Suvorexant Advisory Committee Meeting Briefing Document

Suvorexant Tablets
Insomnia Indication

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Peripheral & Central Nervous System Drugs Advisory Committee Meeting

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LIST OF ABBREVIATIONS

Abbreviation /Term	Definition
ACTH	Adrenocorticotropic hormone
AE	adverse event or experience
AHI	apnea hypopnea index
APaT	all patients as treated
AUC	area under the concentration-time curve
BMI	Body mass index
BZD	benzodiazepines
CFB	change from baseline
CGI-I	Clinical Global Impressions – Improvement of Illness
CGI-S	Clinical Global Impressions – Severity of Illness
CI	confidence interval
Cmax	maximum plasma concentration
CNS	Central Nervous System
COPD	chronic obstructive pulmonary disease
CSS	Controlled Substance Staff
C-SSRS	Columbia Suicidality Severity Rating Scale
CYP	cytochrome P450
DDI	Drug-drug interactions
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorder-Category IV-Text Revision
DSST	Digit Symbol Substitution Test
ECG	Electrocardiogram
ECI	events of clinical interest
EDS	excessive daytime sleepiness
e-diary	electronic diary
EEG	Electroencephalogram
EMG	Electromyelogram
EOG	electro-oculogram
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid receptor alpha 1
HD	high dose
iSAP	Integrated Statistical Analysis Plan
ISE	Integrated Summary of Efficacy
LD	low dose
LDA	longitudinal data analysis
LPS	latency to onset of persistent sleep
LS	least-squares
MK-4305	Suvorexant
MVAV	motor vehicle accidents and violations
NREM	non rapid eye movement
OSA	obstructive sleep apnea

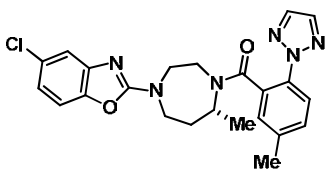
Abbreviation /Term	Definition
OX1R and OX2R	orexin R1 and R2 receptors
P-gp	P-glycoprotein transporter
PBO	Placebo
PD	pharmacodynamics
PDLC	predefined limits of change
PGI-I	Patient Global Impressions – Improvement of Illness
PGI-S	Patient Global Impressions – Severity of Illness
PK	pharmacokinetic
PQ-Cohort	cohort receiving polysomnography and questionnaire assessments
PSG	polysomnography
PSWS	NREM stage 3 percent defined as S3/4 divided by TST
Q-Cohort	cohort receiving questionnaire assessments only
qEEG	quantitative electroencephalogram
QIDS-SR16	Quick Inventory of Depressive Symptomatology
QTc	QT interval corrected for heart rate
REM	rapid eye movement; stage R from lights-off to lights-on
S1	NREM stage 1 duration
S2	NREM stage 2 duration
SAE	Serious adverse events
SaO2	oxygen saturation
SD	standard deviation
SDLP	standard deviation of lane position
SDS	Sheehan Disability Scale
SE	Sleep efficiency
SOL	sleep onset latency
sQUALm	mean subjective sleep quality
sREFRESHEDm	mean subjective refreshed upon awakening
SSRI	selective serotonin reuptake inhibitors
sTSOm	mean subjective time to sleep onset
sTSTm	mean subjective total sleep time
SULTs	Sulfotransferases
Suvo	Suvorexant
sWASOm	mean subjective wake time after sleep onset
SWS	slow wave sleep
$t_{1/2}$	Half life
TQTc	Thorough QTc Study
TSO	time to sleep onset
TST	total sleep time
UGTs	Uridinediphosphoglucuronosyltransferases
US	United States
VAS	visual analog scale
WASO	wakefulness after persistent sleep onset
WSQ	Withdrawal Symptom Questionnaire

1. Executive Summary/Overview

Insomnia affects up to 30% of the adult population, and despite the availability of a number of medical treatments, remains a significant medical problem. Persistent insomnia impacts patients directly through psychiatric and broader health-related risks, as well as society more generally through occupational, public safety, and economic aspects. Insomnia is a risk factor for major depression, anxiety disorder, alcohol and drug abuse and addiction, and diminishes overall quality of life. Insomnia with objective evidence of short sleep duration is associated with increased risk for morbidity (diabetes, hypertension) and mortality risks [1; 2; 3]. The recent American Insomnia Survey reported that of the four DSM-IV-based nighttime insomnia symptom domains evaluated (difficulty initiating sleep, difficulty maintaining sleep, early morning awakenings, and non-restorative sleep), that difficulty maintaining sleep is the strongest predictor of individual perceptions about health [4]. Given the high prevalence of sleep maintenance difficulties among insomnia patients (61% in the survey) and the limited options that address both sleep onset and sleep maintenance insomnia with an acceptable residual effects profile, new treatments with a balanced profile are an important unmet need and could have important medical and societal benefits.

The most commonly used pharmacological treatment options for insomnia are the benzodiazepine (BZD) and the non-BZD GABA-acting hypnotics (e.g., zolpidem, eszopiclone, and zaleplon), all of which enhance the activity of the widespread CNS inhibitory neurotransmitter gamma-aminobutyric acid receptor alpha-1 (GABA). Less frequently prescribed agents include sedating anti-depressants, melatonin agonism, and anti-histamines [5]. However, restricted efficacy profiles (e.g. onset with no or inadequate maintenance, or maintenance without onset efficacy) and/or unwanted side effects limit the use of many of these treatments, narrowing options for many patients. New treatments are therefore needed that are well-tolerated and can provide broader options to patients who have difficulties initiating sleep as well as difficulties maintaining sleep.

Suvorexant, also known as MK-4305, is the first of a new class of drugs, the orexin receptor antagonists (ORAs), being developed for the treatment of insomnia. The chemical formula for suvorexant is $C_{23}H_{23}ClN_6O_2$ and the chemical name is [(7R)-4-(5-chloro-2-benzoxazolyl)hexahydro-7-methyl-1H-1,4-diazepin-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone (chemical structure is provide below).



Suvorexant is a unique alternative to existing therapies, providing improved sleep onset as well as sleep maintenance efficacy that is sustained through the night, and has a favorable tolerability and residual effects profile. Suvorexant is an orally active, highly selective antagonist for orexin receptors OX_1R and OX_2R that transiently inhibits the effects of wakefulness-promoting orexin neurons of the arousal system thus facilitating the natural transition from wake to sleep. Suvorexant's efficacy and safety/tolerability have been studied in multiple placebo-controlled studies for periods up to 12 months.

In a Phase 2b two-period crossover polysomnography (PSG) study (P006), 254 insomnia patients received suvorexant (doses of 10 mg, 20 mg, 40 mg, and 80 mg) and placebo for up to 4 weeks. All four doses of suvorexant were superior to placebo for the co-primary endpoints of sleep efficiency (SE) after Night 1 and Week 4 as assessed by PSG. Overall, the doses of 40 mg and 80 mg demonstrated efficacy most consistently across key objective and subjective endpoints. A dose response was observed with respect to number of patients experiencing one or more AEs, and for specific AEs of somnolence, suggesting that the 80 mg dose offered minimal advantage over 40 mg, whereas a dose of 20 mg would be unlikely to provide maximal benefit on some sleep endpoints. These results along with modeling and simulation, that incorporated data from Phase I studies, guided selection of four doses for evaluation in Phase 3. Examining the totality of the data (efficacy and safety/tolerability), 40 mg appeared to have the best clinical profile, and was selected as the primary dose of suvorexant for Phase 3 evaluation in non-elderly adults (age <65). An analogous dose of 30 mg for elderly patients (age >=65) was selected based on comparable exposure to 40 mg exposure in the non-elderly. These doses (i.e, 40 mg for non-elderly and 30 mg for elderly) are referred to as the high dose (HD). A lower dose (LD) of 20 mg in non-elderly and 15 mg in elderly was also selected for evaluation in the Phase 3 confirmatory trials, to further characterize dose response.

In the worldwide Phase 3 program, 1784 primary insomnia patients from diverse backgrounds received suvorexant. Of the three Phase 3 trials in insomnia patients, two were confirmatory efficacy and safety trials (P028 and P029) that each included 1) a 3-month double-blind core treatment period; 2) combined measures design, in which both objective (PSG) and subjective (patient-reported) measures of efficacy served as primary endpoints; 3) combined age design, with the primary analysis population consisting of combined age groups, e.g. elderly and non-elderly patients; and 4) evaluation of two suvorexant doses for each age group. Thus, this is the first Phase 3 program to incorporate objective and subjective primary endpoints reflecting both onset and maintenance in elderly and nonelderly patients for a full 3 months.

Results of these confirmatory Phase 3 studies demonstrated that suvorexant HD was efficacious for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance; suvorexant was superior to placebo on all objective and subjective measures of sleep maintenance and sleep onset at Night 1/Week 1, Month 1, and Month 3, except for LPS at Month 3 in one of the two studies (P029). The totality of the Phase 3 trial data – including results of pooled data across studies – supports the

efficacy of suvorexant LD, but the magnitude of efficacy effects observed for suvorexant LD was consistently less than for suvorexant HD, confirming the presence of a dose response with increasing efficacy as the dose was increased from the 20/15 mg LD to the 40/30 mg HD.

The third Phase 3 study was a long-term safety trial (P009) that included 779 nonelderly and elderly patients randomized to suvorexant HD or placebo for 12 months of therapy. In addition to long term safety, the data collected in this trial also provide evidence for the long term efficacy of suvorexant HD for up to one year of nightly treatment, with no evidence suggesting a loss of drug efficacy over time relative to baseline as well as placebo. An additional 2-month Randomized Discontinuation Phase of the trial showed that insomnia symptoms returned in patients who were discontinued from suvorexant, without clinically meaningful rebound or withdrawal, whereas those who continued to receive suvorexant maintained the gains they had made during the year of treatment, providing evidence for the continued benefit of treatment with suvorexant beyond one year.

Across the Phase 3 studies, consistent efficacy was also observed in exploratory endpoints which included subjective endpoints of sleep quality (sQUALm) and feeling refreshed upon awakening (sREFRESHEDm), clinician-rated and patient-rated global measures of severity and improvement (CGI, PGI), and patient-rated Insomnia Severity Index (ISI), which assesses insomnia symptoms and the perceived effect on function and quality of life associated with insomnia.

Suvorexant was administered to 2027 insomnia patients in Phase 2b/3 studies, and the safety and tolerability profile was favorable in both elderly and non-elderly patients. The most common adverse event associated with suvorexant treatment was somnolence, which in a combined 0-3 month assessment of the three Phase 3 studies was reported in 10.7% or 6.7% of patients who received suvorexant HD or LD, respectively, versus 3.0% in those receiving placebo. Somnolence typically resolved with continued treatment, was generally mild or moderate in severity, and in the vast majority of instances did not result in discontinuation of therapy. Serious adverse events in the program were rare, and occurred at similar rates between patients who received suvorexant and those receiving placebo, without any pattern of specific events suggesting a suvorexant-associated effect.

In the Phase 1 program that evaluated the PK, PD, drug-drug interaction (DDI) and safety in special populations, suvorexant also had a favorable safety profile. In the Phase 2b/3 program additional systematic safety assessments of Events of Clinical Interest (ECIs) were undertaken to evaluate the potential for safety concerns associated with the use of sleep medications (e.g. complex sleep-related behaviors, driving/residual effects, rebound and withdrawal, respiratory safety), those associated with a novel CNS-active compound (e.g. abuse potential, alcohol interaction, potential for suicidality), and to address theoretical considerations associated with the new ORA mechanism of action (e.g.

cataplexy). The findings of these detailed, prospective ECI assessments support the favorable safety profile of suvorexant across multiple categories of potential concerns.

Overall, these comprehensive assessments demonstrate that suvorexant offers patients an excellent alternative to existing therapies that works through a novel mechanism to provide onset and maintenance efficacy that is sustained through the night, with a favorable tolerability and residual effects profile.

This document provides an overview of the development of suvorexant, including the clinical data supporting the conclusions that suvorexant:

- Fulfills an unmet medical need as a novel treatment for insomnia.
- Has significant efficacy in the treatment of sleep onset and sleep maintenance insomnia.
- Has demonstrated efficacy after short, intermediate and long term use.
- Improves clinically relevant measures including patient- and clinician-reported global measures of insomnia severity and improvement, as well as perceived quality of life, functioning, and stress due to insomnia as assessed by the Insomnia Severity Index.
- Is both efficacious and generally safe and well tolerated in a diverse group of patients representing different genders, races, geographic regions, and age groups (non-elderly and elderly adult patients).
- Has a favorable risk/benefit profile.

The proposed prescribing indication and dosing recommendation for suvorexant is:

<u>INDICATIONS AND USAGE:</u>

Suvorexant is indicated for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

<u>DOSAGE AND ADMINISTRATION:</u>

Non-Elderly Adults (<65 yrs):

The recommended dose is 40 mg once daily. A lower dose of 20 mg once daily may be appropriate for some patients based on individual tolerability.

Elderly Adults (≥ 65 yrs):

The recommended dose is 30 mg once daily. A lower dose of 15 mg once daily may be appropriate for some patients based on individual tolerability.

2. Scientific Background

2.1 Sleep and Insomnia as an Unmet Medical Need

Sleep and Insomnia

Alternation of wake and sleep states is ubiquitous in mammals, and across species the requirement for sleep is absolute. Prolonged sleep deprivation disrupts a variety of essential homeostatic processes [6], and at the extreme is lethal. The function of and necessity for sleep are topics of active scientific debate, but its benefits include daily recalibration and restoration of critical homeostatic mechanisms, facilitation of cyclical energy conservation, and provision for the offline time required by critical neural systems to process information and to encode and consolidate memories and motor programs [7].

Given the clear biological requirement for sleep, it is not surprising that inadequate sleep in humans, as is the case with insomnia, has significant consequences. Chronic insomnia affects about 10% to 30% of adults, with the majority of individuals experiencing significant daytime consequences such as reduced energy, memory problems, and difficulty concentrating [8; 9]. Insomnia may also be associated with broad impairments of physical and mental well-being, reflected in higher levels of depression, anxiety, and diminished quality of life.

The bi-directional relationship between insomnia and other conditions is well-documented and typically does not follow a straightforward cause-effect model. Depression is not only common among patients suffering from insomnia, but insomnia is also a predictor for the later development of depression [10; 11] and episodes of insomnia predict a recurrence of depression in previously recovered individuals [12]. Insomnia may not only increase the risk of psychiatric disorders, but may also be a risk factor for other medical disorders such as hypertension. Patients with insomnia and objective evidence of sleep loss controlled for apnea, had a significant risk for hypertension; the risk of hypertension was inversely related to total sleep time [1]. This increased risk was also greater in patients with insomnia than in short sleepers without insomnia [13]. Furthermore, a meta-analysis of 16 trials has shown that poor sleep is associated with a negative cardiac event outcome, with a typical combined risk ratio of about 1.92 (95% confidence intervals [CI] = 1.62–2.31) [14].

Elderly individuals are somewhat more likely to describe poor sleep (up to 50% of elderly having such complaints at some time) including poor sleep maintenance and early awakenings. In addition, with aging comes fragmentation of the more consolidated sleep architecture pattern seen in younger adults. People with insomnia have more medical complaints and seek medical care more often than people without insomnia.

Insomnia has broad societal and economic impact as well, as its effects on daytime function can impair focus and reduce productivity. For example, based on results obtained in the recent American Insomnia Survey, the estimated annualized costs attributed to lost work performance due to insomnia in the United States is approximately $63 billion [15].

Clinically, insomnia presents as a perception or symptom of inadequate or poor quality sleep that can include difficulty in falling asleep, waking up frequently during the night with difficulty returning to sleep, waking up too early, and/or un-refreshing sleep [9; 16]. While patients typically experience multiple sleep symptoms either at the same time or in the course of their insomnia, epidemiological evidence indicates that sleep maintenance symptoms are the most prevalent (~50-70%), followed by difficulty initiating sleep (35-60%), and non-restorative sleep (20-25%) [17]. Insomnia may occur as a primary disorder or as a component of other medical and psychiatric illnesses, medication use, medication/substance misuse, behavioral or environmental factors, or other sleep disorders, such as obstructive sleep apnea or restless leg syndrome [9]. A Diagnostic Statistical Manual of Mental Disorder-Category IV-Text Revision (DSM-IV-TR) diagnosis of primary insomnia requires that the individual suffer from one or more of these insomnia symptoms, along with subjective daytime impairment, for at least a month, and that the symptoms should not stem from another sleep disorder, another psychiatric problem, a medical illness, or use of a substance [18]. As indicated previously, results from the American Insomnia Survey indicate that due to its high prevalence and strength of individual-level association with perceived health, treatments targeting unmet need for sleep maintenance insomnia are likely to have the most significant societal impact [4].

Treatment of Insomnia

The treatment of insomnia may involve multiple modalities, with non-pharmacological approaches subsumed within the category of cognitive behavioral therapy (CBT) being effective for many patients. For those seeking medical intervention, current pharmacologic treatment options for insomnia are limited and fail to meet the needs of all patients, in part because available mechanisms are unable to deliver adequate efficacy for the substantial proportion of patients who have both sleep induction and sleep maintenance difficulties. The current treatment of insomnia is dominated by benzodiazepines (BZD), including the so-called "Z-drug" non-BZD hypnotics (e.g., zolpidem, eszopiclone, zaleplon), which act to enhance activity of the widespread CNS inhibitory neurotransmitter GABA, inducing sleep as part of a general CNS depression [19; 20]. Due to off-target actions of the BZDs and non-BZDs have a number of properties and side effects that have limited their use: next-day sedation, dizziness, ataxia, memory disturbances, hallucinations, rebound insomnia, potential for withdrawal-related symptoms, as well as physical and psychological dependence in at risk populations [21]. BZD/non-BZDs treat insomnia by increasing sleep, preferentially Stage

2 sleep, but may suppress the deeper stages of sleep and rapid eye movement (REM) sleep.

As GABA agonists are limited by traditional PK, BZD/non-BZD medications can only provide modest sleep maintenance before incurring unwanted side effects, including next-day residual effects [22; 23; 24]. For instance, the product label for zolpidem extended-release (Ambien CR®) with a t½ of 2.8 hours (range 1.6-4.5 hours) states that in a 3-week trial of the 12.5 mg dose in non-elderly adult patients (age 18-64) improvements in the sleep maintenance polysomnographic measure Wake After Sleep Onset (WASO) were only observed during the first 5 hours of the 8-hour sleep period after 2 weeks of nightly treatment, with a reported somnolence AE rate of 15% in those patients taking Ambien CR versus 2% for those taking placebo.

In terms of alternative mechanisms for improving sleep, a low-dose tricyclic antidepressant doxepin (Silenor®) and a melatonin receptor agonist ramelteon (Rozerem®) have been approved by the Food and Drug Administration (FDA) for treatment of specific symptoms of insomnia. However, based on the limitations of their efficacy profiles (e.g low-dose doxepin and ramelteon have only been demonstrated to improve either sleep maintenance or sleep onset, respectively, but not both), these medications cannot provide effective monotherapy treatment for the majority of insomnia patients who suffer from difficulties with both sleep onset and sleep maintenance.

2.2 Rationale for Orexin Receptor Antagonists as a Novel Treatment

Insomnia is a heterogeneous disorder with a variety of potential underlying contributing factors that include genetic, psychological, physical, and environmental components. Emerging data suggests that patients with chronic insomnia exhibit a more generalized state of heightened arousal (or hyperarousal), which can be documented not only during sleep but also throughout the circadian cycle [14; 25]. Data obtained from these patients reveal increased high-frequency electroencephalogram (EEG) activation, abnormal hormone secretion (which includes elevated cortisol and adrenocorticotropin hormone [ACTH]) secretion) and during sleep, attenuated nighttime melatonin secretion, increased whole-body and brain metabolic activation, and elevated heart rate and sympathetic nervous system activation [14; 26]. While the precise causes underlying these observations are being actively explored, it is intriguing to consider the possibility that for many patients persistent activation of the orexin system, a central regulator of wakefulness, may be responsible at least in part for the clinical symptoms of insomnia.

Report of the discovery of the orexin system in 1998 has enabled important new insights into the regulation of wakefulness and sleep [27; 28]. Orexin–expressing neurons originate from the lateral hypothalamus, a control center for sleep and wakefulness. Projections from orexinergic neurons extend widely throughout the brain to signal activation of key neural centers involved in wake-state control, including locus coeruleus and tuberomammillary nucleus, which are nuclei that express orexin peptide receptors and whose function is to mediate wakefulness signaling [29]. Orexinergic neurons first

produce orexin neuropeptide as a preprohormone that is cleaved into two discreet peptide neurotransmitters, orexin A and orexin B [30]. Released orexin peptides selectively bind to two different GPCR transmembrane receptors, OX_1R and OX_2R, found on target afferent neurons in cortical, thalamic and hypothalamic neuronal circuits specifically associated with sleep/wake regulation. The circadian rhythmicity of orexin neuropeptide release, whereby orexins A and B levels rise with waking and decrease during the night, is an important critical feature of the system [31; 32] and should be kept in mind when interpreting effects of pharmacotherapy, particularly with regard to how rising orexin levels can competitively offset residual pharmacology of competitive receptor antagonists, for example.

This background package describes the efficacy and safety of suvorexant, a novel ORA being developed for the treatment of insomnia. As a selective antagonist of the two orexin receptors OX_1R and OX_2R, suvorexant dampens activation of downstream brainstem and cerebral nuclei that mediate wakefulness, thus enabling sleep to occur. Suvorexant is chemically unrelated to ethanol, BZDs, non-BZDs, barbiturates or other drugs with hypnotic properties, and suvorexant does not possess the intrinsic myorelaxant or anxiolytic properties accompanying interaction with the GABA system. The specificity of this targeted approach to facilitating sleep, through antagonism of the wake-inducing output of a relatively limited and discreet pool of ~70,000 orexin neurons, affords potential advantages over the non-selective inactivation of widely distributed GABA receptor expressing neurons [33], offering a unique and selective arousal-pathway-directed therapeutic option for patients in the treatment of insomnia. The data summarized in this package provide substantial and compelling evidence for the acute and chronic efficacy and safety of suvorexant for the treatment of insomnia, as characterized by difficulties with sleep onset and/or sleep maintenance.

2.3 Nonclinical Pharmacology and Toxicology

2.3.1 NonClinical Pharmacology

The selectivity and functional effects of suvorexant were investigated in a series of in vitro and in vivo pharmacological studies. These studies included in vitro evaluation of suvorexant activity at human and non-human orexin receptors (OX_1R and OX_2R), in vivo assays in animals to determine the effects of suvorexant on sleep and wake, and in vitro and in vivo assays for secondary pharmacodynamic profiles. The in vitro pharmacology studies show that the affinity and functional antagonist potency of suvorexant is reversible and is conserved across mouse, rat, rabbit, dog, rhesus monkey and human OX_1R and OX_2R indicating that these species are appropriate for the evaluation of in vivo pharmacodynamic activity and potential mechanism-related toxicities. Suvorexant is a highly selective reversible high affinity orexin receptor antagonist at OX_1R (Ki 0.55 nM) and OX_2R (Ki 0.35 nM) receptors with ~6,000 to10,000 fold intrinsic selectivity for OX_1R and OX_2R over 165 receptors and enzymes in an *in vitro* screening panel.

The ability of suvorexant to modulate the endogenous orexin signaling response was evaluated in multiple in vivo assays across several nonclinical species. Nonclinical assessment in rats, dogs and rhesus monkeys demonstrated that antagonism of the orexin receptors by suvorexant induces rapid sleep in animals and increases non rapid eye movement (NREM) and REM stage sleep. The increases in NREM and REM duration following suvorexant administration in nonclinical species are unique compared to GABA-ergic agonists which increase NREM sleep but decrease REM sleep [34].

The overall nonclinical pharmacology profile supports the conclusion that suvorexant is a highly potent and selective reversible antagonist of OX_1R and OX_2R that has consistent sleep effects across species.

2.3.2 Nonclinical Toxicology

Suvorexant has been extensively evaluated in a series of nonclinical safety pharmacology studies, genetic toxicology studies, repeat-dose toxicity studies up to 6 months in duration in rats and 9 months in duration in dogs, carcinogenicity studies in rasH2 Tg mice and Sprague Dawley rats, fertility studies in female and male rats, embryo-fetal developmental toxicity studies in rats and rabbits, and abuse liability studies in rats and monkeys. In addition, an oral placental and lactational transfer study in rats, an oral pre- and postnatal developmental toxicity study in rats, an oral placental transfer study in rabbits, a three day oral phototoxicity evaluation in pigmented rats and an oral study to assess physical signs in monkeys were completed. Overall, the nonclinical profile of suvorexant supports the safety of suvorexant for the chronic treatment of insomnia in non-elderly and elderly adults.

3. Clinical Development Program for Suvorexant

The clinical development program was designed to evaluate suvorexant's effects on sleep onset and sleep maintenance in primary insomnia, during short-term and long-term use, and to assess its safety and tolerability. The suvorexant clinical development program encompassed extensive patient exposure, duration of treatment, and patient diversity to provide a robust assessment of the efficacy and safety of suvorexant for use in insomnia patients worldwide. Potential safety issues associated with sleep medication use were thoroughly assessed via the prospective and systematic collection of special assessments (related to sleep medications, CNS-active compounds, ORA mechanism) both in Phase I trials in special populations and in the Phase 2b/3 program. The suvorexant clinical program comprised three key phases:

1) In ***Phase 1***, 32 studies were conducted to assess the initial safety and tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of suvorexant, including evaluation of residual effects, abuse potential and respiratory safety.

2) In ***Phase 2***, a dose-ranging clinical trial (P006) was conducted to establish proof-of-concept for suvorexant's efficacy and safety in patients with DSM-IV criteria primary insomnia, and to identify doses for further evaluation in Phase 3.

3) In ***Phase 3***, the efficacy and safety of suvorexant in primary insomnia patients was confirmed via three placebo-controlled, parallel group, multi-center/multi-national trials:

   - Two Phase 3 confirmatory efficacy and safety clinical trials (P028 and P029),
   - One Phase 3 Long-term Safety Trial (P009).

Over the course of Phase 2b/3 clinical development of suvorexant in patients with insomnia, 3063 patients were randomized in 24 countries; 1466 patients were randomized at sites in the U.S. Of these, 2027 insomnia patients overall (1198 non-elderly and 829 elderly patients) received treatment with suvorexant. The key study elements of the Phase 2b/3 trials are summarized in [Table 1].

Table 1
Summary of Key Elements of Phase 2b/3 Clinical Trials with Suvorexant

Trial ID	Design Control Type	Duration	Trial Objective	Trial and Control Drugs Dose, Route & Regimen	No. Patients Treated (Total, by Treatment Arm), and Completed
PHASE 2b					
Dose Finding (P006)	Phase 2b, multicenter, randomized, double-blind placebo- controlled, 2-period adaptive crossover PSG trial in nonelderly patients	4-week treatment phase in each period	- Evaluate Efficacy at Night 1 and Week 4 by endpoints of Sleep Efficiency (SE). - Evaluate the safety and tolerability of suvorexant in patients with chronic insomnia	Suvorexant • 10 mg • 20 mg • 40 mg • 80 mg Placebo	Total: 254 • suvorexant 10 mg: 62 • suvorexant 20 mg: 61 • suvorexant 40 mg: 59 • suvorexant 80 mg: 61 • PBO: 249 Completed: 228
PHASE 3 PIVOTAL STUDIES					
Pivotal Efficacy 1 (P028)	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group, trial in nonelderly and elderly patients	3-month Treatment Phase followed by 3-month Extension Phase	- Evaluate the safety and tolerability of suvorexant in patients with chronic insomnia - Evaluate efficacy at Week 1, Month 1, and Month 3 by patient-reported outcomes of sTSTm, sTSOm, and sWASOm; and at Night 1, Month 1, and Month 3 by PSG endpoints of LPS and WASO.	Suvorexant HD • 40 mg (non-elderly) • 30 mg (elderly) Suvorexant LD • 20 mg (non-elderly) • 15 mg (elderly) Placebo	Treatment Phase (P028) Total: 1021 • suvorexant LD: 254 • suvorexant HD: 383 • PBO: 384 Completed: 916 Extension Phase Total: 423 • suvorexant LD: 100 • suvorexant HD: 172 • PBO: 151 Completed: 377
Pivotal Efficacy 2 (P029)	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group trial in non-elderly and elderly patients	3-month Treatment Phase			Treatment Phase (P029) Total: 1009 • suvorexant LD: 239 • suvorexant HD: 387 • PBO: 383 Completed: 881

Summary of Key Elements of Phase 2b/3 Clinical Trials with Suvorexant (Cont.)

Trial ID	Design Control Type	Duration	Trial Objective	Trial and Control Drugs Dose, Route & Regimen	No. Patients Treated (Total, by Treatment Arm), and Completed
Long Term Safety (P009)	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, long term safety trial in nonelderly and elderly patients	12-month double-blind Treatment Phase followed by a 2-month Randomized Discontinuation Phase	Evaluate long term safety of suvorexant in patients with chronic insomnia and potential discontinuation effects.	Suvorexant HD • 40 mg (non-elderly) • 30 mg (elderly) Placebo	Treatment Phase Total: 779 • suvorexant 521 • PBO: 258 Completed: 484 Randomized Discontinuation Phase Total entered: 484 • suvorexant/suvorexant: 156 • suvorexant/PBO: 166 • PBO/PBO: 162 Completed: 470

HD= high dose, LD= low dose, PBO= placebo; suvorexant/suvorexant= suvorexant / suvorexant, suvorexant / PBO, PBO / PBO = therapy received during Treatment phase / therapy received during Randomized Discontinuation phase.
PSG= polysomnography, PRO= patient-reported outcomes, SE= sleep efficiency, sTSTm = mean subjective total-sleep-time, sTSOm = mean subjective time-to-sleep-onset , sWASOm= mean subjective wake-time-after-sleep-onset , LPS=Latency-to-onset-of-Persistent-Sleep, WASO= Wakefulness-After-persistent-Sleep-Onset

4. Clinical Pharmacology

The suvorexant clinical pharmacology program included 32 studies conducted in a total of 922 subjects. These studies characterized the PK of suvorexant, including the effects of intrinsic factors and extrinsic factors (drug-drug interactions) on suvorexant PK. Pharmacodynamic (PD) and special safety studies were also conducted and are described in [Section 6.10]. The results indicate that suvorexant is generally well tolerated, has low potential to be a perpetrator of drug-drug interactions, and has PK that supports once-daily dosing without regard to food. In Phase 3 in elderly subjects, the reduced low (15 mg) and high (30 mg) dose resulted in similar exposures relative to the doses administered to non-elderly patients (20 mg and 40 mg). No clinically meaningful changes in suvorexant PK based upon intrinsic factors (i.e. gender, BMI, race, hepatic or renal impairment) have been observed.

4.1 Pharmacokinetics of Suvorexant

The PK of suvorexant following single doses up to 240 mg and multiple doses up to 100 mg were evaluated.

Absorption: Oral absorption of suvorexant is relatively rapid, producing median peak plasma concentrations approximately 2 hours (range: 0.5 to 6.0 hours) after dosing under fasted conditions. Food does not have a meaningful effect on suvorexant PK; therefore, suvorexant may be administered without regard to meals.

Distribution: Suvorexant is widely distributed, with a volume of distribution of 105.9 L following oral administration. Suvorexant is extensively bound (99.5%) to plasma protein, primarily serum albumin and α-1 acid glycoprotein, and does not distribute preferentially into red blood cells.

Metabolism: Suvorexant is eliminated via metabolism, primarily by CYP3A4, with considerably less contribution by CYP2C19. M9, a circulating hydroxylated metabolite of suvorexant, is the major metabolite and is not active in vivo. M9 exhibits formation-rate limited PK such that the terminal phase of plasma concentration-time profiles largely parallel those of suvorexant.

Elimination: Suvorexant is predominantly excreted as metabolites in the feces with negligible renal clearance of unchanged suvorexant. The geometric mean terminal half-life ($t_{1/2}$) for suvorexant is 12.2 hours (5^{th}-95^{th} percentile: 8-19 hours) following 40-mg administration. Consistent with the terminal half-life, steady-state is achieved by 3 days of once-daily dosing with minimal accumulation of AUC and Cmax (accumulation ratio: 1.2-1.6).

Linearity/Dose Proportionality: The systemic PK of suvorexant following multiple-dose administration were consistent with those following single-dose administration, indicating time-independent PK. Dose-dependent increases Cmax and AUC are obtained

over the range from 10 to 80 mg, but these changes are less than strictly dose-proportional, and likely attributable to absorption limitations, such that suvorexant exposures increase ~75% with a doubling of dose from 20 mg to 40 mg.

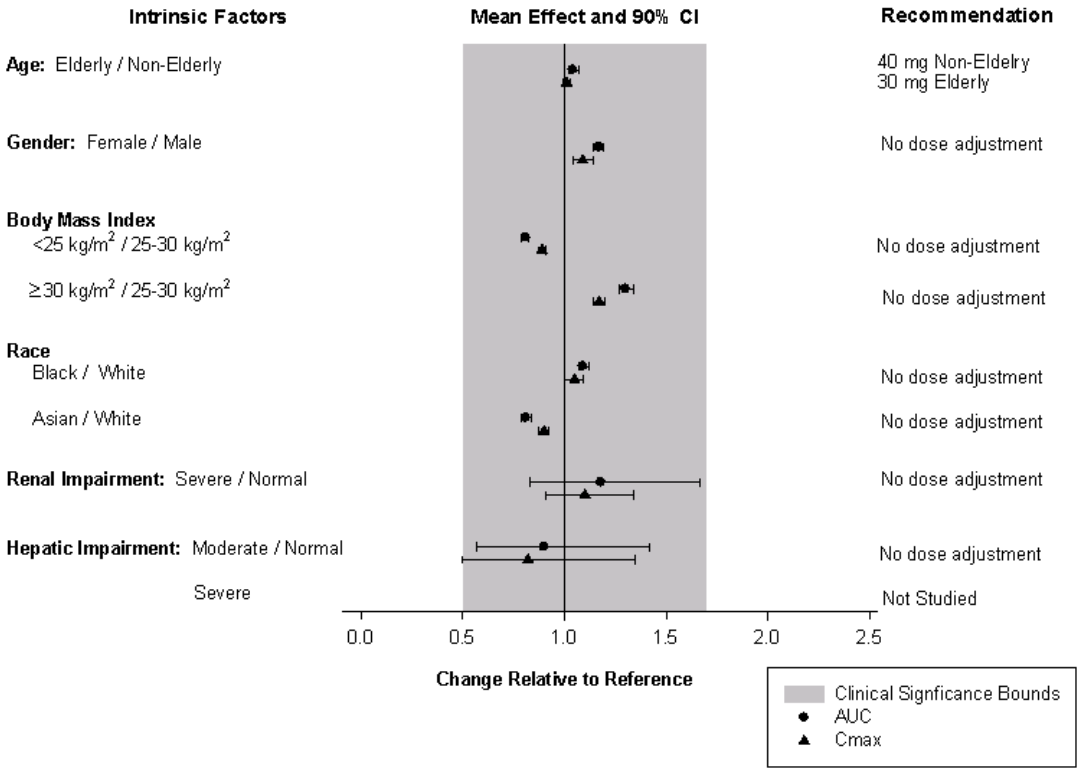
4.2 Intrinsic Factors and Suvorexant Pharmacokinetics

The PK of suvorexant were characterized using population PK analyses across Phase 1 studies and pooled Phase 2/3 studies (samples collected at ~9 hr postdose, or C9hr) to assess potential covariate effects on PK variability over a dose range of 10 mg to 80 mg. For the purposes of assessing the impact of intrinsic and extrinsic factors on suvorexant PK and determination of dose adjustments, where appropriate, the therapeutic window (clinical significance bounds) is defined as 0.5- to-1.7-fold of exposure (AUC) of the recommended clinical doses (40 mg in non-elderly, 30 mg in elderly). The upper clinical bound of 1.7 (i.e., 1.7-fold of the 40 mg exposure) is defined by the mean exposure at 80 mg relative to 40 mg, which is supported by the favorable clinical experience at 80 mg from the Phase 2b study. The lower clinical bound of 0.5 is proposed based on the dose-response on efficacy endpoints which projects clinical benefit to be maintained at ~15 mg (corresponding to ~0.5x AUC of 40 mg)

The plasma PK of suvorexant in patients with insomnia is consistent with that in healthy subjects. Therefore, properties observed in healthy subjects are applicable to patients with insomnia. Gender, BMI, and race were included as factors assessed in the population pharmacokinetic model to evaluate suvorexant pharmacokinetics in healthy subjects and predict exposures in the patient population. None of these factors resulted in clinically meaningful changes in suvorexant pharmacokinetics, as the changes in exposure estimates were contained within the clinical significance bounds of 0.5 to 1.7 [Figure 1].

Lower doses of suvorexant were evaluated in elderly patients (30 and 15 mg) relative to non-elderly (40 and 20 mg) in the Phase 3 studies. This dose reduction was incorporated to match the pharmacokinetic exposures in elderly to non-elderly based on observed age effects on PK in Phase 1 (e.g., elderly had a slightly higher exposure than non-elderly subjects). After completion of Phase 3, population PK analysis of non-elderly (<65 years) and elderly (≥65 years) healthy subjects and patients indicated that doses administered to the elderly provide similar suvorexant exposures to doses in the non-elderly [Figure 1]. There was no clinically meaningful effect of severe renal or moderate hepatic impairment on suvorexant PK based on specific pharmacokinetic studies conducted. Patients with severe hepatic impairment were not studied as this group generally includes patients with encephalopathy. Hypnotics may have more pronounced effects in the setting of encephalopathy and are commonly avoided in this setting; therefore, suvorexant is not recommended in patients with severe hepatic impairment.

Figure 1
Impact of Intrinsic Factors on the PK (AUC and C_{max})
of Suvorexant GMR and 90% CIs



4.3 Extrinsic Factors and Suvorexant Pharmacokinetics: Drug-Drug Interactions

Effects of co-administered drugs on suvorexant PK:

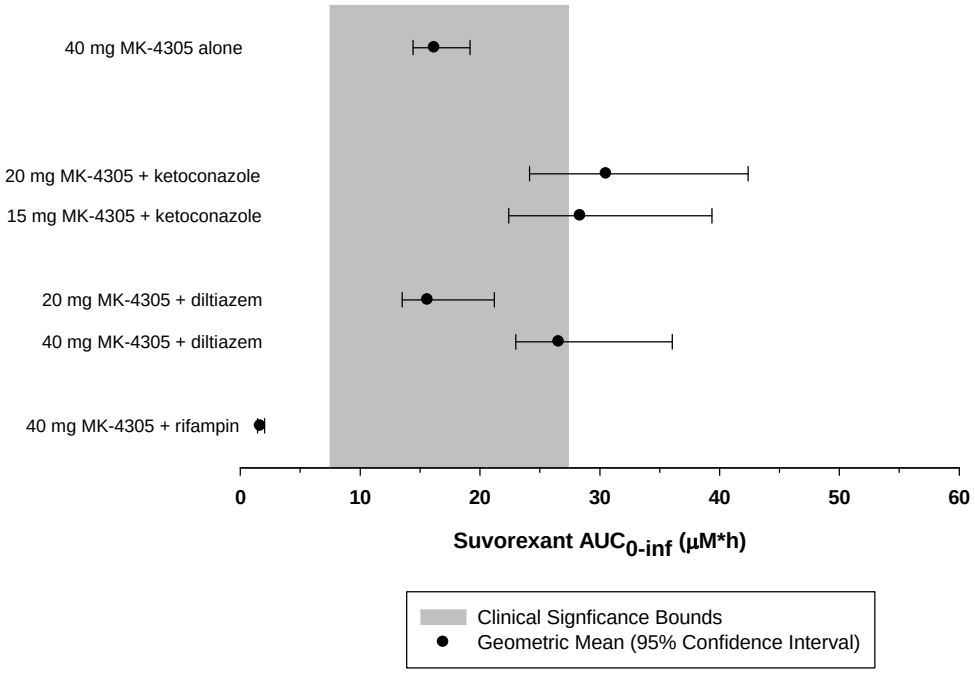
Consistent with CYP3A mediated biotransformation of suvorexant, drug-drug interactions affecting suvorexant PK were observed with ketoconazole (strong CYP3A and/or P-gp inhibitor), diltiazem (moderate CYP3A inhibitor), and rifampin (strong CYP3A inducer). Co-administration of suvorexant with ketoconazole resulted in systemic exposure 2.79-times higher than for suvorexant alone. Co-administration of suvorexant 20 mg with ketoconazole is expected to result in a mean AUC that is 1.89-times greater than that following treatment with 40 mg suvorexant alone, exceeding the clinical significance bound for safe and effective use of suvorexant [Figure 2]. Thus, it is proposed that concomitant use of suvorexant is not recommended in patients taking strong inhibitors of CYP3A.

Concomitant administration of diltiazem with suvorexant resulted in a lesser effect on suvorexant (2.05-fold change in AUC) than that observed with ketoconazole. The

administration of 40 mg (non-elderly) or 30 mg (elderly) suvorexant dose with diltiazem would exceed the predicted AUC upper bound of clinical significance. However, coadministration of 20 mg suvorexant with diltiazem results in a mean AUC and the distribution of AUC largely contained within the clinical significance bounds in non-elderly subjects [Figure 2]. Similarly, the predicted suvorexant exposure for the coadministration of diltiazem with 15 mg suvorexant mg can be supported in the elderly. Therefore, coadministration of these lower doses of suvorexant with moderate CYP3A inhibitors is expected to produce suvorexant plasma concentrations within the therapeutic window [Figure 2].

In the presence of rifampin, a known strong inducer of CYP3A, clinically significant decreases in suvorexant AUC (88%) were observed. As the decreased exposures of suvorexant are below the lower clinical bound, a decrease in the efficacy of suvorexant can be anticipated [Figure 2].

Figure 2
Observed and Predicted Suvorexant Exposure With and Without Concomitant Ketoconazole, Diltiazem and Rifampin Administration in Non-Elderly Subjects Compared to Suvorexant Exposure Applying the Clinical Significance Bounds

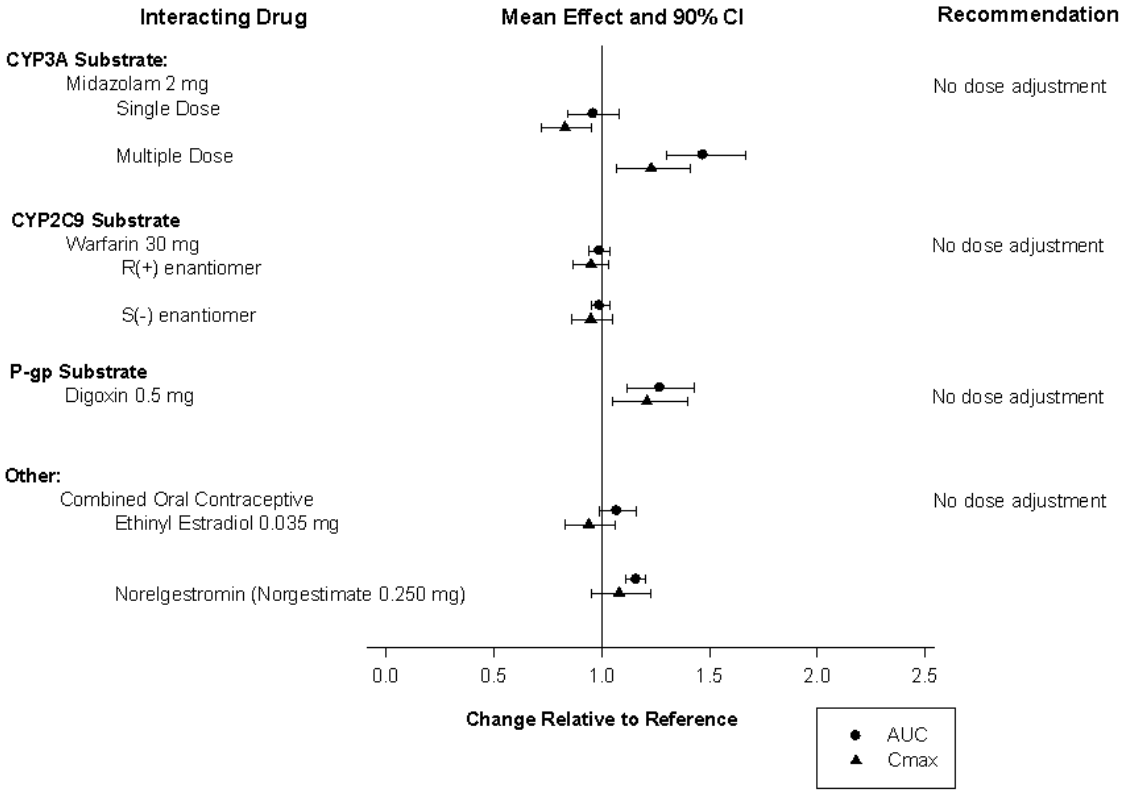


Effects of suvorexant on co-administered drugs:

Overall and consistent with the in vitro projections, suvorexant has a low potential to be a perpetrator of clinically meaningful PK drug interactions. Clinical pharmacokinetic drug-drug interaction studies were conducted to determine the potential perpetrator effects of suvorexant on midazolam (sensitive CYP3A substrate), oral contraceptives (CYP3A, uridinediphosphoglucuronosyltransferases (UGT) and sulfotransferases (SULT) substrate), warfarin (CYP2C9 substrate), and digoxin (P-gp substrate) [Figure 3]. Based on in vitro and/or in vivo data, clinically meaningful effects on the PK of substrates of other CYPs or transporters following co-administration with suvorexant are not anticipated. Based on the results from these studies, together with in vitro studies, suvorexant is regarded as a weak time-dependent inhibitor of CYP3A and a weak inhibitor of intestinal P-gp, likely causing a minor increase in the exposure to drugs metabolized by CYP3A or transported via P-gp. Therefore, restrictions on the co-administration of most drugs that are CYP3A or P-gp substrates with suvorexant are unnecessary. Owing to the narrow therapeutic index of digoxin, when co-administering digoxin with suvorexant, digoxin concentrations should be monitored as clinically

indicated. The PK of warfarin and oral contraceptives are not affected when co-administered with suvorexant.

Figure 3
The Effect of Suvorexant on the PK
of Other Co-Administered Drug



4.4 Pharmacodynamics and Special Safety Studies In Phase 1

Suvorexant demonstrated dose-dependent sleep promoting effects in healthy subjects, regardless of whether dosed during a typical wake or sleep phase. After morning administration of suvorexant, increased somnolence was observed as indicated by subjective measures (e.g. Bond and Lader Visual Analog Scale, or VAS), psychomotor performance tests, and increased delta band power on quantitative electroencephalography (qEEG). Following evening administration to healthy subjects, suvorexant demonstrated dose-dependent decreases in latency to the onset of persistent sleep (LPS), decreases in wake after the onset of persistent sleep (WASO), and increases in total sleep time (TST) as measured by polysomnography (PSG).

Standard safety evaluations demonstrated that suvorexant was generally well tolerated, and the safety profile observed in Phase 1 was similar to that observed in insomnia patients in Phase 2b/3 trials. In addition, pharmacodynamic and special safety studies were conducted to evaluate specific parameters of interest for a sleep medication. A double-blind, 3-period, single dose crossover study in 12 healthy elderly subjects (≥ 65 years) evaluated effects of suvorexant (30 mg), zolpidem (5 mg) or placebo on balance, memory and psychomotor performance (choice reaction time, CRT) during middle-of-the-night awakenings as a pilot safety assessment. Treatments were administered prior to bedtime, and balance and CRT were assessed at predose and 1.5, 4 and 8 hours postdose, with immediate and delayed word recall assessed at predose and 4 hours postdose. As compared to placebo, suvorexant demonstrated minimal impairment on balance; there was a statistically significant increase in body sway area at 1.5 hour, but not at 4 and 8 hours postdose. The impairment was less than that produced by zolpidem. Suvorexant increased CRT at 1.5 hours postdose only, whereas no significant increase was observed for zolpidem. There were no statistically significant effects on immediate and delayed word recall with either suvorexant or zolpidem treatment, although it should be noted that the ability to detect treatment differences in this study were limited by the small sample size.

Additional special safety assessments in Phase 1 included evaluation of residual effects, i.e. next-day effects of suvorexant on driving performance, memory, balance, and psychomotor tests; human abuse potential; respiratory function; and a Thorough QTc Study. Further details regarding these assessments are provided in Section 6.7. Given the possibility of additive effects with other CNS-active agents, the potential for pharmacodynamic and PK interactions were investigated when suvorexant was co-administered with alcohol and paroxetine (see in Section 6.9).

5. Overview of Efficacy

The suvorexant Phase 3 program is unique in that the trials were of long duration (3-month minimum), and the designs utilized a combined-age and combined-measures strategy. Suvorexant was evaluated in four randomized, double-blind, placebo-controlled, multicenter/multinational trials designed to establish its efficacy and safety in non-elderly (18 to <65 years) and elderly (≥65 years) adult patients with insomnia. These include one Phase 2b dose-finding trial (P006), two Phase 3 confirmatory efficacy trials (P028 and P029), and one Phase 3 long-term safety trial (P009). Subjective assessment of efficacy was evaluated by patient-report via an electronic diary in all four trials, and objective assessment was evaluated using sleep lab polysomnography (PSG) in three of the four trials (P006, P028, P029).

From results of the Phase 2b cross-over study in which doses of 10, 20, 40, and 80 were evaluated over four weeks of treatment, 40 mg was identified as the dose likely to provide the ideal benefit to risk ratio for non-elderly patients and this dose served as the anchor point for the other doses selected for Phase 3. Based on observation of slightly higher exposures in elderly patients in Phase 1 studies, the suvorexant HD for elderly

patients was adjusted to 30 mg. By matching exposures, effects of suvorexant HD were anticipated to be similar for both non-elderly and elderly patients, enabling combined-age studies to be conducted with pooling of efficacy and safety data across age groups. A lower dose (LD) of 20 mg in non-elderly and 15 mg in elderly was also evaluated in these two trials with a smaller sample size than HD and the pre-specified intention to pool sample across the two studies for a more precise estimation of LD effects. This type of approach to evaluation of the lower dose was discussed with FDA at the the End of Phase 2 meeting.

In the confirmatory efficacy trials (P028 and P029) suvorexant high dose (HD = 40 mg for non-elderly and an exposure-matched dose of 30 mg for elderly patients) was superior to placebo on all objective (WASO and LPS) and subjective (sTSTm, sWASOm, and sTSOm) measures of sleep maintenance and sleep onset at Night 1/Week 1, Month 1, and Month 3, except for LPS at Month 3 in one of the two studies (P029). It is noteworthy that with 5 endpoints and 3 timepoints in each of the two studies, in total suvorexant HD was significantly superior to placebo (adjusting for multiplicity) in 29 out of 30 contrasts. Improvements in sleep maintenance and sleep onset with suvorexant low dose (LD = 20 mg for non-elderly patients and 15 mg for elderly patients) compared to placebo were generally less than improvements with suvorexant HD. Supportive evidence of long-term efficacy was provided by the results of Protocol 009, which included non-elderly and elderly patients (N=779) treated with either suvorexant (40 mg for non-elderly, or 30 mg for elderly patients) or placebo for 12 months.

5.1 Features of Efficacy Trials

Two Phase 3 confirmatory efficacy trials (P028 and P029) provide the primary evidence for the efficacy of suvorexant in the treatment of insomnia. These two combined-age trials were similarly designed, multinational, randomized, double-blind, parallel-group efficacy trials, conducted in patients with chronic insomnia. Patients received treatment with suvorexant HD (40 mg in non-elderly, 30 mg in elderly), suvorexant LD (20 mg in non-elderly, 15 mg in elderly) or placebo. Consisent with the recommended timing for use of sleep medications and to provide the most conservative estimate of sleep induction effects, patients were instructed to self-administer study drug immediately before going to bed in the outpatient setting. This dosing time differs from dosing conditions in some published trials of other sleep agents where patients were instructed to take study drug earlier in order to achieve drug exposure levels before attempting to sleep. For those patients who underwent overnight PSG in the sleep laboratory, witnessed doses were administered 30 minutes before lights out as is the practice in sleep laboratory studies.

The confirmatory efficacy trials (P028 and P029) were also designed as combined-measures studies in order to provide assessments that support both subjective and objective efficacy measures of insomnia, wherein all patients completed a daily sleep diary in their naturalistic environment and a majority of patients in each trial also underwent PSG in the sleep laboratory. This design was innovative given the historical

framework of hypnotic development, as typically subjective and objective efficacy were assessed in separate trials and separate studies by age (i.e. non-elderly and elderly) were conducted. The combined-measures design has the advantage that an individual trial is sufficiently powered to assess both subjective and objective assessments in the same patient population, negating the need to relate results from separate subjective and objective endpoint trials. The combined-age strategy allows for a pooled assessment of efficacy and safety across the continuous variable of age.

Given the similarity of the pivotal efficacy studies design, an integrated statistical analysis plan pre-specified that pooled data would be evaluated from these two efficacy trials (P028 and P029) to provide a more precise estimate of the treatment differences for the primary and secondary hypotheses and selected exploratory objectives. The pooled evaluation of LD also provides a more robust sample size for estimation of LD effects in comparison to HD, due to the secondary and exploratory nature of the LD comparisons to placebo in P028 and P029, respectively. Long term efficacy data was collected via patient-report in the Phase 3 long-term trial (P009) to provide support in for the sustained subjective efficacy of suvorexant HD for up to 12 months in non-elderly and elderly patients with insomnia. Additional supportive evidence for the efficacy of suvorexant in the treatment of insomnia was obtained in a Phase 2b two-period crossover dose-ranging study conducted in 254 non-elderly patients with primary insomnia, in which suvorexant doses of 10 mg, 20 mg, 40 mg, or 80 mg were evaluated versus placebo.

5.2 Primary Efficacy Endpoints and Timepoints

The primary objective of the program was to evaluate the efficacy of suvorexant HD in non-elderly and elderly patients with insomnia by improvement in sleep maintenance and sleep onset assessed by both polysomnographic (PSG) objective assessments and subjective patient reports. Four variables represent the primary endpoints included in the two confirmatory efficacy trials (P028 and P029). The two key objective maintenance and onset measures in these confirmatory trials were Wakefulness After persistent Sleep Onset (WASO) and Latency to onset of Persistent Sleep (LPS) respectively, data for which were collected via the gold standard technique of PSG in the sleep laboratory. The two key endpoints for the subjective (patient-reported) evaluation of sleep maintenance and onset were subjective Total Sleep Time (sTST) and subjective Time to Sleep Onset (sTSO), respectively. Based on FDA input, supportive analyses of sWASO are also provided as further evidence for the efficacy of suvorexant in sleep maintenance.

Given that patients sometimes use treatments for insomnia for short durations, as well as chronically, these efficacy variables were measured after initial treatment (Night 1 PSG and Week 1 e-diary) and during longer-term treatment (Months 1 and 3) to evaluate both early and sustained efficacy in Protocols 028 and 029. Additionally, in the long-term safety trial (P009), subjective patient reports via e-diary were collected at specified intervals throughout the duration of the study treatment phases. Since some of the subjective measures represent the average value over time (e.g., the average value over 7

days for Week 1) a convention of adding 'm' after the measure is used to denote a mean value over time for this measure (e.g., Week 1 sTSTm).

Sample sizes for the confirmatory trials (P028 and P029) were selected based on power estimates for detection of clinically meaningful differences between suvorexant HD and placebo based on results of the Phase 2b dose-ranging study (see discussion in Section 5.4), in which the primary measure was sleep efficiency (SE), a composite measure that assesses sleep (via polysomnography) across the entire night, encompassing both sleep induction and sleep maintenance. Suvorexant LD was a secondary objective in P028, and an exploratory objective in P029, and a pooled analysis across the two trials was pre-specified in the integrated Statistical Analysis Plan to enable a more precise estimate of LD effects. The primary and/or secondary efficacy endpoints in the Phase 2b/3 trials are summarized in [Table 2].

Table 2
Summary of Phase 2b/3 Trial Endpoints

Protocol 006 – Phase 2b Dose-finding trial					
Suvorexant/placebo or placebo/Suvorexant ▪ Suvo 10 mg ▪ Suvo 20 mg ▪ Suvo 40 mg ▪ Suvo 80 mg Placebo	**OBJECTIVES**				
	Comparison	**Sleep Maintenance**		**Sleep Onset**	
		Variable	Timepoints	Variable	Timepoints
	Primary				
	Suvo vs. placebo	SE	Night 1, Week 4	--	
	Secondary				
	Suvo vs. Placebo	WASO	Night 1, Week 4	LPS	Night 1, Week 4
Protocol P028 & P029– Phase 3 Confirmatory Efficacy Trials					
Nonelderly patients: ▪ Suvo 40 mg (HD) ▪ Suvo 20 mg (LD) ▪ Placebo **Elderly patients** ▪ Suvo 30 mg (HD) ▪ Suvo 15 mg (LD) Placebo	**Primary**				
	HD vs. Placebo	CFB sTSTm	Month 1, 3	CFB sTSOm	Month 1, 3
		CFB WASO	Month 1, 3	CFB LPS	Month 1, 3
	Secondary				
	HD vs. Placebo	CFB sTSTm	Week 1	CFB sTSOm	Week 1
		CFB WASO	Night 1	CFB LPS	Night 1
	LD vs. Placebo (P028 only)	CFB sTSTm	Month 1, 3	CFB sTSOm	Month 1, 3
		CFB WASO	Month 1, 3	CFB LPS	Month 1, 3
		CFB sTSTm	Week 1	CFB sTSOm	Week 1
		CFB WASO	Night 1	CFB LPS	Night 1

Summary of Phase 2b/3 Trial Endpoints (Cont.)

<table>
<tr><td colspan="6">Protocol 009 – Long-term Safety Trial</td></tr>
<tr><td rowspan="8">Nonelderly patients:
▪ Suvo 40 mg
▪ Placebo
Elderly patients
▪ Suvo 30 mg
▪ Placebo</td><td colspan="5">Primary</td></tr>
<tr><td>Suvo (HD) vs. Placebo</td><td colspan="4">Safety and tolerability</td></tr>
<tr><td colspan="5">Secondary</td></tr>
<tr><td>Comparison</td><td>Sleep Maintenance</td><td colspan="3">Sleep Onset</td></tr>
<tr><td></td><td>Variable</td><td>Timepoint</td><td>Variable</td><td>Timepoint</td></tr>
<tr><td>Suvo (HD) vs. Placebo</td><td>CFB sTSTm</td><td>Month 1</td><td>CFB sTSOm</td><td>Month 1</td></tr>
<tr><td colspan="6">CFB=change from baseline
Please note: Analysis of sWASOm as a key supportive endpoint for sleep maintenance was also conducted. In this analysis sTSTm was substituted by sWASO in the multiplicity strategy.</td></tr>
</table>

5.3 Relevance and Key Features of the Patient Population

The Phase 3 program for suvorexant evaluated efficacy in patient samples representative of those meeting DSM-IV criteria primary insomnia (difficulty initiating or maintaining sleep, or non-restorative sleep) that is present for at least 1 month. In the confirmatory trials (P028 and P029), study eligibility also required that patients meet the following insomnia symptom severity thresholds:

- For the "PQ-Cohort" (patients with both PSG and e-diary questionnaire data) entry criteria were only based on objective PSG criteria for WASO and LPS:
    - LPS >20 minutes on both Screening and Baseline PSG nights;
    - mean WASO ≥ 60 minutes on the combined Screening and Baseline PSG nights; neither night was ≤ 45 minutes.
- For the "Q-Cohort" (patients with e-diary questionnaire data only) entry criteria were based on subjective questionnaire (e-diary) criteria for sTST and sTSO:
    - sTST <6.5 hours on at least 4 nights for the week prior to baseline;
    - sTSO ≥ 30 minutes on at least 4 nights for the week prior to baseline.

Support to conduct combined-measures trials, wherein two cohorts with different entry criteria can be reasonably combined to result in a similar insomnia patient population, was based on data from previous Merck PSG insomnia trials with another experimental

sleep medication, gaboxadol (MK-0928 P002 and P004). Based on these prior studies, it was anticipated that for the suvorexant trials patients in the PQ-Cohort who satisfied PSG criteria would also have subjective complaints sufficiently similar in severity to those patients in the Q-Cohort who satisfied subjective entry criteria, thereby allowing these cohorts to be pooled for the evaluation of subjective efficacy. An important and unique aspect of the Phase 3 long-term safety trial (P009) was that study eligibility regarding insomnia only required that patients meet DSM-IV-TR insomnia criteria, e.g. no insomnia severity threshold level was required with respect to sleep onset or sleep maintenance parameters; as such, patients in this study sample closely approximate "real world" insomnia patients.

Patient characteristics across the individual Phase 3 trials were generally similar and included both men and women with a wide age range, having diverse racial backgrounds, and from 24 countries throughout the world; refer to [Table 3]. Overall, there were more female than male patients in each trial with approximately two-thirds of the patients in P028 and P029 being female. The median age was approximately 59 years in P028 and P029, and 66 years in P009. There were no notable differences in baseline characteristics of non-elderly patients (<65 years) as compared with elderly ones (≥ 65 years). A thorough description of the patient characteristics for the primary safety population (combined Phase 3 population - Months 0 to 3) is provided in [Section 6.4].

Table 3
Select Baseline Demographic Characteristics by Trial in the Phase 3 Trials
Treatment Phase (All Patients Treated)

Variable	P028			P029			P009		Total		
	Suvo LD (N=254)	Suvo HD (N=383)	Placebo (N=384)	Suvo LD (N=239)	Suvo HD (N=387)	Placebo (N=383)	Suvo HD (N=521)	Placebo (N=258)	Suvo LD (N=493)	Suvo HD (N=1291)	Placebo (N=1025)
Gender											
Male: n (%)	92(36.2)	153(39.9)	139(36.2)	82(34.3)	120(31.0)	136(35.5)	234(44.9)	109(42.2)	174(35.3)	507(39.3)	384(37.5)
Female: n (%)	162(63.8)	230(60.1)	245(63.8)	157(65.7)	267(69.0)	247(64.5)	287(55.1)	149(57.8)	319(64.7)	784(60.7)	641(62.5)
Age											
Mean	55	56	56	56	57	57	61	62	55	58	58
Median	59	58	58	59	59	59	66	66	59	64	62
Range	20 to 84	18 to 87	21 to 85	18 to 86	20 to 86	20 to 86	18 to 88	18 to 90	18 to 86	18 to 88	18 to 90
Age Category											
<65: n (%)	147(57.9)	222(58.0)	223(58.1)	144(60.3)	229(59.2)	226(59.0)	213(40.9)	107(41.5)	291(59.0)	664(51.4)	556(54.2)
≥65: n (%)	107(42.1)	161(42.0)	161(41.9)	95(39.7)	158(40.8)	157(41.0)	308(59.1)	151(58.5)	202(41.0)	627(48.6)	469(45.8)
Race											
White n (%)	168(66.1)	253(66.1)	244(63.5)	190(79.5)	310(80.1)	309(80.7)	476(91.4)	231(89.5)	358(72.6)	1039(80.5)	784(76.5)
Black n (%)	15(5.9)	18(4.7)	25(6.5)	4(1.7)	20(5.2)	21(5.5)	33(6.3)	24(9.3)	19(3.9)	71(5.5)	70(6.8)
Asian n (%)	66(26.0)	98(25.6)	99(25.8)	27(11.3)	26(6.7)	25(6.5)	6(1.2)	1(0.4)	93(18.9)	130(10.1)	125(12.2)
Other n (%)	5(2.0)	14(3.7)	16(4.2)	18(7.5)	31(8.0)	28(7.3)	6(1.2)	2(0.8)	23(4.7)	51(4.0)	46(4.5)
Cohort											
Q n (%)	61(24.0)	92(24.0)	94(24.5)	89(37.2)	88(22.7)	86(22.5)	521(100.0)	258(100.0)	150(30.4)	701(54.3)	438(42.7)
PQ n (%)	193(76.0)	291(76.0)	290(75.5)	150(62.8)	299(77.3)	297(77.5)	0(0.0)	0(0.0)	343(69.6)	590(45.7)	587(57.3)

Suvo LD = Suvorexant 20 mg for patients <65 years and Suvorexant 15 mg for patients ≥65 years.
Suvo HD = Suvorexant 40 mg for patients <65 years and Suvorexant 30 mg for patients ≥65 years.

Baseline values for the various efficacy measures were generally comparable among treatment groups within the individual trials. Overall, patients in the confirmatory trials (P028 and P029) had substantial impairment with regard to onset and maintenance with less than 5.5 hours of sTSTm, more than 1 hour time to sleep onset as measured by both sTSOm and LPS and nearly 2 hours of WASO. Slightly greater severity of symptoms was observed in P029 compared to P028 as judged by the subjective assessments (sTSTm, sTSOm, and sWASOm), but not based on PSG-measured sleep onset and maintenance (LPS and WASO). Despite the lack of specific entry criteria with regards to symptom severity, patients in P009 showed overall similar impairment at baseline with regards to subjective sleep onset and sleep maintenance (refer to [Table 4]. Some differences were noted in baseline values between non-elderly and elderly in the pooled (P028+P029) population for some efficacy measures; sWASOm and WASO were higher while sTSOm and sTSTm were lower for elderly patients compared with non-elderly ones. This is consistent with the overall age-related increase in sleep maintenance difficulties observed in the general population and the generally higher rate of elderly patients suffering from insomnia characterized by sleep maintenance difficulties [35; 36; 4]. Within each age group, the baseline severities among the treatment groups across the key efficacy measures were generally comparable.

Table 4
Summary Statistics for Efficacy Measures at Baseline in the Phase 3 Trials
Treatment Phase (All Patients Treated)

Protocol #	Endpoint	Suvorexant LD		Suvorexant HD		Placebo	
		N	Mean (minutes)	N	Mean (minutes)	N	Mean (minutes)
Phase 3 – Confirmatory Efficacy							
028	sTSTm	252	322.4	383	316.1	384	315.7
	sTSOm	252	63.3	383	68.0	384	66.9
	sWASOm	252	73.9	381	78.4	384	78.2
	WASO	193	119.2	291	117.7	290	114.9
	LPS	193	68.9	291	61.8	290	66.2
029	sTSTm	238	298.3	386	315.3	383	309.7
	sTSOm	238	86.0	386	74.4	383	81.3
	sWASOm	233	84.8	382	82.1	375	83.3
	WASO	150	119.6	299	119.4	295	118.4
	LPS	150	65.3	299	67.3	295	68.0
Phase 3 – Long-Term Safety							
009	sTSTm	-	-	492	319.5	245	330.0
	sTSOm	-	-	492	65.9	245	65.3
	sWASOm	-	-	488	79.6	241	71.2
	WASO	-	-	-	-	-	-
	LPS	-	-	-	-	-	-

5.4 Overview of Statistical Methodology

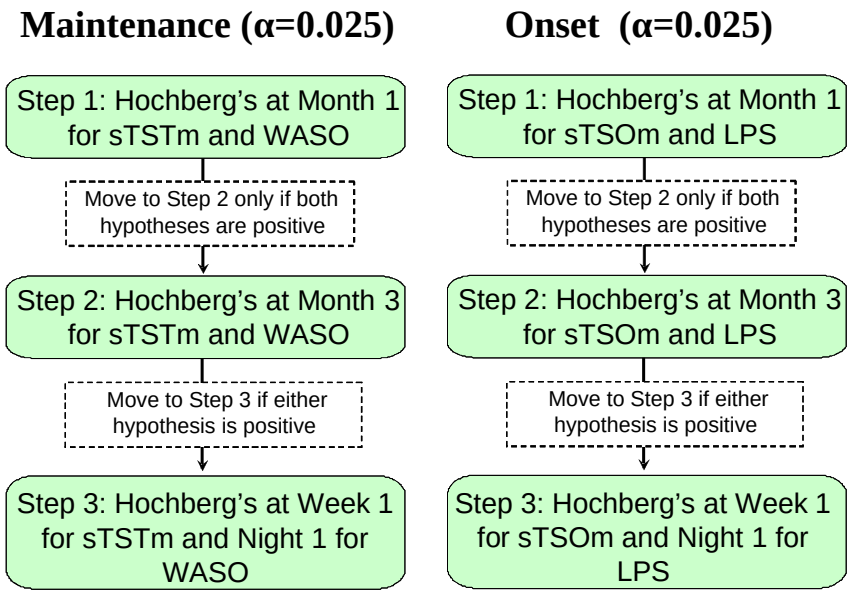
The primary analyses in the Phase 3 trials were based upon the entire trial population (i.e., across non-elderly and elderly age groups) for P028, P029, and P009 using the full analysis set (FAS). For P028 and P029, a longitudinal data analysis (LDA) model was used to evaluate the change from baseline for each of the primary and secondary endpoints. In this model, time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The analysis model included the baseline value of the response variable, age group, region, gender, treatment group, time, and the interaction of treatment group by time; treatment comparisons at specific time points were constructed using the treatment group by time interaction term. An additional term for cohort (PQ; Q) was included in the model for subjective endpoints in P029 (but not P028 due to confounding of region and cohort since all patients in the Q cohort were from Japan). An unstructured covariance matrix was used to model the correlation among repeated measurements. P009 used a similar model to that described for P028.

The evaluation of efficacy for suvorexant focuses on the 3-month Treatment Phase of the confirmatory efficacy trials (P028 and P029). These trials were powered to detect clinically meaningful differences between suvorexant HD and placebo (based on treatment effects observed in the Phase 2b trial and with consideration of treatment effects reported in the labels and trial literature of other sleep agents and as confirmed in consultation with sleep experts), whereas the sample sizes for suvorexant LD were lower in each trial relative to the other treatment groups and intended to provide information on the dose response relationship. Based upon power calculations using data from the Phase 2b trial (with variability estimates supported by other in-house data from a prior insomnia development program), the planned sample size for suvorexant HD and placebo was 360 patients and for suvorexant LD was 240 and 225 patients in P028 and P029, respectively. For PSG endpoints (i.e., collected in the PQ-cohort), the planned sample size for suvorexant HD and placebo was 270 patients and for suvorexant LD was 180 and 135 patients in P028 and P029, respectively. The studies had 91% power to declare all primary maintenance endpoints significant for suvorexant HD in accordance with the multiplicity strategy. The studies had 62% power to declare all primary onset endpoints significant for suvorexant HD in accordance with the multiplicity strategy; the probability of declaring both Month 1 onset endpoints significant and at least one Month 3 onset endpoint significant for suvorexant HD in accordance with the multiplicity strategy was 81%. The treatment differences (suvorexant HD vs. placebo) that the trials were designed to detect (based upon the assumed variability) ranged from 14 to 20 minutes for primary maintenance endpoints and from 11 to 12 minutes for primary onset endpoints.

A multiplicity strategy was used to control the false positive error rate (or Type I error rate) for the primary and key secondary hypotheses in the confirmatory Phase 3 efficacy trials and is shown in [Figure 4]. The overall 5% alpha level was split equally between sleep maintenance and sleep onset hypotheses related to suvorexant HD vs. placebo. Within each sleep indication, the subjective and objective endpoints were tested at the

two-sided 2.5% level according to the following strategy. Within each primary timepoint (i.e., Month 1 and Month 3), a Hochberg approach was used to evaluate the subjective (e.g., sTSTm) and objective (e.g., WASO) endpoints. The Hochberg approach concludes that both endpoints (e.g., sTSTm and WASO at Month 1) are significant if the larger p-value is less than 0.025; if the larger p-value is not less than 0.025, then it concludes that the endpoint associated with the smaller p-value is significant if it is less than 0.0125. (Note that p-values for the efficacy treatment comparisons are provided to the 5th decimal place due to this multiplicity strategy.) A fixed sequential testing procedure was used to move from the first set of primary hypotheses (e.g., sTSTm and WASO at Month 1) to the next set of primary hypotheses (e.g., sTSTm and WASO at Month 3); both hypotheses must have been significant at Month 1 in order to test the Month 3 hypotheses (at the two-sided 2.5% level). This procedure strongly controls the overall Type I error level across indications, endpoints (PSG/e-diary) and timepoints related to the primary hypotheses. If at least one of the Month 3 hypotheses was significant, then the secondary set of hypotheses related to Night 1 (PSG endpoint) and Week 1 (e-diary endpoint) were tested for suvorexant HD vs. placebo at the two-sided 2.5% level. While nominal p-values are provided for other exploratory comparisons and/or endpoints (and for pooled analyses of primary/secondary endpoints), only those defined in the multiplicity strategy for each trial are classified as statistically significant.

Figure 4
Multiplicity Strategy for Phase 3 Confirmatory Efficacy Trials (P028, P029)
for Suvorexant HD vs. Placebo



For Protocol 028, suvorexant LD comparisons to placebo were evaluated as secondary hypotheses. If at least one of the Month 3 endpoints was positive for suvorexant HD vs. placebo (according to the multiplicity strategy described), then suvorexant LD vs. placebo was tested using a similar multiplicity strategy as described for HD, with the additional requirement that for a particular endpoint, the HD comparison to placebo must be positive in order to declare the LD comparison to placebo positive.

To further investigate maintenance effects, additional supportive analyses which focus on sWASOm are provided. In particular, results for sWASOm and WASO are provided using the same multiplicity strategy as outlined for sTSTm above (i.e., replacing sTSTm with sWASOm in the multiplicity strategy).

Pooled analyses of these two trials were performed in accordance with the Integrated Statistical Analysis Plan (iSAP) for efficacy, and serve to: 1) provide more precise estimates of the treatment differences (suvorexant HD vs. placebo, and suvorexant LD vs. placebo) with respect to the primary and secondary efficacy endpoints; and 2) provide a more accurate assessment of the consistency of these treatment differences across subgroups of selected baseline factors. No multiplicity adjustments were applied for the pooled (P028+P029) efficacy analyses since the primary purpose of these analyses was to improve the precision of estimates of the treatment group comparisons. Nominal p-values were provided for all statistical tests.

5.5 Efficacy Results

Following discussion of the Phase 2b study results below, data presentation for the confirmatory Phase 3 studies P028 and P029 that follows is focused first on the primary and secondary sleep maintenance and sleep onset endpoints collected through PSG and patient reports. Sleep maintenance (sTSTm, sWASOm) are discussed initially, followed by the objective sleep maintenance variable (WASO); the subjective variable for sleep onset (sTSOm) is then discussed, followed by the objective sleep onset variable (LPS). Within each endpoint, the suvorexant HD comparisons to placebo are discussed/presented first, followed by suvorexant LD comparisons to placebo Results of other efficacy endpoints are presented for both suvorexant HD and LD for the combined population (P028+P029) in Section [5.5.2.4]. Results of the key efficacy endpoints in P009 are presented in Section [5.5.3 Long Term Efficacy].

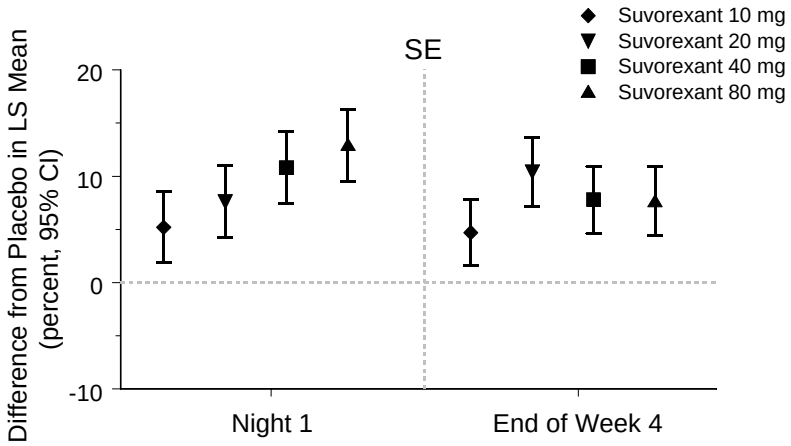
5.5.1 Phase 2b Dose-Ranging Trial (P006) and Rationale for Phase 3 Dose Selection

In the Phase 2b placebo-controlled dose-finding cross-over study, 254 non-elderly patients were treated for 4 weeks with one of four doses of suvorexant (10 mg, 20 mg, 40 mg, or 80 mg) and placebo via four separate two-treatment, two-period crossover groups. Objective endpoints were measured at Night 1 and end of Week 4. All doses of suvorexant were superior to placebo on the primary endpoint measure of sleep efficiency (SE, which is objective TST divided by total time in bed [8 hr] x 100). A display of the

difference for suvorexant compared to placebo for the primary efficacy variable (Sleep efficiency [SE]) and for the secondary efficacy variables (WASO and LPS) are plotted by dose at Night 1 and end of Week 4 in Figure 5]; improvement compared to placebo is represented by positive numbers for SE and by negative numbers for WASO and LPS. All doses of suvorexant (10 mg, 20 mg, 40 mg and 80 mg) were superior to placebo at Night 1 and end of Week 4 as measured by the primary endpoint SE and the secondary efficacy endpoint, WASO. The study was not powered to detect differences in the secondary efficacy endpoint of LPS, and no dose of suvorexant was superior to placebo in improving sleep onset as measured by LPS, according to the study multiplicity strategy. However, the numerical improvement observed provided sufficient information regarding LPS effect sizes to establish power estimates for demonstrating objective sleep induction effects in Phase 3.

As patient-reported efficacy is also essential to demonstrate in Phase 3, exploratory analyses of the subjective sleep variables from the Phase 2b study were conducted and showed that patients reported better sTSTm, sTSOm, and sWASOm [Figure 6,Figure 7, Figure 8] for the two higher doses of suvorexant (40 mg and 80 mg) than for placebo on most weeks (nominal p-values <0.05; improvement compared to placebo is represented by positive numbers for sTSTm and by negative numbers for sTSOm and sWASOm). These data indicated that a minimum dose of 40 mg was most likely to demonstrate subjective efficacy in Phase 3.

Figure 5
Protocol 006
Differences in Least Squares (LS) Means (and 95% CIs) from Placebo
for Sleep Efficiency (SE), WASO, and LPS



Protocol 006
Differences in Least Squares (LS) Means (and 95% CIs) from Placebo
for Sleep Efficiency (SE), WASO, and LPS (Cont.)

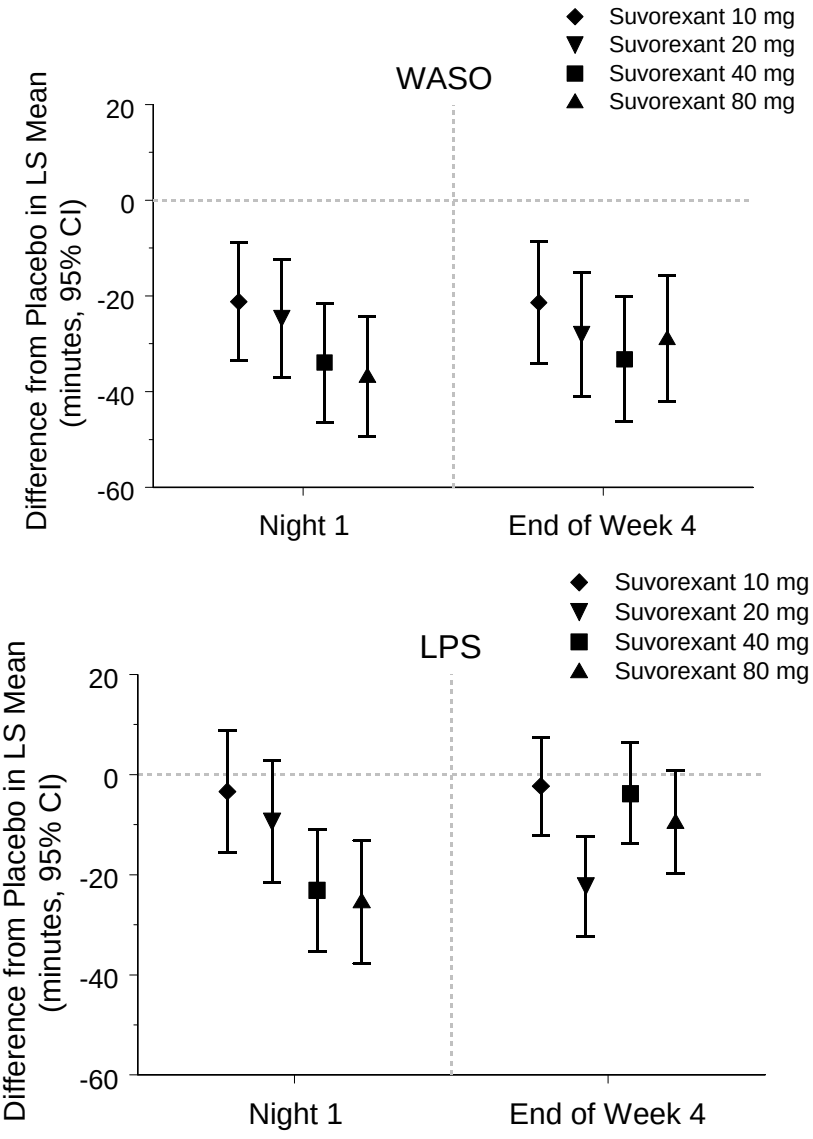


Figure 6
Protocol 006
Differences in LS Means (and 95% CIs) from Placebo for sTSTm

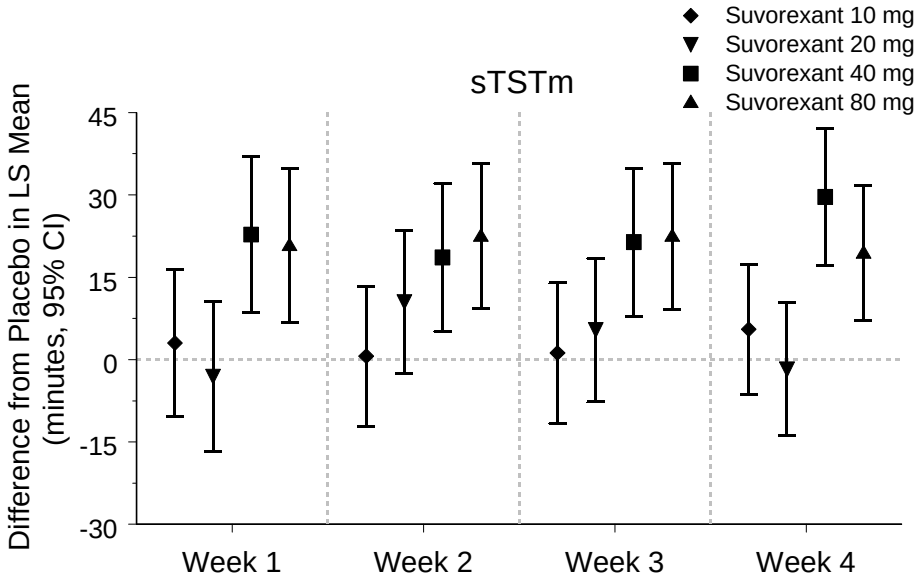


Figure 7
Protocol 006
Differences in LS Means (and 95% CIs) from Placebo for sTSOm

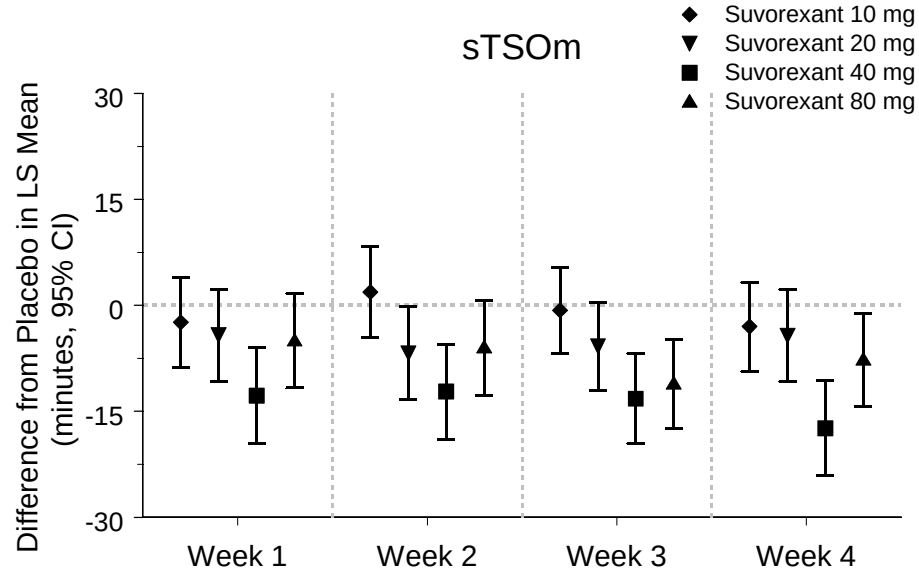
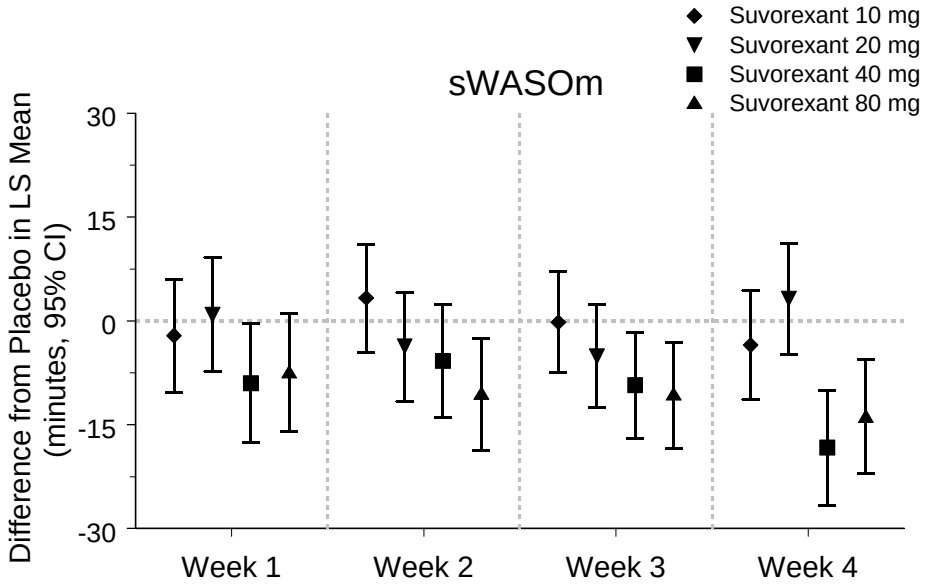


Figure 8
Protocol 006
Differences in LS Means (and 95% CIs) from Placebo for sWASOm



Overall, the doses of 40 mg and 80 mg most consistently demonstrated efficacy across key objective and subjective endpoints in the Phase 2b study, whereas effects were less consistent at the 20 mg dose and either less robust, or absent at the 10 mg dose. With respect to safety considerations, no serious safety or tolerability concerns were observed at any suvorexant dose studied; however, a dose response was observed with respect to number of patients experiencing one or more AEs, AEs in system categories for Neurologic System Disorders and Psychiatric Disorders, and for specific AEs of somnolence, suggesting that with regard to potential benefit-risk the dose of 80 mg offered minimal advantage over 40 mg, whereas a dose of 20 mg would be unlikely to provide maximal benefit on some sleep endpoints (reference Phase 2b safety table in Appendix 1).

In addition to the results observed in this Phase 2b study and taking into account additional data from Phase 1 trials, dose-response modeling and simulation of WASO and LPS was performed to inform the Phase 3 dose selection. The results indicated efficacy response is increased between 20 mg and 40 mg, with further increases between 40 mg and 80 mg being more modest. Taken together, these results suggested 40 mg as the non-elderly adult dose most likely to be well-tolerated and efficacious in Phase 3; this dose was the highest dose of suvorexant (referred to as suvorexant HD) evaluated in the Phase 3 trials. Based on evidence for slightly higher exposures in elderly patients in Phase 1 studies, suvorexant HD in elderly patients was 30 mg. Thus exposure levels for suvorexant HD were anticipated to be similar for non-elderly and elderly patients enabling the pooling of efficacy and safety data across age groups. A lower dose

(referred to as suvorexant LD) of 20 mg for non-elderly and 15 mg dose for elderly patients was also included in the two confirmatory efficacy trials (P028 and P029) to further discern the dose-response relationship in non-elderly adults.

5.5.2 Confirmatory Efficacy Trials (P028, P029, P028+P029 combined)

Two similarly-designed confirmatory efficacy trials (P028 and P029), were conducted that included 2041 randomized patients (1191 non-elderly and 839 elderly treated patients) who received treatment with either suvorexant HD, suvorexant LD, or placebo during a 3-month treatment period. The overall completion rate at the end of the 3-month Treatment Phase was high (consistent with the trial literature in insomnia) and similar in P028 (89.6%) and P029 (86.5%) (refer to [Table 5]. During the 3-month treatment period in these trials, the most common reasons for discontinuations were due to AEs and withdrawal by the patient; less than 2% discontinued due to lack of efficacy.

Table 5
Disposition of Patients by Treatment for P028, P029
Treatment Phase (All Patients Randomized)

Protocol #	Disposition	Suvo LD n (%)	Suvo HD n (%)	Placebo n (%)	Total n (%)
Phase 3 – Confirmatory Efficacy					
028	**Patients in population**	254	383	385	1022
	Not Treated	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
	Completed Treatment	230 (90.6)	345 (90.1)	341 (88.6)	916 (89.6)
	Discontinued during Treatment	24 (9.4)	38 (9.9)	43 (11.2)	105 (10.3)
	Adverse Event	6 (2.4)	15 (3.9)	21 (5.5)	42 (4.1)
	Withdrawal by Subject	6 (2.4)	8 (2.1)	12 (3.1)	26 (2.5)
	Protocol Violation	5 (2.0)	3 (0.8)	1 (0.3)	9 (0.9)
	Lost to Follow-up	1 (0.4)	1 (0.3)	0 (0.0)	2 (0.2)
	Lack of Efficacy	1 (0.4)	7 (1.8)	9 (2.3)	17 (1.7)
	Pregnancy	1 (0.4)	1 (0.3)	0 (0.0)	2 (0.2)
	Physician Decision	4 (1.6)	3 (0.8)	0 (0.0)	7 (0.7)
029	**Patients in population**	240	392	387	1019
	Not Treated	1 (0.4)	5 (1.3)	4 (1.0)	10 (1.0)
	Completed Treatment	205 (85.4)	346 (88.3)	330 (85.3)	881 (86.5)
	Discontinued during Treatment	34 (14.2)	41 (10.5)	53 (13.7)	128 (12.6)
	Adverse Event	10 (4.2)	19 (4.8)	17 (4.4)	46 (4.5)
	Withdrawal by Subject	8 (3.3)	9 (2.3)	19 (4.9)	36 (3.5)
	Protocol Violation	5 (2.1)	4 (1.0)	8 (2.1)	17 (1.7)
	Lost to Follow-up	2 (0.8)	4 (1.0)	1 (0.3)	7 (0.7)
	Lack of Efficacy	7 (2.9)	4 (1.0)	8 (2.1)	19 (1.9)
	Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Physician Decision	2 (0.8)	1 (0.3)	0 (0.0)	3 (0.3)

Each patient is counted once for Study Disposition and Protocol Milestone based on the latest corresponding disposition record.
Suvo LD = Suvorexant 20 mg for patients < 65 years and Suvorexant 15 mg for patients ≥ 65 years.
Suvo HD = Suvorexant 40 mg for patients < 65 years and Suvorexant 30 mg for patients ≥ 65 years

5.5.2.1 Sleep Maintenance

Suvorexant HD

Suvorexant HD demonstrated efficacy in sleep maintenance by both subjective and objective measures in both pivotal studies and at all pre-specified timepoints. Significant differences from placebo in sTSTm and WASO in [
Table 6] were observed at all timepoints for the individual studies (P028 and P029). All comparisons were highly significant ($p<0.00001$) in meeting the pre-specified objectives in both confirmatory trials, P028 and P029. Estimated differences and 95% CIs for HD versus placebo for P028 and P029 in [Figure 9] show that improvements relative to placebo for these two variables (sTSTm, and WASO) were sustained throughout the 3-month Treatment Phase.

Despite having no entry criteria severity threshold for sWASOm, the results for the supportive analysis of sWASOm in [
Table 6]
Table 6 indicate that suvorexant HD was also superior to placebo in decreasing sWASOm at all timepoints with p-values of <0.006, providing further support for the efficacy of suvorexant HD in improving sleep maintenance.

The magnitude of improvements in the objective and subjective maintenance measures observed for suvorexant HD in P028 and P029 was robust. In P028, for the maintenance endpoints, sTSTm was increased 19.7 minutes, sWASOm was reduced 6.9 min, and objective WASO was reduced 22.9 minutes for suvorexant HD as compared to placebo at Month 3. Similar results were observed in P029; sTSTm was increased 25.1 minutes, sWASO was reduced 8.9 minutes, and WASO was reduced 29.4 minutes for suvorexant HD as compared to placebo at Month 3. Maintenance values at earlier timepoints were generally similar indicating that maintenance effects for suvorexant are not diminished over time.

Figure 9
Estimated Difference and 95% Confidence intervals for
Change from Baseline in Sleep Maintenance Efficacy Endpoints
Suvorexant High Dose (HD) versus Placebo – P028, P029

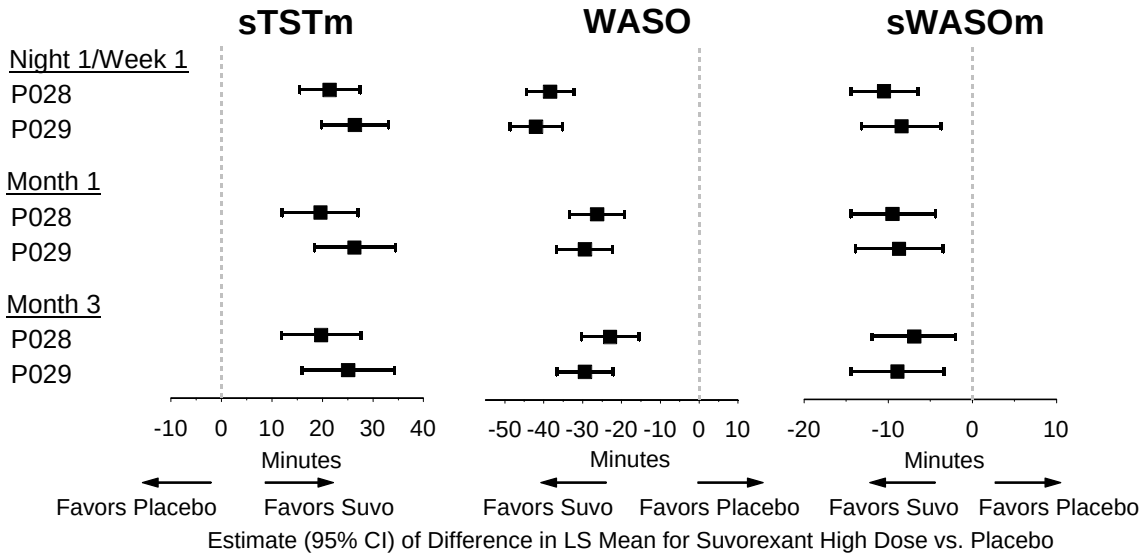


Table 6
Effects of Suvorexant High Dose on Sleep Maintenance Measures (Minutes) – P028, P029 and Pooled (P028+P029)

Endpoint	Timepoint	Protocol	Suvo HD LS Mean Change From Baseline	Placebo LS Mean Change From Baseline	LS Mean Difference From Placebo	P-value
sTSTm†	Week 1	028	36.0	14.6	21.4	<0.00001*
		029	40.4	14.0	26.4	<0.00001*
		Pooled	38.1	14.4	23.7	<0.00001
	Month 1	028	42.6	23.1	19.6	<0.00001*
		029	48.7	22.4	26.3	<0.00001*
		Pooled	45.6	22.9	22.7	<0.00001
	Month 3	028	60.3	40.6	19.7	<0.00001*
		029	62.8	37.7	25.1	<0.00001*
		Pooled	61.4	39.3	22.1	<0.00001
sWASOm‡	Week 1	028	-21.1	-10.6	-10.5	<0.00001*
		029	-22.0	-13.6	-8.4	0.00046*
		Pooled	-21.5	-12.1	-9.5	<0.00001
	Month 1	028	-27.4	-17.9	-9.5	0.00025*
		029	-29.5	-20.8	-8.7	0.00099*
		Pooled	-28.5	-19.4	-9.1	<0.00001
	Month 3	028	-36.5	-29.6	-6.9	0.00565*
		029	-38.7	-29.8	-8.9	0.00167*
		Pooled	-37.6	-29.8	-7.8	0.00003
WASO§	Night 1	028	-58.0	-19.6	-38.4	<0.00001*
		029	-63.3	-21.3	-42.0	<0.00001*
		Pooled	-60.4	-20.5	-39.9	<0.00001
	Month 1	028	-45.0	-18.7	-26.3	<0.00001*
		029	-51.9	-22.5	-29.4	<0.00001*
		Pooled	-48.3	-20.6	-27.6	<0.00001
	Month 3	028	-47.9	-25.0	-22.9	<0.00001*
		029	-54.2	-24.8	-29.4	<0.00001*
		Pooled	-50.9	-25.0	-25.9	<0.00001

* Statistically significant based upon the protocol-specified multiplicity strategy (defined using sTSTm in protocol, but also using sWASOm in a supportive analysis); only nominal p-values are provided for the pooled analyses
† sTSTm is subjective Total Sleep Time (weekly mean of daily measurements)
‡ sWASOm is subjective Wake time After Sleep Onset (weekly mean of daily measurements)
§ WASO is objective Wakefulness After persistent Sleep Onset (PSG)
LS = Least Squares (based upon primary analysis model)

Based on the pre-specified pooled analysis of the two confirmatory trials, patient-reported sleep duration as measured by sTSTm at Month 3 was increased following suvorexant HD treatment, with a difference of 22.1 minutes in favor of suvorexant compared to placebo. Similarly, PSG-measured WASO was improved at Month 3, with a difference of 25.9 minutes favoring suvorexant compared to placebo. The percent reduction from

baseline for sWASOm (47%) by suvorexant HD was similar to that of WASO, but with a more moderate difference of -7.8 minutes favoring suvorexant compared to placebo. Lastly, while evaluation of placebo-subtracted results inform the relative clinical meaning of treatment, change from baseline results of the pooled data inform what an individual patient may experience from treatment, and as indicated LS-mean change from baseline improvements sTSTm, sWASOm, and WASO for the pooled (P028+P029) data for Month 3 were substantial at 61.4, -37.6, and -50.9 minutes, respectively.

For context, the magnitude of these results fall within or beyond effect size ranges identified as clinically meaningful based on the effects reported in peer-reviewed literature for other sleep medications and from input received in consultation with sleep medicine experts. The substantial Month 3 results are comparable to improvements seen with other agents approved with a sleep maintenance insomnia indication, with the caveat that study design, conduct and duration differences limit the interpretation of these comparisons. That these results are clinically meaningful is further supported by consistent evidence for the superiority of outcomes for patients taking suvorexant as compared to placebo on qualitative measures such as the Insomnia Severity Index and patient global impression (results presented in section 5.5.2.4 below).

Suvorexant LD

Suvorexant LD was also efficacious in improving sleep maintenance. For the suvorexant LD comparisons, the results in P028 showed statistically significant differences from placebo for both sTSTm and WASO at all timepoints. Results from P029 and the pooled (P028+P029) analysis were consistent with these findings with p-values of <0.00005. A supportive analysis of sWASOm was also conducted comparing suvorexant LD to placebo for P028, P029 and the pooled (P028+P029) data. As described in Section 5.4, in the supportive analysis for P028, sWASOm and WASO were utilized in the multiplicity strategy (rather than sTSTm and WASO) and resulted in statistically significant differences between suvorexant LD and placebo for only WASO at Month 1; since sWASOm at Month 1 was not positive, no further hypotheses (e.g., sWASOm and WASO at Month 3) were evaluated in accordance with the multiplicity strategy. In exploratory analyses (not multiplicity controlled) of P029 and the pooled (P028+P029) dataset, differences were observed between suvorexant LD and placebo in sWASOm and WASO at all timepoints (nominal $p<0.03$ and $p<0.00001$, respectively) with the exception of sWASOm at Week 1. Refer to [Appendix 2] for a table of the LD effects on maintenance measures.

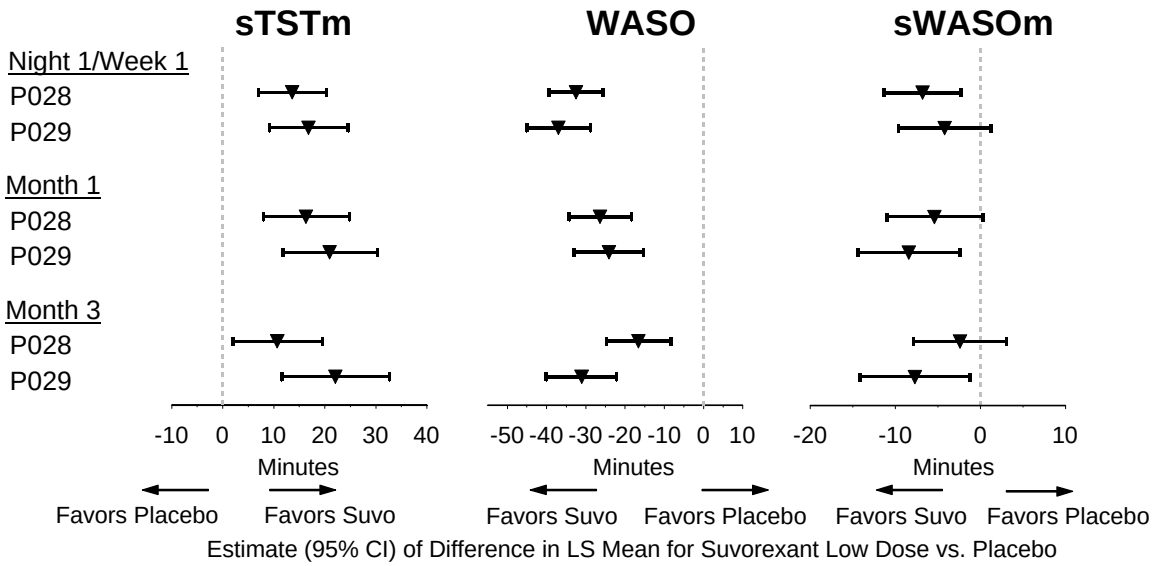
Estimated differences and 95% confidence intervals for suvorexant LD versus placebo for P028 and P029 are presented in [Figure 10].

The magnitude of improvement in sleep maintenance parameters observed with suvorexant LD was greater in P029 than P028. In P028, sTSTm was increased 10.7 minutes and sWASOm was reduced 2.4 minutes, and WASO was reduced 16.6 minutes for suvorexant LD as compared to placebo at Month 3. Similar results were observed in

P029; sTSTm was increased 22.1 minutes, sWASOm was reduced 7.7 minutes, and WASO was reduced 31.1 minutes for suvorexant LD as compared to placebo at Month 3. Based on the pooled (P028+P029) analysis, patient-reported sleep duration as measured by sTSTm was increased at Month 3 for suvorexant LD treatment, having a difference of 16 minutes in favor of suvorexant compared to placebo. Similarly for WASO, a difference of 23.1 minutes favoring suvorexant, compared to placebo, was observed at Month 3. For sWASO, a 4.7-minute advantage was observed for suvorexant LD compared to placebo for the pooled population (P028+P029).

Together, these findings support that suvorexant LD is efficacious in improving sleep maintenance insomnia. A discussion of the effect of suvorexant HD compared with suvorexant LD follows in the discussion of Dose Response in the Confirmatory Trials in [Sec. 5.5.2.3 Dose Response Relationship in the Confirmatory Trials].

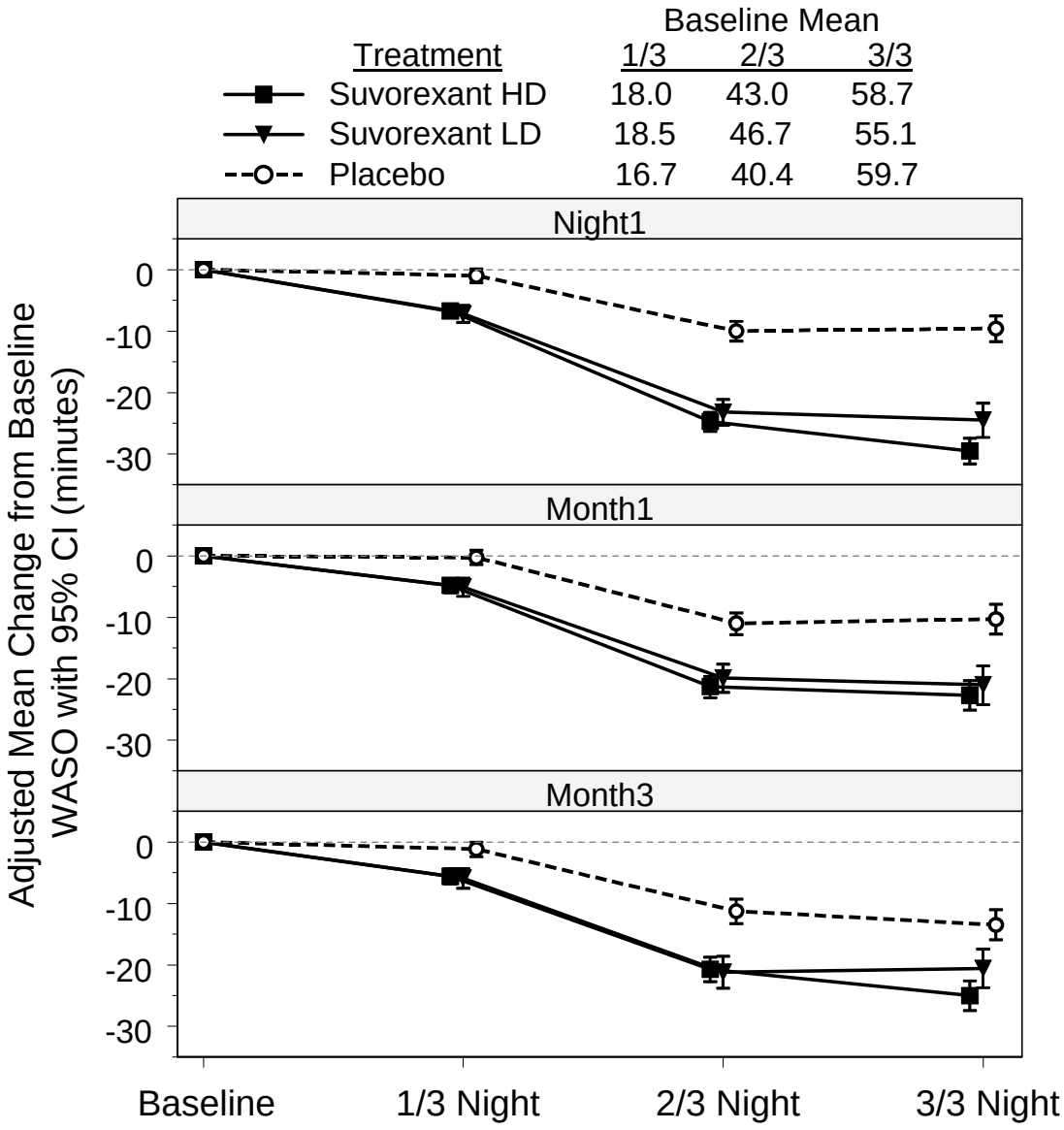
Figure 10
Estimated Difference and 95% Confidence Intervals
for Change from Baseline in Sleep Maintenance Efficacy Endpoints
Suvorexant Low Dose (LD) versus Placebo – P028, P029



Suvorexant Maintenance Efficacy is Sustained through the Night

Lastly, analyses of WASO by thirds of the night during the 8-hour PSG period (T1, T2, and T3) show that suvorexant maintains sleep throughout the night. Adjusted means and 95% CI for change from baseline in WASO by thirds of the night for each timepoint during the Treatment Phase for the pooled population (P028+P029) are presented in [Figure 11]. Greater reductions from baseline in WASO were seen for both doses of suvorexant compared with placebo for each third of the night, and at each timepoint. Similar results were observed for analysis of WASO by hour of the night. These reductions in WASO observed during the latter part of the night provide an important contribution to suvorexant's sleep maintenance profile.

Figure 11
Adjusted Means and 95% Confidence Intervals for Change from Baseline in Wakefulness After Persistent Sleep Onset (WASO; minutes) by One Third of Night at Each Time Point During the Treatment Phase (Pooled P028+P029 / Full Analysis Set PSG / Data-as-Observed)



5.5.2.2 **Sl**eep Onset

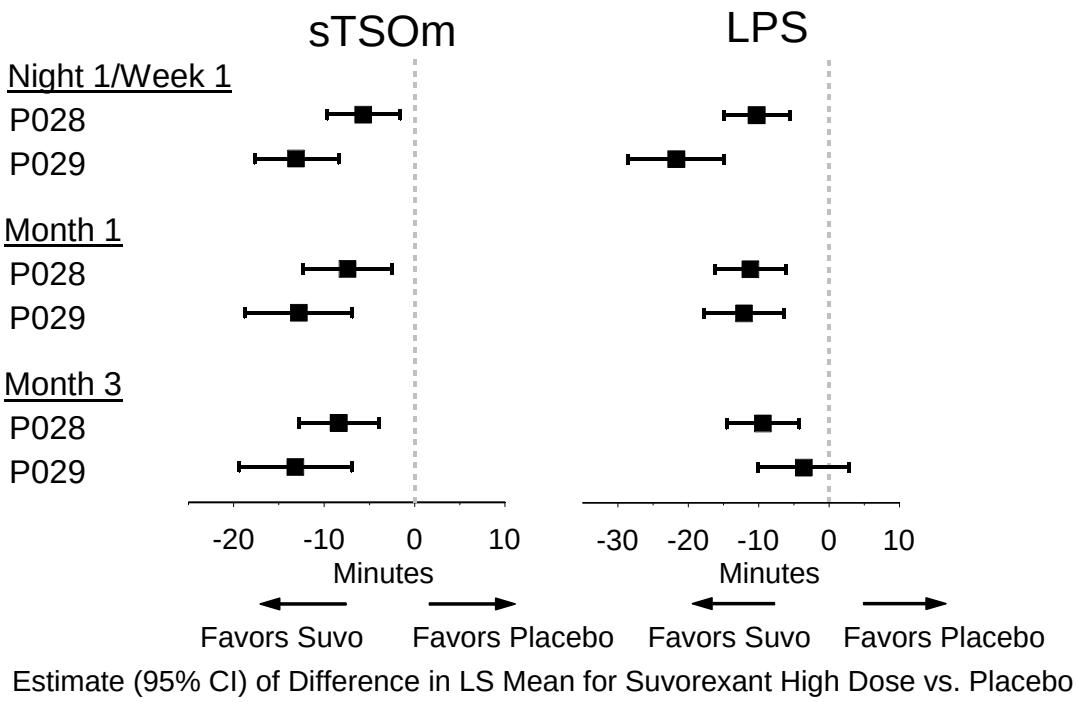
Suvorexant HD

Suvorexant HD was efficacious in improving sleep onset. The analyses in [Table 7] show that suvorexant HD was superior to placebo in decreasing sTSOm at all timepoints in each of the individual studies. All comparisons were statistically significant ($p<0.007$), meeting the pre-specified objectives in both confirmatory trials (P028 and P029). Likewise, suvorexant HD was superior to placebo in decreasing LPS at all timepoints (all p-values <0.0004) with the exception of Month 3 in Protocol 029 (p=0.26510). This diminution of the apparent treatment difference at Month 3 may be partially attributable to the increasing placebo response that was observed in this trial, despite the generally sustained improvements over baseline LPS seen for the suvorexant HD treatment group. The apparent gradual improvement in the placebo group over the course of the 3-month treatment period may be due, in part, to disproportionate discontinuation of non-responder placebo-treated patients and retention of placebo responders. Despite this observation for one timepoint in P029, the pooled (P028+P029) analysis of LPS at Month 3 provides additional support for the beneficial effects observed for suvorexant HD on objective sleep onset (p=0.00235). Estimated differences and 95% CIs for suvorexant HD versus placebo for P028 and P029 are presented in [Figure 12].

The magnitude of improvements observed for suvorexant HD in the subjective onset measure, sTSOm, was consistent across P028 and P029. In P028, sTSOm was reduced by 8.4 minutes for suvorexant HD as compared to placebo at Month 3, while in P029, the corresponding reduction in sTSOm was 13.2 minutes. For objective onset at Month 3 in P028, LPS was reduced by 9.4 minutes for suvorexant HD compared to placebo; in P029, the corresponding reduction in LPS was 3.6 minutes. As discussed above, this smaller difference at Month 3 was due to increased improvements in placebo over time; a more robust effect was observed at Night 1 and Month 1.

For the pooled analysis of the two confirmatory trials, sTSOm following suvorexant HD treatment was decreased by 29.8 minutes (~42% decrease) from baseline at Month 3; a difference of 10.8 minutes from placebo in favor of suvorexant. LPS for the pooled (P028+P029) was reduced by 34 minutes from baseline and was improved by 6.4 minutes compared to placebo at Month 3. For context, the magnitude of these results fall within effect size ranges identified as clinically meaningful based on the effects reported in peer-reviewed literature for other sleep medications and from input received in consultation with sleep medicine experts, with the caveat that study design, conduct and duration differences limit the interpretation of these comparisons. That these results are clinically meaningful is further supported by consistent evidence for the superiority of outcomes for patients taking suvorexant as compared to placebo on qualitative measures such as the Insomnia Severity Index (ISI results presented below).

Figure 12
Estimated Difference and 95% Confidence Intervals
for Change from Baseline in Sleep Onset Efficacy Endpoints
Suvorexant High Dose (HD) versus Placebo – P028, P029



Estimate (95% CI) of Difference in LS Mean for Suvorexant High Dose vs. Placebo

Table 7
Effects of Suvorexant High Dose on Sleep Onset Measures (Minutes) – P028, P029 and Pooled (P028+P029)

Endpoint	Timepoint	Protocol	Suvo HD LS Mean Change From Baseline	Placebo LS Mean Change From Baseline	LS Mean Difference From Placebo	P-value
sTSOm†	Week 1	028	-15.3	-9.6	-5.7	0.00609*
		029	-19.7	-6.7	-13.1	<0.00001*
		Pooled	-17.6	-8.3	-9.4	<0.00001
	Month 1	028	-19.1	-11.7	-7.4	0.00298*
		029	-26.9	-14.1	-12.8	0.00003*
		Pooled	-23.2	-13.0	-10.1	<0.00001
	Month 3	028	-25.7	-17.3	-8.4	0.00019*
		029	-33.7	-20.5	-13.2	0.00003*
		Pooled	-29.8	-19.0	-10.8	<0.00001
LPS‡	Night 1	028	-30.6	-20.3	-10.3	0.00002*
		029	-34.7	-13.0	-21.7	<0.00001*
		Pooled	-32.5	-16.8	-15.8	<0.00001
	Month 1	028	-34.5	-23.3	-11.2	0.00002*
		029	-36.7	-24.6	-12.1	0.00004*
		Pooled	-35.5	-24.1	-11.4	<0.00001
	Month 3	028	-36.0	-26.6	-9.4	0.00037*
		029	-32.2	-28.6	-3.6	0.26510
		Pooled	-34.0	-27.6	-6.4	0.00235

* Statistically significant based upon the protocol-specified multiplicity strategy; only nominal p-values are provided for the pooled analyses
† sTSOm is subjective Time to Sleep Onset (weekly mean of daily measurements)
‡ LPS is objective Latency to onset of Persistent Sleep (PSG)
LS = Least Squares (based upon primary analysis model)

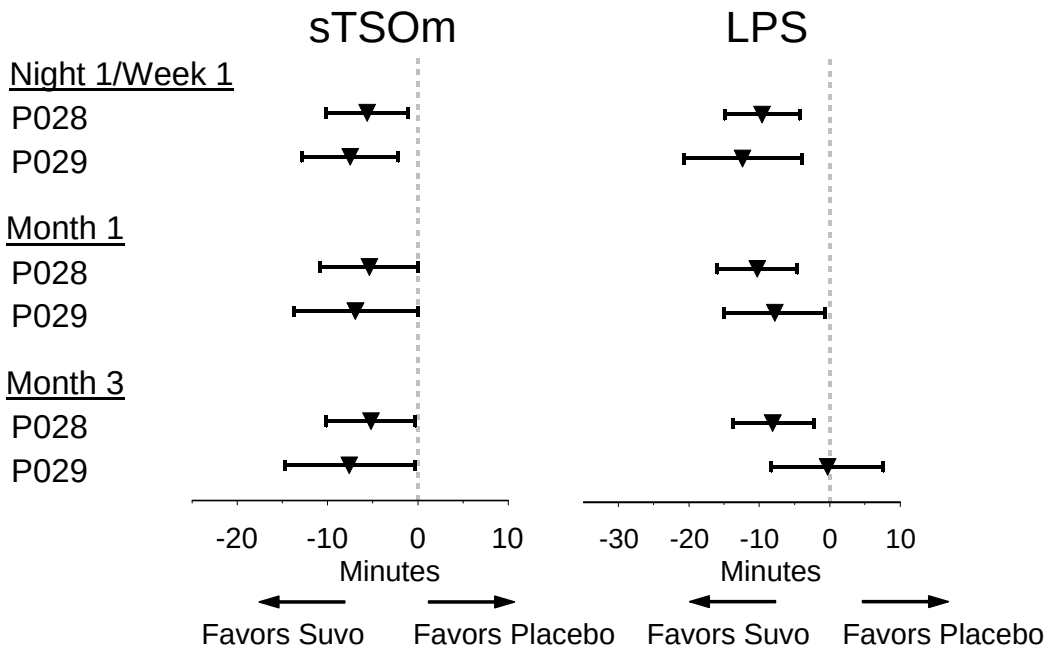
Suvorexant LD

Suvorexant LD was also efficacious in improving sleep onset. The results for P028 show statistically significant differences from placebo for LPS at Month 1, based upon the multiplicity procedure; however, nominal p-values were <0.007 for LPS at all timepoints. While sTSOm results for P028 were not significant according to the multiplicity strategy, nominal p-values suggested evidence of effect for the subjective onset measure ($p<0.052$ for all timepoints). In exploratory analyses of suvorexant LD (not multiplicity controlled) of P029, nominal p-values were generally consistent with those observed for P028 ($p<0.05$ for both sTSOm and LPS at all timepoints except Month 3 [for LPS]). The pre-specified exploratory pooled (P028+P029) analyses provide additional evidence to support the effect of LD vs. placebo on sleep onset measures ($p<0.02$ for all endpoints/timepoints, except LPS at Month 3 [$p=0.06205$]). Refer to [Appendix 3] for a table of the LD effects on sleep onset measures.

Estimated differences and 95% confidence intervals for suvorexant LD versus placebo for P028 and P029 are presented in [Figure 13].

Based on the pooled analysis of the two confirmatory trials, sTSOm was reduced by 5.9 minutes for suvorexant LD as compared to placebo at Month 3. Across the two trials, sTSOm improvement with suvorexant LD, compared to placebo, ranged between 5.2 to 7.6 minutes. In P028, LPS at Month 3 was reduced by 34.7 minutes (53% reduction from baseline) compared to baseline, with a difference from placebo of 8.1 minutes favoring suvorexant. In P029, a more robust effect was observed at Night 1 and Month 1, but at Month 3 the difference from placebo was diminished.

Figure 13
Estimated Difference and 95% Confidence Intervals
for Change from Baseline in Sleep Onset Efficacy Endpoints
Suvorexant Low Dose (LD) versus Placebo – P028, P029



Estimate (95% CI) of Difference in LS Mean for Suvorexant Low Dose vs. Placebo

5.5.2.3 Dose Response Relationship in the Confirmatory Trials

Results of the confirmatory studies provide significant and consistent evidence across multiple endpoints and timepoints for the efficacy of suvorexant HD in improving the sleep maintenance [Figure 14] and sleep onset [Figure 15] difficulties of insomnia. The efficacy evaluation of suvorexant LD was a secondary objective in P028, an exploratory objective in P029, and pre-specified as a pooled analysis across trials in the integrated Statistical Analysis Plan. In the individual confirmatory trials, the magnitude of improvement seen was consistently dose-related. This is illustrated in [Figure 14, Figure 15] , which show that all point estimates for the comparison of HD and LD for each efficacy endpoint favor suvorexant HD.

Figure 14
Estimated Difference and 95% Confidence Intervals
for Change from Baseline in Sleep Maintenance Efficacy Endpoints
Suvorexant High Dose (HD) versus Low Dose (LD)
(Pooled P028+P029)

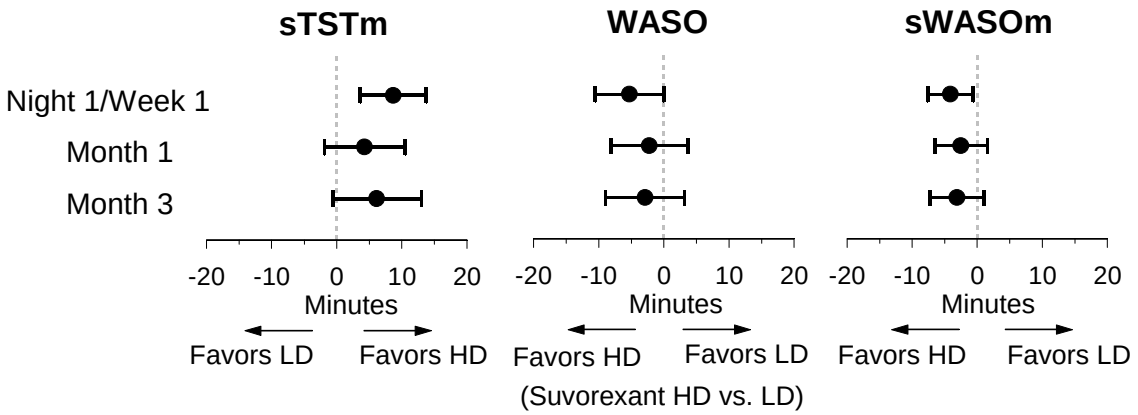
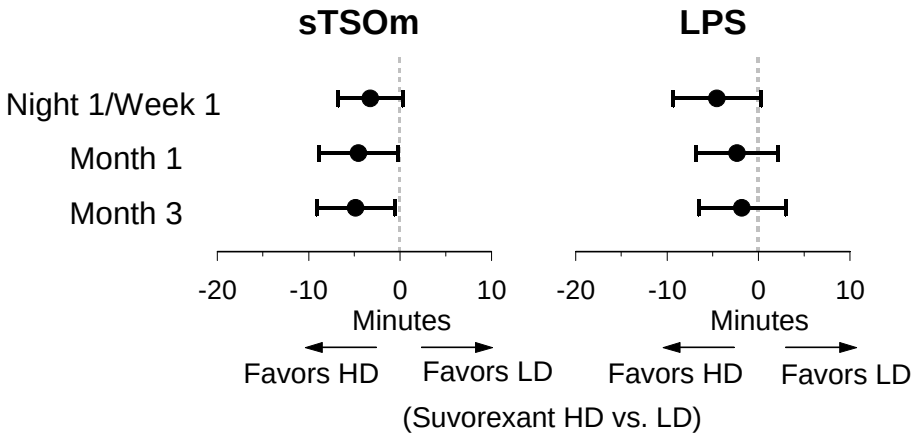


Figure 15
Estimated Difference and 95% Confidence Intervals
for Change from Baseline in Sleep Onset Efficacy Endpoints
Suvorexant High Dose (HD) versus Low Dose (LD)
(Pooled P028+P029)



5.5.2.4 Supportive (Exploratory) Clinical Efficacy Endpoints

In addition to the endpoints discussed thus far, other pre-specified exploratory endpoints evaluated in the Phase 3 trials included:

- Additional objective measures: Total Sleep Time (TST), Sleep Onset Latency (SOL), and sleep architecture (sleep stages: S1, S2, S3, REM) assessed via PSG.

- Additional subjective measures:

    - sleep quality (sQUALm) and feeling refreshed upon awakening (sREFRESHEDm); patient-reported single-item question collected via e-diary

    - global measures: clinician-rated (CGI-S, CGI-I), and patient-rated (PGI-S, PGI-I), single-item measures of insomnia severity(S) and insomnia improvement(I)

    - Insomnia Severity Index (ISI)- 7-item instrument that includes items related to sleep onset, sleep maintenance, and effects of sleep disturbance on daytime functioning, quality of life, and stress levels.

Results from these exploratory endpoints for the pooled data (P028 + P029) are consistent with the results of the primary analyses. These favorable results for clinician- and patient-reported measures, such as the ISI, indicate that suvorexant consistently improves symptoms of insomnia in ways that are noticeable to patients and their care provider and provide additional support for the efficacy and clinical relevance of suvorexant in improving symptoms of insomnia [Appendix 4].

Of particular interest are results of the ISI, a global composite patient-report measure that is recognized and validated in the insomnia research community. Of the seven areas of insomnia interrogated by the scale (falling asleep, staying asleep, early awakening, satisfaction, interference, noticeable, and worry), it is noteworthy that the majority (4) of items in the ISI deal with waking functionality rather than with sleep symptoms, and which makes the scale complementary to the standard primary and secondary sleep onset and sleep maintenance endpoints and therefore serves to bridge between symptom improvement to other domains of important clinical relevance that are meaningful to patients [37; 38; 17].

Analysis of the pooled (P028+P029) pivotal efficacy trials demonstrated sustained improvements in the ISI total score in patients treated with suvorexant HD and LD at the two timepoints (Month 1 and 3) measured during the Treatment Phase of the studies. The percentage of patients who had a clinically meaningful improvement (i.e. responders; defined as ≥6-point improvement from baseline [38] in the ISI total score was higher in the suvorexant HD and LD treatment groups than in the placebo group in both P028 (all

p-values <0.05) and P029 (all p-values <0.006) and for the pooled population (P028+P029) analysis shown in [Table 8]. The odds of being a responder, e.g. achieving a ≥6-point improvement from baseline in ISI total score, was nearly twice that of placebo for both suvorexant HD and LD (as noted by the odds ratios) at Month 1 and at Month 3 and were suggestive of efficacy compared to placebo (all p-values <0.05).

Table 8
Analysis of Response in Insomnia Severity Index Total Score (≥6 point improvement)
(Pooled P028+P029 / GLIMMIX / Full Analysis Set E-Diary / Data-as-Observed)

				Treatment vs. Placebo at Time Point	
Treatment	N	n	(%)	Estimated odds ratio (95% CI)[†]	p-Value [†]
Month 1					
Suvo LD	440	149	(33.9)	1.8 (1.4, 2.4)	0.00004
Suvo HD	699	279	(39.9)	2.4 (1.9, 3.1)	<0.00001
Placebo	685	157	(22.9)		
Month 3					
Suvo LD	411	228	(55.5)	1.8 (1.4, 2.3)	0.00002
Suvo HD	656	360	(54.9)	1.8 (1.4, 2.2)	<0.00001
Placebo	638	269	(42.2)		

[†] Based on a generalized linear mixed model with terms for study (P028, P029), baseline value, age category (<65, ≥65), region (NA, EU, Other), cohort (PQ, Q), gender, treatment, time point, and treatment-by-time point interaction as covariates.
Suvo LD = Suvorexant 20 mg for patients <65 years and Suvorexant 15 mg for patients ≥65 years.
Suvo HD = Suvorexant 40 mg for patients <65 years and Suvorexant 30 mg for patients ≥65 years.

Sleep Architecture

Exploratory analyses were also performed to investigate suvorexant effects on sleep architecture (sleep stages; durations and percents) assessed via PSG. The results of these analyses (in P028, P029, as well as the pooled analysis) suggest that the overall increase in sleep duration affected by suvorexant is generally proportional across sleep stages. Sleep architecture overall appears to be generally preserved with only small differences in the proportions of Stage 2, Stage 3, and REM sleep.

5.5.3 Long Term Efficacy

Long-Term Safety Trial (Protocol 009)

Additional evidence for the ability of suvorexant HD to provide sustained improvements in sleep onset and sleep maintenance was demonstrated over the course of a 1-year placebo-controlled long-term safety trial (P009), conducted in 779 treated-patients with chronic insomnia, wherein 521 patients received suvorexant. It is important to note that this study was not enriched for sleep disturbance, i.e. there were no entry criteria other than an insomnia diagnosis. Therefore not only did this study evaluate effects in the most demanding circumstance of long-term efficacy in terms of duration of use (one year), but

was also essentially an “all comers” study, both of which are firsts based on the current insomnia literature.

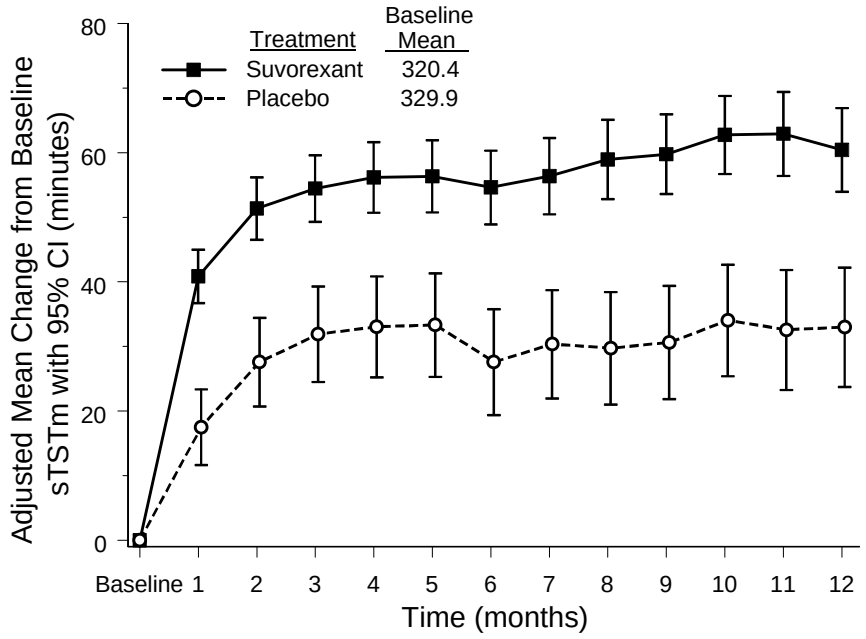
Key patient characteristics and baseline efficacy values are for the Protocol 009 population are provided in [Table 3] and [Table 4]. The percentage of patients who completed 3 months and 12 months of treatment was 81% and 62% respectively. The most common reasons for discontinuation for patients overall were AEs, followed by withdrawal by the patient, and lack of efficacy. Within treatment groups, the proportion of patients who completed was similar (61.7% vs. 62.5% for suvorexant vs placebo). Discontinuations due to AEs and patient withdrawal were modestly higher in the suvorexant group (11.5% and 11.5% vs 8.3% and 9.5% for suvorexant vs placebo), while discontinuations due to lack of efficacy were lower for patients in the suvorexant group compared to placebo (8.4% vs 10.8%).

A secondary objective of this study was evaluation of the short-term efficacy of suvorexant HD during the first month of treatment (average of Weeks 1 to 4), compared to placebo, on subjective measures of sleep maintenance and onset (sTSTm and sTSOm). Regarding maintenance efficacy, suvorexant HD showed improvement in sTSTm and sWASOm during the first month of treatment and at every weekly timepoint during this interval; sTSTm was increased by 22.7 minutes ($p<0.0001$) for suvorexant HD, compared to placebo. For sleep onset, suvorexant HD reduced sTSOm by 9.5 minutes over placebo during the first month of treatment and at every timepoint during this interval ($p< 0.01$).

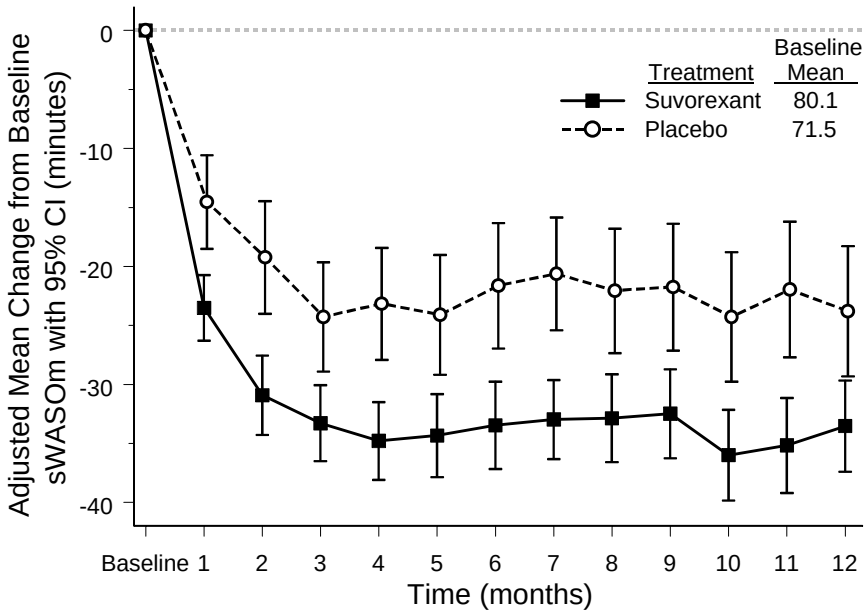
In an exploratory analysis of suvorexant long-term efficacy in this study, improvements in subjective sleep maintenance and onset measures, sTSTm, sTSOm, and sWASOm, were consistently observed for suvorexant HD at each month during the 12-month treatment period; see data displays for sTSTm, sWASOm, and sTSOm in [Figure 16].

Figure 16
Adjusted (LS) Means and 95% Confidence Intervals for Change from Baseline in Mean sTSTm, sTSOm, and sWASOm (minutes) for Suvorexant HD vs. Placebo by Month Treatment Phase (LDA/ Full Analysis Set / Data-as-Observed) – P009

sTSTm

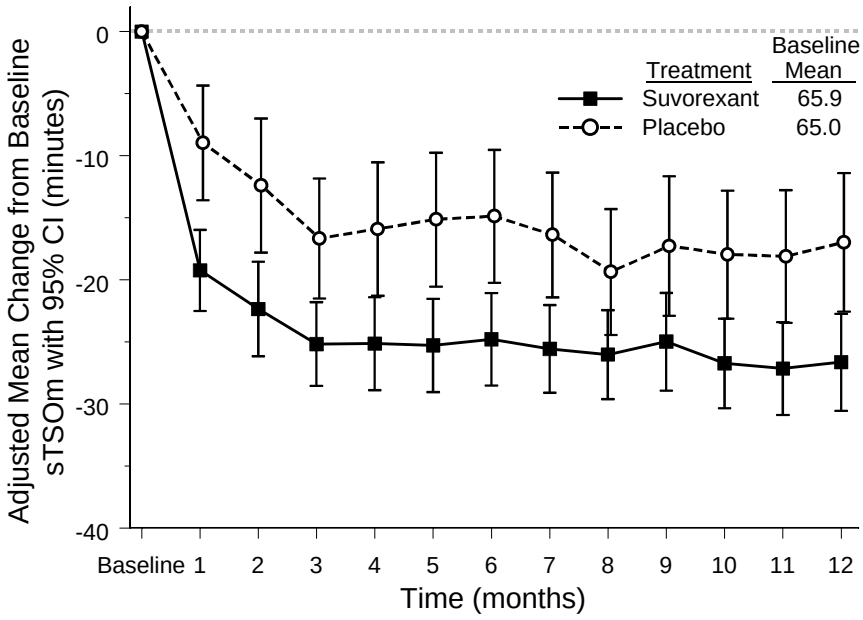


sWASOm



Adjusted (LS) Means and 95% Confidence Intervals for Change from Baseline in Mean sTSTm, sTSOm, and sWASOm (minutes) for Suvorexant HD vs. Placebo by Month Treatment Phase (LDA/ Full Analysis Set / Data-as-Observed) – P009 (Cont.)

sTSOm



Treatment differences in favor of suvorexant HD (nominal p-values <0.05) were consistently demonstrated on these endpoints as well as for other patient-reported exploratory efficacy endpoints (sREFRESHEDm, sQUALm, ISI total, CGI-S, CGI-I, PGI-S, and PGI-I). For the ISI specifically, the total score showed improvement for suvorexant HD over placebo at all timepoints measured over the entire year of assessment (at Months 1, 3, 6, and 12); refer to [Table 9]. Positive results were also observed for sub-item ISI responses for improvements in sleep onset and maintenance, as well as the degree of concern or distress caused by those difficulties. These results providing further evidence that suvorexant's improvements in insomnia disorders were sustained throughout the entire year, and that these improvements were noticeable and clinically meaningful to both patients and clinicians.

Table 9
Analysis of Change from Baseline in ISI Total Score by Month
Treatment Phase
(LDA / Full Analysis Set / Data-as-Observed) – P009

Treatment	N	Baseline Mean (SD)	Treatment Mean (SD)	Change from Baseline Mean (SD)	Change from Baseline LS Mean† (95% CI)†
Month 1					
Suvo HD	488	14.5 (4.5)	10.8 (5.4)	-3.8 (5.0)	-3.6 (-4.0, -3.2)
Placebo	240	13.7 (4.6)	11.7 (4.9)	-2.0 (4.6)	-2.2 (-2.8, -1.6)
Month 3					
Suvo HD	428	14.5 (4.5)	9.5 (5.4)	-5.0 (5.2)	-4.7 (-5.1, -4.2)
Placebo	203	13.6 (4.6)	9.8 (4.8)	-3.8 (5.1)	-3.7 (-4.4, -3.1)
Month 6					
Suvo HD	380	14.3 (4.4)	8.8 (5.4)	-5.5 (5.5)	-5.1 (-5.6, -4.6)
Placebo	185	13.5 (4.7)	9.6 (5.1)	-3.8 (5.5)	-3.6 (-4.3, -3.0)
Month 12					
Suvo HD	332	14.4 (4.4)	8.4 (5.4)	-6.0 (5.7)	-5.3 (-5.8, -4.8)
Placebo	165	13.4 (4.9)	8.7 (5.0)	-4.6 (5.8)	-4.4 (-5.1, -3.7)

Pairwise Comparison	Difference in LS Mean (95% CI)†	p-Value†
Month 1		
Suvo HD vs. Placebo	-1.4 (-2.1, -0.7)	<.0001
Month 3		
Suvo HD vs. Placebo	-0.9 (-1.7, -0.2)	0.0160
Month 6		
Suvo HD vs. Placebo	-1.4 (-2.3, -0.6)	0.0007
Month 12		
Suvo HD vs. Placebo	-0.9 (-1.8, -0.0)	0.0390

† Results based on a mixed effects model with terms for baseline value, gender, region, treatment, time, and treatment-by-time interaction.
Suvo HD = Suvorexant 40 mg for patients < 65 years and Suvorexant 30 mg for patients ≥ 65 years.

Another unique feature of this trial was a 2-month Randomized Discontinuation Phase, which was designed to investigate the potential relapse of insomnia symptoms in patients for whom suvorexant treatment was stopped, and to likewise assess the potential continued benefit of suvorexant treatment for relapse prevention in patients treated beyond one year. The Randomized Discontinuation Phase was conducted in 484 participants who completed the 12-month Treatment Phase, where patients who had received suvorexant during the Treatment Phase either continued on suvorexant (N=156) or were switched to placebo (N=166), and those patients who received placebo in the Treatment Phase continued on placebo (N=162). There were no entry criteria specific to the 2-Month Randomized Discontinuation Phase and this phase was not considered optional; this phase included all patients who were continuing in the study at the end of

Month 12. Further, there was no interruption of treatment between the 2 treatment phases.

During the Randomized Discontinuation Phase, patients treated with suvorexant HD who were switched to placebo (Suvo/PBO) had a worsening in both subjective sleep onset and maintenance measures, indicative of a return of insomnia symptoms, or relapse, as compared with patients who remained on suvorexant or placebo during this phase. This group of patients (Suvo/PBO) experienced substantial declines in sTSTm [Figure 17] and increases in sTSO [Figure 18] and sWASOm; the greatest change was observed at Week 1 of the Randomized Discontinuation Phase. Evaluation of rebound insomnia (i.e. exacerbation of symptoms upon discontinuation compared with pre-treatment baseline) yielded no significant differences indicative of clinically meaningful rebound.

Figure 17
Observed Mean for Subjective Total Sleep Time (sTSTm; minutes) at Baseline (Month 0), Month 12, and during each week of the Randomized Discontinuation Phase (LDA / Randomized Discontinuation Set / Data-as-Observed) – P009

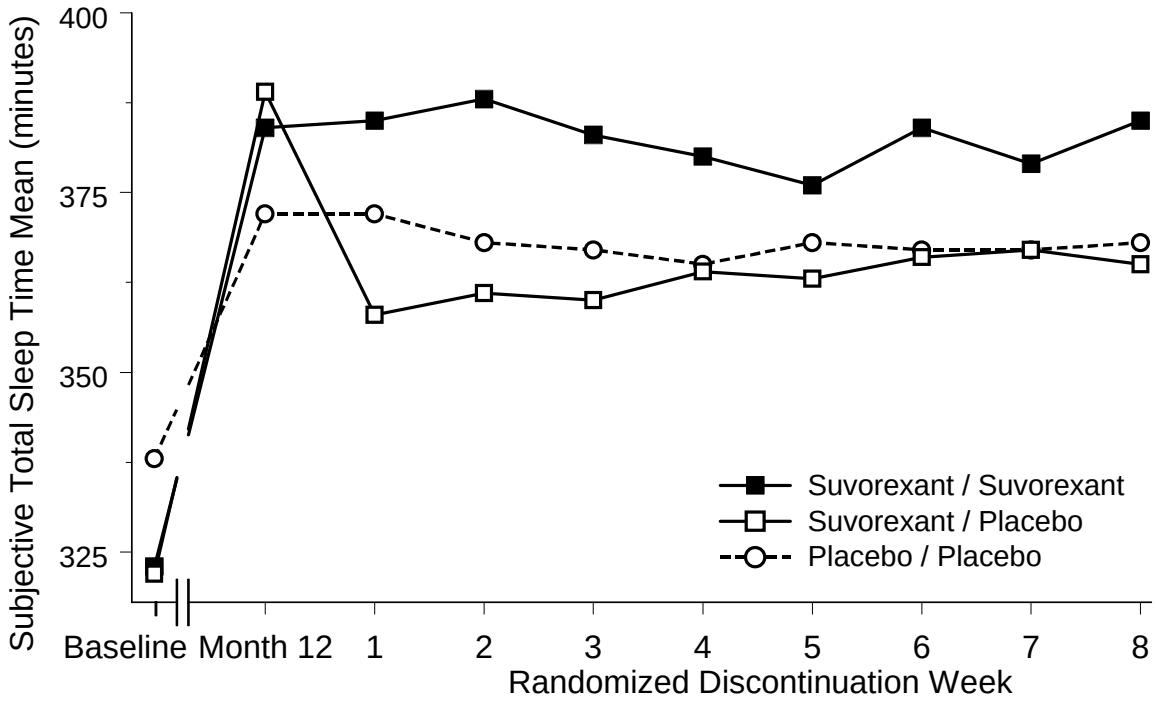
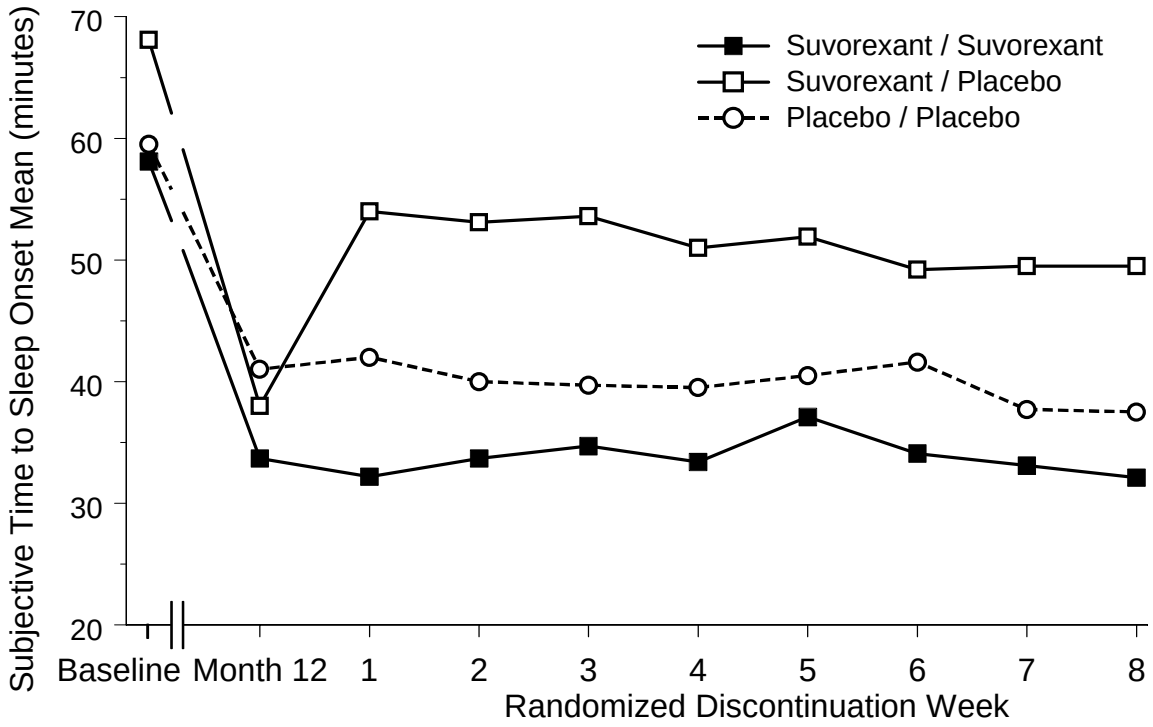


Figure 18
Observed Mean for Subjective Subjective Time to Sleep Onset (sTSOm; minutes) at Baseline (Month 0), Month 12, and during each week of the Randomized Discontinuation Phase (LDA / Randomized Discontinuation Set / Data-as-Observed) – P009



These results indicate that patients with chronic insomnia continue to benefit from suvorexant treatment (beyond a year), and that insomnia symptoms return, with no rebound, in patients upon cessation of suvorexant treatment.

Protocol 028 Extension

The optional 3-month Extension Phase of P028 was designed to provide additional safety data for treatment duration beyond the 3 month core Treatment Phase, where patients from both the (blinded) placebo and suvorexant treatment arms could elect to enter the 3-month extension. Of the patients who completed the Treatment Phase in P028, only about 46% opted to enter the Extension Phase representing 39.4%, 44.9%, and 39.2% of the randomized population in the suvorexant LD, suvorexant HD, and placebo groups, respectively. Assessment of efficacy during the Extension Phase was an exploratory analysis; however, due to higher placebo responses in the relatively small sub-group of patients who elected to continue in the extension, suvorexant treatment differences from placebo were not observed in the planned analysis despite sustained changes from

baseline in the suvorexant HD and LD groups from the core Treatment Phase. Based on the self-selected nature of this population, the P028 Extension Phase sub-group analysis does not provide an opportunity for a valid evaluation of suvorexant efficacy compared to placebo, or its persistence over time.

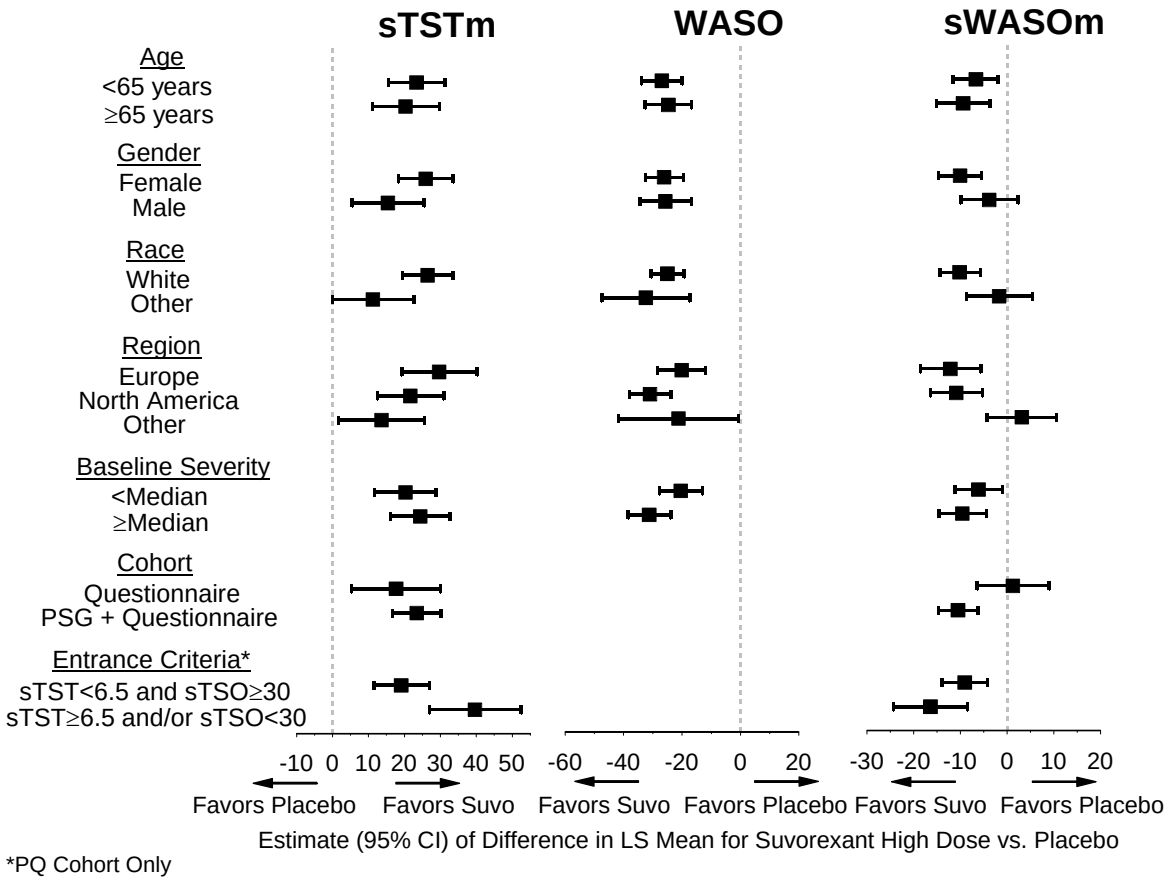
5.5.4 Effects of Important Demographic and Prognostic Factors on Efficacy

Intrinsic and extrinsic factors related to efficacy were evaluated using the pooled (P028+P029) analyses of the two confirmatory efficacy trials for the primary and secondary timepoints (Night1/Week 1, Month 1 and Month 3). Analysis of factors and subgroups included: age (<65; ≥ 65 years), gender, race (white, other), region (North America, Europe, other), baseline severity of insomnia, Q-Cohort vs. PQ-Cohort (for key subjective endpoints), and PQ-Cohort subjective baseline values. Displays of the estimated differences for the subgroup factors for suvorexant HD and LD based upon the pooled data (P028+P029) at the Month 3 timepoint for the maintenance endpoints are provided in [Figure 19], [Figure 20] and for sleep onset endpoints in [Figure 21],[Figure 22] respectively. In general, while smaller sample sizes in some subgroups introduce caveats to interpretation (refer to [Appendix 5] for subgroup sample sizes), subgroup analyses generally mirrored the primary analyses in regards to the efficacy results observed for suvorexant HD and LD on sleep maintenance and sleep onset endpoints across the subgroups evaluated.

The beneficial effects on sleep maintenance and sleep onset were also generally consistent across other subgroups evaluated; 95% CI for the subgroup treatment differences overlapped and frequently excluded zero in favor of suvorexant, with few inconclusive exceptions occurring in sparsely-populated subgroups such as "Other" race and "Other" region.

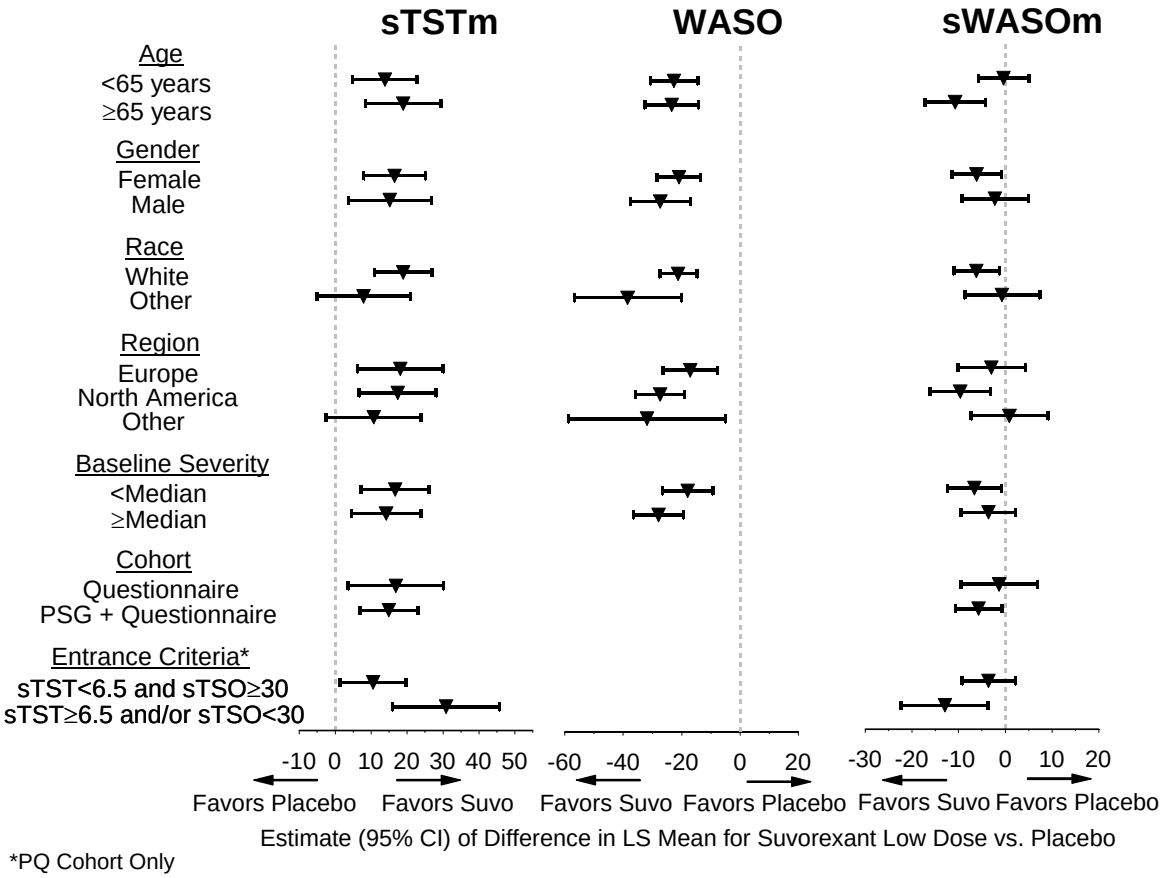
Sleep Maintenance

Figure 19
Estimated Difference and 95% Confidence Intervals for Change from Baseline in Sleep Maintenance Efficacy Endpoints at Month 3 by Subgroup Factors
Suvorexant High Dose (HD) versus Placebo – Pooled P028+P029



*PQ Cohort Only

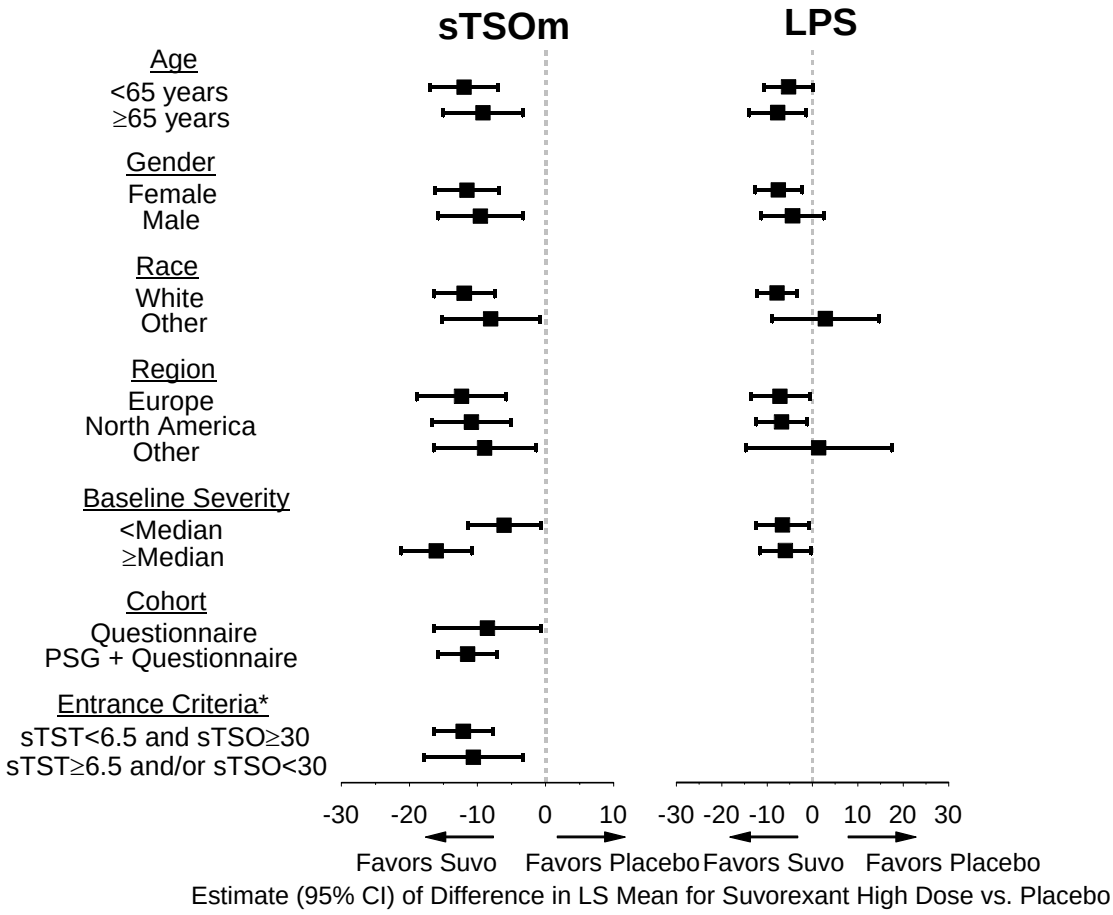
Figure 20
Estimated Difference and 95% Confidence Intervals for Change from Baseline in Sleep Maintenance Efficacy Endpoints at Month 3 by Subgroup Factors
Suvorexant Low Dose (LD) versus Placebo (Pooled P028+P029)



*PQ Cohort Only

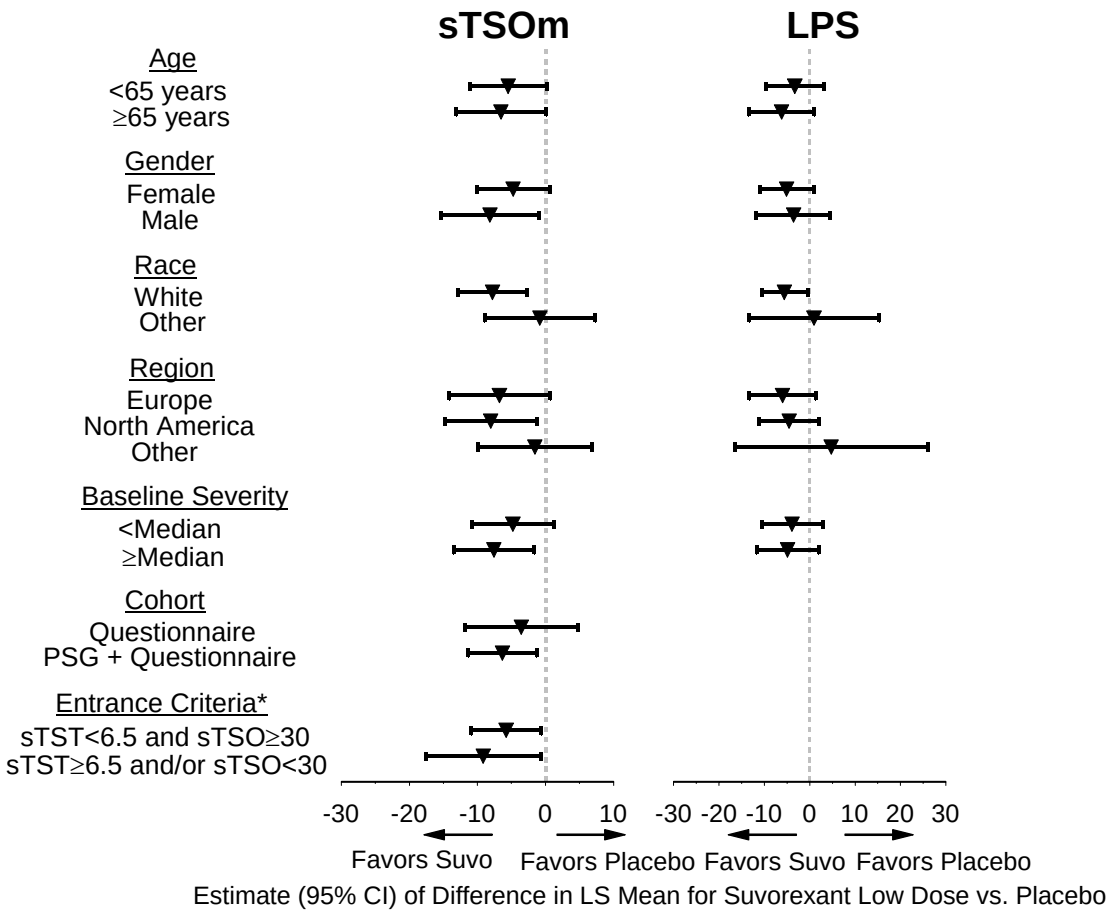
Sleep Onset

Figure 21
Estimated Difference and 95% Confidence Intervals for Change from Baseline in Sleep Onset Efficacy Endpoints at Month 3 by Subgroup Factors
Suvorexant High Dose (HD) versus Placebo – Pooled P028+P029



*PQ Cohort Only

Figure 22
Estimated Difference and 95% Confidence Intervals for Change from Baseline in Sleep Onset Efficacy Endpoints at Month 3 by Subgroup Factors
Suvorexant Low Dose (LD) versus Placebo (Pooled P028+P029)



*PQ Cohort Only

Efficacy in Elderly Patients

The results of a subgroup analysis by age conducted on the pooled data (P028+P029), where a significant proportion of patients were in the elderly subgroup (41%), mirrored the efficacy observed for suvorexant HD and LD over placebo in the primary analyses. In the analysis of age subgroups, suvorexant HD and suvorexant LD improved objective (WASO) and subjective (sTSTm and sWASOm) measures of sleep maintenance at Night

1/Week 1, Month 1, and Month 3 in both non-elderly and elderly. Suvorexant HD was effective in elderly patients in decreasing objective (LPS) and subjective (sTSOm) measures of sleep onset at Night 1/Week 1, Month 1, and Month 3. Given the unique approach of conducting combined-age studies for the Phase 3 suvorexant program, it is important to note that improvements in objective and subjective endpoints in elderly and in non-elderly patients for each of the individual trials (P028, P029, and P009) were consistent with the improvements observed in the overall combined-age populations of each study.

Sleep Maintenance Effects in Elderly

The magnitude of the changes for maintenance endpoints in the elderly are presented in [Table 10]. In elderly, sTSTm improvements from baseline for Suvorexant HD steadily increased from between 36.9 minutes at Week 1, 41.9 min at Month 1 and 54.9 minutes at Month 3. sTSTm was improved 20.4 to 24.9 minutes for Suvorexant HD over placebo. For sWASOm, reductions from baseline ranged between 19.6 minutes (Week 1) and 36.0 minutes (Month 3) for suvorexant HD; differences between suvorexant HD and placebo were ~9 minutes in favor of suvorexant HD at all 3 timepoints. In elderly patients, WASO reductions were 53.5 minutes at Night 1, and 37.5 minutes at Months 3 for suvorexant HD compared to baseline; improvements (reductions) over placebo were 49.4 minutes at Night 1 and 24.7 minutes at Month 3.

Suvorexant LD also showed strong effects on maintenance measures in elderly patients. Most cases showed substantial improvements compared to placebo; the effects were typically smaller than suvorexant HD.

Table 10
Subgroup (Age ≥ 65) Analysis of Change from Baseline in Sleep Maintenance Endpoints (sTSTm, sWASOm, and WASO) at All Time Points During the Treatment Phase
(Pooled P028+P029 / LDA / Full Analysis Set PSG / Data-as-Observed)

			Baseline	Time Point	Change from Baseline at Time Point	Difference from placebo	
	Treatment	N	Mean (SD)	Mean (SD)	LS Mean (95% CI) †	LS Means (95% CI)†	p-Value†
sTSTm	**Week 1**						
	Suvo LD	198	315.1 (60.3)	343.4 (60.5)	28.7 (22.5, 34.8)	16.7 (8.8, 24.6)	0.00003
	Suvo HD	313	314.1 (69.2)	351.5 (71.8)	36.9 (32.0, 41.8)	24.9 (18.0, 31.8)	<0.00001
	Placebo	307	313.2 (66.3)	325.7 (68.8)	12.0 (7.0, 16.9)	--	--
	Month 1						
	Suvo LD	191	315.0 (60.0)	352.2 (64.3)	36.8 (29.2, 44.4)	15.5 (5.8, 25.2)	0.00180
	Suvo HD	304	315.6 (66.6)	358.6 (74.5)	41.9 (35.9, 48.0)	20.6 (12.0, 29.1)	<0.00001
	Placebo	297	314.1 (66.0)	336.4 (67.0)	21.4 (15.3, 27.4)	--	--
	Month 3						
	Suvo LD	182	315.7 (60.5)	369.4 (65.5)	53.5 (45.2, 61.7)	18.9 (8.3, 29.5)	0.00046
	Suvo HD	289	316.8 (65.5)	372.9 (70.5)	54.9 (48.4, 61.5)	20.4 (11.0, 29.7)	0.00002
	Placebo	276	314.4 (66.0)	352.2 (64.7)	34.6 (28.0, 41.2)	--	--
sWASOm	**Week 1**						
	Suvo LD	198	86.7 (52.0)	66.8 (49.2)	-18.5 (-22.8, -14.3)	-9.3 (-14.7, -3.8)	0.00081
	Suvo HD	312	85.1 (53.3)	63.7 (47.0)	-19.6 (-23.0, -16.3)	-10.3 (-15.1, -5.6)	0.00002
	Placebo	303	89.5 (54.4)	77.5 (52.7)	-9.3 (-12.7, -5.9)	--	--
	Month 1						
	Suvo LD	191	85.7 (50.9)	58.0 (42.6)	-26.2 (-31.2, -21.3)	-10.8 (-17.1, -4.4)	0.00086
	Suvo HD	303	84.3 (52.3)	56.7 (47.6)	-25.8 (-29.7, -21.9)	-10.4 (-15.9, -4.8)	0.00027
	Placebo	296	89.1 (54.2)	70.4 (53.2)	-15.5 (-19.4, -11.5)	--	---
	Month 3						
	Suvo LD	182	84.0 (50.3)	46.4 (39.7)	-37.4 (-42.4, -32.3)	-10.8 (-17.2, -4.3)	0.00113
	Suvo HD	289	83.3 (51.9)	45.9 (42.6)	-36.0 (-40.0, -32.0)	-9.4 (-15.1, -3.7)	0.00123
	Placebo	275	89.9 (54.1)	58.8 (44.0)	-26.6 (-30.7, -22.5)	--	--
WASO	**Night 1**						
	Suvo LD	145	133.5 (49.8)	80.4 (43.5)	-42.8 (-49.2, -36.5)	-39.3 (-47.2, -31.3)	<.00001
	Suvo HD	245	130.3 (52.6)	69.2 (38.7)	-53.0 (-57.9, -48.1)	-49.4 (-56.3, -42.6)	<.00001
	Placebo	245	127.1 (50.5)	117.2 (53.7)	-3.6 (-8.4, 1.3)	--	--
	Month 1						
	Suvo LD	134	132.7 (49.6)	94.6 (47.4)	-28.8 (-36.0, -21.6)	-26.9 (-35.9, -17.9)	<.00001
	Suvo HD	234	129.7 (50.8)	88.5 (46.4)	-33.5 (-39.0, -28.1)	-31.6 (-39.3, -23.9)	<.00001
	Placebo	235	125.4 (50.0)	118.0 (56.5)	-1.9 (-7.4, 3.5)	--	--
	Month 3						
	Suvo LD	131	133.7 (50.5)	87.4 (46.4)	-36.2 (-43.6, -28.9)	-23.4 (-32.7, -14.2)	<.00001
	Suvo HD	217	127.6 (48.0)	83.7 (40.8)	-37.5 (-43.2, -31.8)	-24.7 (-32.7, -16.7)	<.00001
	Placebo	218	126.7 (50.5)	108.1 (48.8)	-12.8 (-18.4, -7.1)	--	--

†Based on a mixed effects model with terms for study (P028, P029), baseline value, age category (<65, ≥65), region (NA, EU, Other), gender, treatment, time point, treatment-by-time point and age category-by-treatment-by-time point interaction as covariates.
Suvo LD = Suvorexant 20 mg for patients <65 years and Suvorexant 15 mg for patients ≥65 years.
Suvo HD = Suvorexant 40 mg for patients <65 years and Suvorexant 30 mg for patients ≥65 years.

Sleep Onset Effects in Elderly

Suvorexant HD was effective in elderly patients in decreasing objective (LPS) and subjective (sTSOm) measures of sleep onset at Night 1/Week 1, Month 1, and Month 3. The magnitude of the changes for sleep onset endpoints in the elderly is presented in [Table 11].

In elderly, improvements (decreases) in sTSOm from baseline for Suvorexant HD ranged between 17.1 minutes at Week 1 to 26.7 minutes at Month 3. While improvements in sTSOm increased over time for both suvorexant HD and placebo; differences for suvorexant HD compared to placebo were ~9 (8.7 to 9.6) minutes in favor of suvorexant HD and were significant at all 3 timepoints. For LPS, Suvorexant HD improvements from baseline ranged between 30.4 to 33.5 minutes for Night 1, Months 1 and 3; differences from placebo were 17.5 minutes at Night 1 and decreased to 7.7 minutes by Month 3 due to increasing placebo improvement.

Similar to the overall results, sleep onset results were less consistent with suvorexant LD with regard to the timepoints across age groups, which is not unexpected given the smaller sample sizes and lower dose. The magnitude of sleep onset effects was lower as well; reductions in sTSOm ranged between 14.0 minutes at Week 1 to 24.1 minutes at Month 3; differences from placebo were ~6.5 minutes for Week 1 and Month 3, and 3.6 minutes at Month 1 in favor of suvorexant LD.

Table 11
Subgroup (Age≥65) Analysis of Change from Baseline in Sleep Onset Endpoints (sTSOm, LPS) at All Time Points During the Treatment Phase (Pooled P028+P029 / LDA / Full Analysis Set PSG / Data-as-Observed)

	Treatment	N	Baseline Mean (SD)	Time Point Mean (SD)	Change from Baseline at Time Point LS Mean (95% CI) †	Difference from placebo LS Means (95% CI)†	Difference from placebo p-Value†
sTSOm	Week 1						
	Suvo LD	198	66.1 (39.2)	53.4 (35.3)	-14.0 (-18.3, -9.7)	-6.5 (-12.1, -1.0)	0.02058
	Suvo HD	313	67.0 (45.9)	51.2 (40.1)	-17.1 (-20.5, -13.7)	-9.6 (-14.5, -4.8)	0.00011
	Placebo	307	69.1 (49.4)	62.2 (50.9)	-7.5 (-10.9, -4.0)	--	--
	Month 1						
	Suvo LD	191	64.5 (38.3)	49.8 (32.3)	-16.0 (-21.3, -10.7)	-3.6 (-10.4, 3.2)	0.29721
	Suvo HD	304	65.5 (39.4)	45.3 (37.0)	-21.1 (-25.3, -16.9)	-8.7 (-14.6, -2.7)	0.00429
	Placebo	297	68.2 (49.0)	55.8 (44.6)	-12.4 (-16.6, -8.2)	--	--
	Month 3						
	Suvo LD	182	64.6 (38.7)	41.5 (34.2)	-24.1 (-29.3, -18.9)	-6.5 (-13.2, 0.1)	0.05394
	Suvo HD	289	64.3 (38.7)	37.5 (25.0)	-26.7 (-30.9, -22.6)	-9.2 (-15.0, -3.3)	0.00210
	Placebo	276	68.6 (50.0)	50.3 (44.9)	-17.5 (-21.7, -13.4)	--	--
LPS	Night 1						
	Suvo LD	145	66.5 (49.8)	40.1 (33.5)	-25.9 (-31.8, -20.1)	-10.0 (-17.3, -2.6)	0.00811
	Suvo HD	247	64.6 (43.1)	32.4 (24.5)	-33.5 (-38.0, -29.0)	-17.5 (-23.9, -11.2)	<.00001
	Placebo	247	67.5 (49.1)	50.5 (47.2)	-16.0 (-20.5, -11.5)	--	--
	Month 1						
	Suvo LD	135	65.5 (46.2)	34.6 (24.1)	-31.4 (-36.8, -25.9)	-5.0 (-11.9, 1.8)	0.15101
	Suvo HD	235	63.0 (39.1)	32.6 (29.1)	-33.1 (-37.2, -29.0)	-6.7 (-12.6, -0.9)	0.02388
	Placebo	235	66.9 (48.9)	39.9 (36.4)	-26.3 (-30.5, -22.2)	--	--
	Month 3						
	Suvo LD	131	65.6 (46.4)	37.0 (33.6)	-28.9 (-34.6, -23.2)	-6.2 (-13.5, 1.0)	0.09159
	Suvo HD	219	62.7 (38.7)	35.1 (39.9)	-30.4 (-34.8, -25.9)	-7.7 (-14.0, -1.4)	0.01601
	Placebo	218	67.8 (50.3)	43.8 (40.2)	-22.7 (-27.1, -18.2)	--	--

†Based on a mixed effects model with terms for study (P028, P029), baseline value, age category (<65, ≥65), region (NA, EU, Other), gender, treatment, time point, treatment-by-time point and age category-by-treatment-by-time point interaction as covariates.
Suvo LD = Suvorexant 20 mg for patients <65 years and Suvorexant 15 mg for patients ≥65 years.
Suvo HD = Suvorexant 40 mg for patients <65 years and Suvorexant 30 mg for patients ≥65 years.

5.6 Conclusions

The efficacy of suvorexant in improving sleep maintenance and reducing latency to sleep onset in patients with chronic insomnia has been comprehensively evaluated in one Phase 2b and three Phase 3 randomized, double-blind, placebo-controlled, multicenter/multinational trials of up to 12 months duration involving 3063 patients including 1765 non-elderly and 1298 elderly patients. Following are the efficacy conclusions based on the overall information presented in this efficacy summary:

- In the confirmatory Phase 3 studies, suvorexant HD (40 mg for non-elderly and 30 mg for elderly patients) was superior to placebo on all objective (WASO and LPS) and subjective (sTSTm and sWASOm, sTSOm) measures of sleep

maintenance and sleep onset at Night 1/Week 1, Month 1, and Month 3, except for LPS at Month 3 in one of the two studies (P029).

- In terms of sleep maintenance, the reduction in WASO for both HD and LD is maintained throughout the night.

- The totality of the Phase 2b and Phase 3 trials and pooled results (P028+P029) support the efficacy of suvorexant LD. However, the magnitude of effects observed for suvorexant LD across efficacy measures were less consistent and generally smaller, compared to those observed for suvorexant HD.

- Subgroup analyses of the pooled (P028+P029) data provide evidence that suvorexant HD is effective in improving objective and subjective measures of sleep maintenance and sleep onset for up to 3 months of treatment for non-elderly and elderly patients and for both gender, with the beneficial effects on sleep maintenance and sleep onset being generally consistent across other subgroups as well.
- The results of the long-term trial, P009, additionally support the chronic efficacy observed in the 3-month confirmatory studies P028 and P029, providing evidence for efficacy up to one year of treatment without evidence of tolerance to drug effect with extended treatment.

- The Randomized Discontinuation Phase of the long-term study (P009) reveals return of insomnia symptoms without rebound upon suvorexant cessation, and demonstrates the continued benefit of treatment beyond one year.

- For the Insomnia Severity Index, a measure of important aspects of insomnia beyond simply sleep induction and maintenance, patients on suvorexant consistently reported greater improvement compared to placebo on the ISI score total as well as individual ISI items. The percentage of patients who had a clinically meaningful improvement (defined as ≥6-point improvement from baseline) in the ISI total score (i.e., responders) was also higher in the suvorexant HD and LD treatment groups than in the placebo group.

- Lastly, results from multiple additional exploratory endpoints, which include specific measures of sleep quality (subjective sleep quality [sQUALm], subjective feeling of being refreshed upon waking [sREFRESHEDm]), clinician- and patient- global ratings of illness improvement and severity (CGI-S, CGI-I, PGI-S, PGI-I), are consistent with the results of the primary analyses and provide additional support for the efficacy of suvorexant in improving symptoms of insomnia. These results further suggest that the demonstrated effects of suvorexant to improve both sleep onset and sleep maintenance are clinically relevant.

6. Overview of Safety

The suvorexant development program was designed to enable a comprehensive evaluation of suvorexant safety in non-elderly (< 65 years) and elderly (> 65 years) adults with insomnia, and the results of this extensive evaluation indicate that suvorexant is generally safe and well tolerated with a favorable residual effects profile. In three large Phase 3 trials, rates of discontinuation due to adverse experiences were low and similar across the age subgroups. The most common adverse experience was somnolence, which occurred in a dose-dependent manner and was generally mild to moderate in severity and self-limited.

The suvorexant program also included systematic assessments for a variety of special safety considerations with focus on those associated with the use of sleep medications (e.g. complex sleep-related behaviors, rebound and withdrawal, next day residual effects including effects on psychomotor performance and driving, and respiratory safety), those associated with a novel CNS-active compound (e.g. abuse potential, alcohol interaction, potential for suicidality), and to address theoretical considerations associated with the new orexin receptor antagonist (ORA) mechanism of action (e.g. cataplexy). The results of these detailed prospective assessments support the favorable safety profile of suvorexant.

6.1 Extent of Exposure by Duration and by Suvorexant Dose

Over the course of clinical development of suvorexant, 2027 patients with chronic insomnia (1198 non-elderly and 829 elderly patients) were exposed to any dose of suvorexant. [Table 12] presents exposure data for patients treated with suvorexant in the Phase 3 studies.

Overall, 1784 insomnia patients were treated with suvorexant in Phase 3 at doses ranging from 15 mg to 40 mg. A total of 1218 patients (60.1%) received suvorexant for at least 3 months, including 290 who received suvorexant LD and 927 who received suvorexant HD. A total of 507 patients received suvorexant for 6 months or longer (42 on suvorexant LD and 464 on suvorexant HD); 160 patients received suvorexant HD for 12 months or longer. These data represent 758.2 person years (and over 275,000 patient nights) of exposure to suvorexant in the Phase 3 program, which provides a robust suvorexant safety database in both non-elderly (955 patients, 357.7 person years) and elderly patients (829 patients, 400.5 person years).

In the Phase 1 studies, 842 subjects received at least one dose of suvorexant (either alone or in combination with another drug), with evaluation of single doses up to 240 mg and multiple doses up to 100 mg.

Table 12
Extent of Exposure to Suvorexant by Dose
Treatment, Extension, and Run-out Phases
Phase 3 Trials (P028, P029, and P009)

Suvorexant	1 day to < 1 Week	1 Week to < 1 Month	1 to < 3 Months	3 to < 6 Months	6 to < 9 Months	9 to < 12 Months	≥ 12 Months	Total Patients	Duration Range	Mean Duration
Any Dose	28	94	444	711	170	177	160	1,784	1 to 434 days	155.2 days
10 mg	18	1	0	0	0	0	0	19	1 to 7 days	1.8 days
15 mg	3	10	71	96	22	0	0	202	1 to 189 days	104.9 days
20 mg	7	12	100	152	20	0	0	291	1 to 191 days	98.3 days
30 mg	21	34	123	196	54	107	109	644	1 to 434 days	194.4 days
40 mg	17	41	151	267	73	70	51	670	1 to 426 days	152.1 days
60 mg	11	0	0	0	0	0	0	11	1 to 3 days	1.7 days
80 mg	9	0	0	0	0	0	0	9	1 to 5 days	1.9 days

Each patient is counted once on each applicable dosage category row.
Only patients treated during the indicated phase of the study period are included in the table.
This table also includes doses other than the doses of suvorexant designated in the studies, based on occurrences when patients took more or less than the prescribed dose (i.e., sporadic administrations of 10 mg and 60 mg inadvertently by patients in the Phase 3 trials). Therefore, the individual dose totals during each timeframe may not add up to "any dose" for the corresponding timeframe.

6.2 Approaches for Collection and Evaluation of Safety Data

In the clinical program, safety assessments were based on review of adverse events, review of abnormalities meeting predefined limits of change (PDLC) criteria and mean changes in safety laboratory analytes, ECG intervals, and vital signs. Adverse events, including drug-related AEs, events of clinical interest (ECIs), AEs associated with potential for abuse, residual effects, and withdrawal, serious adverse events (SAEs), and AEs that led to discontinuation of study medication, were identified and summarized. Patient demographics, medical history, study disposition, and exposure also contributed to the evaluation of safety in the study populations. Additional safety parameters evaluated and specific features of safety monitoring in the clinical development program are described below.

6.2.1 Special Considerations in the Assessment of Safety

6.2.1.1 Events of Clinical Interest (ECIs)

Given potential safety-related concerns associated with the use of sleep medications, AEs of special interest, defined as ECIs, were selected for prospective assessment in the suvorexant development program based on review of key topics in prior sleep medication filings and approved product labels. The ECI designation ensured rapid reporting and collection of detailed AE data from these events to support narrative summaries. Analysis of ECIs was pre-specified within the integrated statistical analysis plan (iSAP) for safety. The suvorexant program ECIs were focused on safety considerations associated with 1) events reported with other marketed sleep medications, 2) clinical characterization of a novel CNS-active compound, and 3) theoretical effects related to the orexin receptor antagonist mechanism of action, as summarized in [Table 13].

Table 13
ECIs by Category and Issue for Safety Factor Assessed

Category	Event of Clinical Interest (ECI)	Specific issue addressed by ECI
Safety considerations associated with marketed sleep medications	Complex sleep-related behaviors	Assess potential for sleep-related parasomnias, e.g. sleep walking
	Sleep paralysis (including sleep onset paralysis)	Assess potential for events associated with sleep transitions (i.e., during sleep onset and upon awakening)
	Hypnagogic or hypnopompic hallucinations	
	Excessive daytime sleepiness (EDS)	Assess residual effects
	AEs associated with motor vehicle accidents (when patient is driving)	Assess potential for effects on driving
	Falls	Assess potential effects on balance and investigate any potential relationship to cataplexy
Safety considerations with novel CNS-active compounds	Suicidal ideation and/or behaviors	Assess potential risk for suicidality
	Selected events associated with potential for abuse	Assess potential for abuse liability
Safety considerations with novel mechanism of action	Cataplexy	Assess theoretical effects due to transient inhibition of orexin receptors

Discussions of these individual ECIs are woven in a contextually-appropriate manner with the safety topic relevant to the ECI data (e.g., excessive daytime sleepiness (EDS) discussion is included within the Residual Effects section).

Adjudication of Selected ECIs

In order to enable consistent and impartial expert evaluation of key ECIs, a blinded, independent committee of scientific experts, external to the Sponsor, was established for assessment of selected theoretical mechanism-related AEs reported in the course of the suvorexant clinical program. ECIs identified for adjudication by this committee consisted of cataplexy, falls (to evaluate if the circumstances of a fall event were

suggestive of cataplexy), and sleep onset paralysis. The adjudication process was prospectively described in an adjudication committee charter.

6.2.1.2 Assessments Pertinent to Safety Concerns for Sleep Medications

Withdrawal

The potential for acute withdrawal symptoms was prospectively assessed during the Run-Out Phase in the Phase 3 trials using the Tyrer Withdrawal Symptom Questionnaire (WSQ). Withdrawal symptoms were also evaluated through spontaneous reports during the Run-out Phase of selected AEs prospectively categorized as potentially being associated with withdrawal effects.

Rebound Insomnia

Rebound insomnia was evaluated both objectively (via PSG in P028 and P029) and subjectively (via e-dairy responses in P009, P028 and P029). Objective assessment of rebound, as measured by WASO and LPS comparison to pre-treatment baseline, was carried out on the first night (PSG night) of the Run-out Phase. Subjective evaluation of rebound, as measured by daily assessment of sTST and sTSO, and sWASO compared to the last daily pre-treatment baseline, was conducted on the first 3 nights of the Run-out Phase. Two analytical approaches were used in these evaluations:

1) A categorical approach to compare the proportion of patients in each treatment group who had any worsening from baseline sleep values;

2) A comparison between treatment groups in mean changes from baseline in minutes.

Residual Effects

The comprehensive evaluation of potential residual effects of suvorexant included objective and subjective measurements across the clinical development program in both the non-elderly and elderly age groups. The objective evaluation included assessments of driving performance, psychomotor performance, balance, and memory in Phase 1 studies, and assessment of psychomotor performance using the Digit Symbol Substitution Test (DSST) in Phase 2b/3 studies. The DSST was performed in the morning approximately 8.5-9 hours after study medication was administered; 30 minutes to 1 hour following completion of the overnight PSG. In the insomnia trials, next-day residual effects were also characterized through review of selected spontaneously reported AEs that were categorized as possibly being associated with residual effects. In addition, occurrences of motor vehicle accidents and/or traffic violations (when the patient was a driver) and any associated adverse events were evaluated in Phase 3.

To facilitate collection of detailed information on selected cases of next day somnolence, excessive daytime sleepiness (EDS) was designated as a pre-specified ECI in the

program. EDS in this context was predefined as a form of recurrent and/or persistent residual somnolence beyond the more typical short-lived next-day somnolence indicative of potential drug carryover effect. Note that as defined for this program, the EDS designation is an operational definition for the purpose of detailed AE data collection, but is not synonymous with the clinical diagnostic syndrome of Excessive Daytime Sleepiness seen in conditions of obstructive sleep apnea, narcolepsy, or shift work sleep disorder. In the latter circumstances, EDS symptoms result from and are sustained by the underlying disorder and may require medical intervention, whereas in the suvorexant program the symptoms of sleepiness are likely directly related to the transient pharmacology of the drug, and symptoms abate without need for medical intervention upon discontinuation of therapy.

6.2.1.3 Safety Assessments for Novel CNS-Active Compounds

Assessing the Potential Risk for Suicidal Behavior and Ideation

In accordance with recent FDA requirements for the systematic assessment of suicidal ideation and behavior in trials of investigational CNS-active compounds, including sleep medications, suicidal ideation and behavior were prospectively assessed in the suvorexant Phase 3 studies (and eight of the later Phase 1 studies) via patient interview using the Columbia Suicide Severity Rating Scale (C-SSRS). In addition, suicidal ideation and/or behavior adverse events were pre-identified as ECIs for the suvorexant clinical development program.

Patients with an ongoing episode of major depression were excluded from the confirmatory efficacy trials, but patients with depressive symptoms who did not meet full diagnostic criteria for major depression could have participated in the long-term safety trial (P009). Based on the Quick Inventory of Depression Scale (QIDS-SR 16) total score at baseline, few patients in P009 reported significant symptoms of depression, and among those reported, most were those related to insomnia, and were without clinical evidence of depression (QIDS mean total score: suvorexant HD 4.5, placebo 4.3). Evaluation of change from baseline over time (i.e., Months 1, 3, 6, 9, and 12) was done to assess differences with respect to core mood symptoms and individual items between suvorexant and placebo at any time point with treatment for up to 12 months. To assess whether the presence of baseline depressive symptoms constituted a specific risk factor, subgroup analyses by QIDS severity at baseline (<10 and ≥ 10) were conducted. Note that 4.6% of patients had a QIDS score of ≥ 10 at baseline.

Assessing Potential for Abuse and Other Misuse

To evaluate the potential abuse liability for suvorexant, a broad list of adverse event terms that could potentially be associated with medication abuse or other misuse was established by the Sponsor and refined based on consultation with the FDA CSS subsequent to launching the Phase 3 program. A further refined subset of terms, focused on those which could be considered potentially positively reinforcing and, thereby,

associated with misuse of a medication, was also identified prior to launching the Phase 3 program and also designated as ECIs and included the following:

- Depersonalization;
- Derealization;
- Dissociation;
- Euphoric mood;
- Hallucination;
- Mania; and
- Potential study medication misuse
    - In order to facilitate identification of instances of potential medication diversion or other inappropriate use of study medication, AEs of "drug administration error" were defined as follows: when a patient returned less study medication than expected, denied taking extra study medication beyond that prescribed, and the equivalent of more than one pill per week per study medication bottle dispensed was unaccounted for.

6.3 Safety Evaluation Plan

For the clinical assessment of safety, data were pooled across the three Phase 3 trials (P028, P029, and P009) for both the Treatment and Run-out phases. The pooled safety evaluation provides a comparison of the safety profile of suvorexant with placebo, as well as by the doses (suvorexant HD and suvorexant LD) investigated in the phase 3 trials. This population pooling strategy permits combination of all data from patients receiving common dosages of suvorexant across trials irrespective of differences in trial design, duration, or exposed population. In terms of duration of safety assessed by dose (in comparison to placebo), core treatment data up to 12 months in duration is available for HD since the HD treatment arm was studied in all three trials (including the long-term safety trial, P009), whereas assessment of LD occurred in two studies (P028 and P029) for up to 6 months (in P028).

For the purposes of this safety summary, discussion is focused on pooled safety data for the 0-3 month treatment period for suvorexant HD and suvorexant LD for the Combined Phase 3 trials (P028, P029, P009), which represents the most robust suvorexant safety dataset. Exposure was similar among all 3 treatment groups during this 0-3 month time frame based upon the similar percentage of patients who completed the 3 months of treatment. Pooled data supporting long term treatment with suvorexant HD for up to 12 months are also provided.

Rebound and withdrawal was assessed in the double-blind Run-out Phases of the three Phase 3 trials. Rebound insomnia was evaluated both objectively (PQ-cohort only) and subjectively. Objective assessment of rebound (as measured by wakefulness after persistent sleep onset (WASO) and latency to persistent sleep (LPS) comparison to pre-treatment baseline) was assessed by data collected by PSG on the first night of the Run-out Phase. Subjective evaluation of rebound (as measured by subjective total sleep time (sTST) and subjective time to sleep onset (sTSO), and subjective wake time after sleep onset (sWASO) compared to the last daily pre-treatment baseline) was conducted on the first 3 nights of the Run-out Phase. Acute withdrawal was systematically assessed during the double-blind Run-out Phase of the confirmatory efficacy trials (P028 and P029) and the double-blind Randomized Discontinuation Phase of the long-term safety trial (P009) using the Tyrer WSQ via the evening eDiary over the first three days of these timeframes, with the day following the last night of the Treatment or Extension Phase serving as the baseline. In addition, withdrawal was further characterized through review of spontaneously reported AE reported over the 1-Week Run-out Phase in the confirmatory efficacy trials (P028 and P029).

Statistical Methods

The data from Phase 3 trials are from patients who received at least one dose of double-blind study medication, and are referred to as the All Patients as Treated (APaT) population. Summary statistics are provided for all safety parameters. Additionally, for selected events of interest for the pooled Phase 3 data, 95% CIs are provided for between-treatment differences in the percentage of patients with events; these analyses were performed using the Miettinen and Nurminen method (1985) stratified for study (using sample size as weights). For residual effect data (change from baseline in DSST number of correct and number of attempted responses), estimated treatment differences (e.g., at Month 3) and 95% CIs are provided based upon a longitudinal data analysis model including terms for study, baseline value, age group, region, gender, treatment group, time, and treatment group-by-time interaction.

6.4 Patient Characteristics and Limitations of the Safety Database

The patient characteristics for the pooled Phase 3 safety population for Month 0-3, presented in [Table 14], includes both men and women with a wide age range, having diverse racial backgrounds, and from various regions throughout the world. Age for the pooled safety population ranged from 18 to 90 years, with a mean (median) age of 58 (62) years. The sample is comprised predominantly of female patients (62.1%), consistent with the epidemiology of insomnia. Patients were predominantly White (77.6%) and of Asian (12.4%) race and were largely enrolled at sites in North America, Europe and Japan.

Table 14
Patient Baseline Characteristics
Combined Phase 3 Population Treatment Phase (P028, P029, and P009)
(All Patients as Treated)

	Suvo LD		Suvo HD		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	493		1,291		1,025		2,809	
Gender								
Male	174	(35.3)	507	(39.3)	384	(37.5)	1,065	(37.9)
Female	319	(64.7)	784	(60.7)	641	(62.5)	1,744	(62.1)
Age								
24 and under	13	(2.6)	28	(2.2)	25	(2.4)	66	(2.3)
25 to 34	62	(12.6)	86	(6.7)	71	(6.9)	219	(7.8)
35 to 44	62	(12.6)	148	(11.5)	120	(11.7)	330	(11.7)
45 to 54	77	(15.6)	213	(16.5)	169	(16.5)	459	(16.3)
55 to 64	77	(15.6)	189	(14.6)	171	(16.7)	437	(15.6)
65 to 74	170	(34.5)	500	(38.7)	359	(35.0)	1,029	(36.6)
75 to 84	31	(6.3)	120	(9.3)	102	(10.0)	253	(9.0)
over 84	1	(0.2)	7	(0.5)	8	(0.8)	16	(0.6)
Patients with data	493		1291		1025		2809	
Mean	55		58		58		58	
SD	16		15		15		15	
Median	59		64		62		62	
Range	18 to 86		18 to 88		18 to 90		18 to 90	
Race								
American Indian or Alaska Native	0	(0.0)	2	(0.2)	3	(0.3)	5	(0.2)
Asian	93	(18.9)	130	(10.1)	125	(12.2)	348	(12.4)
Black	19	(3.9)	71	(5.5)	70	(6.8)	160	(5.7)
Multiple	23	(4.7)	48	(3.7)	42	(4.1)	113	(4.0)
Native Hawaiian or Other Pacific Islander	0	(0.0)	1	(0.1)	1	(0.1)	2	(0.1)
White	358	(72.6)	1,039	(80.5)	784	(76.5)	2,181	(77.6)
Ethnicity								
Hispanic or Latino	90	(18.3)	201	(15.6)	154	(15.0)	445	(15.8)
Not Hispanic or Latino	403	(81.7)	1,089	(84.4)	871	(85.0)	2,363	(84.1)

Patient Baseline Characteristics
Combined Phase 3 Population Treatment Phase (P028, P029, and P009)
(All Patients as Treated) (Cont.)

	Suvo LD		Suvo HD		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Ethnicity								
Null	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
Region								
Asia Pacific	26	(5.3)	38	(2.9)	32	(3.1)	96	(3.4)
Central and Eastern Europe	17	(3.4)	24	(1.9)	32	(3.1)	73	(2.6)
Central and South America	27	(5.5)	55	(4.3)	46	(4.5)	128	(4.6)
Europe	165	(33.5)	419	(32.5)	331	(32.3)	915	(32.6)
Japan	61	(12.4)	92	(7.1)	94	(9.2)	247	(8.8)
Middle East / Africa	7	(1.4)	16	(1.2)	18	(1.8)	41	(1.5)
North America	190	(38.5)	647	(50.1)	472	(46.0)	1,309	(46.6)
Body Mass Index (kg / m^2)								
Patients with data	493		1289		1024		2806	
Mean	25.4		26.3		26.0		26.0	
SD	4.1		4.4		4.3		4.3	
Median	25.0		26.0		25.6		25.7	
Range	16 to 39		16 to 40		17 to 40		16 to 40	
BMI Category								
Underweight (BMI < 18.5)	11	(2.2)	21	(1.6)	17	(1.7)	49	(1.7)
Normal range (18.5 ≤ BMI < 25)	232	(47.1)	488	(37.8)	432	(42.1)	1,152	(41.0)
Overweight (25 ≤ BMI ≤ 30)	194	(39.4)	548	(42.4)	405	(39.5)	1,147	(40.8)
Obese (BMI > 30)	56	(11.4)	232	(18.0)	170	(16.6)	458	(16.3)
Null	0	(0.0)	2	(0.2)	1	(0.1)	3	(0.1)

NULL indicates data were not reported for those subjects.
Suvo LD = Suvorexant 20 mg for patients < 65 years and Suvorexant 15 mg for patients ≥ 65 years
Suvo HD = Suvorexant 40 mg for patients < 65 years and Suvorexant 30 mg for patients ≥ 65 years

Use in Pediatric Patients

Suvorexant has not been studied in children and adolescents under the age of 18 years, as all protocols excluded these patients. As the safety and effectiveness of suvorexant in pediatric patients has not been established, treatment of pediatric patients with suvorexant is not recommended.

Use in Elderly Patients

As all Phase 3 trials were combined-age studies with no upper age limit, extensive experience with suvorexant in elderly patients was obtained in the program. Nearly half (46.2%) of the patients that participated in the Phase 3 program were elderly (≥65 years); 1,029 (36.6%) patients were ≥ 65 and <75 years of age, and 269 (9.6%) patients were ≥ 75 years of age.

Use in Pregnancy

Regarding the use of suvorexant in pregnancy, the program study protocols required that women of child-bearing potential be counseled to avoid pregnancy through the use of effective forms of contraception during their participation in clinical trials of suvorexant. There were 5 reports of exposure during pregnancy in women participating in the suvorexant clinical development program. Of these, one was carried to term and resulted in a healthy birth, one was terminated by elective abortion, and one was terminated following administration of misoprostol; a sonogram in this patient suggested a blighted ovum, but was performed after administration of misoprostol. Two pregnancies ended in spontaneous abortions; however of these, one had taken several other concomitant medications including desogestrel. Use in pregnancy will be addressed through labeling.

Use in Patients with Narcolepsy

Because narcolepsy in some cases has been shown to be associated with potential reductions in orexinergic tone, an ORA is unlikely to be of benefit to narcolepsy patients. Therefore, no studies of suvorexant have been conducted in narcolepsy patients. Additionally, patients with a diagnosis of narcolepsy and cataplexy were excluded from participation in all clinical trials of suvorexant. Because suvorexant has not been studied in patients with narcolepsy or cataplexy, treatment with suvorexant is not recommended in these patients.

6.5 Patient Disposition

The majority of patients treated with suvorexant in the combined Phase 3 population completed at least 3 months of treatment (86.4%); refer to [Table 15]. The most common reasons for discontinuation were AEs, withdrawal by subject, and lack of efficacy. The incidences of specific reasons for discontinuation were similar between suvorexant and placebo treatment groups, with no tolerability concerns with continued treatment for up to 12 months. Note that the completion rate was somewhat lower in patients treated with suvorexant for at least 12 months (78.4%) in the pooled population, but this is consistent with the higher rates of discontinuation observed in trials of extended duration. Note also that in the long-term safety trial, 62.0% of patients completed. In addition, nearly all (99%) patients who entered the Run-out Phase completed it, regardless of treatment, indicating good tolerability upon abrupt cessation of suvorexant.

Table 15
Disposition of Patients
Combined Phase 3 Population 0-3 Months (P028, P029, and P009)
(All Patients as Treated)

	Protocols 028+029+009							
	Suvo LD		Suvo HD		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	493		1291		1025		2809	
Trial Disposition								
Completed	435	(88.2)	1117	(86.5)	874	(85.3)	2426	(86.4)
Discontinued	58	(11.8)	174	(13.5)	151	(14.7)	383	(13.6)
Adverse Event	16	(3.2)	70	(5.4)	48	(4.7)	134	(4.8)
Lack of Efficacy	8	(1.6)	33	(2.6)	37	(3.6)	78	(2.8)
Lost to Follow-up	3	(0.6)	10	(0.8)	8	(0.8)	21	(0.7)
Physician Decision	6	(1.2)	11	(0.9)	3	(0.3)	20	(0.7)
Pregnancy	1	(0.2)	2	(0.2)	0	(0.0)	3	(0.1)
Protocol Violation	10	(2.0)	7	(0.5)	10	(1.0)	27	(1.0)
Withdrawal by Subject	14	(2.8)	41	(3.2)	45	(4.4)	100	(3.6)

Each patient is counted once for Study Disposition based on the latest corresponding disposition record.
Suvo LD = Suvorexant 20 mg for patients < 65 years and Suvorexant 15 mg for patients ≥ 65 years.
Suvo HD = Suvorexant 40 mg for patients < 65 years and Suvorexant 30 mg for patients ≥ 65 years.

6.6 Analysis of Adverse Events

6.6.1 Adverse Event Summary

In the 0-3 Month Combined Phase 3 population, the percentage of patients that reported any AE was greater for suvorexant HD compared to placebo; however, the treatment difference was not striking (51.0% and 46.6% respectively for the 0-3 Month Treatment Phase), whereas the percentage for suvorexant LD (46.5%) was similar to placebo; see [Table 16]. AEs assessed as treatment-related by the investigator occurred more commonly with suvorexant in a dose-related manner. The proportions of patients reporting SAEs, and discontinuation due to an AE, drug-related AE, or SAE were low and similar between all treatment groups.

In elderly patients, the incidence of any AE was similar across all the treatment groups (49.0%, 50.4%, and 49.5% for suvorexant LD, HD, and placebo, respectively). As in non-elderly patients, elderly patients treated with suvorexant HD (23.8%) reported a higher incidence of drug-related AEs than those treated with placebo (14.7%), while the incidence in elderly patients treated with suvorexant LD (20.8%) was not different from placebo (confidence interval included zero). No other differences were observed between the treatment groups with respect to the other AE categories in elderly patients. The incidence of events in the various other AE categories was generally similar between the age subgroups. Further, the incidence of events across the AE categories was generally

comparable for both suvorexant LD and HD across the age subgroups, with no evidence to suggest tolerability differences between the age subgroups.

For patients treated with suvorexant HD for up to 12 months, the AE summary profile was similar to that observed for 0 to 3 months. In general, the incidences of events in the various AE summary categories were somewhat higher than was observed from 0-3 months, likely due to the additional months of exposure in this population. Compared to patients treated with placebo, patients treated with suvorexant HD had a higher incidence of AEs overall (59.9% vs. 52.7%) and of drug-related AEs (28.5% vs. 16.9%); the incidence of other categories of AEs was similar between treatment groups.

Table 16
Adverse Event Summary
Combined Phase 3 Population: 0-3 Months (P028, P029, and P009)
All Patients as Treated

Protocols 028+029+009	n	(%)	Difference in % vs. Placebo Estimate (95% CI)[†]
Patients in population			
Suvo LD	493		
Suvo HD	1,291		
Placebo	1,025		
with one or more adverse events			
Suvo LD	229	(46.5)	-0.3 (-5.9, 5.3)
Suvo HD	658	(51.0)	4.2 (0.1, 8.4)
Placebo	478	(46.6)	
with no adverse events			
Suvo LD	264	(53.5)	0.3 (-5.3, 5.9)
Suvo HD	633	(49.0)	-4.2 (-8.4, -0.1)
Placebo	547	(53.4)	
with drug-related[‡] adverse events			
Suvo LD	109	(22.1)	7.0 (2.7, 11.6)
Suvo HD	329	(25.5)	10.2 (6.9, 13.5)
Placebo	154	(15.0)	
with serious adverse events			
Suvo LD	3	(0.6)	-1.5 (-2.8, -0.1)
Suvo HD	18	(1.4)	-1.0 (-2.2, 0.1)
Placebo	23	(2.2)	
with serious drug-related adverse events			
Suvo LD	0	(0.0)	0.0 (-0.5, 0.8)
Suvo HD	0	(0.0)	-0.1 (-0.6, 0.1)
Placebo	1	(0.1)	
who died			
Suvo LD	0	(0.0)	-0.1 (-0.7, 0.6)
Suvo HD	1	(0.1)	-0.0 (-0.5, 0.4)
Placebo	1	(0.1)	

Adverse Event Summary
Combined Phase 3 Population 0-3 Months (P028, P029, and P009)
(All Patients as Treated) (Cont.)

Protocols 028+029+009	n	(%)	Difference in % vs. Placebo Estimate (95% CI)[†]
discontinued[§] due to an adverse event			
Suvo LD	15	(3.0)	-2.2 (-4.4, 0.2)
Suvo HD	80	(6.2)	1.2 (-0.8, 3.1)
Placebo	50	(4.9)	
discontinued due to a drug-related adverse event			
Suvo LD	13	(2.6)	0.3 (-1.4, 2.3)
Suvo HD	53	(4.1)	1.4 (-0.1, 2.9)
Placebo	25	(2.4)	
discontinued due to a serious adverse event			
Suvo LD	1	(0.2)	-1.2 (-2.4, -0.2)
Suvo HD	9	(0.7)	-0.4 (-1.3, 0.4)
Placebo	12	(1.2)	
discontinued due to a serious drug-related adverse event			
Suvo LD	0	(0.0)	0.0 (-0.5, 0.8)
Suvo HD	0	(0.0)	-0.1 (-0.6, 0.1)
Placebo	1	(0.1)	

[†] Based on Miettinen & Nurminen method stratified by study (using sample size as weight); if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
[‡] Determined by the investigator to be related to the drug.
[§] Study medication withdrawn.
Suvo LD=Suvorexant 20 mg for patients < 65 years and Suvorexant 15 mg for patients ≥ 65 years.
Suvo HD=Suvorexant 40 mg for patients < 65 years and Suvorexant 30 mg for patients ≥ 65 years.

6.6.2 Common Adverse Experiences

Treatment for up to 3 months

Treatment for up to 3 months in the Combined Phase 3 Population yielded few treatment-emergent AEs (having an incidence of 2% in any treatment group as presented in [Table 17] and for most of these events, the incidence was similar across treatment groups. The most common (≥2%) AEs that were more frequent in suvorexant-treated patients were somnolence and fatigue; headache was common and not different among all treatment groups. The reported rates for somnolence were 6.7% and 10.7% for suvorexant LD and HD respectively vs. 3.0% for placebo, for fatigue 2.2% and 3.8% for suvorexant LD and HD respectively vs. 1.8% for placebo. Somnolence and fatigue are responsible for the difference observed in the Nervous System and General Disorders and Site Administration Conditions system organ class (SOC) categories. Results for elderly patients ≥ 65 years of age were generally similar and displayed in [Appendix 6]. In elderly patients, somnolence and fatigue were reported more frequently by suvorexant HD-treated (8.8% and 3.8%, respectively) than placebo-treated (3.2% and 1.7%, respectively) patients, and with similar frequency to placebo in patients treated with

suvorexant LD (somnolence 5.4% and fatigue 1.5%). Note that dizziness was reported less commonly in elderly patients treated with suvorexant HD than in those treated with placebo (2.2% vs. 4.9%, respectively).

Overall, similar results were observed for treatment-related AEs.

Table 17
Patients With Specific Adverse Events
(Incidence ≥ 2% in One or More Treatment Groups)
Combined Phase 3 Population 0-3 Months (P028, P029, and P009)
(All Patients as Treated)

Protocols 028+029+009	Suvo LD		Suvo HD		Placebo	
	n	(%)	n	(%)	n	(%)
Patients in population	493		1,291		1,025	
with one or more adverse events	229	(46.5)	658	(51.0)	478	(46.6)
with no adverse events	264	(53.5)	633	(49.0)	547	(53.4)
Eye disorders	**11**	**(2.2)**	**23**	**(1.8)**	**18**	**(1.8)**
Gastrointestinal disorders	**39**	**(7.9)**	**121**	**(9.4)**	**82**	**(8.0)**
Diarrhoea	12	(2.4)	21	(1.6)	15	(1.5)
Dry mouth	9	(1.8)	36	(2.8)	14	(1.4)
Nausea	7	(1.4)	27	(2.1)	16	(1.6)
General disorders and administration site conditions	**31**	**(6.3)**	**92**	**(7.1)**	**46**	**(4.5)**
Fatigue	11	(2.2)	49	(3.8)	18	(1.8)
Infections and infestations	**70**	**(14.2)**	**161**	**(12.5)**	**147**	**(14.3)**
Nasopharyngitis	26	(5.3)	49	(3.8)	56	(5.5)
Upper respiratory tract infection	8	(1.6)	28	(2.2)	12	(1.2)
Urinary tract infection	8	(1.6)	15	(1.2)	20	(2.0)
Injury, poisoning and procedural complications	**31**	**(6.3)**	**62**	**(4.8)**	**57**	**(5.6)**
Drug administration error	16	(3.2)	25	(1.9)	23	(2.2)
Investigations	**22**	**(4.5)**	**57**	**(4.4)**	**39**	**(3.8)**
Metabolism and nutrition disorders	**4**	**(0.8)**	**31**	**(2.4)**	**9**	**(0.9)**
Musculoskeletal and connective tissue disorders	**25**	**(5.1)**	**107**	**(8.3)**	**80**	**(7.8)**

Patients With Specific Adverse Events
(Incidence ≥ 2% in One or More Treatment Groups)
Combined Phase 3 Population 0-3 Months (P028, P029, and P009)
(All Patients as Treated) (Cont.)

Protocols 028+029+009	Suvo LD		Suvo HD		Placebo	
	n	(%)	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**25**	**(5.1)**	**107**	**(8.3)**	**80**	**(7.8)**
Back pain	7	(1.4)	16	(1.2)	23	(2.2)
Nervous system disorders	**83**	**(16.8)**	**276**	**(21.4)**	**135**	**(13.2)**
Dizziness	15	(3.0)	32	(2.5)	29	(2.8)
Headache	36	(7.3)	85	(6.6)	61	(6.0)
Somnolence	33	(6.7)	138	(10.7)	31	(3.0)
Psychiatric disorders	**28**	**(5.7)**	**85**	**(6.6)**	**32**	**(3.1)**
Abnormal dreams	9	(1.8)	27	(2.1)	10	(1.0)
Respiratory, thoracic and mediastinal disorders	**18**	**(3.7)**	**48**	**(3.7)**	**28**	**(2.7)**
Skin and subcutaneous tissue disorders	**18**	**(3.7)**	**34**	**(2.6)**	**29**	**(2.8)**

Every patient is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Suvo LD=Suvorexant 20 mg for patients < 65 years and Suvorexant 15 mg for patients ≥ 65 years.
Suvo HD=Suvorexant 40 mg for patients < 65 years and Suvorexant 30 mg for patients ≥ 65 years.

Treatment for up to 1 year

The overall AE profile of suvorexant HD in the Combined Phase 3 Population with continued treatment for up to 1 year was similar to results observed during the first 3 months of treatment. In general, the incidence of events overall was somewhat higher for all treatment groups, likely due to the extended duration of treatment. Somnolence and fatigue were more frequently reported in patients treated with suvorexant HD than placebo, with little change in incidence compared to 0-3 months (see ([Appendix 7]).

Based on review of other AEs, including events not observed from 0-3 months, AEs were generally similarly distributed between the treatment groups, without evidence of clinically concerning events to suggest emergence of treatment-duration AEs with longer-term use.

The profile of drug-related AEs with suvorexant was similar to that of the common AEs.

6.6.3 Deaths, Serious Adverse Experiences, and Discontinuations Due to Adverse Events

Deaths (Pooled Phase 3 Data up to 12 months)

Two deaths occurred over the course of all the trials; one each on suvorexant HD and placebo, and neither were considered related to study medication.

- One death occurred in P028 in a patient who was assigned to placebo that experienced a SAE of cerebrovascular accident that resulted in death.

- One death occurred in P029 in a patient who was assigned to suvorexant HD that died from hypoxic-ischemic encephalopathy, subsequent to a near drowning accident that involved getting caught in rip tide.

Serious Adverse Events (Pooled Phase 3 Data up to 12 Months)

Over the entire exposure period for suvorexant HD (maximum exposure of 12 months, Suvorexant HD N=1291; placebo N=1025), the incidence of SAEs was low and was similar between patients treated with suvorexant HD (2.8%) and placebo (3.2%); refer to [Appendix 8]. There were no specific SAEs with an incidence >0.2% (i.e., >2 patients) among those treated with suvorexant HD. The highest incidence of SAEs occurred in the Neoplasms, Benign, Malignant, and Unspecified SOC, with comparable rates for suvorexant HD (0.6%, n=6) and placebo (1.0%, n=8). The specific SAEs reported within this SOC varied, were similarly distributed between treatment arms, and in general may be anticipated in trials of extended duration, especially given participation of a sizeable proportion of elderly patients in the 12-month safety trial. Other specific SAEs were infrequent and similarly distributed between suvorexant HD and placebo. The SAE profile (suvorexant HD) over 12 months was generally similar between elderly and non-elderly patients.

Overall, the incidence of SAEs was lower with suvorexant LD for the maximum exposure duration of treatment for up to 6 months (0.6% [n=3] vs. 2.1% [n=16] for placebo), with no events reported in the Neoplasms SOC and no treatment-related SAEs in patients treated with suvorexant LD [Appendix 9]. The SAE profile (suvorexant LD) over 6 months was generally similar between elderly and non-elderly patients.

Adverse Events Leading to Discontinuation of Study Medication

Overall, the rate of AEs leading to discontinuation during the first 3 months of treatment was low and generally comparable across the treatment groups: 3.0% for suvorexant LD; 6.2% for suvorexant HD; and 4.9% for placebo (see Table 18). While of low incidence (<2%), somnolence and fatigue were more frequently associated with discontinuation in patients treated with suvorexant HD; discontinuation rates due to these events with suvorexant LD were similar to placebo. Other individual AEs leading to discontinuation

varied, with very low incidence in any one treatment group. The incidence of AEs resulting in discontinuation for treatment up to 12 months was comparable to the rate observed during the first 3 months of treatment. Similar results were seen for non-elderly and elderly patients.

Table 18
Patients With Discontinuation Due to Adverse Events
(Incidence ≥ 0.2% in One or More Treatment Groups)
Combined Phase 3 Population 0-3 Months (P028, P029, and P009)
(All Patients as Treated)

Protocols 028+029+009	Suvo LD		Suvo HD		Placebo	
	n	(%)	n	(%)	n	(%)
Patients in population	493		1,291		1,025	
with one or more adverse events	15	(3.0)	80	(6.2)	50	(4.9)
with no adverse events	478	(97.0)	1,211	(93.8)	975	(95.1)
Cardiac disorders	**1**	**(0.2)**	**3**	**(0.2)**	**2**	**(0.2)**
Tachycardia	1	(0.2)	0	(0.0)	1	(0.1)
Gastrointestinal disorders	**2**	**(0.4)**	**3**	**(0.2)**	**4**	**(0.4)**
Constipation	2	(0.4)	0	(0.0)	0	(0.0)
Dyspepsia	1	(0.2)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	**2**	**(0.4)**	**10**	**(0.8)**	**3**	**(0.3)**
Asthenia	1	(0.2)	0	(0.0)	0	(0.0)
Fatigue	1	(0.2)	9	(0.7)	0	(0.0)
Infections and infestations	**0**	**(0.0)**	**2**	**(0.2)**	**3**	**(0.3)**
Injury, poisoning and procedural complications	**1**	**(0.2)**	**2**	**(0.2)**	**3**	**(0.3)**
Ankle fracture	1	(0.2)	0	(0.0)	1	(0.1)
Investigations	**1**	**(0.2)**	**2**	**(0.2)**	**0**	**(0.0)**
Blood creatine phosphokinase increased	1	(0.2)	0	(0.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**4**	**(0.3)**	**4**	**(0.4)**
Pain in extremity	0	(0.0)	3	(0.2)	1	(0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**1**	**(0.1)**	**4**	**(0.4)**

Patients With Discontinuation Due to Adverse Events
(Incidence ≥ 0.2% in One or More Treatment Groups)
Combined Phase 3 Population 0-3 Months (P028, P029, and P009)
(All Patients as Treated)

Protocols 028+029+009	Suvo LD		Suvo HD		Placebo	
	n	(%)	n	(%)	n	(%)
Nervous system disorders	**5**	**(1.0)**	**42**	**(3.3)**	**14**	**(1.4)**
Cerebrovascular accident	0	(0.0)	0	(0.0)	2	(0.2)
Depressed level of consciousness	1	(0.2)	0	(0.0)	0	(0.0)
Dizziness	1	(0.2)	2	(0.2)	4	(0.4)
Headache	2	(0.4)	0	(0.0)	3	(0.3)
Lethargy	0	(0.0)	3	(0.2)	0	(0.0)
Memory impairment	0	(0.0)	3	(0.2)	0	(0.0)
Migraine	1	(0.2)	1	(0.1)	0	(0.0)
Paraesthesia	0	(0.0)	2	(0.2)	1	(0.1)
Sedation	0	(0.0)	3	(0.2)	0	(0.0)
Sleep paralysis	0	(0.0)	2	(0.2)	0	(0.0)
Somnolence	1	(0.2)	22	(1.7)	3	(0.3)
Psychiatric disorders	**2**	**(0.4)**	**13**	**(1.0)**	**8**	**(0.8)**
Depression	0	(0.0)	2	(0.2)	1	(0.1)
Insomnia	0	(0.0)	2	(0.2)	4	(0.4)
Nightmare	1	(0.2)	2	(0.2)	0	(0.0)
Suicidal ideation	1	(0.2)	1	(0.1)	0	(0.0)
Skin and subcutaneous tissue disorders	**3**	**(0.6)**	**0**	**(0.0)**	**2**	**(0.2)**
Eczema	1	(0.2)	0	(0.0)	1	(0.1)
Rash	1	(0.2)	0	(0.0)	0	(0.0)
Rash macular	1	(0.2)	0	(0.0)	0	(0.0)
Vascular disorders	**0**	**(0.0)**	**1**	**(0.1)**	**3**	**(0.3)**

Every patient is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Suvo LD=Suvorexant 20 mg for patients < 65 years and Suvorexant 15 mg for patients ≥ 65 years.
Suvo HD=Suvorexant 40 mg for patients < 65 years and Suvorexant 30 mg for patients ≥ 65 years.

6.7 Vital signs, Laboratory and ECG Findings

No clinically meaningful changes or trends in vital signs (i.e., blood pressure, heart rate, respiratory rate, weight, temperature) were observed for suvorexant in the combined Phase 3 population, or within age subgroup. These evaluations include mean changes from baseline over time (0-3 month data) and patients with values that met predetermined criteria relative to normal range.

Overall, clinical laboratory parameters were similar for suvorexant and placebo; no clinically meaningful changes or consistent trends in laboratory values were observed for suvorexant for continued treatment for up to 12 months in patients overall, or within the

age subgroups. During the 0-12 month period with suvorexant, a total of 17 patients (nine patients treated with suvorexant HD, three with suvorexant LD, and five with placebo) met PDLC criteria for elevations in hepatic transaminases (≥ 3 x ULN for ALT and/or AST). The maximum elevation in the suvorexant group was a 7.6X ULN elevation in ALT in a patient treated with placebo. None of these cases met criteria for Hy's Law.For the majority of patients (15/17), the elevations resolved without interruption of treatment and patients completed the study (12/17) or discontinued for unrelated reasons (3/17). Regarding the two cases not cited in the 15/17, one patient had elevated hepatic transaminases (ALT and AST) attributed to diagnosis of fatty liver and the other was discontinued based on an increased transaminase levels (ALT) prior to dosing with study medication. Mean values for hepatic transaminases were similar between groups, providing additional evidence that suvorexant is not associated with an increased risk for hepatotoxicity with continued treatment for up to 12 months.

In a Thorough QTc study (P022) the effects of suvorexant on QTc interval were evaluated in a randomized, placebo-, and active-controlled (moxifloxacin 400 mg) crossover study in healthy subjects. The upper bound of the one-sided 95% confidence interval for the largest placebo-adjusted, baseline-corrected QTc interval was below 10 msec for both suvorexant dose levels (low dose was 60 mg; high dose was pooled data from 150 mg and 240 mg doses). Thus, suvorexant was not associated with QTc prolongation at doses higher than the maximum recommended dose. Suvorexant exposures at the doses of 150/240 mg are generally 2 to 3x those anticipated in patients with insomnia receiving the highest recommended dose (HD).

In the Phase 2b/3 trials of suvorexant, no clinically meaningful changes or trends in ECG parameters were seen with suvorexant. Additionally, no pattern in cardiac system organ class AEs or other laboratory abnormalities were observed to suggest any treatment-related cardiovascular effects. Taken together, these Phase 2b/3 clinical data support that suvorexant has no untoward cardiac effects.

6.8 Intrinsic Factors

Effects by Age

The overall tolerability profile of suvorexant was comparable between the age subgroups, recognizing the age-related differences in PK and associated dose adjustment (see section 4.2), and was similar to the Combined Phase 3 population, without clinically meaningful differences between the non-elderly and elderly patients treated for up to 12 months. Further assessment of the tolerability of suvorexant in elderly patients age >65 and <75 years vs. ≥ 75 years did not provide evidence to suggest clinically meaningful differences in safety between these elderly subgroups. Age-related effects reported as somnolence AEs are further discussed in section 6.10.3.

Effects by Gender

With respect to gender effects in comparison to the Combined Phase 3 population, dose-related effects for somnolence were observed with suvorexant in both males and females without gender differences. Additionally, population PK analyses demonstrated that there are no meaningful differences in PK based on gender (see section 4.2). A comparison of gender within age groups found that the incidence of any adverse event was generally higher in elderly females in all treatment groups as compared to elderly males; AE summaries were comparable between male and female non-elderly patients.

Effects in Other Subgroups

No clinically important differences in tolerability were observed in other subgroups based on race, ethnicity, BMI; although the small sample sizes for some subgroups may not be sufficient for a clinically meaningful assessment. Lastly, in Phase 1 studies in subjects with moderate hepatic or severe renal impairment, PK was not meaningfully altered and suvorexant was generally well-tolerated.

6.9 Extrinsic Factors

No clinically important differences were observed across subgroups based on geographic region for Phase 3 data.

The PK and pharmacodynamic interaction between suvorexant and alcohol was evaluated in a clinical pharmacology study. When suvorexant is co-administered with alcohol, an additive impairment on psychomotor performance was demonstrated. There was no PK interaction between alcohol and suvorexant. An interaction study between suvorexant and paroxetine (a selective serotonin reuptake inhibitor) did not demonstrate clinically important PD interactions on a digit vigilance task or on other measures of psychomotor performance. There was also no meaningful PK interaction with paroxetine.

The use of concomitant psychotropic and other CNS active drugs was largely prohibited in the Phase 2b/3 trials, so information regarding the safety of these treatments when used concomitantly with suvorexant in patients is limited. In the long-term safety study (P009), short-term use of some CNS-active drugs was permitted (e.g. limited use of centrally acting analgesics and muscle relaxants, pseudoephedrine, sedating antihistamines, as well as the continued use of SSRIs and SNRIs); however, use was infrequent.

6.10 Safety Considerations Associated with Sleep Medications

6.10.1 Withdrawal

Withdrawal was systemically assessed in the Phase 3 studies using the Tyrer Withdrawal Symptom Questionnaire (WSQ), and defined as the presence of three or more treatment

emergent (or worsened) symptoms on any night during the first three nights of the Run-out Phase. Based on this definition, ≤ 7% of patients experienced at least three withdrawal symptoms on any particular night and < 9% of patients in any treatment group experienced at least three withdrawal symptoms across the three nights during the Run-out Phase, and no significant differences were noted at any timepoint or by suvorexant dose between patients switched from suvorexant to placebo compared to those who continued suvorexant (Table 19). In addition, no AEs associated with potential withdrawal (based on a predefined list of terms) were reported during the Run-out Phase. Findings by age subgroups were comparable to those for the overall population. Given the low incidence of withdrawal symptoms overall, the absence of patterns observed in mean change in individual WSQ item responses, and lack of subjective reports of AEs associated with potential withdrawal, no clinically important evidence of withdrawal was observed following abrupt cessation of treatment with suvorexant.

Table 19

Analysis of Withdrawal (Yes if 3 or more Emergent or Worsening Withdrawal Symptom Out of 20 Withdrawal Symptom Questionnaire Items) by Time Point
Combined Phase 3 Population Run-out Phase Following Treatment Phase
(P028, P029, and P009)
(All Patients as Treated / Data-as-Observed)

Protocols 028+029+009	Night of Run-out							
	Night 1		Night 2		Night 3		Across Nights 1, 2, and 3[†]	
Treatment	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Suvo LD / Suvo LD	157	6 (3.8)	160	5 (3.1)	151	7 (4.6)	172	11 (6.4)
Suvo LD / PBO	184	7 (3.8)	186	13 (7.0)	182	9 (4.9)	197	17 (8.6)
Suvo HD / Suvo HD	398	6 (1.5)	396	16 (4.0)	387	9 (2.3)	424	23 (5.4)
Suvo HD / PBO	393	12 (3.1)	383	13 (3.4)	381	8 (2.1)	414	22 (5.3)
PBO / PBO	677	17 (2.5)	681	19 (2.8)	664	18 (2.7)	726	36 (5.0)

Pairwise Comparison	Point Differences (%)	95% CI[‡]
Night 1		
Suvo HD / Suvo HD versus Suvo HD / PBO	-1.6	(-4.0, 0.5)
Suvo LD / Suvo LD versus Suvo LD / PBO	0.1	(-4.3, 4.8)
Night 2		
Suvo HD / Suvo HD versus Suvo HD / PBO	0.6	(-2.2, 3.4)
Suvo LD / Suvo LD versus Suvo LD / PBO	-3.9	(-8.9, 0.9)
Night 3		
Suvo HD / Suvo HD versus Suvo HD / PBO	-0.7	(-4.0, 2.4)
Suvo LD / Suvo LD versus Suvo LD / PBO	-0.2	(-5.0, 5.1)
Night 1, 2, or 3		
Suvo HD / Suvo HD versus Suvo HD / PBO	0.2	(-3.0, 3.3)
Suvo LD / Suvo LD versus Suvo LD / PBO	-2.1	(-7.7, 3.5)

Worsening or emerging were compared to end of treatment.

[†] Total of three or more symptoms across the three nights (e.g., one withdrawal symptom on Night 1 and 2 other withdrawal symptoms on Night 3). Worsening or emerging when compared to end of treatment.

[‡] 95% Confidence Interval computed using a method by Miettinen and Nurminen stratified for study (using sample size as weight).

Suvo LD = Suvorexant 20 mg for patients < 65 years and Suvorexant 15 mg for patients ≥ 65 years.

Suvo HD = Suvorexant 40 mg for patients < 65 years and Suvorexant 30 mg for patients ≥ 65 years.

PBO = Placebo.

Suvo LD / Suvo LD, Suvo LD / PBO, Suvo HD / Suvo HD, Suvo HD / PBO, PBO / PBO = therapy received during Treatment phase / therapy received during Run-out phase.

n = Number of patients with withdrawal.

6.10.2 Rebound Insomnia

In the pooled analysis of the Phase 3 studies, rebound insomnia following discontinuation of suvorexant relative to placebo and baseline was assessed. Objective assessments (in P028 and P029) were based on the PSG measures of sleep onset (LPS) and maintenance

(WASO) performed the night after treatment discontinuation at Month 3 and compared to pre-treatment baseline. Subjective assessments (in P028, P029, and P009) were based on patient-reported measures of sleep onset (sTSO) and maintenance (sTST) in the first three nights following treatment discontinuation at Month 3, Month 6, or Month 12.

No effects were seen on measures of sleep onset in these analyses. Based on the overall assessment of both doses of suvorexant evaluated in non-elderly and elderly patients, effects observed for some sleep maintenance measures following suvorexant discontinuation had the characteristics of the return of insomnia symptoms, but did not exhibit a consistent pattern suggestive of rebound insomnia.

6.10.3 Assessment of Residual Effects

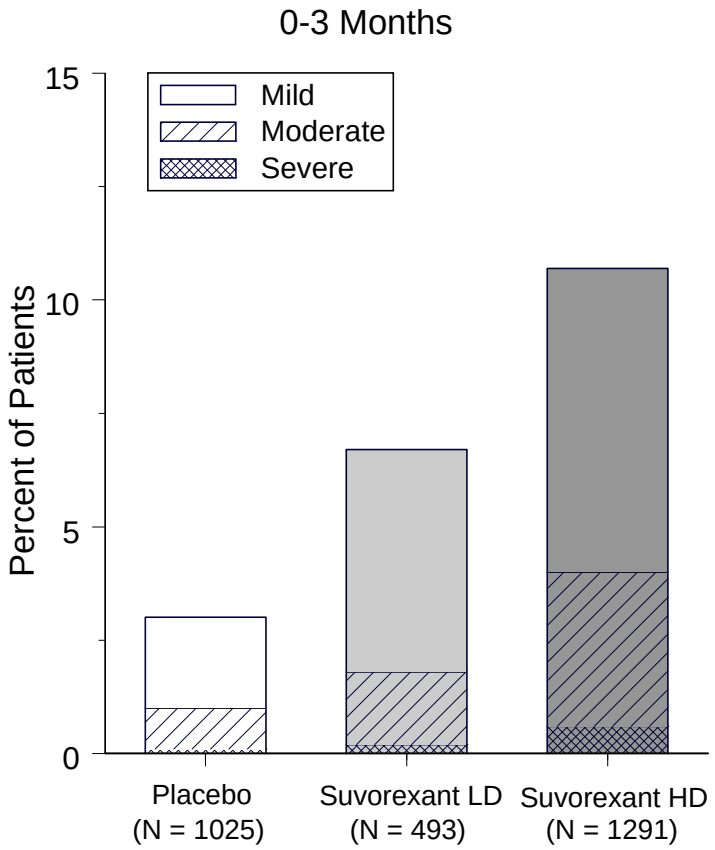
Hypnotics can be associated with next-day residual effects for some patients, which can be manifested as feelings of residual sedation and/or alterations in cognition (e.g., reduced alertness, slowed thinking) the morning after administration. More acutely, these effects may interfere with the ability to drive or operate machinery.

Assessment of residual effects in the suvorexant program included systematic evaluation of the effects of suvorexant on memory, balance, psychomotor performance, and driving performance. Also, investigation of PK/PD relationships for next day residual effects associated with the suvorexant use in the Phase 2 and 3 studies was conducted using both the objective Digit Symbol Substitution Test (DSST) data and the subjective spontaneously reported AE data. The findings of various evaluations to assess residual effects are summarized below.

<u>Adverse Events Associated with Potential Residual Effects</u>

Of the AE terms prespecified as being associated with potential residual effects, somnolence was reported most frequently. In patients treated for up to 3 months, the 0-3 Month Combined Phase 3 population, the incidence of somnolence for suvorexant LD, suvorexant HD, and placebo was 6.7%, 10.7%, and 3.0%, respectively.

Figure 23
Incidence and Severity Of Somnolence
Combined Phase 3 Population 0-3 Months (P028, P029, and P009)
(All Patients as Treated)



The severity of somnolence was reported as mild-to-moderate in the majority of occurrences, with the incidence of severe somnolence being low at 0.2% (1 patient) for suvorexant LD, 0.6% (8 patients) for suvorexant HD, and 0.1% (1 patient) for placebo [Figure 23]. The median duration of these events was 53.0 days for suvorexant LD, 30.5 days for suvorexant HD, and 16.5 days for placebo. In most cases, occurrence of somnolence was reported within the first week after initiating treatment and resolved spontaneously without medication interruption, with few events of somnolence reported after one month of treatment.

The incidence at which patients discontinued due to somnolence in the 0-3 month Combined Phase population was also low at 0.2% (1 patient), 1.7%, (22 patients) and 0.3% (3 patients) for suvorexant LD, suvorexant HD, and placebo, respectively. Twenty-three total patients on suvorexant discontinued due to somnolence, including 11 patients (6 non-elderly and 5 elderly) with symptoms classified as excessive daytime sleepiness as

defined for the suvorexant program (see below). For patients continuing treatment after 3 months, the incidence of somnolence with suvorexant was essentially unchanged, without an increase in somnolence-related AEs.

Fatigue was the next most frequently reported residual effect AE term, with an incidence of 2.2%, 3.8%, and 1.8% for suvorexant LD, suvorexant HD, and placebo, respectively. Other AEs associated with potential residual effects occurred infrequently (<1%).

Examination of residual effects AEs by-age subgroup revealed that results were generally comparable to the overall population. For example, in treatment for up to 12 months, somnolence rates were only somewhat lower in elderly patients (5.4% and 8.8% for suvorexant LD and HD, respectively) compared to non-elderly (7.6% and 12.5% for suvorexant LD and HD, respectively). The incidence of fatigue was more similar between elderly (1.5% and 3.8% for suvorexant LD and HD, respectively) and non-elderly (2.7% and 3.8% for suvorexant LD and HD, respectively).

Excessive Daytime Sleepiness ECIs

The incidence of excessive daytime sleepiness (EDS), defined as a subjective report of recurrent, persistent sleepiness throughout the day, was low overall in the first 3 months of treatment, with slightly more reports among patients treated with suvorexant HD (1.1% [n=14]) than for placebo (0.2% [n=2]) and suvorexant LD (0.6% [n=3]). In those patients who experienced EDS, onset generally occurred during the first week of treatment. For patients taking suvorexant, the intensity of EDS was mild in _ 25% of cases (2 on suvorexant LD, 2 on suvorexant HD, 1 on placebo), moderate in _ 50% of cases (1 on suvorexant LD, 7 on suvorexant HD, 1 on placebo) and severe in _ 25% of cases (5 on suvorexant HD only). In the first 3 months of treatment, 11 of 17 patients on suvorexant (most taking suvorexant HD) discontinued due to the EDS; with symptoms resolving following treatment discontinuation. With continued treatment up to 12 months, 6 additional patients on suvorexant HD (1.5% total) reported EDS (compared to 1 on placebo (0.3% total) and none on suvorexant LD); of these, four discontinued treatment due to EDS. See [Appendix 10] for counts of excessive daytime sleepiness and all Events of Clinical Interest for 0-6 months and 0-12 months.

In summary, only a small minority of patients reported somnolence or other adverse events suggestive of residual effects in the suvorexant Phase 3 program, and among these few had symptoms severe or persistent enough to require stopping treatment. The lower incidence of both somnolence and EDS observed with suvorexant LD suggests that a dose adjustment may be a useful treatment strategy for those patients who do experience tolerability issues with the higher dose.

Effects of Suvorexant on Psychomotor Performance

The potential effect of suvorexant on psychomotor performance was systematically evaluated using a variety of testing modalities including standard performance tests and assessments of memory and balance conducted the morning after treatment administration. Based on these assessments in healthy subjects and in patients with insomnia, there was no consistent evidence of impairment in next day psychomotor performance. The results of these studies are summarized below.

In Phase I, potential residual effects were evaluated in the morning after night-time administration of suvorexant using tests of memory (immediate and delayed word recall) and balance in four double-blind studies (N = 103), and psychomotor performance (DSST +/- simple and choice reaction time) in 5 double-blind studies (N=125). Overall, there was no consistent evidence of significant residual effects at therapeutic doses of suvorexant as assessed by these tests. In one of the five studies (P035, non-elderly driving study), statistically significant next-day effects were observed on some endpoints (DSST and delayed word recall after a 40 mg single dose, and body sway after a single 20 mg or 40 mg dose, without impairment after multiple doses). However, there were no significant effects on these endpoints in the other studies.

Patients in the confirmatory efficacy studies who participated in the PQ-Cohort (N=1493) completed the DSST in the morning following overnight PSG assessments, approximately 9 hours postdose. While a small increase in the mean number of correct items compared to baseline was observed with both suvorexant and placebo with repeated measures, consistent with the established learning effect seen with this assessment, no differences were observed between suvorexant and placebo to suggest next-day impairment in psychomotor performance based on DSST on the morning following acute treatment with suvorexant (Night 1) or at subsequent timepoints (Months 1 and 3) in patients treated with suvorexant for up to 3 months; see [Table 20]. In elderly patients, the degree of improvement for DSST on Night 1 was greater for those on placebo compared to those taking suvorexant. However, the magnitude of the difference observed (~2 items) was small, and this difference was not observed at subsequent assessments at the Month 1 or Month 3 assessments, and is therefore likely not clinically meaningful. DSST results for the non-elderly patients were similar to those for the overall population.

Table 20

Analysis of Digit Symbol Substitution Test Number of Correct Responses by Time Point
Combined Phase 3 Population: 0-3 Months
(All Patients as Treated - PQ Cohort / Data-as-Observed)

Treatment	N	Baseline Mean (SD)	Time Point Mean (SD)	Change from Baseline at Time Point Mean (SD)	Change from Baseline at Time Point LS Mean (95% CI)[†]
Night 1					
Suvo LD	338	50.8 (14.7)	52.7 (15.4)	1.9 (8.9)	1.6 (0.8, 2.5)
Suvo HD	577	52.8 (17.2)	54.1 (16.8)	1.3 (8.6)	1.5 (0.8, 2.1)
Placebo	578	51.7 (15.9)	54.1 (15.7)	2.4 (8.3)	2.3 (1.7, 3.0)
Month 1					
Suvo LD	321	51.1 (14.4)	53.1 (16.2)	2.0 (10.5)	1.8 (0.8, 2.8)
Suvo HD	560	52.7 (16.7)	54.4 (16.6)	1.7 (10.4)	1.9 (1.1, 2.7)
Placebo	551	51.8 (15.9)	54.0 (15.5)	2.2 (9.0)	2.2 (1.4, 2.9)
Month 3					
Suvo LD	307	50.8 (14.1)	53.5 (14.7)	2.7 (8.6)	2.4 (1.3, 3.4)
Suvo HD	526	53.0 (16.9)	54.9 (16.9)	1.9 (10.7)	2.1 (1.3, 2.9)
Placebo	516	51.7 (15.8)	54.7 (15.9)	3.0 (9.9)	2.9 (2.1, 3.7)

Pairwise Comparison	Difference in LS Means (95% CI)[†]
Night 1	
Suvo HD vs. Placebo	-0.9 (-1.8, 0.1)
Suvo LD vs. Placebo	-0.7 (-1.8, 0.4)
Month 1	
Suvo HD vs. Placebo	-0.3 (-1.4, 0.8)
Suvo LD vs. Placebo	-0.4 (-1.7, 0.9)
Month 3	
Suvo HD vs. Placebo	-0.8 (-1.9, 0.3)
Suvo LD vs. Placebo	-0.5 (-1.9, 0.8)

[†] Based on a mixed effects model with terms for baseline value, age category (<65, ≥65), region, gender, treatment, time point, and treatment-by-time point interaction as covariates.

Suvo LD = Suvorexant 20 mg for patients < 65 years and Suvorexant 15 mg for patients ≥ 65 years.

Suvo HD = Suvorexant 40 mg for patients < 65 years and Suvorexant 30 mg for patients ≥ 65 years.

Exposure-Response Modeling of Residual Effects

Exposure-response modeling of next day residual effects from pooled Phase 2 and 3 data was conducted for the objective measure Digit Symbol Substitution Test (DSST) and spontaneously reported next day residual effects of somnolence and fatigue (any occurrence including short duration and mild severity). Next day residual effects were related to suvorexant concentration in the morning (9 hours postdose -C9hr). The DSST exposure-response relationship was best characterized by a linear C9hr-response drug model with a shallow slope that increased modestly in elderly relative to non-elderly. Somnolence incidence rates with C9hr gradually increase in incidence across the clinical

exposure range. Fatigue incidence vs. C9hr was well described by a bi-phasic model, consistent with the incidence of fatigue initially increases with increasing C9hr, but then falling at higher C9hr values. Notably the elderly were not found to be more sensitive to somnolence or fatigue than non-elderly. EDS-C9hr relationship was explored graphically and the results suggest a gradually increasing trend with C9hr. Dose simulations using these exposure-response models support that DSST changes (e.g. a >3 decrease in number correct) are unlikely at high doses in Phase 3 for both non-elderly and elderly, and that most patients will not experience residual effects (e.g., somnolence, fatigue) at the recommended clinical doses although there is a modest exposure-dependency

Falls

The potential exists for patients taking sleep medications to be at increased risk for falls, particularly when getting out of bed during the night. This risk is of particular concern for the elderly, due to the increased propensity for fall-associated morbidity in this population. For the Combined Phase 3 Population from 0-3 months, the incidence of falls was low overall and similar across the treatment groups: 0.8% (n=4) for suvorexant LD, 0.7% (n=9) for suvorexant HD and 0.9% (n=9) for placebo. In patients treated for up to 12 months, the incidence of falls was low and similar between treatment groups: 1.6% (n=21) for suvorexant HD and 1.5% (n=15) for placebo. Based on review of information provided in the narrative summaries, all falls reported appeared to be associated with circumstances which contributed to or triggered the fall (e.g., faulty ladder or other unstable footing, icy or other slippery conditions, etc), and no falls were related to residual somnolence or impaired coordination. Based on review by the adjudication committee, none of the falls were related to cataplexy. See [Appendix 10] for counts of falls and all Events of Clinical Interest for 0-6 months and 0-12 months. Consistent with observations in the general population, falls occurred more frequently in the elderly (three patients (1.5%) on suvorexant LD, four patients (0.6%) on suvorexant HD, and seven patients (1.5%) on placebo). In addition, there were no reports of falls in the Run-out Phase or in the Phase 1 or 2b studies. Taken together, these data do not suggest any increased risk of falls associated with suvorexant treatment.

Effects on Ability to Drive or Operate Machinery

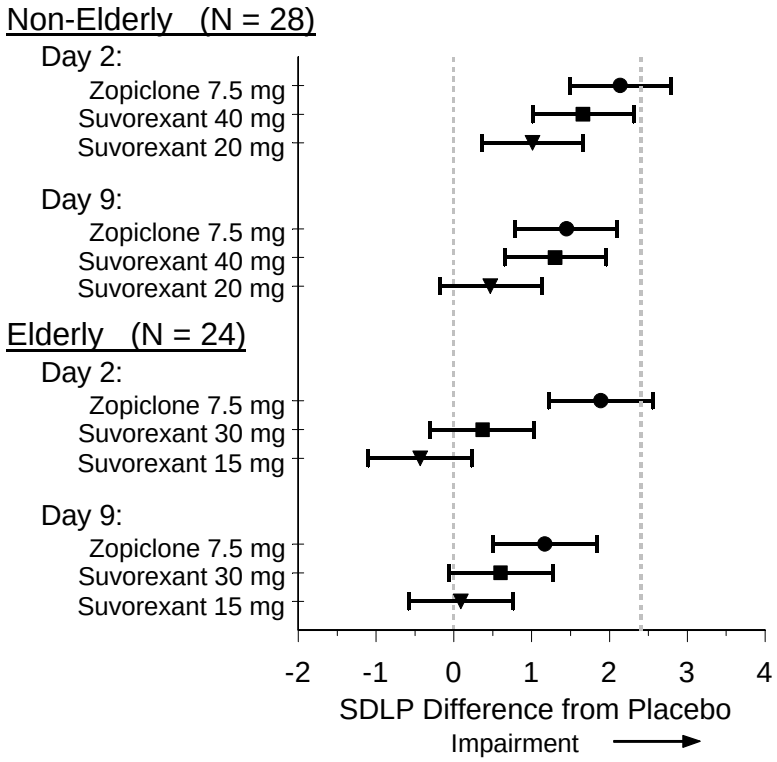
In order to further evaluate the residual effect profile, a model on-the-road driving platform was used to assess driving performance in the morning 9 hours after night-time administration of suvorexant. Next-day driving performance was assessed with this platform in two studies, in non-elderly subjects (21-64 years, P035) and elderly subjects (≥65 years, P039), and both studies included driving assessments after single doses and multiple doses, and at the LD and HD of suvorexant.

Both studies had a similar design: randomized, double-blind, placebo- and positive-controlled, 4-period crossover studies. Zopiclone 7.5 mg, administered double-blind as a single dose on Day 1 and again on Day 8, was included as an active control. The primary endpoint was standard deviation of lane position (SDLP), a measure of road tracking

error or "weaving," on Day 2 (after a first, ie. single dose) and Day 9 (after 8 consecutive doses). An increase in SDLP of 2.4 cm or greater is considered clinically meaningful, based on literature data indicating a blood alcohol concentration of 0.05% increases SDLP by 2.4 cm. The primary hypothesis in both studies was that there would be no clinically meaningful increases in SDLP, i.e. the mean difference from placebo and 90% CI would lie below 2.4 cm for both LD and HD, on both Day 2 and on Day 9. In addition to mean analysis, a symmetry analysis was conducted to evaluate potential effects on the population distribution: for each treatment comparison it was determined if there was a significant difference in the number of individuals with an increase in SDLP >2.4 cm (worsening) vs. the number of subjects who had a decrease in SDLP below -2.4 cm (improvement). Standard deviation of speed (SDS), memory, balance, psychomotor tests and PK were also assessed.

Results: In both studies, zopiclone demonstrated assay sensitivity, and symmetry analyses showed significant effects of zopiclone at all time points. In the elderly subjects, there was no clinically meaningful impairment of next-day driving performance at either dose level of suvorexant (LD or HD) as assessed by mean or symmetry analysis of SDLP [Figure 24]. In the non-elderly subjects, there was no clinically meaningful impairment of next-day driving performance at either dose level based on the primary endpoint [Figure 24], since the 90% confidence intervals of SDLP were <2.4 cm. Symmetry analysis of SDLP revealed a statistically greater number of subjects with SDLP treatment difference of >2.4 cm (indicating impairment) than those with SDLP < -2.4 cm on Day 2 for both suvorexant doses and on Day 9 for 40 mg.

Figure 24
Plot of SDLP Difference from Placebo Following Single Dose (Day 2) and Multiple Doses (Day 9) of Suvorexant in Healthy Non-elderly and Elderly Subjects
(vertical dotted line at 2.4 cm indicates the prespecified clinical significance bound)



Five subjects on treatment had their driving tests prematurely stopped due to somnolence in the two driving studies. The SDLP and secondary endpoint data from four of five stopped driving tests were included in the analyses. One elderly female subject had her driving test prematurely terminated due to somnolence after 45 minutes driving on Day 2 during the placebo treatment period. In the non-elderly driving study, four female subjects requested to have driving tests prematurely stopped due to self-reported somnolence after driving for 29-57 minutes. Three driving tests were stopped following the 40 mg dose, and two following the 20 mg dose. The absolute SDLP values obtained during the prematurely stopped driving tests were generally consistent with the median SDLP values in this study, and the individual SDLP differences from placebo did not always exceed the clinical significance bound of 2.4 cm. This lack of relationship between SDLP and prematurely stopped driving is consistent with that reported in literature [39]. Furthermore, there was no apparent trend for increased suvorexant plasma concentration in the subjects whose driving was prematurely stopped, and no consistent effects on other measurements of next-day effects such as memory and balance. Plasma concentrations were obtained one hour after completion of the driving tests in both

studies, and the PK-PD relationship was explored for SDLP. However, only a very weak correlation between plasma suvorexant concentration and treatment difference on SDLP was observed, and no threshold concentration for SDLP increases >2.4 cm could be identified.

Phase 3:

To evaluate the potential effects of suvorexant on driving-related safety in the Phase 3 trials and in response to feedback from the FDA, occurrences of motor vehicle accidents (MVAs) and moving traffic violations were collected for patients who drove a motor vehicle. Accident-related injuries were designated as ECIs. The incidence of MVAs and citations was generally similar across the treatment groups in patients treated for up to 3 months [Table 21]. Differences in the occurrence of MVAs and citations for 0-12 months were also generally comparable between the treatment groups.

Table 21
Patients with Motor Vehicle Accidents and/or Violations (MVAV)
Combined Phase 3 Population 0-3 Months (P028, P029, and P009)
(All Patients as Treated)

	Suvo LD n (%)	Suvo HD n (%)	Placebo n (%)
Patients in population	342	569	531
with one or more MVAV events	10 (2.9)	13 (2.3)	12 (2.3)
with no MVAV event	332 (97.1)	556 (97.7)	519 (97.7)
Number of MVAV events	11	14	13
Number of Patients with Accidents	4 (1.2)	7 (1.2)	5 (0.9)
Number of Accidents	4	7	5
Number of Patients with citations†	6 (1.8)	7 (1.2)	7 (1.3)
Number of citations†	7	7	8

Only patients who were treated and drove during the indicated phase of the study period were included in the table. For Protocol 009, only 12 patients were included in the 0-3 month interval due to a protocol amendment that added the MVAV form; this was implemented after enrollment completed.

Percents of sub-category levels calculated using the total number of patients in that sub-category as the denominator.

† Citation = violation.

Suvo LD = Suvorexant 20 mg for patients < 65 years and Suvorexant 15 mg for patients ≥ 65 years.

Suvo HD = Suvorexant 40 mg for patients < 65 years and Suvorexant 30 mg for patients ≥ 65 years.

For non-elderly patients, the incidence of MVAs and/or citations was comparable across the treatment groups: suvorexant LD, 3.0%; suvorexant HD, 3.2% ; and placebo, 3.1%. In elderly patients, the incidence of accidents and citations were also comparable between treatment groups and somewhat lower than those in non-elderly patients treated with suvorexant: suvorexant LD, 2.8%; suvorexant HD, 0.9% ; and placebo, 1.0% .

As described above, the safety profile of suvorexant relative to next-day functioning was studied using multiple different tools and methodologies. For the great majority of patients, suvorexant was not associated with detectable or problematic next-day impairment, as evidenced by performance on cognitive and psychomotor tasks, adverse event reporting, and driving performance. However, as noted above, a small minority of patients did experience some next-day somnolence which was generally mild and self-limited, and an even smaller number experienced more pronounced and/or persistent daytime sleepiness. While the majority of patients taking suvorexant nightly for extended periods had no complaints of residual morning sleepiness or impairment in tasks such as driving, a few individuals did experience somnolence that they felt might impair their ability to drive. This can be addressed through labeling.

6.10.4 Other Sleep-Related Events

Complex sleep-related behaviors, in which patients have reported engaging in activities while asleep (such as sleepwalking), may occur in the persons not taking sleep medications but are also identified as an issue of concern with the use of hypnotics and are reflected in class labeling. As such, complex sleep-related behavior events were pre-specified as ECIs in the suvorexant clinical development program. Based on the data collected, the risk for such events related to suvorexant treatment is low. Two patients experienced a complex sleep-related behavior in the Phase 2b/3 insomnia program; there was one event of somnambulism and one event of parasomnia (described as somnambulism). Both events occurred in Phase 3 trials in patients taking suvorexant HD, and occurred within the first 3 months of treatment. Complex sleep related behaviors will be addressed through labeling.

Sleep-related hallucinations and sleep paralysis are events that may occur during or around transitions between states of wake to sleep and vice versa, and can occur in normal individuals taking no medication, and are sometimes reported in association with other sleep-related perceptual experiences. In the Phase 3 studies, five patients treated with suvorexant (one for LD, four for HD, none on placebo) reported AEs of sleep paralysis in the 0-3 month Combined Phase 3 Population, with one additional event reported in the period of up to Month 12 with suvorexant HD. Four of the six events submitted for adjudication were confirmed to be sleep onset paralysis. These AEs were generally isolated events without recurrence, not associated with other adverse events, occurred within 2 to 3 months of treatment initiation, with no pattern of increasing incidence associated with extended treatment duration, and overall suggest no important safety concern. Sleep paralysis was reported as an AE in the Phase I studies with an incidence of 1.7% (13/782 subjects) following suvorexant alone and 0.3% (1/365 subjects) following placebo. All but one of the Phase 1 reports of sleep paralysis on suvorexant occurred after morning administration and/or after supratherapeutic doses: twelve of the 13 subjects were administered suvorexant in the morning at doses ranging from 40 mg to 240 mg, and one of the 13 subjects experienced sleep paralysis following nighttime dosing. All sleep paralysis AEs occurred in an in-patient setting, and in studies

involving morning administration, and it should be noted that subjects were awakened frequently for assessments which likely increased the chance of these events occurring for those administered suvorexant. These events were anticipated given the sedative properties of the drug and other evidence that subjects were frequently falling in and out of sleep in these studies, providing opportunities to experience the phenomenon. None of the sleep paralysis events in Phase I studies were submitted for adjudication.

Five ECIs of hypnagogic and hypnopompic hallucinations were reported in the Combined Months 0 to 3 period, with 2 additional events reported in patients receiving treatment for up to 1 year. While the overall incidence of these events was low (~0.3%), these five events occurred in patients treated with suvorexant (2 on suvorexant LD and 3 on suvorexant HD). These ECIs occurred sporadically and were generally mild, without evidence of increased occurrence with extended treatment duration. With one exception, (suvorexant HD) these events did not lead to discontinuation of suvorexant.

Overall, the incidence of sleep-related events was low, events were generally mild, did not recur, and the frequency of such events did not increase in the setting of chronic treatment. The safety profile associated with sleep-related events in Phase 1 and Phase 2b studies is consistent with the pooled Phase 3 data.

See [Appendix 10] for counts of complex sleep behaviors, sleep paralysis, hypnagogic and hypnopompic hallucinations and all Events of Clinical Interest for 0-6 months and 0-12 months.

6.10.5 Respiratory Safety Data

No significant respiratory depressant effects of ORAs have been reported in animal studies in the literature, and no significant effects were observed with suvorexant in preclinical safety/pharmacology studies. However, because of concern regarding potential for respiratory depression with hypnotics in general, clinical pharmacology studies were conducted to evaluate the effects of HD suvorexant on respiratory function in patients with mild to moderate COPD (N=25, 21 with moderate COPD), and in patients with mild to moderate OSA (N=26, 12 with moderate OSA). The mean oxygen saturation (SaO2) and Apnea/Hypopnea Index (AHI) were primary or secondary endpoints in these studies. A 2% drop in mean SaO2 during total sleep time and an increase in mean AHI of 5 were prespecified as clinically significant changes. In subjects with COPD there were no clinically significant effects following single or multiple doses of suvorexant on oxygen saturation (SaO_2) or on apnea-hypopnea index (AHI), as the 90% CI for mean change excluded -2% for SaO2 and 5 for AHI.

In subjects with OSA, a small mean increase in AHI was observed with suvorexant compared to placebo following four consecutive nights of treatment (mean treatment difference [90% CI] was 2.66 [0.22, 5.09]), but no significant effects were observed on AHI after a single dose, nor on SaO_2 following single and multiple doses. The percentage of total sleep time that SaO2 was less than 90%, 85% and/or 80% were also analyzed in

both studies, and no significant differences from placebo were observed. Furthermore, in healthy subjects (N=12), no clinically meaningful effects on SaO_2 or AHI were observed at therapeutic (40 mg) or supratherapeutic (150 mg) doses of suvorexant. Overall, the totality of data supports the conclusion that suvorexant does not produce clinically significant respiratory suppressant effects.

6.11 Safety Related to Novel Medications with CNS Mechanism of Action

6.11.1 Overdose

In the suvorexant development program, an overdose was defined as ingestion of a dose of study medication (accidental or intentional) exceeding the specified dose to be administered nightly in each protocol. Reporting was based on patient report; therefore, an AE of "overdose" was only reported when a patient reported taking more medication than prescribed. Relatively few overdoses were reported in the suvorexant development program and the numbers/proportion of events were higher for placebo than for suvorexant. During the treatment phase and extension phase for the Phase 3 trials, eleven patients in the suvorexant group (9 on suvorexant HD [0.7%] and 2 on suvorexant LD [0.4%]) and 10 patients in the placebo group reported overdose (1.0 %). There were no reports of intentional overdose in the suvorexant development program and no other AEs were associated with the overdoses. In the clinical pharmacology studies, one subject (in the COPD Study) was accidentally overdosed by the study site, and received 280 mg total exposure on a single evening. The patient did not report any AEs or have other complications following the overdose or upon awakening the following morning.

General medical practice recommends that in cases of possible overdose where medical treatment is deemed appropriate, gastric lavage with supportive care is recommended; however, no data for these interventions are available for suvorexant. The value of dialysis in the treatment of overdosage with suvorexant has not been determined. As suvorexant is highly protein bound, hemodialysis is not expected to contribute to elimination of suvorexant.

6.11.2 Assessment of Abuse Potential

Hypnotics used for the treatment of insomnia have been associated with misuse, including the potential for abuse. Suvorexant is a new molecular entity which has not yet been marketed in any country, so the use or potential abuse in society in a real world setting is unknown. Based on a comprehensive nonclinical and clinical assessment, the potential abuse liability of suvorexant in patients with insomnia is considered to be low. In particular, suvorexant has a mechanism of action that is distinct from that of benzodiazepine and non-benzodiazepine sedative-hypnotic drugs and a high degree of selectivity as an antagonist of the orexin receptors. The chemical structure of suvorexant does not have a high degree of structural similarity to any controlled substance, and suvorexant cannot be used as a precursor of any controlled substance. Synthesis of suvorexant is complex and it is not readily extracted from the tablet formulation.

Preclinical abuse studies, a clinical abuse liability study in connoisseurs, and program-wide assessment of adverse experiences, rebound and withdrawal all indicate that while individuals with a history of sedative-hypnotic abuse may be at risk, in general suvorexant appears to have a low potential for abuse.

Nonclinical Abuse Liability Assessment

The nonclinical abuse liability assessment for suvorexant included a physical dependence study in rats, a drug discrimination study in rats, and an intravenous self-administration study in non-human primates. In all of these studies suvorexant was tested up to the maximum feasible dose. In the rat physical dependence study there was no evidence of tolerance, dependence, or withdrawal. In the rat drug discrimination study, animals were trained to recognize subjective internal cues resulting from administration of a morphine or zolpidem training drug. In these animals at doses that resulted in sedation, subjective internal cues resulting from suvorexant administration partially overlapped with those recognized by zolpidem-trained rats (partial cross-generalization). In contrast, suvorexant administration at all dose levels did not result in subjective internal cues that were similar to those recognized by morphine trained rats (no cross-generalization). In the physical dependence and drug discrimination studies, suvorexant plasma concentrations in rats reached levels 39- to 66-fold higher than the clinical C_{max} at 40 mg. Suvorexant was not self-administered in non-human primates and suvorexant plasma concentrations attained in this study were 4-fold the clinical C_{max} at 40 mg. Based on the outcome of these studies, there was no evidence that suvorexant has the potential for abuse or dependence.

Phase 1 Human Abuse Liability Study (P025)

The relative abuse potential of suvorexant, as compared to placebo and zolpidem (a Schedule IV drug in the U.S.A.), was evaluated in healthy male and female subjects who are recreational polydrug users with a history of sedative-hypnotic abuse. Subjects first participated in a Qualification Session (Part I), during which each subject received zolpidem 20 mg or placebo in a two-period, double-blind, crossover manner. Subjects who discriminated zolpidem from placebo on the "Drug Liking" Visual Analogue Scale (VAS) were eligible for the Treatment session (Part II). Thirty-six subjects were randomized to enter Part II, a double-blind, placebo- and active-comparator controlled 6-way crossover study. Each subject received 6 single-dose treatments, which included placebo, 2 doses of zolpidem (15 mg and 30 mg), and three doses of suvorexant (40, 80 and 150 mg) in a randomized order. Abuse potential was evaluated via multiple subjective and objective PD measures. The primary endpoint was "Drug Liking" VAS. There were a number of secondary endpoints which were divided into three categories: positive measures, negative measures and other measures of abuse potential.

Suvorexant showed greater effects than placebo, but similar effects as zolpidem on the primary endpoint, "Drug Liking" VAS. On the secondary subjective measures of abuse potential, suvorexant generally produced effects similar to zolpidem. However, on “High” VAS (a “positive effects” measure), Addiction Research Center Inventory

morphine-benzedrine group subscale (a measure of euphoria) and Bowdle VAS (a measure of psychedelic effects), all doses of suvorexant showed statistically significantly less effect than zolpidem 30 mg. There was no apparent dose-response for suvorexant on positive measures of drug abuse potential, whereas higher dose of zolpidem appeared to have greater effects than the low dose on most measures. Adverse experiences potentially related to abuse liability were also assessed in this study and were nominally less frequent on suvorexant than on zolpidem. When pooled across all doses evaluated, the incidences of any abuse potential AE were 30.6% for suvorexant and 58.3% for zolpidem. The incidence of typical abuse potential AEs such as euphoric mood (11.1% for suvorexant vs. 19.4% for zolpidem) and hallucination were lower for suvorexant than zolpidem.

Assessment of Potential for Abuse Based on Adverse Events

In the suvorexant Phase 3 program, abuse potential was assessed by spontaneously reported AEs associated with the potential for abuse (e.g., euphoria, mania, dissociation, derealization, depersonalization). One assessment involved a broad list of AE terms (based on input received from the CSS at the FDA subsequent to launching the Phase 3 program), suggestive of an experience which may be considered pleasant and/or positively reinforcing by some individuals so as to potentially lead to misuse of a drug. A subset of these terms were designated as ECIs identified prior to launching the Phase 3 program (depersonalization, derealization, dissociation, euphoric mood, hallucination, mania, potential study medication misuse) and were analyzed.

Based on review of the AEs/ECIs associated with potential for abuse, there did not appear to be signal that suvorexant promotes drug-liking. Drug administration error was the most frequently reported AE for the both the selected ECI terms as well as the broad list of terms associated with this category. Reports for this specific event were prompted by drug accountability measures, specified in the protocol, in order to assess the potential for drug diversion and misuse. The incidence for this AE/ECI was low (2% to 3% during the 0-3 month period) and was similar between suvorexant and placebo. Narrative information collected to further characterize these events indicates that most cases occurred as isolated events and, in the majority of cases, patients reported loss of pills and denied taking additional medication. See [Appendix 10] for counts of ECIs of abuse potential and all Events of Clinical Interest for 0-6 months and 0-12 months.

Of the broader list of pre-specified AE terms associated with potential for abuse, dizziness (reported as lightheadedness and wooziness) was the second most frequently reported AE; incidence was low (<0.4% in any treatment group) and similar between groups. Other AEs within this category were reported as isolated events with no clear or consistent patterns observed between treatment groups. Results were generally similar with treatment for up to 12 months, with no evidence of intention to abuse suvorexant with continued treatment. Results in the age subgroups were comparable to the overall population. For the ECIs in this category other than drug maladministration discussed above, two additional events were reported in Phase 3 studies, both in the long term

safety study in patients taking suvorexant HD: an AE of derealization in 1 patient and AEs of auditory and visual hallucination in another patient. In addition, review of potential withdrawal-related symptoms based on responses to the Tyrer Withdrawal Symptom Questionnaire and on reports of adverse events, there was no evidence of withdrawal-related events which may be a concern with respect to potential abuse or other misuse of suvorexant.

Across the Phase 1 program, the incidence of AE's of abuse potential, including euphoria, was low. For subjects receiving suvorexant alone, a total of 5 subjects reported an AE of euphoria (0.6%). Among these five cases, four were reported in the Human Abuse Liability study by recreational drug users following suvorexant (40 mg, 80 mg or 150 mg). For subjects receiving suvorexant co-administered with another drug, one subject reported euphoric mood when suvorexant 40 mg was coadministered with alcohol in the alcohol DDI Study, and one subject reported feeling high when suvorexant 20 mg was coadministered with diltiazem in an open-label DDI study. No reports of euphoria were reported in the Phase 2b/3 studies.

In summary, based on the totality of data available, including the absence of withdrawal effects described earlier (Section 6.10.1), suvorexant does not appear to be associated with a significant risk for abuse in the treatment of insomnia.

6.11.3 Suicidal Ideation and/or Behavior

Suvorexant is a novel CNS-active compound representing an entirely new class of sleep medications. Recognizing that new mechanisms may influence mood and potentially self injurious behaviors, and to ensure a thorough evaluation of this possibility, suicidal ideation and/or behavior were prespecified as ECIs for the suvorexant clinical development program. In accordance with recommendations per FDA draft guidance (issued in 2010; revised 2012: Guidance for Industry Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials), suicidal thoughts and behaviors were prospectively assessed using the Columbia Suicide Severity Rating Scale (C-SSRS) at all visits in the Phase 3 program. Patients reporting a positive response on the C-SSRS were to be further evaluated by the investigator and additional information regarding the event was collected. Note that this is the first hypnotic development to include this prospective evaluation.

There were no reports of suicidal ideation that included intent with a formal plan or actual suicidal behaviors in the suvorexant clinical development program. In total, based on events identified by both the ECI and C-SSRS reporting mechanisms, 11/2809 (0.4%) patients in the Combined Phase 3 population had an event of suicidal ideation, inclusive of 9/1291 (0.7%) on suvorexant HD, 1/493 (0.2%) on suvorexant LD, and 1/1025 (0.1%) on placebo. While all events were reported on the C-SSRS, 3 occurrences (all on suvorexant HD) were not considered in the investigator's judgment to be adverse events. One event of suicidal ideation with intent without a plan was reported (suvorexant HD) and all other occurrences were of suicidal ideation without intent. Most events were

transient, with the majority of events lasting minutes to hours and were mild to moderate in intensity. With the exception of three patients with recurrent thoughts within a limited timespan (2 occurrences over 6 days in a patient on suvorexant LD, 2 occurrences over 62 days in a patient on suvorexant HD, and three occurrences over 15 days in a patient on suvorexant HD), all patients reported single, isolated episodes of ideation without recurrence. Events did not cluster either early or late in treatment, with onset ranging from day 9 to day 269. Four of nine patients on suvorexant HD remained on drug and in those patients, symptoms resolved spontaneously and did not recur. Five patients on suvorexant HD discontinued for the following reasons: suicidal ideation (n=1), depression (n=1), lack of efficacy (n=2), and patient no longer wanting to continued in the study (n=1). The one patient on suvorexant LD discontinued due to suicidal ideation. The one patient on placebo was discontinued due to depressed mood and was later hospitalized for treatment of depression. All occurrences in all groups were confounded by a prior history of depression and suicidality, current depression, and/or precipitating life events. Individual narratives for these events are provided in [Appendix 11].

In addition to the CSSRS, mood symptoms were monitored longitudinally in the long term safety study using the Quick Inventory of Depression Scale (QIDS), a validated instrument for the assessment of depressive symptom severity. There was no evidence based on change in mean scores, either in the overall group or in those patients who entered the study with a QIDS score ≥10 (i.e., patients with prominent depressive symptomatology at baseline) [Table 22] and [Table 23].

See [Appendix 10] for counts of suicidal ideation and all Events of Clinical Interest for 0-6 months and 0-12 months.

Table 22
Analysis of Change from Baseline in QIDS Total Score by Month
Treatment Phase
(Data-as-Observed)

Treatment	N	Baseline Mean (SD)	Treatment Mean (SD)	Change from Baseline Mean (SD)	Change from Baseline LS Mean[†] (95% CI)[†]
Month 1					
Suvo	490	4.5 (2.5)	4.0 (2.3)	-0.5 (2.4)	-0.4 (-0.6, -0.2)
Placebo	240	4.3 (2.4)	4.2 (2.4)	-0.2 (2.3)	-0.2 (-0.4, 0.1)
Month 3					
Suvo	431	4.5 (2.5)	3.9 (2.4)	-0.6 (2.4)	-0.5 (-0.7, -0.3)
Placebo	204	4.3 (2.4)	3.9 (2.3)	-0.4 (2.6)	-0.3 (-0.6, -0.1)
Month 6					
Suvo	381	4.4 (2.4)	3.9 (2.4)	-0.5 (2.6)	-0.4 (-0.6, -0.2)
Placebo	186	4.2 (2.3)	3.7 (2.3)	-0.4 (2.6)	-0.4 (-0.7, -0.1)
Month 9					
Suvot	352	4.4 (2.4)	3.7 (2.2)	-0.7 (2.5)	-0.5 (-0.7, -0.3)
Placebo	173	4.1 (2.3)	3.7 (2.2)	-0.4 (2.6)	-0.4 (-0.7, -0.1)
Month 12					
Suvo	329	4.4 (2.5)	3.6 (2.3)	-0.8 (2.6)	-0.5 (-0.7, -0.2)
Placebo	163	4.2 (2.4)	3.8 (2.8)	-0.4 (2.7)	-0.3 (-0.7, 0.0)

Pairwise Comparison	Difference in LS Mean (95% CI)[†]	p-Value[†]
Month 1		
Suvo vs. Placebo	-0.2 (-0.5, 0.1)	0.1655
Month 3		
Suvo vs. Placebo	-0.1 (-0.5, 0.2)	0.5011
Month 6		
Suvo vs. Placebo	0.1 (-0.3, 0.4)	0.7644
Month 9		
Suvo vs. Placebo	-0.1 (-0.4, 0.3)	0.6743
Month 12		
Suvo vs. Placebo	-0.1 (-0.6, 0.3)	0.5188

[†]Results based on a mixed effects model with terms for baseline value, gender, region, treatment, time, and treatment-by-time interaction.
Suvo = suvorexant 40 mg for patients < 65 years and suvorexant 30 mg for patients ≥ 65 years.

Table 23
Analysis of Change from Baseline in QIDS Total Score by Month
Treatment Phase Baseline Total Score ≥ 10
(Data-as-Observed)

Treatment	N	Baseline Mean (SD)	Treatment Mean (SD)	Change from Baseline Mean (SD)	Change from Baseline LS Mean[†] (95% CI)[†]
Month 1					
Suvo	26	11.9 (2.1)	7.8 (3.9)	-4.1 (3.9)	0.0 (-0.9, 1.0)
Placebo	12	11.3 (1.4)	7.4 (3.8)	-3.9 (3.8)	-0.0 (-1.3, 1.2)
Month 3					
Suvo	22	12.0 (2.2)	7.5 (4.3)	-4.5 (4.1)	-0.1 (-1.1, 0.9)
Placebo	11	11.5 (1.4)	6.0 (3.8)	-5.5 (4.2)	-1.3 (-2.7, 0.0)
Month 6					
Suvo	17	12.1 (2.5)	7.2 (3.3)	-4.9 (4.0)	-0.3 (-1.5, 0.8)
Placebo	9	11.2 (1.4)	6.8 (4.4)	-4.4 (4.7)	-0.7 (-2.2, 0.8)
Month 9					
Suvo	17	12.1 (2.5)	6.6 (3.1)	-5.5 (3.7)	-1.0 (-2.0, 0.1)
Placebo	8	11.4 (1.4)	5.4 (3.5)	-6.0 (3.7)	-1.9 (-3.3, -0.4)
Month 12					
Suvo	17	12.1 (2.5)	7.8 (4.1)	-4.3 (4.7)	0.3 (-0.9, 1.5)
Placebo	9	11.2 (1.4)	7.8 (4.6)	-3.4 (4.7)	0.4 (-1.2, 2.0)

Pairwise Comparison	Difference in LS Mean (95% CI)[†]	p-Value[†]
Month 1		
Suvo vs. Placebo	0.1 (-1.3, 1.4)	0.9137
Month 3		
Suvo vs. Placebo	1.2 (-0.3, 2.7)	0.1088
Month 6		
Suvo vs. Placebo	0.3 (-1.4, 2.1)	0.6987
Month 9		
Suvo vs. Placebo	0.9 (-0.7, 2.6)	0.2754
Month 12		
Suvo vs. Placebo	-0.1 (-1.9, 1.7)	0.8991

[†] Results based on a mixed effects model with terms for baseline value, gender, region, treatment, time, and treatment-by-time interaction.

Suvo = suvorexant 40 mg for patients < 65 years and suvorexant 30 mg for patients ≥ 65 years.

In the Phase 1 program, the C-SSRS was prospectively assessed in 9 studies. No subject experienced suicidal ideation during the treatment phase of any study, although there was one report of suicidal ideation in a patient with a series of precipitating life events 4 days after the last dose of suvorexant with paroxetine in a drug-drug interaction study. No adverse events of suicidal ideation or behavior was reported in the earlier studies that did not include the C-SSRS.

In summary, this program was to our knowledge the first hypnotic development program to use the C-SSRS systematic surveillance methodology to assess suicidal ideation prospectively. Events of suicidal ideation when they occurred were transient, with the majority lasting minutes to hours and were mild to moderate in intensity and were not associated with active intent or with action. All occurred in the context of factors typically associated with increased risk for suicidal ideation (e.g., history of depression, acute stressors). Even though a highly sensitive and systematic method of monitoring for suicidal ideation (i.e., CSSRS) was used in the program, the absolute number of ideation events across all groups was low, and consistent with the number of events that might be expected, given the ubiquity of suicidal ideation as a transient symptom in the general population. For example, the 12-month exposure-adjusted rate of suicidal ideation in the combined Phase 3 Population was 0.6%, which is in line with 12-month prevalence rates of 2-4% reported in the general adult population [40; 41; 42]. Several biases also confound the interpretation of the higher number of cases of suicidal ideation in the suvorexant HD. First, all suicidal ideation events occurred in the presence of confounding factors, including pre-existing and/or current depression, a history of suicidal ideation, or clear external precipitants, each of which is an established risk factor for future instances of suicidal ideation independent of medication use. Second, there is more person-time of exposure to suvorexant HD in the pooled safety database (622 person years exposure at HD vs 136 person years at LD vs 455 person years on placebo). There was no temporal pattern suggesting an association with drug (i.e. events occurred at various times during the study, and events were not associated with starting or stopping treatment, or with any particular duration of treatment). In those patients who continued in the study, the events resolved despite continuing treatment with study drug. Finally, as assessed by the QIDS, there was no evidence that suvorexant was associated with deleterious general effects on mood or anxiety that could have increased risk for suicidality. Thus the overall weight of evidence suggests that that the risk of suicidal ideation is low, consistent with expected background rates, and does not have a specific association with suvorexant..

6.11.4 Safety Related to Orexin Mechanism of Action

Orexinergic signaling has been implicated in animal models of narcolepsy, and low cerebrospinal fluid (CSF) orexin-A levels have been reported in narcolepsy patients, especially in narcolepsy patients with cataplexy [43; 44; 45; 46; 47; 48; 49; 50]. Thus the theoretical possibility exists that antagonism of normal orexinergic tone, especially for prolonged and continuous periods of time, may lead to adverse events similar to symptoms of narcolepsy, including cataplexy. Cataplexy, the abrupt intrusion of REM-related muscle atonia into wakefulness, typically prompted by a positive emotional trigger, is a symptom seen in some patients with narcolepsy. Evidence for cataplexy or cataplexy-like events warrant careful examination because of the potential for abrupt onset, potential lack of antecedent aura, and potential for secondary adverse events related to abrupt muscle atonia, such as falls or other injuries. In narcolepsy patients with cataplexy, however, it is demonstrated that pathological loss of orexin neurons occurs over time, resulting in significant and permanent reductions in the production of orexin

ligands. This loss is associated with impairments in wakefulness functions dependent on orexins, manifested clinically by symptoms such as EDS and cataplexy. This progression is in contrast to the setting for the intended clinical use of ORAs for the treatment of insomnia, where the intention of transient cyclical pharmacologic antagonism of downstream orexin receptors on afferent neurons during the period intended for sleep is anticipated to have no effect on upstream orexin neurons and their orexin ligand production. Due to declining exposure levels of the antagonist over the sleep period, offset by rising orexin ligand upon awakening, the function of the orexin system is anticipated to remain fully intact during the wake period, with no basis to expect that under these circumstances patients would experience the wake phenomenon of cataplexy.

In preclinical safety assessment studies, transient pharmacologically-mediated behavioral changes (limb buckling, unsteady gait, decreased activity, recumbency) were observed in a small number of orexin (OX1R/OX2R and OX2R) antagonist-treated dogs in response to a food treat routinely provided post dose as an animal socialization tool. Pharmacology studies were performed to characterize the behavioral changes in telemeterized dogs, and these studies demonstrated that the behavioral and EEG, EOG, and EMG changes observed in orexin antagonist-treated dogs reflect an increased sleep drive that significantly reduces time to sleep onset and are not consistent with changes described in the literature for genetically narcoleptic dogs with cataplexy, nor did ORAs show performance decrement in the literature standard food elicited cataplexy test [51; 52]. Behavioral changes were not observed in orexin receptor antagonist-treated rhesus monkeys under similar testing conditions, suggesting that these changes are dog-specific.

For the suvorexant clinical development program, falls, cataplexy, or other reports (such as leg weakness) appropriate to be evaluated as cataplexy were predefined as ECIs and adjudicated, with falls adjudicated to establish if the fall was due to cataplexy; see [Sec. 6.10.3 above]. No AEs reported at any time were adjudicated as cataplexy in the Combined Phase 3 Population with treatment for up to 12 months or in the post-study period. In P009, one AE of "muscle weakness in legs" in a patient treated with suvorexant HD was reported, and upon review was adjudicated as not cataplexy. Additionally, no events of cataplexy were reported in patients treated in any of the Phase 1 or 2b studies (up to a dose of 240 mg). See [Appendix 10] for counts of cataplexy and all Events of Clinical Interest for 0-6 months and 0-12 months.

In summary, based on the extensive data evaluated in the suvorexant program, including the results of careful analysis of non-clinical effects in canine, the absence of findings in non-human primate, and with the perspective that cataplexy has not been observed in humans treated with suvorexant or any other Merck ORA to date, there is no identified risk for cataplexy associated with the intended clinical use of suvorexant in the treatment of insomnia.

6.12 Conclusions Regarding the Clinical Safety of Suvorexant

- Throughout the comprehensive Phase 2b/3 clinical experience with suvorexant in 2027 insomnia patients, of whom 1198 were non-elderly and 829 elderly, the safety and tolerability profile was demonstrated to be favorable in both age groups and across the doses studied. Tolerability differences between doses were modest but generally favored LD; no serious safety concerns were observed with either dose.

- Suvorexant exhibits a favorable safety profile in non-elderly adults <65 years old (up to 40 mg) and elderly adults ≥ 65 years old (up to 30 mg) with primary insomnia treated nightly for up to 12 months. The safety profile is consistent irrespective of age, gender, race, ethnicity, BMI, and geographic region.

- Across the Phase 3 studies, the low frequency of discontinuations due to adverse experiences and the similarity of discontinuations across treatment groups provide evidence suvorexant is generally safe and well-tolerated when used for the treatment of insomnia.

- Serious adverse events were rare, balanced across treatment groups, and showed no clustering or patterns suggesting any concern of safety issues related to suvorexant treatment. Neither were there patterns of change in vital signs (including weight), laboratory values, or ECGs were observed at acute, intermediate, or longer term timepoints to suggest emergent safety concerns.

- The most common tolerability complaint associated with suvorexant treatment was next day somnolence. In patients treated up to 12 months, somnolence was reported in a maximum of approximately 12% of patients in a dose-related manner, was most often self-limited and only mild or moderate in severity, and in the vast majority of instances did not require stopping or otherwise altering treatment. A small proportion of patients treated with suvorexant may experience more severe next-day somnolence, and a dose reduction to the lower dose of suvorexant may be appropriate for these patients.

- Systematic evaluation of next-day residual effects did not show consistent evidence for clinically meaningful impairment of psychomotor performance, memory, or balance. On the whole, suvorexant was not associated with clinically meaningful impairment of next-day driving performance.

- Systematic assessments for a variety of other special safety considerations including those associated with the use of sleep medications and related to sleep (e.g. complex sleep-related behaviors, hypnogogic and hypnopompic phenomena, sleep paralysis, falls, respiratory safety) and those associated with a novel CNS-

active compound (e.g. potential for suicidality) yielded no serious safety concerns related to suvorexant.

- Regarding potential for adverse events which could be theoretically related to suvorexant's mechanism of action, no events of cataplexy were observed based on a prospective evaluation. As patients with a history of narcolepsy or cataplexy were not included in the suvorexant development program, use in this patient population is not recommended.

- Results from studies in animals and in patients with primary insomnia are consistent with a low risk of abuse potential. As with other hypnotics, care should be taken when prescribing suvorexant to individuals with a history of addiction to, or abuse of, drugs or alcohol due to potential for misuse or abuse.

- Discontinuation of suvorexant following chronic administration is not associated with withdrawal effects or consistent rebound insomnia, supportive of low potential for dependence or abuse.

7. Benefits and Risks Conclusions

Insomnia is a significant medical problem, and although a number of drug therapies have been approved for its treatment, a significant medical need remains unmet. Many patients respond inadequately to available treatments, particularly among those who experience both sleep onset and sleep maintenance insomnia, as few available treatment options have a profile that addresses both . This is likely due in part to the fact that the most commonly used agents of the GABA agonist class (BZD, non-BZD) are constrained in the profile they can deliver (e.g. sleep onset efficacy with limited sleep maintenance efficacy in order to manage next-day effects) because GABA is widely distributed throughout the CNS, leading to a global CNS depressant effect and associated potential side effects. GABA agonists must have rapid elimination PK to minimize next-day effects, at the expense of sleep maintenance. Suvorexant, however, represents a completely novel ORA class of therapeutics for sleep grounded in the advancing science made possible by the relatively recent discovery of the orexins and their receptors.

Benefit Risk Profile of Suvorexant

The primary benefit of suvorexant is its consistent, sustained, and clinically meaningful efficacy on the broad constellation of signs and symptoms of chronic insomnia, in particular improving both sleep onset and sleep maintenance, with an acceptable residual effects profile. This overall clinical profile is unique among currently available sleep agents, and is likely due to the fundamentally unique biology made possible with a neuropeptide antagonist mechanism of action, whereby sleep maintenance efficacy throughout the night is possible without undue next day effects because increased

production of endogenous ligand in the morning has the potential to offset the pharmacological effects of any residual drug exposure.

The efficacy of suvorexant was studied in three large Phase 3 placebo-controlled combined-age clinical trials in non-elderly and elderly patients with chronic insomnia. The evidence from the two similarly-designed confirmatory efficacy trials supports the conclusion that suvorexant significantly improves objective and subjective measures of both sleep onset and sleep maintenance in the setting of chronic administration for up to 3 months with effect size magnitudes consistent with clinically meaningful effects. Further, efficacy was demonstrated for the LD, based on data from the Phase 2b study as well as the secondary, exploratory, and pre-specified pooled analyses conducted for protocols P028 and P029. The sleep maintenance efficacy was evident across the entire sleep period. These effects of suvorexant HD are sustained and consistent during chronic use as demonstrated by the fact that initial treatment gains were preserved throughout the duration of the 12 month study. The value of continued treatment with suvorexant is supported by the observation that even after a full year of treatment, in patients who were randomized under double blind conditions for an additional two months to continue on suvorexant or switch to placebo, symptoms returned in the patients switched to placebo but not for those who continued on suvorexant.

Based on the point estimate comparisons in the confirmatory efficacy trials, suvorexant HD was consistently favored over suvorexant LD, suggesting that HD provides further additional benefit (Figures 14 and 15, section 5.5.2.3). Based upon these placebo-corrected mean results, suvorexant LD provided 55%, 72%, and 60% of the effect that suvorexant HD produced at Month 3 for the subjective measures of sTSOm, sTSTm, and sWASOm, respectively. By these assessments suvorexant HD is anticipated to deliver a larger magnitude efficacy benefit for a majority of patients.

In addition to clinically relevant magnitudes of effect observed on standard sleep endpoints, data obtained from the administration of the Insomnia Severity Index (ISI), a validated composite patient-report measure of the degree of impairment due to insomnia and response to treatment, was consistently in favor of both HD and LD suvorexant over placebo across the Phase 3 trials, providing supportive alignment of a global insomnia measure with the improvements observed across the various individual sleep parameters assessed in the program. Finally, this efficacy profile was attained in the context of a highly tolerable drug, as judged by adverse event reports and the evidence that discontinuations for any reason, including adverse events, were not different from placebo. Efficacy was seen at both the low and high dose, but was generally of greater magnitude and delivered more clinical benefit at the high dose with only minimal differences in tolerability. Tolerability differences between doses were modest but generally favored LD; no serious safety concerns were observed with either dose.

The extensive safety database acquired across the Phase 1-3 program indicates that suvorexant is well-tolerated acutely and during long-term use. Discontinuations due to adverse events were consistently low and similar across treatment groups, and there was no evidence of increased risk in subgroups such as age or gender. Serious adverse events occurred infrequently and were balanced across treatment groups without clustering suggestive of clinical concern. With chronic nightly dosing in Phase 3, the most frequently reported adverse events associated with the use of suvorexant were somnolence and fatigue, which were dose-related, generally mild to moderate in severity and short-lived, occurring primarily in the first few months of treatment. While next-day residual effects were not an issue for the great majority of patients (>95%) in the setting of chronic nightly treatment, a minority who reported next-day somnolence or EDS in a few instances also reported impairment of next day performance with tasks like driving. Importantly, when this effect occurred, it was generally early in treatment, short-lived, and recognizable by patients. Due to individual variation, patients should be advised not to drive, operate machinery or engage in other activities requiring full mental alertness until they feel fully awake.

Of the other identified or potential risks including assessment of safety considerations associated with use of other marketed sleep medications (e.g. complex sleep-related behaviors, potential for rebound and withdrawal, residual effects, respiratory safety), those associated with novel CNS-active compounds (e.g. abuse liability and suicidality), and considerations of theoretical considerations for the ORA mechanism (e.g. cataplexy), no serious or unusual safety concerns were observed at either the high or low dose.

Dose Recommendation Based on Benefits and Risks

Both the high and low doses are efficacious, safe and well-tolerated in their respective age groups and should be available to patients and their physicians to allow individualized dosing.

Given the favorable tolerability/safety of the higher dose and consistently better efficacy, we propose the dose recommendation to initiate treatment at the higher dose, with dose reduction as an option to improve tolerability.

Overall Benefits and Risks Conclusion

Overall, the recommended doses of 40 mg and 30 mg in non-elderly and elderly patients respectively show a favorable benefit-risk profile in the treatment of insomnia. Suvorexant is efficacious in improving the symptoms of insomnia, including both sleep onset and sleep maintenance. It is well-tolerated during chronic use, and demonstrates an acceptable next day residual effects profile without withdrawal or rebound effects of clinical concern upon cessation of use. For the small number of patients who experience tolerability problems that preclude continued treatment, the lower dose of 20 mg (non-elderly)/15 mg (elderly) may potentially provide an efficacious alternative with satisfactory tolerability. Suvorexant, by virtue of its unique pharmacology compared

with currently approved drugs for insomnia, provides a new and attractive alternative that expands the therapeutic options available to patients and physicians.

8. List of References

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9. Appendices

Appendix 1
Patients with Adverse Events for System Organ Categories of Nervous system disorders and Psychiatric disorders (Incidence ≥ 2% for One or More Treatments)
Protocol 006 – Treatment Periods 1 and 2 (All Patients as Treated)

	Placebo		Suvo 10 mg		Suvo 20 mg		Suvo 40 mg		Suvo 80 mg		Total Suvo	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	249		62		61		59		61		243	
with ≥ AE	50	(20.1)	11	(17.7)	12	(19.7)	18	(30.5)	22	(36.1)	63	(25.9)
with no AEs	199	(79.9)	51	(82.3)	49	(80.3)	41	(69.5)	39	(63.9)	180	(74.1)
Nervous system disorders	9	(3.6)	2	(3.2)	5	(8.2)	9	(15.3)	12	(19.7)	28	(11.5)
Dizziness	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)	3	(4.9)	4	(1.6)
Headache	6	(2.4)	0	(0.0)	1	(1.6)	3	(5.1)	3	(4.9)	7	(2.9)
Sedation	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	2	(3.3)	2	(0.8)
Somnolence	1	(0.4)	1	(1.6)	3	(4.9)	6	(10.2)	7	(11.5)	17	(7.0)
Psychiatric disorders	3	(1.2)	1	(1.6)	0	(0.0)	2	(3.4)	5	(8.2)	8	(3.3)
Abnormal dreams	2	(0.8)	1	(1.6)	0	(0.0)	0	(0.0)	3	(4.9)	4	(1.6)

Every patient is counted a single time for each applicable specific adverse event and treatment. A patient with multiple adverse events within a system organ class is counted a single time for that system organ class.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.

Appendix 2
Effects of Suvorexant Low Dose on Sleep Maintenance Measures (Minutes)

Endpoint	Timepoint	Protocol	Suvo LD LS Mean Change From Baseline	Placebo LS Mean Change From Baseline	LS Mean Difference From Placebo	P-value
sTSTm[†]	Week 1	028	28.2	14.6	13.6	0.00007*
		029	30.8	14.0	16.8	0.00002
		Pooled	29.4	14.4	15.0	<0.00001
	Month 1	028	39.4	23.1	16.3	0.00016*
		029	43.4	22.4	20.9	<0.00001
		Pooled	41.3	22.9	18.4	<0.00001
	Month 3	028	51.2	40.6	10.7	0.01711*
		029	59.8	37.7	22.1	0.00004
		Pooled	55.3	39.3	16.0	<0.00001
sWASOm[‡]	Week 1	028	-17.3	-10.6	-6.8	0.00330
		029	-17.8	-13.6	-4.2	0.12680
		Pooled	-17.4	-12.1	-5.3	0.00281
	Month 1	028	-23.3	-17.9	-5.4	0.06168
		029	-29.2	-20.8	-8.4	0.00626
		Pooled	-26.0	-19.4	-6.6	0.00159
	Month 3	028	-32.0	-29.6	-2.4	0.38819
		029	-37.5	-29.8	-7.7	0.01885
		Pooled	-34.5	-29.8	-4.7	0.02680
WASO[§]	Night 1	028	-52.1	-19.6	-32.5	<0.00001*
		029	-58.3	-21.3	-37.0	<0.00001
		Pooled	-55.1	-20.5	-34.6	<0.00001
	Month 1	028	-45.0	-18.7	-26.4	<0.00001*
		029	-46.6	-22.5	-24.1	<0.00001
		Pooled	-46.1	-20.6	-25.4	<0.00001
	Month 3	028	-41.6	-25.0	-16.6	0.00009*
		029	-56.0	-24.8	-31.1	<0.00001
		Pooled	-48.0	-25.0	-23.1	<0.00001

* Statistically significant based upon the protocol-specified multiplicity strategy (or for the sWASOm supportive analysis, statistically significant after substituting sWASOm for sTSTm in the protocol-specified multiplicity strategy); LD vs. placebo comparisons were not primary or secondary objectives of P029; therefore, statistical significance (*) was not assessed for this treatment comparison in P029; only nominal p-values are provided for the pooled analyses

[†] sTSTm is subjective Total Sleep Time (weekly mean of daily measurements)

[‡] sWASOm is subjective Wake time After Sleep Onset (weekly mean of daily measurements)

[§] WASO is objective Wakefulness After persistent Sleep Onset (PSG); asterisks for WASO represent statistical significance based on protocol-specified primary analysis (i.e., using sTSTm and WASO in the multiplicity strategy)

LS = Least Squares (based upon primary analysis model)

Appendix 3
Effects of Suvorexant Low Dose on Sleep Onset Measures (Minutes)

Endpoint	Timepoint	Protocol	Suvo LD LS Mean Change From Baseline	Placebo LS Mean Change From Baseline	LS Mean Difference From Placebo	P-value
sTSOm†	Week 1	028	-15.2	-9.6	-5.6	0.01564
		029	-14.2	-6.7	-7.5	0.00593
		Pooled	-14.4	-8.3	-6.1	0.00081
	Month 1	028	-17.1	-11.7	-5.4	0.05191
		029	-21.0	-14.1	-6.9	0.04975
		Pooled	-18.6	-13.0	-5.6	0.01209
	Month 3	028	-22.5	-17.3	-5.2	0.03771
		029	-28.1	-20.5	-7.6	0.03894
		Pooled	-24.9	-19.0	-5.9	0.00675
LPS‡	Night 1	028	-29.9	-20.3	-9.6	0.00041
		029	-25.3	-13.0	-12.4	0.00392
		Pooled	-28.0	-16.8	-11.2	<0.00001
	Month 1	028	-33.6	-23.3	-10.3	0.00040*
		029	-32.5	-24.6	-7.8	0.03063
		Pooled	-33.2	-24.1	-9.1	0.00007
	Month 3	028	-34.7	-26.6	-8.1	0.00606
		029	-28.9	-28.6	-0.3	0.93219
		Pooled	-32.2	-27.6	-4.6	0.06205

* Statistically significant based upon the protocol-specified multiplicity strategy; LD vs. placebo comparisons were not primary or secondary objectives of P029; therefore, statistical significance (*) was not assessed for this treatment comparison in P029; only nominal p-values are provided for the pooled analyses
† sTSOm is subjective Time to Sleep Onset (weekly mean of daily measurements)
‡ LPS is objective Latency to onset of Persistent Sleep (PSG)
LS = Least Squares (based upon primary analysis model)

Appendix 4
Analysis of Exploratory Endpoints
Suvorexant vs. Placebo at Key Time Points during the Treatment Phase – Pooled (Protocols 028 + P029)

Endpoint	Suvo Dose	Week 2		Month 1		Month 3	
		Difference in LS Means (95% CI)†	p-Value†	Difference in LS Means (95% CI)†	p-Value†	Difference in LS Means (95% CI)†	p-Value†
sQUALm	HD	0.12 (0.08, 0.17)	<0.00001	0.16 (0.11, 0.21)	<0.00001	0.11 (0.06, 0.16)	0.00005
	LD	0.12 (0.07, 0.17)	<0.00001	0.14 (0.08, 0.19)	<0.00001	0.10 (0.04, 0.16)	0.00090
sREFRESHEDm	HD	0.16 (0.10, 0.22)	<0.00001	0.16 (0.09, 0.22)	<0.00001	0.12 (0.04, 0.19)	0.00161
	LD	0.15 (0.09, 0.22)	<0.00001	0.16 (0.08, 0.23)	0.00003	0.13 (0.05, 0.21)	0.00205
ISI Total Score	HD	--	--	-1.8 (-2.2, -1.3)	<0.00001	-1.8 (-2.3, -1.3)	<0.00001
	LD	--	--	-1.4 (-1.9, -0.9)	<0.00001	-1.3 (-1.8, -0.7)	0.00004
CGI-S	HD	-0.4 (-0.5, -0.3)	<.00001	-0.5 (-0.6, -0.3)	<.00001	-0.5 (-0.6, -0.3)	<.00001
	LD	-0.3 (-0.5, -0.2)	<.00001	-0.4 (-0.5, -0.3)	<.00001	-0.3 (-0.4, -0.2)	<.00001
CGI-I	HD	-0.5 (-0.6, -0.4)	<.00001	-0.5 (-0.6, -0.4)	<.00001	-0.5 (-0.6, -0.4)	<.00001
	LD	-0.4 (-0.5, -0.3)	<.00001	-0.4 (-0.5, -0.3)	<.00001	-0.4 (-0.5, -0.3)	<.00001
PGI-S	HD	-0.5 (-0.6, -0.4)	<.00001	-0.5 (-0.6, -0.4)	<.00001	-0.4 (-0.5, -0.3)	<.00001
	LD	-0.3 (-0.4, -0.2)	<.00001	-0.4 (-0.5, -0.3)	<.00001	-0.3 (-0.4, -0.2)	<.00001
PGI-I	HD	-0.5 (-0.6, -0.4)	<.00001	-0.5 (-0.6, -0.4)	<.00001	-0.5 (-0.6, -0.4)	<.00001
	LD	-0.3 (-0.5, -0.2)	<.00001	-0.4 (-0.6, -0.3)	<.00001	-0.4 (-0.5, -0.2)	<.00001

†Based on a mixed effects model with terms for study (P028, P029), baseline value (except for CGI-I and PGI-I), age category (<65, ≥65), region (NA, EU, Other), cohort (PQ, Q), gender, treatment, time point, and treatment-by-time point interaction as covariates.
sQUALm - sleep quality (via e-diary); sREFRESHEDm - feeling refreshed upon awakening (via e-diary)
CGI-S, CGI-I: clinician global impressions of insomnia severity (S) and improvement(I)
PGI-S, PGI-I: patient global impressions of insomnia severity (S) and improvement(I)
ISI: Insomnia Severity Index
Suvo LD=Suvorexant 20 mg for patients < 65 years and Suvorexant 15 mg for patients ≥ 65 years.
Suvo HD=Suvorexant 40 mg for patients < 65 years and Suvorexant 30 mg for patients ≥ 65 years.
Note: change from baseline was evaluated as the response variable for each endpoint with the exception of CGI-I and PGI-I which already measure improvement

Appendix 5
Sample Sizes for Subgroup Analyses Conducted by Endpoint (Pooled P028+P029)

Baseline Factor	Sample Size for[†]														
	sTSTm			sWASOm			WASO			sTSOm			LPS		
Subgroups	LD	HD	PBO	LD	HD	PBO	LD	HD	PBO	LD	HD	PBO	LD	HD	PBO
Age (years)															
<65	281	439	433	276	434	426	191	331	325	281	439	433	192	333	327
≥65	198	313	307	198	312	303	145	245	245	198	313	307	145	247	247
Gender															
Females	309	484	471	307	479	464	216	374	368	309	484	471	216	376	371
Males	170	268	269	167	267	265	120	202	202	170	268	269	121	204	203
Race															
Whites	346	548	530	346	546	526	302	510	498	346	548	530	303	514	501
Other	133	204	210	128	200	203	34	66	72	133	204	210	34	66	73
Region															
Europe	161	248	241	161	246	237	147	234	232	161	248	241	148	235	234
North America	187	322	305	187	322	305	173	306	299	187	322	305	173	309	301
Other	131	182	194	126	178	187	16	36	39	131	182	194	16	36	39
Baseline Severity															
<Median	254	359	378	243	365	363	162	291	282	229	375	347	175	296	272
≥Median	225	393	362	231	381	366	174	285	288	250	377	393	162	284	302
Cohort															
Q-Cohort	147	177	176	142	173	169	-	-	-	147	177	176	-	-	-
PQ-Cohort	332	575	564	332	573	560	-	-	-	332	575	564	-	-	-
Entrance Criteria[‡]															
More severe	237	402	428	237	400	424	-	-	-	237	402	428	-	-	-
Less severe	95	173	136	95	173	136	-	-	-	95	173	136	-	-	-

[†]Based upon number of patients with Week 1 data for subjective endpoints and Night 1 data for objective endpoints; sample sizes at Month 1 and Month 3 are lower than sample sizes at Week 1/Night 1 due to dropout.

[‡]The baseline factor of "Entrance Criteria" was evaluated for subjective endpoints for the PQ-cohort only; more severe = sTST<6.5 hours on at least 4 of 7 days and sTSO≥30 minutes on at least 4 of 7 days; less severe = did not meet severe criteria

LD=Suvorexant 20 mg for patients < 65 years and Suvorexant 15 mg for patients ≥ 65 years.

HD=Suvorexant 40 mg for patients < 65 years and Suvorexant 30 mg for patients ≥ 65 years.

Appendix 6
Patients with Specific Adverse Events
(Incidence ≥2% in One or More Treatment Groups)
Combined Phase 3 Population 0-3 Months (P028, P029, and P009)
Age ≥65
(All Patients as Treated)

Protocols 028+029+009	Suvo LD		Suvo HD		Placebo	
	n	(%)	n	(%)	n	(%)
Patients in population	202		627		469	
with one or more adverse events	99	(49.0)	316	(50.4)	232	(49.5)
with no adverse events	103	(51.0)	311	(49.6)	237	(50.5)
Cardiac disorders	**6**	**(3.0)**	**11**	**(1.8)**	**13**	**(2.8)**
Ear and labyrinth disorders	**4**	**(2.0)**	**4**	**(0.6)**	**6**	**(1.3)**
Eye disorders	**5**	**(2.5)**	**8**	**(1.3)**	**10**	**(2.1)**
Gastrointestinal disorders	**19**	**(9.4)**	**57**	**(9.1)**	**36**	**(7.7)**
Diarrhoea	8	(4.0)	14	(2.2)	7	(1.5)
Dry mouth	5	(2.5)	18	(2.9)	8	(1.7)
Nausea	4	(2.0)	7	(1.1)	6	(1.3)
General disorders and administration site conditions	**12**	**(5.9)**	**38**	**(6.1)**	**27**	**(5.8)**
Fatigue	3	(1.5)	24	(3.8)	8	(1.7)
Infections and infestations	**36**	**(17.8)**	**71**	**(11.3)**	**60**	**(12.8)**
Gastroenteritis	4	(2.0)	2	(0.3)	3	(0.6)
Nasopharyngitis	7	(3.5)	18	(2.9)	19	(4.1)
Upper respiratory tract infection	6	(3.0)	16	(2.6)	6	(1.3)
Urinary tract infection	6	(3.0)	8	(1.3)	11	(2.3)
Injury, poisoning and procedural complications	**7**	**(3.5)**	**26**	**(4.1)**	**30**	**(6.4)**
Drug administration error	1	(0.5)	8	(1.3)	10	(2.1)
Investigations	**5**	**(2.5)**	**26**	**(4.1)**	**20**	**(4.3)**

Patients With Specific Adverse Events
(Incidence ≥2% in One or More Treatment Groups)
Combined Phase 3 Population 0-3 Months (P028, P029, and P009)
Age ≥65
(All Patients as Treated) (Cont.)

Protocols 028+029+009	Suvo LD		Suvo HD		Placebo	
	n	(%)	n	(%)	n	(%)
Metabolism and nutrition disorders	**0**	**(0.0)**	**13**	**(2.1)**	**6**	**(1.3)**
Musculoskeletal and connective tissue disorders	**12**	**(5.9)**	**56**	**(8.9)**	**46**	**(9.8)**
Back pain	4	(2.0)	7	(1.1)	13	(2.8)
Nervous system disorders	**33**	**(16.3)**	**119**	**(19.0)**	**63**	**(13.4)**
Dizziness	8	(4.0)	14	(2.2)	23	(4.9)
Headache	14	(6.9)	35	(5.6)	25	(5.3)
Somnolence	11	(5.4)	55	(8.8)	15	(3.2)
Psychiatric disorders	**14**	**(6.9)**	**33**	**(5.3)**	**12**	**(2.6)**
Abnormal dreams	5	(2.5)	10	(1.6)	4	(0.9)
Respiratory, thoracic and mediastinal disorders	**7**	**(3.5)**	**22**	**(3.5)**	**16**	**(3.4)**
Cough	5	(2.5)	7	(1.1)	5	(1.1)
Skin and subcutaneous tissue disorders	**10**	**(5.0)**	**18**	**(2.9)**	**19**	**(4.1)**
Pruritus	4	(2.0)	2	(0.3)	4	(0.9)
Vascular disorders	**4**	**(2.0)**	**9**	**(1.4)**	**8**	**(1.7)**

Every patient is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Suvo LD=Suvorexant 20 mg for patients < 65 years and Suvorexant 15 mg for patients ≥ 65 years.

Suvo HD=Suvorexant 40 mg for patients < 65 years and Suvorexant 30 mg for patients ≥ 65 years.

Appendix 7
Patients With Specific Adverse Events
(Incidence ≥ 2% in One or More Treatment Groups)
Combined Phase 3 Population High Dose 0-12 Months (P028, P029, and P009)
(All Patients as Treated)

Protocols 028+029+009	Suvo HD		Placebo	
	n	(%)	n	(%)
Patients in population	1,291		1,025	
with one or more adverse events	773	(59.9)	540	(52.7)
with no adverse events	518	(40.1)	485	(47.3)
Cardiac disorders	**26**	**(2.0)**	**24**	**(2.3)**
Eye disorders	**35**	**(2.7)**	**25**	**(2.4)**
Gastrointestinal disorders	**160**	**(12.4)**	**98**	**(9.6)**
Diarrhoea	26	(2.0)	20	(2.0)
Dry mouth	43	(3.3)	15	(1.5)
Nausea	33	(2.6)	20	(2.0)
General disorders and administration site conditions	**120**	**(9.3)**	**53**	**(5.2)**
Fatigue	61	(4.7)	19	(1.9)
Infections and infestations	**257**	**(19.9)**	**194**	**(18.9)**
Influenza	30	(2.3)	16	(1.6)
Nasopharyngitis	95	(7.4)	67	(6.5)
Upper respiratory tract infection	37	(2.9)	19	(1.9)
Urinary tract infection	21	(1.6)	26	(2.5)
Injury, poisoning and procedural complications	**99**	**(7.7)**	**78**	**(7.6)**
Drug administration error	32	(2.5)	31	(3.0)
Investigations	**85**	**(6.6)**	**57**	**(5.6)**
Metabolism and nutrition disorders	**38**	**(2.9)**	**15**	**(1.5)**
Musculoskeletal and connective tissue disorders	**163**	**(12.6)**	**104**	**(10.1)**
Arthralgia	29	(2.2)	18	(1.8)

Patients With Specific Adverse Events
(Incidence ≥ 2% in One or More Treatment Groups)
Combined Phase 3 Population High Dose 0-12 Months (P028, P029, and P009)
(All Patients as Treated) (Cont.)

Protocols 028+029+009	Suvo HD		Placebo	
	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	**163**	**(12.6)**	**104**	**(10.1)**
Back pain	25	(1.9)	29	(2.8)
Nervous system disorders	**322**	**(24.9)**	**157**	**(15.3)**
Dizziness	41	(3.2)	35	(3.4)
Headache	101	(7.8)	68	(6.6)
Somnolence	151	(11.7)	33	(3.2)
Psychiatric disorders	**107**	**(8.3)**	**36**	**(3.5)**
Abnormal dreams	34	(2.6)	11	(1.1)
Nightmare	27	(2.1)	7	(0.7)
Respiratory, thoracic and mediastinal disorders	**72**	**(5.6)**	**39**	**(3.8)**
Skin and subcutaneous tissue disorders	**42**	**(3.3)**	**37**	**(3.6)**
Vascular disorders	**29**	**(2.2)**	**17**	**(1.7)**

Every patient is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Suvo HD=Suvorexant 40 mg for patients < 65 years and Suvorexant 30 mg for patients ≥ 65 years.

Appendix 8
Patients with Serious Adverse Events
(Incidence ≥ 0.2% in One or More Treatment Groups)
Combined Phase 3 Population High Dose 0-12 Months (P028, P029, and P009)
(All Patients as Treated)

Protocols 028+029+009	Suvo HD		Placebo	
	n	(%)	n	(%)
Patients in population	1,291		1,025	
with one or more serious adverse events	36	(2.8)	33	(3.2)
with no serious adverse events	1,255	(97.2)	992	(96.8)
Cardiac disorders	**2**	**(0.2)**	**4**	**(0.4)**
Atrial fibrillation	1	(0.1)	3	(0.3)
Ear and labyrinth disorders	**2**	**(0.2)**	**0**	**(0.0)**
Gastrointestinal disorders	**2**	**(0.2)**	**3**	**(0.3)**
Infections and infestations	**4**	**(0.3)**	**5**	**(0.5)**
Diverticulitis	2	(0.2)	1	(0.1)
Gastroenteritis	0	(0.0)	2	(0.2)
Injury, poisoning and procedural complications	**5**	**(0.4)**	**3**	**(0.3)**
Fall	1	(0.1)	2	(0.2)
Musculoskeletal and connective tissue disorders	**4**	**(0.3)**	**3**	**(0.3)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**8**	**(0.6)**	**10**	**(1.0)**
Basal cell carcinoma	3	(0.2)	3	(0.3)
Malignant melanoma	0	(0.0)	2	(0.2)
Nervous system disorders	**6**	**(0.5)**	**3**	**(0.3)**
Cerebrovascular accident	0	(0.0)	2	(0.2)
Renal and urinary disorders	**0**	**(0.0)**	**2**	**(0.2)**

Every patient is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Suvo HD=Suvorexant 40 mg for patients < 65 years and Suvorexant 30 mg for patients ≥ 65 years.

Appendix 9

Patients with Serious Adverse Events
(Incidence ≥ 0.2% in One or More Treatment Groups)
Combined Phase 3 Population Low Dose 0-6 Months (P028 and P029)
(All Patients as Treated)

Protocols 028+029	Suvo LD		Placebo	
	n	(%)	n	(%)
Patients in population	493		767	
with one or more serious adverse events	3	(0.6)	16	(2.1)
with no serious adverse events	490	(99.4)	751	(97.9)
Cardiac disorders	**1**	**(0.2)**	**1**	**(0.1)**
Atrial fibrillation	1	(0.2)	0	(0.0)
Infections and infestations	**1**	**(0.2)**	**3**	**(0.4)**
Gastroenteritis	0	(0.0)	2	(0.3)
Pneumonia	1	(0.2)	0	(0.0)
Injury, poisoning and procedural complications	**1**	**(0.2)**	**2**	**(0.3)**
Ankle fracture	1	(0.2)	0	(0.0)
Fall	0	(0.0)	2	(0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**6**	**(0.8)**
Nervous system disorders	**0**	**(0.0)**	**2**	**(0.3)**
Cerebrovascular accident	0	(0.0)	2	(0.3)

Every patient is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Suvo LD=Suvorexant 20 mg for patients < 65 years and Suvorexant 15 mg for patients ≥ 65 years.

Appendix 10
Events of Clinical Interest in the Combined Phase 3 Population from
0-6 Months (Suvorexant LD) and 0-12 months (Suvorexant HD)

ECIs	**Phase 3 Totals n (%)**			
	0-6 Months[1]		**0-12 Months[1]**	
(Events of Clinical Interest)	**Suvo LD (n=493)**	**Placebo[2] (n=767)**	**Suvo HD (n=1291)**	**Placebo (n=1025)**
	n (%)	n (%)	n (%)	n (%)
Complex Sleep Behaviors	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)
Hypnagogic/Hypnopompic Hallucinations	2 (0.4)	0 (0.0)	5 (0.4)	0 (0.0)
Sleep Paralysis	1 (0.2)	0 (0.0)	5 (0.4)	0 (0.0)
Sleep Onset Paralysis (adjudicated)	0 (0.0)	0 (0.0)	4 (0.3)	0 (0.0)
Excessive daytime sleepiness	3 (0.6)	1 (0.1)	20 (1.5)	3 (0.3)
Cataplexy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Falls	5 (1.0)	7 (0.9)	21 (1.6)	15 (1.5)
Abuse potential	20 (4.1)	19 (2.5)	34 (2.6)	31 (3.0)
Suicidal ideation[3]	1 (0.2)	1 (0.1)	9 (0.7)[4]	1 (0.1)

[1]Not adjusted for exposure
[2]Subset of 0-12 month data
[3] Not captured as unsolicited adverse events. Data are based on responses to the C-SSSRS
[4] includes 3 patients with suicidal ideation not considered adverse event by investigator
Suvo LD=Suvorexant 20 mg for patients < 65 years and Suvorexant 15 mg for patients ≥ 65 years.
Suvo HD=Suvorexant 40 mg for patients < 65 years and Suvorexant 30 mg for patients ≥ 65 years.

Appendix 11
Narratives for Suicidal Ideation*

*Detailed identifying information has been redacted from these narrative summaries.

Phase 3 Narratives.

Suvorexant LD

- Patient #1 is a 30-40 year-old male with a prior history of suicidal ideation and seasonal affective disorder. The patient was treated with suvorexant LD. Baseline QIDS score was 5. The reported events of suicidal ideation occurred on Study Day 25 and Study Day 31. The patient reported feeling depressed due to his janitorial job, which he hated. These feelings were associated with fleeting thoughts of self-harm which were controlled with some difficulty, and included thoughts of shooting himself, but without a specific plan and without intent. The first occurrence ended after he quit his job on Study Day 28. The second report of suicidal ideation was described by the patient as a thought, lasting approximately 1 minute on Study Day 31. The patient's circumstances at the time of the event were that he was at training for his new job, and he briefly thought that if the new job did not work he would rather die than return to his former job as a janitor. The first event of suicidal ideation was reported to be moderate in intensity and lasted 3 days and the second report was described as mild in intensity and lasted 1 minute. Neither episode was associated with intent. The last dose of suvorexant LD was taken on Study Day 30. On study day 36, the patient initiated treatment with bupropion hydrochloride and aripiprazole. In the investigator's opinion, the adverse events of suicidal ideation were not related to study medication. The patient discontinued the study due to the adverse event of suicidal ideation.

Suvorexant HD

- Patient #2 is a 20-30 year old male assigned to suvorexant HD, with a prior history of suicidal ideation and an aborted suicide attempt by suffocation who reported mild suicidal ideation on Study Day 269. Baseline QIDS score was 7. In response to the C-SSRS at the Month 9 visit, the patient reported a vague feeling of "not being worthwhile" related to difficulties gaining employment, citing numerous job interview rejections as cause for the ideation. These thoughts were noted as fleeting, lasting 10 seconds, were controlled with some difficulty, and resolved with no intent to act on these thoughts. The patient reported the frustration he felt led to regressive thoughts that were controlled without progression to any planning or instigation. The QIDS score at the Month 9 visit was 4. The investigator reported that the adverse event of suicidal ideation was not related to study medication. The patient completed the study per protocol.

- Patient #3 is a 60-70 year old male assigned to suvorexant HD, with a history of two episodes of major depression and a past suicide attempt by intentional overdose. Baseline QIDS score was 11. The patients reported three occurrences of severe suicidal ideation at the clinic visit on Study Day 29. The QIDS score at this visit was 14. Suicidal ideation occurred on Study Days 21, 22, and 26. The patient reported "feeling down" about an upcoming birthday and how this event would signify to him that he has accomplished "nothing with his life". He these thoughts lasted less than an hour and he had difficulty controlling the thoughts. He denied any intent to act on any of his ideation. Note that based on the C-SSRS responses, the greatest intensity of ideation as assessed by the rater was “ideation with any method, without a plan and intent”, however, in discussion with the investigator, the patient denied suicidal intent and no method was reported. The patient discontinued study medication on Study Day 29 due to the adverse event of suicidal ideation. The outcome of each event was ongoing as of the post-study visit. The investigator reported that the suicidal ideation was not related to study medication.

- Patient #4 is a 30-40 year old male assigned to suvorexant HD, without a prior history of suicidal ideation who reported mild suicidal ideation on Study Day 9. Baseline QIDS score was 4. At an unscheduled visit on Study Day 10, the patient presented with complaints of anergia, family problems, and business problems with his accountant. The QIDS score at this visit was 11. On the C-SSRS, the patient reported "wishing to be dead", with fleeting thoughts over 2 days which were controlled with little difficulty. As reported by the site, the patient returned for followup for this event on Study Day 15 and the patient reported feeling better after the visit. The patient continued taking study medication. The investigator reported that the adverse event of suicidal ideation was not related to study medication. The patient was discontinued from the study due to lack of efficacy on Study Day 179.

- Patient #5 is a 70-80 year old male assigned to suvorexant HD, with a history of past suicidal ideation (death by drowning) who reported mild suicidal ideation on Study Day 81. Baseline QIDS score was 4. The patient reported these thoughts upon learning that one of his sons had esophageal cancer and with concerns about his other son, who was being deployed to Afghanistan. The QIDS score at this visit was 7. The patient reported thoughts of jumping into the water from a cruise ship and leaving behind a note to the captain stating his suicidal intent. These thoughts lasted 2 hours, were easily controlled and were without suicidal intent. The patient was seen by a psychiatrist who diagnosed a depressive episode and recommended treatment. The patient discontinued study medication on Study Day 111. The adverse event of suicidal ideation was not considered to be related to study medication. The patient discontinued from the study due to the adverse event of depressive episode.

- Patient #6 is a 40-50 year-old female assigned to suvorexant HD, without a past history of suicidal ideation who reported mild suicidal ideation with intent on Study Day 66. Baseline QIDS score was 3. At the scheduled Month 2 visit, the patient

reported "love pain" and broken-heartedness following the end of a romantic relationship and stated on the C-SSRS “wanting to have serenity”. The patient acknowledged thoughts of a possible method (i.e., as taking medication to end her life), with intent, “but not for a long time”, and without a specific plan. Per the C-SSRS, the patient reported “ideation with any method and intent, but no plan”, occurring 2-5 times per week, less than an hour at a time, and these thoughts were controlled with a lot of difficulty. In the rater’s assessment of greatest intensity of suicidal ideation, the rater recorded “ideation with any method, without a plan and intent”. The event resolved in 32 days when the patient started a new romantic relationship. Patient's study medication has not changed. On Study Day 102, the patient showed no evidence of suicidal ideation per the C-SSRS. The investigator reported that the adverse event of suicidal ideation was not related to study medication. The patient completed the study per protocol.

- Patient #7 is a 50-60 year-old female assigned to suvorexant HD, with no known history of suicidal ideation who reported mild suicidal ideation on Study Day 91. Baseline QIDS score was 3. Shortly after an argument with her daughter, the patient briefly felt like she wanted to die, without any intent to act on these thoughts. These thought lasted one minute and were easily controllable. Due to travel, treatment with suvorexant HD was interrupted the evening prior to the event (i.e., the patient did not take study medication on Study Day 90). The investigator reported that the adverse event of suicidal ideation was not related to study medication. The patient completed the study per protocol.

- Patient #8 is a 60-70 year-old female with a history of autoimmune thyroiditis assigned to suvorexant HD who had prior suicidal thoughts attributed to hyperthyroidism. Prior to beginning the Run-in Period, the patient reported suicidal ideation, with thoughts of jumping from a bridge, but without intent. She also reported these thoughts during the placebo Run-in Phase, as well as at the Month 2 visit after randomization. Per responses to the C-SSRS, these thought occurred less than once a week, lasted less than an hour, and were easily controllable. The investigator determined that these thoughts were part of the mood changes related to the patients history of autoimmune thyroiditis and did not report this as an adverse event. The patient completed the study with no additional changes to baseline C-SSRS responses. Baseline QIDS was not done for this patient.

- Patient #9 is a 50-60 year-old male assigned to suvorexant HD, with a history of depression and anxiety who reported a "wish to be dead" on the C-SSRS at the end of Month 3 visit. Baseline QIDS score was 8. Per the C-SSRS, these thoughts occurred less than once a week, were fleeting, and easily controllable. In the investigator's judgment, this was a "fleeting thought" and not suicidal ideation and, was therefore determined not to be an adverse event. The QIDS score at this visit was 13. Note that based on the C-SSRS responses, the greatest intensity of ideation as assessed by the rater was “ideation with any method, without a plan and intent”, however, the

highest level of ideation reported by the patient was a "wish to be dead, with no mention of a method or intent. The patient withdrew from the study for unknown reasons.

- Patient #10 is a 50-60 year-old female assigned to suvorexant HD, with no known psychiatric history who reported suicidal thoughts per the C-SSRS at the end of Months 1 and 3. Baseline QIDS score was 13. Per the C-SSRS, the patient experienced fleeting suicidal thoughts 2-5 times per week which were controllable with little difficulty. The QIDS score at Month 3 was 21. The investigator determined that the patient was never at risk of suicide and this was assessment confirmed by other site physicians. Given these considerations, the investigator did not report this as an adverse event. The patient subsequently discontinued from the study due to lack of efficacy.

Placebo

- Patient #11 is a 40-50 year-old male assigned to placebo, with a history of depression and suicidal ideation who reported moderate suicidal ideation on Study Day 16. Baseline QIDS score was 6. The actual event started on Study Day 8 in the setting of interfamilial relationship problems and on Study Day 9, the patient was admitted to the psychiatric ward for further evaluation and treatment. The patient was hospitalized for 6 days and was started on antidepressant medication. The last dose of study medication was taken on Study Day 8. The patient recovered on Study Day 34. Of note, the patient had experienced problems prior to the study (the nature of which was not specified), but had not disclosed this information to the site at the screening or initiation visits. For this patient, the C-SSRS was not performed until 8 days after the last dose of study medication. Therefore, while the event occurred within the 0-3 month period, the C-SSRS was completed after study discontinuation and the corresponding data were thereby not reflected in the C-CASA Treatment Phase data. The investigator reported that the adverse event of suicidal ideation was not related to study medication. The patient discontinued from the study due to an adverse event of depressed mood.

<u>Phase 1 Narrative</u>

Patient #12 is a 20-30 year old female without a prior history of suicidal ideation and with a history of miscarriage, polycystic ovarian syndrome, and lower abdominal pain, reported an adverse event of suicidal ideation and depression beginning poststudy, 4 days after the final dose of study medication in Period 3 in a drug-drug interaction study of suvorexant and paroxetine. In Period 3, the patient received suvorexant 40 mg and paroxetine 20 mg. Per responses to the C-SSRS, the patient noted that she "wanted to die" and "felt lonely all the time." The event was mild in intensity and lasted for 10 days (8-10 hours intermittently through the day). She stated that she had no plans to commit suicide and that she was just "really depressed" because of her situation. She stated that

she didn't really "want" to die. The subject had recently had a series of major life changes (new house and strained relationship with her husband) which the subject considered to be the primary cause of her suicidal ideation. She stated that she felt that it was "the house" that was depressing her so much. She felt that if she had a job and/or a car, she would be fine. The Investigator considered the event possibly related to the study drug.