAK-861 C_{max} by ~56% and AUC_{∞} by ~81%. These results confirm clinically significant CYP3A-mediated induction of TAK-861 metabolism by phenytoin. Such lower exposures could cause substantial loss of efficacy. Therefore, avoiding use of TAK-861 with strong CYP3A4 inhibitors is recommended.

Group 4—DDI With Itraconazole (Strong CYP3A Inhibitor)

In 3 participants, a single 1-mg TAK-861 T2 dose was administered alone (Day 1) and co-administered with itraconazole (200 mg QD oral solution Days 6 to 22, with TAK-861 on Day 9). The TAK-861 dose was reduced to 1 mg (from 10 mg) after review of Groups 1 to 3 data and updated PBPK modeling to ensure adequate safety margins. Concentrations were higher throughout the sampling period following itraconazole co-administration; all 3 participants had quantifiable concentrations through 336 h post-dose. Mean $t_{½z}$ increased markedly to ~125 h vs. ~27 h.

Reference ID: 5847402

Table 136. Summary of Plasma TAK-861 Pharmacokinetic Parameters Following a Single Oral Dose of 1 mg TAK-861 T2 IR Tablets on Day 1, and Following an Oral Dose of 200 mg Itraconazole Oral Solution on Days 6 to 22 Coadministered With a Single Oral Dose of 1 mg TAK-861 T2 IR Tablets on Day 9 in Healthy Participants (Group 4)

Pharmacokinetic Parameters	TAK-861 Alone	TAK-861 + Itraconazole
t_{max} (hr)	1.500 (1.09, 1.50) [n=3]	1.503 (1.50, 2.06) [n=3]
C_{max} (ng/mL)	7.698 (49.9) [n=3]	12.83 (34.6) [n=3]
AUC_{∞} (ng•hr/mL)	87.29 (62.1) [n=3]	648.6 (48.0) [n=3]
AUC_{last} (ng•hr/mL)	81.27 (62.7) [n=3]	605.0 (49.4) [n=3]
$AUC_{extrap\%}$ (%)	6.877 ± 2.4074 [n=3]	6.713 ± 1.7493 [n=3]
$t_{½z}$ (hr)	27.278 ± 11.2944 [n=3]	124.745 ± 24.3026 [n=3]
CL/F (L/hr)	12.85 ± 7.8223 [n=3]	1.652 ± 0.75141 [n=3]
V_z/F (L)	422.6 ± 43.661 [n=3]	281.3 ± 76.762 [n=3]

TAK-861 Alone: a single oral dose of 1 mg TAK-861 T2 IR tablets on Day 1
TAK-861 + Itraconazole: oral doses of 200 mg itraconazole oral solution on Days 6 to 22 coadministered with a single oral dose of 1 mg TAK-861 T2 IR tablets on Day 9
AUCs and C_{max} are presented as geometric mean and geometric CV%.
t_{max} values are presented as median (min, max).
All other parameters are presented as arithmetic mean (± SD).
Source: Clinical Study Report TAK-861-1007, Table 11.t, page 119

Co-administration with the strong CYP3A inhibitor itraconazole increased the C_{max} of TAK-861 by ~67% and AUC_{∞} by ~7.5-fold, with $t_{½z}$ prolonged to ~125 h. Even though the DDI with strong CYP3A inhibitors was studied in only 3 subjects, the magnitude of this interaction is consistent with itraconazole's strong inhibitory effect on CYP3A4/5 and confirms TAK-861 as a sensitive CYP3A substrate. The results suggest that concomitant use of TAK-861 with strong CYP3A4 inhibitor is contraindicated.

Clinical Study TAK-861-1010

Title

A Phase 1, Open-Label, Randomized, Crossover Trial to Evaluate the Effect of Food on the Pharmacokinetics of TAK-861 in Healthy Adult Participants

Study Objectives

Primary Objective:

- To evaluate the effect of food on the oral bioavailability of a single dose of 2 mg TAK-861 administered under fed conditions compared to fasted conditions in healthy adult participants. Primary PK endpoints: C_{max}, AUC_{inf}, and AUC_{last}.

Secondary Objective:

- To evaluate the safety and tolerability of TAK-861 following a single oral administration of 2 mg TAK-861 under fed and fasted conditions.

Reference ID: 5847402

Exploratory Objectives:

- Characterize additional plasma PK parameters (t_{max}, $t_{½z}$, CL/F, V_z/F) and additional safety parameters (MAVs for laboratory, vital signs, ECG, and C-SSRS; change from baseline).

Study Design

A phase 1, open-label, randomized, 2-way crossover food effect trial. Twelve healthy adult male participants were enrolled and randomized 1:1 to one of two treatment sequences (AB or BA) with a 5-day washout between periods. All participants were confined to the CRU for each treatment period (Day -1 through Day 6 of each period).

Treatments Administered

Treatment A (Reference): Single oral dose of 2 mg TAK-861 (1 × 2 mg T3 tablet) under fasted conditions (overnight fast ≥10 h; continued fast for ≥4 h post-dose).
Treatment B (Test): Single oral dose of 2 mg TAK-861 (1 × 2 mg T3 tablet) under fed conditions (overnight fast ≥10 h; standard FDA high-fat, high-calorie breakfast [800 to 1000 kcal, ≥50% fat] consumed within 30 minutes immediately before dosing).

PK Sampling Schedule

Blood samples for plasma TAK-861 PK collected pre-dose (0 h) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 h post-dose in each period. The 120 h sample from Period 1 also served as the pre-dose sample for Period 2.

Subject Disposition and Demographics

All 12 enrolled participants received both treatments and completed the trial (100% completion). No participants withdrew or discontinued. There were no protocol deviations.

Table 137. Subject Demographic Summary

Parameter	Sequence AB (N=6)	Sequence BA (N=6)	Overall (N=12)
Sex: Male (%)	100%	100%	100%
Race: White (%)	83%	100%	92%
Race: Black/African Am. (%)	17%	0%	8%
Ethnicity: Hispanic/Latino (%)	83%	83%	83%
Mean Age (yrs)	37.5	31.5	34.5
Mean BMI (kg/m²)	26.00	24.07	25.03
Mean Weight (kg)	81.1	71.3	76.2

Source: Clinical Study Report TAK-861-1010, Table 8, pages 26–27

Bioanalytical Methods

The bioanalytical methods used in Study TAK-861-1005 are the same as those described in the bioanalytical report section (Section 16.4.2) of this Appendix (b) (4) Study No. CB210057). Total and unbound plasma TAK-861 concentrations were quantified by

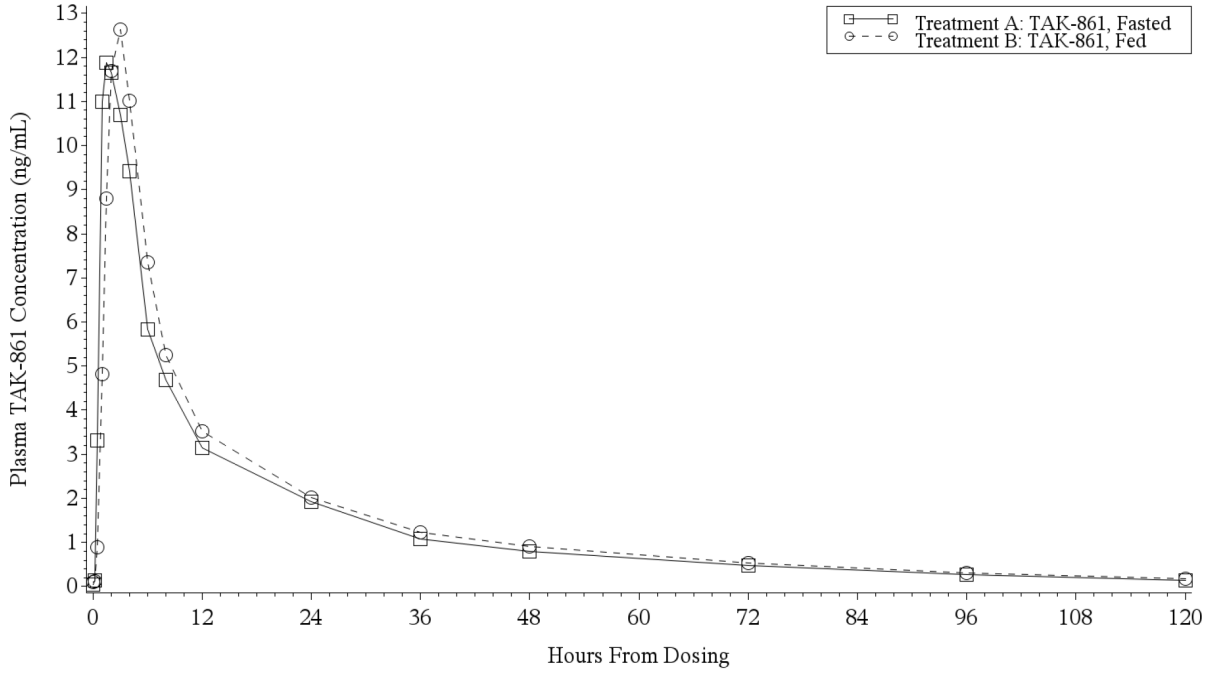
Reference ID: 5847402

validated LC-MS/MS methods at [redacted] (b) (4)

Pharmacokinetic Results

Plasma TAK-861 concentration-time profiles were characterized following both treatments. Most participants had quantifiable concentrations at the first postdose time point (0.25 h): 92% under fasted conditions and 73% under fed conditions. Concentrations remained quantifiable for all participants through 72 h and all but 1 participant through 96 and 120 h post-dose. One participant (Participant [redacted] (b) (6)) was excluded from Treatment B (Period 2, fed) PK analysis due to a predose concentration >5% of C_{max} (N=11 for Treatment B). Concentrations under fed conditions showed a delayed initial absorption but overall similar exposure to fasted conditions.

Figure 42. Mean Plasma Concentration Versus Time Profiles of TAK-861 After a Single Oral Dose of 2 mg TAK-861 Under Fasted (Treatment A) and Fed (Treatment B) Conditions in Healthy Adult Participants (Linear Scale)



Source: Clinical Study Report TAK-861-1010, Figures 2, page 29

Table 138. Summary of Plasma Pharmacokinetic Parameters of TAK-861 After a Single Oral Dose of 2 mg TAK-861 Under Fasted (Treatment a) and Fed (Treatment B) Conditions in Healthy Adult Participants.

Pharmacokinetic parameter (unit)	Treatment A (N=12)	Treatment B* (N=11)
t_{max} (h)	1.530 (1.00, 4.00)	3.004 (1.99, 4.00)
t_{lag} (h)	0.000 (0.00, 0.25)	0.000 (0.00, 0.50)
C_{max} (ng/mL)	13.24 (21.9)	12.95 (19.6)
AUC_{last} (ng•h/mL)	158.2 (29.8)	168.2 (37.7)
AUC_{inf} (ng•h/mL)	162.9 (32.9)	174.9 (40.9)
$t_{1/2z}$ (h)	21.801 ± 8.5333	26.040 ± 11.1679
CL/F (L/h)	12.86 ± 4.0720	12.26 ± 4.8473
V_z/F (L)	364.3 ± 68.242	437.6 ± 270.60

Source: Table 15.2.1.3 and Table 15.2.1.4
Treatment A: 2 mg TAK-861 (1 × 2 mg TAK-861 T3 tablet) on Day 1 under fasted conditions
Treatment B: 2 mg TAK-861 (1 × 2 mg TAK-861 T3 tablet) on Day 1 under fed conditions
t_{max} and t_{lag} values are presented as median (minimum, maximum).
C_{max}, AUC_{last}, and AUC_{inf} are presented as geometric mean (geometric percent coefficient of variation).
$t_{1/2z}$, CL/F, and V_z/F values are presented as arithmetic mean ± standard deviation.

Source: Clinical Study Report TAK-861-1010, Table 9, page 31

No clinically meaningful food effect was observed on the PK of T3 tablet formulation of TAK-861. C_{max}, AUC_{last}, and AUC_{inf} were equivalent under fed and fasted conditions (the GMRs and 90% CIs of PK parameters were within 80 to 125%). Absorption was slightly delayed under fed conditions (median t_{max} ~3.0 h vs. ~1.5 h fasted), but this was not statistically significant. These data support that T3 tablets of TAK-861 can be administered without regard to food.

16.4.4. Pharmacometrics Assessment

Executive Summary

Table 139. Model Risk Assessment for Pharmacometrics Analysis

Question of interest	Is the dose adjustment needed for the patents with mild to moderate hepatic impairment or moderate to severe renal impairment?
Context of use	Population PK and exposure-response analyses for safety were conducted
Model influence	Moderate. PK data were collected from patients with mild to moderate hepatic impairment or moderate to severe renal impairment. The studied PK exposure range was relatively large in pivotal trials (1 mg BID and 2 mg BID).
Consequence of wrong decision	Moderate. Wrong decision may increase the risk of safety outcomes in patients with patients with mild to moderate hepatic impairment or moderate to severe renal impairment.
Model risk	Moderate. By combining the moderate model influence and moderate consequence of wrong decision, the overall model risk is moderate.

Source: Pharmacometrics Reviewer's analysis

The effect of HI on oveporexton PK was evaluated in a dedicated study (TAK-861-1004) in patients with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) HI. In participants

Reference ID: 5847402

with mild HI, total oveporexton AUC_∞ was 28% higher and C_{max} was 17% higher compared to participants with normal hepatic function. In participants with moderate HI, AUC_∞ was 23% higher and C_{max} was 15% lower compared to controls. RI was evaluated in a reduced design study (TAK-861-1005). In participants with severe RI (estimated glomerular filtration rate [eGFR] ≥15 to <30 mL/min; not requiring dialysis), oveporexton AUC_∞ was 45% higher, AUC_t was 35% higher, and C_{max} was 16% lower compared to matched participants with normal renal function (eGFR 90 mL/min or greater). Population PK analysis, based on data from patients enrolled in the dedicated PK trials as well as from patients with HI or RI in pivotal trials, confirmed the PK exposures of oveporexton were increased in patients with mild to moderate HI or moderate to severe RI.

Exposure-response analysis suggests that the probability of insomnia, urinary events, and micturition urgency increased with increasing exposures of oveporexton. The predicted probability of insomnia for median $C_{avg,ss}$ of 1 mg BID and 2 mg BID were 49.2% [95% CI: 42.2%-56.3%] and 56.1% [95% CI: 50.4%-61.7%], respectively. The predicted probability of urinary events for median $C_{avg,ss}$ of 1 mg BID and 2 mg BID in North America were 43.6% [95% CI: 30.6%-57.6%] and 48.4% [95% CI: 35.4%-61.7%], respectively. The predicted probability of micturition urgency for median $C_{avg,ss}$ of 1 mg BID and 2 mg BID in North America were 16% [95% CI: 11.7%-21.5%] and 20.5% [95% CI: 16.2%-25.6%], respectively. However, the predicted difference between two dosing regimens were relatively close. In addition, the observed percentage of events as well as the percentage of resolved events for insomnia, urinary events, and micturition urgency were comparable between 1 mg BID and 2 mg BID based on pooled data from Study TAK-861-3001 and TAK-861-3002. The event duration for these three safety events were comparable as well between 1 mg BID and 2 mg BID.

The probabilities to have insomnia, urinary events, and micturition urgency in patients with HI (mild to moderate) or RI (moderate to severe) were largely within the range of those in patients with normal hepatic and renal function. Based on the comparable dose-response for safety as well as the limited increase in the probability of safety events in patients with hepatic or renal impairment, dose adjustment based on HI (mild and moderate) and RI (moderate and severe) is not recommended.

Population PK Analysis

In total, the population PK model was developed using 8535 PK observations of 494 subjects from phase 1 studies TAK-861-1001 and TAK-861-1007, TAK-861-1004, and TAK-861-1005 as well as from non-placebo arms in studies TAK-861-2001, TAK-861-2002, TAK-861-3001, and TAK-861-3002. The baseline characteristics stratified by study are summarized in Table 140 and Table 141.

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Table 140. Summary of Continuous Baseline Characteristics Stratified by Study

Characteristic	TAK-861-1001 [N=97]	TAK-861-1004 [N=33]	TAK-861-1005 [N=20]	TAK-861-1007 [N=12]	TAK-861-2001 [N=90]	TAK-861-2002 [N=46]	TAK-861-3001 [N=126]	TAK-861-3002 [N=70]	TOTAL [N=494]
Albumin (g/L)	44.9 (3.19) [36-52]	42.5 (2.84) [37-48]	40.6 (4.07) [32-46]	47.8 (3.41) [44-55]	45.4 (3.12) [38-53]	44.6 (2.88) [40-51]	45.7 (3.1) [37-55]	46.6 (2.63) [42-53]	45.1 (3.35) [32-55]
Aspartate Aminotransferase (U/L)	17.6 (3.76) [10-31]	22.9 (9.34) [13-43]	17.4 (6.75) [8-38]	18.3 (3.94) [13-24]	18.8 (6.69) [10-48]	18.9 (6.32) [9-44]	20.3 (5.48) [11-37]	20.2 (7.98) [10-59]	19.4 (6.39) [8-59]
Alanine Aminotransferase (U/L)	18.7 (9.72) [6-50]	21.6 (17.1) [5-77]	22.3 (14.4) [8-67]	14.6 (3.37) [9-19]	20.9 (10.7) [8-56]	20.2 (12.2) [6-69]	20.5 (11.4) [5-62]	21.3 (11.6) [7-55]	20.3 (11.6) [5-77]
Alkaline Phosphatase (U/L)	66.2 (13.6) [38-96]	72 (19.2) [36-112]	80.2 (28.2) [45-157]	87.4 (31.7) [46-151]	68.1 (20.5) [31-121]	66.8 (17.4) [35-111]	72 (20.2) [37-155]	74.9 (25.5) [29-151]	70.8 (20.8) [29-157]
Bilirubin (umol/L)	13 (4.45) [3.42-26.5]	13.4 (6.6) [5.13-32.5]	8.64 (4.42) [5.13-22.2]	9.69 (6.29) [5.13-27.4]	6.61 (5) [1.25-28.2]	6.04 (3.72) [1.25-22.9]	6.04 (4.58) [1.25-25.7]	5.24 (4.1) [1.25-17.8]	8.08 (5.61) [1.25-32.5]
Gamma Glutamyl Transferase (U/L)	20.4 (11.6) [5-64]	44.2 (58.4) [7-314]	35 (40.1) [10-195]	15.2 (4.35) [10-25]	21.5 (19.9) [4-147]	17 (10.4) [6-61]	19.3 (16.1) [3-109]	19.8 (15.4) [3-79]	22 (23.2) [3-314]
Prothrombin Time (sec)	11.5 (1.93) [9.6-30]	11.9 (1.05) [9.7-14.6]	11.1 (0.687) [9.8-12.4]	11 (0.674) [9.9-12.2]	11.5 (0.61) [10-14]	11.6 (0.63) [11.2-14.8]	11.5 (0.886) [9.7-13.8]	11.5 (0.607) [10.1-13.5]	11.5 (1.1) [9.6-30]
Age at baseline (years)	32.8 (12.8) [18-72]	62.6 (5.88) [43-73]	60.9 (9) [38-78]	35.8 (9.76) [25-54]	33.1 (11.3) [18-59]	36 (11.3) [21-64]	31.6 (10.9) [16-65]	29.1 (9.62) [18-62]	35.5 (14.3) [16-78]
Weight at baseline (kg)	69.9 (12) [42.3-112]	77.3 (12.9) [56.3-104]	83.2 (12.9) [61.4-104]	74.6 (11.5) [59.3-91.6]	78.4 (16.1) [47-120]	75.6 (17.2) [43.9-108]	79 (16.5) [47.4-126]	79.9 (17.6) [48-145]	76.9 (15.8) [42.3-145]
Total daily dose (mg)	19.7 (19.2) [0.5-75]	4 (0) [4-4]	4 (0) [4-4]	10 (0) [10-10]	4.77 (2.53) [1-7]	5.57 (1.52) [4-7]	3.05 (1) [2-4]	4 (0) [4-4]	7.27 (10.6) [0.5-75]
Estimated creatinine clearance using Cockcroft-Gault Equation (mL/min)	131 (11) [86-151]	98 (26.3) [62-162]	65.9 (46.2) [14-146]	121 (17) [93-145]	142 (40.2) [77-253]	135 (40.7) [61-228]	157 (44.6) [80-347]	161 (42.4) [64-294]	139 (43.1) [14-347]
eGFR MDRD formula (mL/min)	102 (17.4) [66.6-171]	99.8 (25) [52.6-143]	64.7 (47.6) [10.4-140]	103 (15.6) [70.1-121]	117 (28.1) [70.9-182]	112 (29.7) [49.6-173]	127 (31.5) [72.3-267]	130 (30.9) [57.2-207]	114 (32) [10.4-267]

N: Number of subjects
Entries represent: Mean (Standard deviation) [Minimum-Maximum]
Source: study-tak-861-poppk-analysis, Table 6

Table 141. Summary of Categorical Baseline Characteristics Stratified by Study

Characteristic	Category	TAK-861-1001 [N=97]	TAK-861-1004 [N=33]	TAK-861-1005 [N=20]	TAK-861-1007 [N=12]	TAK-861-2001 [N=90]	TAK-861-2002 [N=46]	TAK-861-3001 [N=126]	TAK-861-3002 [N=70]	TOTAL [N=494]
Female	No	79 (81.4%)	19 (57.6%)	16 (80%)	9 (75%)	46 (51.1%)	15 (32.6%)	53 (42.1%)	33 (47.1%)	270 (54.7%)
	Yes	18 (18.6%)	14 (42.4%)	4 (20%)	3 (25%)	44 (48.9%)	31 (67.4%)	73 (57.9%)	37 (52.9%)	224 (45.3%)
Prior use of narcolepsy medications	No	83 (85.6%)	0 (0%)	0 (0%)	0 (0%)	43 (47.8%)	0 (0%)	25 (19.8%)	11 (15.7%)	162 (32.8%)
	Yes	14 (14.4%)	0 (0%)	0 (0%)	0 (0%)	47 (52.2%)	0 (0%)	101 (80.2%)	59 (84.3%)	221 (44.7%)
	Undefined	0 (0%)	33 (100%)	20 (100%)	12 (100%)	0 (0%)	46 (100%)	0 (0%)	0 (0%)	111 (22.5%)
Region is East Asia	No	29 (29.9%)	33 (100%)	20 (100%)	12 (100%)	86 (95.6%)	41 (89.1%)	107 (84.9%)	56 (80%)	384 (77.7%)
	Yes	68 (70.1%)	0 (0%)	0 (0%)	0 (0%)	4 (4.44%)	5 (10.9%)	19 (15.1%)	14 (20%)	110 (22.3%)
Region is Asia Pacific	No	29 (29.9%)	33 (100%)	20 (100%)	12 (100%)	86 (95.6%)	41 (89.1%)	107 (84.9%)	56 (80%)	384 (77.7%)
	Yes	68 (70.1%)	0 (0%)	0 (0%)	0 (0%)	4 (4.44%)	5 (10.9%)	19 (15.1%)	14 (20%)	110 (22.3%)
Region is Europe	No	97 (100%)	33 (100%)	20 (100%)	12 (100%)	24 (26.7%)	31 (67.4%)	43 (34.1%)	14 (20%)	274 (55.5%)
	Yes	0 (0%)	0 (0%)	0 (0%)	0 (0%)	66 (73.3%)	15 (32.6%)	83 (65.9%)	56 (80%)	220 (44.5%)
Region is North America	No	68 (70.1%)	0 (0%)	0 (0%)	0 (0%)	70 (77.8%)	20 (43.5%)	102 (81%)	70 (100%)	330 (66.8%)
	Yes	29 (29.9%)	33 (100%)	20 (100%)	12 (100%)	20 (22.2%)	26 (56.5%)	24 (19%)	0 (0%)	164 (33.2%)
Region is China	No	88 (90.7%)	33 (100%)	20 (100%)	12 (100%)	90 (100%)	46 (100%)	126 (100%)	60 (85.7%)	475 (96.2%)
	Yes	9 (9.28%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	10 (14.3%)	19 (3.85%)
Region is Japan	No	38 (39.2%)	33 (100%)	20 (100%)	12 (100%)	86 (95.6%)	41 (89.1%)	107 (84.9%)	70 (100%)	407 (82.4%)
	Yes	59 (60.8%)	0 (0%)	0 (0%)	0 (0%)	4 (4.44%)	5 (10.9%)	19 (15.1%)	0 (0%)	87 (17.6%)
Asian	No	27 (27.8%)	32 (97%)	19 (95%)	11 (91.7%)	83 (92.2%)	40 (87%)	106 (84.1%)	56 (80%)	374 (75.7%)
	Yes	70 (72.2%)	1 (3.03%)	1 (5%)	1 (8.33%)	7 (7.78%)	6 (13%)	20 (15.9%)	14 (20%)	120 (24.3%)
Hepatic impairment flag	No	97 (100%)	13 (39.4%)	20 (100%)	12 (100%)	90 (100%)	46 (100%)	126 (100%)	70 (100%)	474 (96%)
	Yes	0 (0%)	20 (60.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	20 (4.05%)
Mild hepatic impairment flag	No	97 (100%)	23 (69.7%)	20 (100%)	12 (100%)	90 (100%)	46 (100%)	126 (100%)	70 (100%)	484 (98%)
	Yes	0 (0%)	10 (30.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	10 (2.02%)
Moderate hepatic impairment flag	No	97 (100%)	23 (69.7%)	20 (100%)	12 (100%)	90 (100%)	46 (100%)	126 (100%)	70 (100%)	484 (98%)
	Yes	0 (0%)	10 (30.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	10 (2.02%)
Renal impairment flag	No	97 (100%)	31 (93.9%)	10 (50%)	12 (100%)	90 (100%)	45 (97.8%)	126 (100%)	69 (98.6%)	480 (97.2%)
	Yes	0 (0%)	2 (6.06%)	10 (50%)	0 (0%)	0 (0%)	1 (2.17%)	0 (0%)	1 (1.43%)	14 (2.83%)
Japanese subjects in ph3 studies flag	No	97 (100%)	33 (100%)	20 (100%)	12 (100%)	90 (100%)	46 (100%)	107 (84.9%)	70 (100%)	475 (96.2%)

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Healthy Volunteer*	No	22 (22.7%)	0 (0%)	0 (0%)	0 (0%)	90 (100%)	46 (100%)	126 (100%)	70 (100%)	354 (71.7%)
	Yes	75 (77.3%)	33 (100%)	20 (100%)	12 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	140 (28.3%)
NT1 subject	No	75 (77.3%)	33 (100%)	20 (100%)	12 (100%)	0 (0%)	46 (100%)	0 (0%)	0 (0%)	186 (37.7%)
	Yes	22 (22.7%)	0 (0%)	0 (0%)	0 (0%)	90 (100%)	0 (0%)	126 (100%)	70 (100%)	308 (62.3%)
NT2 subject	No	97 (100%)	33 (100%)	20 (100%)	12 (100%)	90 (100%)	0 (0%)	126 (100%)	70 (100%)	448 (90.7%)
	Yes	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	46 (100%)	0 (0%)	0 (0%)	46 (9.31%)
T1 formulation	No	9 (9.28%)	33 (100%)	20 (100%)	6 (50%)	90 (100%)	46 (100%)	126 (100%)	70 (100%)	400 (81%)
	Yes	88 (90.7%)	0 (0%)	0 (0%)	6 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	94 (19%)
T2 formulation	No	88 (90.7%)	33 (100%)	20 (100%)	6 (50%)	0 (0%)	0 (0%)	126 (100%)	70 (100%)	343 (69.4%)
	Yes	9 (9.28%)	0 (0%)	0 (0%)	6 (50%)	90 (100%)	46 (100%)	0 (0%)	0 (0%)	151 (30.6%)
T3 formulation	No	97 (100%)	0 (0%)	0 (0%)	12 (100%)	90 (100%)	46 (100%)	0 (0%)	0 (0%)	245 (49.6%)
	Yes	0 (0%)	33 (100%)	20 (100%)	0 (0%)	0 (0%)	0 (0%)	126 (100%)	70 (100%)	249 (50.4%)
Severe renal impairment	No	97 (100%)	33 (100%)	10 (50%)	12 (100%)	90 (100%)	46 (100%)	126 (100%)	70 (100%)	484 (98%)
	Yes	0 (0%)	0 (0%)	10 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	10 (2.02%)
Moderate renal impairment	No	97 (100%)	31 (93.9%)	20 (100%)	12 (100%)	90 (100%)	45 (97.8%)	126 (100%)	69 (98.6%)	490 (99.2%)
	Yes	0 (0%)	2 (6.06%)	0 (0%)	0 (0%)	0 (0%)	1 (2.17%)	0 (0%)	1 (1.43%)	4 (0.81%)
Mild renal impairment	No	73 (75.3%)	22 (66.7%)	18 (90%)	10 (83.3%)	72 (80%)	35 (76.1%)	116 (92.1%)	65 (92.9%)	411 (83.2%)
	Yes	24 (24.7%)	11 (33.3%)	2 (10%)	2 (16.7%)	18 (20%)	11 (23.9%)	10 (7.94%)	5 (7.14%)	83 (16.8%)
Black or African American	No	89 (91.8%)	29 (87.9%)	11 (55%)	10 (83.3%)	86 (95.6%)	40 (87%)	123 (97.6%)	70 (100%)	458 (92.7%)
	Yes	8 (8.25%)	4 (12.1%)	9 (45%)	2 (16.7%)	4 (4.44%)	6 (13%)	3 (2.38%)	0 (0%)	36 (7.29%)
Caucasian**	No	83 (85.6%)	5 (15.2%)	10 (50%)	3 (25%)	13 (14.4%)	14 (30.4%)	83 (65.9%)	42 (60%)	253 (51.2%)
	Yes	14 (14.4%)	28 (84.8%)	10 (50%)	9 (75%)	77 (85.6%)	32 (69.6%)	43 (34.1%)	28 (40%)	241 (48.8%)

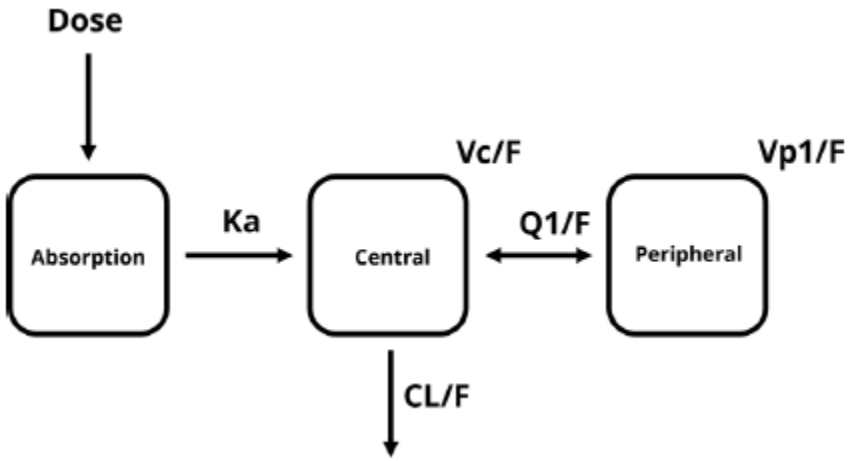
N: Number of subjects
Number of subjects in each category and percentage within this category
*The healthy volunteer category includes participants with renal (severe) or hepatic (mild or moderate) impairment from dedicated hepatic impairment Study TAK-861-1004 and renal impairment Study TAK-861-1005.
**Caucasian (White race) was not included in the analysis dataset but was added here for completeness
Source: study-tak-861-poppk-analysis, Table 19

The selected base model is characterized as follows (Figure 43):

- Absorption: first-order absorption from depot compartment to central compartment with a lag time,
- Distribution: two-compartment model,
- Elimination: linear elimination from central compartment,
- Estimated interindividual variability (IIV) on all parameters except F (fixed to zero),
- Mixed absolute-proportional residual error model,
- Covariate effect of Tablet T1 and T2 on F,
- Covariate effect of total dose on K_a

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Figure 43. Population PK Model Structure



Abbreviations: Ka: absorption rate constant, Vc/F: apparent volume of distribution for central compartment, CL/F: apparent CL from central compartment, Q1/F: apparent inter-compartment CL, Vp1/F: apparent volume of distribution for peripheral compartment
Source: study-tak-861-poppk-analysis, Figure 3

The covariate model development was conducted following a step-wise full covariate modeling approach with an inclusion step building the full covariate model followed by an elimination step to select the final covariate model. The final model included the following covariates:

- Body weight at baseline on V_c/F, Q1/F, and V_p1/F,
- Tablet T1 formulation on relative bioavailability F
- Total daily dose on K_a (total dose below 1 mg or above 25 mg changed K_a by more than 20%),
- Asian race on V_c/F,
- Female sex on V_c/F, V_p1/F, and Q1/F,
- Hepatic impairment (mild or moderate) on CL/F,
- Renal impairment (moderate or severe) on CL/F.

The final model parameter estimates are summarized in Table 142.

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Table 142. Summary of Final Model Parameter Estimates

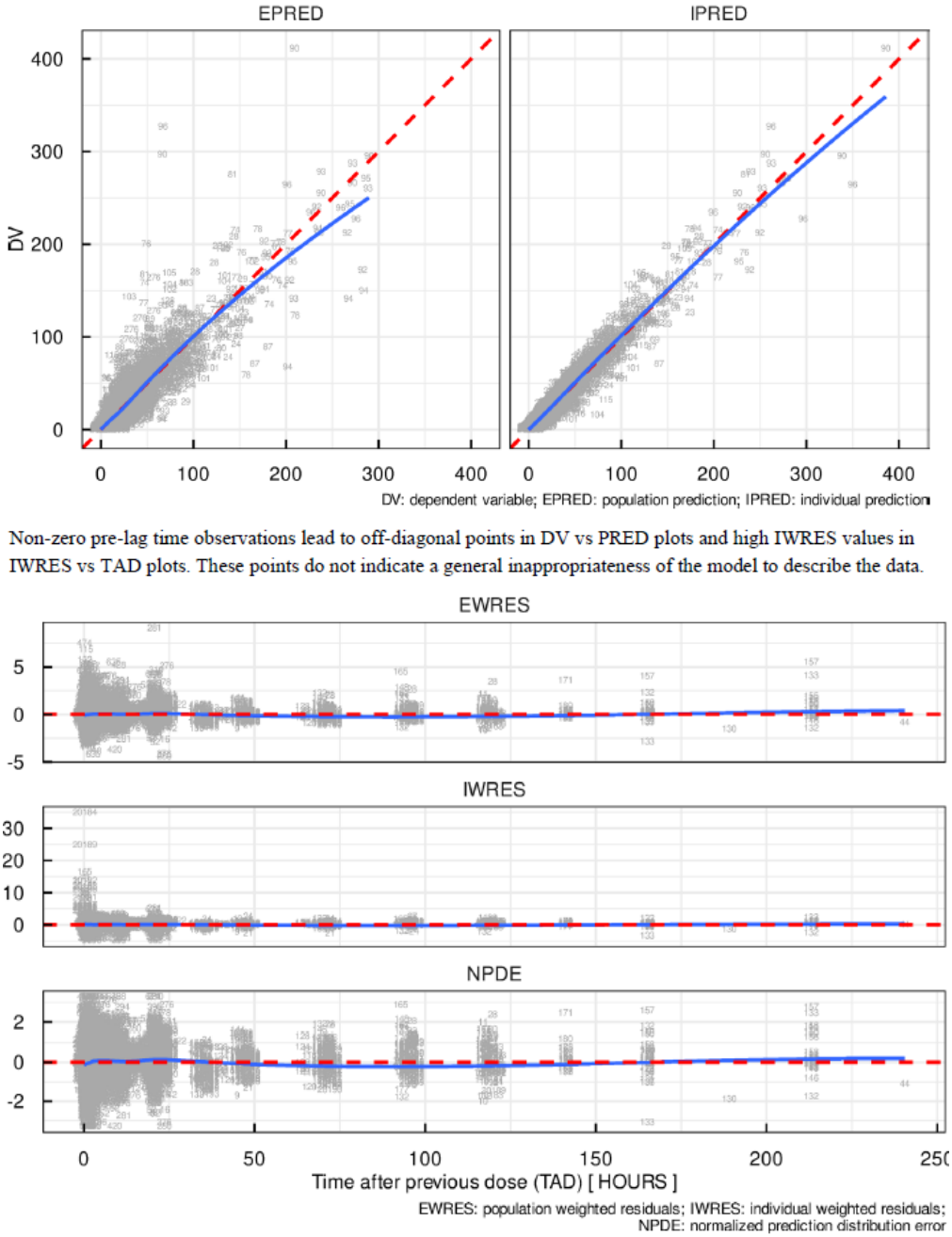
PARAMETER	VALUE	RSE	SHRINKAGE	COMMENT
Typical parameters				
CL/F	11.5	1.8%	-	Apparent clearance (L/hour)
Vc/F	139	2.67%	-	Apparent central volume (L)
Q1/F	22.8	4.7%	-	Apparent intercompartmental clearance (L/hour)
Vp1/F	186	3.47%	-	Apparent peripheral volume (L)
F	1 (FIX)	-	-	Relative bioavailability with T3 formulation as reference (-)
Ka	2.16	6.37%	-	Absorption rate parameter (1/hour)
Tlag1	0.38	3.35%	-	Absorption lag time (hours)
Inter-individual variability				
omega(CL/F)	0.354	3.18%	2.5%	LogNormal
omega(Vc/F)	0.205	8.52%	15.8%	LogNormal
omega(Q1/F)	0.302	7.81%	24.1%	LogNormal
omega(Vp1/F)	0.258	8.18%	38.6%	LogNormal
omega(F)	0 (FIX)	-	-	LogNormal
omega(Ka)	0.598	5.13%	25.7%	LogNormal
omega(Tlag1)	0.488	3.92%	35.4%	LogNormal
Correlation of random effects				
corr(CL/F,Vc/F)	0.694	8.64%	-	Correlation coefficient
corr(CL/F,Q1/F)	0.177	54.1%	-	Correlation coefficient
corr(Vc/F,Q1/F)	0.525	32.2%	-	Correlation coefficient
corr(CL/F,Vp1/F)	0.0526	173%	-	Correlation coefficient
corr(Vc/F,Vp1/F)	0.218	57.3%	-	Correlation coefficient
corr(Q1/F,Vp1/F)	0.403	28.1%	-	Correlation coefficient
Parameter-Covariate relationships**				
beta_CL/F(ISHI_1)	-0.363	18.9%	-	Hepatic impairment flag Yes on CL/F
beta_CL/F(ISRI_1)	-0.402	15.5%	-	Renal impairment flag Yes on CL/F
beta_Vc/F(WTKGBL)	0.437	19.8%	-	Weight at baseline in kg on Vc/F (centered around: 75.4 kg)
beta_Vc/F(SEXF_1)	-0.187	19.1%	-	Female Yes on Vc/F
beta_Vc/F(ASIAN_1)	-0.0947	37.6%	-	Asian Yes on Vc/F
beta_Q1/F(WTKGBL)	0.657	23.7%	-	Weight at baseline in kg on Q1/F (centered around: 75.4 kg)
beta_Q1/F(SEXF_1)	0.394	13.6%	-	Female Yes on Q1/F
beta_Vp1/F(WTKGBL)	1.36	10.4%	-	Weight at baseline in kg on Vp1/F (centered around: 75.4 kg)
beta_Vp1/F(SEXF_1)	0.515	9.72%	-	Female Yes on Vp1/F
beta_F(FORMUT1_1)	-0.346	7.55%	-	T1 formulation Yes on F
beta_Ka(TOTDOSE)	-0.213	18%	-	Total daily dose in mg on Ka (centered around: 4 mg)
Residual Variability				
error_ADD1	0.0779	4.56%	-13.9%*	Additive Error (ng/mL) - Compound concentration (ng/mL)
error_PROP1	0.202	0.374%	-	Proportional Error (fraction) - Compound concentration (ng/mL)
Objective function	28773	-	-	-
AIC	28835	-	-	-
BIC	29053	-	-	-

Source: study-tak-861-poppk-analysis, Table 8

Reference ID: 5847402

No major bias was observed based on goodness-of-fit plots (Figure 44) and the predictive capability is relatively reasonable (Figure 45).

Figure 44. Goodness-of-Fit Plots for Final Population PK Models

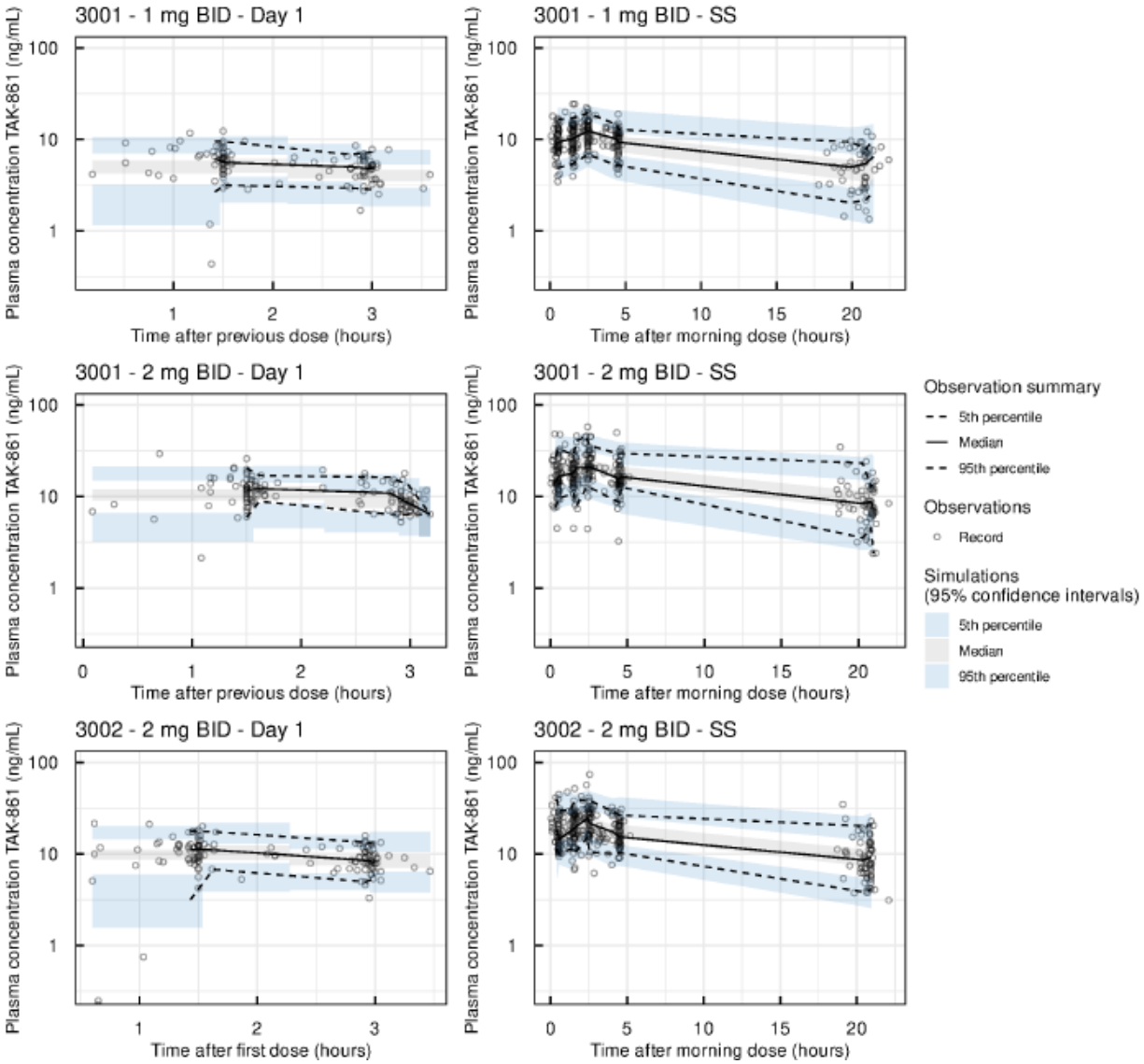


Non-zero pre-lag time observations lead to off-diagonal points in DV vs PRED plots and high IWRES values in IWRES vs TAD plots. These points do not indicate a general inappropriateness of the model to describe the data.

Source: study-tak-861-poppk-analysis, Figure 43

Reference ID: 5847402

Figure 45. Prediction-Corrected Visual Predictive Check for Phase 3 Studies TAK-861-3001 and TAK-861-3002

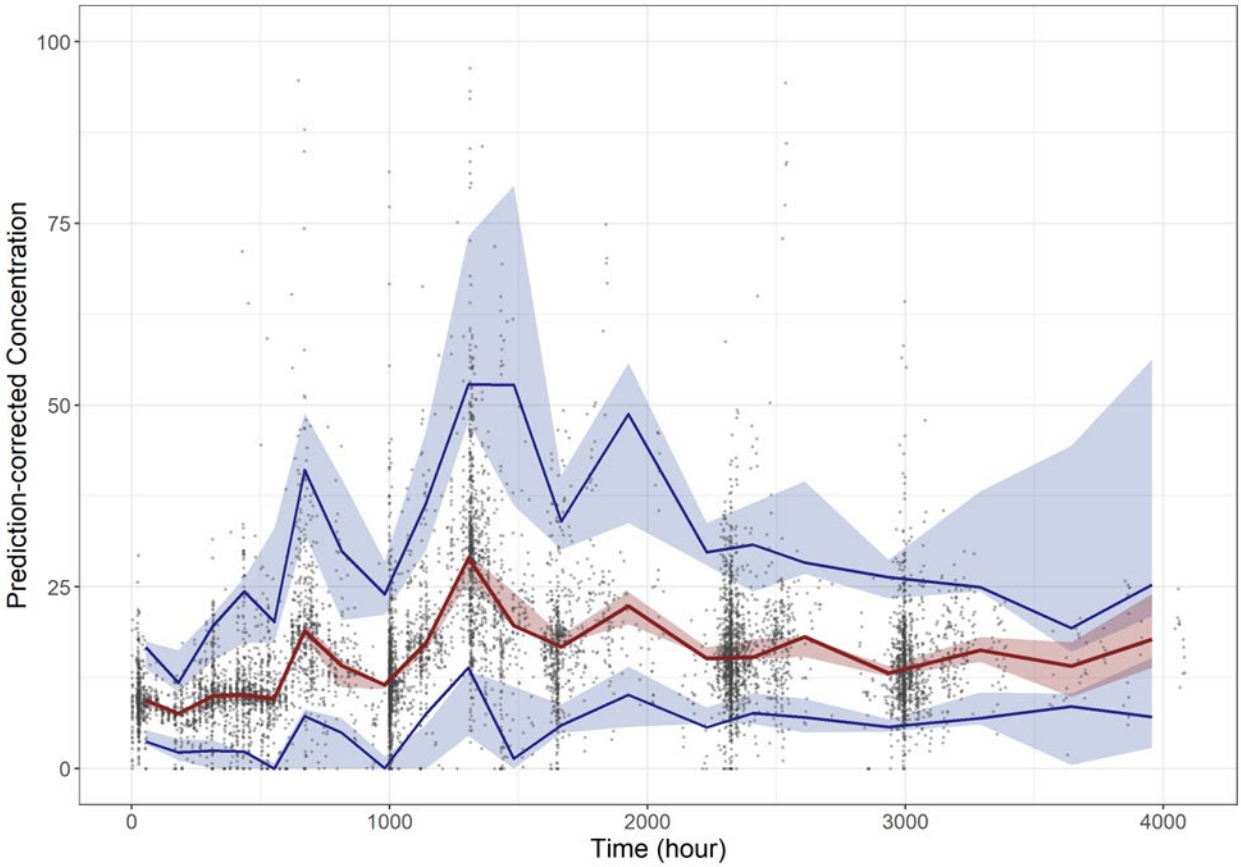


Source: study-tak-861-poppk-analysis, Figure 4

In general, the proposed population PK model is acceptable. Iterative two-stage estimation was run first to obtain stable starting values for the subsequent stochastic approximation expectation-maximization (SAEM) step to get final parameter estimates. The importance sampling was performed to get objective function value. During reproducing the Applicant's model, the pharmacometrics reviewer changed SAEM from using one Metropolis-Hastings chain to using two chains for the stochastic individual-parameter sampling step. Increasing ISAMPLE from 1 to 2 (default) improved the robustness of the SAEM search. The parameter estimates of the pharmacometrics reviewer's reproduced model were reasonably close to those estimated by Applicant. The predictive capability of reproduced model appeared to be reasonable (Figure 46). All the subsequent population PK model related evaluations were performed using the reviewer's reproduced model.

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Figure 46. Prediction-Corrected Visual Predictive Check for Reviewer Reproduced Population PK Model

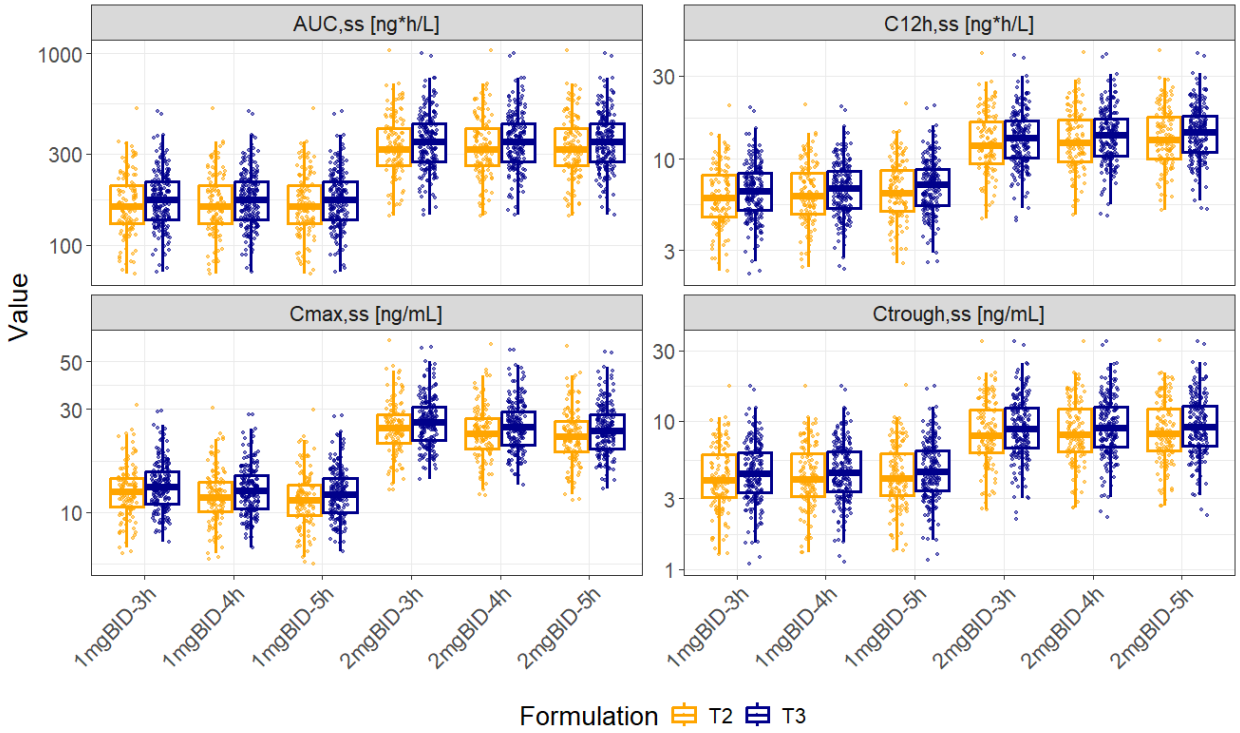


Dark grey dots represent individual prediction-corrected observations. Solid lines represent the 5th (blue), 50th (red), and 95th (blue) percentiles of the observed data. The corresponding shaded regions indicate the 95% confidence intervals for the model-simulated percentiles.
Source: Pharmacometric Reviewer's analysis

In the development program of oveporexton, three immediate-release (IR) formulations (T1 [phase 1 tablets], T2 [phase 2 tablets], and T3 [phase 3 tablets]) were used. A comparative bioavailability study (TAK-861-1007) was conducted to establish the PK bridge between T1 and T2 formulations. However, a comparative bioavailability study for T2 versus T3 was not performed. Both pivotal safety and efficacy studies (TAK-861-3001 and TAK-861-3002), the food effect study (TAK-861-1010), and hepatic and renal impairment studies (TAK-861-1004 and TAK-861-1005) were conducted with the T3 formulation, which shares the same core tablet composition as the registration and commercial tablets. As a result, it is practical to bridge the T2 and T3 using population PK analysis. The T2 and T3 were not estimated to have different impact on PK parameters, and the simulation suggested the PK exposures of T2 and T3 were comparable (Figure 47).

Reference ID: 5847402

Figure 47. PK Exposures at Steady State for T2 and T3

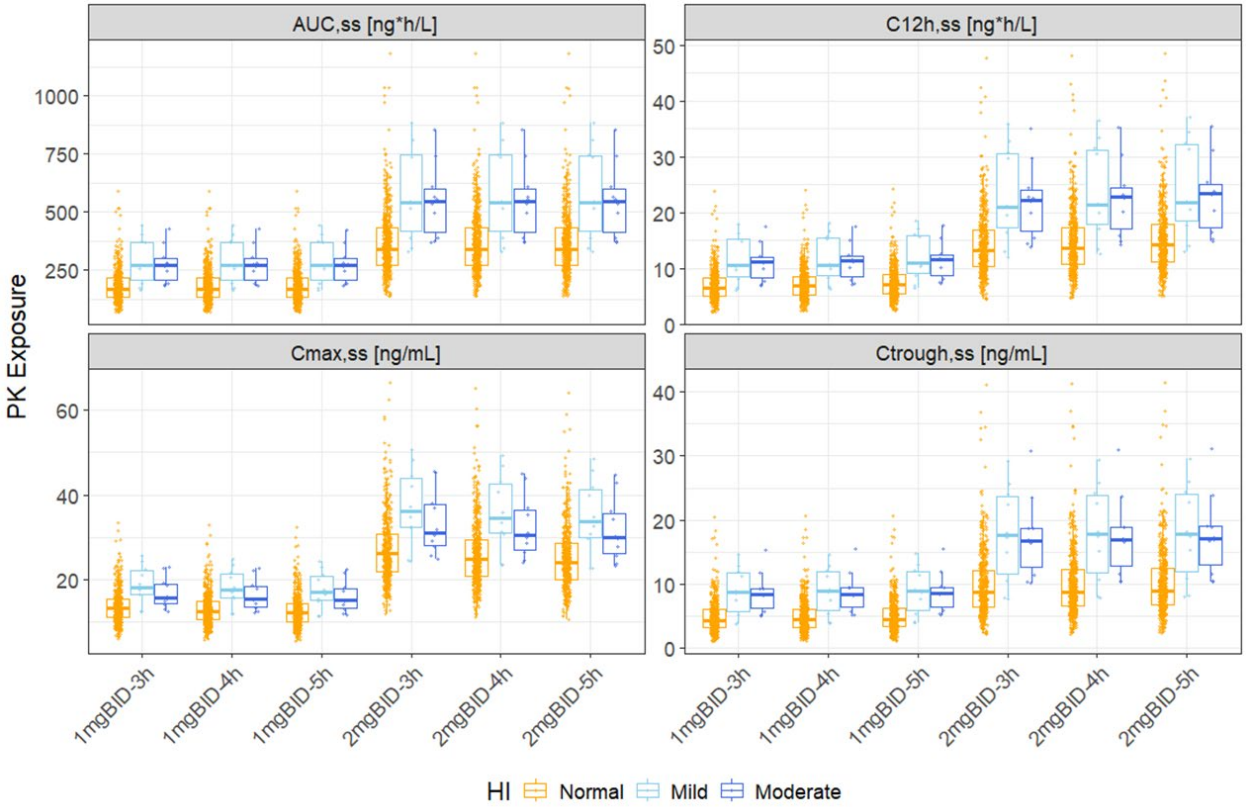


Main rectangular box represents the interquartile range (IQR): upper edge represents the 75th percentile, middle line represents median, lower edge represents the 25th percentile. Upper whisker extends to the largest data point that is no larger than 1.5*IQR from 75th percentile and lower whisker extends to the smallest data point that is no smaller than 1.5*IQR from 25th percentile. Dots: individual prediction.
Source: Pharmacometric Reviewer's analysis

The effect of HI on oveporexton PK was evaluated in a dedicated study (TAK-861-1004) in patients with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) HI. RI was evaluated in a reduced design study (TAK-861-1005). Population PK analysis was performed to further evaluate the impact of HI and RI on PK. Mild and moderate HI as well as moderate and severe RI were estimated to decrease the apparent clearance. Population PK analysis included patients with HI or RI from dedicated PK trials as well as the patients with RI or HI from pivotal trials. PK simulation using the studied subjects suggested PK exposures at steady state increased in the patients with mild and moderate HI (Figure 48) as well as in patients with moderate and severe RI (Figure 49). Substantial overlaps in exposures to oveporexton were observed in patients with HI or RI compared to those in subjects with normal organ function.

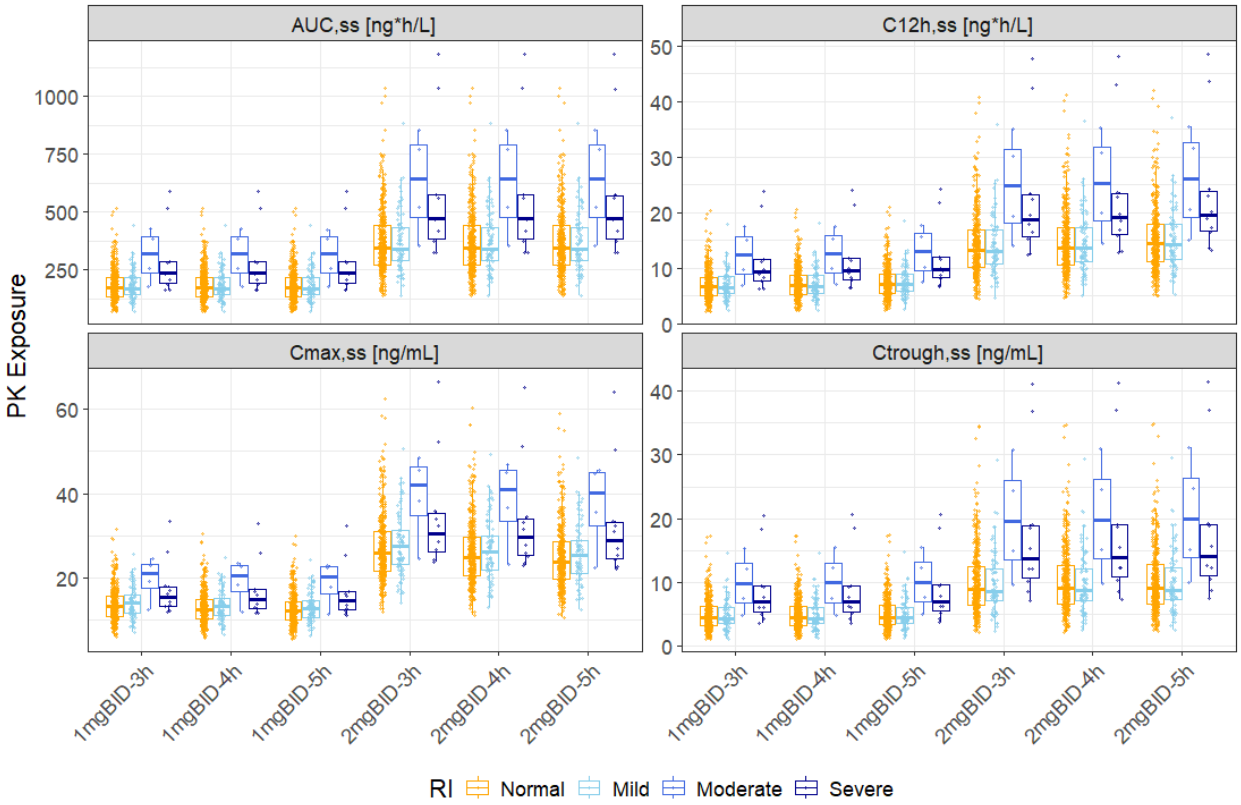
Reference ID: 5847402

Figure 48. Steady State PK Exposures Stratified by Hepatic Impairment Category



Main rectangular box represents the interquartile range (IQR): upper edge represents the 75th percentile, middle line represents median, lower edge represents the 25th percentile. Upper whisker extends to the largest data point that is no larger than 1.5*IQR from 75th percentile and lower whisker extends to the smallest data point that is no smaller than 1.5*IQR from 25th percentile. Dots: individual prediction.
Source: Pharmacometric Reviewer's analysis

Figure 49. Steady State PK Exposures Stratified by Renal Impairment Category

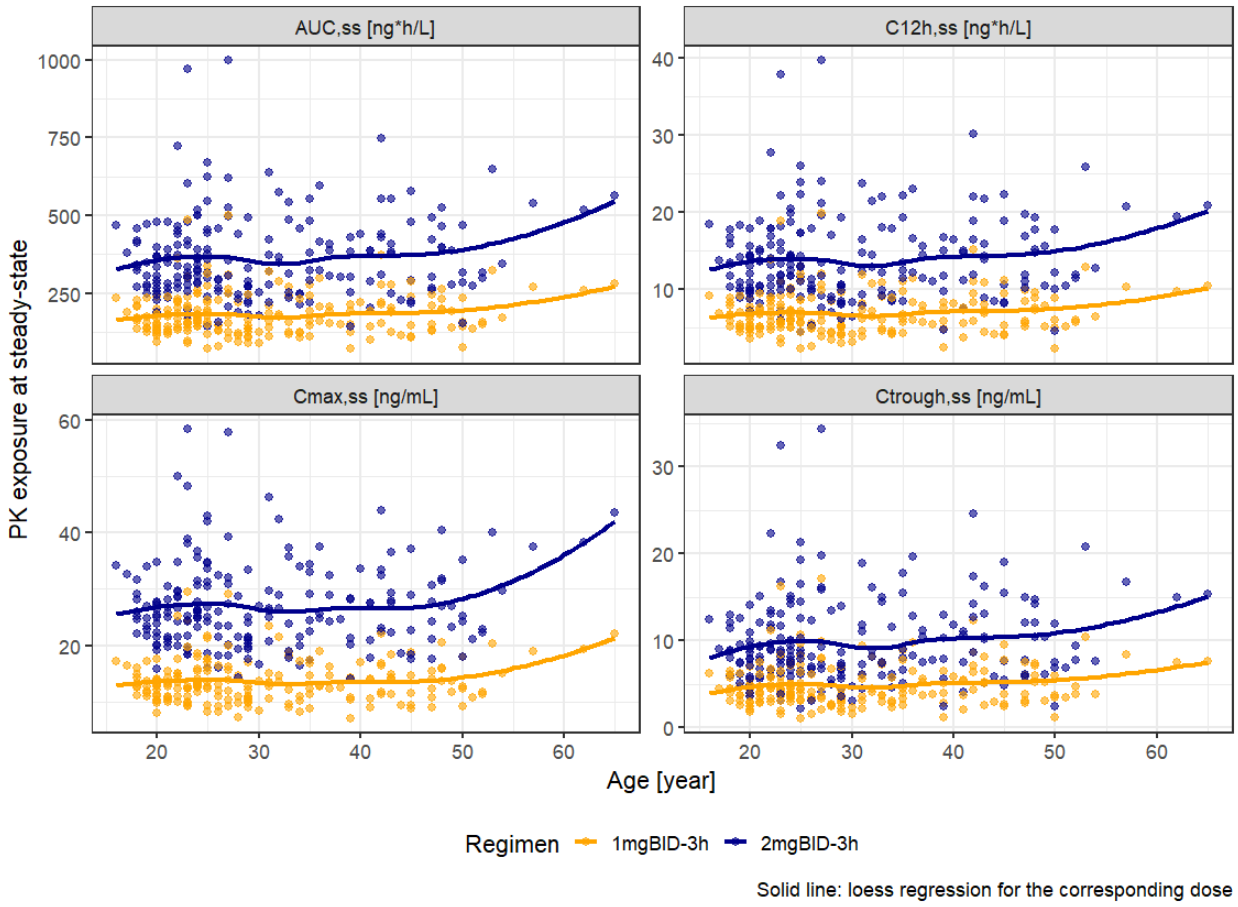


Main rectangular box represents the interquartile range (IQR): upper edge represents the 75th percentile, middle line represents median, lower edge represents the 25th percentile. Upper whisker extends to the largest data point that is no larger than 1.5*IQR from 75th percentile and lower whisker extends to the smallest data point that is no smaller than 1.5*IQR from 25th percentile. Dots: individual prediction.
Source: Pharmacometric Reviewer's analysis

No apparent clinically relevant effect of age (Figure 50), weight (Figure 51), sex (Figure 52), and race (Figure 53) on PK were estimated based on the population PK simulation using data from two pivotal trials.

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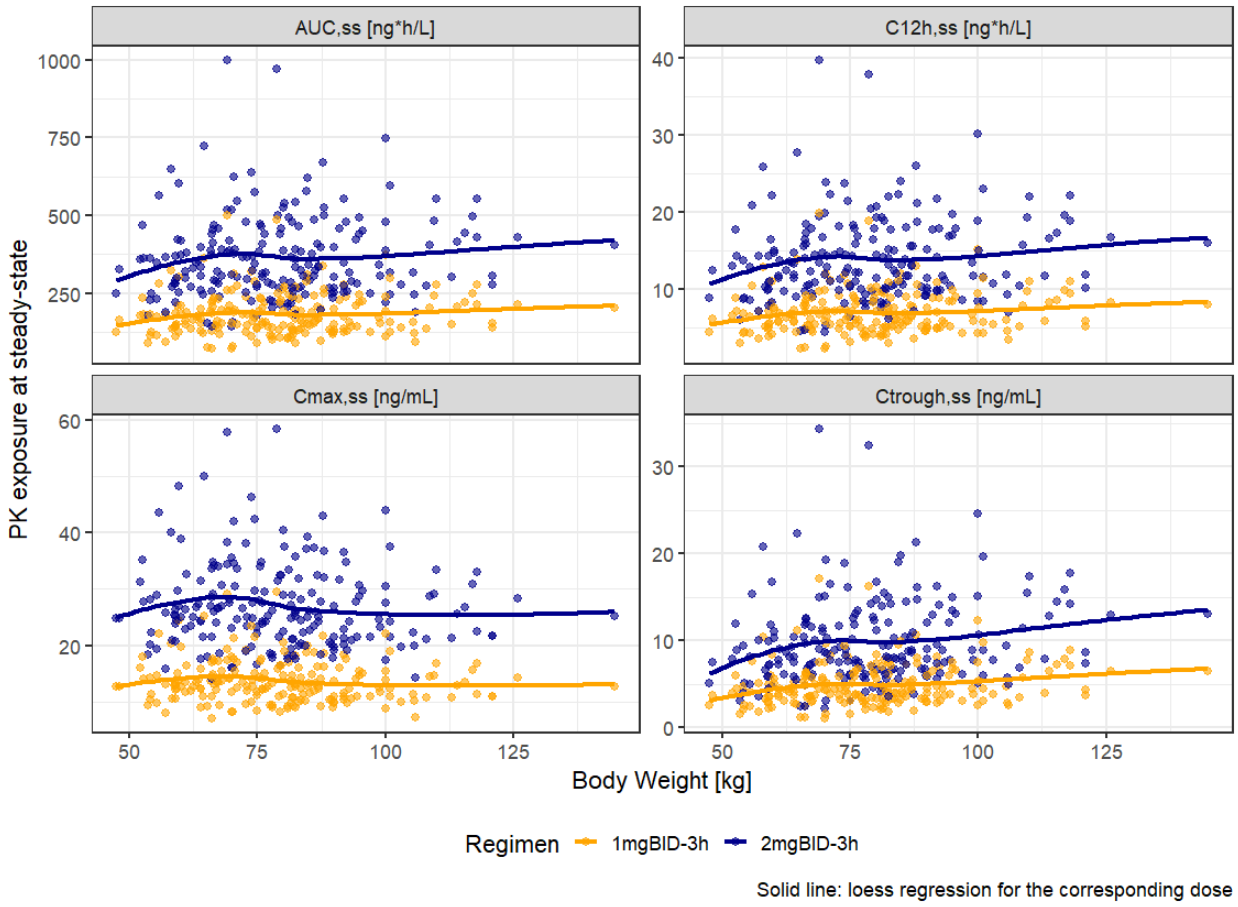
Figure 50. PK Exposures at Steady-State vs. Age



Source: Pharmacometric Reviewer's analysis

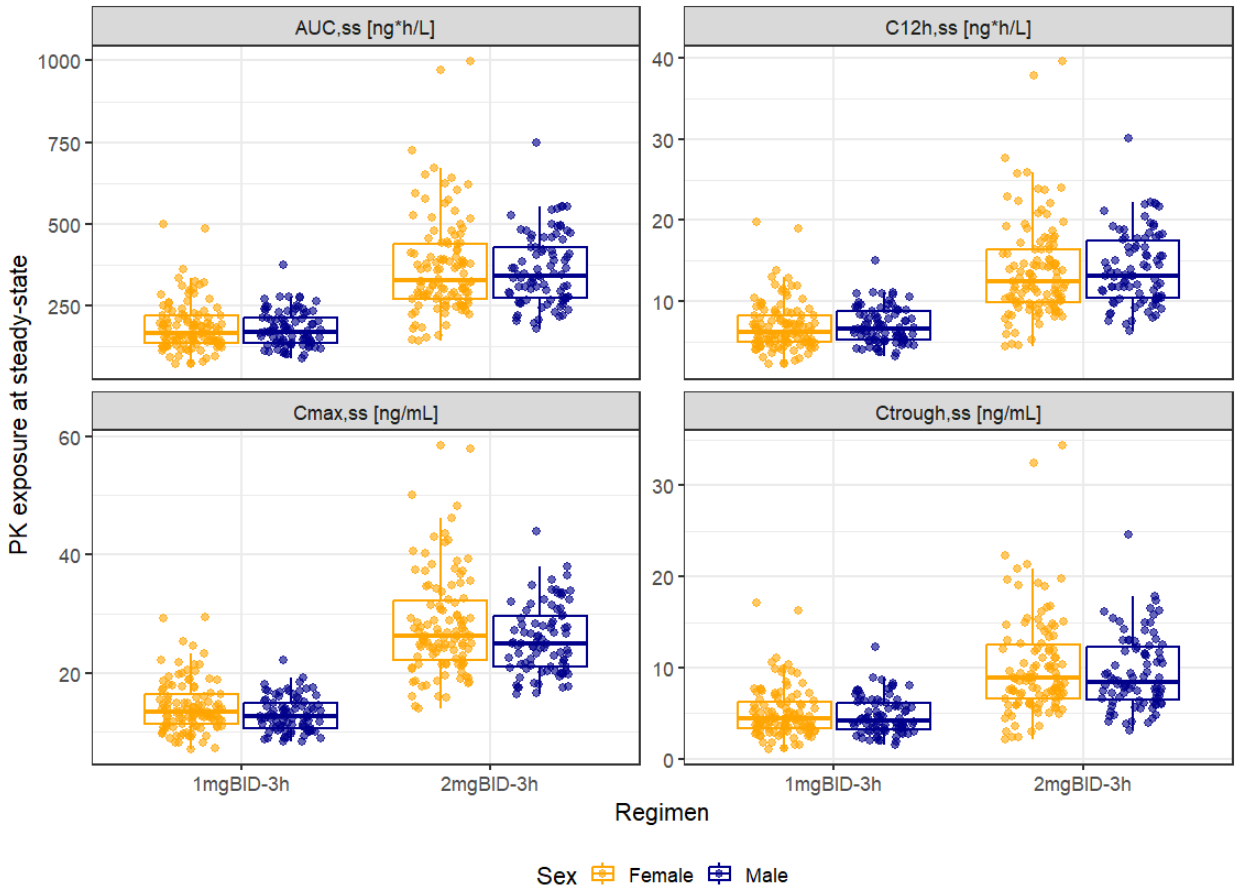
Reference ID: 5847402

Figure 51. PK Exposures at Steady-State vs. Body Weight



Source: Pharmacometric Reviewer's analysis

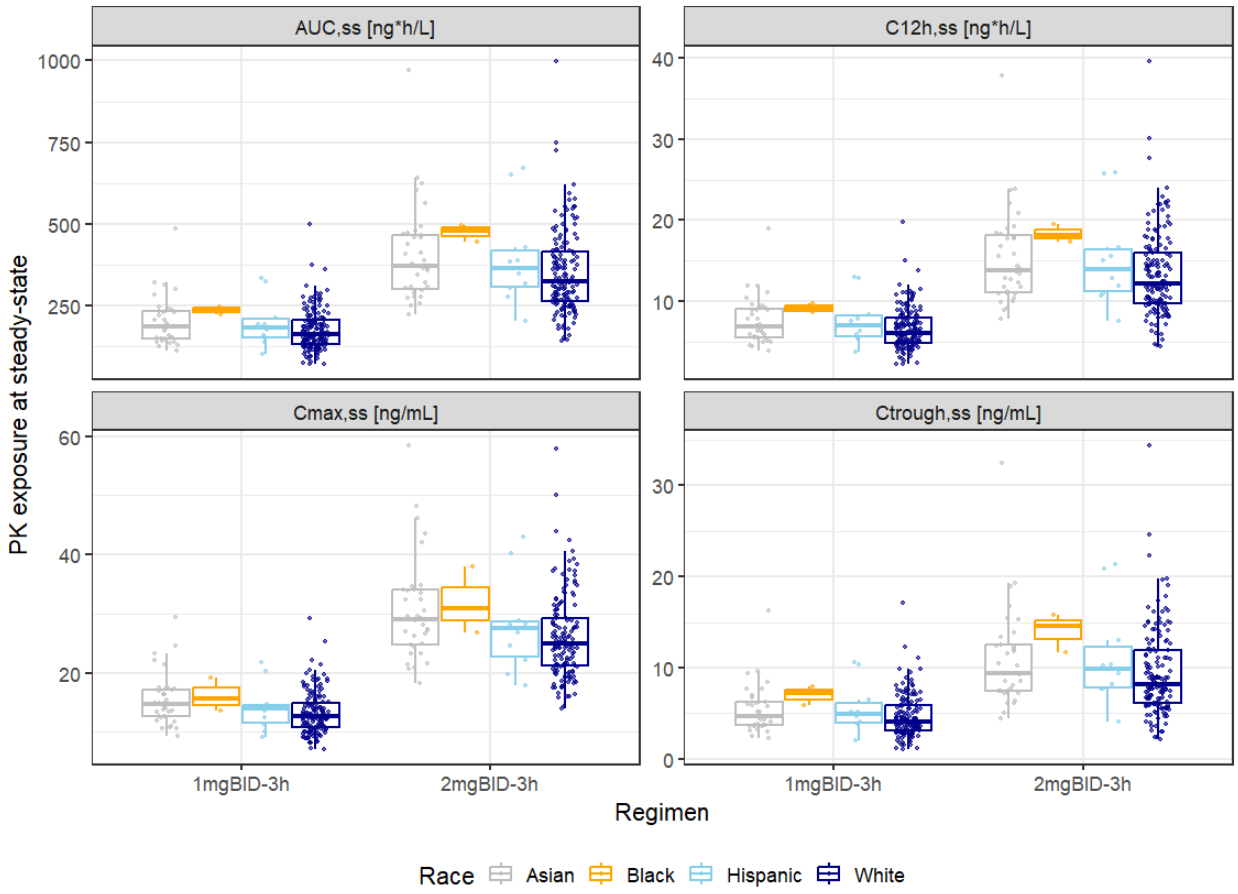
Figure 52. PK Exposures at Steady-State vs. Sex



Main rectangular box represents the interquartile range (IQR): upper edge represents the 75th percentile, middle line represents median, lower edge represents the 25th percentile. Upper whisker extends to the largest data point that is no larger than 1.5*IQR from 75th percentile and lower whisker extends to the smallest data point that is no smaller than 1.5*IQR from 25th percentile. Dots: individual prediction.
Source: Pharmacometric Reviewer's analysis

Reference ID: 5847402

Figure 53. PK Exposures at Steady-State vs. Race



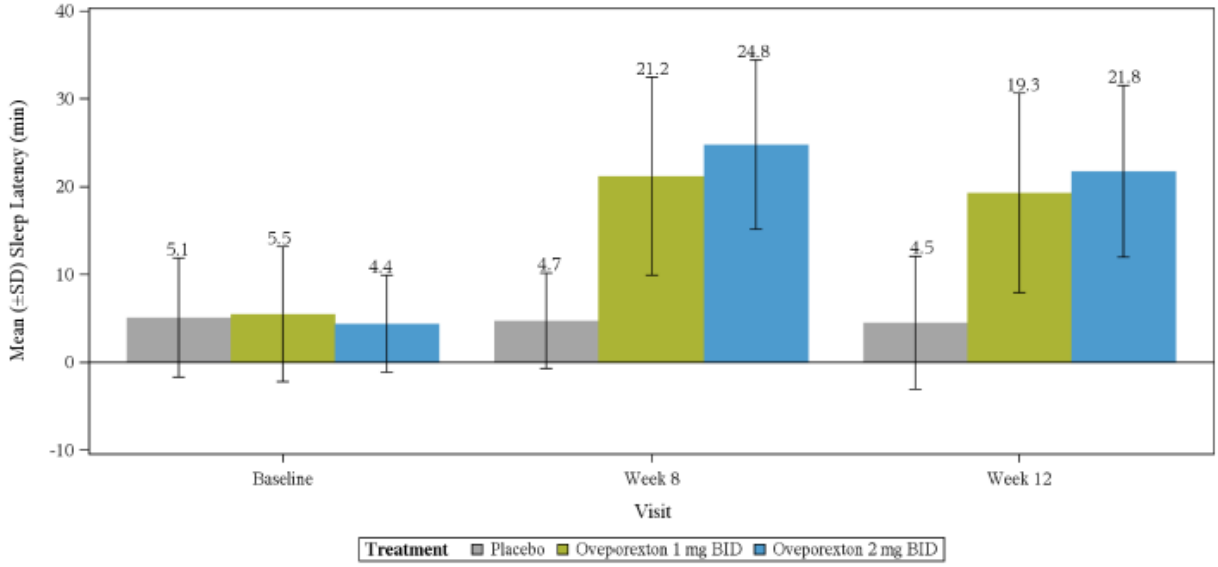
Main rectangular box represents the interquartile range (IQR): upper edge represents the 75th percentile, middle line represents median, lower edge represents the 25th percentile. Upper whisker extends to the largest data point that is no larger than 1.5*IQR from 75th percentile and lower whisker extends to the smallest data point that is no smaller than 1.5*IQR from 25th percentile. Dots: individual prediction.
Source: Pharmacometric Reviewer's analysis

Dose-Response for Efficacy Based on Data From TAK-861-3001

Study TAK-861-3001 was conducted to evaluate the efficacy and safety of oveporexton for the treatment of narcolepsy with cataplexy (narcolepsy type 1). The primary efficacy endpoint was change from Baseline to Week 12 in mean sleep latency from the four maintenance of wakefulness test (MWT) trials. Oveporexton, at the doses of 1 and 2 mg BID, demonstrated statistically significant improvements compared with placebo for the change from Baseline to Week 12 in mean sleep latency on the MWT (Figure 54).

Reference ID: 5847402

Figure 54. Mean Sleep Latency From the MWT in Study TAK-861-3001



Source: Study TAK-861-3001 report, Figure 3

Both 1 mg BID and 2 mg BID demonstrated effectiveness in pivotal trial TAK-861-3001, supporting the approval of both dosage regimens. The response of 2 mg BID arm was numerically better than that of 1 mg BID arm at both Week 8 and Week 12, suggesting potential dose-response relationship in MWT.

Applicant's Exposure-Response for Safety

All participants from Study TAK-861-1001 Parts D and G, as well as Studies TAK-861-2001, TAK-861-3001, and TAK-861-3002 were included in Applicant's safety analysis population. The number of subjects per study as well as the baseline characteristics are summarized in Table 143, Table 144, and Table 145.

Table 143. Number of Participants Per Study and Dose Group for ER Analysis for Safety

Treatment	TAK-861-1001_D [N=18]	TAK-861-1001_G [N=13]	TAK-861-2001 [N=112]	TAK-861-3001 [N=167]	TAK-861-3002 [N=105]	TOTAL [N=415]
0.5 mg BID	0 (0%)	0 (0%)	23 (20.5%)	0 (0%)	0 (0%)	23 (5.54%)
0.5 mg QD	5 (27.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (1.2%)
1 mg BID	0 (0%)	0 (0%)	0 (0%)	60 (35.9%)	0 (0%)	60 (14.5%)
2 mg BID	0 (0%)	0 (0%)	21 (18.8%)	66 (39.5%)	70 (66.7%)	157 (37.8%)
2+5 mg BID	0 (0%)	0 (0%)	23 (20.5%)	0 (0%)	0 (0%)	23 (5.54%)
4 mg BID	5 (27.8%)	9 (69.2%)	0 (0%)	0 (0%)	0 (0%)	14 (3.37%)
4 mg QD	3 (16.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (0.723%)
7 mg QD	0 (0%)	0 (0%)	23 (20.5%)	0 (0%)	0 (0%)	23 (5.54%)
Placebo	5 (27.8%)	4 (30.8%)	22 (19.6%)	41 (24.6%)	35 (33.3%)	107 (25.8%)

N: Number of subjects
Number of subjects in each category and percentage within this category
QD: Once daily treatment, BID: Twice daily treatment
Source: study-tak-861-safety-er-analysis, Table 4

Table 144. Summary of Continuous Covariates for ER Analysis for Safety

Characteristic	Placebo [N=107]	0.5 mg BID [N=23]	1 mg BID [N=60]	2 mg BID [N=157]	2+5 mg BID [N=23]	4 mg BID [N=14]	0.5 mg QD [N=5]	4 mg QD [N=3]	7 mg QD [N=23]	TOTAL [N=415]
Age at baseline (years)	33.1 (12.6) [16-61]	32.7 (11.1) [18-59]	33.7 (11.8) [16-65]	29.7 (9.84) [17-62]	34.7 (11.5) [18-58]	32.4 (11.8) [19-59]	34.4 (17.7) [19-64]	34 (14.4) [18-46]	33.3 (11.9) [18-57]	32 (11.4) [16-65]
Weight at baseline (kg)	81.6 (19.2) [48-138]	77.2 (17.4) [51-111]	82.3 (18.5) [47.4-126]	78 (15.8) [47-145]	79.9 (16.3) [50.6-114]	75.4 (14.8) [56-112]	66.2 (14.1) [51.7-84.5]	79.1 (4.26) [74.7-83.2]	79 (17) [52.7-120]	79.4 (17.3) [47-145]

N: Number of subjects
Entries represent: Mean (Standard deviation) [Minimum-Maximum]
Source: study-tak-861-safety-er-analysis, Table 5

Table 145. Summary of Categorical Covariates for ER Analysis for Safety

Characteristic	Category	Placebo [N=107]	0.5 mg BID [N=23]	1 mg BID [N=60]	2 mg BID [N=157]	2+5 mg BID [N=23]	4 mg BID [N=14]	0.5 mg QD [N=5]	4 mg QD [N=3]	7 mg QD [N=23]	TOTAL [N=415]
Female	No	52 (48.6%)	12 (52.2%)	33 (55%)	65 (41.4%)	9 (39.1%)	5 (35.7%)	1 (20%)	3 (100%)	13 (56.5%)	193 (46.5%)
	Yes	55 (51.4%)	11 (47.8%)	27 (45%)	92 (58.6%)	14 (60.9%)	9 (64.3%)	4 (80%)	0 (0%)	10 (43.5%)	222 (53.5%)
Region	Asia	18 (16.8%)	0 (0%)	9 (15%)	24 (15.3%)	2 (8.7%)	10 (71.4%)	3 (60%)	1 (33.3%)	2 (8.7%)	69 (16.6%)
	North America	18 (16.8%)	5 (21.7%)	11 (18.3%)	18 (11.5%)	5 (21.7%)	4 (28.6%)	2 (40%)	2 (66.7%)	5 (21.7%)	70 (16.9%)
	Europe	71 (66.4%)	18 (78.3%)	40 (66.7%)	115 (73.2%)	16 (69.6%)	0 (0%)	0 (0%)	0 (0%)	16 (69.6%)	276 (66.5%)

N: Number of subjects
Number of subjects in each category and percentage within this category
Source: study-tak-861-safety-er-analysis, Table 6

The model-based analysis of the ER relationship was conducted for insomnia, all urinary events, micturition urgency, and pollakiuria using PK exposures predicted by the final population PK model.

Reference ID: 5847402

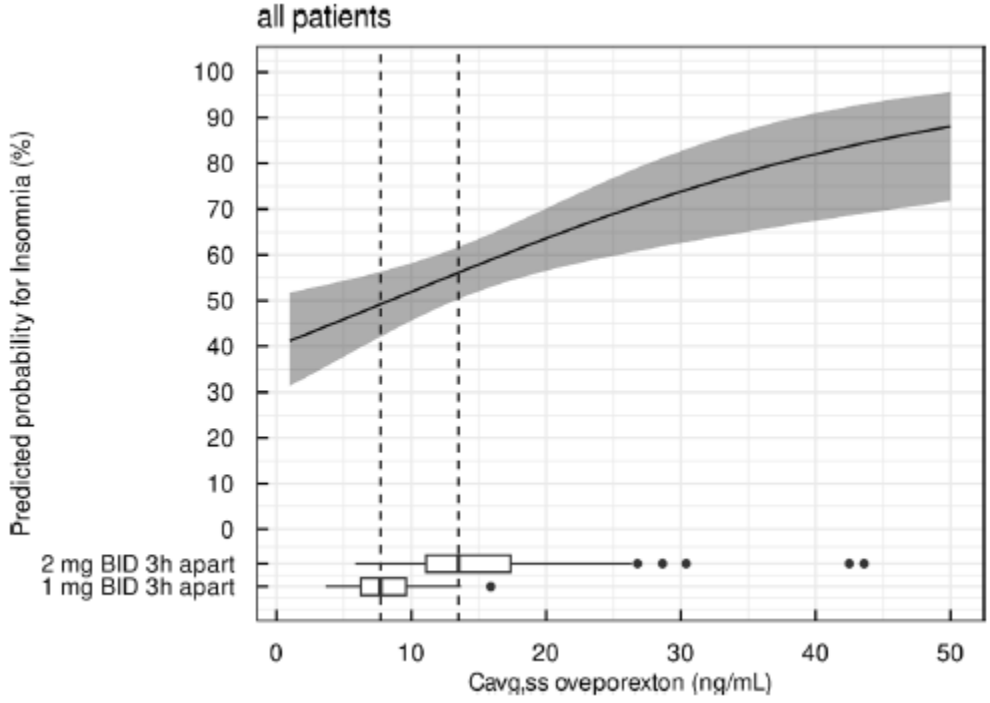
After accounting for treatment (treated versus placebo), average steady-state concentration ($C_{avg,ss}$) was a statistically significant (p=0.048) predictor for insomnia based on logistic regression (Figure 55). The predicted probability of insomnia for median $C_{avg,ss}$ of 1 mg BID and 2 mg BID were 49.2% [95% CI: 42.2%-56.3%] and 56.1% [95% CI: 50.4%-61.7%], respectively.

After accounting for treatment (treated versus placebo) and region (North America versus other regions), $C_{avg,ss}$ was a statistically significant (p=0.034) predictor for urinary events based on logistic regression (Figure 56). The predicted probability of urinary events for median $C_{avg,ss}$ of 1 mg BID and 2 mg BID in North America were 43.6% [95% CI: 30.6%-57.6%] and 48.4% [95% CI: 35.4%-61.7%], respectively.

After accounting for treatment (treated versus placebo), there was a trend (p=0.052) that increased $C_{avg,ss}$ was associated with increased probability of micturition urgency based on logistic regression (Figure 57). The predicted probability of micturition urgency for median $C_{avg,ss}$ of 1 mg BID and 2 mg BID in North America were 16% [95% CI: 11.7%-21.5%] and 20.5% [95% CI: 16.2%-25.6%], respectively.

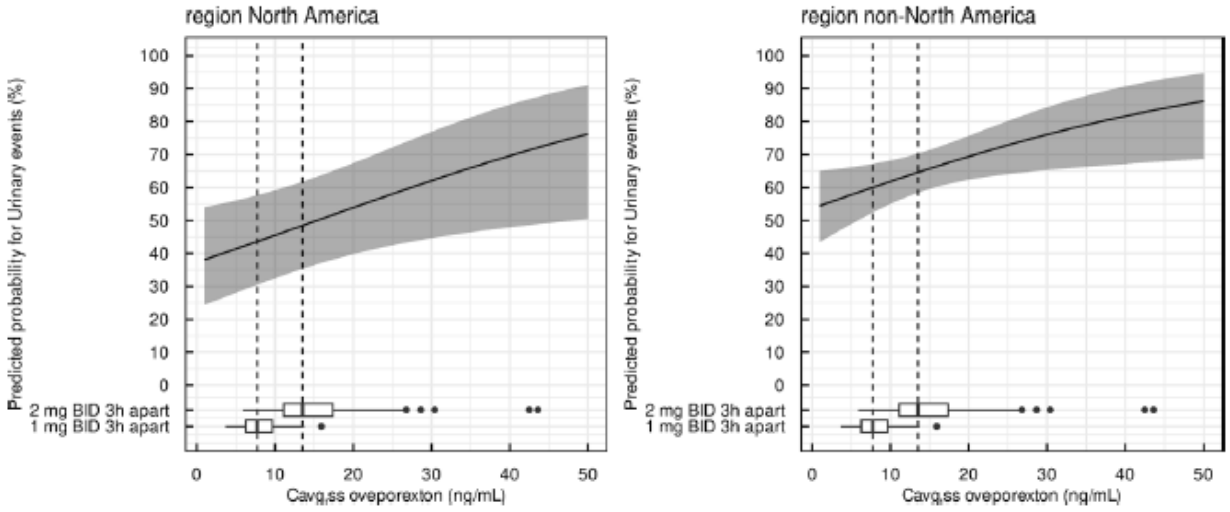
PK exposures were not associated with the probability of pollakiuria after accounting for treatment (treated versus placebo).

Figure 55. Predicted Oveporexton ER Relationship for Insomnia in Participants With NT1



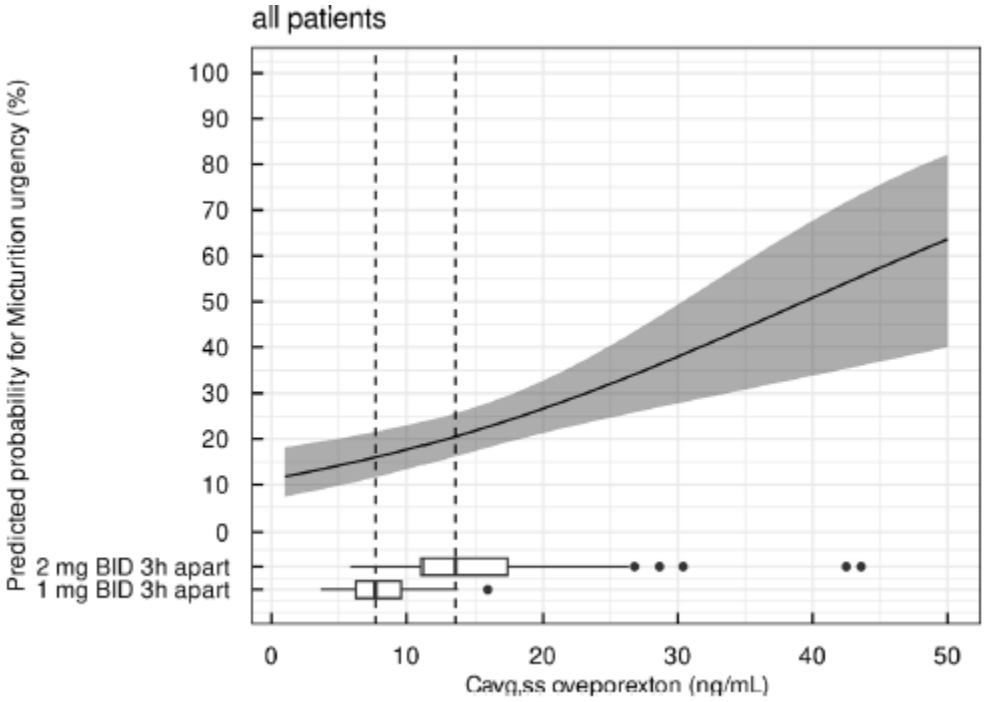
Line and shaded areas indicate prediction with 95% confidence interval. For the boxplots, thick lines and boxes indicate median and interquartile range (IQR). Whiskers extend to 1.5x of the IQR.
Source: study-tak-861-safety-er-analysis, Figure 4

Figure 56. Predicted Oveporexton ER Relationship for Urinary Events in Participants With NT1



Line and shaded areas indicate prediction with 95% confidence interval. For the boxplots, thick lines and boxes indicate median and interquartile range (IQR). Whiskers extend to 1.5x of the IQR.
Source: study-tak-861-safety-er-analysis, Figure 5

Figure 57. Predicted Oveporexton ER Relationship for Micturition Urgency in Participants With NT1



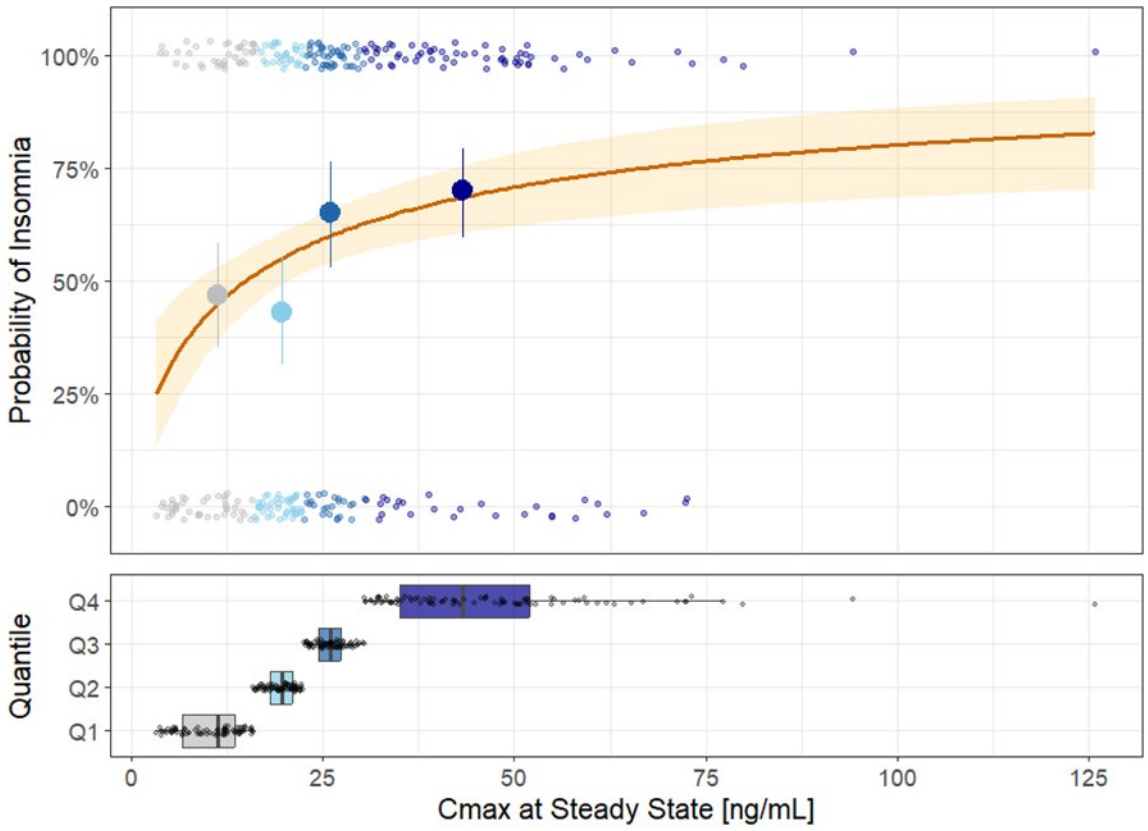
Line and shaded areas indicate prediction with 95% confidence interval. For the boxplots, thick lines and boxes indicate median and interquartile range (IQR). Whiskers extend to 1.5x of the IQR.
Source: study-tak-861-safety-er-analysis, Figure 6

The Applicant proposed ER analysis for safety appears acceptable. The pharmacometric reviewer performed sensitivity analysis using the patients from treated arms. PK exposure metrics at steady-state, including AUC over 12 hours (AUC_{ss}), maximum concentration

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($C_{max,ss}$), trough concentration ($C_{trough,ss}$), and concentration 12 hours post-last dose ($C_{12h,ss}$), were positively associated with the probability of insomnia (Figure 58), urinary events (Figure 59), and micturition urgency (Figure 60), which were consistent with Applicant's findings. A similar trend was observed for all four PK metrics. All subsequent plots will use $C_{max,ss}$ as representative.

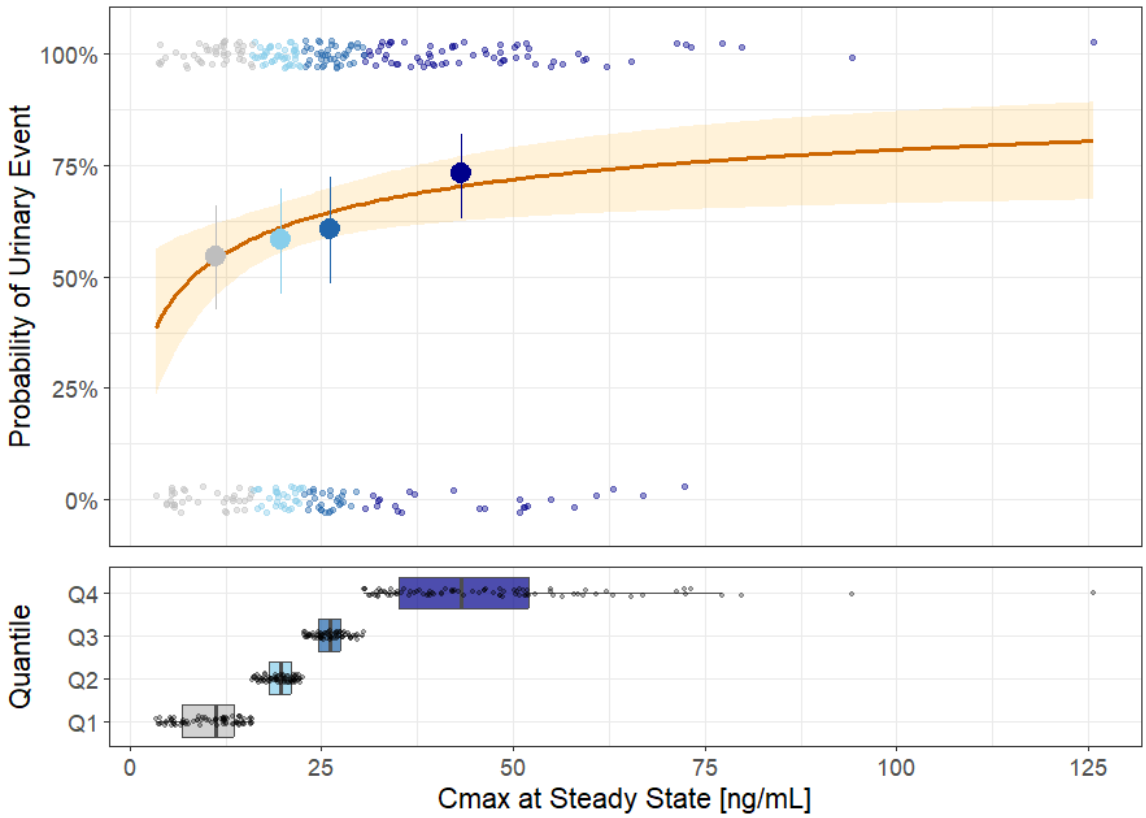
Figure 58. Probability of Insomnia Against $C_{max,ss}$ Based on Studied Patient Population



Upper panel: large dots and error bar: observed probability of event for the corresponding Cmax,ss quantiles and 95% confidence interval; small dots: individual event outcome; orange curve and shaded area: model predicted probability of event following the increase of Cmax,ss and 95% predictive interval
Lower panel: distribution of model predicted Cmax,ss among the studied patients
Source: Pharmacometrics Reviewer's analysis

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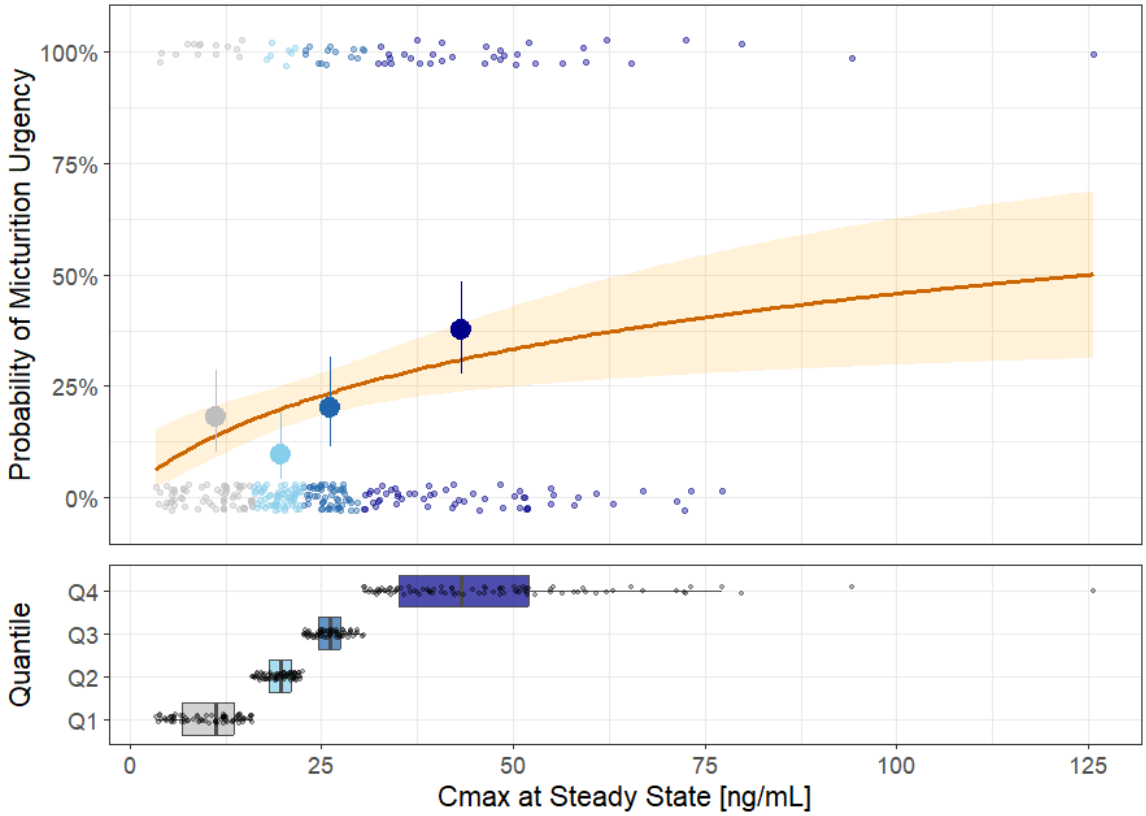
Figure 59. Probability of Urinary Event Against $C_{max,ss}$ Based on Studied Patient Population



Upper panel: large dots and error bar: observed probability of event for the corresponding $C_{max,ss}$ quantiles and 95% confidence interval; small dots: individual event outcome; orange curve and shaded area: model predicted probability of event following the increase of $C_{max,ss}$ and 95% predictive interval
Lower panel: distribution of model predicted $C_{max,ss}$ among the studied patients
Source: Pharmacometrics Reviewer's analysis

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Figure 60. Probability of Micturition Urgency Against $C_{max,ss}$ Based on Studied Patient Population



Upper panel: large dots and error bar: observed probability of event for the corresponding $C_{max,ss}$ quantiles and 95% confidence interval; small dots: individual event outcome; orange curve and shaded area: model predicted probability of event following the increase of $C_{max,ss}$ and 95% predictive interval
Lower panel: distribution of model predicted $C_{max,ss}$ among the studied patients
Source: Pharmacometrics Reviewer's analysis

Although the positive exposure-response relationships were identified for insomnia, urinary event, and micturition urgency, the overall percentage of events (Table 146) as well as the percentage of patients with events resolved (Table 147) for these three safety outcomes were comparable between 1 mg BID and 2 mg BID based on pooled data from Study TAK-861-3001 and TAK-861-3002. In addition, the event duration for these three safety events were comparable between 1 mg BID and 2 mg BID (Figure 61).

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Table 146. Percentage of Event in Pooled Patients From Studies TAK-861-3001 and TAK-861-3002

	Insomnia	Micturition urgency	Urinary event
Placebo	1.32%	1.32%	6.58%
1 mg BID	55%	15%	63.3%
2 mg BID	59.6%	16.2%	63.2%

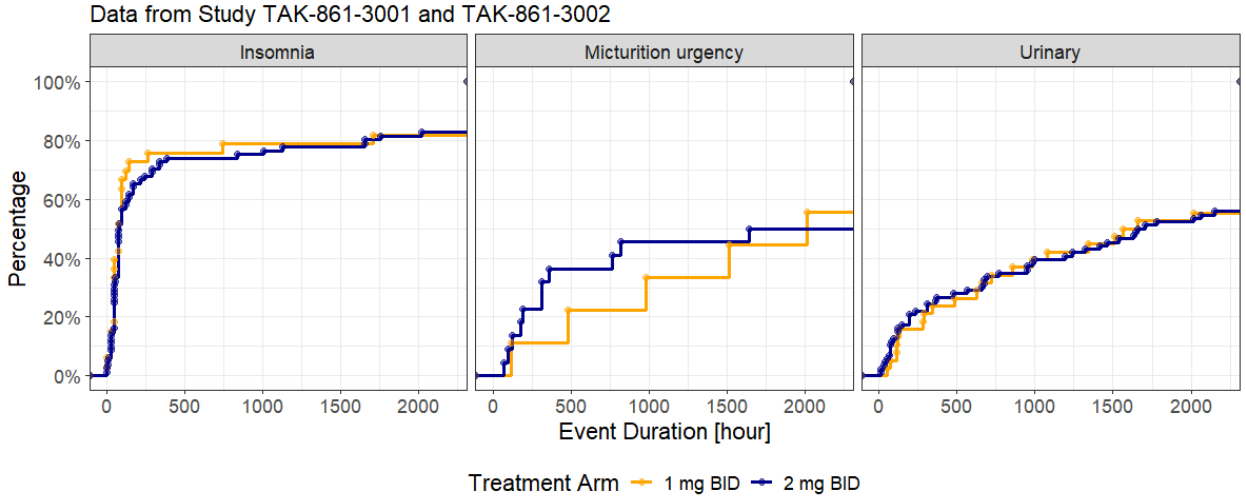
Source: Pharmacometrics Reviewer's analysis

Table 147. Percentage of Patients Resolved for Insomnia, Micturition Urgency and Urinary Events From Studies TAK-861-3001 and TAK-861-3002

	Insomnia	Micturition urgency	Urinary event
Placebo	100%	100%	60%
1 mg BID	75.8%	55.6%	55.3%
2 mg BID	81.5%	50%	55.8%

Source: Pharmacometrics Reviewer's analysis

Figure 61. Empirical Cumulative Distribution of Event Duration

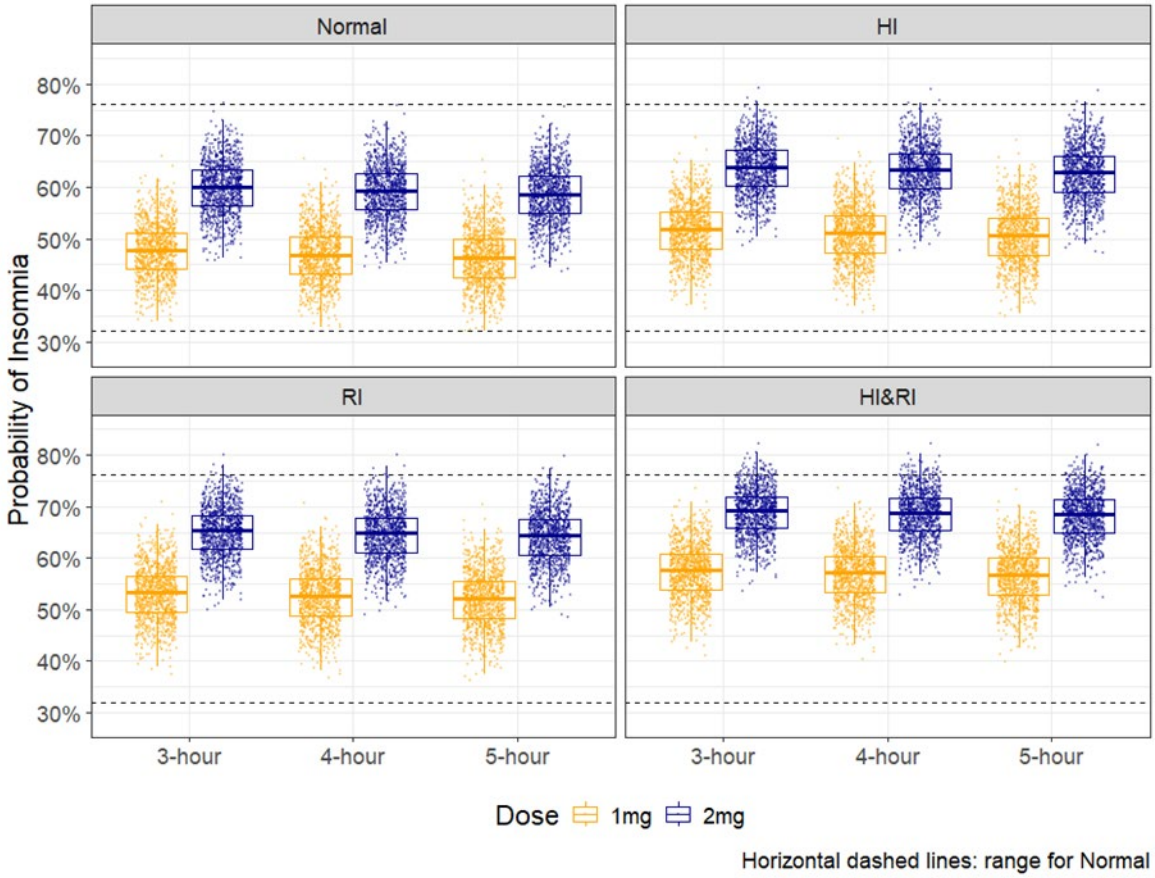


Source: Pharmacometrics Reviewer's analysis

Since the patients with HI and RI were predicted to have increased PK exposures compared to patients with normal hepatic and renal function, the probability of safety events were

simulated to compare the risk between patients with HI (pooled mild and moderate HI) or RI (pooled moderate and severe RI) and patients with normal hepatic and renal function, respectively. Patients with HI and RI were predicted to have increased probability of insomnia (Figure 62), urinary event (Figure 63), and micturition urgency (Figure 64). However, the probability range in patients with HI or RI were largely within the range of that in patients with normal hepatic and renal function. Based on the comparable dose-response as well as the limited increase in the probability of safety events in patients with HI and RI, the dosage adjustment based on HI (mild and moderate) and RI (moderate and severe) is not recommended.

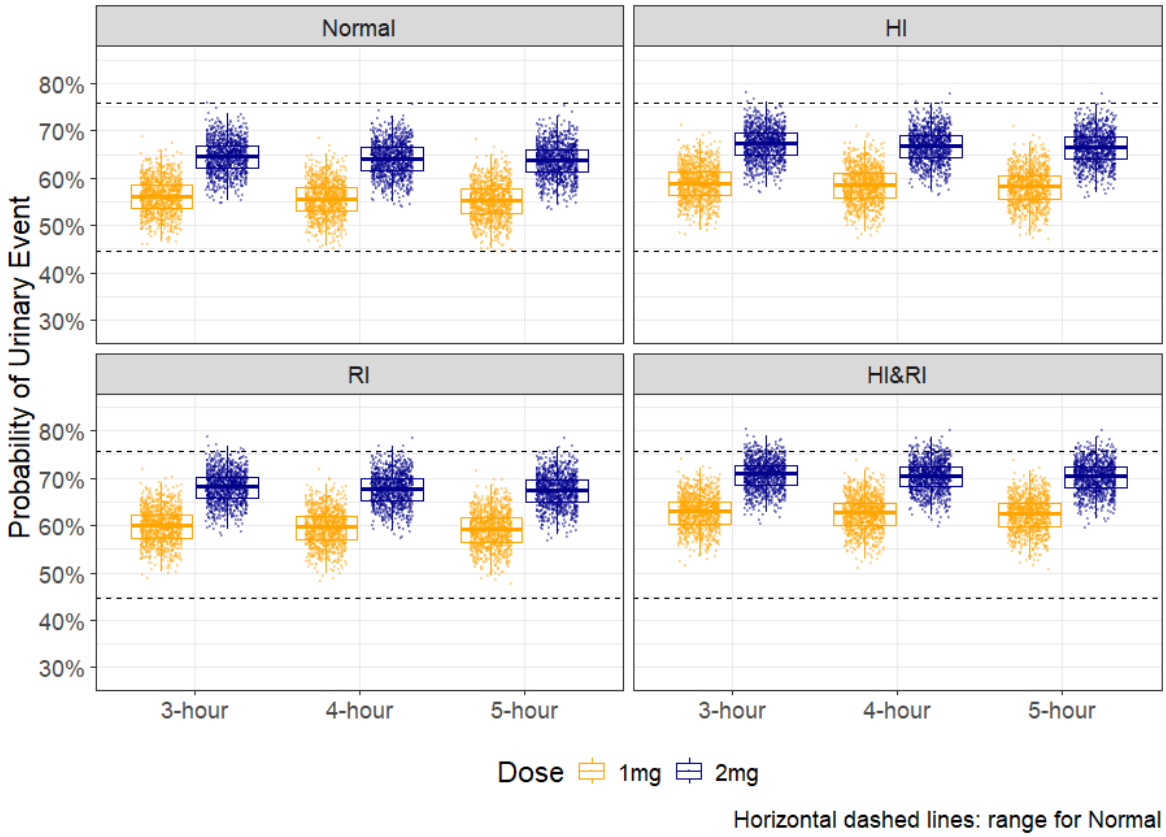
Figure 62. Simulated Probability of Insomnia in Patients With Different Categories of Hepatic and Renal Function



Normal: subjects with normal hepatic and renal function; HI: subjects with hepatic impairment; RI: subjects with renal impairment; HI&RI: patients with hepatic impairment and renal impairment
Source: Pharmacometrics Reviewer's analysis

Reference ID: 5847402

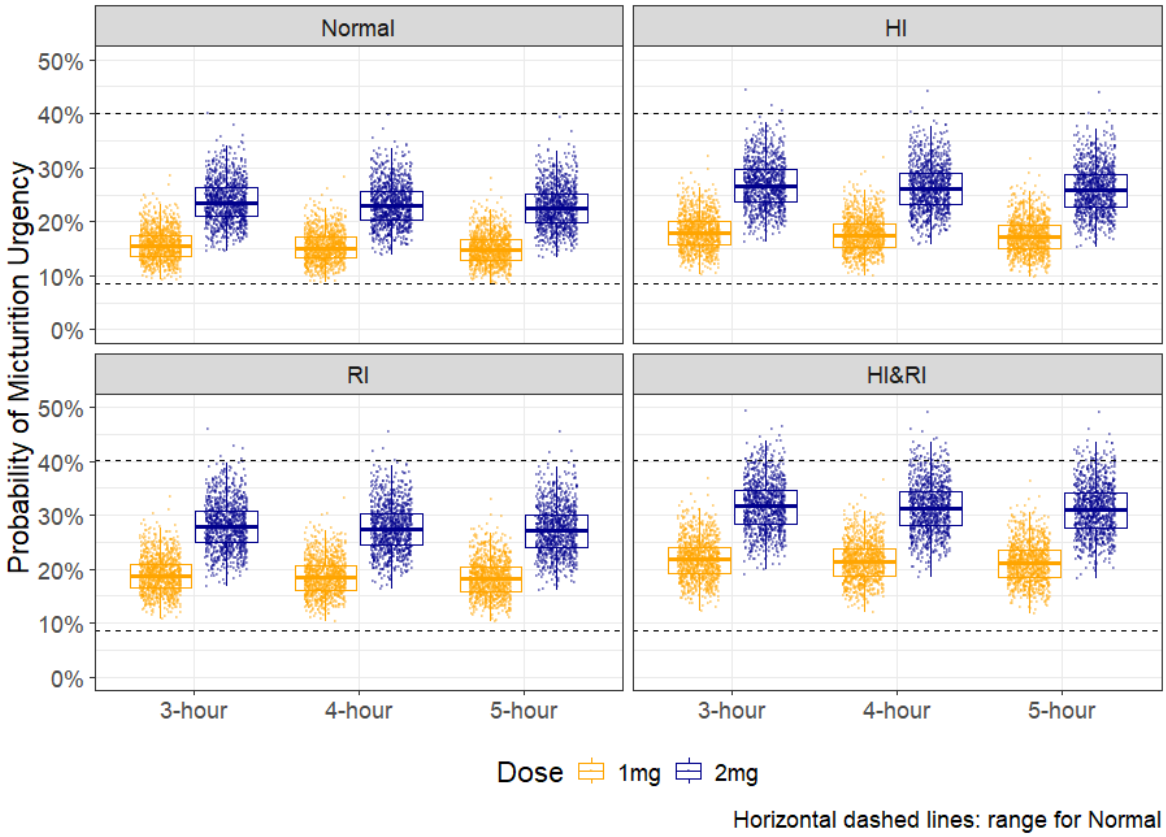
Figure 63. Simulated Probability of Urinary Event in Patients With Different Categories of Hepatic and Renal Function



Normal: subjects with normal hepatic and renal function; HI: subjects with hepatic impairment; RI: subjects with renal impairment; HI&RI: patients with hepatic impairment and renal impairment
Source: Pharmacometrics Reviewer's analysis

Reference ID: 5847402

Figure 64. Simulated Probability of Urinary Micturition Urgency in Patients With Different Categories of Hepatic and Renal Function



Normal: subjects with normal hepatic and renal function; HI: subjects with hepatic impairment; RI: subjects with renal impairment; HI&RI: patients with hepatic impairment and renal impairment
Source: Pharmacometrics Reviewer's analysis

16.4.5. Physiologically-Based Pharmacokinetic Analyses Review

Executive Summary

The objective of this review was to evaluate the adequacy of the Applicant's Physiologically based Pharmacokinetic (PBPK) modeling analyses to predict the following:

- Interaction effect of a weak CYP3A4 inhibitor on the exposure of oveporexton
- Interaction effect of moderate and weak CYP3A4 inducers on the exposure of oveporexton
- Interaction effect of oveporexton on the exposure of a CYP3A substrate

The Division of Pharmacometrics has reviewed the PBPK submission (Reports TAK/25/A associated modeling files and response to FDA IR dated February 17, 2026) and concludes:

- A weak interaction effect on oveporexton exposure was predicted with coadministration of a weak CYP3A inhibitor (AUC increase <2-fold) or weak CYP3A4 inducer (AUC decreased by <50%).
- Coadministration of oveporexton with a moderate CYP3A inducer was predicted to decrease oveporexton AUC_{tau} and C_{max} by 72% and 55%, respectively.
- Co-administration of oveporexton 2 mg BID (3 h apart) with a strong or moderate CYP3A inducer was predicted to result in approximately 2-fold and 5-fold lower AUC, compared to administration of oveporexton 1 mg and 2 mg BID (3 h apart), respectively.
- Co-administration of oveporexton 0.5 mg BID (3 h apart) with a moderate CYP3A inhibitor was predicted to result in a similar oveporexton AUC compared to oveporexton 1 mg BID (3 h apart) dosing alone.
- The PBPK analysis, in combination with clinical PK data of oveporexton at steady state, indicated a low likelihood for a clinically relevant interaction of oveporexton 2 mg BID with a substrate of CYP3A4.

Methods

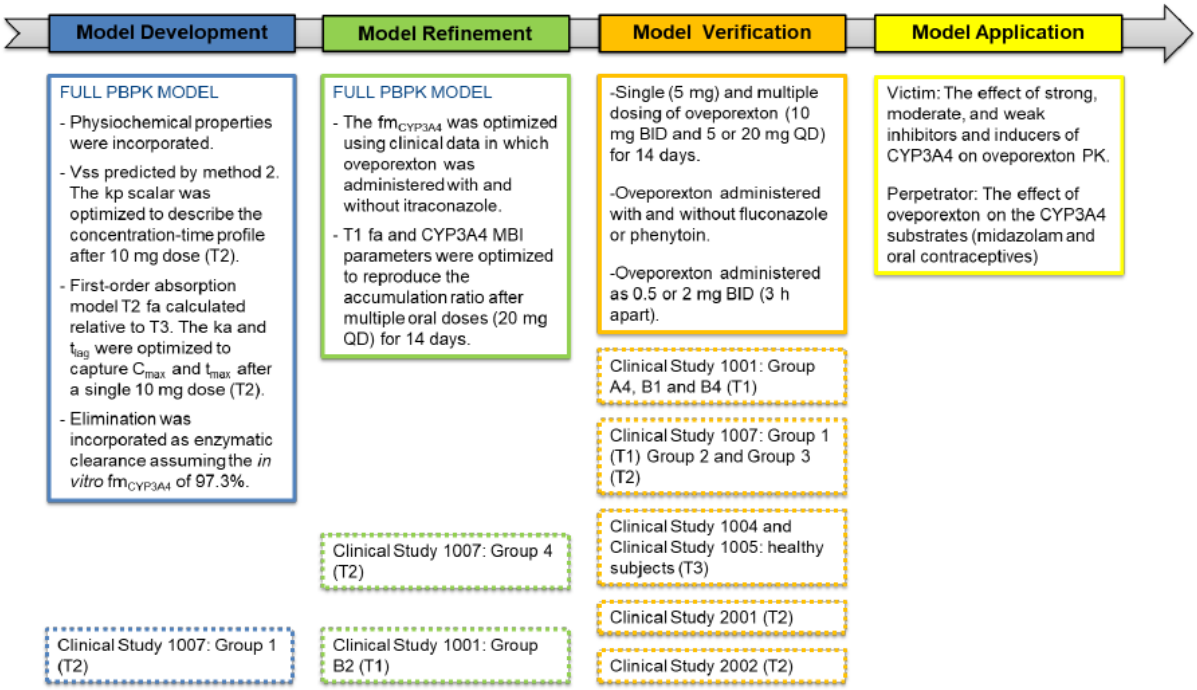
Oveporexton PBPK Modeling

The PBPK analyses were performed using the software Simcyp® version 23. The oveporexton PBPK model consisted of a first-order absorption model and a full PBPK distribution model.

A schematic representation of the PBPK modeling strategy, including the key PBPK modeling steps and clinical studies used in the model development, verification and application, is shown in Figure 65. The input parameters for oveporexton PBPK model are listed in Table 148.

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Figure 65. Schematic of PBPK Modeling Strategy



Abbreviations: fa: fraction absorbed; fm: fraction metabolized; ka: first order absorption rate constant; Kp: tissue-to-plasma partition coefficient; MBI: mechanism-based inhibition; tlag: lag time; VSS: steady-state volume of distribution.
Clinical Study TAK-861-1001 Group A1: a single 5 mg dose of oveporexton (T1), Group B1: 5 mg oveporexton (T1) QD for 14 days, Group B2: 20 mg oveporexton QD (T1) for 14 days, and Group B4: 10 mg oveporexton (T2) BID for 14 days; Clinical Study TAK-861-1007 Group 1: relative bioavailability of a single 10 mg dose of the T1 versus T2 formulations of oveporexton, Group 2: a single 10 mg dose of oveporexton (T2) with and without fluconazole (200 mg QD), Group 3: a single 10 mg dose of oveporexton (T2) with and without phenytoin (100 mg TID), Group 4: a single 1 mg dose of oveporexton (T2) with and without itraconazole (200 mg QD); Clinical Study TAK-861- 1004: two 2 mg doses of oveporexton (T3) administered 3 h apart; Clinical Study TAK-861-1005: two 2 mg doses of oveporexton (T3) administered 3 h apart; Clinical Study TAK-861-2001 (T2): 0.5 or 2 mg BID (3 h apart) oveporexton (T2); Clinical Study TAK-861-2002: 2 mg BID (3 h apart) oveporexton (T2).
Source: Figure 1 of PBPK report TAK/25/A

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Table 148. Input Parameters for the PBPK Model of Oveporexton

PARAMETER	Value	Reference
Physicochemical and Binding Parameters		
Molecular weight (g/mol)	520.51	Global Investigator's Brochure
Log P	4.1	Report 24-0429-01-02-R01
Compound type	Monoprotic acid	Global Investigator's Brochure
pKa	8.4	TAK-861 General Properties
B:P	0.749	Report DDA-A41-058
fu	0.037	Report DDA-A41-006
Main binding protein	HSA	Report DDA-A41-059
Absorption Model – First Order		
P_{app} (A->B) (x10^{-6} cm/s) (1 µM)	17	Report DDA-041-015
Calibrator P_{app} (A->B) (x10^{-6} cm/s) = Atenolol	0.492	Report DDA-041-015
Calibrator P_{app} (A->B) (x10^{-6} cm/s) = Propranolol	24.5	Report DDA-041-015
P_{eff} (x10^{-4}cm/s)	3.2595	Predicted in Simcyp version 23
Q_{gut} (L/h)	12.867	
ka (h^{-1})	1.15	Optimised to fit clinical data after a 10 mg dose of oveporexton (T2) (Clinical Study TAK-861-1007)
t_{lag} (h)	0.6	
T1 fa	0.6	Optimised to fit clinical data after multiple 20 mg doses of oveporexton (T1) (Clinical Study TAK-861-1001)
T2 fa	0.897	Calculated based on the dose-normalised exposure of T2 relative to T3 (Section 3.4.1)
T3 fa	1.00	Assumed (Section 3.4.1)
fu_{gut}	1.00	Assumed
F_G	0.902	Retrograde output
Distribution Model – Full PBPK Model		
V_{SS} (L/kg)	2.47	Optimised to fit clinical data after a 10 mg dose of oveporexton (T2) (Clinical Study TAK-861-1007)
K_p scalar	0.12	
Elimination Parameters		
CL/F (L/h)	11.81	Clinical Study TAK-861-1007
fm_{CYP3A4}	0.91	Clinical Study TAK-861-1007, DDI with itraconazole
CYP3A4 CL_{int} (µL/min/pmol)	0.4243	Retrograde model. CL/F obtained from Clinical Study TAK-861-1007 (11.81 L/h); fm_{CYP3A4} = 0.91
Additional HLM CL_{int} (µL/min/mg)	5.2933	
fu_{mic}	1	Assumed

PARAMETER	Value	Reference
CL_R (L/h)	0	Clinical Study TAK-861-1001
Interaction Parameters		
CYP3A4 K_i (µM)	9	Report DDA-A41-016
fu_{mic}	0.850	Protein concentration (b) (4) mg/mL protein; Report DDA-A41-016
CYP3A4 K_{app} (µM)	11.83	Report DDA-A41-016
CYP3A4 K_{inact} (1/h)	1.17	Report DDA-A41-016; reduced 2.6-fold (Mao *et al.*, 2016)
fu_{mic}	0.322	Protein concentration (b) (4) mg/mL protein; Report DDA-A41-016
CYP3A4 Ind_{max}	15.01	Report DDA-A41-016
CYP3A4 $IndC_{50}$ (µM)	2.75	Report DDA-A41-016
fu_{inc}	0.511	Cell density of (b) (4) cells/mL; Report DDA-A41-016

Source: Table 3 of the PBPK report TAK/25/A

Simulations were conducted using the default population model for healthy volunteers. For model verification, simulations of 10 virtual trials of each clinical study were generated to assess variability across groups. A fixed-trial design was used in which individual simulated ages, weights, heights, and sexes were matched to the clinical study demographics.

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For model application, 10 virtual trials of 20 healthy subjects (50% female) aged 18 to 70 years receiving multiple oral doses of oveporexton (administered as formulation T3) in the absence and presence of CYP3A4 inhibitors or inducers administered for 28 days were generated.

The default library models (Simcyp version 23) of itraconazole, fluconazole, efavirenz, modafinil, dexamethasone, and midazolam were used without modification. The library model of phenytoin was modified (CYP2C9 and CYP3A4 Indmax values) to improve model predictive performance of multiple-dose exposure of phenytoin. The modified phenytoin model predicted all the CYP3A4 DDIs for model verification within 0.7- to 1.5-fold of the observed value. The library model of cimetidine was modified (CYP3A Ki value), by the PBPK reviewer, based on version 25 model. All simulations were performed under steady-state conditions for the CYP3A4 inhibitor or inducer.

Additional Comments

In vitro studies in human hepatocytes, hepatic microsomes, and recombinant CYP expressing microsomes indicated oveporexton clearance is primarily mediated by CYP metabolism. In vitro recombinant CYP data were used to assign the initial value for the relative contribution of CYP3A4 to the clearance of oveporexton (fmCYP3A =97.3%) (Report DDA-A41-011). The fmCYP3A value was further optimized to 91% using the clinical DDI effect of itraconazole on single-dose oveporexton PK (Study TAK-861-1007). The in vitro estimated fmCYP3A4 value overpredicted the interaction effect of itraconazole on oveporexton AUC by more than 2-fold in the initial PBPK model of oveporexton. The in vivo optimized fmCYP3A4 value was verified using the clinical DDI effect of fluconazole or phenytoin on single-dose oveporexton PK (Study TAK-861-1007). Additionally, the metabolite profiling from human mass balance study (Study TAK-861-1007) indicated the primary metabolites M16 and M17 accounted for 7% and 4.5% of total metabolites in urine and feces, for 91.5% of total percentage dose recovered. M16 and M17 are carboxylic acid derivates which metabolism could potentially be mediated by non-CYP pathways (e.g., carboxylesterases). Thus, in vivo metabolite data support the percentage decrease of relative CYP3A contribution to parent clearance compared to in vitro data.

Oveporexton exhibited time-dependent inhibition of CYP3A4 in vitro (Report DDA-A41-017), with estimates of apparent enzyme inhibition constant (Ki) and inactivation rate (kinact) values of 11.83 µM and 3.047 1/h, respectively (Report TKD-BCS-00565-R1). Oveporexton also exhibited concentration dependent induction of CYP3A4 mRNA in human hepatocytes, with estimates of CYP3A4 Indmax of 44.1 and IndC50 of 2.75 µM (from one donor) (Report DDA-A41-016). For model input, the in vitro estimated CYP3A4 Indmax was calibrated to 15.01, using the in vitro rifampin data. The in vitro estimate for competitive inhibition of CYP3A4 IC_{50} of 18 µM (Report DDA-A41-017) was adjusted to Ki of 9 µM using the Cheng-Prusoff equation. For modeling purposes, all in vitro estimates for the CYP3A4 interaction constants were corrected by the unbound fraction. These input parameters were evaluated by comparison of predicted oveporexton plasma concentration-time profiles (visual check) and PK parameters to observed data after multiple-dose administration, as autoinduction and autoinhibition

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were simulated within oveporexton model. The CYP3A4 kinact value was optimized to 1.17 1/h (reduced by 2.6-fold, as described by Mao et al. 2016) to better describe the observed PK data following 20 mg QD dosing, including accumulation ratio.

Formulation was identified as a covariate affecting oveporexton exposure in the population PK analysis (Applicant's population PK report). The formulation T1 resulted in approximately 29% lower $C_{max,ss}$ and $C_{avg,ss}$ compared to the formulation T3, while oveporexton PK following formulation T2 were comparable to those of T3 (GMRs $C_{max,ss}$ and $AUC_{24,ss}$ T3/T2=1.13 and 1.14, respectively) (See Section 6.3.1 for more information). For PBPK modeling, it was assumed that formulation-dependency in oveporexton exposure was attributed solely to changes in the fraction absorbed (fa) among formulations and not changes in the rate of absorption (ka), lag time (t_{lag}) or first-pass metabolism. The formulation with the highest dose-normalized exposure, T3, was assumed an fa value of 1. Estimates of fa values for T1 and T2 were subsequently calculated based on their dose-normalized exposure relative to T3, as follows: the fa of T2 was set to 0.897 (T2 exposure, 10 mg SD, Study -1007 relative to T3 exposure for two 2 mg doses Study -1005). The exposure for T1 was 91.7% of the exposure with the T2 formulation in the comparative BA study (TAK-861-1007). Thus, the initial estimate of fa for T1 was calculated to be 0.822 (0.917 * 0.897). The fa for T1 was further optimized to 60% to capture the Day 1 AUC of oveporexton observed for 20 mg oveporexton T1 in the clinical study TAK-861-1001. The values of ka (1.15 1/h) and tlag (0.6 h) used in the PBPK model were comparable to the estimates of ka (2.16 1/h) and tlag (0.38 h) from population PK analysis.

Membrane permeability and P-gp-mediated transport of oveporexton were investigated using Caco-2 cell monolayers (Report DDA-041-015). The results indicated that oveporexton has high apparent permeability and does not appear to be a substrate for P-gp.

Results

Performance of PBPK Model To Predict Oveporexton PK

The predictive performance of the PBPK model of oveporexton was evaluated by comparing predictions to observed PK following single and multiple oral doses of oveporexton in the clinical studies TAK-861-1001, TAK-861-1007 (T1 formulation, healthy subjects), TAK-861-1004 and TAK-861-1005 (T3 formulation, healthy subjects), and TAK-861-2001 and TAK-861-2002 (T2 formulation, patients with narcolepsy).

Overall, the predicted values for AUC and C_{max} were ≤ ±25% of the observed values, across the dose range simulated. Predicted and observed PK values are listed in Table 149. After multiple doses (5 mg QD or 10 mg BID) of oveporexton, the predicted accumulation ratios for AUC_{24h} and C_{max} were ≤±20% of the observed values. The predicted and observed T_{max} values (median) for two doses of 2 mg oveporexton (administered 3 hours apart, as formulation T3, to healthy subjects) were 4.20 h and 4.50 h, respectively. A comparison of predicted versus observed plasma concentration-time profiles following single and multiple doses of oveporexton are shown in Figure 66 and Figure 67.

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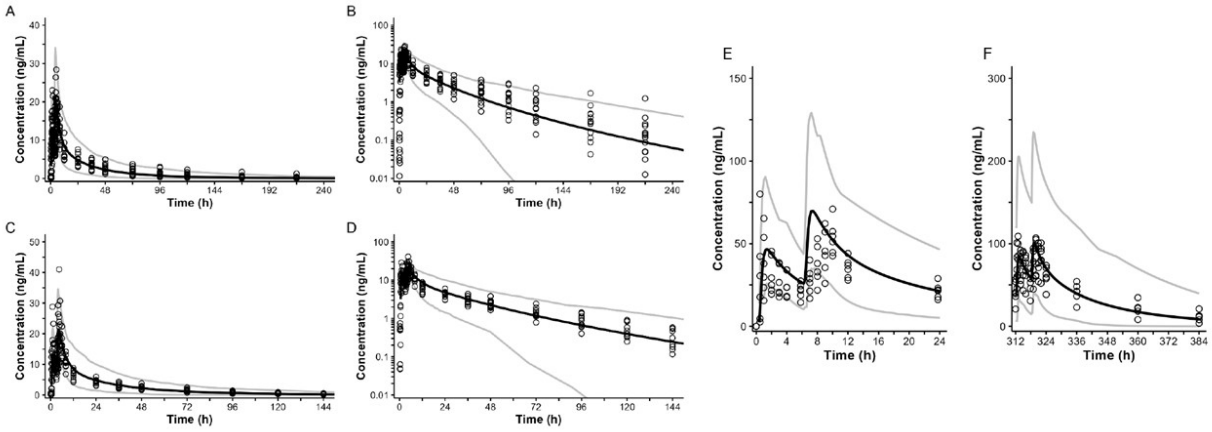
Table 149. Predicted and Observed PK Parameters for Oveporexton

Oveporexton Dose (Formulation) Clinical Study		AUC0-3 (h.ng/mL)	AUC3-144 (h.ng/mL)	AUC (h.ng/mL)	Cmax (ng/mL)	AUC24 Accumulation ratio	Cmax Accumulation ratio
5 mg SD (T1) TAK-861-1001	Predicted	-	-	333	23.9	-	-
	Observed	-	-	371	25.0	-	-
	Pred/Obs	-	-	0.897	0.958	-	-
5 mg QD Day 1 (T1) TAK-861-1001	Predicted	-	-	222	24.4	-	-
	Observed	-	-	208	25.1	-	-
	Pred/Obs	-	-	1.07	0.970	-	-
5 mg QD Day 14 (T1) TAK-861-1001	Predicted	-	-	334	31.6	1.51	1.30
	Observed			338	31.7	1.63	1.26
	Pred/Obs	-	-	0.990	0.999	0.926	1.03
10 mg SD (T1) TAK-861-1007	Predicted	-	-	634	45.7	-	-
	Observed	-	-	785	50.9	-	-
	Pred/Obs	-	-	0.807	0.898	-	-
10 mg SD (T2) TAK-861-1007 (fluconazole control)	Predicted	-	-	881	64.1	-	-
	Observed	-	-	847	53.1	-	-
	Pred/Obs	-	-	1.04	1.20	-	-
10 mg SD (T2) TAK-861-1007 (phenytoin control)	Predicted	-	-	880	64.4	-	-
	Observed	-	-	1039	59.4	-	-
	Pred/Obs	-	-	0.847	1.08	-	-
10 mg BID (6 hours apart) Day 1 (T1) TAK-861-1001	Predicted	-	-	784	66.1	-	-
	Observed	-	-	709	53.8	-	-
	Pred/Obs			1.11	1.23	-	-
10 mg BID Day 14 (T1) TAK-861-1001	Predicted	-	-	1271	90.9	1.62	1.38
	Observed	-	-	1426	87.4	2.01	1.63
	Pred/Obs	-	-	0.891	1.04	0.806	0.847
2 mg (2 doses 3 hours apart) (T3) TAK-861-1004	Predicted	26.6	317	355	20.8	-	-
	Observed	25.1	433	447	20.0	-	-
	Pred/Obs	1.06	0.732	0.793	1.04	-	-
2 mg (2 doses 3 hours apart) (T3) TAK-861-1005	Predicted	26.7	313	350	19.6	-	-
	Observed	26.6	339	383	20.8	-	-
	Pred/Obs	1.01	0.923	0.914	0.938	-	-

Values are geometric means. AUC = AUC inf for single-dose, AUC24 for Day 1 of multiple-doses and $AUC_{24,ss}$ for Day 14 of multiple-doses.
Observed data from TAK-861-1001, TAK-861-1004, TAK-861-1005 and TAK-861-1007.
Abbreviations: C_{max}: maximal drug concentration, AUC: Area under the curve, SD: single-dose, BID: twice a day, QD: once daily, T1, T2, T3: formulations T1, T2 or T3.
Source: PBPK report TAK/25/A

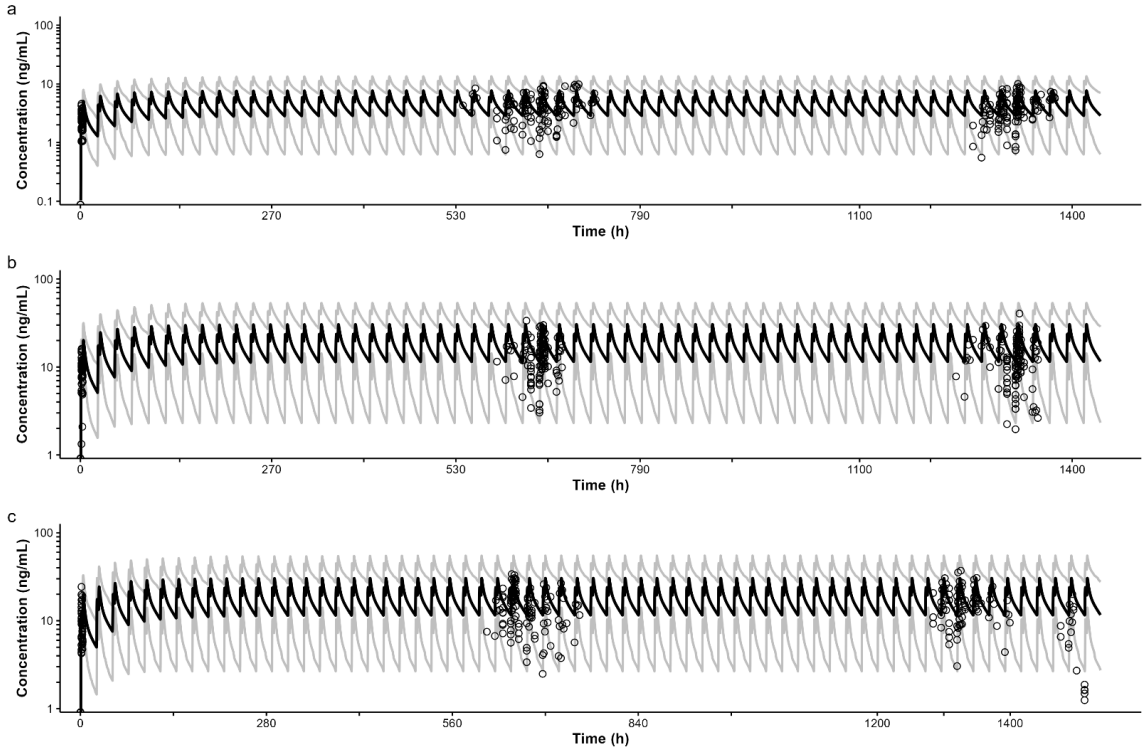
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Figure 66. Predicted and Observed Plasma PK Profiles of Oveporexton Following Two Oral Doses of 2 mg (3 Hours Apart) or 10 mg BID (6 Hours Apart for 14 Days) in Healthy Subjects



A-D: Linear (A, C) and log-linear (B, D) PK profiles after two doses of 2 mg oveporexton (formulation T3) administered three hours apart (A, B: Study TAK-861-1004 and C, D: Study TAK-861-1005) in healthy subjects. Predicted (lines) and observed data (circles, n=10, TAK-861-1004 or n=13, TAK-861-1005). E, F: Predicted (lines) and observed (circles, n=6, TAK-861-1001) PK profiles of 10 mg oveporexton (formulation T1) administered twice a day, 6 hours apart for 14 days, Day 1 (E) and Day 14 (F) in healthy subjects. Grey lines: predicted 5th- 95th percentiles. Solid black line: predicted mean data for the simulated population (10 x n).
Source: Figures 14 and 18 of the PBPK report TAK/25/A

Figure 67. Predicted and Observed Plasma PK Profiles Following Multiple Doses of Oveporexton in Patients With Narcolepsy



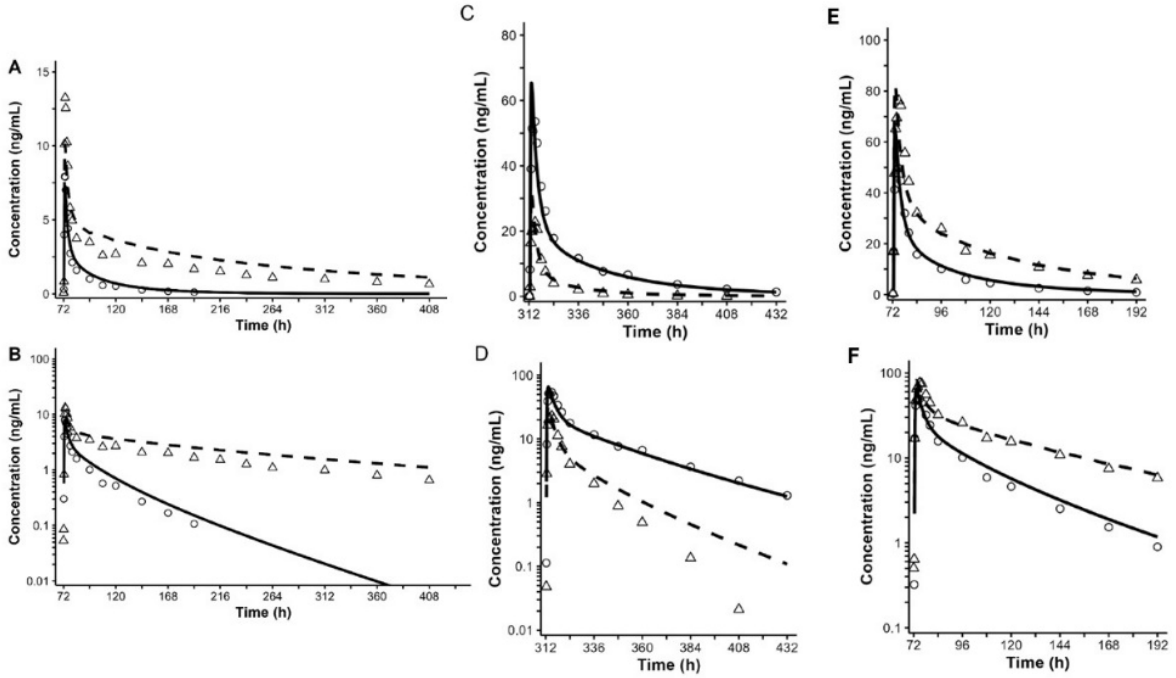
Log-linear predicted and observed plasma PK profiles of multiple doses of oveporexton (formulation T2) for 0.5 mg BID (A, Study TAK-861-2001), 2 mg BID (B, Study TAK-861-2001), and 2 mg BID (C, Study TAK-861-2002) in patients with narcolepsy. Predicted (lines) and observed data (circles; Study TAK-861-2001, 0.5 mg BID (n=23), Study TAK-861-2001, 2 mg BID (n=21) and Study TAK-861-2002, 2 mg BID (n=22)). Grey lines: predicted 5th- 95th percentiles. Solid black line: predicted mean data for the simulated population.
Source: Figure 20 of the PBPK report TAK/25/A

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Prediction of Interaction Effect of CYP3A Modulators on the PK of Oveporexton

The predicted changes on oveporexton PK following single oral dose with coadministration of the strong CYP3A inhibitor, itraconazole (200 mg QD for Days 1-17), moderate CYP3A inhibitor, fluconazole (400 mg on Day 1 and 200 mg QD for Days 2 through 8) or strong CYP3A inducer, phenytoin (100 mg TID for Days 1 through 18) compared with observed data (Study TAK-861-1007) are shown in Table 150 and Figure 68. The predicted geometric mean ratios (GMRs) of AUC_{inf} and C_{max} for single dose oveporexton in the presence of each of these CYP3A modulators were within 25% of the observed values.

Figure 68. Predicted and Observed Plasma PK Profiles of Oveporexton With Co-Administration of Itraconazole, Phenytoin and Fluconazole in Healthy Subjects



Linear (A, C, E) and log-linear (B, D, F) predicted (lines) and observed (symbols; Study TAK-861-1007) plasma PK profiles of oveporexton following a single dose of oveporexton (T2) in the absence of itraconazole (A, B), phenytoin (C,D) or fluconazole (E, F) (solid line; circles) and on Day 4 of 17 days of itraconazole dosing, Day 4 of 8 days of fluconazole dosing or Day 14 of 18 days of phenytoin dosing (dashed line; triangles). Lines: predicted mean data of the simulated population (n=30 or 120).
Source: Figures 5 and 15 of the PBPK report TAK/25/A.

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Table 150. Observed and Predicted PK Changes of Oveporexton With Co-Administration of CYP3A Inhibitors or Inducers

CYP3A Modulator Class	CYP3A Modulator	Oveporexton Dose	Oveporexton PK parameters			
			Observed		Predicted	
			GMR Cmax	GMR AUC	GMR Cmax	GMR AUC
Strong CYP3A inhibitor	Itraconazole 200 mg QD	1 mg SD	1.67	7.43	1.39	8.94
	Itraconazole 200 mg QD	0.5 mg BID	NA	NA	5.24	8.48
Moderate CYP3A inhibitor	Fluconazole 200 mg QD	10 mg SD	1.50	2.87	1.27	2.65
	Fluconazole 200 mg QD	0.5 mg BID	NA	NA	2.05	2.74
Weak CYP3A inhibitor	Cimetidine 400 mg TID	2 mg BID	NA	NA	1.30*	1.43*
Strong CYP3A inducer	Phenytoin 100 mg TID	10 mg SD	0.460	0.231	0.439	0.187
		2 mg BID	NA	NA	0.34	0.22
Moderate CYP3A inducer	Efavirenz 600 mg QD	2 mg BID	NA	NA	0.45	0.28
Weak CY3A inducer	Modafinil 200 mg QD	2 mg BID	NA	NA	0.73	0.82
	Dexamethasone 9 mg QD	2 mg BID	NA	NA	0.77	0.66
	Dexamethasone 8 mg BID*	2 mg BID	NA	NA	0.67*	0.55*

Abbreviations: GMR: geometric mean ratio; Cmax: maximal drug concentration, CYP: Cytochrome P450, AUC: Area under the curve, SD: single-dose, BID: twice a day, QD: once daily, NA: not available.
Data are geometric means ratios of Cmax and AUC, calculated as with/without modulator. AUCinf for oveporexton single dose, AUC24,ss Day 28 for oveporexton BID. Observed PK from clinical study TAK-861-1007.
Source: PBPK report TAK/25/A, Response to IR dated February 17, 2026, and *PBPK Reviewer's analysis

Simulations were conducted to predict the effect of strong, moderate, and weak CYP3A inhibitors or inducers on the PK of oveporexton following multiple doses of 0.5 mg BID (3 hours apart) or 2 mg BID (3 hours apart, for 28 days) in healthy subjects. The predicted GMRs of steady state AUC_{24h} and C_{max} values with coadministration of a CYP3A precipitant are listed in Table 150.

The analysis predicted that coadministration of oveporexton at steady state with a strong CYP3A inhibitor would result in a strong interaction effect (AUC GMR ≥5). While coadministration of a moderate CYP3A inhibitor would result in a moderate interaction effect (oveporexton AUC GMR around 3). No relevant changes on oveporexton exposure were predicted with coadministration of a weak CYP3A inhibitor (PK change fell within the no interaction effect boundaries of 80 to 125%). A moderate interaction effect was predicted with coadministration of with either the strong CYP3A inducer, phenytoin or the moderate CYP3A inducer, efavirenz (AUC GMR decreased by ≥50 to <80%). A weak interaction effect was predicted with coadministration of a weak CYP3A inhibitor (AUC GMR ≥1.25 to <2) or weak CYP3A inducer (AUC GMR decreased by ≥20 to <50%).

The predicted steady state AUC_{24h} and C_{max} of oveporexton (formulation T3) in the presence of CYP3A4 precipitants were compared to the AUC and C_{max} of oveporexton dosing of 1 mg or 2 mg BID (3 h apart) alone (Table 151).

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Table 151. Predicted $AUC_{,ss}$ and C_{max} Values of Oveporexton in the Presence of CYP3A4 Inhibitors and Inducers Compared to Oveporexton Administered Alone

Oveporexton Dose	Oveporexton PK parameters		PK relative to 1 mg BID Dose		PK relative to 2 mg BID Dose	
	AUC,ss (ng/mL.h)	Cmax,ss (ng/mL)	AUC,ss	Cmax,ss	AUC,ss	Cmax,ss
1 mg BID (3 h apart)	213	16.4	-	-	-	-
2 mg BID (3 h apart)	430	33.0	-	-	-	-
0.5 mg BID + itraconazole	896	42.8	4.2	2.6	2.1	1.3
0.5 mg BID + fluconazole	290	16.8	1.4	1.0	0.67	0.51
2 mg BID + phenytoin	93.9	11.0	0.44	0.67	0.21	0.33
2 mg BID + efavirenz	118	14.8	0.56	0.90	0.28	0.45

Abbreviations: $C_{max,ss}$: maximal drug concentration at steady state, $AUC_{,ss}$: Area under the curve at 24 hours dosing interval at steady state, BID: twice a day.
Values are geometric means.
Source: Table 22 of the PBPK report TAK/25/A.

In the presence of a strong CYP3A inhibitor, at the lowest available tablet strength (0.5 mg), the AUC of oveporexton was predicted to be 2-fold higher than the proposed therapeutic dosing regimen of 2 mg BID (3 h apart). In the presence of a moderate CYP3A inhibitor, 0.5 mg BID (3 h apart) dosing of oveporexton was predicted to result in a similar AUC to oveporexton 1 mg BID (3 h apart) dosing alone. In the presence of CYP3A inducers, oveporexton 2 mg BID (3 h apart) with a strong or moderate inducer were predicted to result in approximately 2-fold and 5-fold lower AUC compared to dosing oveporexton 1 mg or 2 mg BID (3 h apart) without inducers, respectively.

Prediction of Drug-Interaction Risk of Oveporexton With a CYP3A4 Substrate

Oveporexton was determined to be an in vitro inhibitor and inducer of CYP3A4. The potential for clinical interaction with a CYP3A4 substrate was evaluated using the index substrate midazolam and the oveporexton CYP3A4 inhibition and induction parameters evaluated to recover oveporexton PK (base model). Sensitivity analysis was also conducted to evaluate the CYP3A4 inhibition and induction potential independently and uncertainty associated with in vitro determined parameters. Table 152 lists the predicted changes on the PK of midazolam (5 mg SD) with co-administration of oveporexton (2 mg BID 3 h apart, Day 14 of 17 days of dosing of formulation T3 to healthy subjects).

The predicted GMRs of AUC_{inf} and C_{max} for midazolam in the presence of oveporexton were within the no interaction effect boundaries of 80 to 125%, when considering the base model and optimized induction and inhibition parameters simultaneously or independently. Sensitivity analysis simulations predicted weak inhibitory effect on midazolam (GMR AUC_{inf} <2-fold), when considering only inhibition via a CYP3A4 Ki reduced 10-fold and in vitro CYP3A4 kinact value. Similarly, SA predicted a weak induction effect on midazolam (GMR AUC_{inf} =0.7) when considering only induction via uncalibrated in vitro E_{max} value.

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Table 152. Predicted Changes on Midazolam PK With Co-Administration of Oveporexton for Different Scenarios of CYP3A4 Interaction Parameters

	CYP3A4 Interaction Parameters				2 mg BID Oveporexton	
Scenarios	**$k_{i,u}$ (μM)**	**$K_{app,u}$ (μM)**	**k_{inact} (1/h)**	**$Ind_{max,u}$**	**AUC_{inf} GMR**	**C_{max} GMR**
Base Model	7.65	3.81	1.17	15.01	1.02 (1.02 to 1.03)	1.01 (1.01 to 1.02)
Inhibition Only	7.65	3.81	1.17	-	1.14 (1.13 to 1.15)	1.12 (1.11 to 1.13)
Induction Only	-	-	-	15.01	0.874 (0.864 to 0.884)	0.879 (0.870 to 0.889)
Inhibition Only (*in vitro* k_i and k_{inact})	0.765[a]	3.81	3.047[b]	-	1.31 (1.29 to 1.34)	1.26 (1.24 to 1.28)
Induction Only (*in vitro* Ind_{max})	-	-	-	44.1[c]	0.695 (0.676 to 0.715)	0.708 (0.690 to 0.727)
Inhibition and Induction (*in vitro* k_i, k_{inact}, and Ind_{max})	0.765[a]	3.81	3.047[b]	44.1	1.03 (1.02 to 1.05)	1.01 (0.999 to 1.02)

[a]10-fold reduction in the in vitro value, [b]in vitro value before optimization, [c]in vitro value before calibration. PK data are geometric means ratios (90% confidence interval) of C_{max} and AUC, calculated as with/without oveporexton administration.
Abbreviations: AUC_{inf}: area under the curve, BID: twice a day, C_{max}: maximal drug concentration, CYP3A4: Cytochrome P450 3A4 enzyme, Kapp,u: Apparent enzyme inhibition constant for unbound drug, ki,u: enzyme competitive inhibition constant for unbound drug, kinact: inactivation rate of enzyme; GMR: geometric mean ratio, Indmax,u: maximal fold induction over vehicle for unbound drug.
Source: Table 29 of the PBPK report TAK/24/A

The low likelihood for clinically relevant interaction with a CYP3A4 substrate is also supported by the following data: Oveporexton is a sensitive CYP3A4 substrate, as determined in vitro (fm_{CYP3A} =97%) and optimized in vivo (fm_{CYP3A} =91%), with no apparent dose- and time-dependent changes in oveporexton clearance and PK. Oveporexton administered as 2 mg BID (3 hours apart) had an accumulation ratio of approximately 1.6 consistent with terminal half-life. Optimization of model CYP3A4 interaction parameters adequately describe the steady-state PK of oveporexton (e.g., predicted accumulation ratio within 20% of observed data).

Reference ID: 5847402

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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 Sciences
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 220860
Drug Name:	Orzeyful (TAK-861)
Indication:	Treatment of Narcolepsy Type 1
Studies:	Carcinogenicity Studies in Rats for 104 weeks and Mice for 26 weeks
Applicant:	Study Sponsor: Takeda Pharmaceutical Company Limited 26-1, Muraoka-Higashi 2-chome, Fujisawa Kanagawa 251-8555, Japan Testing Facility: (b) (4)
Documents Reviewed:	Electronic submission: Submitted on January 9th,2026
Review Priority:	Standard
Biometrics Division:	Division of Biometrics - VI
Statistical Reviewer:	Dr. Hepei Chen
Concurring Reviewer:	Dr. Atiar Mohammad Rahman
Medical Division:	Division of Pharmacology Toxicology for Neuroscience (DPTN)
Reviewing Pharmacologist:	Dr. Sonia Tabacova
Keywords:	Carcinogenicity, Dose response

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1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were to assess the potential carcinogenicity of TAK-861 in rats and mice. TAK-861 was administered by oral gavage once daily to Sprague-Dawley rats for 24 months and to CByB6F1-Tg(HRAS)2Jic mice (Tg rasH2 mice) for up to 26 weeks.

In this review the phrase "dose response relationship" refers to the linear component (trend) of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Rat Study

Two separate experiments, one in male rats and one in female rats were conducted. As indicated in Table 1, in the experiment there were three treated groups, and one vehicle control group. Two hundred and fourty Sprague-Dawley rats of each sex were assigned randomly in size of 60 rats per group. TAK-861 was administered in a vehicle of 0.5% (weight-to-volume ratio [w/v]) methylcellulose (MC) solution at 0, 1, 20, and 100 mg/kg by oral gavage once daily for 24 months. In this review the three treated groups were referred to as the low (Group 2), mid (Group 3), and high (Group 4) dose groups, respectively. The rats in the vehicle control group (Group 1) were administrated with 0.5% (weight-to-volume ratio [w/v]) methylcellulose (MC) solution, and handled for the same duration and in the same manner as the treated groups.

Table 1: Experimental Design in Rat Study

Group No.	No. of Toxicity Animals		Test Material	Dosage Level (mg/kg/day)	
	Male	Female		Male	Female
1	60	60	Vehicle control	0	0
2	60	60	TAK-861 Low	1	1
3	60	60	TAK-861 Mid	20	20
4	60	60	TAK-861 High	100	100

The following parameters were evaluated in all animals for the evidence of carcinogenicity and toxicity: mortality, clinical signs including evidence of palpable masses, body weights, food consumption, hematology, macroscopic observations, and microscopic findings.

2.1. Sponsor's analyses

2.1.1. Survival analysis

In the sponsor’s report, the survival function was estimated by Kaplan-Meier’s method (product limit estimator) and graphed (Kaplan-Meier’s curve). The positive trend of survival rate to dose level was analyzed by Tarone-type method, and then the difference between the vehicle control group and each TAK-861 group was compared using the log-rank test (level of significance: 0.05). The above analyses were performed by the integrated statistical package, SAS release 9.1.3 (SAS Institute Inc.).

Sponsor's findings:

The sponsor's analysis (page 29) showed that the numbers of rats surviving to their terminal necropsy were 38 (63%), 32 (53%), 27 (45%), and 28 (47%) in the vehicle control, low, mid, and high dose groups, respectively, for male rats, and 29 (48%), 25 (42%), 22 (37%), and 28 (47%) in the vehicle control, low, mid, and high dose groups, respectively, for female rats.

Although a statistically significant decrease in survival rate at the end of the dosing period was recorded in the mid dose group of male rats, it was judged to be incidental because it was not dose related. No other statistically significant findings were noted in mortality for either male or female rats.

2.1.2. Tumor data analysis

In the sponsor's analysis, for tumors that occurred with high incidence (incidence of 10/sex or above), positive trend to dose level and pairwise comparison between the vehicle control group and each TAK-861 group were conducted using the asymptotic survival-adjusted Peto's method. For tumors that occurred with low incidence (incidence of less than 10/sex), positive trend to dose level and pairwise comparison between the vehicle control group and each test article group were conducted using the Peto's exact test. Incidental tumors were analyzed in the following partitions: Week 1 to Week 52, Week 53 to Week 78, Week 79 to Week 92, Week 93 to Week 104, and terminal necropsy period.

Tumors that can occur anywhere in the body were also analyzed for their total incidence over the entire body. The total incidence of benign/malignant tumors and the tumors that have the same origin were also analyzed. The above analyses were performed by the integrated statistical package, SAS Release 9.4 (SAS Institute Inc.) and EXSUS Version 10.2 (CAC Croit Corporation).

Adjustment for multiple testing:

In the sponsor's report, analyses of positive trend and pairwise comparison were both performed at the significance levels of 0.01 (one-tailed) for common tumors and 0.05 (one tailed) for rare tumors. Common tumors were defined as those with a historical incidence in controls at (b) (4) exceeding 1% (>1%) and rare tumors as 1% or less (⩽1%).

Sponsor's findings:

In the sponsor's report (pages 31, 64, 256), for female rats, the incidence of follicular cell adenoma of the thyroid gland was statistically significant in the trend test, but not in the pairwise comparison test. The combined incidence of follicular cell adenoma and carcinoma was not statistically significant in either the trend or pairwise comparison tests. The incidence of endometrial stromal polyp and combined tumors (endometrial stromal polyp and sarcoma) was statistically significant in the trend test, but not in the pairwise comparison test. The incidences of follicular cell hyperplasia and endometrial stromal hyperplasia did not differ from those in the

control group. Therefore, the incidences of follicular cell adenoma of the thyroid gland and endometrial stromal polyp were not considered TAK-861-related.

2.2. Reviewer's analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing toxicologist, this reviewer independently performed the survival and tumor data analyses using the data provided by the sponsor electronically.

2.2.1. Survival analysis

In the reviewer's analysis, the survival distributions of rats in all four groups (Groups 1, 2, 3, and 4) were estimated using the Kaplan-Meier product limit method. The dose response relationship was tested across Groups 1, 2, 3, and 4 using the likelihood ratio test, and the homogeneity of survival distributions was tested using the log-rank test.

Reviewer's findings:

The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for all four groups in male and female rats, respectively. The intercurrent mortality data of all four groups and the results of the tests for dose response relationship and homogeneity of survivals for Groups 1, 2, 3, and 4 are given in Tables 1A and 1B in the appendix for male and female rats, respectively.

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy were 38 (63%), 32 (53%), 27 (45%), and 28 (47%) in the vehicle control, low, mid, and high dose groups, respectively, for male rats, and 29 (48%), 25 (42%), 22 (37%), and 28 (47%) in the vehicle control, low, mid, and high dose groups, respectively, for female rats.

A statistically significant increase in mortality ($p = 0.0304$) was observed in the mid dose group (Group 3) of male rats when compared to the vehicle control group (Group 1), without a corresponding statistically significant positive dose response relationship. No statistically significant dose response relationship or pairwise comparisons in mortality was observed for female rats.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships across the vehicle control, low, mid, mid-high, and high dose groups, and pairwise comparisons of each of the three treated groups against the vehicle control group, using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993).

In the poly-k method, the adjustment for differences in mortality among treatment groups is made by modifying the number of animals at risk in the denominators in the calculations of overall tumor rates in the Cochran-Armitage test to reflect less-than-whole-animal contributions for animals that die without tumor before the end of the study (Bailer and Portier 1988). The modification is made by defining a new number of animals at risk for each treatment group. The

number of animals at risk for the *i*-th treatment group R^* i is defined as $R^*_i = \sum W_{ij}$ where w_{ij} is the weight for the *j*-th animal in the *i*-th treatment group, and the sum is over all animals in the group.

Bailer and Portier (1988) proposed the weight w_{ij} as follows:

$w_{ij} = 1$ to animals dying with the tumor, and

$w_{ij} = (t_{ij} / tsacr)^k$ to animals dying without the tumor,

where t_{ij} is the time of death of the *j*-th animal in the *i*-th treatment group, and tsacr is the planned (or intended) time of terminal sacrifice. The above formulas imply that animals living up to the end of the planned terminal sacrifice date without developing any tumor will also be assigned $w_{ij} = 1$ since t_{ij} = tsacr. Also animals developed the tumor type being tested before the end of the study will be assigned as $w_{ij} = 1$.

Certain treatment groups of a study or the entire study may be terminated earlier than the planned (or intended) time of terminal sacrifice due to excessive mortalities. However, based on the principle of the Intention-to-treat (ITT) analysis in randomized trials, the tsacr should not be affected by the unplanned early terminations. The tsacr should always be equal to the planned (or intended) time of terminal sacrifice. For those animals that were sacrificed later than tsacr, regardless their actual terminal sacrifice time, tsacr was used as their time of terminal sacrifice in the analysis.

One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data.

Multiple testing adjustment:

For a submission with one two-year study in one species and one short-term study with another species, in order to keep the overall false-positive rate at the nominal level of approximately 10%, as indicated in Table 2, this reviewer used the methodologies suggested in the Expanded Statistical Decision Rules for Interpretations of Results of Rodent Carcinogenicity Studies of Pharmaceuticals by Lin and Rahman (2018).

A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. However, if the background information for the common or rare tumor is not available, the number of animals bearing tumors in the vehicle control group in the present study was used to determine the common or rare tumor status in the review report. That is, if the number of animals bearing tumors in the vehicle control group is 0, then this tumor is considered as the rare tumor; otherwise, if the number of animals bearing tumors in the control group is greater than or equal to 1, then this tumor is considered as the common tumor.

Table 2. Recommended decision rules for controlling the overall false positive rates

	Tests for positive trend alone	Control-high pairwise comparison alone	Tests for positive trend and control-high pairwise comparison jointly
Alternative ICH studies (one two-year study in one species and one short- or medium-term alternative study, two sexes)	Common and rare tumors are tested at 0.005 and 0.025 significance levels, respectively, in the two-year study, and at 0.05 and 0.05 significance levels, respectively, in the alternative study	Common and rare tumors are tested at 0.01 and 0.05 significance levels, respectively, in the two-year study, and at 0.05 and 0.05 significance levels, respectively, in the alternative study	Common and rare tumors are tested at 0.005 and 0.025 significance levels, respectively, in trend test, and at 0.05 and 0.10 significance levels, respectively, in control-high pairwise comparison in the two-year study, and at 0.05 and 0.05 significance levels, respectively, in both trend test and control-high pairwise comparison in the alternative study

Reviewer's findings:

The tumor rates and the p-values of the tested tumor types are listed in Tables 2A and 2B in the appendix for male and female rats, respectively.

Based on the criteria of adjustment for multiple testing discussed above, for male rats, as indicated in Table 3, a statistically significant increase (p-value = 0.0477) was noted in medium dose group in the incidence of adenoma hepatocellular in liver, without the corresponding statistically significant dose response relationship if this tumor is considered rare. No other statistically significant dose response relationship or pairwise comparisons were observed in the tumor data for either male or female rats.

Table 3: Summary Table of Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Vehicle Group

Organ name	Tumor name	0 mg Vehicle (VC) P - Trend	1 mg Low (L) P - VC vs. L	20 mg Mid (M) P - VC vs. M	100 mg High (H) P - VC vs. H
Male					
Adrenal Gland	Adenoma, Cortex/ Carcinoma, Cortex (C)	2/60 (53) 0.0486 @	0/60 (48) 0.7271	1/60 (47) 0.4546	4/60 (49) 0.3023
Liver	Adenoma, Hepatocellular (R)	0/60 (53) 0.3658	0/60 (48) NC	4/60 (48) 0.0477 $	1/60 (49) 0.4804
Female					
Ovary	Tumor, Sex Cord Stromal, Mixed, Benign (R)	0/60 (49) 0.0484 @	2/60 (44) 0.2211	2/60 (46) 0.2318	4/60 (50) 0.0612
Thyroid Gland	Adenoma, Follicular Cell (C)	0/60 (49) 0.0094 @	1/59 (43) 0.4674	2/60 (46) 0.2318	5/60 (51) 0.0312 @
Uterus	Polyp, Endometrial Stromal (C)	5/60 (49) 0.0111 @	5/60 (44) 0.5592	3/60 (46) 0.6066	12/60 (51) 0.0649
	Adenocarcinoma, Endometrium/ Polyp, Endometrial Strom/ Sarcoma, Endometrial Stromal (C)	5/60 (49) 0.0059 @	5/60 (44) 0.5592	3/60 (46) 0.6066	13/60 (52) 0.0451 @

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable. VC = Vehicle Control;
$ = Statistically significant at 0.005 level in common tumor or 0.025 level in rare tumor for test of dose response relationship or at 0.01 level in common tumor or 0.05 in rare tumor for test of pairwise comparisons;
@ = Not statistically significant at 0.005 level in common tumor or 0.025 level in rare tumor for test of dose response relationship or at 0.01 level in common tumor or 0.05 in rare tumor for test of pairwise comparisons;

3. Mouse Study

Two separate experiments were conducted, one in male mice and one in female mice. As indicated in Table 4, the male mouse experiment included four treatment groups, one vehicle control group, and one positive control group. The female mouse experiment included three treatment groups, one vehicle control group, and one positive control group. A total of 140 male and 115 female transgenic CByB6F1/Tg rasH2 hemizygous mice were randomly assigned to groups of 25 mice each, except for the positive control groups, which contained 15 mice each.

TAK-861 was administered by oral gavage once daily as a solution in a vehicle at 0, 6, 20, 60, and 600 mg/kg for males and 0, 3, 30, and 300 mg/kg for females for up to 26 weeks at a dose volume of 10 mL/kg. In this review, the four treatment groups in male mice are referred to as the low-dose (Group 2), mid-dose (Group 3), mid-high-dose (Group 4), and high-dose (Group 5) groups, respectively. The three treatment groups in female mice are referred to as the low-dose (Group 2), mid-dose (Group 3), and high-dose (Group 4) groups, respectively. The rats in the vehicle control group (Group 1) were administrated with 0.5% (weight-to-volume ratio [w/v]) methylcellulose (MC) solution, and handled for the same duration and in the same manner as the treated groups.

In addition, 15 male and female mice were used for the positive control group (N-Methyl-Nnitrosourea (MNU) in a vehicle of citrate buffer solution, single intraperitoneal dose at 75

mg/kg at a dose volume of 10 mL/kg) to confirm the carcinogenic susceptibility of the Tg rasH2 mice used in this study.

Table 4: Experimental Design in Mouse Study (Page 64)

Group No.		No. of Toxicity Animals		Test Material	Dosage Level (mg/kg/day)	
Male	Female	Male	Female		Male	Female
1	1	25	25	Vehicle control	0	0
2	2	25	25	TAK-861 Low	6	3
3	3	25	25	TAK-861 Mid	20	30
4		25		TAK-861 Mid-high	60	
5	4	25	25	TAK-861 High	600	300
6	5	15	15	Positive control MNU	0	0

The following parameters were evaluated in all main study animals for evidence of carcinogenicity and toxicity: mortality, clinical signs (including observations of palpable masses, body weight, food consumption, hematology, blood chemistry, macroscopic observations, and microscopic evaluation of tissues.

3.1. Sponsor's analyses

3.1.1. Survival analysis

In the sponsor's report, the survival function was estimated by Kaplan-Meier's method (product limit estimator) and graphed (Kaplan-Meier's curve). The positive trend of survival rate to dose level was analyzed by Tarone-type method, and then the difference between the vehicle control group and each TAK-861 group was compared using log-rank test (level of significance: 0.05). The above analyses were performed by the integrated statistical package, SAS release 9.1.3 (SAS Institute Inc.).

Sponsor's findings:

The sponsor's analysis showed that the numbers of mice surviving to their terminal necropsy were 24 (96%), 24 (96%), 25 (100%), 24 (96%), and 23 (77%) in the vehicle control, low, mid, mid-high, and high dose groups, respectively, for male mice, and 24 (96%), 24 (96%), 23 (92%), and 23 (96%) in the vehicle control group, the low, mid, and high dose groups, respectively, for female mice. In the sponsor's report (page 29), there were no TAK-861-related effects on survival rate at any dose. In the positive control group (MNU), 15/15 males and 14/15 females died or were euthanized as moribund during the study period due to neoplasm as expected.

3.1.2. Tumor data analysis

In the sponor's report (page 67), positive trend to dose level and pairwise comparison between the vehicle control group and each TAK-861 group was conducted by Peto's exact test. Analysis of positive trend was conducted at the significance level of 0.01 (one tailed-level) for common

tumors and 0.05 (one tailed-level) for rare tumors. Tumors that can occur anywhere in the body were also analyzed for their total incidence over the entire body. The total incidence of benign and malignant tumors was also analyzed. The above analyses were performed by the integrated statistical package, SAS Release 9.1.3 (SAS Institute Inc.) and EXSUS Version 7.6 (EPS Corporation).

Multiple testing adjustment:

In the sponsor's report, analysis of pairwise comparison was conducted at the significance level of 0.05 (one tailed-level). Common tumors were defined as those with a historical incidence in controls at (b) (4) exceeding 1% (>1%) and rare tumors as 1% or less (⩽ 1%).

Sponsor's findings:

In the sponsor's report (pages 36, 111), there were no TAK-861-related tumors at any dose. In the positive control group, malignant lymphoma was observed in 13/15 males and 10/15 females, and papilloma/carcinoma of the squamous cells in the forestomach was observed in 14/15 males and 14/15 females. Thus, a high susceptibility to a known carcinogen of the test animals used in this study was confirmed because both tumors were induced at remarkably high incidences..

3.2. Reviewer's analyses

Similar to the rat study, this reviewer independently performed survival and tumor data analyses of mouse data to verify sponsor's analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

For the analysis of both the survival data and the tumor data in mice, this reviewer used similar methodologies that were used for the analyses of the rat survival and tumor data.

3.2.1. Survival analysis

Reviewer's findings:

The Kaplan-Meier curves for survival rates are given in Figures 2A and 2B in the appendix for all four groups in male and female mice, respectively. The intercurrent mortality data of all groups and the results of the tests for dose response relationship and homogeneity of survivals are given in Tables 3A and 3B in the appendix for male and female mice, respectively.

The reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 24 (96%), 24 (96%), 25 (100%), 24 (96%), and 23 (77%) in the vehicle control, low, mid, mid-high, and high dose groups, respectively, for male mice, and 24 (96%), 24 (96%), 23 (92%), and 23 (96%) in the vehicle control group, the low, mid, and high dose groups, respectively, for female mice. No statistically significant dose response relationship or pairwise comparisons in mortality was observed for either male or female mice.

3.2.2. Tumor data analysis

Reviewer's findings:

The tumor rates and the p-values of the tested tumor types are listed in Tables 4A and 4B in the appendix for male and female mice, respectively.

In the reviewer's analysis, based on the criteria of adjustment for multiple testing discussed above, no statistically significant dose response relationship or pairwise comparisons in any tested tumor was noted in either male or female mice. For both male and female mice, the pairwise compairons between the positive control group (Group 5) and the vehicle control group (Group 1) showed p-values less than 0.05 for many tumors, confirming animal expressed oncogenes and responded to carcinogenic insult as expected.

4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were to assess the potential carcinogenicity of TAK-861 in rats and mice. TAK-861 was administered by oral gavage once daily to Sprague-Dawley rats for 24 months and to CByB6F1-Tg(HRAS)2Jic mice (Tg rasH2 mice) for up to 26 weeks.

Rat Study:

Two separate experiments, one in male rats and one in female rats were conducted. In each of the experiment there were three treated groups, and one vehicle control group. Two hundred and fourty Sprague-Dawley rats of each sex were assigned randomly in size of 60 rats per group. TAK-861 was administered in a vehicle of 0.5% (weight-to-volume ratio [w/v]) methylcellulose (MC) solution at 0, 1, 20, and 100 mg/kg by oral gavage once daily for 24 months.

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy were 38 (63%), 32 (53%), 27 (45%), and 28 (47%) in the vehicle control, low, mid, and high dose groups, respectively, for male rats, and 29 (48%), 25 (42%), 22 (37%), and 28 (47%) in the vehicle control, low, mid, and high dose groups, respectively, for female rats. A statistically significant increase in mortality ($p = 0.0304$) was observed in the mid dose group (Group 3) of male rats when compared to the vehicle control group (Group 1), without a corresponding statistically significant positive dose response relationship. No statistically significant dose response relationship or pairwise comparisons in mortality was observed for female rats.

In the reviewer's analysis, a statistically significant increase (p-value = 0.0477) was noted in the medium dose group in the incidence of adenoma hepatocellular in liver of male rats, without the corresponding statistically significant dose response relationship if this tumor is considered rare. No other statistically significant dose response relationship or pairwise comparisons were observed in the tumor data for either male or female rats.

Mouse Study:

Two separate experiments, one in male mice and one in female mice were conducted. The male mouse experiment included four treatment groups, one vehicle control group, and one positive control group. The female mouse experiment included three treatment groups, one vehicle control group, and one positive control group. A total of 140 male and 115 female transgenic CByB6F1/Tg rasH2 hemizygous mice were randomly assigned to groups of 25 mice each, except for the positive control groups, which contained 15 mice each. TAK-861 was administered by oral gavage once daily as a solution in a vehicle at 0, 6, 20, 60, and 600 mg/kg for males and 0, 3, 30, and 300 mg/kg for females for up to 26 weeks at a dose volume of 10 mL/kg..

The reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 24 (96%), 24 (96%), 25 (100%), 24 (96%), and 23 (77%) in the vehicle control, low, mid, mid-high, and high dose groups, respectively, for male mice, and 24 (96%), 24 (96%), 23 (92%), and 23 (96%) in the vehicle control group, the low, mid, and high dose groups, respectively, for female mice. No statistically significant dose response relationship or pairwise comparisons in mortality was observed for either male or female mice.

In the reviewer's analysis, no statistically significant dose response relationship or pairwise comparisons in any tested tumor was noted in either male or female mice. For both male and female mice, the pairwise compairons between the positive control group (Group 5) and the vehicle control group (Group 1) showed p-values less than 0.05 for many tumors, confirming animal expressed oncogenes and responded to carcinogenic insult as expected.

Dr. Hepei Chen.
Mathematical Statistician

Concur: Dr. Atiar Mohammad Rahman.

Cc: Archival NDA 220860
Dr. Sonia Tabacova

5. Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

	0 mg/kg/day Vehicle Control		1 mg/kg/day Low		20 mg/kg/day Mid		100 mg/kg/day High	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52			1	5.00	2	3.33		
53 - 78	7	11.67	6	15.00	4	10.00	7	11.67
79 - 91	3	16.67	13	36.67	9	25.00	6	21.67
92 - 104	12	36.67	6	46.67	18	55.00	19	53.33
>105			2	3.33				
Terminal sacrifice	38	63.33	32	53.33	27	45.00	28	46.67
Total	60		60		60		60	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.2474	0.2143	0.0304*	0.0579
Homogeneity (Log-Rank)	0.1687	0.2100	0.0288*	0.0553

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

* = Significant at 5% level; ** = Significant at 1% level.

Table 1B: Intercurrent Mortality Rate in Female Rats

	0 mg/kg/day Vehicle Control		1 mg/kg/day Low		20 mg/kg/day Mid		100 mg/kg/day High	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	2	3.33	3	5.00	1	1.67		
53 - 78	7	15.00	12	25.00	6	11.67	4	6.67
79 - 91	5	23.33	6	35.00	13	33.33	8	20.00
92 - 104	17	51.67	14	58.33	18	63.33	20	53.33
Terminal sacrifice	29	48.33	25	41.67	22	36.67	28	46.67
Total	60		60		60		60	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.4618	0.2662	0.1524	0.8984
Homogeneity (Log-Rank)	0.3494	0.2599	0.1465	0.8969

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats

Organ name	Tumor name	0 mg Vehicle (VC) P - Trend	1 mg Low (L) P - VC vs. L	20 mg Mid (M) P - VC vs. M	100 mg High (H) P - VC vs. H
Adrenal Gland	Adenoma, Cortex	1/60 (53)	0/60 (48)	1/60 (47)	3/60 (49)
		0.0599	0.4752	0.7216	0.2796
	Carcinoma, Cortex	1/60 (53)	0/60 (48)	0/60 (47)	1/60 (49)
		0.4365	0.4752	0.4700	0.7325
	Adenoma, Cortex/ Carcinoma, Cortex	2/60 (53)	0/60 (48)	1/60 (47)	4/60 (49)
		0.0486	0.7271	0.4546	0.3023
	Pheochromocytoma, Benign	12/60 (53)	10/60 (49)	10/60 (48)	5/60 (49)
		0.9613	0.5124	0.4905	0.9229
	Pheochromocytoma, Malignant	2/60 (53)	1/60 (48)	2/60 (47)	0/60 (48)
		0.8393	0.4625	0.6445	0.7271
	Pheochromocytoma, Benign/ Pheochromocytoma, Malignant	12/60 (53)	10/60 (49)	11/60 (48)	5/60 (49)
		0.9638	0.5124	0.5801	0.9229
Brain	Glioma, Not Otherwise Specified	1/60 (53)	2/60 (48)	2/60 (48)	0/60 (48)
		0.8112	0.4625	0.4625	0.4752
	Reticulosis, Malignant	0/60 (53)	1/60 (48)	0/60 (47)	0/60 (48)
		0.4847	0.4752	NC	NC
	Tumor, Granular Cell, Benign	0/60 (53)	0/60 (48)	2/60 (48)	1/60 (48)
		0.1909	NC	0.2234	0.4752
	Tumor, Granular Cell, Malignant	0/60 (53)	1/60 (48)	1/60 (47)	0/60 (48)
		0.4873	0.4752	0.4700	NC
	Tumor, Granular Cell, Benign/ Tumor, Granular Cell, Malignant	0/60 (53)	1/60 (48)	3/60 (48)	1/60 (48)
		0.3746	0.4752	0.1038	0.4752
Cecum	Leiomyosarcoma	1/60 (53)	0/59 (47)	0/58 (46)	0/58 (47)
		0.7254	0.4700	0.4646	0.4700
Harderian Gland	Adenoma	0/60 (53)	1/60 (48)	0/60 (47)	0/59 (48)
		0.4847	0.4752	NC	NC
Heart	Schwannoma, Endocardial	0/60 (53)	0/60 (48)	2/60 (47)	0/60 (48)
		0.4308	NC	0.2184	NC
	Schwannoma, Intramural	0/60 (53)	0/60 (48)	1/60 (47)	0/60 (48)
		0.2449	NC	0.4700	NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (VC) P - Trend	1 mg Low (L) P - VC vs. L	20 mg Mid (M) P - VC vs. M	100 mg High (H) P - VC vs. H
Hemolymphoreticular (All Sites)	Leukemia, L Granular Lymphocyt	0/60 (53)	1/60 (48)	0/60 (47)	1/60 (48)
		0.2976	0.4752	NC	0.4752
	Leukemia, Myeloid	2/60 (54)	0/60 (48)	4/60 (50)	2/60 (49)
		0.3332	0.7222	0.3031	0.6536
	Leukemia, L Granular Lymphocyt/Leukemia, Myeloid	2/60 (54)	1/60 (48)	4/60 (50)	3/60 (49)
		0.2413	0.4555	0.3031	0.4536
	Lymphoma	0/60 (53)	2/60 (49)	0/60 (47)	0/60 (48)
		0.7332	0.2283	NC	NC
	Sarcoma, Histiocytic	2/60 (53)	1/60 (49)	3/60 (48)	2/60 (49)
		0.3938	0.4703	0.4527	0.6610
Jejunum	Adenocarcinoma	0/60 (53)	1/57 (46)	0/55 (44)	0/56 (47)
		0.4789	0.4646	NC	NC
Kidney	Lipoma	0/60 (53)	0/60 (48)	1/60 (47)	0/60 (48)
		0.2449	NC	0.4700	NC
	Liposarcoma	1/60 (53)	1/60 (48)	0/60 (47)	0/60 (48)
		0.7948	0.7271	0.4700	0.4752
	Lipoma/Liposarcoma	1/60 (53)	1/60 (48)	1/60 (47)	0/60 (48)
		0.7160	0.7271	0.7216	0.4752
Liver	Adenoma, Hepatocellular	0/60 (53)	0/60 (48)	4/60 (48)	1/60 (49)
		0.3658	NC	0.0477	0.4804
Lymph Node, mesenteric	Hemangioma	1/60 (53)	0/60 (48)	0/60 (47)	0/60 (48)
		0.7296	0.4752	0.4700	0.4752
	Hemangiosarcoma	0/60 (53)	0/60 (48)	1/60 (48)	0/60 (48)
		0.2437	NC	0.4752	NC
	Hemangioma/Hemangiosarcoma	1/60 (53)	0/60 (48)	1/60 (48)	0/60 (48)
		0.6067	0.4752	0.7271	0.4752
Lymph Node, nos	Hemangiosarcoma	1/2 (1)	0/3 (1)	0/5 (4)	0/1 (1)
		0.8571	0.5000	0.8000	0.5000
Mammary Gland	Adenoma	0/60 (53)	0/60 (48)	0/60 (47)	1/60 (49)
		0.2487	NC	NC	0.4804
	Fibroadenoma	1/60 (53)	2/60 (48)	0/60 (47)	1/60 (48)
		0.5579	0.4625	0.4700	0.7271

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor Name	0 mg Vehicle (VC) P - Trend	1 mg Low (L) P - VC vs. L	20 mg Mid (M) P - VC vs. M	100 mg High (H) P - VC vs. H
Pancreas	Adenoma, Acinar Cell	4/58 (51)	1/60 (48)	5/59 (47)	1/60 (49)
		0.8370	0.7994	0.4477	0.8062
	Adenoma, Acinar-Islet Cell	1/58 (51)	0/60 (48)	0/59 (46)	0/60 (48)
		0.7358	0.4848	0.4742	0.4848
	Adenoma, Acinar Cell/ Adenoma, Acinar-Islet Cell	5/58 (51)	1/60 (48)	5/59 (47)	1/60 (49)
		0.8807	0.8833	0.5763	0.8883
	Adenoma, Islet Cell	13/58 (51)	17/60 (49)	13/59 (47)	16/60 (49)
		0.3394	0.2161	0.4938	0.2849
	Carcinoma, Islet Cell	3/58 (51)	1/60 (48)	0/59 (46)	2/60 (49)
		0.4695	0.6681	0.8588	0.4809
	Adenoma, Islet Cell/ Carcinoma, Islet Cell	16/58 (51)	18/60 (50)	13/59 (47)	18/60 (50)
		0.3363	0.3892	0.5711	0.3892
Parathyroid Gland	Adenoma	0/59 (52)	1/57 (45)	1/58 (46)	1/58 (47)
		0.2815	0.4639	0.4694	0.4747
Pituitary Gland	Adenoma, Pars Distalis	31/60 (56)	34/60 (54)	26/60 (52)	34/60 (54)
		0.2537	0.2687	0.6421	0.2687
	Carcinoma, Pars Distalis	0/60 (53)	1/60 (48)	1/60 (48)	0/60 (48)
		0.4873	0.4752	0.4752	NC
	Adenoma, Pars Distalis/ Carcinoma, Pars Distalis	31/60 (56)	35/60 (55)	27/60 (52)	34/60 (54)
		0.2779	0.2437	0.5653	0.2687
Prostate	Adenocarcinoma	1/60 (53)	1/60 (48)	0/60 (47)	0/60 (48)
		0.7948	0.7271	0.4700	0.4752
	Adenoma	1/60 (53)	0/60 (48)	0/60 (47)	0/60 (48)
		0.7296	0.4752	0.4700	0.4752
	Adenocarcinoma/Adenoma	2/60 (53)	1/60 (48)	0/60 (47)	0/60 (48)
		0.9275	0.4625	0.7216	0.7271
	Carcinosarcoma	0/60 (53)	0/60 (48)	1/60 (48)	0/60 (48)
		0.2437	NC	0.4752	NC
Seminal Vesicle	Adenocarcinoma	1/60 (53)	0/60 (48)	0/60 (47)	0/60 (48)
		0.7296	0.4752	0.4700	0.4752

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (VC) P - Trend	1 mg Low (L) P - VC vs. L	20 mg Mid (M) P - VC vs. M	100 mg High (H) P - VC vs. H
Skin	Carcinoma, Basal Cell	1/60 (53)	1/60 (48)	0/60 (47)	0/60 (48)
		0.7948	0.7271	0.4700	0.4752
	Carcinoma, Squamous Cell	0/60 (53)	0/60 (48)	1/60 (47)	0/60 (48)
		0.2449	NC	0.4700	NC
	Fibroma	5/60 (53)	4/60 (48)	5/60 (48)	4/60 (49)
		0.5552	0.4367	0.5646	0.4498
	Fibrosarcoma	3/60 (53)	2/60 (48)	4/60 (47)	1/60 (49)
		0.7981	0.4527	0.4326	0.6610
	Fibroma/Fibrosarcoma	8/60 (53)	6/60 (48)	8/60 (48)	5/60 (50)
		0.7671	0.5337	0.5213	0.6835
	Keratoacanthoma	1/60 (53)	4/60 (48)	5/60 (47)	1/60 (49)
		0.8129	0.1518	0.0772	0.7325
	Papilloma, Squamous Cell	0/60 (53)	0/60 (48)	1/60 (47)	1/60 (48)
		0.1771	NC	0.4700	0.4752
	Keratoacanthoma/ Papilloma, Squamous Cell	1/60 (53)	4/60 (48)	5/60 (47)	2/60 (49)
		0.6208	0.1518	0.0772	0.4703
	Lipoma	0/60 (53)	3/60 (48)	0/60 (47)	0/60 (48)
		0.8651	0.1038	NC	NC
	Liposarcoma	0/60 (53)	0/60 (48)	0/60 (47)	1/60 (49)
		0.2487	NC	NC	0.4804
	Lipoma/Liposarcoma	0/60 (53)	3/60 (48)	0/60 (47)	1/60 (49)
		0.5505	0.1038	NC	0.4804
	Neuroendocrine Tumor, Benign	0/60 (53)	0/60 (48)	1/60 (48)	0/60 (48)
		0.2437	NC	0.4752	NC
	Polyp	0/60 (53)	1/60 (48)	0/60 (47)	0/60 (48)
		0.4847	0.4752	NC	NC
	Sarcoma, Nos	1/60 (53)	1/60 (48)	0/60 (47)	0/60 (48)
		0.7948	0.7271	0.4700	0.4752
Spinal Cord	Glioma, Not Otherwise Specified	0/60 (53)	0/60 (48)	0/60 (47)	1/60 (49)
		0.2487	NC	NC	0.4804
Spleen	Hemangiosarcoma	1/60 (53)	0/60 (48)	0/60 (47)	0/60 (48)
		0.7296	0.4752	0.4700	0.4752

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (VC) P - Trend	1 mg Low (L) P - VC vs. L	20 mg Mid (M) P - VC vs. M	100 mg High (H) P - VC vs. H
Stomach	Leiomyosarcoma	0/60 (53)	0/60 (48)	0/60 (47)	1/60 (48)
		0.2449	NC	NC	0.4752
	Papilloma, Squamous Cell	0/60 (53)	0/60 (48)	0/60 (47)	1/60 (48)
		0.2449	NC	NC	0.4752
Testis	Adenoma, Leydig Cell	1/60 (53)	2/60 (48)	2/60 (48)	2/60 (48)
		0.3353	0.4625	0.4625	0.4625
Thymus	Thymoma, Malignant	1/60 (53)	0/60 (48)	0/60 (47)	0/60 (48)
		0.7296	0.4752	0.4700	0.4752
Thyroid Gland	Adenoma, C-Cell	6/60 (53)	8/60 (49)	8/60 (48)	9/60 (50)
		0.2525	0.3276	0.3124	0.2482
	Carcinoma, C-Cell	0/60 (53)	1/60 (48)	1/60 (47)	2/60 (49)
		0.1128	0.4752	0.4700	0.2283
	Adenoma, C-Cell/ Carcinoma, C-Cell	6/60 (53)	9/60 (49)	9/60 (48)	11/60 (50)
		0.1407	0.2346	0.2212	0.1162
	Adenoma, Follicular Cell	2/60 (53)	2/60 (48)	4/60 (48)	5/60 (50)
		0.0974	0.6529	0.2929	0.1949
	Carcinoma, Follicular Cell	1/60 (53)	0/60 (48)	2/60 (48)	0/60 (48)
		0.6264	0.4752	0.4625	0.4752
	Adenoma, Follicular Cell/ Carcinoma, Follicular Cell	3/60 (53)	2/60 (48)	6/60 (49)	5/60 (50)
		0.1953	0.4527	0.2060	0.3254
Tongue	Tumor, Granular Cell, Benign	0/60 (53)	1/60 (48)	0/60 (47)	0/59 (48)
		0.4847	0.4752	NC	NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats

Organ name	Tumor name	0 mg Vehicle (VC) P - Trend	1 mg Low (L) P - VC vs. L	20 mg Mid (M) P - VC vs. M	100 mg High (H) P - VC vs. H
Abdominal Cavity	Fibrosarcoma, Pleomorphic	0/1 (1)	0/1 (1)	0/4 (3)	1/1 (1)
		0.1667	NC	NC	0.5000
	Sarcoma, Nos	0/1 (1)	1/1 (1)	0/4 (3)	0/1 (1)
		0.6667	0.5000	NC	NC
Adrenal Gland	Adenoma, Cortex	2/60 (49)	2/60 (43)	1/60 (46)	1/60 (50)
		0.7207	0.6406	0.4761	0.5077
	Carcinoma, Cortex	0/60 (49)	0/60 (43)	1/60 (46)	0/60 (50)
		0.2660	NC	0.4842	NC
	Adenoma, Cortex/ Carcinoma, Cortex	2/60 (49)	2/60 (43)	2/60 (46)	1/60 (50)
		0.7160	0.6406	0.6672	0.5077
	Pheochromocytoma, Benign	5/60 (49)	1/60 (43)	1/60 (46)	0/60 (50)
		0.9910	0.8654	0.8830	0.9733
	Pheochromocytoma, Complex, M	1/60 (49)	0/60 (43)	0/60 (46)	0/60 (50)
		0.7394	0.4674	0.4842	0.5051
	Pheochromocytoma, Malignant	0/60 (49)	0/60 (43)	1/60 (46)	0/60 (50)
		0.2660	NC	0.4842	NC
	Pheochromocytoma, Benign/ Pheochromocytoma, Complex, M	6/60 (49)	1/60 (43)	2/60 (46)	0/60 (50)
		0.9912	0.9216	0.8447	0.9875
Brain	Glioma, Not Otherwise Specified	0/60 (49)	1/60 (44)	1/60 (46)	1/60 (50)
		0.3096	0.4731	0.4842	0.5051
	Meningioma, Benign	1/60 (50)	0/60 (43)	0/60 (46)	0/60 (50)
		0.7354	0.4624	0.4792	0.5000
	Tumor, Granular Cell, Benign	0/60 (49)	1/60 (43)	0/60 (46)	0/60 (50)
		0.5106	0.4674	NC	NC
Duodenum	Leiomyoma, Benign	0/60 (49)	0/60 (43)	2/60 (46)	0/60 (50)
		0.4622	NC	0.2318	NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (VC) P - Trend	1 mg Low (L) P - VC vs. L	20 mg Mid (M) P - VC vs. M	100 mg High (H) P - VC vs. H
Hemolymphoreticular (All Sites)	Leukemia, L Granular Lymphocyt	0/60 (49)	0/60 (43)	3/60 (46)	2/60 (50)
		0.1282	NC	0.1097	0.2525
	Leukemia, Myeloid	0/60 (49)	0/60 (43)	1/60 (46)	0/60 (50)
		0.2660	NC	0.4842	NC
	Leukemia, L Granular Lymphocyt/ Leukemia, Myeloid	0/60 (49)	0/60 (43)	4/60 (46)	2/60 (50)
		0.1959	NC	0.0513	0.2525
	Lymphoma	1/60 (49)	0/60 (43)	0/60 (46)	0/60 (50)
		0.7394	0.4674	0.4842	0.5051
	Sarcoma, Histiocytic	0/60 (49)	0/60 (43)	1/60 (46)	2/60 (50)
		0.0697	NC	0.4842	0.2525
Ileum	Leiomyoma, Benign	0/57 (47)	1/54 (41)	0/51 (40)	0/54 (45)
		0.4913	0.4659	NC	NC
Jejunum	Leiomyoma, Benign	1/56 (45)	1/54 (41)	0/55 (43)	0/58 (48)
		0.8180	0.7291	0.4886	0.5161
	Leiomyosarcoma	0/56 (45)	0/54 (41)	1/55 (43)	0/58 (48)
		0.2712	NC	0.4886	NC
	Leiomyoma, Benign/ Leiomyosarcoma	1/56 (45)	1/54 (41)	1/55 (43)	0/58 (48)
		0.7532	0.7291	0.7414	0.5161
Kidney	Adenoma	2/60 (49)	0/60 (43)	0/60 (46)	0/60 (50)
		0.9331	0.7191	0.7366	0.7576
	Carcinoma	1/60 (49)	0/60 (43)	0/60 (46)	1/60 (50)
		0.4622	0.4674	0.4842	0.2525
	Adenoma/Carcinoma	3/60 (49)	0/60 (43)	0/60 (46)	1/60 (50)
		0.6948	0.8533	0.8669	0.6990
	Carcinoma, Urothelial	1/60 (49)	0/60 (43)	0/60 (46)	0/60 (50)
		0.7394	0.4674	0.4842	0.5051
Liver	Adenoma, Hepatocellular	0/60 (49)	0/60 (43)	0/60 (46)	2/60 (50)
		0.0697	NC	NC	0.2525
Lymph Node, mesenteric	Hemangiosarcoma	0/59 (48)	0/59 (43)	1/58 (44)	0/60 (50)
		0.2703	NC	0.4783	NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (VC) P - Trend	1 mg Low (L) P - VC vs. L	20 mg Mid (M) P - VC vs. M	100 mg High (H) P - VC vs. H
Mammary Gland	Adenocarcinoma	16/60 (50)	15/60 (48)	13/60 (48)	16/60 (52)
		0.5018	0.4452	0.6220	0.4686
	Adenocarcinoma In Fibroadenoma	12/60 (50)	6/60 (44)	10/60 (46)	4/60 (50)
		0.9729	0.8441	0.5073	0.9731
	Carcinoma, Adenosquamous Cell	0/60 (49)	3/60 (44)	0/60 (46)	0/60 (50)
		0.8828	0.1021	NC	NC
	Adenocarcinoma/ Adenocarcinoma In Fibroadenoma	28/60 (51)	20/60 (48)	21/60 (48)	20/60 (53)
		0.8954	0.8678	0.8180	0.9407
	Adenoma	1/60 (49)	1/60 (44)	1/60 (46)	0/60 (50)
		0.7444	0.7251	0.7366	0.5051
	Carcinosarcoma	0/60 (49)	1/60 (44)	0/60 (46)	0/60 (50)
		0.5079	0.4731	NC	NC
	Adenoma/Carcinosarcoma	1/60 (49)	2/60 (44)	1/60 (46)	0/60 (50)
		0.8392	0.4593	0.7366	0.5051
	Fibroadenoma	30/60 (52)	30/60 (49)	34/60 (51)	24/60 (55)
		0.9828	0.4372	0.2311	0.8963
	Fibroma	1/60 (49)	0/60 (43)	0/60 (46)	0/60 (50)
		0.7394	0.4674	0.4842	0.5051
	Fibrosarcoma	0/60 (49)	0/60 (43)	1/60 (46)	0/60 (50)
		0.2660	NC	0.4842	NC
	Fibroma/Fibrosarcoma	1/60 (49)	0/60 (43)	1/60 (46)	0/60 (50)
		0.6336	0.4674	0.7366	0.5051
	Liposarcoma	0/60 (49)	1/60 (44)	0/60 (46)	0/60 (50)
		0.5079	0.4731	NC	NC
	Sarcoma A In Fibroadenoma	1/60 (49)	0/60 (43)	0/60 (46)	0/60 (50)
		0.7394	0.4674	0.4842	0.5051

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (VC) P - Trend	1 mg Low (L) P - VC vs. L	20 mg Mid (M) P - VC vs. M	100 mg High (H) P - VC vs. H
Ovary	Granulosa Cell Tumor, Benign	0/60 (49)	0/60 (43)	1/60 (46)	0/60 (50)
		0.2660	NC	0.4842	NC
	Granulosa Cell Tumor, Malignant	0/60 (49)	1/60 (43)	0/60 (46)	0/60 (50)
		0.5106	0.4674	NC	NC
	Granulosa Cell Tumor, Benign/ Granulosa Cell Tumor, Malignant	0/60 (49)	1/60 (43)	1/60 (46)	0/60 (50)
		0.5211	0.4674	0.4842	NC
	Leiomyoma, Benign	1/60 (50)	0/60 (43)	0/60 (46)	0/60 (50)
		0.7354	0.4624	0.4792	0.5000
	Tumor, Sex Cord Stromal, Mixed, Benign	0/60 (49)	2/60 (44)	2/60 (46)	4/60 (50)
		0.0484	0.2211	0.2318	0.0612
Pancreas	Adenoma, Acinar Cell	0/58 (47)	0/60 (43)	1/60 (46)	0/60 (50)
		0.2688	NC	0.4946	NC
	Adenoma, Islet Cell	5/58 (47)	2/60 (43)	2/60 (46)	2/60 (50)
		0.8028	0.7444	0.7736	0.8070
	Carcinoma, Islet Cell	1/58 (47)	0/60 (43)	0/60 (46)	1/60 (50)
		0.4664	0.4778	0.4946	0.2631
	Adenoma, Islet Cell/ Carcinoma, Islet Cell	5/58 (47)	2/60 (43)	2/60 (46)	3/60 (50)
		0.6247	0.7444	0.7736	0.6770
Parathyroid Gland	Adenoma	0/56 (45)	2/56 (40)	1/58 (44)	0/59 (49)
		0.7232	0.2185	0.4944	NC
Pituitary Gland	Adenoma, Pars Distalis	39/60 (56)	46/60 (55)	46/60 (55)	47/60 (57)
		0.2152	0.0642	0.0642	0.0841
	Carcinoma, Pars Distalis	8/60 (51)	3/60 (44)	2/60 (46)	0/60 (50)
		0.9991	0.8473	0.9355	0.9968
	Adenoma, Pars Distalis/ Carcinoma, Pars Distalis	47/60 (58)	49/60 (55)	48/60 (55)	47/60 (57)
		0.6851	0.1754	0.2591	0.5177
Site, uncertain Primary	Tumor, Sex Cord Stromal, Mixed, M	0/60 (49)	0/60 (43)	1/60 (46)	0/60 (50)
		0.2660	NC	0.4842	NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (VC) P - Trend	1 mg Low (L) P - VC vs. L	20 mg Mid (M) P - VC vs. M	100 mg High (H) P - VC vs. H
Skin	Carcinoma, Basal Cell	0/60 (49)	0/60 (43)	1/60 (46)	0/60 (50)
		0.2660	NC	0.4842	NC
	Tumor, Basal Cell, Benign	0/60 (49)	1/60 (43)	0/60 (46)	0/60 (50)
		0.5106	0.4674	NC	NC
	Tumor, Basal Cell, Benign/ Carcinoma, Basal Cell	0/60 (49)	1/60 (43)	1/60 (46)	0/60 (50)
		0.5211	0.4674	0.4842	NC
	Fibroma	0/60 (49)	0/60 (43)	0/60 (46)	1/60 (50)
		0.2660	NC	NC	0.5051
	Fibrosarcoma	0/60 (49)	0/60 (43)	0/60 (46)	1/60 (50)
		0.2660	NC	NC	0.5051
	Fibroma/Fibrosarcoma	0/60 (49)	0/60 (43)	0/60 (46)	2/60 (50)
		0.0697	NC	NC	0.2525
	Keratoacanthoma	0/60 (49)	0/60 (43)	0/60 (46)	1/60 (50)
		0.2660	NC	NC	0.5051
	Tumor, Granular Cell, Benign	0/60 (49)	1/60 (43)	0/60 (46)	0/60 (50)
		0.5106	0.4674	NC	NC
Stomach	Papilloma, Squamous Cell	0/60 (49)	1/60 (44)	0/60 (46)	0/60 (50)
		0.5079	0.4731	NC	NC
Submandibular Gland	Adenoma	0/60 (49)	0/59 (43)	0/60 (46)	1/60 (50)
		0.2660	NC	NC	0.5051
Thymus	Thymoma, Benign	1/60 (49)	0/60 (43)	0/60 (46)	0/60 (50)
		0.7394	0.4674	0.4842	0.5051

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (VC) P - Trend	1 mg Low (L) P - VC vs. L	20 mg Mid (M) P - VC vs. M	100 mg High (H) P - VC vs. H
Thyroid Gland	Adenoma, C-Cell	8/60 (49)	9/59 (43)	5/60 (46)	6/60 (51)
		0.8123	0.3817	0.6811	0.6438
	Carcinoma, C-Cell	0/60 (49)	1/59 (43)	1/60 (46)	0/60 (50)
		0.5211	0.4674	0.4842	NC
	Adenoma, C-Cell/ Carcinoma, C-Cell	8/60 (49)	10/59 (43)	6/60 (46)	6/60 (51)
		0.8580	0.2831	0.5630	0.6438
	Adenoma, Follicular Cell	0/60 (49)	1/59 (43)	2/60 (46)	5/60 (51)
		0.0094	0.4674	0.2318	0.0312
	Carcinoma, Follicular Cell	2/60 (49)	0/59 (43)	0/60 (46)	0/60 (50)
		0.9331	0.7191	0.7366	0.7576
	Adenoma, Follicular Cell/ Carcinoma, Follicular Cell	2/60 (49)	1/59 (43)	2/60 (46)	5/60 (51)
		0.0608	0.4506	0.6672	0.2349
Tongue	Tumor, Granular Cell, Benign	1/60 (49)	2/59 (43)	0/60 (46)	0/60 (50)
		0.8961	0.4506	0.4842	0.5051
Urinary Bladder	Papilloma, Urothelial Cell	0/60 (49)	0/60 (43)	0/60 (46)	1/59 (49)
		0.2620	NC	NC	0.5000
Uterus	Adenocarcinoma, Endometrium	1/60 (49)	0/60 (43)	0/60 (46)	1/60 (50)
		0.4622	0.4674	0.4842	0.2525
	Polyp, Endometrial Stromal	5/60 (49)	5/60 (44)	3/60 (46)	12/60 (51)
		0.0111	0.5592	0.6066	0.0649
	Sarcoma, Endometrial Stromal	0/60 (49)	0/60 (43)	0/60 (46)	1/60 (50)
		0.2660	NC	NC	0.5051
	Adenocarcinoma, Endometrium/ Polyp, Endometrial Strom/ Sarcoma, Endometrial Stromal	5/60 (49)	5/60 (44)	3/60 (46)	13/60 (52)
		0.0059	0.5592	0.6066	0.0451
	Carcinosarcoma	0/60 (49)	0/60 (43)	1/60 (46)	0/60 (50)
		0.2660	NC	0.4842	NC
	Leiomyosarcoma	1/60 (49)	0/60 (43)	0/60 (46)	0/60 (50)
		0.7394	0.4674	0.4842	0.5051
	Papilloma, Squamous Cell	0/60 (49)	1/60 (44)	0/60 (46)	0/60 (50)
		0.5079	0.4731	NC	NC
	Schwannoma, Malignant	0/60 (49)	1/60 (44)	1/60 (46)	1/60 (51)
		0.3147	0.4731	0.4842	0.5100
	Tumor, Granular Cell, Benign	2/60 (49)	1/60 (43)	6/60 (46)	5/60 (50)
		0.1355	0.4506	0.1143	0.2264

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	0 mg Vehicle (VC) P - Trend	1 mg Low (L) P - VC vs. L	20 mg Mid (M) P - VC vs. M	100 mg High (H) P - VC vs. H
Uterus/Vagina	Leiomyosarcoma	1/60 (49)	0/60 (43)	1/60 (46)	0/60 (50)
		0.6336	0.4674	0.7366	0.5051
	Schwannoma, Malignant	0/60 (49)	1/60 (44)	3/60 (47)	2/60 (51)
		0.2125	0.4731	0.1135	0.2576
	Tumor, Granular Cell, Benign	8/60 (50)	4/60 (44)	9/60 (47)	9/60 (51)
		0.2692	0.7539	0.4436	0.5180
Vagina	Leiomyosarcoma	0/60 (49)	0/60 (43)	1/60 (46)	0/60 (50)
		0.2660	NC	0.4842	NC
	Polyp, Vaginal	0/60 (49)	0/60 (43)	1/60 (46)	1/60 (51)
		0.2038	NC	0.4842	0.5100
	Schwannoma, Malignant	0/60 (49)	0/60 (43)	2/60 (47)	1/60 (50)
		0.2203	NC	0.2371	0.5051
	Tumor, Granular Cell, Benign	6/60 (49)	3/60 (44)	4/60 (46)	5/60 (51)
		0.4863	0.7002	0.5888	0.5285

& X/YY (ZZ): X=number of tumor bearing animals; YY=unweighted total number of animals observed; ZZ=mortality weighted total number of animals;
NC = Not calculable.

Table 3A: Intercurrent Mortality Rate in Male Mice

	Vehicle Control		0.02 mg/kg/day Low		0.1 mg/kg/day Mid		0.8 mg/kg/day Mid-High		4/7 mg/kg/day High		Positive Control	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	No. of Death	Cum %
0 - 13									1	4.00	2	
14 - 27	1	4.00	1	4.00			1	4.00	1	8.00	13	
Terminal sacrifice	24	96.00	24	96.00	25	100.00	24	96.00	23	92.00	0	0
Total	25		25		25		25		25		15	

Test	All Dose Groups	Vehicle vs. Low	Vehicle vs. Mid	Vehicle vs. MId-high	Vehicle vs. High	Vehicle vs. Positive Control
Dose-Response (Likelihood Ratio)	0.2869	0.9885	0.2390	1.0000	0.5362	<.0001
Homogeneity (Log-Rank)	0.7118	0.9885	0.3173	1.0000	0.5396	<.0001

#All Cum. % Cumulative Percentage except for Terminal sacrifice;
* = Significant at 5% level; ** = Significant at 1% level.

Table 3B: Intercurrent Mortality Rate in Female Mice

	Vehicle Control		1 mg/kg/day Low		3 mg/kg/day Mid		10 mg/kg/day High		Positive Control	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 13					1	4.00			1	6.67
14 - 27	1	4.00	1	4.00	1	8.00	2	8.00	13	93.33
Terminal sacrifice	24	96.00	24	96.00	23	92.00	23	92.00	1	6.67
Total	25		25		25		25		15	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High	Vehicle Control vs. Positive Control
Dose-Response (Likelihood Ratio)	0.5891	0.9885	0.5521	0.5521	<.0001
Homogeneity (Log-Rank)	0.8671	0.9885	0.5557	0.5557	<.0001

#All Cum. % Cumulative Percentage except for Terminal sacrifice;
* = Significant at 5% level; ** = Significant at 1% level.

Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice

		Vehicle (C)	Low (L)	Mid (M)	Mid-High (MH)	High (H)	Positive (P)
		0 mg	6 mg	20 mg	60 mg	600 mg	
Organ name	Tumor name	P-Trend	LP-L vs C	P-M vs C	P-MH vs C	P-H vs C	P-P vs C
Kidney	Hemangioma	0/25 (25)	0/25 (24)	0/25 (25)	1/25 (25)	0/25 (24)	0/15 (5)
		0.3984	NC	NC	0.5000	NC	NC
	Hemangiosarcoma	0/25 (25)	1/25 (24)	0/25 (25)	0/25 (25)	0/25 (24)	0/15 (5)
		0.7967	0.4898	NC	NC	NC	NC
	Hemangioma/ Hemangiosarcoma	0/25 (25)	1/25 (24)	0/25 (25)	1/25 (25)	0/25 (24)	0/15 (5)
		0.5567	0.4898	NC	0.5000	NC	NC
Lung(Including Bronchus)	Adenoma,bronchiolo-Alveolar	1/25 (25)	4/25 (24)	1/25 (25)	1/25 (25)	1/25 (24)	0/15 (5)
		0.7595	0.1616	NC	NC	0.7449	1.0000
	Carcinoma,bronchiolo-Alveolar	0/25 (25)	1/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/15 (5)
		0.7984	0.5000	NC	NC	NC	NC
	Adenoma,bronchiolo-Alveolar/ Carcinoma,bronchiolo-Alveolar	1/25 (25)	5/25 (25)	1/25 (25)	1/25 (25)	1/25 (24)	0/15 (5)
		0.8146	0.0947	NC	NC	0.7449	1.0000
	Hemangioma	0/25 (25)	0/25 (24)	0/25 (25)	1/25 (25)	0/25 (24)	0/15 (5)
		0.3984	NC	NC	0.5000	NC	NC
Prostate	Adenoma	1/25 (25)	0/25 (24)	0/25 (25)	0/25 (25)	0/25 (24)	0/15 (5)
		1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
Spleen	Hemangiosarcoma	2/25 (25)	2/25 (24)	0/25 (25)	1/25 (25)	2/25 (24)	0/15 (5)
		0.3477	0.6798	1.0000	0.8827	0.6798	1.0000
Spleen/Thymus	Lymphoma,malignant	0/25 (25)	0/25 (24)	0/25 (25)	0/25 (25)	0/25 (24)	13/15 (13)
		NC	NC	NC	NC	NC	<.0001$
Stomach	Carcinoma,squamous Cell	0/25 (25)	0/25 (24)	0/25 (25)	0/25 (25)	0/25 (24)	5/15 (7)
		NC	NC	NC	NC	NC	0.0001$
	Papilloma,squamous Cell	0/25 (25)	0/25 (24)	0/25 (25)	0/25 (25)	0/25 (24)	14/15 (14)
		NC	NC	NC	NC	NC	<.0001$
	Carcinoma,squamous Cell/ Papilloma,squamous Cell	0/25 (25)	0/25 (24)	0/25 (25)	0/25 (25)	0/25 (24)	19/20 (19)
		NC	NC	NC	NC	NC	<.0001$
Submandibular Lymph Node	Lymphangioma	0/25 (25)	1/25 (24)	0/25 (25)	0/25 (25)	0/25 (24)	0/15 (5)
		0.7967	0.4898	NC	NC	NC	NC
Testis	Hemangiosarcoma	0/25 (25)	0/25 (24)	1/25 (25)	0/25 (25)	0/25 (24)	0/15 (5)
		0.6016	NC	0.5000	NC	NC	NC
Thymus	Thymoma,benign	1/25 (25)	0/25 (24)	0/25 (25)	0/25 (25)	0/25 (24)	0/15 (5)
		1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
Tongue	Hemangioma	0/25 (25)	1/25 (24)	0/25 (25)	0/25 (25)	0/25 (24)	0/15 (5)
		0.7967	0.4898	NC	NC	NC	NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice (Continued)

		Vehicle (C)	Low (L)	Mid (M)	Mid-High (MH)	High (H)	Positive (P)
		0 mg	6 mg	20 mg	60 mg	600 mg	
Organ name	Tumor name	P-Trend	LP-LvsC	P-MvsC	P-MHvsC	P-HvsC	P-PvsC
Whole Body	Hemangioma	0/25 (25)	1/25 (24)	0/25 (25)	2/25 (25)	0/25 (24)	0/15 (5)
		0.5379	0.4898	NC	0.2449	NC	NC
	Hemangioma/ Hemangiosarcoma	2/25 (25)	3/25 (24)	1/25 (25)	3/25 (25)	2/25 (24)	0/15 (5)
		0.4809	0.4800	0.8827	0.5000	0.6798	1.0000

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 3 mg P - VC vs. L	Mid (M) 30 mg P - VC vs. M	High (H) 300 mg P - VC vs. H	Positive (PC) 0 mg P - VC vs. PC
Cecum	Leiomyosarcoma	1/25 (24) 1.0000	0/25 (25) 1.0000	0/24 (24) 1.0000	0/24 (23) 1.0000	0/15 (6) 1.0000
Harderian Gland	Adenoma	0/25 (24) 0.1853	2/25 (25) 0.2551	0/25 (24) NC	2/25 (24) 0.2447	0/15 (6) NC
Lung(Including Bronchus)	Adenoma,bronchiolo-Alveolar	1/25 (24) 0.5332	1/25 (25) 0.7653	0/25 (24) 1.0000	1/25 (24) NC	0/15 (6) 1.0000
	Carcinoma,bronchiolo-Alveolar	0/25 (24) 0.4948	0/25 (25) NC	1/25 (24) 0.5000	0/25 (24) NC	0/15 (6) NC
	Adenoma,bronchiolo-Alveolar /Carcinoma,bronchiolo- Alveolar	1/25 (24) 0.5124	1/25 (25) 0.7653	1/25 (24) NC	1/25 (24) NC	0/15 (6) 1.0000
Skin/Subcutis	Hemangiosarcoma	0/25 (24) 0.7526	1/25 (25) 0.5102	0/25 (24) NC	0/25 (24) NC	0/15 (6) NC
Spleen	Hemangiosarcoma	1/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (24) 1.0000	0/25 (24) 1.0000	0/15 (6) 1.0000
Spleen/Thymus	Lymphoma,malignant	0/25 (24) NC	0/25 (25) NC	0/25 (24) NC	0/25 (24) NC	10/15 (12) 0.0000 $
Stomach	Carcinoma,squamous Cell	0/25 (24) NC	0/25 (25) NC	0/25 (24) NC	0/25 (24) NC	3/15 (7) 0.0078 $
	Papilloma,squamous Cell	0/25 (24) NC	0/25 (25) NC	0/25 (24) NC	0/25 (24) NC	14/15 (14) 0.0000 $
	Carcinoma,squamous Cell/ Papilloma,squamous Cell	0/25 (24) NC	0/25 (25) NC	0/25 (24) NC	0/25 (24) NC	14/15 (14) 0.0000 $
Thymus	Thymoma,benign	1/25 (24) 0.1504	0/25 (25) 1.0000	0/25 (24) 1.0000	2/25 (24) 0.5000	0/15 (6) 1.0000

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Figure 1A: Kaplan-Meier Survival Functions for Male Rats

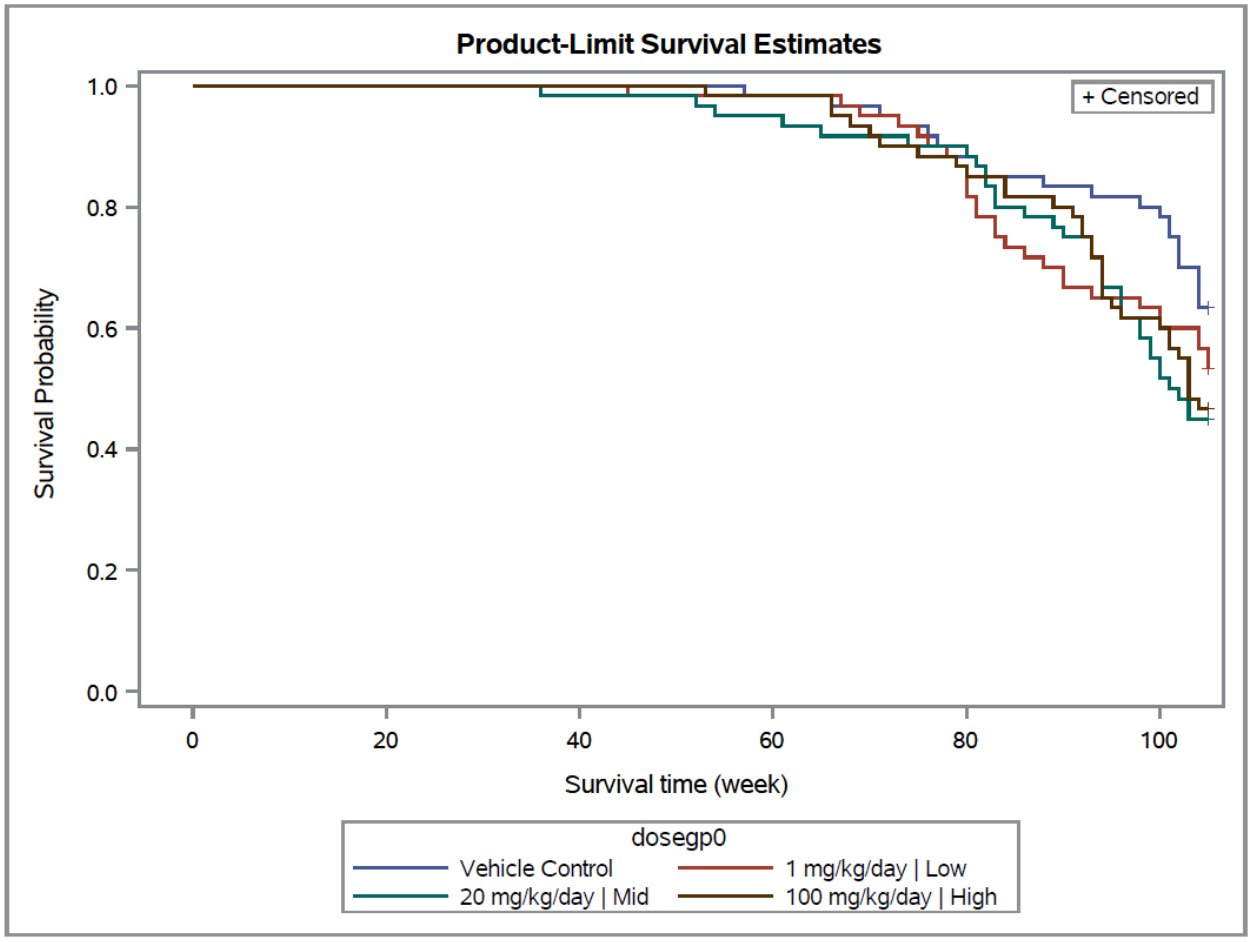


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

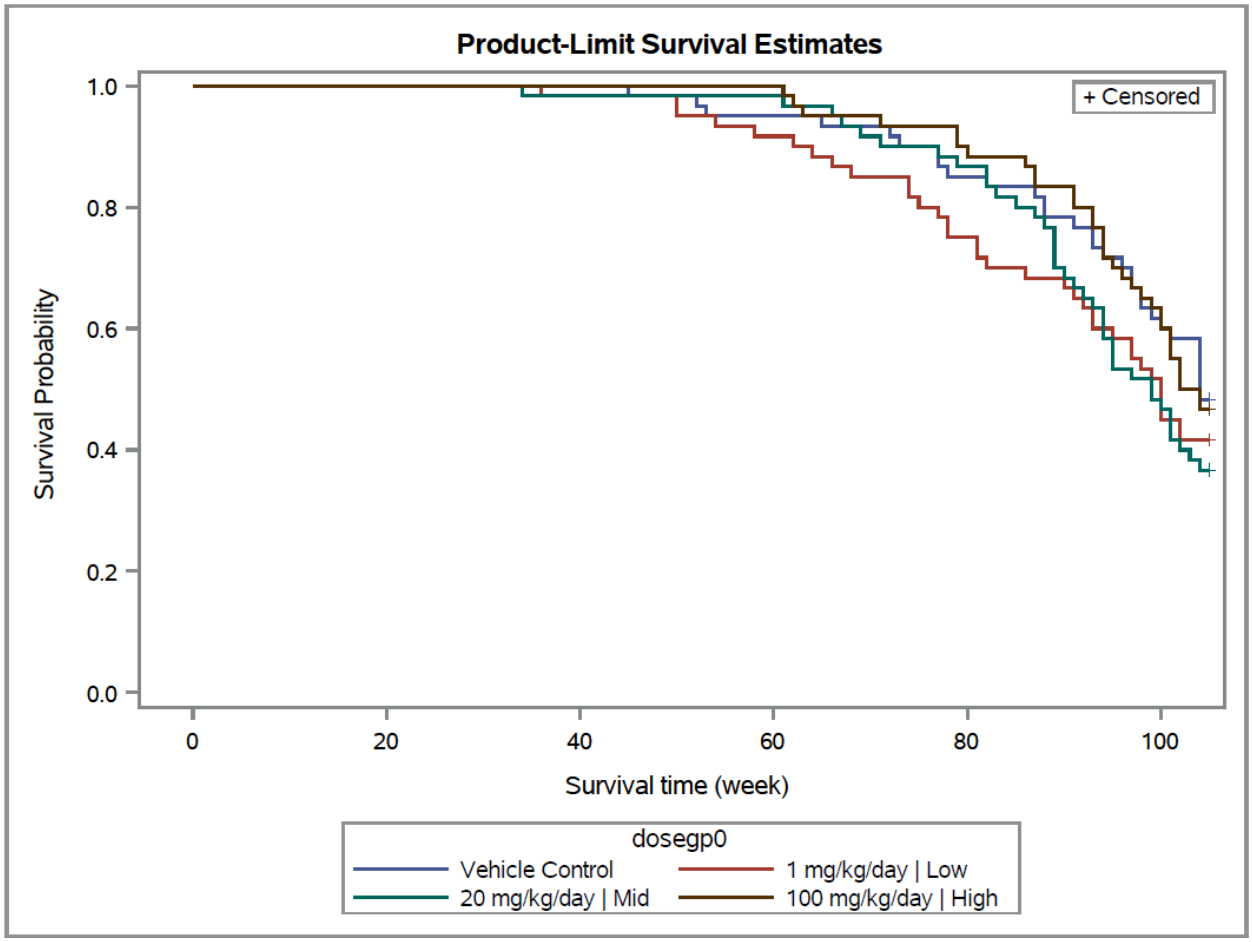


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

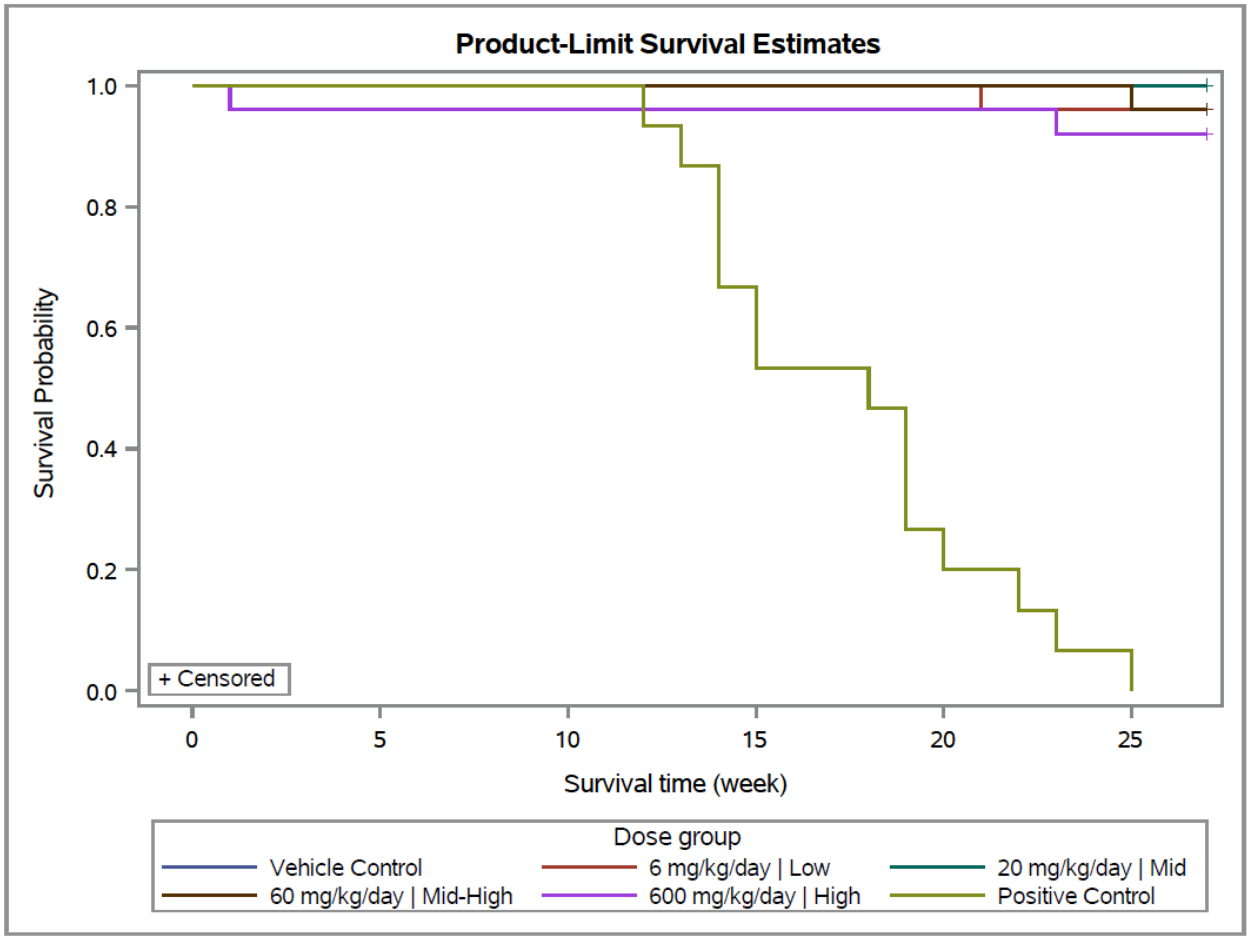
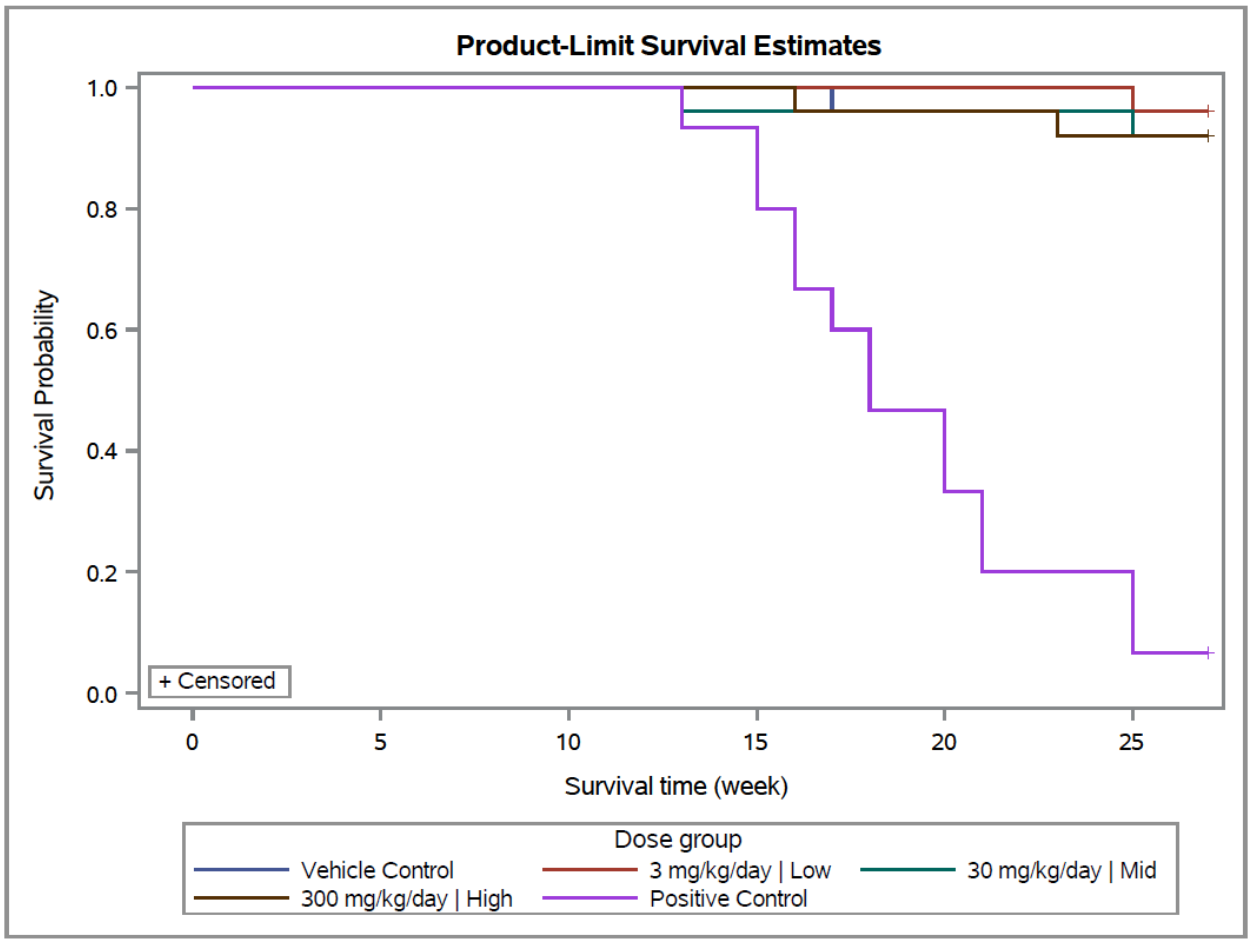


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	220860/0002
Drug Name:	oveporexton (TAK-861)
Indication(s):	Treatment of narcolepsy with cataplexy (NT1)
Applicant:	Takeda Pharmaceuticals USA
Date(s):	Date of Document: 12/10/2025 Consult received date: 1/28/2026 Completion date: 5/29/2026
Review Priority:	Standard review
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Wei Liu, Ph.D., OB/DBVI
Concurring Reviewers:	Qianyu Dang, Ph.D., Team Leader, OB/DBVI
Medical Division:	Office of Neuroscience/Division of Psychiatry (ONDP) and Controlled Substance Staff (CSS)
The CSS Team:	Neil Varshneya, PhD/MBA, Senior Pharmacologist, CDER/OD/CSS Chad J. Reissig, Pharmacologist, CDER/OD/CSS Silvia Calderon, Pharmacologist, CDER/OD/CSS Dominic Chiapperino, Ph.D., Director, CDER/OD/CSS
Project Manager:	Diana Walker, CDER/OCD/CSS
Keywords: NDA review, clinical studies, Crossover design; Self-reported endpoint; Multiple endpoints; human drug abuse study; Central Nervous System; Stimulant	

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EXECUTIVE SUMMARY

The applicant, Takeda Pharmaceuticals USA, submitted data for Study TAK-861-1009 in NDA 220860 for the assessment of abuse potential for Oveporexton (TAK-861) (IND 154232). The Study TAK-861-1009 was a phase 1, randomized, double-blind, double-dummy, active- and placebo-controlled, 5-way crossover trial evaluating the abuse potential of Oveporexton in healthy adult nondependent recreational drug users with CNS stimulant experience. A total of 50 subjects were randomized into the treatment phase and forty-seven (47) participants (94.0%) completed the treatment phase. A total of 43 subjects (86%) were included in the Modified Completer Population (MCP).

The primary endpoint of this study was the maximum effect (Emax) for Drug Liking ("at this moment") of Oveporexton, as assessed by a bipolar (0–100 point) visual analog scale (VAS). The key secondary endpoints were VAS Emax of Overall Drug Liking, Take Drug Again, and High. Other secondary endpoints included VAS Emax of Good Drug Effects and Bad Drug Effects, and the occurrence of at least 1 TEAE during the study including the follow-up period, as applicable. Data for the endpoints of Any Drug Effects, and the VAS Emax of Alertness/Drowsiness, and time-averaged area under the effect-time curve [TA_AUE]) are also available.

The reviewer's primary analysis was conducted on Modified Completers population Set (n=43). Considering the overall evidence from the data, this reviewer confirmed the following findings:

1. The validation test for comparing the mean difference of Drug Liking VAS Emax between Phentermine 75 mg and placebo with a test margin of 15 points was statistically significant at alpha level of 0.05 (1-sided) and the lower 95% confidence limit (one-sided) of the mean difference was 20.8, supporting the study validity.

2. For the relative abuse potential of Oveporexton at each dose in this study compared to Phentermine 75 mg with a margin of 0 point, the data rejected the hypothesis of the mean Emax score of Drug Liking VAS in subjects receiving Phentermine 75 mg being less than or equal to those receiving Oveporexton 6 mg at alpha level of 0.05 (one-sided), suggesting that the subjects in this study prefer Phentermine 75 mg to Oveporexton 6 mg. However, the data failed to reject the null hypothesis of the relative abuse potential of the higher doses of Oveporexton (18 mg, or 30 mg) compared to Phentermine 75 mg with p-value > 0.05 (1-sided), suggesting that the subjects in this study liked Oveporexton no less than Phentermine 75 mg.

   Furthermore, analyses of the key and other secondary endpoints showed consistent patterns as seen in the relative abuse potential analysis of the primary analysis.

   Since only the low dose of Oveporexton demonstrated a significant difference relative to Phentermine 75 mg while the analysis failed to reject the null hypothesis at the medium and high doses of the test drug, this is sufficient to draw the conclusion about the potential for abuse of Oveporexton. Therefore, the analysis of absolute abuse potential of Oveporexton would be exploratory.

3. Exploratory analysis: At alpha level of 0.05 (one-sided), there was no sufficient evidence to reject the null hypothesis of the mean Emax of Drug Liking VAS to the treatment of each Oveporexton dose is higher than that of placebo by 11 points, suggesting that the subjects in the treatment phase more like Oveporexton than placebo.

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In summary, the data suggested that Oveporexton has higher abuse potential than placebo when assessed on the mean Emax score of Drug Liking VAS and other secondary endpoints. Relative to the positive control treatment, data from both the primary and secondary endpoints support that Oveporexton at either 18 mg or 30 mg has no less potential for abuse than Phentermine 75 mg, while Oveporexton 6 mg has a lower abuse potential than Phentermine 75 mg.

Summary: Results of Primary Analysis on Drug Liking VAS Emax (MCP, N=43)

					95% CI*		95% CI**	
Pairwise Comparison	**δ**	Mean diff	SE	p-value	LCL	UCL	LCL	UCL
Phentermine 75 mg - Placebo	15	24.3	2.1	<0.0001	20.8	Inf	20.2	28.5
Phentermine 75 mg - Oveporexton 6 mg	0	9.7	2.7	0.0004	5.1	Inf	4.2	15.2
Phentermine 75 mg - Oveporexton 18 mg	0	3.7	2.9	0.1020	-1.1	Inf	-2.0	9.4
Phentermine 75 mg - Oveporexton 30 mg	0	-1.5	2.6	0.7175	-5.8	Inf	-6.6	3.7
Oveporexton 6 mg – Placebo***	11	14.6	2.4	0.9312	-Inf	18.7	9.8	19.5
Oveporexton 18 mg – Placebo***	11	20.7	2.5	0.9998	-Inf	24.9	15.6	25.8
Oveporexton 30 mg – Placebo***	11	25.8	2.3	>0.9999	-Inf	29.6	21.3	30.4

Note: Analyses were carried out on the Modified Completers Population.
test: mixed-effects model
δ: the Sponsor preselected margin
p-value and one-sided confidence limit (*) were from the tests of the following null hypothesis at alpha=0.05:
Positive control vs. placebo (validation), H_0: $\mu_C - \mu_P \leq \delta$, δ=15
Positive control vs. test drug (Relative Abuse Potential), H_0: $\mu_C - \mu_T \leq \delta$, δ=11, 0
Test drug vs. Placebo (Absolute Abuse Potential), H_0: $\mu_T - \mu_P \geq \delta$, δ=11
** two-sided confidence limit for the pairwise comparison.
*** exploratory.
LCL: lower confidence limit; UCL: upper confidence limit; Inf represents infinity.

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2. INTRODUCTION

2.1 Overview

Oveporexton (TAK-861) is developed for the treatment of narcolepsy with cataplexy (NT1), a rare neurological disorder characterized by EDS and associated rapid eye movement phenomena including cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and disturbed nighttime sleep.

This study had been conducted to assess the relative abuse potential of TAK-861 in healthy adult nondependent recreational drug users with central nervous system (CNS) stimulant experience.

The primary purpose of this study was to evaluate the abuse potential of oveporexton, in comparison to placebo and an active control with Phentermine, which is a Schedule IV controlled substance.

2.2 Data Source

Application:	NDA220860
Company	Takeda Pharmaceuticals USA
Drug	Oveporexton (TAK-861)
CDER EDR link	file://cdsesub1/evsprod/NDA220860/0002/m5/datasets/tak-861-1009/analysis/adam/datasets/
Letter date	12/10/2025

3. REVIEW REPORT on STUDY TAK-861-1009

3.1 STUDY OBJECTIVES

Primary Objective:

To evaluate the relative abuse potential of oveporexton as measured by the VAS for Drug Liking (“at this moment”).

Key Secondary Objectives:

To evaluate the relative abuse potential of oveporexton as measured by the VAS for Overall Drug Liking, Take Drug Again, and High.

Other Secondary Objectives:

- To evaluate the relative abuse potential of oveporexton as measured by the VAS for Bad Drug Effects and Good Drug Effects.
- To evaluate the safety/tolerability of oveporexton as measured by TEAE incidence.

3.2 STUDY DESIGN

This was a phase 1, randomized, double-blind, double-dummy, active- and placebo-controlled, 5-way crossover trial evaluating the abuse potential of oveporexton in healthy adult nondependent recreational drug users with CNS stimulant experience.

An overview of the study design is presented in Figure 1.

Figure 1 Study Design Schematic

Screening Phase	Randomization to Sequence Q1-Q2	Randomization Sequence	Qualification Phase		Randomization to Sequence 1-10	Sequence	Treatment Phase					Follow-up Phase
			Day 1	Day 2			Period 1	Period 2	Period 3	Period 4	Period 5	
Within 28 days of Qualification Phase		Q1	Phentermine	Placebo		1	A	B	E	C	D	Discharge
		Q2	Placebo	Phentermine		2	B	C	A	D	E	–7 ±3 days after final dose given at the last treatment period
						3	C	D	B	E	A	
						4	D	E	C	A	B	
						5	E	A	D	B	C	
						6	D	C	E	B	A	
						7	E	D	A	C	B	
						8	A	E	B	D	C	
						9	B	A	C	E	D	
						10	C	B	D	A	E	

Qualification phase: 2 period, 2 sequence cross-over with 5-day washout before treatment period.
Treatment phase: 5-period, 10 sequence cross-over.
Treatment A: Oveporexton 6 mg.
Treatment B: Oveporexton 18 mg.
Treatment C: Oveporexton 30 mg.
Treatment D: Phentermine (active comparator) 75 mg.
Treatment E: Placebo.

Qualification Phase

Eligible participants underwent screening (within 28 days before dosing) and an inpatient qualification phase (Day –1 through Day 3) to determine their ability to discriminate the drug effects of phentermine 75 mg versus placebo and tolerate phentermine.

- Treatment QA: 75 mg of phentermine
- Treatment QP: matching placebo

Participants will be required to meet all of the following qualification criteria to be eligible to enter the treatment phase:

1. The participant continues to meet all of the inclusion criteria and none of the exclusion criteria.
2. The participant satisfactorily completes the qualification phase, is able to tolerate phentermine, and general behavior suggests that the participant could successfully complete the trial, as judged by the investigational site staff.
3. On the assessment of drug liking (“at the moment” Drug Liking VAS):
   a) The participant ’ s Emax in response to phentermine is numerically ⩾15 points higher than that of placebo, and the participant has an Emax ⩾65 points with phentermine.
   b) The participant has an acceptable placebo response, defined as an Emax between 40 and 60 points inclusive (that is, a score considered neutral on the scale, meaning neither like nor dislike).
4. The participant has acceptable overall responses to phentermine and placebo on the VAS measures, as judged by the investigational site staff.

After the qualification phase, eligible participants who meet these qualification criteria will remain confined until the end of the treatment phase. The last trial intervention administration in the

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qualification phase and the first trial intervention administration in the treatment phase will be separated by a washout interval of at least 5 days, exceeding 5 half-lives of phentermine (~20 hours).

Treatment Phase

The treatment phase is based on a 5-treatment, 10-sequence, 5-period Williams square crossover design. Treatments were:

- Treatment A: Oveporexton 6 mg
- Treatment B: Oveporexton 18 mg
- Treatment C: Oveporexton 30 mg
- Treatment D: Phentermine 75 mg (active comparator)
- Treatment E: placebo

Participants received each treatment as a single oral dose in randomized sequence (double-dummy). Each treatment period was separated by a ≥7-day washout based on the oveporexton half-life (16–28 hours). PD, PK, and safety assessments were performed up to 24 hours postdose.

Approximately 50 qualified participants will be randomized equally to the 10 sequences in the treatment phase with the intent to ensure that at least 40 participants are in the modified completer analysis set.

For the Day 43 follow-up visit, a minimum of 3 documented telephone calls must be attempted to contact any participant (or their legally authorized representative) for the last scheduled visit.

Participants will be considered as having completed the trial if they successfully complete the Treatment phase and are discharged from the site.

The Schedule of assessments is presented in Table 1 and Table 2 for different Phases, respectively.

Table 1. Schedule of Activities Part A: Schedule of Procedures for the Screening and Qualification Phases (partial)

	Screening [a]	Qualification Phase													
			Trial Days 1 and 2												
			Hours Postdose [b]												
Day	Trial Days -28 to -2	Trial Day -1 (Check-in)	Pre	0	0.5	1	1.5	2	2.5	3	4	6	8	Trial Day 2 (~23 h After Day 1 Dose)	Trial Day 3 (≥23 h After Day 2 Dose)	ET [c]
Pharmacodynamic Assessments																
THC impairment assessment (if UDS positive for THC) [p]		X														
PD (instrument) training/practice session [q]		X														
VAS [r]			X [s]		X	X	X	X	X	X	X	X	X	X	X	
Take Drug Again VAS, Overall Drug Liking VAS													X	X [t]	X [t]	

a The 28-day screening window may be extended upon sponsor approval. Screening visit assessments can be distributed over multiple days upon clinical investigator discretion.
b For this trial, the critical components are the VAS assessments, and these should be performed as close to the scheduled times defined in this protocol as possible. All other trial assessments to be performed in a consistent order per site's standard practice.
c If a participant should discontinue early during the qualification phase, ET procedures should be performed before discharge (if possible). Timing of discharge is to be determined by the investigator. Timing of ET procedures may also be determined by the investigator. Participants who discontinue after the qualification phase (after Day 3) and before receiving their first dose of trial intervention in the treatment phase need not attend an ET visit.
p Conducted by a clinical investigator using clinical judgment when participant is positive for THC/cannabinoids.
q Retraining is allowed, as needed.
r Includes VASs for Drug Liking, High, Good Effects, Alertness/Drowsiness, Bad Effects, and Any Effects measured at the nominal timepoints.
s At predose, only the VASs for High and Alertness/Drowsiness are administered.
t For Day 2, should be conducted before the Day 2 dosing. For Day 3, site may collect VAS anytime between 23 and 24 hours after dosing. Site should try and complete as close to the Day 2 timing as possible.
Source: Table 1.a in the Sponsor's Protocol Amendment 1.

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Table 2. Schedule of Activities Part B: Schedule of Procedures for the Treatment Phase (partial)

Day	Qualification Washout (Trial Days 4 to 6)	Baseline (Trial Day 7)	Trial Days 8, 15, 22, 29, 36 (Day 1 of Treatment Periods 1, 2, 3, 4, and 5)														Treatment Washout: Trial Days 9, 16, 23, and 30	Treatment Washout: (Days 3-7 of treatment periods) Trial Days 10-14, 17-21, 24-28, and 31-35	Trial Day 37	FU Trial Day 43	ET [b]
			Hours Postdose [a]																		
			Pre	0	0.5	1	1.5	2	2.5	3	3.5	4	6	8	10	12	24				
Window (days)																				±3 [c]	
Pharmacodynamic Assessments																					
PD (instrument) training/practice session		X [d]																			
Drug Liking at this moment VAS, Good, Bad, and Any Effects VAS [a]					X	X	X	X	X	X	X	X	X	X	X	X	X		X [g]		
High, Alertness/Drowsiness VAS [a]			X		X	X	X	X	X	X	X	X	X	X	X	X	X		X [g]		
Take Drug Again VAS, Overall Drug Liking VAS [a]																X	X		X [g]		
Drug Similarity VAS																X					

There will be a minimum of 5-day washout between dosing in the qualification phase and treatment phase. Participants will enter the site the day before dosing (Day -1) of the qualification phase and be confined until the end of the treatment phase (Trial Day 37). In some cases, the site may need to postpone dosing in the treatment phase and in such cases, site may release participant and repeat the baseline/treatment Day -1 procedures upon return to clinic and recheck the participant into the site. Treatment periods will be separated by a minimum of 7 days between dosing.

a For this trial, the critical component are the VAS assessments, and these assessments should be performed as close to the scheduled times defined in this protocol as possible. All other trial assessments to be performed in a consistent order per site's standard practice.

b If a participant should discontinue early during the treatment phase, ET procedures should be performed before discharge (if possible). Timing of discharge is to be determined by the investigator. Timing of ET procedures may also be determined by the investigator.

c The time window for this visit (7 days ±3 days) is measured from Day 1 of Treatment Period 5, which is the last dose given in the trial.

d Predose or Day -1 of treatment period 1 only. Site may randomize participants anytime between confirming eligibility and before dosing.

e Vital signs including pulse rate, respiratory rate, temperature, systolic and diastolic BPs are measured at the nominal time points (±30 minutes). Predose vital signs should be collected within 1 hour prior to dosing. Pulse rate, respiratory rate, systolic and diastolic BP (single measurement) should be measured after a resting period of at least 5 minutes in a supine position. If systolic BP measurement is >160 mm Hg or diastolic BP measurement >100 mm Hg, BP measurement must be repeated in approximately 15 minutes to assess trial intervention discontinuation criteria, as described in the protocol.

f Site should try to complete vital sign assessments within 30 minutes before 2-hour postdose timepoint. If this cannot occur before completing the VAS assessments, site may perform vital sign assessments within approximately 30 minutes after the VAS assessments.

g Performed at 24 hours post Trial Day 36 assessment. For vitals: site should try to complete vital sign assessments within 30 minutes before 24-hour postdose timepoint. If this cannot occur before completing the VAS assessments, site may perform vital sign assessments within approximately 30 minutes after the VAS assessments.

Source: Table 1.b in the Sponsor's Protocol Amendment 1.

3.3 Statistical Methodologies of the Sponsor

Primary endpoint:

- Maximum effect (Emax) for Drug Liking ("at this moment") as assessed by a bipolar VAS (0-100 points).

Key secondary endpoints:

- Overall Drug Liking (Emax), assessed by a bipolar VAS (0-100 points).
- Take Drug Again (Emax), assessed "overall" by a bipolar VAS (0-100 points).
- High (Emax), assessed "at this moment" by a unipolar VAS (0-100 points).

Other secondary endpoints:

- Bad Drug Effects (Emax) assessed "at this moment" by a unipolar VAS (0-100 points).
- Good Drug Effects (Emax) assessed "at this moment" by a unipolar VAS (0-100 points).
- Occurrence of at least 1 TEAE during the study including the follow-up period, as applicable.

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3.3.1 Sample Size Determination

Assuming the true difference in Drug-Liking VAS peak score (maximum effect, Emax) between phentermine 75 mg and placebo is 25, and the true standard deviation of within participant differences is 21, it was estimated that, in the treatment phase, a sample size of 40 participants in the modified completers analysis set would provide at least 90% power to test each hypothesis for the primary PD endpoint.

3.3.2 Analysis population

Randomized Analysis Set

The Randomized Analysis Set consisted of all participants who were randomized in the Treatment Phase.

Safety Set

The Safety Analysis Set consisted of all participants who received at least 1 dose of trial intervention in the Treatment phase.

Completer Set

The Completer Analysis Set consisted of all participants in the Randomized Analysis Set who completed all treatment periods of the Treatment Phase and had at least 1 response on the VAS for Drug Liking "at this moment" within 2 hours postdose for each treatment.

Stat comment: This definition of a treatment completer is problematic. The correct definition is that a completer should have at least 1 observation within 2 hours of the median Tmax for each active treatment and within 4-hours post dose for placebo for Drug Liking VAS.

Modified Completer Set

The Modified Completer Analysis Set consisted of all participants in the completer analysis set, excluding those whose Drug Liking "at this moment" VAS Emax scores meet any one of the elimination criteria:

- Similar Emax scores (within a 5-points difference) for a participant across all trial treatments (including placebo)
- Emax(phentermine) ≤ 55
- Emax (placebo) - Emax (phentermine) ≥ 5

3.3.3 Statistical Analysis

Primary Analysis

Analysis of the primary endpoint will be performed on the modified completer analysis set. A linear mixed effects model containing treatment, period, sequence, and first-order carryover (if applicable) as fixed effects, and participant as random effect, is planned to be used to evaluate the hypotheses for the primary endpoint. The Kenward-Roger method for calculating denominator degrees of freedom will be used.

Prior to applying the model, homogeneity of variances across treatments will be tested using a restricted likelihood ratio test. If the test is statistically significant at the 0.05 level, variances will be considered heterogeneous. Otherwise, variances will be considered homogeneous.

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If the variances are homogeneous, the model will constrain variances to be equal across treatment groups. If variances are heterogeneous, the model will allow unequal variances across treatment groups.

After determining whether the treatment variance is homogeneous or heterogeneous, the residuals from the model will be investigated for normality using the Shapiro-Wilk W-test. If the test has p-value <0.05, the residuals will be considered not normally distributed. Otherwise, the residuals will be considered normally distributed.

If the residuals are normally distributed, it will be determined whether the carryover effects should be included in the model. Carryover effects are defined as the effect of the treatment administered in the previous treatment period. If the carryover effect is found to be significant at a level of 0.25, then it will be included in the mixed-effects model as a fixed effect. Otherwise, carryover effect will be dropped from the model.

If the residuals are not normally distributed, the distribution of the paired difference for each contrast will be examined in terms of normality and skewness. Each paired difference will be investigated for normality using the Shapiro-Wilk W-test. If the test has p-value ≥0.05, the paired difference will be considered normally distributed, and a paired t-test will be used for analysis. If the paired difference is not normally distributed, that is, the W-test has p-value <0.05, the following criteria on skewness will be used to determine whether the paired t-test or sign test is used for testing:

a) If the alternative hypothesis is upper-tailed, and skewness is [0, 0.5], the paired t-test will be used.

b) If the alternative hypothesis is upper-tailed, and skewness <0 or skewness >0.5, the sign test will be used.

c) If the alternative hypothesis is lower-tailed, and skewness is [-0.5, 0], the paired t-test will be used.

d) If the alternative hypothesis is lower-tailed, and skewness <-0.5 or skewness >0, the sign test will be used.

e) If the alternative hypothesis is two-tailed, and skewness is [-0.5, 0.5], the paired t-test will be used.

f) If the alternative hypothesis is two-tailed, and skewness <-0.5 or skewness >0.5, the sign test will be used.

If the sign test is used for analysis, the median of the paired difference, first quartile (Q1), third quartile (Q3), 1-sided 95% confidence interval (CI), and p-value from the sign test will be displayed (Hollander and Wolfe 1999). Note that the p-value of the sign test excludes paired differences in scores that are equal to zero after subtracting the margin from the differences. The calculation of the CI does not exclude any paired differences (Hollander and Wolfe 1999). The conclusions will be based on p-values.

If the paired t-test is used for analysis, the mean difference, SE, 1-sided 95% CI, and p-value from the t-test will be displayed.

If a mixed effects model is used for analysis, the least squares mean difference, SE, 1-sided 95% CI, and p-value from the contrast test will be displayed.

3.3.4 Hypothesis testing

Primary Endpoint Analysis

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• Positive control phentermine (C) vs placebo (P)

Does phentermine (C) produce mean responses that show a greater abuse potential compared to placebo (P)?

$$H_o: \mu_C - \mu_P \leq 15 \text{ vs. } H_a: \mu_C - \mu_P > 15, \ \delta_1 = 15 \qquad (1)$$

where μ_C and μ_P are the mean Drug Liking VAS Emax for phentermine and placebo, respectively. The margin of 15 aligns with previous studies of this type (Braeckman et al. 2019; Shram et al. 2022).

• Test drug TAK-861 (T) vs positive control phentermine (C)

Does TAK-861 produce mean responses that show less abuse potential compared to positive control, phentermine (C)?

$$H_o: \mu_C - \mu_T \leq \delta_2 \text{ vs. } H_a: \mu_C - \mu_T > \delta_2, \quad \delta_2 = 0 \qquad (2)$$

where μ_C and μ_T are the mean Drug Liking VAS Emax for phentermine and TAK-861, respectively. This hypothesis will be tested separately for each TAK-861 dose. Rejection of each null hypothesis would suggest lower relative abuse potential of TAK-861 compared to phentermine.

The evaluation of absolute abuse potential of OVEPOREXTON will be the comparison of OVEPOREXTON versus placebo. The following hypothesis will be tested for each dose level of OVEPOREXTON compared to placebo:

1. A: OVEPOREXTON dose 1 vs. D: placebo
2. B: OVEPOREXTON dose 2 vs. D: placebo

• Test drug TAK-861 (T) vs placebo (P)

Does TAK-861 produce mean responses that show similar abuse potential compared to placebo (P)?

$$H_o: \mu_T - \mu_P \geq \delta_3 \text{ vs. } H_a: \mu_T - \mu_P < \delta_3, \ \delta_3 = 11 \qquad (3)$$

where μ_T and μ_P are the mean Drug Liking VAS Emax for placebo and TAK-861, respectively. This hypothesis will be tested separately for each TAK-861 dose. Rejection of each null hypothesis would suggest that TAK-861 does not produce an abuse-related signal. The margin of 11 was selected based on Chen and Boson (Chen and Bonson 2013). Assuming the true difference in Drug-Liking VAS peak score (maximum effect, Emax) between phentermine 75 mg and placebo is 25, and the true standard deviation of within-participant differences is 21, a total of 40 participants in the modified completers analysis set is needed to ensure at least 90% power with a margin of 15 and an upper-tailed test with significance level of 0.05, using a paired t-test.

The above hypotheses will be tested sequentially, and no adjustments will be made for multiplicity.

Secondary Endpoints

The following hypotheses will be evaluated for key and other secondary endpoints. Comparisons among treatments will be evaluated at 1-sided significance level 0.05 for hypothesis 1 and 2, and 2-sided significance level 0.10 for hypothesis 3.

Hypothesis 1, Positive control (phentermine) (C) versus placebo (P):

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$$H_0: \mu_C - \mu_P \leq 0 \text{ vs. } H_a: \mu_C - \mu_P > 0$$

Hypothesis 2, Positive control (phentermine) (C) versus each dose of TAK-861 (T):

$$H_0: \mu_C - \mu_T \leq 0 \text{ vs. } H_a: \mu_C - \mu_T > 0$$

Hypothesis 3, Each dose of TAK-861 (T) versus placebo (P):

$$H_0: \mu_T - \mu_P = 0 \text{ vs. } H_a: \mu_T - \mu_P \neq 0$$

No adjustments to p-values will be made. All hypotheses will be evaluated using nominal pvalues.

Key and other secondary PD endpoints will be analyzed with the same linear mixed effects model or nonparametric approaches (as appropriate) as the primary endpoint analysis, using the modified completer analysis set and following the same strategy for determining the analysis method. If a PD endpoint is based on a VAS that has a baseline (pre-dose) measurement, the mixed effects model for that endpoint will include baseline as a covariate.

Changes in Planned Analysis

No changes were made to the planned analyses described in SAP Version 1.

3.5 Disposition of Subjects

In the qualification phase, a total of 125 participants were randomized and all received at least 1 dose of trial intervention. Fifty (50) participants (40.0%) were eligible for the treatment phase upon completing the qualification phase, while 75 (60%) participants did not meet the criteria to continue into the treatment phase. The most common reason for discontinuation was failure to meet qualification criteria (38.4%), followed by protocol-specified withdrawal criteria (15.2%). Other reasons included withdrawal of consent (5 participants, 4.0%), physician decision (2 participants, 1.6%), and failure to meet continuation criteria (1 participant, 0.8%) (Table 3).

The 50 participants who completed the qualification phase were randomized to treatment sequences in the Treatment Phase, and all (100%) received at least 1 dose of trial intervention. Forty-seven (47) participants (94.0%) completed the treatment phase, and 3 participants (6.0%) discontinued. Reasons for discontinuation were withdrawal of consent (2 participants, 4.0%) and other reasons (1 participant, 2.0%). No discontinuations occurred due to AEs. No participants were randomized but not treated (Table 4).

Table 3 Disposition of Subjects - Treatment Phase (Part 2)

Category	Overall (N=50) n (%) [a]
Randomized	50 (100.0)
Randomized but not treated	0
Dosed	50 (100.0)
Completed phase	47 (94.0)
Discontinued from phase	3 (6.0)
Other [b]	1 (2.0)
Withdrawal of consent	2 (4.0)

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a Percentages are based on the number of participants who were randomized in the treatment phase.
b Reason for discontinuation: participant non-compliance; unable or unwilling to follow the rules.
Source: Table 6 in the Sponsor's study report body

A total of 41 protocol deviations by 28 participants were identified during the treatment phase. All were assessed as minor in severity, with no impact on participant safety or trial integrity.

Table 4 Analysis Sets (Randomized Analysis Set – Treatment Phase)

	Overall (N=50)
Randomized Analysis Set	50 (100.0)
Safety Analysis Set	50 (100.0)
Completer Analysis set	47 (94.0)
Modified Completer Analysis Set	43 (86.0)
PK Analysis Set	50 (100.0)

Source: Table 8 in the Sponsor's study report body

Demographics

The randomized analysis set included 50 participants, most of whom were male (88.0%) and Black or African American (60.0%). The mean (SD) age was 35.0 (6.66) years, and the mean (SD) BMI was 26.81 (3.969) kg/m^2. Additional demographic and baseline characteristics are summarized in Table 5.

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Table 5. Demographic Summary (Randomized Analysis Set – Treatment Phase)

Trait	Category/Statistic	Overall (N=50)
Sex	Female	6 (12.0%)
	Male	44 (88.0%)
Race	Black or African American	30 (60.0%)
	Black or African American, American Indian or Alaska Native	1 (2.0%)
	White	13 (26.0%)
	White, American Indian or Alaska Native	1 (2.0%)
	White, Black, or African American	1 (2.0%)
	White, Native Hawaiian or Other Pacific Islander	1 (2.0%)
	American Indian or Alaska Native	1 (2.0%)
	Asian	1 (2.0%)
	Unknown	1 (2.0%)
White Sub-category	European	7 (14.0%)
	Not Reported	9 (18.0%)
Asian Sub-category	Filipino	1 (2.0%)
Ethnicity	Hispanic or Latino	2 (4.0%)
	Not Hispanic or Latino	48 (96.0%)
Age (yr)	n	50
	Mean	35.0
	SD	6.66
	Minimum	23
	Median	34.0
	Maximum	46
BMI (kg/m^2)	n	50
	Mean	26.81
	SD	3.969
	Minimum	20.3
	Median	26.50
	Maximum	34.0
Height (cm)	n	50
	Mean	175.68
	SD	8.399
	Minimum	153.4
	Median	176.40
	Maximum	195.5
Weight (kg)	n	50
	Mean	82.93
	SD	14.319
	Minimum	53.0
	Median	82.80
	Maximum	112.4

Descriptive statistics for BMI, height, and weight are calculated using the last measurements prior to first dosing.
Percentages are based on the number of participants in the treatment randomization analysis set.
Source: Table 9 in the Sponsor's study report body.

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3.6 Sponsor's Pharmacodynamic Summary and Conclusions

- Primary Endpoint (Drug Liking Emax):
  - The positive control phentermine showed greater drug liking compared to placebo, thereby confirming trial validity.
  - At the 6 mg dose of oveporexton, Emax for Drug Liking "at this moment" was significantly lower than phentermine, supporting lower drug liking relative to active control. Supratherapeutic doses (18 and 30 mg) did not demonstrate abuse potential less than that of phentermine. None of the oveporexton doses showed abuse potential similar to placebo.
- Secondary Endpoints (Overall Drug Liking, Take Drug Again, " High " VAS):
  - Phentermine demonstrated significantly greater effects than placebo on key secondary endpoints, further demonstrating the sensitivity of the endpoints and trial.
  - At 6 mg, oveporexton consistently demonstrated lower effects than phentermine for all 3 key secondary endpoints (Overall Drug Liking, Take Drug Again and High VAS).
  - At higher doses (18 and 30 mg), oveporexton were similar to those of phentermine, with no statistically significant differences.
- Additional Subjective Measures (Good/Bad Drug Effects, Any Drug Effects, Alertness/Drowsiness):
  - Results for Good Drug Effects were similar to those of High VAS.
  - Bad Drug Effects were minimal with phentermine and oveporexton doses and comparable to placebo.
  - Dose-related increases were observed for Any Drug Effects and Alertness/Drowsiness, with higher oveporexton doses showing effects comparable to phentermine.
- Drug Similarity VAS: Phentermine and oveporexton were both rated as having similarity to stimulants.

Stat comment: The statement regarding the validity of the study is valid only for the analysis based on the primary endpoint, but for the secondary endpoints, the validity of this statement may be uncertain due to the unadjusted margins used in the analyses.

3.7 Reviewer's Assessment

The statistical analysis by this reviewer used the modified completer population (MCP).

There was one subject receiving oveporexton 6 mg with missing visit at hour 1 in the Treatment Phase.

This missing outcome occurred within two hours of Tmax for determining the Emax score of drug liking VAS (the primary endpoint), therefore, they could affect the primary analysis.

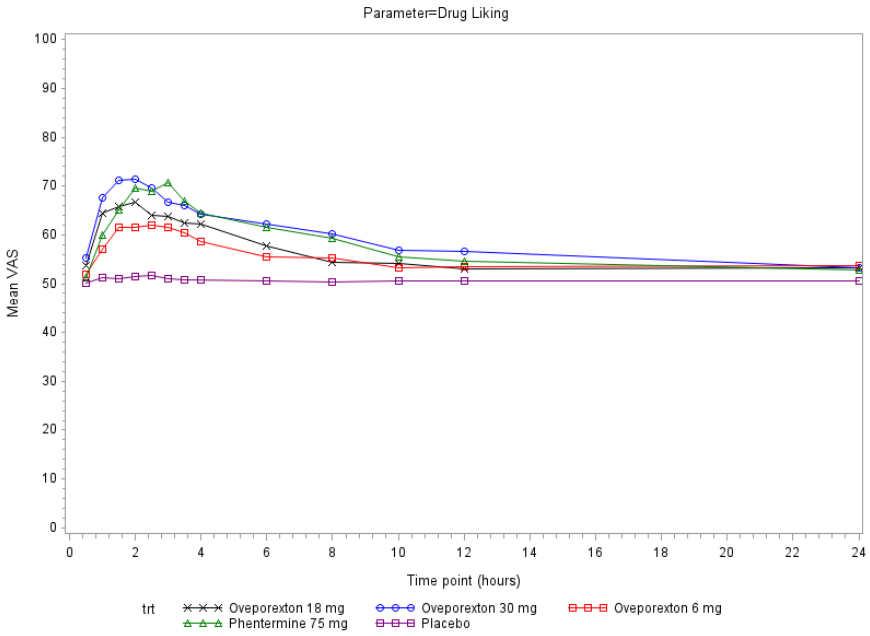
3.7.1 Descriptive Analysis

Time Course of Outcomes: The mean time course profiles by treatment for Drug Liking VAS (Figure 2), Overall Drug Liking VAS (Figure 3) and Take Drug Again VSA (Figure 4), High VAS (Figure 5), Good Effects VAS (Figure 6), Bad Effects VAS (Figure 7), Any Effects VAS (Figure 8), Alertness/Drowsiness VAS (Figure 9), show that the mean responses to different measurements peaked around 2 to 3 hours after treatment administration, and the peak time for Oveporexton came earlier than for Phentermine 75 mg.

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All showed more similar trends among oveporexton doses and phentermine 75 mg, distinct from that of placebo.

Figure 2: Mean Time course of Drug Liking VAS (bipolar) (MCP, N=43**).**



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Figure 3: Mean Time course of Overall Drug Liking VAS (bipolar) (MCP, N=43**).**

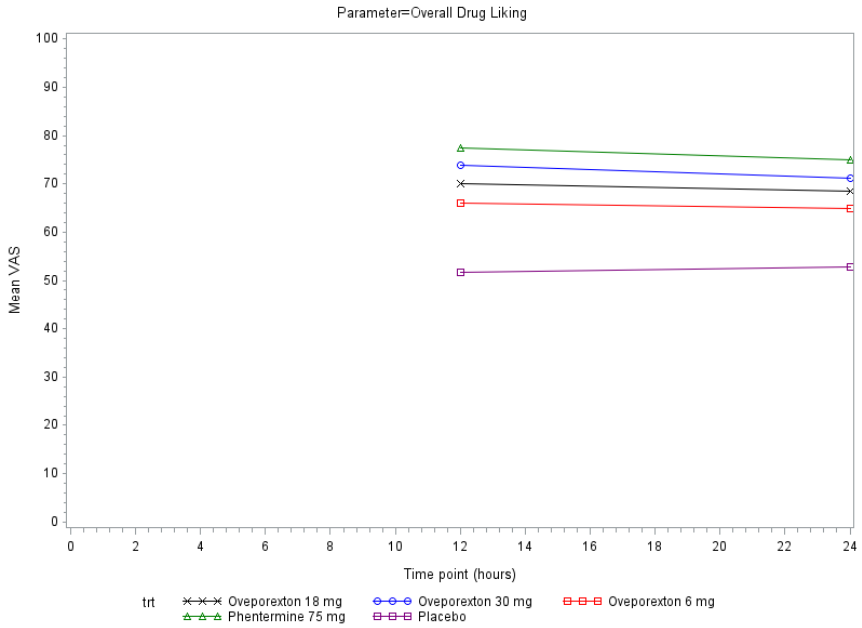


Figure 4: Mean Time course of Take Drug Again VAS (bipolar) **(MCP, N=43)**.

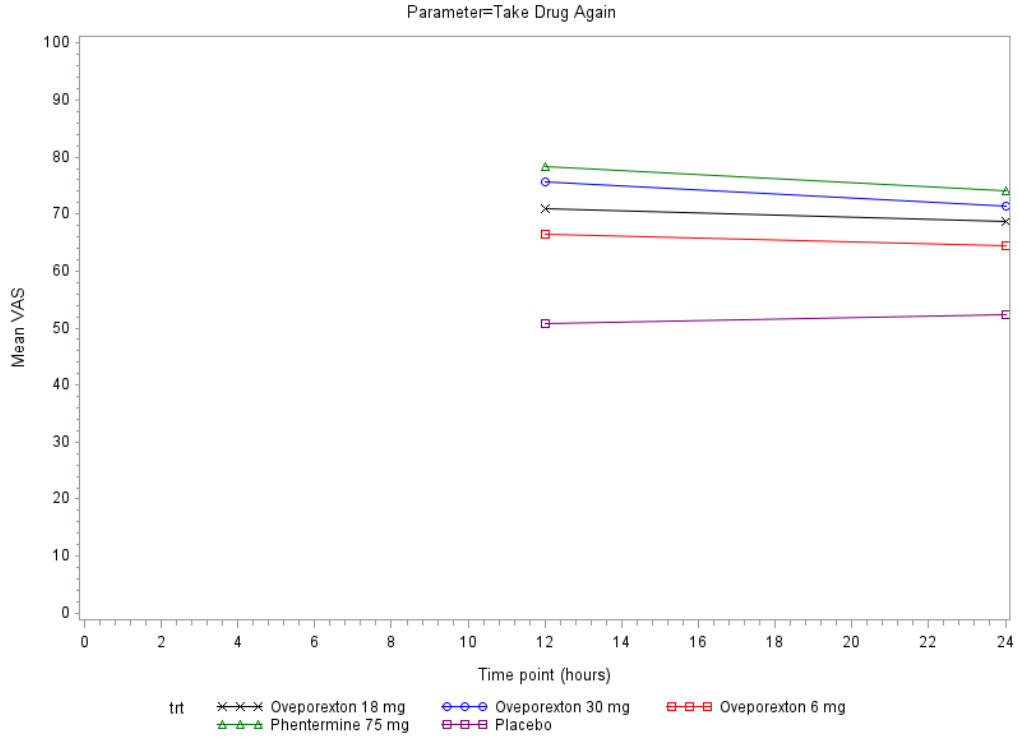
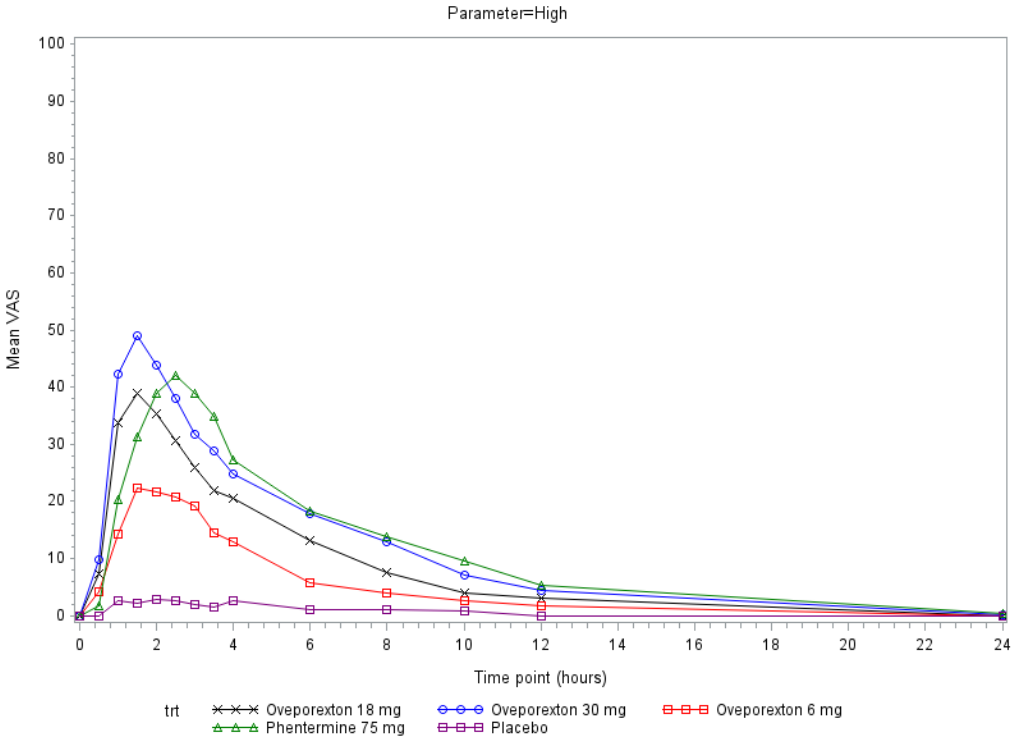


Figure 5: Mean Time course of Feeling High VAS (unipolar) (MCP, N=43).



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Figure 6: Mean Time courses of Good Drug Effects VAS (unipolar) (MCP, N=43).

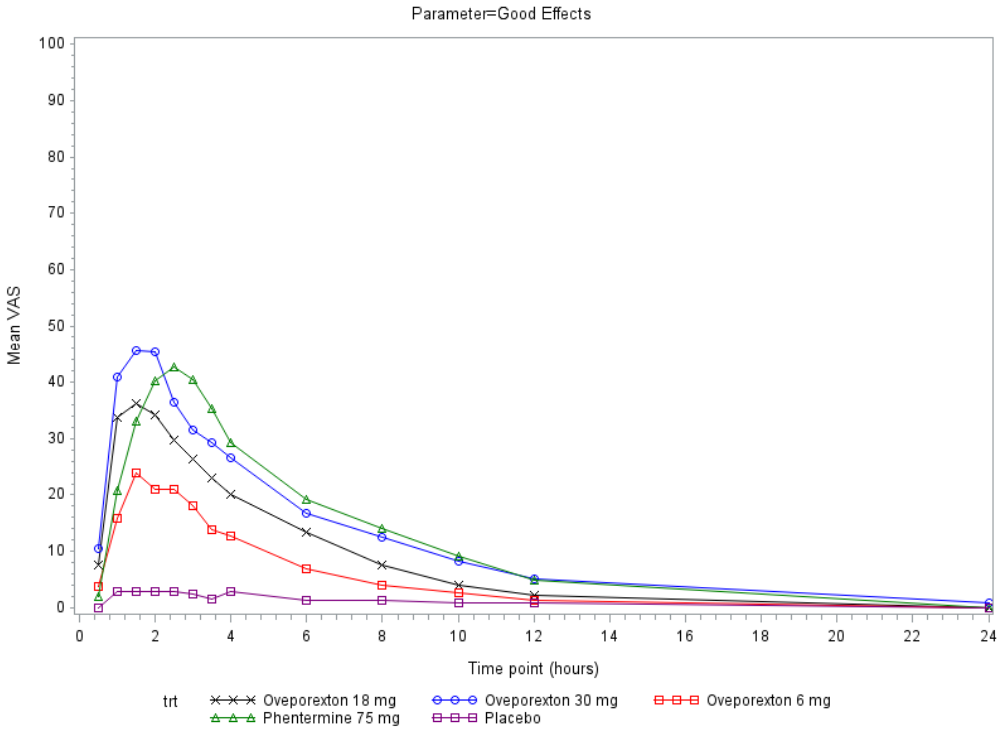


Figure 7: Mean Time courses of Bad Drug Effects VAS (unipolar) (MCP, N=43).

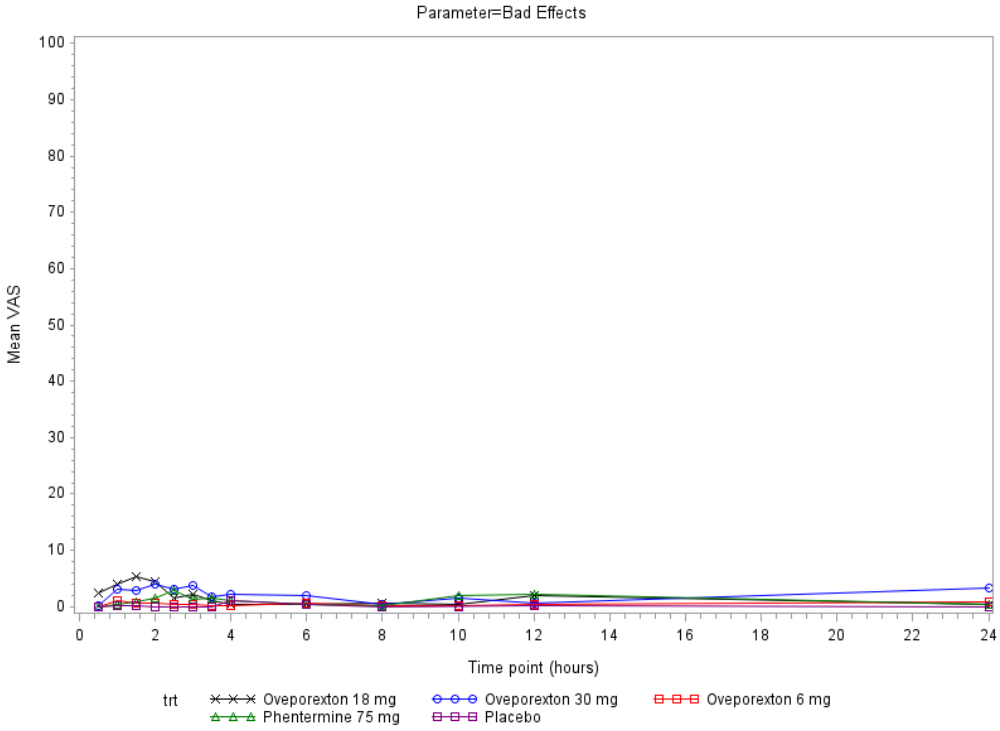


Figure 8: Mean VAS Time courses of Any Effects (unipolar VAS) **(MCP, N=43)**.

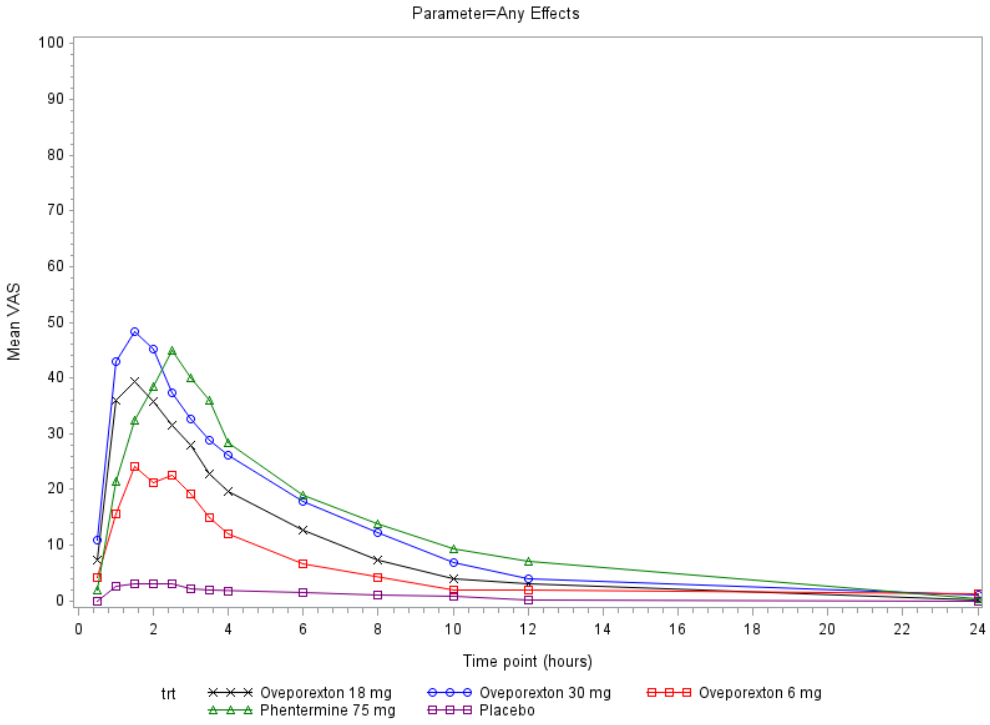
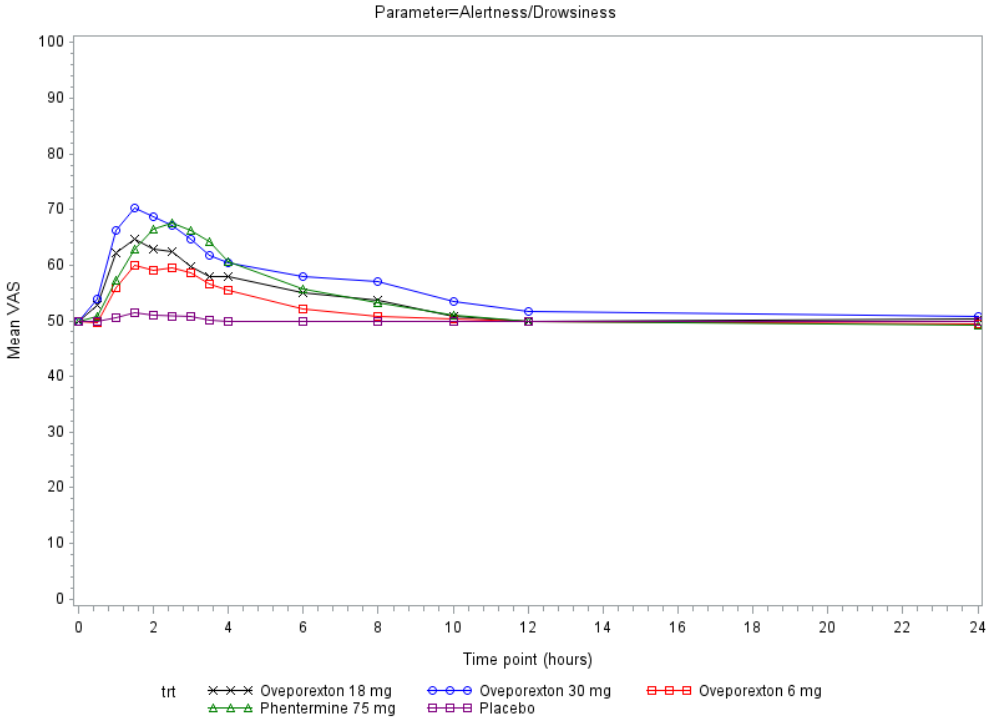


Figure 9: Mean VAS Time courses of Alertness/Drowsiness (Bipolar VAS) (MCP, N=43).



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Abnormal responses of subjects to propofol and placebo:

Figure 10 compared the subjects' Drug Liking VAS Emax scores between the positive control (phentermine) and placebo in the Qualification (subplot A) and Treatment phases (subplot B), respectively. Based on the predefined Qualification criteria for selecting subjects to enter the Treatment Phase, the Emax scores to the placebo should fall in the region 40-60 (the two blue lines) while the Emax scores to the positive control should be above 65 (the green line).

For Drug Liking VAS, this reviewer identified that few subjects had abnormal responses to phentermine and placebo in the completer population:

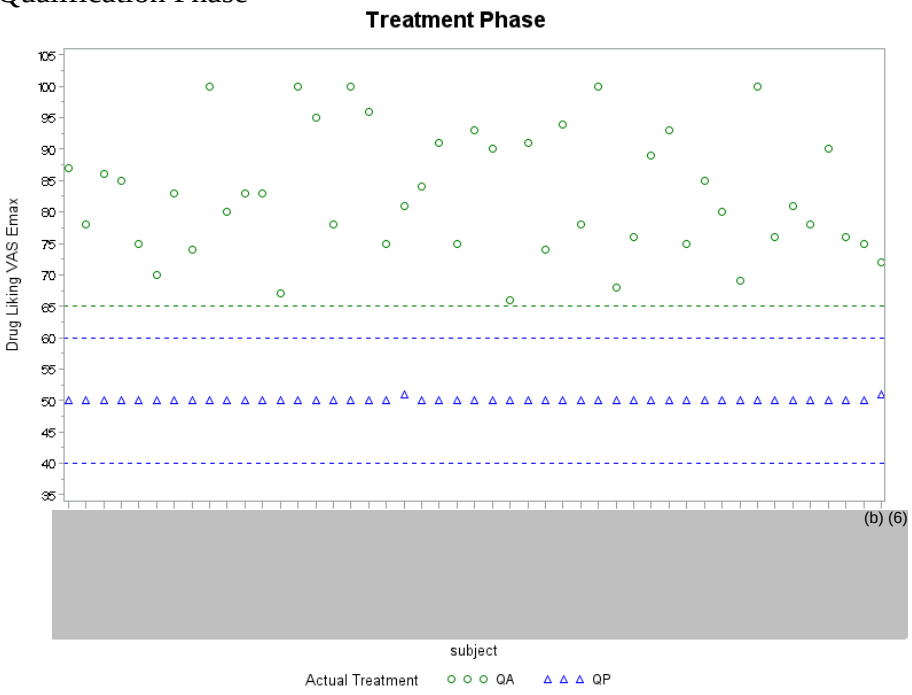
In the Qualification Phase, no abnormal responses to treatments were observed.

In the Treatment Phase, two subjects ((b) (6)), had their Emax(Phentermine) ≤ Emax(placebo), two subjects ((b) (6) ,) had Emax scores to placebo larger than 65, and four subjects, (b) (6) with Emax(phentermine) ⩽55 who were excluded from Modified Completer Population as seen in Figure 12B.

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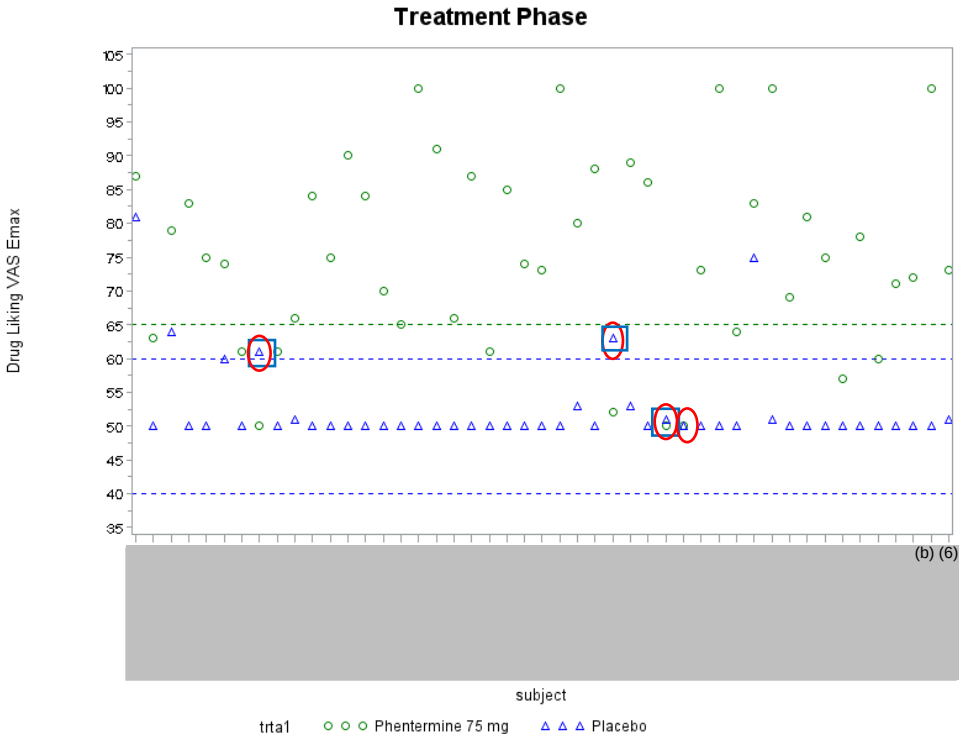
Figure 10: Drug Liking VAS Emax to The Positive Control and Placebo Treatment in A: Qualification and B: Treatment Phase (Completer population, N=47)

A. Qualification Phase



QP: Phentermine 75 mg (Qual); QA: Placebo (Qual)

B: Treatment Phase

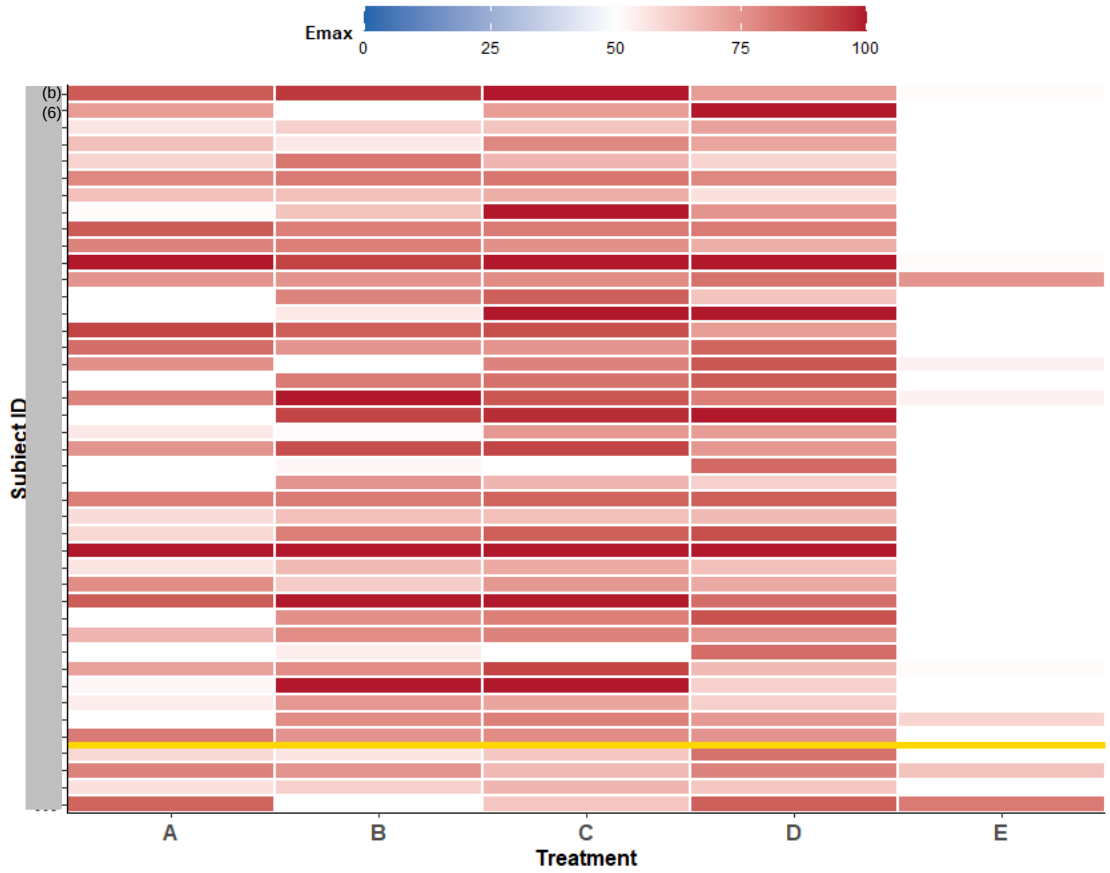


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◯: excluded from completer population; ☐ : Emax(Phentermine 75 mg) ≤Emax(placebo)

The heatmap of Emax for Drug Liking VAS by treatment is shown in Figure 11. Note the orange line on the heat map separates females from males. It is obvious that subjects have similar responses to oveporexton doses and phentermine 75 mg, distinct from that of the placebo.

Figure 13: Heatmap for Drug Liking VAS Emax in the Treatment Phase (Completer population, N=47)



Treatment A: Oveporexton 6 mg. Treatment B: Oveporexton 18 mg. Treatment C: Oveporexton 30 mg.
Treatment D: Phentermine (active comparator) 75 mg. Treatment E: Placebo.

The descriptive statistics of the primary and the key and other secondary endpoints are summarized in Table 6. The table lists the mean, standard deviation (SD), minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3), and maximum (Max) for the treatments in the study. These results are consistent with those of the sponsor's summary statistics on MCP II, showing similar responses to oveporexton in the respective doses and phentermine 75 mg but distinct from that of the placebo for all these PD endpoints.

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Table 6. Descriptive Analysis of the Primary and Secondary Endpoints (MCP, N=43)

Endpoint	Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Drug Liking - Emax	Oveporexton 6 mg	43	67.8	15.5	50	52.0	65	79.0	100
Drug Liking - Emax	Oveporexton 18 mg	43	73.9	15.2	50	61.0	75	81.0	100
Drug Liking - Emax	Oveporexton 30 mg	43	79.6	13.6	50	69.0	79	91.0	100
Drug Liking - Emax	Phentermine 75 mg	43	78.0	12.2	57	69.0	75	87.0	100
Drug Liking - Emax	Placebo	43	52.1	6.4	50	50.0	50	50.0	81
Overall Drug Liking - Emax	Oveporexton 6 mg	43	67.6	16.7	43	50.0	66	80.0	100
Overall Drug Liking - Emax	Oveporexton 18 mg	43	72.5	22.4	0	58.0	75	89.0	100
Overall Drug Liking - Emax	Oveporexton 30 mg	43	76.1	22.0	0	65.0	78	97.0	100
Overall Drug Liking - Emax	Phentermine 75 mg	43	79.0	14.9	51	68.0	77	92.0	100
Overall Drug Liking - Emax	Placebo	43	53.0	10.7	38	50.0	50	50.0	98
Take Drug Again - Emax	Oveporexton 6 mg	43	67.6	18.2	44	50.0	64	79.0	100
Take Drug Again - Emax	Oveporexton 18 mg	43	72.9	22.8	0	58.0	73	94.0	100
Take Drug Again - Emax	Oveporexton 30 mg	43	78.3	22.3	0	66.0	78	100.0	100
Take Drug Again - Emax	Phentermine 75 mg	43	80.4	15.9	39	69.0	77	96.0	100
Take Drug Again - Emax	Placebo	43	53.2	10.2	50	50.0	50	50.0	93
Feeling High - Emax	Oveporexton 6 mg	43	30.8	29.9	0	4.0	23	57.0	97
Feeling High - Emax	Oveporexton 18 mg	43	48.2	29.6	0	17.0	52	73.0	100
Feeling High - Emax	Oveporexton 30 mg	43	60.9	27.3	0	37.0	66	82.0	100
Feeling High - Emax	Phentermine 75 mg	43	52.4	27.1	0	36.0	57	73.0	97
Feeling High - Emax	Placebo	43	4.3	13.9	0	0.0	0	0.0	63

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Table 6. Descriptive Analysis of the Primary and Secondary Endpoints (MCP, N=43) (Continued)

Endpoint	Treatment	N	Mean	SD	Min	Q1	Median	Q3	Max
Good Drug Effect: Emax	Oveporexton 6 mg	43	31.2	30.0	0	1.0	26	64.0	93
Good Drug Effect: Emax	Oveporexton 18 mg	43	47.1	29.9	0	16.0	51	73.0	95
Good Drug Effect: Emax	Oveporexton 30 mg	43	58.9	28.9	0	33.0	65	79.0	100
Good Drug Effect: Emax	Phentermine 75 mg	43	54.7	25.4	7	35.0	57	74.0	100
Good Drug Effect: Emax	Placebo	43	4.7	14.6	0	0.0	0	0.0	66
Bad Drug Effects: Emax	Oveporexton 6 mg	43	2.6	7.2	0	0.0	0	0.0	37
Bad Drug Effects: Emax	Oveporexton 18 mg	43	8.5	20.4	0	0.0	0	7.0	100
Bad Drug Effects: Emax	Oveporexton 30 mg	43	11.7	23.1	0	0.0	0	9.0	97
Bad Drug Effects: Emax	Phentermine 75 mg	43	5.8	15.2	0	0.0	0	3.0	83
Bad Drug Effects: Emax	Placebo	43	1.7	7.7	0	0.0	0	0.0	48
Drowsiness/Alertness: Emax	Oveporexton 6 mg	43	64.6	13.6	50	50.0	60	77.0	94
Drowsiness/Alertness: Emax	Oveporexton 18 mg	43	71.4	13.9	50	60.0	71	81.0	100
Drowsiness/Alertness: Emax	Oveporexton 30 mg	43	76.2	11.7	50	70.0	76	83.0	100
Drowsiness/Alertness: Emax	Phentermine 75 mg	43	73.5	11.1	50	65.0	74	83.0	99
Drowsiness/Alertness: Emax	Placebo	43	51.6	3.8	50	50.0	50	50.0	65
Any Drug Effects: Emax	Oveporexton 6 mg	43	32.5	31.3	0	3.0	25	64.0	95
Any Drug Effects: Emax	Oveporexton 18 mg	43	49.4	30.3	0	18.0	55	75.0	100
Any Drug Effects: Emax	Oveporexton 30 mg	43	59.8	25.8	8	34.0	63	83.0	100
Any Drug Effects: Emax	Phentermine 75 mg	43	53.8	26.1	4	36.0	59	75.0	96
Any Drug Effects: Emax	Placebo	43	3.9	13.1	0	0.0	0	0.0	61
AUEC - Drug Liking	Oveporexton 6 mg	43	447.5	82.1	378	388.0	406	489.5	681
AUEC - Drug Liking	Oveporexton 18 mg	43	468.1	81.8	363	402.0	451	522.0	700
AUEC - Drug Liking	Oveporexton 30 mg	43	498.6	97.9	362	417.0	478	568.8	775
AUEC - Drug Liking	Phentermine 75 mg	43	489.5	77.7	392	432.5	465	545.0	702
AUEC - Drug Liking	Placebo	43	393.2	26.8	381	387.5	388	387.5	553
Drug Liking: TEmax	Oveporexton 6 mg	43	1.9	1.4	1	0.5	2	2.5	6
Drug Liking: TEmax	Oveporexton 18 mg	43	2.5	3.7	1	1.0	2	2.5	24
Drug Liking: TEmax	Oveporexton 30 mg	43	3.0	4.2	1	1.0	2	2.5	24
Drug Liking: TEmax	Phentermine 75 mg	43	2.9	2.1	1	2.0	3	3.0	12
Drug Liking: TEmax	Placebo	43	0.8	1.2	1	0.5	1	0.5	8

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3.7.2 Statistical Testing

This reviewer's analysis was first carried out using the mixed-effects model proposed by the sponsor, including treatment, sequence, period and first-order carryover as fixed effects, and subject as a random effect. The assumption of normality for the mixed-effects model was met in either the primary endpoint or the key secondary endpoint Feeling High, but not in the Overall Drug liking and Take Drug Again, as listed in Table 7 at a significant level of 0.05 using Shapiro-Wilk W-test. The null and alternative hypotheses for the normality analysis are:

H_0: Distribution of residuals is normal
H_a: Distribution of residuals is not normal

Table 7 also shows the skewness and p-values of the Shapiro-Wilk W-test for the residual distribution in the mixed-effects model on other secondary endpoints. The endpoints with p-value >0.05 from the normality test were analyzed using the mixed-effects model. The analysis of the mixed-effects model on the primary endpoint showed no concern regarding the carryover effects (p-value=0.1487).

Table 7: The W-Test results for the primary and Key secondary endpoints (MCP, N=43)

Endpoint	skewness	W-statistics	p-value
Drug Liking VAS Emax	-0.01387805	0.992205384	0.310636509
Overall Drug Liking VAS Emax	-0.884698264	0.957647175	5.34612E-06
Take Drug Again VAS Emax	-0.926037709	0.943915711	2.19565E-07
Feeling High VAS	0.064177733	0.995634911	0.8009002
Good Drug Effect VAS Emax	-0.082083105	0.995542153	0.787066405
Bad Drug Effects VAS Emax	3.237687431	0.65545841	0
Alertness/Drowsiness Emax	0.234128435	0.986268347	0.035796013
Any Effects VAS Emax	0.088785341	0.991657855	0.257583026
AUEC - Drug Liking	0.795633623	0.95826837	6.25348E-06
Drug Liking VAS TEmax	5.190644245	0.572662301	0

For the endpoints whose p-values of the Shapiro-Wilk W-test for the residual distribution in the mixed-effects model <0.05, the distribution of the paired difference for each contrast were examined in terms of normality and skewness using the Shapiro-Wilk W-test. Provided N=43 for MCP and based on the normality tests, this reviewer used t-test analysis (one-sample t-test) on paired differences for each contrast, either with a p-value of the normality test >0.05 or those with a p-value <0.05 but satisfying a skewness within [-0.5, 0.5] (ref. Linsen Liu, 2024). Otherwise, the non-parametric sign test was used on those paired differences.

The results of the primary analysis are summarized in Table 8 at a significance level of 0.05 (1-sided) using the sponsor preselected margins for these tests. The null hypothesis of the validation test was rejected with a highly significant level of p-value<.0001. The lower 95% confidence limit of the median difference is 20.8 (see Table 8), suggesting that the median difference between Phentermine 75 mg and placebo is more than 15 points. This analysis supports the study validity.

For testing whether the abuse potential of the positive control Phentermine 75 mg is no higher than the test drug Oveporexton at each planned dose at least 0 point, the data failed to reject the null hypothesis of the relative abuse potential for each Oveporexton dose, except for Oveporexton 6 mg, compared to

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Phentermine 75 mg with p-value > 0.05 (1-sided). As seen in Table 8 for Drug Liking VAS Emax, the lower 95% confidence limit (1-sided) of Phentermine 75 mg – OVEPOREXTON 6 mg was 5.1, suggesting the difference greater than the pre-specified margin of 0 point by the subjects in the treatment phase; while that for Phentermine 75 mg – OVEPOREXTON 18 mg was -1.1, and for Phentermine 75 mg – OVEPOREXTON 30 mg was -5.8, respectively, suggesting the difference less than the pre-specified margin of 0 point by the subjects in the treatment phase.

Since only the low dose of Oveporexton demonstrated a significant difference relative to Phentermine 75 mg while the analysis failed to reject the null hypothesis at the medium and high doses of the test drug, this is sufficient to draw the conclusion about the potential for abuse of Oveporexton. Therefore, the analysis of absolute abuse potential of Oveporexton would be exploratory.

At a level of 0.05 (one-sided), there was no sufficient evidence to reject the null hypothesis of the mean Emax of Drug Liking VAS to the treatment of each Oveporexton dose is higher than that of placebo by 11 points, suggesting that the subjects in the treatment phase more like Oveporexton than placebo.

Table 8: Results of Primary Analysis on Drug Liking VAS Emax (MCP, N=43)

					95% CI*		95% CI**	
Pairwise Comparison	**δ**	Mean diff	SE	p-value	LCL	UCL	LCL	UCL
Phentermine 75 mg - Placebo	15	24.3	2.1	<0.0001	20.8	Inf	20.2	28.5
Phentermine 75 mg - Oveporexton 6 mg	0	9.7	2.7	0.0004	5.1	Inf	4.2	15.2
Phentermine 75 mg - Oveporexton 18 mg	0	3.7	2.9	0.1020	-1.1	Inf	-2.0	9.4
Phentermine 75 mg - Oveporexton 30 mg	0	-1.5	2.6	0.7175	-5.8	Inf	-6.6	3.7
Oveporexton 6 mg - Placebo	11	14.6	2.4	0.9312	-Inf	18.7	9.8	19.5
Oveporexton 18 mg - Placebo	11	20.7	2.5	0.9998	-Inf	24.9	15.6	25.8
Oveporexton 30 mg - Placebo	11	25.8	2.3	>0.9999	-Inf	29.6	21.3	30.4

Note: Analyses were carried out in the Modified Completers Population. p-value was one-sided at alpha=0.05.
test: mixed-effects model
p-value and one-sided confidence limit (*) were from the tests of the following null hypothesis at alpha=0.05:
Positive control vs. placebo (validation), H_0: $\mu_C - \mu_P \leq 15$
Positive control vs. test drug GE-IR (Relative Abuse Potential), H_0: $\mu_C - \mu_T \leq 0$
Test drug vs. Placebo (Absolute Abuse Potential), H_0: $\mu_T - \mu_P \geq 11$
** two-sided confidence limit for the pairwise comparison.
LCL: lower confidence limit, UCL: upper confidence limit. Inf represents infinity.

Table 9 summarized the results of the key secondary endpoints analysis. The results of other secondary endpoints analysis are summarized in Table 10. The analyses were carried out using a margin of 0 for all these analyses, either 1-sided or 2-sided at the significance level of 0.05. Since the margins used for testing the validation and absolute abuse potential by the sponsor were not adjusted to align with the corresponding margins of the primary analysis, the validity of these results on the secondary endpoints remains uncertain as to whether they support the findings of the primary analysis.

For the hypothesis test of the relative abuse potential, the Drug Liking VAS TEmax analyses of all secondary endpoints showed consistent patterns for relative abuse potential between the positive control Phentermine 75 mg and each corresponding dose of Oveporexton:

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- the data rejected the null hypothesis of the relative abuse potential of Oveporexton 6 mg compared to Phentermine 75 mg with a p-value < 0.05 (one-tailed), suggesting that the subjects in this study prefer Phentermine 75 mg to Oveporexton 6 mg;

- the data failed to reject the null hypothesis of the relative abuse potential of Oveporexton (18 mg, or 30 mg) compared to Phentermine 75 mg with p-value > 0.05 (1-sided), suggesting that the subjects' preference for Oveporexton (18 mg, or 30 mg) is not less than their preference for Phentermine 75 mg.

Table 9. Results of Analysis on Key Secondary Endpoints (MCP, n=43).

						95% CI*		95% CI**	
Endpoint	Pairwise Comparison	test	Mean/ Median diff	SE/ Q1,Q3	p-value	LCL	UCL	LCL	UCL
Overall Drug Liking Emax	Phentermine 75 mg - Placebo	t	26.0	2.6	<0.0001	21.6	Inf	20.7	31.3
Overall Drug Liking Emax	Phentermine 75 mg - Oveporexton 6 mg	t	11.4	3.1	0.0004	6.1	Inf	5.0	17.7
Overall Drug Liking Emax	Phentermine 75 mg - Oveporexton 18 mg	s	2.0	-8, 8	0.1620	0	Inf	0	6
Overall Drug Liking Emax	Phentermine 75 mg - Oveporexton 30 mg	s	0.0	-4, 7	0.5000	-1	Inf	-1	3
Overall Drug Liking Emax	Oveporexton 6 mg - Placebo	t	14.6	3.1	>0.9999	9.4	19.8	8.3	20.9
Overall Drug Liking Emax	Oveporexton 18 mg - Placebo	s	26.0	6, 39	>0.9999	16	36	16	36
Overall Drug Liking Emax	Oveporexton 30 mg - Placebo	s	28.0	10, 46	>0.9999	22	38	22	38
Take Drug Again Emax	Phentermine 75 mg - Placebo	s	26.0	15, 46	<0.0001	19	Inf	19	40
Take Drug Again Emax	Phentermine 75 mg - Oveporexton 6 mg	t	12.8	3.2	0.0001	7.3	Inf	6.2	19.3
Take Drug Again Emax	Phentermine 75 mg - Oveporexton 18 mg	s	0.0	-5, 10	0.4340	-1	Inf	-1	4
Take Drug Again Emax	Phentermine 75 mg - Oveporexton 30 mg	s	0.0	-8, 5	0.5000	-3	Inf	-3	4
Take Drug Again Emax	Oveporexton 6 mg - Placebo	t	14.4	3.1	>0.9999	9.1	19.7	8.1	20.8
Take Drug Again Emax	Oveporexton 18 mg - Placebo	s	22.0	5, 44	>0.9999	12	35	12	35
Take Drug Again Emax	Oveporexton 30 mg - Placebo	s	28.0	12, 50	>0.9999	22	47	22	47
Feeling High Emax	Phentermine 75 mg - Placebo	m	48.0	4.1	<0.0001	41.0	Inf	39.7	56.3
Feeling High Emax	Phentermine 75 mg - Oveporexton 6 mg	m	21.6	5.2	0.0001	12.9	Inf	11.2	32.0
Feeling High Emax	Phentermine 75 mg - Oveporexton 18 mg	m	4.1	5.3	0.2238	-4.9	Inf	-6.6	14.8
Feeling High Emax	Phentermine 75 mg - Oveporexton 30 mg	m	-8.6	5.1	0.9513	-17.0	Inf	-18.7	1.6
Feeling High Emax	Oveporexton 6 mg - Placebo	m	26.4	4.4	>0.9999	19.0	33.8	17.5	35.2
Feeling High Emax	Oveporexton 18 mg - Placebo	m	43.9	4.6	>0.9999	36.2	51.5	34.7	53.1
Feeling High Emax	Oveporexton 30 mg - Placebo	m	56.5	4.2	>0.9999	49.4	63.6	48.0	65.0

Note: Analyses were carried out on the Modified Completers Population.
test m: mixed-effects model
t: paired t-test
s: sign-test
p-value and one-sided confidence limit (*) were from the tests of the following null hypothesis at alpha=0.05:
Positive control vs. placebo (validation), H_0: $\mu_C - \mu_P \leq 0$
Positive control vs. test drug GE-IR (Relative Abuse Potential), H_0: $\mu_C - \mu_T \leq 0$
Test drug vs. Placebo (Absolute Abuse Potential), H_0: $\mu_T - \mu_P = 0$
** two-sided confidence limit for the pairwise comparison.
LCL: lower confidence limit, UCL: upper confidence limit. Inf represents infinity.

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Table 10. Results of Analysis on Other Secondary Endpoints (MCP, n=43).

						95% CI*		95% CI**	
Endpoint	Pairwise Comparison	test	Mean/ Median diff	SE/ Q1,Q3	p-value	LCL	UCL	LCL	UCL
Good Drug Effect Emax	Phentermine 75 mg - Placebo	m	49.9	4.0	<0.0001	43.1	Inf	41.8	57.9
Good Drug Effect Emax	Phentermine 75 mg - Oveporexton 6 mg	m	23.3	5.2	<0.0001	14.6	Inf	12.9	33.8
Good Drug Effect Emax	Phentermine 75 mg - Oveporexton 18 mg	m	7.5	5.4	0.0826	-1.4	Inf	-3.2	18.3
Good Drug Effect Emax	Phentermine 75 mg - Oveporexton 30 mg	m	-4.4	5.3	0.7939	-13.2	Inf	-15.0	6.2
Good Drug Effect Emax	Oveporexton 6 mg - Placebo	m	26.5	4.6	>0.9999	18.9	34.2	17.4	35.7
Good Drug Effect Emax	Oveporexton 18 mg - Placebo	m	42.3	4.7	>0.9999	34.4	50.2	32.8	51.8
Good Drug Effect Emax	Oveporexton 30 mg - Placebo	m	54.2	4.6	>0.9999	46.5	62.0	44.9	63.5
Bad Drug Effects Emax	Phentermine 75 mg - Placebo	s	0	0, 3	0.0021	0.0	Inf	0.0	0.0
Bad Drug Effects Emax	Phentermine 75 mg - Oveporexton 6 mg	s	0.0	0, 2	0.0835	0.0	Inf	0.0	0.0
Bad Drug Effects Emax	Phentermine 75 mg - Oveporexton 18 mg	s	0.0	0, 1	0.3238	0.0	Inf	0.0	0.0
Bad Drug Effects Emax	Phentermine 75 mg - Oveporexton 30 mg	s	0.0	-4, 0	0.0758	-1.0	Inf	-1.0	0.0
Bad Drug Effects Emax	Oveporexton 6 mg - Placebo	s	0.0	0, 0	0.8867	0.0	0.0	0.0	0.0
Bad Drug Effects Emax	Oveporexton 18 mg - Placebo	s	0.0	0, 4	0.9824	0.0	0.0	0.0	0.0
Bad Drug Effects Emax	Oveporexton 30 mg - Placebo	s	0.0	0, 6	0.9993	0.0	4.0	0.0	4.0
Alertness/Drowsiness Emax	Phentermine 75 mg - Placebo	t	21.9	1.6	<0.0001	19.1	Inf	18.6	25.2
Alertness/Drowsiness Emax	Phentermine 75 mg - Oveporexton 6 mg	t	9.0	2.0	<0.0001	5.5	Inf	4.9	13.1
Alertness/Drowsiness Emax	Phentermine 75 mg - Oveporexton 18 mg	t	2.1	2.4	0.1845	-1.8	Inf	-2.6	6.9
Alertness/Drowsiness Emax	Phentermine 75 mg - Oveporexton 30 mg	t	-2.7	2.3	0.1198	-6.5	Inf	-7.3	1.9
Alertness/Drowsiness Emax	Oveporexton 6 mg - Placebo	t	13.0	2.1	>0.9999	9.4	16.5	8.7	17.2
Alertness/Drowsiness Emax	Oveporexton 18 mg - Placebo	t	19.8	2.2	>0.9999	16.1	23.4	15.4	24.1
Alertness/Drowsiness Emax	Oveporexton 30 mg - Placebo	t	24.6	2.0	>0.9999	21.3	27.9	20.6	28.6
Any Drug Effects Emax	Phentermine 75 mg - Placebo	m	49.7	4.1	<0.0001	42.9	Inf	41.6	57.9
Any Drug Effects Emax	Phentermine 75 mg - Oveporexton 6 mg		21.3	5.4	0.0001	12.3	Inf	10.5	32.2
Any Drug Effects Emax	Phentermine 75 mg - Oveporexton 18 mg		4.2	5.5	0.2204	-4.9	Inf	-6.7	15.2
Any Drug Effects Emax	Phentermine 75 mg - Oveporexton 30 mg	m	-6.0	5.0	0.8808	-14.4	Inf	-16.0	4.1
Any Drug Effects Emax	Oveporexton 6 mg - Placebo	m	28.4	4.7	>0.9999	20.5	36.4	18.9	37.9
Any Drug Effects Emax	Oveporexton 18 mg - Placebo	m	45.5	4.8	>0.9999	37.5	53.5	35.9	55.1
Any Drug Effects Emax	Oveporexton 30 mg - Placebo	m	55.7	4.3	>0.9999	48.6	62.8	47.2	64.2

Note: Analyses were carried out on the Modified Completers Population.
test m: mixed-effects model; t: paired t-test; s: sign-test
p-value and one-sided confidence limit (*) were from the tests of the following null hypothesis at alpha=0.05:
Positive control vs. placebo (validation), H_0: $\mu_C - \mu_P \leq 0$
Positive control vs. test drug GE-IR (Relative Abuse Potential), H_0: $\mu_C - \mu_T \leq 0$
Test drug vs. Placebo (Absolute Abuse Potential), H_0: $\mu_T - \mu_P = 0$
** two-sided confidence limit for the pairwise comparison.
LCL: lower confidence limit, UCL: upper confidence limit. Inf represents infinity.

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Table 10. Results of Analysis on Other Secondary Endpoints (MCP, n=43). Cont.

						95% CI*		95% CI**	
Endpoint	Pairwise Comparison	test	Mean/ Median diff	SE/ Q1,Q3	p-value	LCL	UCL	LCL	UCL
AUEC - Drug Liking	Phentermine 75 mg - Placebo	s	74.0	41.5, 154.5	<0.0001	51.8	Inf	51.8	98.8
AUEC - Drug Liking	Phentermine 75 mg - Oveporexton 6 mg	s	30.8	2.3, 78.5	0.0003	14.3	Inf	14.3	50.3
AUEC - Drug Liking	Phentermine 75 mg - Oveporexton 18 mg	t	21.4	14.0	0.0674	-2.2	Inf	-6.9	49.7
AUEC - Drug Liking	Phentermine 75 mg - Oveporexton 30 mg	t	-9.1	11.6	0.2189	-28.6	Inf	-32.5	14.3
AUEC - Drug Liking	Oveporexton 6 mg - Placebo	s	15.0	0, 80.3	>0.9999	3.0	59.5	3.0	59.5
AUEC - Drug Liking	Oveporexton 18 mg - Placebo	s	51.8	14.5, 132.0	>0.9999	18.3	100.0	18.3	100.0
AUEC - Drug Liking	Oveporexton 30 mg - Placebo	s	77.3	27.5, 159.8	>0.9999	44.0	110.8	44.0	110.8
Drug Liking VAS TEmax	Phentermine 75 mg - Placebo	t	2.1	0.4	<0.0001	1.4	Inf	1.3	2.8
Drug Liking VAS TEmax	Phentermine 75 mg - Oveporexton 6 mg	s	0.5	0, 1.5	0.0001	0.5	Inf	0.5	1.0
Drug Liking VAS TEmax	Phentermine 75 mg - Oveporexton 18 mg	s	0.5	0, 1.5	<0.0001	0.5	Inf	0.5	1.5
Drug Liking VAS TEmax	Phentermine 75 mg - Oveporexton 30 mg	s	0.5	0, 1.5	0.0008	0.5	Inf	0.5	1.0
Drug Liking VAS TEmax	Oveporexton 6 mg - Placebo	s	1.0	0, 2	>0.9999	0.5	2.0	0.5	2.0
Drug Liking VAS TEmax	Oveporexton 18 mg - Placebo	s	1.0	0.5, 2	>0.9999	0.5	1.5	0.5	1.5
Drug Liking VAS TEmax	Oveporexton 30 mg - Placebo	s	1.0	0.5, 2	>0.9999	0.5	1.5	0.5	1.5

Note: Analyses were carried out on the Modified Completers Population.
test m: mixed-effects model
t: paired t-test
s: sign-test
p value and one sided confidence limit (*) were from the tests of the following null hypothesis at alpha 0.05:
Positive control vs. placebo (validation), H_0: $\mu_C - \mu_P \leq 0$
Positive control vs. test drug GE-IR (Relative Abuse Potential), H_0: $\mu_C - \mu_T \leq 0$
Test drug vs. Placebo (Absolute Abuse Potential), H_0: $\mu_T - \mu_P = 0$
** two-sided confidence limit for the pairwise comparison.
LCL: lower confidence limit, UCL: upper confidence limit. Inf represents infinity.

Sensitivity Analysis

Currently we recommend all statistical analyses in a HAP study being conducted on a Modified

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Completer Population (MCP). A sensitivity analysis is carried out here based on the Completers population to see the data robustness.

The analysis results of completers population for the primary outcome of Drug Liking Emax are summarized in Table 11.

Table 11: Results of Primary Analysis on Drug Liking VAS Emax (Completers Population, N=47)

					95% CI*		95% CI**	
Pairwise Comparison	δ	Mean diff	SE	p-value	LCL	UCL	LCL	UCL
Phentermine 75 mg - Placebo	15	21.7	2.2	0.0018	18.0	Inf	17.3	26.1
Phentermine 75 mg - Oveporexton 6 mg	0	7.8	2.8	0.0032	3.2	Inf	2.3	13.4
Phentermine 75 mg - Oveporexton 18 mg	0	2.0	2.9	0.2489	-2.9	Inf	-3.8	7.8
Phentermine 75 mg - Oveporexton 30 mg	0	-3.6	2.8	0.8988	-8.4	Inf	-9.3	2.0
Oveporexton 6 mg - Placebo	11	13.9	2.3	0.8924	-Inf	17.7	9.3	18.5
Oveporexton 18 mg - Placebo	11	19.7	2.4	0.9996	-Inf	23.8	14.8	24.6
Oveporexton 30 mg - Placebo	11	25.3	2.4	>0.9999	-Inf	29.3	20.6	30.1

Note: Analyses were carried out in the Completers population. p-value was one-sided at alpha=0.05.
test: mixed-effects model
p-value and one-sided confidence limit (*) were from the tests of the following null hypothesis at alpha=0.05:
Positive control vs. placebo (validation), H_0: $\mu_C - \mu_P \leq 15$
Positive control vs. test drug GE-IR (Relative Abuse Potential), H_0: $\mu_C - \mu_T \leq 0$
Test drug vs. Placebo (Absolute Abuse Potential), H_0: $\mu_T - \mu_P \geq 11$
** two-sided confidence limit for the pairwise comparison.
LCL: lower confidence limit, UCL: upper confidence limit. Inf represents infinity.

The Drug Liking Emax analysis for the completers population was consistent with that of the modified completers population.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues

There was one subject receiving oveporexton 6 mg with missing visit at hour 1 in the Treatment Phase. This missing outcome in responses to drug liking VAS occurred within two hours of Tmax to determine the corresponding Emax, that might affect the primary analysis of this treatment. However, it was not sufficient to change the conclusion.

4.2 Conclusions and Recommendations

The reviewer's primary analysis was conducted on Modified Completers population Set (n=43). Considering the overall evidence from the data, this reviewer confirmed the following findings:

1. The validation test for comparing the mean difference of Drug Liking VAS Emax between Phentermine 75 mg and placebo with a test margin of 15 points was statistically significant at alpha level of 0.05 (1-sided) and the lower 95% confidence limit (one-sided) of the mean difference was 20.8, supporting the study validity.

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2. For the relative abuse potential of Oveporexton at each dose in this study compared to Phentermine 75 mg with a margin of 0 point, the data rejected the hypothesis of the mean Emax score of Drug Liking VAS in subjects receiving Phentermine 75 mg being less than or equal to those receiving Oveporexton 6 mg at alpha level of 0.05 (one-sided), suggesting that the subjects in this study prefer Phentermine 75 mg to Oveporexton 6 mg. However, the data failed to reject the null hypothesis of the relative abuse potential of the higher doses of Oveporexton (18 mg, or 30 mg) compared to Phentermine 75 mg with p-value > 0.05 (1-sided), suggesting that the subjects in this study liked Oveporexton no less than Phentermine 75 mg.

   Furthermore, analyses of the key and other secondary endpoints showed consistent patterns as seen in the relative abuse potential analysis of the primary analysis.

   Since only the low dose of Oveporexton demonstrated a significant difference relative to Phentermine 75 mg while the analysis failed to reject the null hypothesis at the medium and high doses of the test drug, this is sufficient to draw the conclusion about the potential for abuse of Oveporexton. Therefore, the analysis of absolute abuse potential of Oveporexton would be exploratory.

3. Exploratory analysis: At alpha level of 0.05 (one-sided), there was no sufficient evidence to reject the null hypothesis of the mean Emax of Drug Liking VAS to the treatment of each Oveporexton dose is higher than that of placebo by 11 points, suggesting that the subjects in the treatment phase more like Oveporexton than placebo.

In summary, the data suggested that Oveporexton has higher abuse potential than placebo when assessed on the mean Emax score of Drug Liking VAS and other secondary endpoints. Relative to the positive control treatment, data from both the primary and secondary endpoints support that Oveporexton at either 18 mg or 30 mg has no less potential for abuse than Phentermine 75 mg, while Oveporexton 6 mg has a lower abuse potential than Phentermine 75 mg.

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Appendix

Appendix Table 1. Results of Analysis on Other Secondary Endpoints (MCP, n=43).

						95% CI*		95% CI**	
Endpoint	Pairwise Comparison	test	Mean/ Median diff	SE/ Q1,Q3	p-value	LCL	UCL	LCL	UCL
Drug Liking VAS TEmax	Phentermine 75 mg - Placebo	t	2.1	0.4	<0.0001	1.4	Inf	1.3	2.8
Drug Liking VAS TEmax	Phentermine 75 mg - Oveporexton 6 mg	s	0.5	0, 1.5	0.0001	0.5	Inf	0.5	1.0
Drug Liking VAS TEmax	Phentermine 75 mg - Oveporexton 18 mg	s	0.5	0, 1.5	<0.0001	0.5	Inf	0.5	1.5
Drug Liking VAS TEmax	Phentermine 75 mg - Oveporexton 30 mg	s	0.5	0, 1.5	0.0008	0.5	Inf	0.5	1.0
Drug Liking VAS TEmax	Oveporexton 6 mg - Placebo	s	1.0	0, 2	>0.9999	0.5	2.0	0.5	2.0
Drug Liking VAS TEmax	Oveporexton 18 mg - Placebo	s	1.0	0.5, 2	>0.9999	0.5	1.5	0.5	1.5
Drug Liking VAS TEmax	Oveporexton 30 mg - Placebo	s	1.0	0.5, 2	>0.9999	0.5	1.5	0.5	1.5

Note: Analyses were carried out on the Modified Completers Population.
test m: mixed-effects model
t: paired t-test
s: sign-test
p-value and one-sided confidence limit (*) were from the tests of the following null hypothesis at alpha=0.05:
Positive control vs. placebo (validation), H_0: $\mu_C - \mu_P \leq 0$
Positive control vs. test drug GE-IR (Relative Abuse Potential), H_0: $\mu_C - \mu_T \leq 0$
Test drug vs. Placebo (Absolute Abuse Potential), H_0: $\mu_T - \mu_P \geq 0$
** two-sided confidence limit for the pairwise comparison.
LCL: lower confidence limit, M represents negative infinity; UCL: upper confidence limit, I represents infinity.

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