CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204569Orig1s000

MEDICAL REVIEW(S)

Cross-Discipline Team Leader Review

Date	June 29, 2013
From	Ronald Farkas, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 204569
Applicant	Merck
Date of Submission	August 29, 2012
PDUFA Goal Date	June 29, 2013
Proprietary Name / Established (USAN) names	Proprietary name to be determined Established name: suvorexant
Dosage forms / Strength	15 mg, 20 mg, 30 mg, 40 mg
Proposed Indication(s)	Insomnia
Recommended:	Complete response

1. Introduction

Orexin A and orexin B are hypothalamic neuropeptides that play a critical role in the maintenance of wakefulness. Orexins are also thought to play an important role in modulation of feeding behavior and energy balance. Loss of orexin-containing neurons in humans is associated with narcolepsy, a disease characterized by excessive daytime sleepiness, cataplexy, hypnagogic and hypnopompic hallucinations, sleep paralysis, and other symptoms. Suvorexant antagonizes the two orexin receptors, orexin 1 receptor and orexin 2 receptor. Based on the involvement of orexins in the maintenance of wakefulness, suvorexant was developed by Merck for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance.

Suvorexant is both a new molecular entity and first-in-class.

2. Background

In the NDA the sponsor proposed an initial dose of 40 mg for adults, and 30 mg for elderly patients (≥ 65 years of age), taken immediately before bed, with a lower dose of 20 mg for adults and 15 mg for elderly based on individual tolerability. However, during the review cycle, the sponsor informed the Division that, based on public statements made by the Division about the safety of zolpidem products, the sponsor was changing the dosing recommendation to initial dosing with the lower doses above, with the option to increase to the higher doses if necessary for efficacy

Primary clinical review was conducted by Kachi Illoh, MD, and statistical review was conducted by Tristan Massie, PhD. Clinical pharmacology review was conducted by Hristina Dimova, PhD, and pharmacometrics review was conducted by Joo-Yeon Lee. Chemistry review was conducted by Akm Khairuzzaman, PhD., Biopharmaceutics review was conducted by Sandra Suarez, PhD, and drug substance quality aspects were reviewed by Mohan Sapru, PhD. Controlled Substance Staff review was conducted by Chad Reissig, PhD, and Non-Clinical review was conducted by Richard Siarey.

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3. CMC/Device

Dr. Khairuzzaman found the drug product portion of the NDA to be acceptable, and without need for phase 4 commitments.

Dr. Sapru's review stated that with the exception of a pending issue concerning the control of potential genotoxic impurity (b) (4) the NDA was approvable in terms of drug substance.

Dr. Suarez found that the NDA was acceptable from a biopharmaceutics perspective.

The Office of Compliance issuance of an acceptable recommendation for drug substance manufacturing and testing facilities was pending at the time of this review.

4. Nonclinical Pharmacology/Toxicology

Dr. Richard Siarey completed the primary nonclinical review, and Dr. Lois Freed completed a supervisory memo.

Dr. Siarey's overall conclusion was that from a nonclinical perspective, approval of the suvorexant NDA was recommended. However, he found evidence that catapelxy was observed in dogs exposed to MK-4305 (suvorexant) near Tmax, although he concluded that additional information could have been gained by studying the drug in an experimental model that has been used for diagnosing cataplexy in dogs. Dr. Siarey suggested that since cataplexy occurred in dogs near Tmax, a time at which if used for insomnia patients would ordinarily be in bed, safety concern for humans was reduced. Dr. Siarey also found that the neurobehavioral assessment in the pre- and post-natal developmental study was not complete, as the passive avoidance tests was performed too early in development, while learning/acquisition tests and retention/memory tests were not conducted. He recommended that these studies be repeated/conducted.

Dr. Freed agreed that nonclinical studies suggested a theoretical safety concern for cataplexy, concluding that clinical implications, if any, are an issue for the clinical team to decide. She suggested that findings of cataplexy in dog be described in labeling, but would not require additional nonclinical studies of cataplexy, and concluded that the neurobehavioral assessments were sensitive enough to detect at least some adverse effects, and since none were observed, the studies were minimally acceptable. Therefore, the nonclinical team had no suggested post-marketing requirements.

5. Clinical Pharmacology/Biopharmaceutics

A single Clinical Pharmacology review combined the findings of Dr. Dimova and Dr. Lee.

Half life and accumulation

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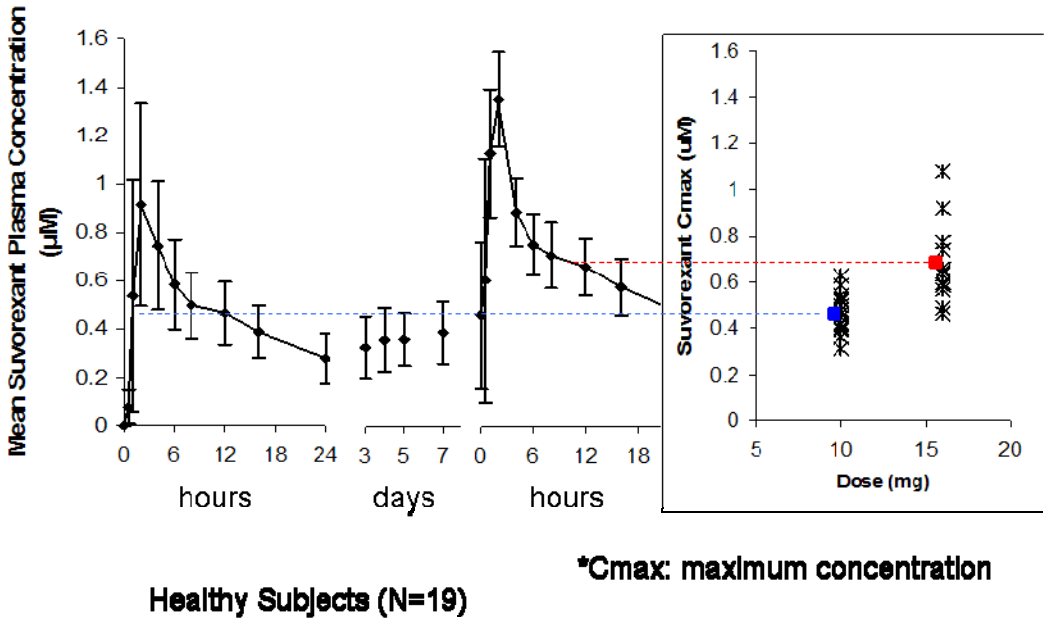
The half-life of suvorexant is about 12 hours, such that levels accumulate to steady state over several days of dosing.

Figure 1: Suvorexant PK, 40 mg



CDTL: Figure 1 illustrates how the long half-life of suvorexant may impact both safety and efficacy. Suvorexant blood level about 12 hours after a single dose is about the same as the Cmax of a single 10 mg dose (blue dashed line in figure). As discussed below in Section 7, the 10 mg dose appears to be effective for inducing and maintaining sleep. While circadian effects might make patients less sensitive to somnolence during the day versus at night, it is concerning that 'effective' levels are present during the day. With repeat dosing, daytime levels increase due to drug accumulation, such that suvorexant levels about 12 hours after the previous night's dose are similar to Cmax from the 15 mg dose, again a dose found to be effective for sleep latency and maintenance.

The long half-life also is likely to affect efficacy, particularly for sleep latency, which is more dependent than sleep maintenance on the time between dosing and blood levels reaching an effective level. At the first dose, suvorexant blood level must go from zero to some level before the drug could be effective. However, with chronic dosing of 40 mg, suvorexant blood level at bedtime, *before* taking that night's dose, is already about the same as Cmax from the 10 mg dose, a dose seemingly effective for sleep latency. This same relationship holds for any dose (with the steady-state suvorexant level proportional to the dose), such that potentially even *if* a low dose (10 mg or even lower) is less effective on night 1 for sleep latency than a high dose, on subsequent nights of chronic dosing, accumulation of suvorexant would allow suvorexant blood levels to more quickly reach an effective level. The difference in efficacy between low and high dose would diminish because, while the high dose would also lead to accumulation of suvorexant, the exposure from the high dose would already have been in or near the plateau region of the dose-response relationship, such that higher exposure would lead to little if any greater efficacy.

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Intrinsic factors

Table 1 shows effect of gender and BMI on suvorexant exposure. Exposure is increased in obesity and in women compared to men.

Table 1: Gender and BMI

	reference	test	ratio of exposure metric	
Single Dose	*non-obese male*	*Obese* male*	AUC	1.14
			Cmax	1.07
			C9 hours	1.03
	non-obese female	*obese female*	AUC	1.18
			Cmax	1.09
			C9 hours	1.04
Multiple Dose	*non-obese male*	*obese male*	AUC	1.39
			Cmax	1.12
			C9 hours	1.1
	non-obese female	*obese female*	AUC	1.45
			Cmax	1.17
			C9 hours	1.12

Overall female vs male

AUC	1.17
Cmax	1.09
C9	1.04

*Definition of obese (>30 kg/m2)

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CDTL: Increased exposure in women vs. men and obese vs. non-obese patients are potentially clinically important. The clinical pharmacology review recommended a 50% lower (e.g. 10 mg) starting dose in obese females based on the approximate doubling of suvorexant exposure vs. non-obese males, and the approximate 20% increase in blood levels the morning after dosing at steady state.

If the initial recommended dose is 10 mg with the option of increasing the dose if clinically indicated, it is not clear that specific dose adjustment needs to be made for these differences; instead, labeling indicating that such exposure differences occur, and should enter into clinical judgments about dose escalation, appears adequate.

Age

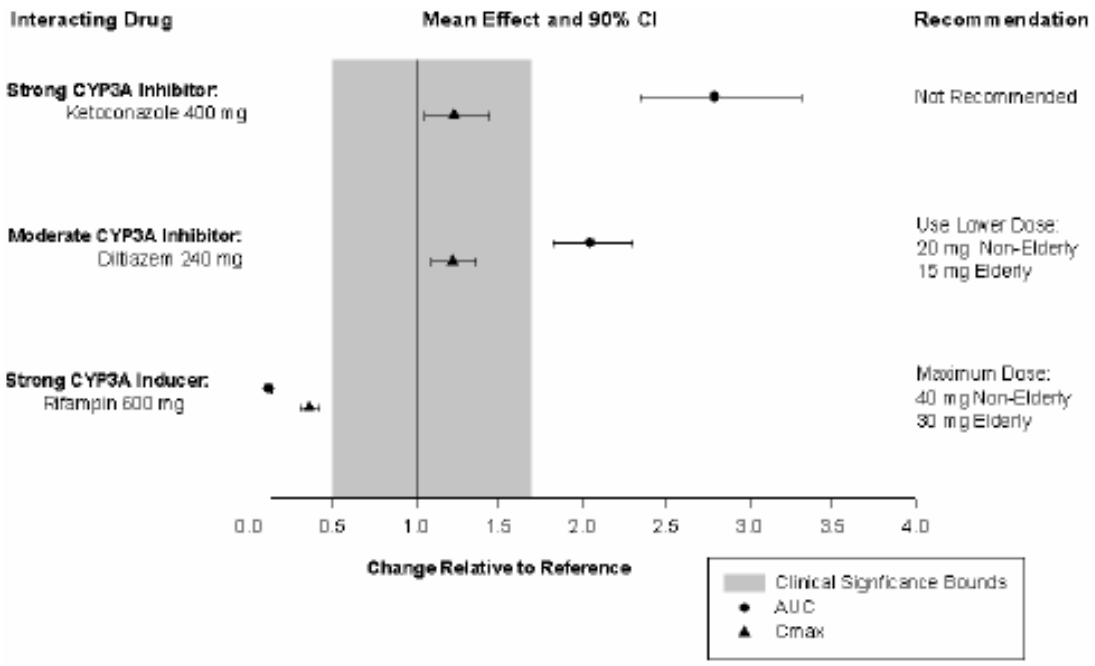
Elderly patients were predicted by the sponsor to have about 15% higher blood levels 9 hours after dosing versus non-elderly patients based on a combination of covariate effects of age, BMI, and creatinine clearance. However, Dr. Dimova found that data from phase 1 studies suggested that age alone did *not* have an effect on suvorexant PK.

CDTL: The Clinical Pharmacology review concludes dose-adjustment for age is not necessary. I agree.

CYP3A inhibition

Exposure (AUC) of suvorexant is increased about 3-fold by strong CYP3A inhibitors and about 2-fold by moderate CYP3A inhibitors (Figure 2).

Figure 2: Effect of CYP3A Inhibition on Suvorexant Exposure



The Clinical Pharmacology review concluded the following regarding CYP3A:

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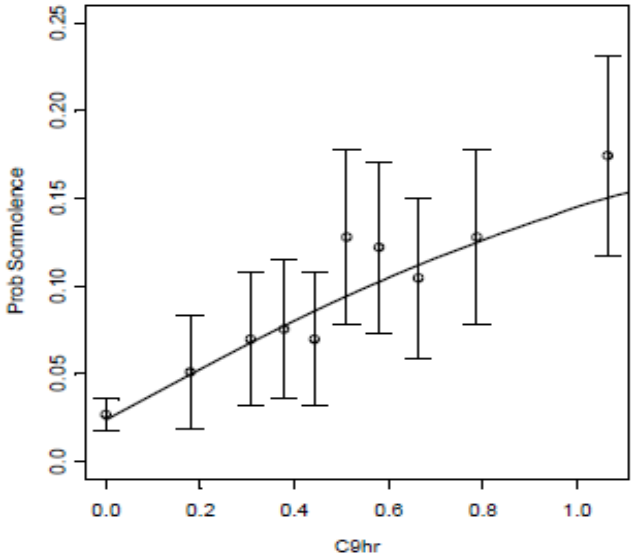
- Exposure is increased about 3-fold by strong CYP3A inhibitors, and suvorexant should not be co-administered with strong CYP3A inhibitors
- Exposure is increased about 2-fold by moderate CYP3A inhibitors, and dosing should be adjusted accordingly
- Efficacy may be reduced by CYP3A inducers

CDTL: I agree with the recommendations regarding CYP3A inhibitors; with 10 mg dosing and strong CYP3A inhibotors, exposure would be similar to that from high dose suvorexant (30 mg/ 40 mg), which this review concludes is not safe, while exposure from the 10 mg dose used with moderate inhibitors would be similar to that from 20 mg suvorexant, which this review concludes is adequately safe so long as patients refrain from driving.

Exposure vs. Somnolence

Analysis from combined controlled trials showed that adverse events of somnolence were exposure-related (Figure 3).

Figure 3: Suvorexant Exposure vs. Incidence of Somnolence



CDTL: Next-day suvorexant blood levels in adults after nighttime administration of the 15 mg dose overlap with blood levels from the 20 mg dose that caused driving impairment in the formal driving study (not shown), as discussed in Section 8. The observation above that exposure and somnolence are correlated supports concern that patients at the higher end of the population distribution of exposure from the 15 mg dose are more likely to be at similar risk of adverse effects to patients with similar exposure from the 20 mg dose. As discussed in Section 7, a starting dose of 10 mg would likely be effective for many patients who would be at the high end of exposure, thus reducing risk of driving impairment while not diminishing efficacy for these patients.

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6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

The sponsor conducted two similarly designed phase 3 efficacy trials of 3 months duration, study 028 and 029. The studies enrolled both adult patients 18- to 64 years of age, and elderly patients age 65 and above. About 40% of the subjects in each study were elderly. Two doses were tested in each age group: for adults, 40 mg or 20 mg suvorexant, and for elderly patients, 30 mg or 15 mg. Randomization was to low dose, high dose, or placebo in a 2:3:3 ratio, respectively. The 40 mg and 30 mg 'high' doses (HD) in adults were expected to result in similar exposure, as were the 20 mg and 15 mg 'low' doses (LD), and for analysis the high doses were pooled and the low doses were pooled. The studies were powered for the high dose sleep maintenance endpoints.

CDTL: As noted in Dr. Massie's review, the sponsor's goals for the phase 3 studies were ambitious, in that they aimed to demonstrate effects for both elderly and non-elderly patients on both sleep maintenance and sleep onset, in terms of both an objective and a subjective assessment for each, in the same study. The sponsor also powered the studies for the high dose (the low dose had 30- to 40% less patients), and the multiplicity method tested the high dose first. The studies were thus underpowered for the low dose, such that non-statistically significant findings for some endpoints at some time points for the low dose is unsurprising, and in no way provides interpretable evidence *against* efficacy. Likewise, the phase 2 study was powered for objective sleep maintenance, but not latency or subjective sleep endpoints, such that non-statistically significant findings can not be taken as meaningful evidence of lack of efficacy at lower suvorexant doses. The question, discussed below, then becomes if enough evidence has been provided in the overall database for appropriate dose-selection, even though studies were underpowered to provide this data in the form of consistently statistically positive endpoints.

Patients used suvorexant immediately before bedtime when at home, but during inpatient polysomnography nights, suvorexant was dosed 30 minutes before lights out and initiation of recording.

Sleep maintenance, phase 3 studies

Objective evidence of benefit for sleep maintenance, as measured by Polysomnographic (PSG) Wake After Sleep Onset (WASO) was positive in both study 28 and 29 at each time point (night 1, month 1, and month 3) for both high dose (HD)(30 and 40 mg combined) and low dose (LD)(15 and 20 mg combined)(Table 2, Table 3).

Table 2: Study 28 PSG-WASO

Night 1	Difference (min)	p-value
HD vs Pbo	-38.4	<0.00001
LD vs Pbo	-32.5	<0.00001
Month 1		
HD vs Pbo	-26.3	<0.00001

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LD vs Pbo	-26.4	<0.00001
Month 3		
HD vs Pbo	-22.9	<0.00001
LD vs Pbo	-16.6	0.000009

Table 3: Study 29 PSG-WASO

Night 1	Difference (min)	p-value
HD vs Pbo	-42.0	<0.00001
LD vs Pbo	-37.0	<0.00001
Month 1		
HD vs Pbo	-29.4	<0.00001
LD vs Pbo	-24.1	<0.00001
Month 3		
HD vs Pbo	-29.4	<0.00001
LD vs Pbo	-31.1	0.000009

Subjective perception of minutes awake at night, as measured by subjective WASO, was positive for most time points, but not month 3 for LD in study 28, or week 1 for LD in study 29 (Table 4, Table 5).

Table 4: Study 28, Subjective WASO

Week 1	Difference (min)	p-value
HD vs Pbo	-10.5	<0.00001
LD vs Pbo	-6.8	0.003
Month 1		
HD vs Pbo	-9.5	0.00025
LD vs Pbo	-5.4	0.06
Month 3		
HD vs Pbo	-6.9	0.006
LD vs Pbo	-2.4	0.39

Table 5: Study 29, Subjective WASO

Week 1	Difference (min)	p-value
HD vs Pbo	-8.4	0.0005
LD vs Pbo	-4.2	0.13
Month 1		
HD vs Pbo	-8.7	0.001
LD vs Pbo	-8.4	0.006

Month 3		
HD vs Pbo	-8.9	0.002
LD vs Pbo	-7.7	0.02

Sleep latency, phase 3 studies

Objective evidence of benefit for sleep latency, as measured by PSG-LPS, was positive in study 28 for each time point, for both HD and LD, but in study 29, while PSG-WASO was positive for each time point for HD, it was positive for LD only at night 1 (Table 6, Table 7).

Table 6: Study 28, LPS

Night 1	Difference (min)	p-value
HD vs Pbo	-10.3	0.00002
LD vs Pbo	-9.6	0.0004
Month 1		
HD vs Pbo	-11.2	0.00002
LD vs Pbo	-10.3	0.0004
Month 3		
HD vs Pbo	-9.4	0.0004
LD vs Pbo	-8.1	0.0061

Table 7: Study 29, LPS

Night 1	Difference (min)	p-value
HD vs Pbo	-21.7	<0.00001
LD vs Pbo	-12.4	0.004
Month 1		
HD vs Pbo	-12.1	0.00004
LD vs Pbo	-7.8	0.03
Month 3		
HD vs Pbo	-3.6	0.27
LD vs Pbo	-0.3	0.9

Subjective perception of sleep latency, as measured by subjective time sleep onset (sTSO), was positive in study 28 and 29 for each time point for HD, but negative for each time point for LD (although nominal p-values were about 0.05 or less for all LD time points)(Table 8, Table 9).

Table 8: Study 28, Subjective Sleep Latency (sTSO)

Week 1	Difference (min)	p-value
HD vs Pbo	-5.7	0.0061
LD vs Pbo	-5.6	0.016

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Month 1		
HD vs Pbo	-7.4	0.003
LD vs Pbo	-5.4	0.052
Month 3		
HD vs Pbo	-8.4	0.0002
LD vs Pbo	-5.2	0.04

Table 9: Study 29, Subjective Sleep Latency (sTSO)

Week 1	Difference (min)	p-value
HD vs Pbo	-13.1*	<0.00001
LD vs Pbo	-7.5	0.006
Month 1		
HD vs Pbo	-12.8*	0.00003
LD vs Pbo	-6.9	0.05
Month 3		
HD vs Pbo	-13.2*	0.00003
LD vs Pbo	-7.6	0.04

Dr. Massie's review analyzed results for elderly and adult separately, pooling results for study 28 and 29 (Table 10)(the sponsor was not required to demonstrate statistical significance separately in the two age groups, so only point estimates are shown in the table). The effects in adult and elderly patients are generally similar.

Table 10: Efficacy by Age (Adult, Elderly)

	Adult	Elderly	Adult	Elderly
	Low Dose (min)		High Dose (min)	
PSG-WASO				
Day 1	-27	-40	-33	-45
Day 30	-26	-27	-26	-26
Day 90	-18	-15	-27	-17
Subjective total sleep time				
Week 1	13	17	23	25
Month 1	20	16	24	21
Month 3	13	19	23	21
PSG-LPS				

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Day 1	-12	-10	-15	-18
Day 30	-12	-5	-15	-7
Day 90	-3	-6	-5	-8
Subjective latency (sLSO)				
Week 1	-6	-7	-9	-9
Month 1	-7	-4	-11	-9
Month 3	-6	-7	-12	-9

Phase 2 Study 006

The sponsor also conducted a phase 2 dose-finding two-period cross-over study that examined the efficacy of 10 mg, 20 mg, 40 mg, and 80 mg suvorexant. A total of 254 patients were randomized, with about 60 patients in each dose arm. PSG-WASO was statistically significantly reduced ($p<0.001$) for all doses, with the following point estimates (Table 11):

Table 11: PSG-WASO, Study 006

Dose	Night 1 (min)	Week 4 (min)
10 mg	-21	-21
20 mg	-25	-28
40 mg	-34	-33
80 mg	-37	-29

In contrast, by the multiplicity strategy no dose was positive for PSG-LPS, with following point estimates and nominal p-values (Table 12):

Table 12: PSG-LPS, Study 006

Dose	Night 1 (min)	p-value	Week 4 (min)	p-value
10 mg	-3	0.6	-2	0.6
20 mg	-9	.13	-22	<0.001
40 mg	-23	<0.001	-4	0.5
80 mg	-25	<0.001	-10	0.07

Dr. Massie's review found evidence of a carryover effect between the first- and second study periods, and therefore performed an analysis of LPS restricted to period 1. Applying the pre-specified multiplicity testing strategy to this alternative analysis, the 80 mg dose significantly improved LPS, and the nominal p-values were <0.05 for all other comparisons of drug vs. placebo except for 40 mg at week 4 (p-value 0.06), with point estimates as follows:

Dose	Night 1 (min)	p-value	Week 4 (min)	p-value
10 mg	-19	0.02	-20	0.02
20 mg	-17	.03	-25	0.003
40 mg	-31	<0.001	-16	0.06
80 mg	-22	0.007	-20	0.02

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Dr. Massie's review also found unexpected variability between placebo groups for the different doses tested, and that results for the 10 mg dose were particularly sensitive to the placebo group involved in the comparison. Based on pooled placebo, the 10 mg dose was nominally positive for PSG-LPS at both day 1 and week 4 ($p = 0.01$ for each).

Dr. Massie's review found little statistical evidence for efficacy of the 10 mg dose on subjective endpoints in study 006 beyond results that were directionally consistent with efficacy. The overall conclusion was that the application overall provided clear evidence for the efficacy of suvorexant for sleep maintenance, and weaker evidence for efficacy for sleep latency, citing the failure to reach statistical significance at the 3-month time point for PSG-LPS. He also concluded that study 006 provided a suggestion of efficacy for 10 mg, particularly for WASO, but notes that no other study examined 10 mg to provide replication of findings, and that efficacy of 10 mg was not studied in elderly patients. He concluded that if the phase 3 doses (15 through 40 mg) are considered to have too much risk of next-day driving impairment then another study of the 10 mg dose may be needed.

Dr. Illoh's review found substantial evidence of efficacy for the high doses only (30 and 40 mg). It notes that suvorexant high dose failed to significantly improve LPS at month 3 in trial 29, but finds subjective endpoints to be more important than objective because they measure patient perception not a biomarker, such that positive findings for subjective time to sleep onset provide in study 29 provide, in combination with positive findings in study 28, adequate evidence of efficacy. For the low doses, the review notes that because in study 28, low doses did not improve sleep onset endpoints beyond month 1, efficacy of low doses for sleep onset remains uncertain. In another section, the review states that suvorexant low dose may be considered in sleep maintenance insomnia, but its benefit for sleep onset insomnia remains uncertain.

CDTL Discussion:

Efficacy

To support a claim for insomnia the Division required that efficacy be demonstrated in at least two studies of 3-months duration, in both adult and elderly patients. The 3-month duration was intended to be a sufficient duration to demonstrate efficacy for chronic insomnia, which is often treated with drugs for 3 months or longer.

Due to concern about possible age-related differences in efficacy and safety of drugs for insomnia, the sponsor was expected to provide enough evidence to allow the Division to conclude that suvorexant was safe and effective in both adult and elderly patients. The Division did not, however, require separate positive studies for adult and elderly patients.

For a claim in sleep latency, the Division required positive findings on both an objective polysomnographic measure of sleep latency, latency to persistent sleep (LPS), and the patient's subjective estimation of the time taken to fall asleep, sleep onset latency (SOL). For a claim in sleep maintenance, the Division required positive findings on both an objective polysomnographic measure of sleep maintenance, wake after sleep onset (WASO), and the

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patient's subjective estimation of wake after sleep onset, subjective WASO (sWASO). The objective and subjective endpoints were required to demonstrate, respectively, that the drug did, in fact, treat insomnia through positive effect on sleep latency and/or maintenance, and that this positive effect was large enough to be apparent to the patient, as a marker of clinical meaningfulness.

While subjective estimation of sleep time has been an endpoint required by the Division, it is known to be an inaccurate reflection of objective sleep time, and thought to be even less reflective of objective benefit due to psychoactive effects of insomnia drugs themselves, including amnestic effects. Thus, there is even concern that sleep might be misperceived due to what would ordinarily be considered an adverse drug effect (amnesia). Thus, there is increased realization that while subjective estimates of sleep remain useful markers, they should be interpreted with these cautions in mind. Historically, no requirement has been set by the Division for either objective or subjective benefit for daytime function, or more global patient reported outcomes for insomnia, like the Insomnia Severity Index. However, particularly in the context of increased FDA focus on patient perspective on disease symptoms, the Division is putting increasing emphasis on such endpoints because they appear to be clearly clinically meaningful to patients.

The discussion below of efficacy evidence is based in particular on situations when substantial evidence of efficacy can be established based on less than two positive studies through reliance on conclusive findings of efficacy in related settings, as described in the FDA Guidance for evidence of effectiveness[1].

For sleep maintenance, the high dose arms of suvorexant were effective for both objective and subjective endpoints, in two studies, with efficacy maintained through the full 3 month study duration. With these findings suvorexant meets the basic legal standard for quantity (and quality) of evidence to support that the drug is effective for sleep maintenance.

For objective sleep latency, HD was positive through the full 3 month study duration in study 28, while study 29 was positive for night 1 and day 30. Subjective sleep latency was positive for HD through the full 3 month duration in both study 28 and 29. Sleep latency and sleep maintenance are closely related indications; sleep maintenance in many respects can be considered as difficulty with sleep latency when trying to fall back asleep after middle-of-the-night awakenings. Given the demonstrated efficacy of suvorexant in sleep maintenance, it is therefore reasonable to accept a single additional study positive for both objective and subjective endpoints, study 29, as adequate support for the sleep latency claim.

The point estimates are similar for the effect of suvorexant on adult versus elderly patients (Table 10), and from this it is reasonable to conclude that study 28 and 29 provide enough evidence to conclude that suvorexant is effective in both adult and elderly patients, for both sleep onset and sleep maintenance.

Dose/response

[1] Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products

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While insomnia is associated with an increased incidence of long-term adverse health outcomes, data is currently lacking that would justify using a higher (and less safe) drug dose for insomnia than necessary to satisfactorily treat current symptoms. The Guidance for evidence of effectiveness cited above notes that information about effectiveness of one dose is relevant to the effectiveness of other doses, and describes a flexible approach to determining efficacy for different doses based on not only additional clinical efficacy data but also pharmacokinetic and dose/response data, sometimes even in the absence of clinical efficacy data.

In the phase 3 trials (28 and 29), the combined low dose arms were positive at all time points for PSG-WASO in both studies, and for subjective WASO at all time points in study 29. Given the demonstrated effectiveness of suvorexant for sleep maintenance (at the high doses), this additional data (more than one additional positive study) is thus more than sufficient to conclude efficacy of the lower doses for sleep maintenance.

For the low doses, PSG-LPS was positive at all time points in study 28, but only night 1 in study 29. Subjective sleep latency was positive at week 1 in both studies, but at month 1 and month 3, in both studies, the p-values were only nominally positive (0.04 in both studies at month 3). In the context of positive findings for the high dose, positive findings in only one study would be necessary to support efficacy of the low dose. Objective findings are provided by study 28. For the subjective endpoint, it seems reasonable to consider *two* nominally positive studies to be of similar persuasiveness as a single study positive on a pre-specified positive endpoint, as replication provides important, qualitatively different, reassurance in addition to the p-value. Thus, I conclude that the phase 3 studies adequately support the efficacy of doses as low as 15 mg for chronic sleep latency and/or sleep maintenance.

Efficacy data is available for the 10 mg dose from study 006, the phase 2 dose finding study. Study 006 was positive for the 10 mg dose by the pre-specified analysis for objective sleep maintenance, and as described by Dr. Massie's review by reasonable post-hoc sensitivity analyses for objective sleep latency. Efficacy of the 10 mg dose is also supported by the exposure/response analysis conducted by Dr. Lee on data from the pivotal studies 28 and 29. She found no clear evidence of decreased efficacy for objective sleep maintenance or latency in patients who had suvorexant exposures (after dosing with 15 mg or higher dosage forms) similar to exposures that, from PK studies, occur after the 10 mg dose.

Dr. Massie's review found that for the 10 mg and 20 mg doses there was little evidence from study 006 of efficacy on subjective total sleep time or subjective time to sleep onset, although subjective time to sleep onset was nominally positive (p = 0.03) at week 4. Some evidence for subjective benefit from the 10 mg (and 20 mg) dose is provided by the Insomnia Severity Index (ISI), a patient-reported outcome of objective complaints in insomnia consisting of seven questions including patient satisfaction and worry about sleep, and perception of how insomnia interferes with their functioning. Figure 4 shows ISI results for study 006. Benefit on ISI appeared to be similar for all doses, noting however that the p-value was *not* nominally positive for 10 mg.

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Figure 4: Insomnia Severity Index, Study 006, Period 1

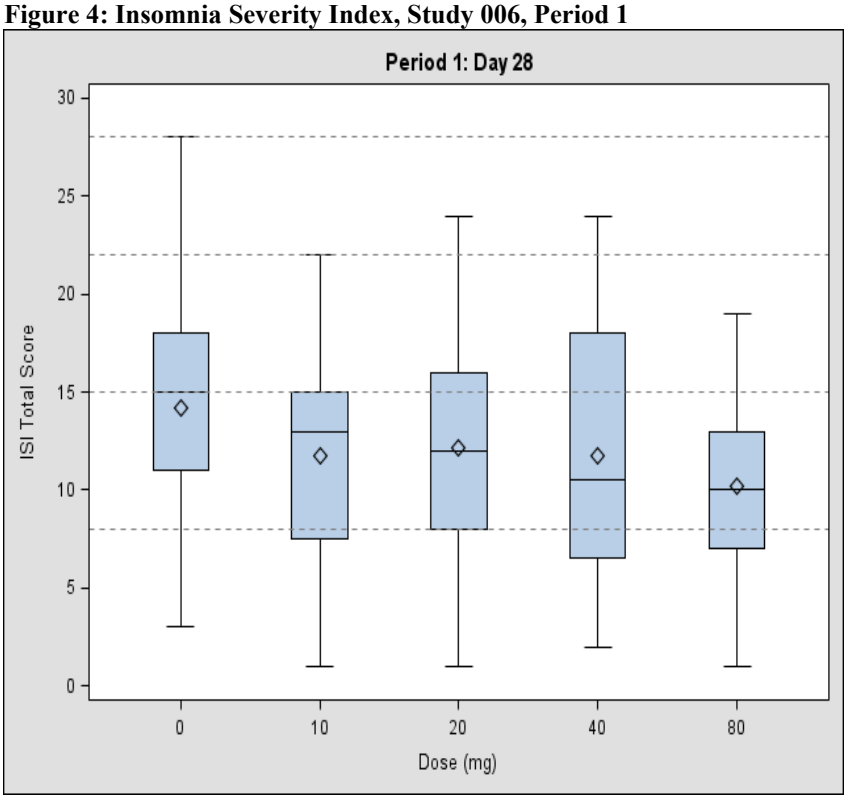

Figure 4 legend: The correlation between ISI total score and insomnia severity is generally considered to be the following: 0-7, no clinically significant insomnia; 8-14, subthreshold insomnia; 15-21, moderate insomnia; 22-28, severe insomnia.

As also discussed in section 5, based on pharmacokinetics, many patients taking the 10 mg dose would have exposure to suvorexant as higher or higher that from the 15 mg or even 20 mg dose, including obese females, a key demographic that would use suvorexant if approved, and who have exposure (AUC) about 1.5-fold higher than non-obese men. This supports efficacy of the 10 mg dose based on PK.

More generally, as shown in Figure 6, because of variability across the population in exposure to a given dose, there is considerable overlap of suvorexant exposure among

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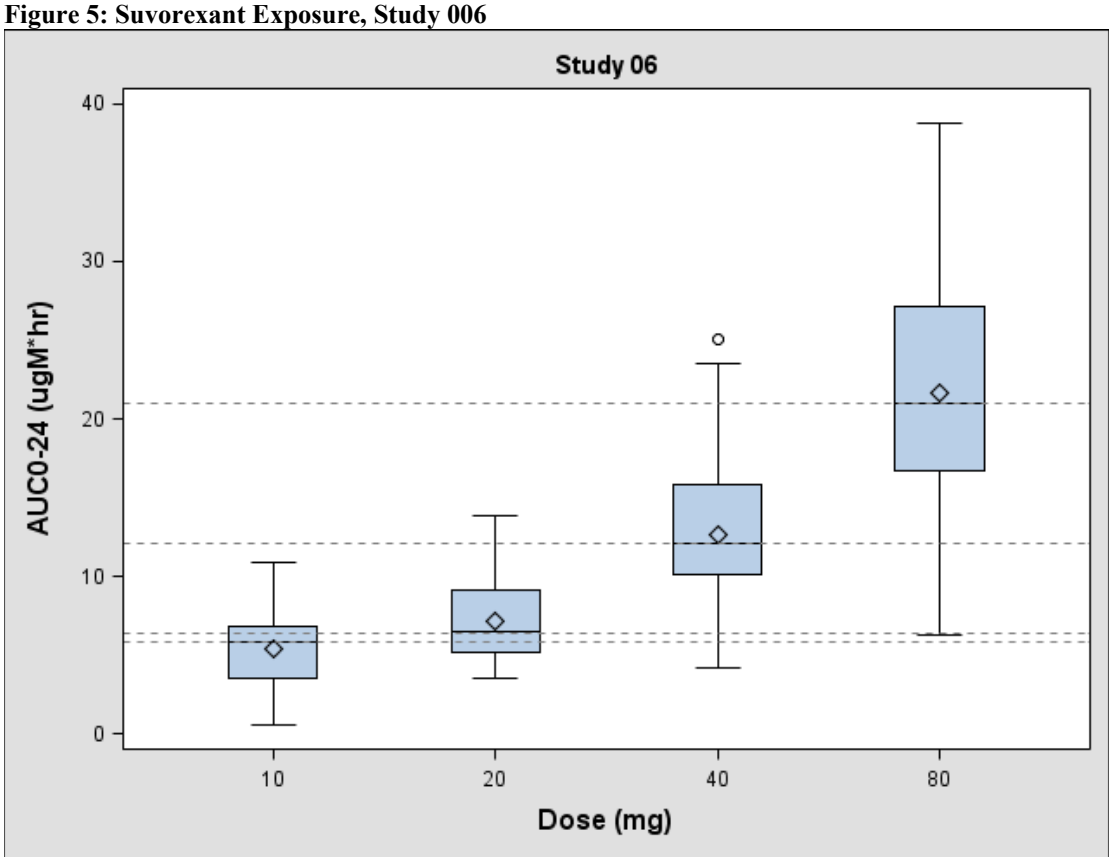
subjects receiving the 10 and 20 mg doses. Thus, logically, if the 20 mg dose is effective, then many patients at the higher end of the distribution of exposures after receiving the 10 mg dose (perhaps the top half of patients) will have to a similarly effective exposure to suvorexant. The above argument represents the same fundamental logic broadly used by FDA to recommend dose adjustment based on PK alone for particular populations with differences in exposure, such as patients with renal or hepatic impairment.

Figure 5: Suvorexant Exposure, Study 006



Finally, in the context of the above discussion about *exposure* experienced by the individual patient in response to a fixed dose, it's also reasonable to consider that the *average efficacy in a population* at a fixed dose does *not* represent the efficacy experienced by individual patients, who, given inter-individual variation in both PK and PD, may experience considerably higher or lower efficacy than the mean. Thus, a statement like 'efficacy was less at 10 mg than 20 mg' is incomplete and potentially misleading because the dose-response relationship in the steep part of the curve might better be stated in terms of the *percentage of patients* at a given dose that obtain effective treatment of their symptoms. At 10 mg, this percentage might be smaller than at 15 or 20 mg, which would, of course, lead to the *average*

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efficacy decreasing, but the goal is to treat the individual patient, who, in a binary fashion, will either obtain efficacy, or have the option of increasing the dose to achieve efficacy. Thus, 10 mg is a reasonable starting dose that will be effective for many patients while minimizing the risk of dose-related adverse effects.

8. Safety

Exposure
The sponsor powered the phase 3 studies for the high dose (30 and 40 mg), and conducted long-term safety studies at the high dose (40 mg). Patient exposure in phase 2 and 3 studies is shown in Table 13. The longest exposure to the 10 mg dose was in the phase 2 study, in which 62 patients were exposed for 1 month.

Table 13: Suvorexant Exposure

	Duration (in Months)		
Dose	3-<6	6-<9	>9
10 mg	0	0	0
15 mg	96	22	0
20 mg	152	20	0
30 mg	196	54	216
40 mg	267	73	121

Deaths
Dr. Illoh's review notes that two deaths occurred, a 40 year old woman who died in the hospital after near-drowning in the ocean (AN 12028), and a 58 year old woman on placebo who died of a stroke (AN 07315). The review notes that the patient that died after near drowning was on a leisure ocean swim when she was caught in a rip-current. The review concludes that it was unclear if a residual effect of suvorexant might have contributed to the death after near-drowning.

CDTL: My review found that the patient who died after near-drowning experienced no other adverse events before her death, such as daytime somnolence. Combined with the circumstances of the near drowning, I conclude it is unlikely that the death was drug-related.

There is essentially no evidence that suvorexant contributed to the stroke death.

Serious Adverse Events
Dr. Illoh's review states that nonfatal serious adverse events were uncommon in the suvorexant trials, that there were fewer serious adverse events in suvorexant arms compared with placebo, and that there is limited ability to make any other meaningful interpretation.

CDTL: My review found that diverticulitis affected 2 suvorexant patients (0.2%) vs. 1 placebo patient (0.1%). In addition, diverticulitis as a *non*-serious adverse event occurred in 2 additional suvorexant patients, versus one additional placebo patient. Diverticulitis was

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found to be a drug-related adverse effect of eplivanserin, an insomnia drug acting as a 5-HT_{2A} receptor antagonist. Increased vigilance for diverticulitis and related events appears warranted.

There was one serious adverse event of suicidal ideation on suvorexant high dose, and one on placebo. My review found that the suvorexant patient was a 61 year old man in study 009 taking 40 mg with a past history of suicidal ideation and remote history of suicide attempt. Suicidal ideation as a non-serious adverse event appeared to be increased by suvorexant, mainly in patients with underlying history or risk factors for such events, such as for this patient.

Dr. Illoh's review identified spontaneous abortion in 3 patients during post-treatment follow-up, out of a total of 5 pregnancies. His review notes, however, that in one of these cases the subject had taken misoprostol to terminate the pregnancy. Of the two others, one was a 19 year old who took suvorexant for 18 days had a spontaneous abortion at estimated 32 days of gestation, and the other was a 25 year old who took suvorexant for 54 days and had a spontaneous abortion on day 97, at estimated 10 weeks of gestation. His review states that the abortions pose some concern because all three occurred in subjects treated with suvorexant, and that this may be an issue for surveillance.

CDTL: My review examined nonclinical findings, which did not reveal teratogenicity, and which showed that developmental toxicity was limited to decrease in fetal body weight in rats, with no evidence of developmental toxicity in rabbits. The primary non-clinical review indicated that maternal exposure at the no-effect dose in rats and rabbits was 16-times and 25-times the clinical exposure at the maximum recommended human dose chosen by the sponsor, 40 mg. Given the lack of a signal for pregnancy risk from nonclinical studies, and rate of occurrence of spontaneous abortion that was not distinguishable from the background population rate, my review concludes there isn't meaningful evidence of pregnancy risk from suvorexant.

Adverse Events Leading to Discontinuation

The percent of patients that discontinued due to an adverse event during phase 3 controlled trials is shown in Table 14.

Table 14: Incidence of Discontinuation, Phase 3 studies

	Placebo	LD	HD
0-3 Months	4.7%	3.2%	5.4%
0-12 Months	6.0%	NA	7.8%

The largest causes of discontinuations that occurred in a dose-dependent manner for suvorexant are shown in Table 15, with the top four (somnolence, fatigue, sedation, lethargy) representing likely overlapping concepts reflecting the primary CNS/wakefulness-depressant effect of suvorexant.

Table 15: Adverse Events Leading to Withdrawal, 0-3 months

Adverse Event	Pbo (N)	LD (N)	HD (N)

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N	1025 %	493 %	1291 %
Somnolence	0.3 (3)	0.2 (1)	1.7 (22)
Fatigue	0	0.2 (1)	0.7 (9)
Sedation	0	0	0.2 (3)
Lethargy	0	0	0.2 (3)
Nightmare	0	0.2 (1)	0.2 (2)
Sleep Paralysis	0	0	0.2 (2)
Memory Impairment	0	0	0.2 (3)
Depression	0.1 (1)	0	0.2 (2)

Dr. Illoh's review comments that the incidence of discontinuation because of adverse events was generally highest with suvorexant high dose compared to low dose and placebo, but the differences between treatment groups were small.

CDTL: My review found that two patients on suvorexant withdrew due to depression vs. 1 on placebo, but as discussed directly below (under *Other causes of Discontinuation*), an additional patient would seemingly have been more appropriately categorized as discontinuing due to suicidal ideation. Thus, discontinuations appear to support the concern that suvorexant increases the risk of suicidal ideation.

While somnolence was the most common adverse event leading to discontinuation, it is notable that the incidence of *withdrawal* for somnolence, 1.7% for high dose and 0.2% for low dose, was much less than the overall incidence of the event of somnolence in treated patients, 11% and 7%, respectively. Somnolence may increase the risk of more serious adverse events, like motor vehicle accidents, and it is concerning that most patients with somnolence continued the drug.

Other causes of discontinuation

Dr Illoh's review found that more subjects withdrew from the placebo group compared to suvorexant groups, and that more subjects withdrew from the placebo group because of lack of efficacy. His review states that the difference in discontinuations is unlikely to inflate suvorexant treatment effect.

CDTL: Roughly 8% of patients discontinued for reasons other than adverse events. Suvorexant dose-related patterns were observed for withdrawal due to 'physician decision' and 'protocol violation'. The sponsor seems to suggest that 'physician decision' might have been used for some cases when 'non-compliance' was potentially appropriate, noting that to be discontinued for non-compliance required a discussion between the investigator and the sponsor.

My search of patients with narrative information available that experienced adverse events during the study revealed one patient on high dose suvorexant (AN 02671) who reported "wish to be dead" at the end of month 3, and was then categorized as leaving the study for

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unknown reasons. Suicidal ideation would seemingly have been a more appropriate reason for discontinuation for this patient.

There was also a patient with moderate neutropenia who was lost to follow-up, with no additional testing. In addition, a 34 year old male with elevated ALT was lost to follow-up, with no additional testing. As noted below under *laboratory evaluations*, there is a potential signal for decreased neutrophil count for suvorexant, with follow-up testing not available for about half of the affected patients. Increased vigilance for neutropenia appears warranted.

Common Adverse Events

Common adverse events in the phase 3 trials are shown in Table 16 and Table 17, and common adverse events for the phase 2 trail (006) are shown in Table 18. While headache was slightly more common in drug- versus placebo arms, the most common drug related adverse effects appear to be somnolence and fatigue, likely related to the primary pharmacodynamic effect of suvorexant.

Table 16: Common Adverse Events, 3-Month Controlled Trial Data

Adverse Event	Pbo (N=1025)	LD (N=493)	HD (N=1291)
Somnolence	3%	7%	11%
Headache	6%	7%	7%
Fatigue	2%	2%	4%
Dry Mouth	1%	2%	3%
Abnormal Dream	1%	2%	2%
URI	1%	2%	2%

Table 17: Common Adverse Events, 12 Month Controlled Trial Data

Adverse Event	Pbo (N=1025)	HD (N=1291)
Somnolence	3%	12%
Headache	7%	8%
Fatigue	2%	5%
Abnormal Dreams	1%	3%
Nightmares	1%	2%
Nausea	2%	3%
Dry Mouth	2%	3%
URI	2%	3%

Table 18: Common Adverse Events, Phase 2 Dose-Finding Study 006

Adverse event	Pbo	10 mg	20 mg	40 mg	80 mg
	N=249	N=62	N=61	N=59	N=61

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Somnolence	0.4%	2%	5%	10%	12%
Abnormal Dreams	1%	2%	0	0	5%
Headache	2%	0	2%	5%	5%
Dizziness	0	0	2%	0	5%

Somnolence was more common in women, and more common in adults (versus elderly), as shown in Table 19

Table 19: Somnolence by age and gender

	Placebo (N=1025)	**Low Dose (N=493)**	**High Dose (N=1291)**
Somnolence by age >=65 y <65 y	 3% 3%	 5% 8%	 9% 13%
Somnolence by sex F M	 2% 4%	 9% 3%	 11% 10%

Somnolence was *not* more common in overweight and obese subjects (Table 20).

Table 20: Somnolence by BMI Category

Variable Category	**Placebo**	**Suvorexant LD**	**Suvorexant HD**
Somnolence in Non-Obese Subjects (BMI <25)	2.2% (10/449)	7.4% (18/243)	11.0% (56/509)
Somnolence in Over-weight Subjects (BMI 25-30)	3.0% (12/405)	7.2% (14/194)	8.9% (49/548)
Somnolence in Obese Subjects (BMI >30)	5.3% (9/170)	1.8% (1/56)	13.4% (31/232)

Dr Illoh's review presents both overall common adverse events and Merck's analysis of adverse events related to drug. His review states that the procedures used to determine and analyze the drug-relatedness of adverse events appear appropriate.

CDTL: The most common adverse event, somnolence, was strongly dose-related, with an incidence decreasing by roughly half between 40 mg and 20 mg, and again by half between 20 mg and 10 mg (study 006).

Somnolence appeared to be more common in women, although this was more striking for low dose vs. high dose. Potentially, increased somnolence in women could be related to higher exposure in women, as discussed in Section 5.

Elderly patients experienced less somnolence than adult patients, however, they received a lower dose (30 mg vs. 40 for high dose, and 15 vs. 20 for low dose). Of note, though, the incidence of somnolence was about the same in elderly patients at the high dose (30 mg) as in adult patients at the low dose (20 mg), suggesting that, at least based on adverse events reporting, elderly patients do *not* have increased pharmacodynamic sensitivity to somnolence from suvorexant (this conclusion is supported by objective findings in the driving study discussed below). Exposure to suvorexant is not higher in elderly vs. adult (see Section 5) and in combined with no evidence of increased pharmacodynamic sensitivity, there appears to be no reason to recommend lower doses of suvorexant in the elderly.

Increased incidence of nightmares and abnormal dreams is associated with narcolepsy, and could be related to the anti-orexin effect of suvorexant. Suvorexant also caused hypnagogic/hypnopompic hallucinations, and it isn't clear if hallucinations around the time of sleep/wake transition could have been recorded as nightmares and abnormal dreams instead of as hallucinations.

Dr. Illoh's review lists drug-related adverse events as reported by Merck. It is not clear from the review the degree to which independent analysis of this data was conducted. The Clinical Review Manuel of Policy and Procedures (MaPP) notes that the analyses of drug-related adverse events presented by applicants are usually based on assessments made by investigators at the time of an event, are highly dependent on information about the side effect profile of the drug available at the time of the clinical trial (e.g., what is in the investigator's brochure), and are not informed by awareness of the entire safety database. The MaPP further states that generally, these analyses are not expected to provide much useful information in assessing causality and should be disregarded.

Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS) was defined for the investigators determining if the event occurred as chronic or persistent sleepiness during the day, possibly starting as sudden involuntary sleep episodes occurring throughout the day or over multiple consecutive days, with the sleepiness often associated with impairment in daytime function. The sponsor explained that EDS was intended to capture patients whose somnolence was beyond what would be expected from residual drug effect.

The incidence of EDS was dose related, occurring in 1.1% of high dose, 0.6% of low dose, and 0.2% of placebo patients.

Dr. Illoh's review states that apart from severity of EDS, there was considerable overlap in other characteristics of the EDS among the treated groups, noting that in the placebo group was reported one case each of mild and moderate EDS. Narrative descriptions of the events were not presented

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except for one patient, AN02642, a 59 year old male who experienced the following: daytime sleepiness episodes occurred variously at work. One episode occurred at a traffic stop; another episode of microsleep, which was witnessed by his wife, occurred while he was driving. The EDS resolved after he discontinued the trial medication

CDTL: The sponsor provided narratives of all the patients who investigators concluded had experienced EDS. My review found that about a third of all patients with EDS taking the high dose expressed that severe sleepiness occurred while driving, sometimes suddenly, with one patient reporting the need to pull over and rest while driving. Descriptions of the EDS and driving risk include the following:

- **AN 07433 was a 61-year-old male assigned to suvorexant HD who reported severe excessive daytime sleepiness (EDS) on Study Day 2 (P028). He experienced severe excessive daytime sleepiness with variation in intensity over the next 30 days. The patient explained he once had difficulties staying awake while driving his car. This AE resolved on Study Day 31, two days after discontinuation of study medication.**
- **AN 02615 was a 60-year old male assigned to suvorexant HD who reported moderate excessive daytime sleepiness (EDS) on Study Day 1 (P009). The event began approximately 15 hours after taking study medication, occurring after lunch at approximately 1 PM and lasting until bedtime. Otherwise, the patient reported a delay in initiating sleep, less awakening during the night and ultimately feeling alert and oriented in the mornings. The patient's daytime circumstances varied, but usually included driving, working or socializing at home. He reported a need to pull over to rest while driving, or to stop daily activities.**

There is also concern that EDS from the low dose puts patients at risk of harm from accidents. For example a 69 year old woman (AN 11697) taking suvorexant 15 mg reported that by study day 52 she had begun taking naps for 2-3 hours due to the sleepiness, and was worried about the sleepiness because it interfered with her daily activities and she "thought she could suffer an accident."

The narratives of EDS for placebo patients suggest that the event was far less severe compared to drug-treated patients, in particular *not* involving situations like driving or severity suggestive of increased risk from accidents. One of the three cases (AN 074440) was reported as moderate EDS, but contained no description of the event. Another case reported as mild was described as 'feeling irritable, cranky, and tired' (AN 02670). The third case, an 87 year old women (AN 04294), reported that she felt weak and had started needing naps daily.

My review found that patients with EDS did *not* discontinue medication at the onset of symptoms, but instead continued treatment for many days, and sometimes weeks or even months, while continuing daily activities like driving. There was evidence of prolonged duration of EDS in patients that continued suvorexant despite this AE; for example, a 65-year old man (AN 04579) reported feeling uncomfortable with driving because of EDS that started on day 65, and continued until suvorexant was discontinued on day 163.

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EDS symptoms could take several days to resolve, raising additional concern that even if drug is stopped for somnolence, patients may remain at risk of impaired driving for several days; this appears to be consistent with suvorexant's long half-life.

EDS was determined by the investigator based on seemingly difficult to define judgments about patient condition including 'beyond what would be expected from residual drug effect.' The case reports suggest that the effort the investigator took to understand the patient's symptoms was a key factor in the events being detected. For example, the level of detail about the symptoms of the 59 year old male described above occurred when "a very careful history including cataplexy aspect was undertaken" after the patient told the investigator that he kept falling asleep while driving. Thus, there is substantial concern that patients with similarly severe symptoms remained undiagnosed for EDS, perhaps including patients with 'severe somnolence' or patients that discontinued due to fatigue. Severe somnolence occurred in 0.6% of high dose patients, 0.2% of low dose patients, and 0.1% of placebo patients. Fatigue leading to discontinuation occurred in 0.7% of high dose, 0.2% of low dose, and 0% of placebo patients.

Cataplexy

The sponsor reports that expert adjudication identified no patients with cataplexy out of 45 that were submitted for review. The sponsor specifically noted that experts had concluded that patient AN02642, a 59 year old man who experienced weak knees when laughing, and who also had EDS, did not experience cataplexy. The narrative describes the events as follows:

> "The event occurred when the patient was at work and fully awake. It resulted when the patient was laughing with his coworkers, and the event was described as a feeling of being weak in the knees. Throughout the episode, the patient could hear and see, and at no time was there a loss of consciousness. He did not stumble or need to grab onto objects to retain his posture, and did not have to sit down to avoid falling down. The patient reported that he continued to feel weak until 19:00 that night. He stated that 1 to 1 ½ weeks after resuming study medication (interrupted due to amylase elevation), he had a total of three episodes of leg weakness, as well as increased tiredness. All episodes of leg weakness occurred in the morning when laughing with coworkers and while on blinded study medication. He described them as a feeling of being weak in the knees and lasting for only a "split second". The patient reported that it was his "whole leg, thigh and calf"."

The sponsor states that the other 44 cases submitted for adjudication of cataplexy were falls that were concluded to be due to tripping or other clear outside physical forces.

Dr. Illoh's review states that there were no 'confirmed' cases of cataplexy. The review states that to be considered a cataplexy event the event had to be preceded by an emotional trigger. In another section the review states 'the absence of cataplexy in the development programs does not necessarily exclude the risk of drug-induced narcolepsy from exposure to ORAs [orexin receptor antagonists]. Although, the external adjudication committee concluded that the muscle weakness event summarized above [the 59 year old man described above] was not cataplexy, features of the

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event present concerns for a narcoleptic process that may be associated with trial treatment.' (bracketed statements inserted for clarification).

CDTL: Dr. Illoh's review identified and discussed AN02642 described above, and also identified and discussed cases of fall, concluding that none of the falls suggested cataplexy. I agree that the falls in the suvorexant studies were not suspicious for cataplexy-like events. However, after review of the episodes of leg weakness in patient AN02642 described above I conclude that the episode was clearly cataplexy-like, as brief leg weakness occurring when laughing is classic for cataplexy in narcoleptics, and in this patient the event occurred in the background of EDS that was also narcolepsy-like in severity. The report for this patient of a feeling of weakness that lasted most of the day appears to be clearly different from the brief (5 seconds to 30 seconds) leg weakness when laughing, and may reflect the patient's somnolence and tiredness, which was a separate adverse event that occurred for many hours during the day.

Additional patients found by my review had symptoms that resemble cataplexy:

- **A 60 year old women (AN 06058) taking 40 mg suvorexant experienced a feeling of weakness in both knees of moderate intensity and 1 minute in duration, about 3 hours after taking study drug, when she was taking her husband to the hospital at 2 AM.**
- **A 24 year old man (AN 00857) taking 80 mg suvorexant reported 'attack of muscle weakness, right knee', of mild intensity, experienced 2 to 3 times a week in the middle of the night upon standing when the patient would awaken and get out of bed. The patient also experienced sleep paralysis about once a week.**
- **A 60 year old women (AN 12108) taking 30 mg suvorexant experienced 2 brief episodes of 'weakness of her right leg, a sensation that her leg was giving out' while walking alone, that lasted between 5 and 30 seconds (as reported on Modified Cataplexy Questionnaire).**

The sponsor appears to assert that these cases do not represent cataplexy because they were not triggered by emotion; however, cataplexy is well-documented as occurring without a clear trigger. The sponsor asserts that the 60 year old woman did not experience any emotional stimulus prior to the event, but this seems unclear, as going to the hospital in the middle of the night was presumably due to an event capable of triggering strong emotions. Also, cataplexy can be triggered by physical exertion, which need not be intense or unexpected. With regard to the 60 year old women with leg weakness while walking, cataplexy occurring during walking in the presence of no other triggers is well-documented.

In the phase 1 studies suvorexant was dosed in the morning, and events considered sleep paralysis by the sponsor might have been cataplexy, as it is not clear that patients were asleep near the time of the events:

- **A 67 year old man (AN 0001) was unable to raise his arms or speak 50 minutes following a dose of 40 mg suvorexant. The subject was reported to be awake but somnolent. The episode lasted about 2 minutes.**
- **A 65 year old man (AN 0008) reported going into a "trance-like, helpless state" after a staff member knocked on the door for vital sign collection. The subject was**

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noted to have slurred speech following the event. The subject appeared to be asleep, but was aware of his surroundings, was unable to mover or talk, and was shaking. The episode lasted about 1 minute.

Particularly for the second subject above, being startled by the knock on the door might have been a trigger for cataplexy.

None of the possible cases of cataplexy appear to have resulted in a fall or other injury, which provides some reassurance of safety. However, it seems reasonable to be concerned that in actual clinical use more severe cataplexy-like events might occur, with more serious consequences, particularly since suvorexant will be taken by patients with more concomitant disease and medication use.

Dr Illoh's review states that there were no 'confirmed' cases of cataplexy, but the review does not define the meaning of the term 'confirmed' adequately, other than to suggest it meant confirmed by the sponsor's adjudication committee. The meaning is also not clear of the review's conclusion about cataplexy that 'features of the event present concerns for a narcoleptic process that may be associated with trial treatment,' particularly since the review makes other statements like 'there was no confirmed case of narcolepsy'. The review notes that the sponsor used terms like 'narcolepsy-like' events and 'cataplexy-like' events in pre-specifying events of clinical interest, but the review does not make clear what, if any, relationship there might be in the review's use of 'confirmed' vs '-like' in reference to events of clinical interest.

Hypnagogic/hypnopompic hallucinations and sleep paralysis

In the 3-month phase 3 population, 3 high dose (0.4%) and 2 low dose (0.2%) suvorexant patients experienced hypnogogic or hypnopompic hallucinations, versus no placebo patients (N = 1,025 placebo patients). Two additional high dose patients in study 009 experienced this adverse event. A similar incidence was observed in phase 1 studies with morning dosing. The hallucinations were frightening to patients, involving sensations like another person was in bed with the patient, or intended to harm them.

In the 3-month phase 3 population, sleep paralysis occurred in 1 low dose (0.2%) and 4 high dose patients (0.3%), and no placebo patients (N = 1,025 placebo patients). One additional high dose patient experienced sleep paralysis in study 0009. Two additional cases occurred in phase 2 studies, one after 40 mg and the other after 80 mg suvorexant.

The sponsor reports that in phase 1 studies, sleep paralysis occurred in 2% of suvorexant patients, 6 at the 40 mg dose, and the remainder at doses of from 80 to 240 mg, versus in 1 subject treated with placebo.

Dr. Illoh's review notes that the incidence of hallucinations in this program was small, and published literature cited by the sponsor indicates prevalence of hypnagogic and hypnopompic hallucinations can be as high as 12.5% in the general population. The review concludes that the small numbers of cases in this program make it difficult to determine the relationship of hallucinations with suvorexant, while seeming to note that the events might be dose-related.

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CDTL: Hypnogogic/hypnopompic hallucinations appear clearly to be a dose-related risk of suvorexant, and might roughly be estimated to increase 10-fold between the lowest and highest doses tested.

The events do not put patients at risk of *physical* harm, but nonetheless can be psychologically traumatic; for example some patients with idiopathic narcolepsy report increased anxiety about sleep because of the fear of such hallucinations. Anxiety surrounding sleep is a key problem for many patients with insomnia, and concern seems appropriate that experiencing this type of hallucination may have the potential to worsen this anxiety and the overall insomnia condition.

Suicidal Ideation (as non-serious adverse event)
In the 3-month controlled trial experience, adverse events of suicidal ideation and/or behavior occurred in 0.1% of placebo patients (1 patient), 0.2% of low dose patients (1 patients), and 0.4% of high dose patients (5 patients). In the 12-month high dose experience, one additional suvorexant patient had an adverse even of suicidal ideation.

There was one event of suicidal ideation in phase 1 trials, 4 days after the final dose of study medication (40 mg suvorexant + 20 mg paroxetine).

Suicidal ideation was also prospectively assessed at each visit in the phase 2b/3 trials with the Columbia Suicidality Severity Rating Scale (C-SSRS), with results then mapped to the Columbia Classification Algorithm for Suicide Assessment (C-CASA). This prospective assessment identified an additional 4 patients treated with high dose suvorexant that had suicidal ideation not considered to investigators to constitute an adverse event.

CDTL: Increased risk of suicidal ideation appears to be a dose-related risk of suvorexant.

Motor Vehicle Accidents (MVAs)
The incidence of motor vehicle accidents was as follows: 1.2% for low dose vs. 1.3% for matched placebo, and 1.5% for high dose, and 1.4% for matched placebo. In addition, 2.7% of suvorexant high dose patients vs. 2.0% of placebo patients received citations for moving violations.

Dr. Illoh's review concluded that the trend may suggest a suvorexant dose effect on occurrence of MVAs, in contrast to the sponsor's position that the incidence of accidents and citations were generally comparable between treatment arms. Dr. Illoh's review suggested that cautionary language that patients avoid driving until fully awake seemed appropriate.

CDTL: My review found that study patients were not 'at fault' for most of the MVA's in the database, and that no events of the type more clearly associated with falling asleep while driving, like single-car accidents, was recorded in any study arm. The database thus appears not to be large enough to capture events of most interest, or to exclude even large adverse effects of suvorexant on such events. That said, the higher incidence of driving events that

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was observed in suvorexant patients would only serve to increase concern about this safety risk.

Unconscious nighttime activity
There were two cases of unconscious nighttime activity.

- A 65 year old man taking 30 mg suvorexant on a PSG night first talked in his sleep, then later in the night lunged out of bed and hit his head and face against a wall. The patient also experienced sleep walking 2 weeks after stopping suvorexant. The patient had a history of sleep talking, but not of sleep walking.
- A 58 year old women taking 40 mg suvorexant experienced sleep paralysis and hypnagogic hallucination, and several hours later found herself standing at the window without knowing how she got there.

CDTL: The first case above may resemble REM sleep behavior disorder (RBD), which is characterized by intense motor or verbal paroxysmal dream-enacting episodes, thought to be due to individuals acting out dreams. RBD occurs at increased frequency in narcolepsy and other sleep disorders, and can result in serious injury to the patient and to others.

The unconscious activity of the 58 year old woman is a concern largely because any potentially dangerous activity that occurred remains unknown.

While sleepwalking is reported to occur in up to 15% of the normal population, patients that had a history of sleepwalking or any other parasomnia were specifically excluded from suvorexant studies, increasing concern that the above events were drug-related.

Laboratory evaluations
Dr Illoh's review notes that in study 006, suvorexant increased serum cholesterol levels in a dose-related manner with the maximum mean increase of 6.0 mg/dL at a suvorexant dose of 80 mg, versus 3.7 mg/dL decrease in placebo (table below). Cholesterol was apparently not measured in phase 3 studies.

	placebo	10 mg	20 mg	40 mg	80 mg
cholesterol	-3.7	1.2	2.3	3.1	6

Dr. Illoh's review suggested that including this effect in labeling would be appropriate, as this magnitude of effect might be clinically meaningful.

CDTL: My review found that orexins are thought to be involved in the modulation of feeding behavior and energy balance, including through interaction with other hormone systems. Patients with narcolepsy have been reported to have BMI-independent metabolic alterations including increased cholesterol. Narcolepsy due to orexin deficiency is also associated with obesity and a high prevalence of metabolic syndrome and type 2 diabetes.

However, the effect of suvorexant on cholesterol was strongly dose-related, and if only the lower doses are approved, it is not clear that increased monitoring of cholesterol would be necessary, particular as patients at greatest risk of clinically meaningful harm would

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seemingly be patients with established abnormalities, and these patients would already be undergoing periodic monitoring unrelated to suvorexant.

My additional review of other laboratory values identified that reductions in absolute neutrophil count to less than 37% of normal occurred in 1.0% (N = 5) of LD patients, 0.5% (N = 6) of HD patients, and 0.1% (N = 1) of placebo patients. Three patients had pre-existing mild or moderate neutropenia. In 5 of the 11 suvorexant patients, return to baseline neutrophil count was *not* documented, with 1 patient with moderate neutropenia lost to follow-up, and the low neutrophil count occurring in 3 patients at the last study visit, without further follow-up. The lowest neutrophil count was 0.2 x 10^3 cells/microliter. The sponsor noted that low neutrophil count occurred sporadically over the course of treatment, without apparent worsening, and that no adverse events associated with infection occurred in these patients. In the context of the multiple comparisons made for safety, whether decreased neutrophil count was due to drug or chance can't be clearly determined. Increased vigilance for this adverse effect appears warranted.

Studies in specific populations

Suvorexant was studied in patients with chronic obstructive pulmonary disease (COPD)(study P032), and obstructive sleep apnea (OSA)(study P036). In OSA, the mean apnea/hypopnea index (AHI) increased by 2.7 after 4 days of treatment. In COPD, oxygen saturation and AHI did not change significantly.

CDTL: AHI values in OSA are typically categorized as 5-15/yr = mild, 15-30/hr = moderate, and >30/hr = severe. The sponsor aimed to exclude a change of 5 on the AHI with 90% confidence, but this difference was not excluded. The mean change observed was still small, (+2.7), and some patients might experience larger, more meaningful worsening of OSA. This should be indicated in labeling, along with recommendation for re-evaluation of OSA severity and treatment efficacy in OSA patients using suvorexant. While the COPD study did not reveal significant change, similar advice appears reasonable for patients with COPD.

Test of daytime function

Laboratory-based tests of daytime function

In one of four phase 1 studies in which next-day memory and balance were evaluated after single-dose of 40 mg suvorexant, there was a statistically significant decrease in word recall, and a statistically significant increase in body sway following single dose of 20 or 40 mg suvorexant.

Pyschomotor performance measured by digit symbol substitution test (DSST) showed no clear change from suvorexant.

CDTL: The effect of suvorexant on body sway was inconsistently observed, and appears to be small. An increased incidence of falls was not observed for suvorexant vs. placebo, suggesting that the possible effect is not likely to be clinically meaningful. The possible effect on memory also appears to be small and of uncertain clinical meaningfulness. However,

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these types of laboratory tests are thought to have little sensitivity for impairment caused by sleepiness because over the brief period of time in which these tests are conducted (only a minute or two for the DSST) patients can maintain their performance even if, for example, somnolent from residual drug effect.

On-the-road driving study
The sponsor conducted two similar on-the-road driving studies of the effect of suvorexant, study 039 in 24 healthy elderly subjects >65 years old, and study 035 in 28 healthy adults age 21 to 64 years. Tested suvorexant doses were 15 mg and 30 mg in elderly subjects, and 20 and 40 mg in adult subjects. A one-hour duration drive was conducted in the morning about 9 hours after dosing.

The primary outcome measure was Standard Deviation of Lateral Position (SDLP), a measure of the ability of the driver to maintain a constant position of the car in the driving lane. The positive control was zopiclone 7.5 mg. Four women asked for the driving test to be stopped because they felt somnolent: on day 2, two after a dose of 40 mg, and one after a dose of 20 mg, and on day 9, one after a dose of 20 mg.

Table 21 and Table 22 show results of the driving studies analyzed by a symmetry analysis that compared the proportion of patients that worsened by a threshold of 2.4 cm compared to placebo (the level of impairment generally taken to represent that of 0.05% blood ethanol) to the proportion that improved by that amount.

Table 21: Symmetry Analysis of Change in SDLP, Adult Driving Study

Day 2	Zopiclone	20 mg	40 mg
# + subjects	14	6	10
# - subjects	1	0	2
Reject Null	Yes	Yes	Yes
Day 9			
# + subjects	8	2	6
# - subjects	0	1	0
Reject Null	Yes	No	Yes

Table 22: Symmetry Analysis of Change in SDLP, Elderly Driving Study

Day 2	Zopiclone	15 mg	30 mg
# + subjects	8	0	3
# - subjects	0	3	1
Reject Null	Yes	No	No
Day 9			
# + subjects	6	0	5
# - subjects	1	0	1
Reject Null	Yes	No	No

The sponsor analyzed mean SDLP as the primary endpoint in both studies. Dr Illoh's review states that another key pharmacodynamic assessment was symmetry analysis of SDLP. His review reports that based on the primary hypothesis results for both the adult and elderly driving study suggest a lack of next-day residual effect of either high or low-dose suvorexant. His review notes that the symmetry analysis was positive for 40 mg in adults on day 2 and 9, and for 20 mg on day 2, and that there was a lean towards positive findings on the symmetry analysis in the elderly study for 30 mg on days 2 and 9. His review concludes that assessing the driving study results beyond the primary hypothesis (mean SDLP) is problematic because of the sheer number of comparisons and the small sample sized, but that the symmetry analysis provides a suggestion of driving impairment, though without statistical significance.

CDTL: The Division's approach to this type of driving study has been that evaluating mean SDLP impairment in a test population is not sensitive to clinically important impairment in individuals, such that the Division considers the symmetry analysis to be more appropriate than the mean analysis.

Figure 6 and

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Figure 7 **show the distribution of change in SDLP for the adult and elderly studies, respectively; multiple subjects experienced increase in SDLP greater than 5 cm, or more than double the cutoff generally considered to be clinically meaningful.**

Figure 6: Adult Driving Study Results

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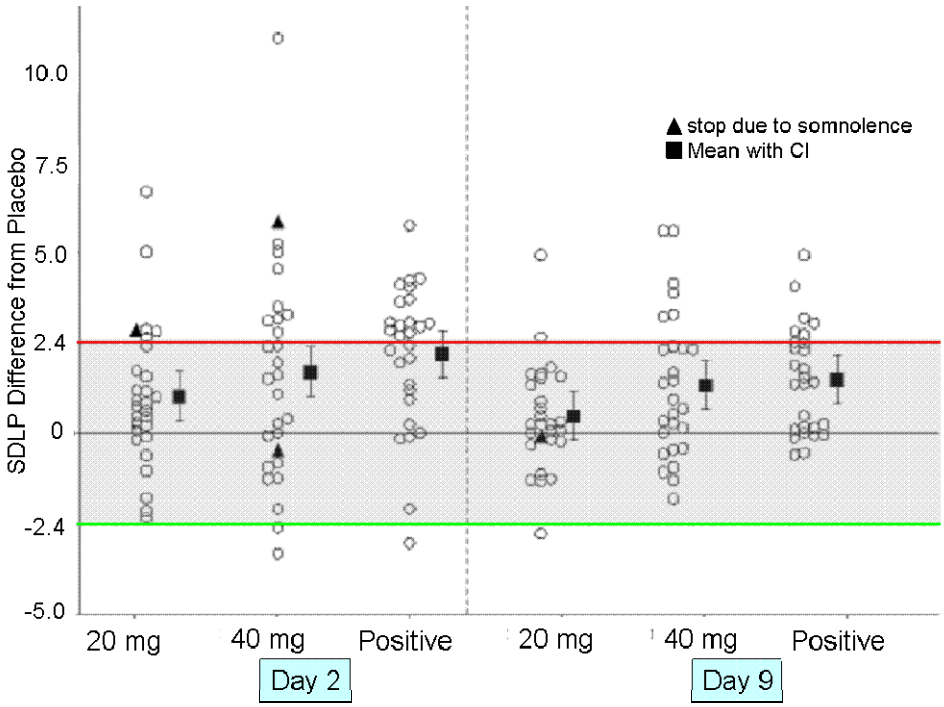


Figure 7: Eldery Driving Study Results

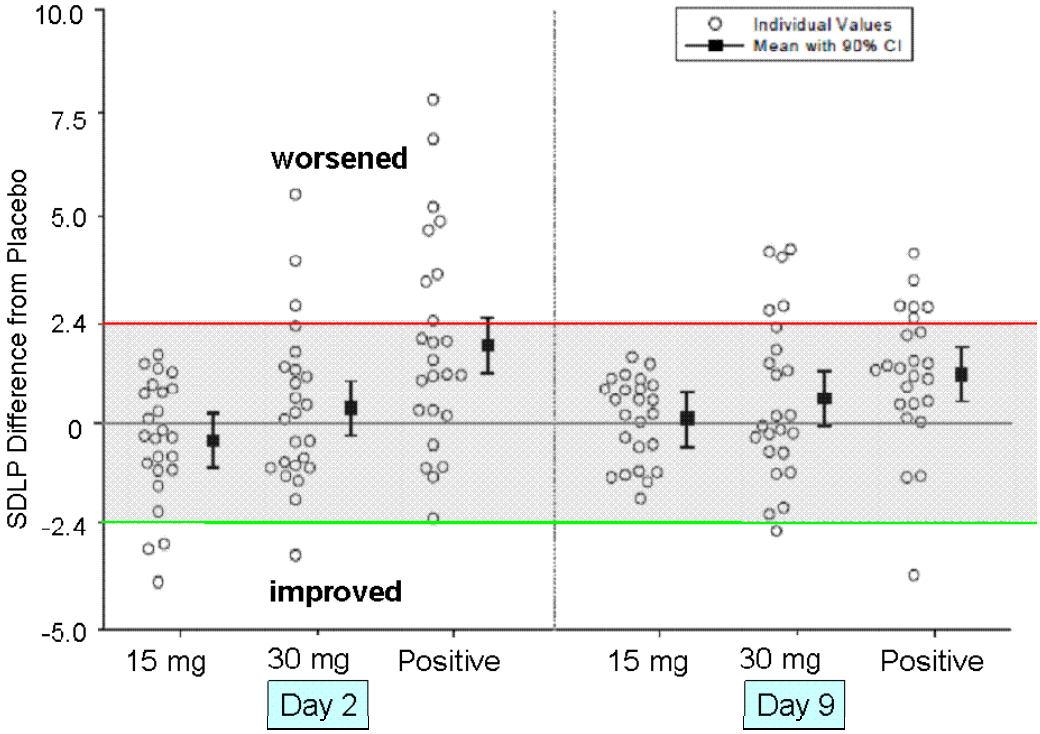
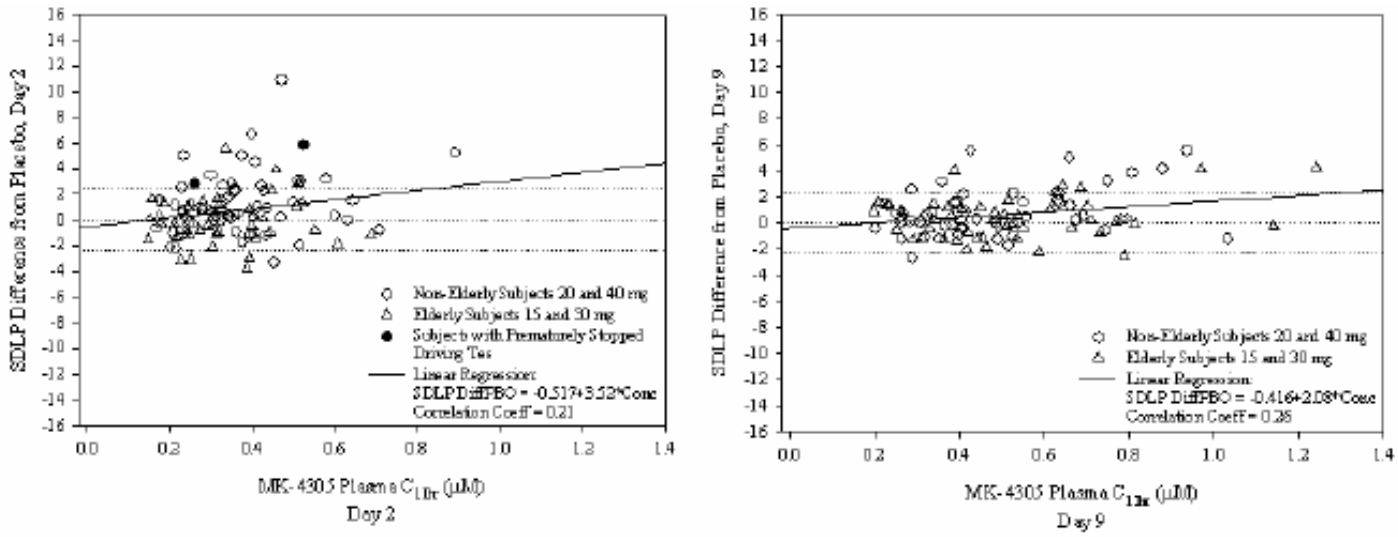


Figure 8 shows the relationship between morning suvorexant levels and change in SDLP, combining results for adult and elderly studies. There is a positive correlation between suvorexant blood level and SDLP impairment, but little indication of a clear cut-off blood level below which impairment does not occur.

Figure 8: Suvorexant Plasma Level vs. SDLP Change



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The driving study in adults was positive for clinically meaningful impairment by the symmetry analysis[2] on day 2 for both 20 mg and 40 mg suvorexant, and on day 9 for 40 mg suvorexant. When results were positive, about 20% to 30% of individual subjects had impairment over the 2.4 cm cutoff, with some subjects worsening by 5 cm or more. To put the 5 cm change in perspective, a blood alcohol level of 0.08, the *per se* limit in the United States, is considered to increase SDLP by about 4 cm.

The driving study in elderly was *not* positive by the symmetry analysis for either dose at either day, but for the 30 mg dose, there were more subjects above (impaired) than below (improved) the SDLP threshold at both day 2 (3 above, 1 below) and day 9 (5 above, 1 below). In the context of the positive studies in adults, and the small sample size typical of this type of driving study (N = 24) this suggest that clinically meaningful impairment may have been present in a proportion of patients, but that the study was not adequately powered to detect this effect. Of note, some elderly patients worsened by about 4 or 5 cm, raising concern that perhaps 5% of elderly patients could still be considered legally impaired when driving after the 30 mg dose of suvorexant, even though the study was not powered to detect this.

Notably, after the 15 mg dose in elderly *no* subjects exceeded the 2.4 cm SDLP cutoff. This is reassuring of safety of the 15 mg dose in elderly, but it is not clear that a 15 mg dose in adults would also find no evidence of impairment, as there is some evidence that elderly patients are less sensitive than younger adults to the next-day impairing effects of suvorexant. Subjectively, elderly subjects had a similar incidence of somnolence from the 30 mg dose as adults had from the 20 mg dose. Objectively, in these driving studies the impairment after 30 mg in elderly was roughly similar to the impairment after 20 mg in adults. Of perhaps greater concern for the safety of the 15 mg dose in adults, a positive correlation was observed between morning suvorexant blood level and SDLP impairment. On day 2, it appears that blood levels as low as 0.2 to 0.3 µM are associated with clinically meaningful impairment, while on day 9 levels beginning at about 0.3 to 0.4 µM appear to correlate with impairment. The 15 mg dose of suvorexant is, of course, only 25% lower than the 20 mg dose, and not unexpectedly blood levels in adults the morning after the 15 mg show considerable overlap with blood levels after the 20 mg dose. Based on this overlap of blood levels, there is concern that perhaps 10% of adults taking the 15 mg dose would be impaired the next day (compared to about 20% above the 2.4 cm threshold observed directly after the 20 mg dose). Suvorexant blood levels the morning after a *10 mg* dose averaged about 0.2 to 0.3 µM, and up to about 0.4 µM, in adult patients in study 006, raising concern that even after the 10 mg dose some adults might experience clinically meaningful driving impairment.

Importantly, sleepiness causes MVA's because it impairs the type of performance measured by SDLP, but also because it can lead to patients experiencing brief sleep episodes (microsleep) while driving. The adverse effect profile of suvorexant suggests the binary transition from wakefulness to sleep while driving, with subsequent *complete* loss of vehicle control, may very well be as large or a larger safety risk than the continuous decrement in

[2] The sponsor designated mean change in SDLP as the primary endpoint, but the symmetry analysis is discussed here because it is more sensitive to clinically important impairment in individual patients, the main concern of adverse event analysis.

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driving ability measured by SDLP. The risk of this type of risk from suvorexant remains largely unknown.

9. Advisory Committee Meeting

The suvorexant NDA was considered at a meeting of the Peripheral and Central Nervous System Advisory Committee on May 22, 2013, and had the following major recommendations:

- Most Committee members agreed that there was substantial evidence of efficacy for suvorexant at the doses studied, for both sleep onset (12 yes/4 no) and sleep maintenance (16 yes/0 no).
- Most Committee members agreed that doses of 15 mg and 20 mg were acceptably safe, by a vote of 15 yes/ 3 no.
- Most Committee members agreed that an additional study of 10 mg was not necessary to establish efficacy of that dose, by a vote of 11 'no', 5 'yes' and 1 abstention, but reasons for this recommendation differed. About 1/3rd of the members voted no because they thought existing evidence was adequate to support efficacy of the 10 mg dose, while about another 1/3rd voted yes because they thought inadequate evidence of efficacy had been presented, although several of these members expressed that with more study the 10 mg dose seemed likely to be found effective. The remaining 1/3rd generally expressed that the 10 mg dose was either not effective, or not of sufficient efficacy to merit further study.
- The Committee was of divided opinion about if safety was adequate for the 30 mg and 40 mg doses, with 7 voting 'yes', and 8 voting 'no'.

10. Pediatrics

The sponsor submitted (b) (4) to the suvorexant IND on July 26, 2011 (b) (4)

The Division responded (b) (4) on October 31, 2011 (b) (4)

CDTL: Based on expert opinion DNP had previously concluded that pediatric patients with insomnia co-morbid with ADHD constituted an appropriate population for studies of insomnia medications under PREA. Pediatric studies were conducted for Ambien (zolpidem) and for Lunesta (eszopiclone) in these patients, but both studies were negative for efficacy, and safety concerns were raised about CNS adverse effects, particularly hallucinations, which appeared to be both more frequent and more disturbing in children than adults.

Dr. Veneeta Tandon reviewed pediatric insomnia in the context of the PREA requirement for another insomnia drug (b) (4)

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(b) (4)

For the suvorexant application, the Division similarly concluded that an appropriate pediatric population had not been identified, and discussed this with PeRC on June 5, 2013. PeRC agreed that a full waiver of pediatric studies was appropriate because studies were impossible or highly impractical given lack of an appropriate identified pediatric population

11. Other Relevant Regulatory Issues

- Office of Scientific Investigations review conducted by Dr. Antoine El-Hage found no deviations likely to have affected the integrity of study conclusions.
- Comments from the Office of Medication Error Prevention and Risk Management review by Dr. Julie Neshiewat were sent to the sponsor regarding specific presentation of labels and labeling.
- Controlled Substance Staff (CSS) review by Dr Chad Reissig concluded that suvorexant produces reinforcing effects and has a potential for abuse. In the human abuse potential study, 'drug liking' of suvorexant was similar to that of zolpidem. In clinical trials, euphoria and other adverse events suggestive of abuse were observed infrequently. Suvorexant was not self-administered in Rhesus monkeys, but the predictive validity of this finding is uncertain. Suvorexant did not appear to produce physical dependence or withdrawal. Based on the above, CSS recommended scheduling suvorexant as a Schedule IV substance under the Controlled Substances Act.

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Complete response

- Risk Benefit Assessment

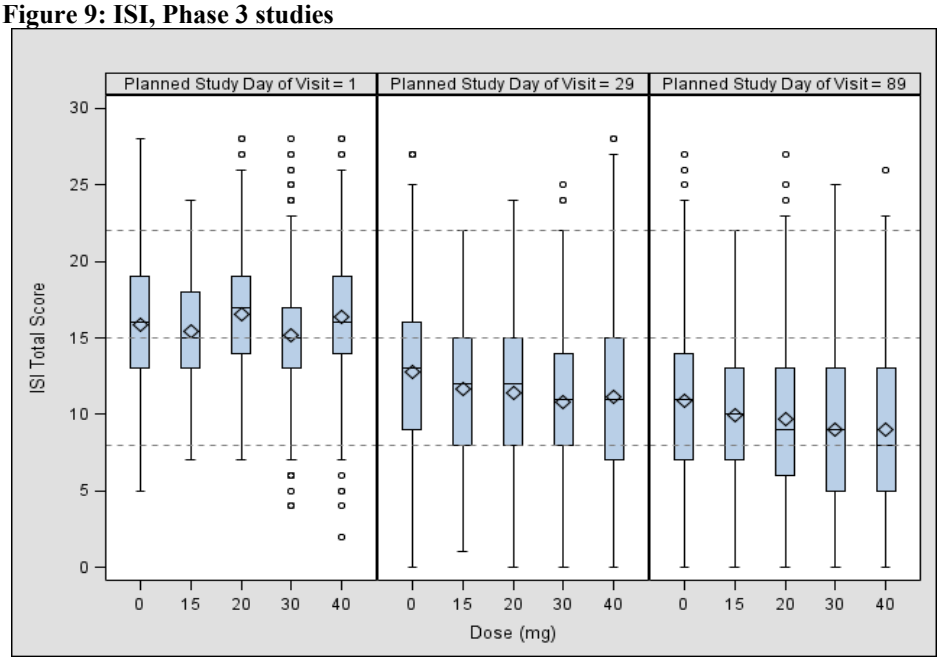
Efficacy

Suvorexant is associated with potentially serious dose-related adverse effects, and there appears to be little justification for patients to use a higher (and less safe) dose for insomnia than necessary to satisfactorily treat their symptoms. As discussed in Section 7, I conclude that there is both objective and subjective evidence from phase 3 trials for efficacy for doses

of 15 mg and greater. The 10 mg dose was only studied in a small phase 2 study with about 60 patients per arm (006). The study was positive for the primary endpoint of objective sleep maintenance, but was negative for subjective sleep endpoints. Importantly, however, the study was not powered for these endpoints. It might not be unreasonable to require the sponsor to conduct an additional efficacy studied adequately powered for subjective sleep endpoints for the 10 mg dose, but I conclude the objective endpoints, combined with an analysis of PK and PD variability as described in Section 7, provides enough evidence to recommend 10 mg as the initial dose, in the context of labeling that specifies that the dose for the individual patient can be increased necessary for efficacy.

In considering benefit from insomnia treatment, it seems relevant to consider that even in patients with the relatively severe insomnia enrolled in the suvorexant studies, insomnia signs and symptoms improved over a few weeks to months. Figure 9 shows that ISI for placebo at month 3 is at least as improved, or even more improved, than any suvorexant dose at month 1. Similarly, for subjective total sleep time, improvement at month 1.5 in study 028 in the placebo arm was about 30 minutes, essentially the same as improvement from low or high-dose suvorexant, and in study 029, LPS at month 3 was indistinguishable for placebo, low- and high-dose suvorexant.

Figure 9: ISI, Phase 3 studies



Subjective daytime function is a key measure of efficacy not captured by other endpoints, and is represented by the following question in the ISI: *to what extent do you consider your sleep problem to interfere with your daily functioning currently*? Figure 10 shows the data for adult patients in the phase 3 studies. Notably, while there was some evidence of a dose effect, the effect of time was much larger than the effect of drug, and there was little difference between the 20 mg and 40 mg doses, particularly for the more severely affected patients.

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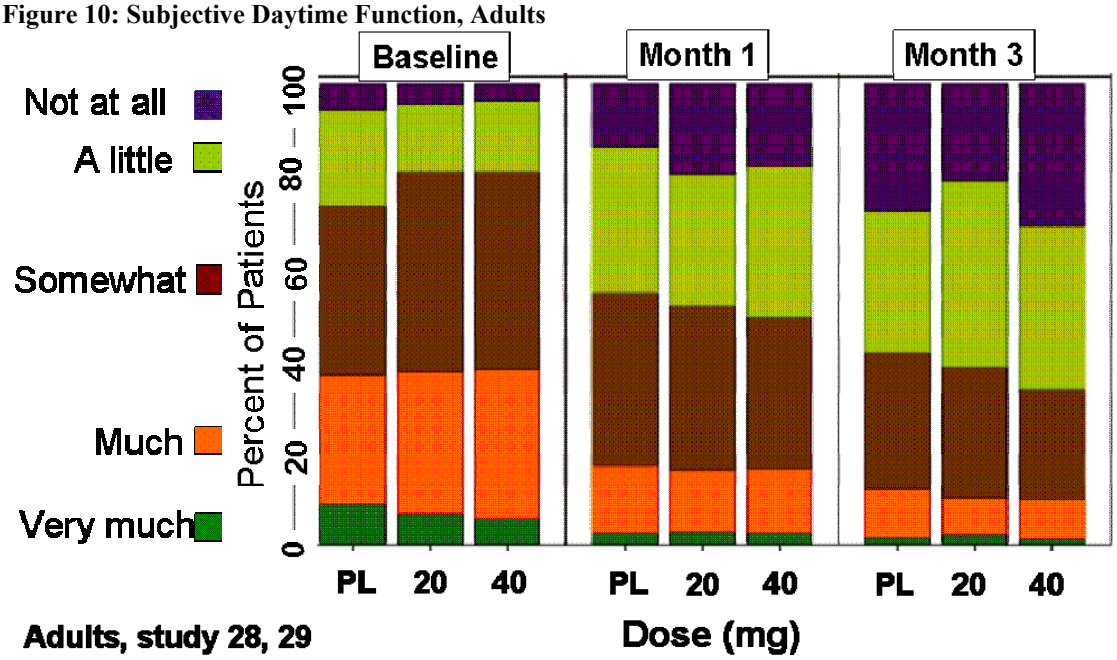
Figure 10: Subjective Daytime Function, Adults



Safety

Adverse effects of suvorexant were strongly dose-related, such that risk-benefit would improve by selecting the lowest dose that is effective for the patient. Key adverse effects included the following:

- **Daytime somnolence/Excessive daytime sleepiness; driving impairment**
- **Suicide risk**
- **Unconscious nighttime activity**
- **Narcolepsy-like events other than daytime somnolence: cataplexy, hypnagogic hallucinations, and sleep paralysis**

Daytime Somnolence/Excessive Daytime Sleepiness (EDS)

Somnolence and EDS were dose-related, and data from study 006 suggest that there is a large difference in risk between 10 mg and 20 mg; the incidence of somnolence was 0.4% for placebo, 1.6% for 10 mg suvorexant, and 4.9% for 20 mg suvorexant.

Daytime somnolence can lead to serious injury, most clearly through increased risk of MVA's. It has recently become clear that drivers can poorly predict their own driving impairment, and that labeling recommendations that patients should not drive until fully awake or otherwise free of impairment are not adequate of themselves to protect patients and the community[3]. A recommendation not to drive the day after use of a drug for insomnia might appear to address the risk, but may not be effective, as driving is an integral part of most patients lives.

[3] Verster JC and Roth T (2011) Drivers can poorly predict their own driving impairment: a comparison between measurements of subjective and objective driving quality. Psychopharmacology. 219(3):775-781.

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In the recently released FDA document *Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision Making: Draft PDUFA Implementation Plan*[4] the FDA proposes that it should consider in benefit-risk assessment how patients actually use a drug, including cognitive and behavioral factors affecting human judgment and decision-making. FDA concluding that a new insomnia drug is safe, yet recommending that patients using the drug not drive, seemingly presents a confusing message to patients that, in the context of actual use, would likely result in the warning often being ignored.

The Division *did* recently revise labeling of Ambien CR with warnings not to drive the day after use, and perhaps it could be argued that if driving risk is adequately addressed by such labeling for Ambien CR, then similar language can be used to address similar risk from suvorexant. However, it is not clear that the risk from suvorexant is adequately similar to the risk from Ambien CR to support addressing the risk through similar recommendations against driving. Suvorexant acts on the orexin system, which is an integral part of a sleep-wake *switch* that appears to specifically function to allow *rapid* transition from wakefulness to sleep; this risk of sleep, particularly microsleep while driving, plausibly poses a greater risk than the type of psychomotor impairment that has been documented to occur from zolpidem.

A key question is therefore if an effective dose of suvorexant has been shown to be adequately free of next-day driving impairment to not require a specific warning against driving. The lowest dose tested in the adult driving study was 20 mg, which was found to significantly impair driving as measured by change in SDLP. While the 15 mg dose in patients ≥ 65 years old did not impair driving, it isn't clear that the same result would occur for younger patients, as comparison of driving studies in adults at 20 mg and elderly at 30 mg suvorexant suggest that elderly patients might be less sensitive to next day impairment from suvorexant compared to non-elderly adults (also the exposure-response curve for somnolence as an adverse event in controlled trials was steeper for adults than for elderly patients). Importantly, there is considerable overlap in exposure from 15 mg and 20 mg, suggesting that many adults would be at risk of impaired driving from the 15 mg dose. Suvorexant blood levels the morning after a *10 mg* dose averaged about 0.2 to 0.3 µM, and up to about 0.4 µM, in adult patients in study 006, raising concern that even after the 10 mg dose some adults might experience clinically meaningful driving impairment; however, this level of risk appears to be acceptable in the context of the benefit for sleep provided by suvorexant.

Suicidal Ideation

The risk of suicidal ideation from suvorexant was evident mainly for the high dose. For low dose suvorexant (15 and 20 mg) there was 1 patient positive for the prospective suicidality assessment (0.2%), versus 1 event for placebo (0.1%) – an insufficient number of events to determine relative risk with confidence. Suvorexant studies generally excluded patients taking antidepressants and patients with active depressive symptoms or suicidal ideation, such that there is no experience with an important segment of the intended clinical population. The potential therefore remains that suvorexant at doses of 15 to 20 mg increases

[4] http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm329758.pdf

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the risk of suicidal ideation to a larger degree that expected from the clinical trials. There were about 34,000 suicides in the US in 2010[5], such that even a small increase in risk for this relatively common cause of death would be highly clinically relevant. Doses of suvorexant as low as 10 mg, and perhaps lower, are effective, and since suicidal ideation appears to be dose related, such lower doses are likely to decrease risk relative to 15 and 20 mg. While not well-characterized, the absolute risk of suicidal ideation appears small enough to be acceptable, with appropriate labeling directed at increased effort to identify patients with suicidal ideation from suvorexant as early as possible.

Unconscious Nighttime Activity
There were two cases of unconscious nighttime activity, one in a patient on 40 mg suvorexant, and the other in a patient on 30 mg. Even though similar cases did not occur in placebo arms, because there were only two cases in suvorexant arms it is not entirely clear that these events represent a drug-related risk and not chance events; however, patients with a history of sleep walking or similar conditions were excluded from the studies, increasing concern that the events were drug related.

Unconscious nighttime activity has the potential to result in serious and life-threatening adverse events, depending on the specific setting and events that occur, and therefore remains of great concern even though the two patients in suvorexant trials did not experience serious harm. It seems clear, for example, that for the patient that lunged out of bed, small factors, like the arrangement of furniture in the room, could have made the difference between minor vs. serious injury. For the case of 'sleepwalking' in some sense the main question is what the patient was doing, or could have been doing, between the time the patient left her bed and the time she found herself near the window. Other insomnia medications can cause 'complex sleep-related behavior' such as sleep driving, and this case of sleepwalking suggests a similar risk may exist for suvorexant.

Narcolepsy-like events
Sleep paralysis and hypnagogic/hynopompic hallucinations appeared to be dose-related. These events, while not likely to cause physical harm, are potentially very distressing to patients, again supporting use of the lowest dose effective for the patient.

<u>Overall Conclusions:</u>

- **The totality of efficacy evidence is adequate to conclude that the 10 mg dose is likely to be effective for many patients, and is an appropriate initial dose, with the option for the individual patient to increase to higher doses if necessary for efficacy, and if the lower doses are well-tolerated.**
- **The 15 mg dose is adequately safe for patients in whom lower doses are not effective, and who have not experienced daytime somnolence or other drug-related adverse effects from lower doses. The driving study at 15 mg was conducted only in elderly subjects, and there is concern that adults at the higher end of exposure from 15 mg could experience clinically meaningful driving impairment. However, this risk is partly mitigated by escalating only patients without adverse events at lower doses,**

[5] CDC Morbidity and Mortality Weekly Report, http://www.cdc.gov/mmwr

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although recognizing that some patients will not be aware of drug impairment and will not be identified.

- **The 20 mg dose should be reserved for patients that did not benefit from lower doses and that do not drive or engage in other activities requiring full mental alertness.**
- **The 30 and 40 mg doses are not associated with greater objective benefit, and the larger benefit on subjective perception of minutes slept is of unclear clinical meaning. Other subjective endpoints relating to patient perception of benefit, including daytime function, show little difference between the 30 and 40 mg doses and lower doses. In contrast, adverse effects, including effects with potential serious or fatal consequences, sharply increase between the lower and higher doses studied. The benefit-risk profile therefore does not support approval of the 30 and 40 mg doses.**

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None

Reference ID: 3331162

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/s/

RONALD H FARKAS
06/25/2013

MEMORANDUM

DATE: June 23, 2013

FROM: Director
Division of Neurology Products

TO: File, NDA 204569

SUBJECT: Recommendation for action on NDA 204569, for the use of Suvorexant in the Treatment of Insomnia characterized by difficulty falling asleep and/or staying asleep

NDA 204569, for the use of Suvorexant in the Treatment of Insomnia characterized by difficulty falling asleep and/or staying asleep, was submitted by Merck Sharp and Dohme Corp., on 8/29/12, and contains three controlled trials that, by design, could contribute to a finding of substantial evidence of effectiveness for Suvorexant in the treatment of insomnia characterized by difficulty falling asleep (sleep latency) and/or staying asleep (sleep maintenance). Suvorexant is a selective antagonist of orexin receptors OX1R and OX2R, and blocks binding of orexin A and B to these receptors, presumably inhibiting activation of neurons of the arousal system. It is the first member of this class to be submitted for the treatment of insomnia.

The application has been reviewed by Dr. Kachi Illoh, medical officer, Dr. Tristan Massie, statistical reviewer, Drs. Hristina Dimova, Xinning Yang, Joo-Yeon Lee, and Satjit Brar, clinical pharmacology and pharmacometrics reviewers, Dr. Richard Siarey, pharmacology, Dr. Lois Freed, pharmacology team leader, the Interdisciplinary Review Team for QT Studies, Dr. Ling Chen, statistician (for studies of abuse), Dr. Chad Reissig, Controlled Substances Staff, Dr. Mohammad Rahman, statistical reviewer (non-clinical carcinogenicity), Drs. Akm Khairuzzaman and Mohan Sapru, Office of New Drug Quality Assessment, Dr. Sandra Suarez, biopharmaceutics, Twanda Scales, Division of Medical Policy Programs, Dr. Melinda McLawhorn, Office of Prescription Drug Promotion, Dr. Julie Neshiewat, Division of Medication Error Prevention and Analysis, Dr. Antoine El-Hage, Office of Scientific Investigations, and Dr. Ron Farkas, neurology team leader and Cross-Discipline Team Leader (CDTL). The review team recommends that the application be approved. This application was also discussed at a meeting of the Peripheral and Central Nervous Systems Drugs Advisory Committee (PCNS AC) at a meeting on 5/22/13. In this memo, I will briefly describe the relevant effectiveness and safety issues presented in the application, and offer the division's recommendation for action on the application.

Reference ID: 3330895

Effectiveness

As noted above, the sponsor has submitted the results of three controlled trials that are relevant for the determination of effectiveness. Studies 28 and 29 were parallel group studies of very similar design; Study 006 was a two-period cross-over study.

Study 28

This was a parallel group, fixed dose study in which patients with insomnia were randomized to one of two fixed doses of suvorexant or placebo for three months. Specifically, patients were randomized into low dose or high dose (or placebo) in a 2:3:3 ratio in the following manner:

	Low dose	High dose
Ages 18-<65	20 mg	40 mg
Ages >65	15 mg	30 mg

Patients were assessed either with questionnaires only (Q-cohort) or PSG and questionnaires (PQ-cohort). The dose was to be taken right before bedtime.

Patients were assessed at baseline and Night 1, the end of Week 1, and Months 1, 2, and 3. In the PQ-cohort, PSG was performed on Night 1, and Months 1 and 3.

The primary hypothesis compared the high dose on Change from Baseline on mean Subjective Total Sleep Time (sTST) and Change from Baseline on (objective) Wakefulness After Sleep Onset (WASO) (both measures of sleep maintenance) and Change from Baseline in mean Subjective Time to Sleep Onset (sTSO) and Change from Baseline in (objective) Latency to Onset to Persistent Sleep (LPS) (measures of sleep latency), all at Months 1 and 3. High dose secondary hypotheses were sTST and sTSO at Week 1, and WASO and LPS at Night 1.

Because of the multiple time points and outcomes tested, the following approach was taken to protect the experiment-wise Type I error rate at 5%:

High Dose:

The endpoints for sleep maintenance (sTST and WASO) were tested at a two-sided 2.5% as were the sleep latency endpoints (sTSO and LPS). Within each indication, a sequential testing procedure was used to move from the first set of primary hypotheses (Month 1) to the Month 3 contrasts. At each time point, a Hochberg approach was used to test the subjective (sTST, sTSO) and objective

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(WASO, LPS) endpoints. To move from Month 1 to Month 3, both subjective and objective outcomes had to be significant. If only one endpoint was significant at Month 1, testing was not done at Month 3. Levels of significance were two sided, alpha of 2.5%

If either hypothesis (sTST or WASO for maintenance and sTSO or LPS for latency) was significant at Month 3, then the secondary hypotheses (Week 1, Night 1) were tested using the Hochberg approach at a two-sided alpha level of 2.5%.

Low Dose:

A similar approach was taken for the Low Dose-placebo comparisons as described above, if the Month 3 outcome was positive for that particular endpoint at the high dose.

Results

A total of 1022 patients were randomized at 79 centers in Asia/Eastern Europe/Africa (4%), Europe (35%), Japan (24%), North America (34%), and Central and South America (3%). The following chart displays the disposition of patients:

	Placebo	LD	HD
Randomized	385	254	383
Completed Treatment	341 (89%)	230 (91%)	345 (90%)
Discontinued due to:			
Adverse event	21	6	15
W/D by Subject	12	6	8
Lack of efficacy	9	1	7

Patients ranged from 18-87 years old. A total of 42% (N=429) were greater than 65 years old. A total of 776 were randomized to the PQ-cohort, and 247 to the Q cohort. The entire Q-cohort consisted of patients from Japan.

The following chart displays the results for sTST and WASO (measures of sleep maintenance):

	Difference in LS Means (minutes)	P-value
sTST		
Week 1		
HD vs Pbo	21.4*	<0.00001

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LD vs Pbo	13.6*	0.00007
Month 1		
HD vs Pbo	19.6*	<0.00001
LD vs Pbo	16.3*	0.00016
Month 3		
HD vs Pbo	19.7*	<0.00001
LD vs Pbo	10.7*	0.017

*-statistically significant

	Difference in LS Means (minutes)	P-value
WASO		
Night 1		
HD vs Pbo	-38.4*	<0.00001
LD vs Pbo	-32.5*	<0.00001
Month 1		
HD vs Pbo	-26.3*	<0.00001
LD vs Pbo	-26.4*	<0.00001
Month 3		
HD vs Pbo	-22.9*	<0.00001
LD vs Pbo	-16.6*	0.000009

*-statistically significant

The following chart displays the results of the comparisons on sTSO and LPS (measures of sleep latency):

	Difference in LS Means (minutes)	P-value
sTSO		
Week 1		
HD vs Pbo	-5.7*	0.0061
LD vs Pbo	-5.6	0.016

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Month 1

HD vs Pbo	-7.4*	0.0030.
LD vs Pbo	-5.4	0.052

Month 3

HD vs Pbo	-8.4*	0.0002
LD vs Pbo	-5.2	0.04

*-statistically significant

	Difference in LS Means (minutes)	P-value
LPS		
Night 1		
HD vs Pbo	-10.3*	0.00002
LD vs Pbo	-9.6*	0.0004
Month 1		
HD vs Pbo	-11.2*	0.00002
LD vs Pbo	-10.3*	0.0004
Month 3		
HD vs Pbo	-9.4*	0.0004
LD vs Pbo	-8.1*	0.0061

*-statistically significant

Study 29

This study had a similar design as Study 28. A total of 1019 patients were randomized at 90 centers in Asia/Central and Eastern Europe (14%), Europe (30%), and North America (48%). The following chart displays patient disposition in this study:

Reference ID: 3330895

	Placebo	LD	HD
Randomized	387	240	392
Completed Treatment	330 (85%)	205 (85%)	346 (88%)
Discontinued due to:			
Adverse event	17	10	19
W/D by Subject	19	8	9
Lack of efficacy	8	7	4

Patients ranged from 18-86 years old. A total of 41% (N=410) were greater than 65 years old. A total of 753 patients were randomized to the PQ cohort, and 268 to the Q cohort.

The following chart displays the results of the measures of sleep maintenance (sTST and WASO):

	Difference in LS Means (minutes)	P-value
sTST		
Week 1		
HD vs Pbo	26.4*	<0.00001
LD vs Pbo	16.8*	0.00002
Month 1		
HD vs Pbo	26.3*	<0.00001
LD vs Pbo	20.9*	<0.00001
Month 3		
HD vs Pbo	25.1*	<0.00001
LD vs Pbo	22.1*	0.00004

*-statistically significant

	Difference in LS Means (minutes)	P-value
WASO		
Night 1		
HD vs Pbo	-42.0*	<0.00001
LD vs Pbo	-37.0*	<0.00001

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Month 1		
HD vs Pbo	-29.4*	<0.00001
LD vs Pbo	-24.1*	<0.00001
Month 3		
HD vs Pbo	-29.4*	<0.00001
LD vs Pbo	-31.1*	0.000009

*-statistically significant

The following chart displays the results of the comparisons on sTSO and LPS (measures of sleep latency):

	Difference in LS Means (minutes)	P-value
sTSO		
Week 1		
HD vs Pbo	-13.1*	<0.00001
LD vs Pbo	-7.5	0.006
Month 1		
HD vs Pbo	-12.8*	0.00003
LD vs Pbo	-6.9	0.05
Month 3		
HD vs Pbo	-13.2*	0.00003
LD vs Pbo	-7.6	0.04

*-statistically significant

	Difference in LS Means (minutes)	P-value
LPS		
Night 1		
HD vs Pbo	-21.7*	<0.00001
LD vs Pbo	-12.4	0.004

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Month 1

HD vs Pbo	-12.1*	0.00004
LD vs Pbo	-7.8	0.03

Month 3

HD vs Pbo	-3.6*	0.27
LD vs Pbo	-0.3	0.93

*-statistically significant

Study 6

This was a two-period counter-balanced cross-over study in which patients received one of 4 doses of Suvorexant (10, 20, 40, or 80 mg) and placebo. Each treatment period was 4 weeks, with a single-blind placebo washout period of at least one week between periods. Patients were assessed with a PSG on Nights 1and 28 of each period. The primary outcome was Sleep Efficiency (SE), defined as 100 X Total Sleep Time/Time in Bed (in minutes). The Time in Bed was fixed at 8 hours. Secondary outcomes were WASO and LPS.

In order to protect the experiment-wise Type I error of 5%, the highest dose was compared to placebo, and needed to be significant (p=0.05) at both time points (Night 1 and Week 4) in order to test the next highest dose in the same way. Doses significant at both time points for SE were then tested for WASO, and doses significant for SE and WASO were tested for LPS.

Results

A total of 254 patients were randomized at 41 centers; 243 and 249 patients received at least one dose of drug and placebo, respectively, and 228 patients completed the study. Patients ranged in age from 18-64 years old.

The following charts display the results of the primary and secondary outcomes:

SE

	LS Mean Change From Placebo Night 1	P-value
10 mg	5.2	<0.002
20 mg	7.6	<0.002
40 mg	10.8	<0.002
80 mg	12.9	<0.002

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	LS Mean Change from Placebo at Week 4	P-value
10 mg	4.7	<0.003
20 mg	10.4	<0.003
40 mg	7.8	<0.003
80 mg	7.6	<0.003

WASO

	Difference in LS Means at Night 1	P-value
10 mg vs Pbo	-21.2	<0.001
20 mg vs Pbo	-24.7	<0.001
40 mg vs Pbo	-33.9	<0.001
80 mg vs Pbo	-36.8	<0.001

	Difference in LS Means at Week 4	
10 mg vs Pbo	-21.4	0.001
20 mg vs Pbo	-28.1	<0.001
40 mg vs Pbo	-33.2	<0.001
80 mg vs Pbo	-28.9	<0.001

LPS

	Difference in LS Means at Night 1	P-value
10 mg vs Pbo	-3.4	0.6
20 mg vs Pbo	-9.4	0.13
40 mg vs Pbo	-23.1	<0.001
80 mg vs Pbo	-25.4	<0.001

	Difference in LS Means at Week 4	
10 mg vs Pbo	-2.3	0.6
20 mg vs Pbo	-22.3	<0.001
40 mg vs Pbo	-3.8	0.46
80 mg vs Pbo	-9.5	0.07

Reference ID: 3330895

Dr. Massie noted a potential carryover effect for LPS. As he notes (page 51-52 of his review) “Patients who received placebo in Period 1 had further improvement in LPS when they received [drug] in Period 2; however, for patients who received [drug] in Period 1 improvement in LPS did not diminish in Period 2, even though patients received placebo in Period 2.”, though there was no carryover effect if only the sequences including 10 mg were examined. The p-value for the interaction between period and treatment was p=0.01. As result of this effect, he performed several different analyses of first period data.

Analyses of the first period data for only the two sequences that included the 10 mg dose revealed no significant effects on either Night 1 or Week 4 for the 10 mg dose. The effect of the 10 mg dose on LPS in the first period when pooling all placebo groups was as follows:

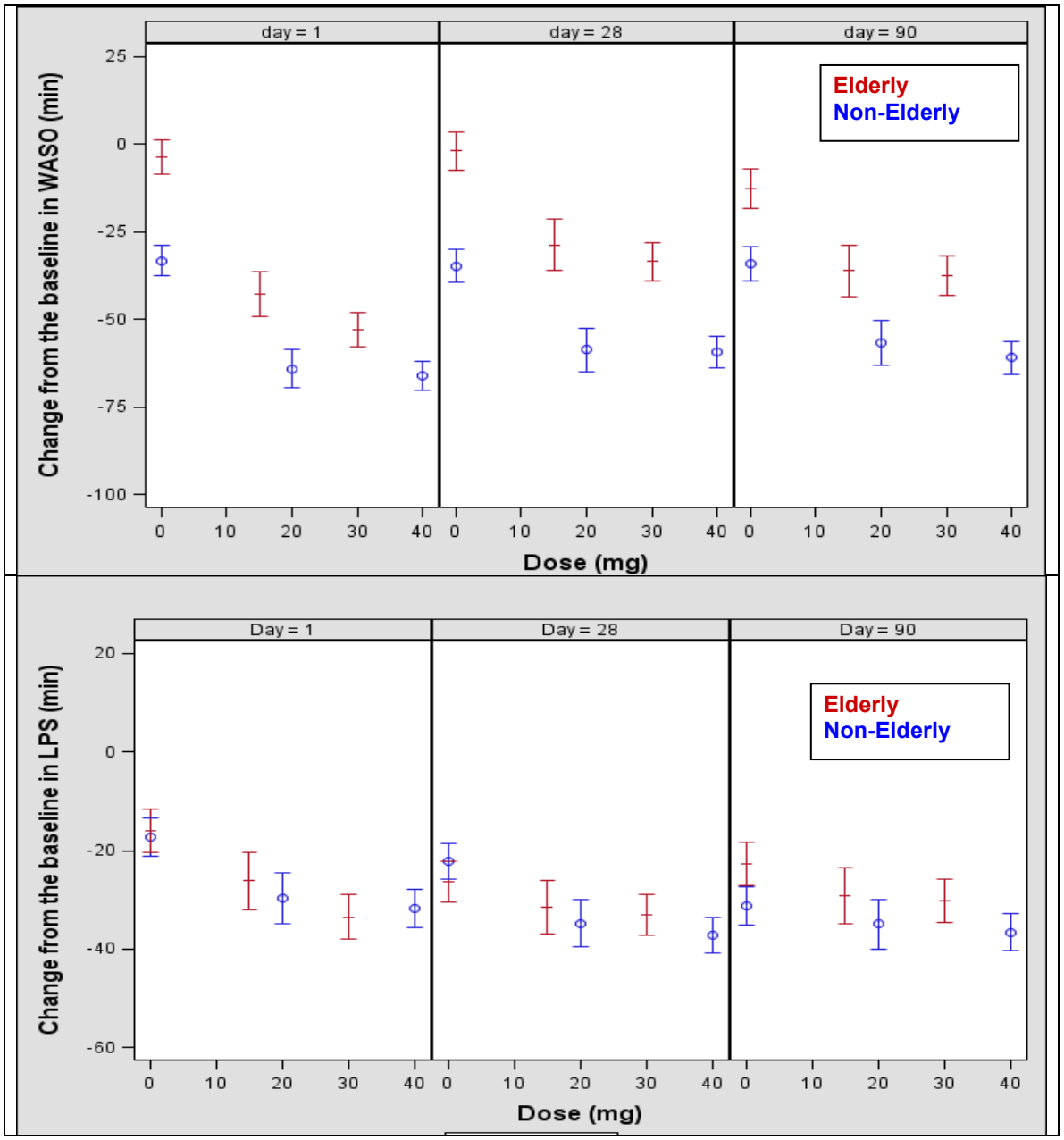
First Period Effect on LS Mean Change from Placebo for LPS

Night 1		P-value
10 mg vs Pbo	-21.7	0.011
Night 28		
10 mg vs Pbo	-20.6	0.013

Our Clinical Pharmacology reviewers performed analyses of the objective measures (WASO, LPS) by dose and by plasma levels (the latter divided into “bins”, based on median AUC [not percentiles, despite the labeling of the graphs]). These analyses combined data from Studies 006, 28, and 29, and were divided by age (elderly, non-elderly). The following graphs, taken from the Clinical Pharmacology review) display these analyses:

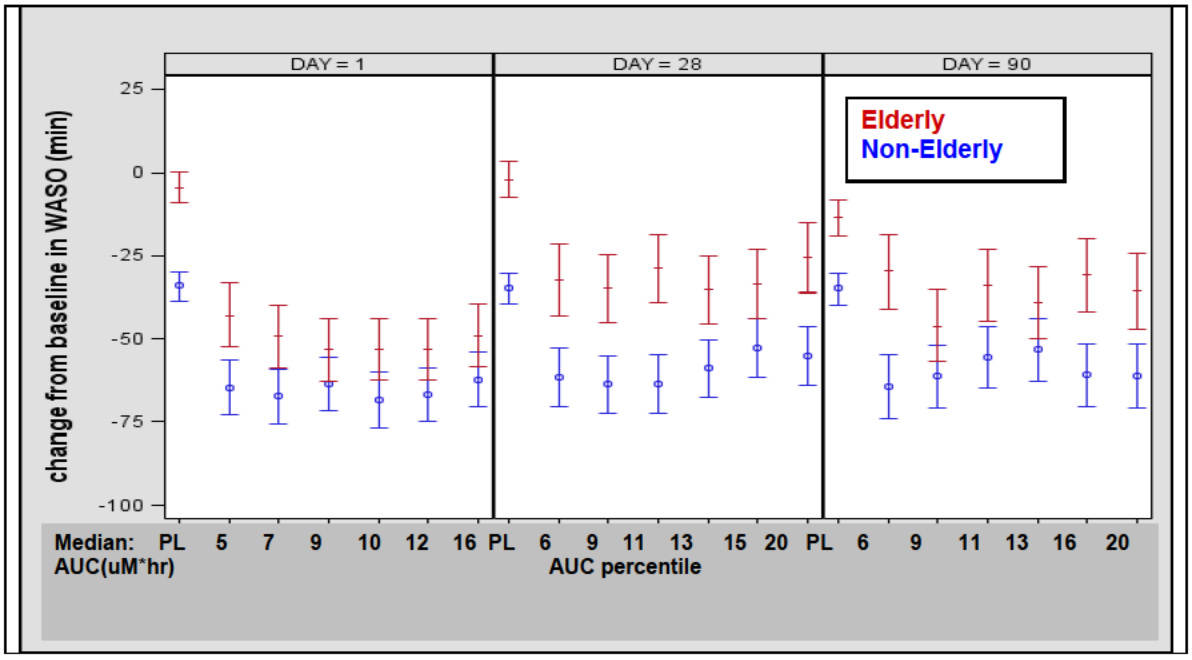
Reference ID: 3330895

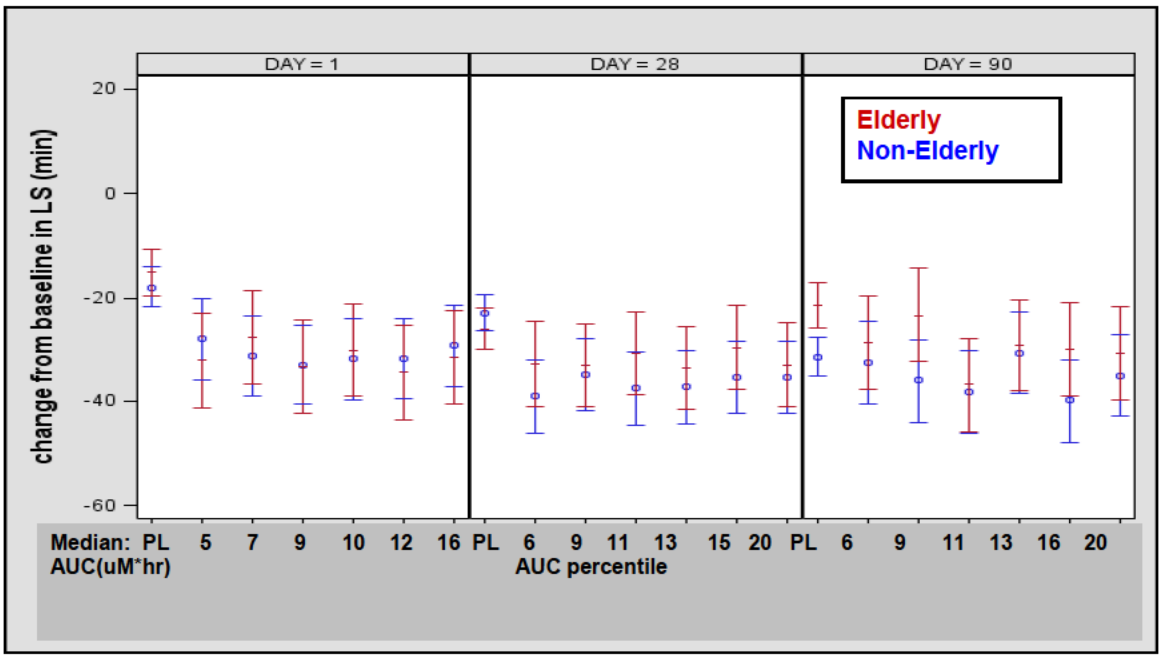
Figure 1: LS mean with 95% CI for Δ WASO (top) and Δ LPS (bottom) vs. Dose by day. LS means were adjusted by baseline value, age group, region and gender



Reference ID: 3330895

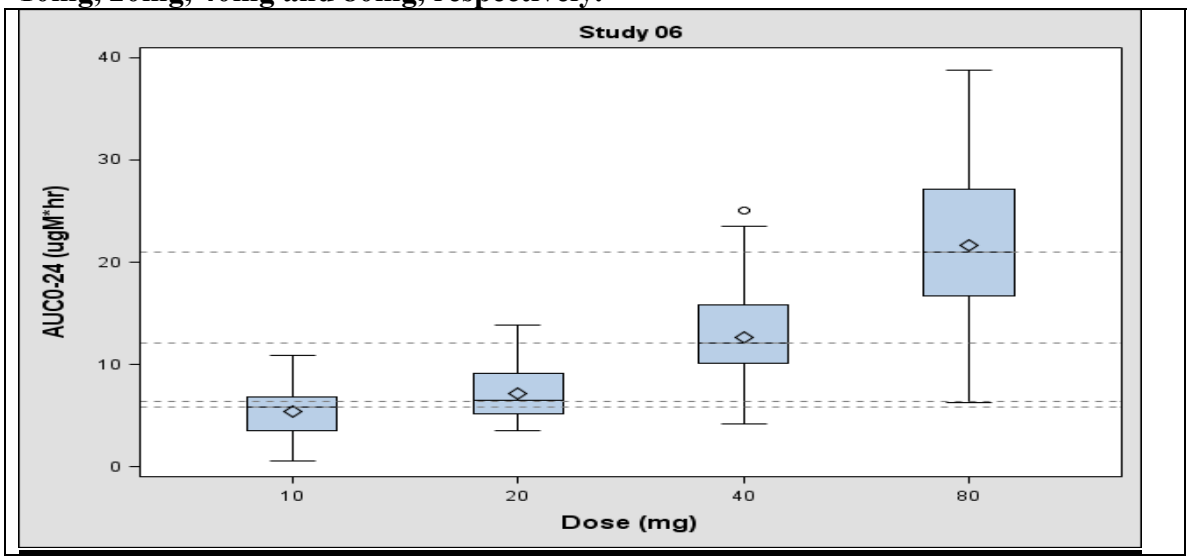
Figure 2: LS mean with 95% CI for Δ WASO (top) and Δ LPS (bottom) vs. exposure (AUC_{0-24}) by day by elderly and non-elderly patients. LS means were adjusted by baseline value, age group, region and gender to be consistent with dose-response analysis.





Reference ID: 3330895

Figure 3: Distribution of AUC_{0-24} (µM*hr) at each dose (data from 1st period of Study 006). The dotted horizontal lines on the top indicate the median AUC_{0-24} at each dose: The median AUC_{0-24} is 5 µM*hr, 6 µM*hr, 12 µM*hr and 21 µM*hr at 10mg, 20mg, 40mg and 80mg, respectively.



Note that the median suvorexant AUC is 5 microM*hr, and that this is similar to the lowest AUC examined in the previous two graphs, which showed effectiveness at all plasma levels, with no concentration response.

Safety

In Phase 2 and 3 studies, a total of 2027 patients with insomnia have received at least one dose of suvorexant; 1218 for at least 3 months, 507 for at least 6 months, and 160 for at least one year. Studies 28 and 29 had extension phases in which patients were treated up to 6 months (the Extension Phases only included the LD), and Study 009 was a double-blind safety study in which patients received either placebo or Suvorexant HD.

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The following chart displays the numbers of patients in Phase 2 and 3 studies who received the given dose of suvorexant for various durations:

	Duration (in Months)		
Dose	3-<6	6-<9	>9
10 mg	0	0	0
15 mg	96	22	0
20 mg	152	20	0
30 mg	196	54	216
40 mg	267	73	121

Deaths

There were 2 deaths in the development program:

1) a 40 year old woman who received 40 mg for 34 days and almost drowned in the ocean the day after her last dose; she was admitted to the ICU and had cardiac arrest
2) a 58 year old woman who received placebo and who died of a stroke.

Serious Adverse Events (SAE)

Over the 12 months of controlled trial data, 2.8% and 3.2% of suvorexant HD (N=1291) and placebo (N=1025) patients, respectively, had a serious adverse event. The only single SAE that occurred more than once in the HD group and more frequently than in the placebo group was diverticulitis (N=2 vs N=1).

Over 6 months of controlled trial data, 0.6% and 2.1% of suvorexant LD (N=493) and placebo (N=767) patients, respectively, experienced a serious adverse event. No single SAE occurred more than once in the suvorexant LD group.

Some SAEs are discussed below under specific adverse events.

Discontinuations

The following chart displays the percent of patients who discontinued during Phase 3 controlled trials due to an adverse event:

	Placebo	LD	HD
0-3 Months	4.7%	3.2%	5.4%
0-6 Months	5.2%	3.2%	NA
0-12 Months	6.0%	NA	7.8%

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In the 3 Month controlled trial data, few AEs led to discontinuation in more than one patient. Those of interest are described below:

Adverse Event	Pbo (N)	LD (N)	HD (N)
N	1025	493	1291
	%	%	%
Somnolence	0.3 (3)	0.2 (1)	1.7 (22)
Fatigue	0	0.2 (1)	0.7 (9)
Sedation	0	0	0.2 (3)
Lethargy	0	0	0.2 (3)
Nightmare	0	0.2 (1)	0.2 (2)
Sleep Paralysis	0	0	0.2 (2)
Memory Impairment	0	0	0.2 (3)
Depression	0.1 (1)	0	0.2 (2)

In general, the adverse events leading to discontinuation of suvorexant in the 3 Month controlled trial cohort were similar to those seen in the 6 and 12 Months controlled trials cohorts. Of interest, the incidence of Somnolence in the 12 Month cohort was 2.2% and 0.4% in the suvorexant HD and placebo groups, respectively.

Some other discontinuations are discussed below under specific adverse events of interest.

Common Adverse Events

The following chart displays the common adverse events seen in the 3 month controlled trial experience:

Adverse Event	Pbo (N=1025)	LD (N=493)	HD (N=1291)
Somnolence	3%	7%	11%
Headache	6%	7%	7%
Fatigue	2%	2%	4%
Dry Mouth	1%	2%	3%
Abnormal Dream	1%	2%	2%
URI	1%	2%	2%

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The following chart displays common adverse events in the 6 Month controlled trial experience:

Adverse Event	Pbo (N=767)	LD (N=493)
Somnolence	3%	7%
Headache	6%	8%
Abnormal Dreams	1%	2%
Diarrhea	1%	2%
Cough	1%	2%

The following chart displays the common adverse events seen in the 12 Month controlled trial data:

Adverse Event	Pbo (N=1025)	HD (N=1291)
Somnolence	3%	12%
Headache	7%	8%
Fatigue	2%	5%
Abnormal Dreams	1%	3%
Nightmares	1%	2%
Nausea	2%	3%
Dry Mouth	2%	3%
URI	2%	3%

Additional adverse events of interest seen in Study 006, the cross-over trial, are listed below:

AE	Pbo N=249	10 mg N=62	20 mg N=61	40 mg N=59	80 mg N=61
Somnolence	0.4%	2%	5%	10%	12%
Abnormal Dreams	1%	2%	0	0	5%
Headache	2%	0	2%	5%	5%
Dizziness	0	0	2%	0	5%

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Laboratory Findings

Mean Changes

mean changes from baseline in routine laboratory measures. The following chart displays those tests with even minimal between-treatment changes in the 3 Month controlled trial data:

	Mean Change From Baseline		
Measure	Pbo N=875	LD N=424	HD N=1118
Hematocrit (%)	-0.07	-0.42	-0.16
Hemoglobin (g/L)	-0.07	-0.18	-0.12
Platelets (10^3/microL)	-0.4	-1.2	-2.5
ALT (U/L)	0.5	-0.5	-0.6
AST (U/L)	0.3	-0.3	-0.1
Calcium (mg/dL)	-0.06	-0.08	-0.12
Creatine Kinase (mg/dL)	-0.5	-2.4	-3.0
LDH (U/L)	-0.5	-2.9	-1.8

The following chart displays the mean change from baseline in serum cholesterol in Study 006:

Treatment	Mean Change from Baseline (g/dL)
Placebo	-3.7
Suv 10 mg	1.2
Suv 20 mg	2.3
Suv 40 mg	3.1
Suv 80 mg	6.0

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Outlier Analyses

The following percent of patients met criteria for potentially significant change from baseline in the 3 Month controlled trial data:

Test	Placebo	LD	HD
Hematocrit (<94.9 LLN)	2%	0.6%	3%
Hemoglobin (<90.5% LLN)	1%	0.6%	2%
Neutrophils (<37% LLN)	0.1%	1%	0.5%
Potassium (>111.1% ULN)	1%	1%	2%

EKG

The sponsor performed a Thorough QT study in which they compared single doses of Suvorexant of 60 mg, 160 mg, and 240 mg to Moxifloxacin 400 mg; there were no significant QT effects in the suvorexant-treated subjects. The study did demonstrate the expected QT-prolonging effect of moxifloxacin.

The following chart displays mean changes from baseline for various EKG parameters in the 3 Month controlled trial data:

	Mean Change from Baseline		
Measure	Placebo	LD	HD
Heart Rate (BPM)	0.1	-0.5	-1.1
PR Interval (msec)	-0.1	0.2	1.0
QT Interval (msec)	0.4	3.1	2.7
QT_cB (msec)	0.4	1.2	-0.5
RR Interval (msec)	0.3	7.4	17.0

There was no difference between treatments in the percent of patients with QT increases of 30-60 msec or greater than 60 msec. There were no meaningful differences in the percent of patients who had a QT interval of >500 msec between treatments.

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Adverse Events of Special Interest

Somnolence

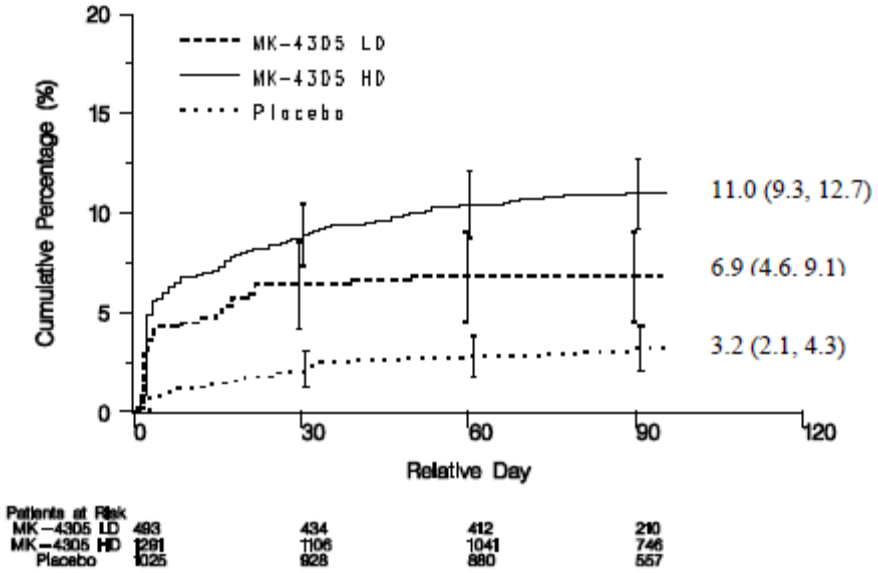
As noted earlier, there was a dose-related increased incidence of next-day somnolence in the 3 Month controlled trial data:

	Placebo N=1025	LD N=493	HD N=1291
Somnolence	3%	7%	11%
Discontinued due to Somnolence	0.3%	0.2%	2%
Severe Somnolence	0.1%	0.2%	0.6%
Somnolence			
>65 years old	3%	5%	9%
<65 years old	3%	8%	12.5%

The relationships seen above between age (inverse), dose (direct), and incidence of somnolence persisted in the 6 and 12 Month controlled trials data.

The following chart displays the time course of the onset of somnolence:

Figure 11: Cumulative Percentage of Subjects Who Reported Somnolence of over 0-3 Months among all Subjects in the Combined Phase 3 Population (P028, P029, and P009)



(Source: Sponsor's submission ISS Page 650 Figure 5.3.5.3.3.:5)

Reference ID: 3330895

Generally speaking, there was little difference in the incidence of somnolence at a given dose of Suvorexant between women and men in the 3 Month controlled trials data:

	Placebo	LD	HD
Men	4%	3%	10%
Women	2%	8.5%	11%

The difference in incidence of somnolence was also seen in the 6 and 12 month controlled trial data:

	Placebo	LD	HD
6 Month	3%	7%	NA
12 Month	3%	NA	12%

Patients treated with suvorexant experienced longer durations of somnolence than placebo patients who experienced somnolence. This can be seen in the following plot of the duration of somnolence in individual patients in the 12 Month controlled trials data:

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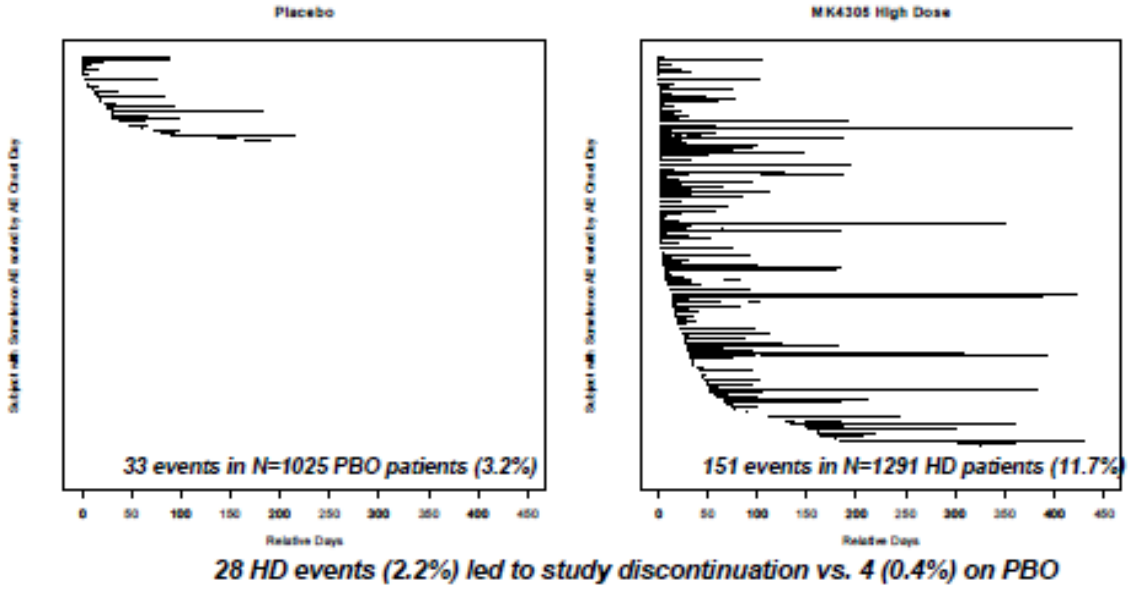
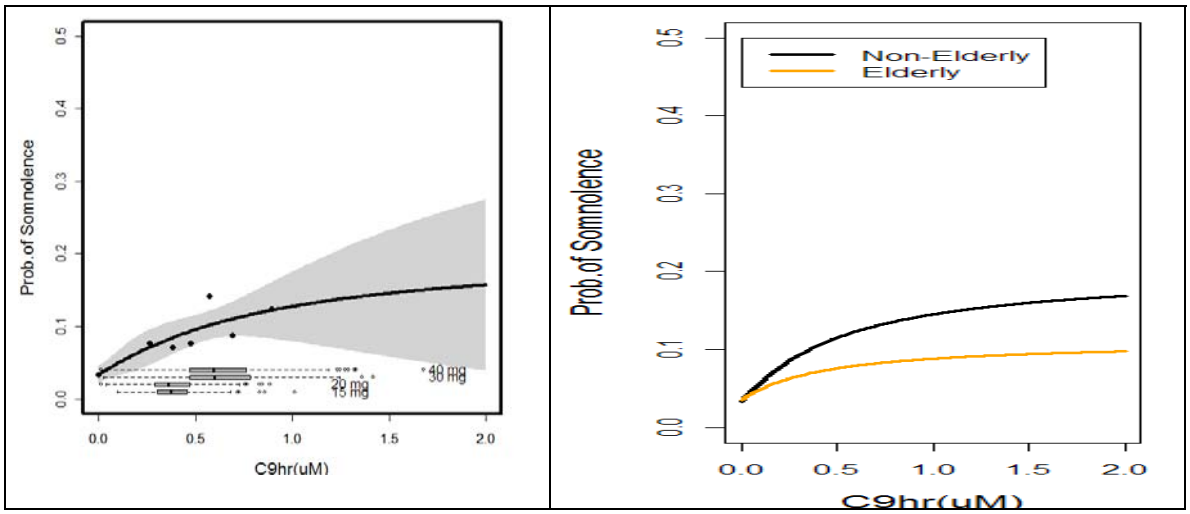
Figure 13: Subject Plots of Somnolence Events over 0-12 Months among all Subjects in the Combined Phase 3 Population (P028, P029, and P009)



(Source: Sponsor's submission ISS Page 654 Figure 5.3.5.3.3:7)

The following graphs display a model predicted relationship between somnolence and C9hr for the overall population and for elderly vs non-elderly:

Figure 4: Left: Overall model-predicted relationship for probability of somnolence and suvorexant concentration (C_{9hr}). Right: model-predicted relationship for probability of somnolence and suvorexant concentration (C_{9hr}) by elderly and non-elderly patients



Suicidal Ideation and/or Behavior

The sponsor monitored clinical trials according to a current Agency draft guidance that requires such monitoring and suggests that suicidal ideation/behavior be assessed using the Columbia Suicidality Severity Rating Scale (C-SSRS). Based on these ratings, events are categorized using the Columbia Classification Algorithm for Suicide Assessment (C-CASA), which rates the events as suicidal ideation or suicidal behavior (or not), or indeterminate.

The incidence of events classified as suicidal ideation on clinical grounds (not according to the C-CASA classification) in the 3 Month controlled trial data were:

Placebo	LD	HD
0.1% (N=1)	0.2% (N=1)	0.4% (N=5)

Both the placebo and LD patients had a history of suicidal ideation, as did one of the HD patients. One patient each in the LD and HD dose groups discontinued treatment due to this AE.

According to the C-CASA classification, the following event rate was seen in the 12 Month controlled trials data:

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	Placebo (N=1012)	HD (N=1268)
Suicidal Ideation	0	0.6% (N=8)

Complex Sleep-Related Behaviors

There were 2 patients who reported complex sleep-related behaviors in the 3 Month controlled trial data.

1) A 65 year old man with a history of sleep talking experienced sleep talking about 2 ½ hours after a dose of 30 mg (Day 85) and then about 90 minutes later lunged out of bed. Sixteen days later, about 2 weeks off of drug, he had an episode of sleep walking.
2) A 58 year old woman experienced sleep walking and sleep paralysis on Day 52 on a dose of 40 mg. The sleep paralysis occurred after a dream, and then hours later found herself standing be a window, unaware of how she got there. Drug was discontinued because of the event

Excessive Daytime Sleepiness (EDS)

The following chart displays the incidence of EDS in the 3 and 12 Month controlled trial data:

Duration of Study	Pbo	LD	HD
3 Month	0.2%	0.6%	1.1% (N=14)
12 Month	0.3%	NA	1.5% (N=20)

In the 12 Month, HD patients, 36% of the episodes of EDS were rated as severe; none of those in the other groups were rated as severe. In the 3 Month data, 10/14 (71%) of HD patients discontinued due to EDS. In the 12 Month controlled trial data, 11 Suvorexant HD (0.9%) and 2 placebo (0.2%) patients discontinued due to EDS.

In Study 006, a 63 year old woman experienced EDS after 2 days of 80 mg, and in a Phase 1 study of patients with COPD, a 63 year old woman experienced 5 days of EDS after a dose of 40 mg.

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Hypnagogic and Hypnopompic Hallucinations

Hypnagogic (dreamlike experiences during sleep onset) and hypnopompic (dreamlike experiences upon awakening) hallucinations were seen in the following incidences:

Duration of Study	Placebo	LD	HD
3 Month	0	0.4%	0.2%
12 Month	0	NA	0.4%

In the 3 Month cohort, two patients (1 LD, 1 HD) experienced sleep paralysis with the event. One HD patient discontinued due to hypnagogic hallucinations (a 73 year old man).

Six subjects in Phase 1 studies also experienced hallucinations after doses of 40-60 mgs.

Sleep paralysis

The following chart displays the incidence of sleep paralysis in controlled trial data:

Duration of Study	Placebo	LD	HD
3 Month	0	0.2%	0.3%
12 Month	0	NA	0.3%

In Study 006, one patient on 40 mg and one patient on 80 mg developed sleep paralysis. Each patient experienced multiple episodes.

In Phase 1 studies, 13/662 (2%) of suvorexant and 1/365 (0.3%) of placebo-treated patients experienced sleep paralysis. Of the suvorexant subjects, 6/13 experienced the events at 40 mg. Of the 6, subjects, 4 had multiple events.

Driving

The sponsor performed two similar studies evaluating highway driving behavior.

Study P039 evaluated driving behavior in 24 healthy subjects >65 years old, and Study P035 evaluated driving in 28 healthy subjects ages 21-64 years old. In these studies, subjects' driving was evaluated in the morning, about 9 hours after nighttime dosing, on Days 2 and 9, after 8 days of dosing. In Study 039, subjects received either 15 mg, 30 mg, or placebo and in Study P035, they received either

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20 mg, 40 mg, or placebo. The studies were 4 period cross-over studies, in which all patients received all treatments.

The primary endpoint was the standard deviation of lane position (SDLP), a standard measure in this type of driving study. Zopiclone 7.5 mg was used as an active control; this is also standard in these studies.

A SDLP of 2.4 cm or greater is considered clinically meaningful in these studies (this is the SDLP associated with a blood alcohol level of 0.05%). In addition to examining the mean SDLP, the number of patients with an SDLP of >2.4 (indicating impairment) was compared to the number of patients with an SDLP <-2.4 under each treatment condition (so-called symmetry analysis). The null hypothesis for this measure is that the percent of patients above the 2.4 SDLP and the percent of subjects below -2.4 is symmetric around zero.

Results

Study P039

The following chart displays the results of the LS Means of SDLP and the results of the symmetry analyses:

	LS Mean SDLP
Day 2	
Pbo	16.67
Zopiclone	18.56
Suv 15 mg	16.24
Suv 30 mg	17.04
Day 9	
Pbo	15.41
Zopiclone	16.58
Suv 15 mg	15.50
Suv	16.01

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Symmetry Analysis (difference from placebo)

Day 2	Zopiclone	15 mg	30 mg
# + subjects	8	0	3
# - subjects	0	3	1
Reject Null	Yes	No	No

Day 9

# + subjects	6	0	5
# - subjects	1	0	1
Reject Null	Yes	No	No

Study P035

	LS Mean SDLP
Day 2	
Pbo	15.53
Zopiclone	17.66
Suv 20 mg	16.54
Suv 40 mg	17.19
Day 9	
Pbo	15.47
Zopiclone	16.91
Suv 20 mg	15.94
Suv 40 mg	16.77

Symmetry Analysis (difference from placebo)

Day 2	Zopiclone	20 mg	40 mg
# + subjects	14	6	10
# - subjects	1	0	2
Reject Null	Yes	Yes	Yes

Day 9

# + subjects	8	2	6
# - subjects	0	1	0
Reject Null	Yes	No	Yes

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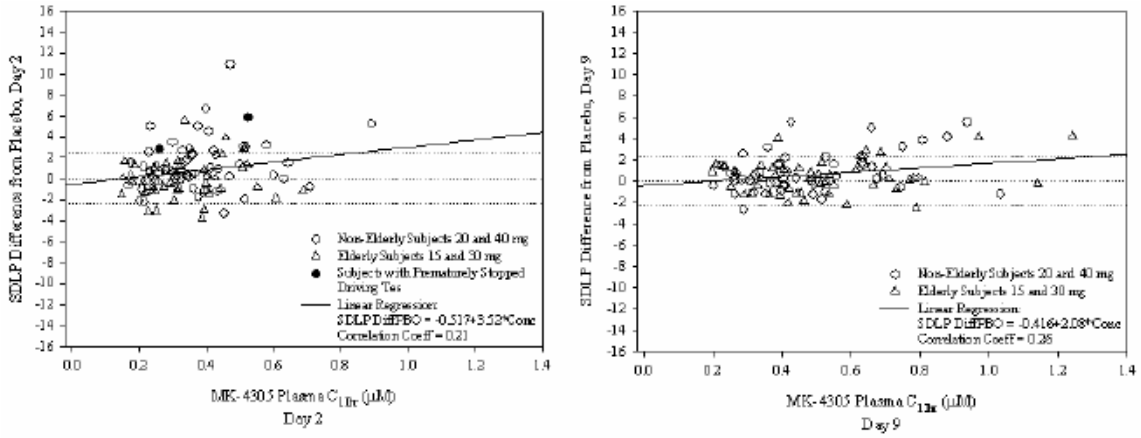
Four (4) women stopped 5 driving tests because of somnolence: two after 40 mg on Day 2; one after 20 mg on Day 2, and one woman stopped tests after 40 mg on Day 2 and after 20 mg on Day 9. These tests were stopped between 29 and 57 minutes after the start of the tests.

In these studies, blood levels were measured at 11 hours after drug ingestion. The following graphs display the differences from placebo in C11 plasma levels and SDLP:

SDLP Differences From Placebo vs Suvorexant Plasma Concentrations (C_{11hr}) in Non-Elderly and Elderly Subjects on Day 2 (left panel) and Day 9 (right panel). Subjects whose driving was prematurely stopped due to somnolence were identified (no PK sample was available for AN007, AN016 repeat period data is shown)



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In addition to the formal driving study, the sponsor presented results on reported motor vehicle accidents (MVAs), as well as data derived from questionnaires. There were no more reported MVAs in suvorexant-treated patients compared to placebo-treated patients in controlled trials overall, but in a 12 month-safety study, 5.5% of suvorexant HD patients and 4.1% of placebo-treated patients reported at least one MVA.

In Phase 3 trials, patients were asked about their driving experiences via a specific Motor Vehicle Accidents and Violations (MVAV) Questionnaire. The following chart displays the results of this testing for the various controlled trials cohorts:

Duration of Study	Placebo	LD	HD
3 Month			
Patients with Accidents	0.9%	1.2%	1.2%
Patients with Citations	1.3%	1.8%	1.2%

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6 Months			
Patients with Accidents	1.3%	1.2%	NA
Patients with Citations	1.5%	2.3%	NA
12 Months			
Patients with Accidents	1.4%	NA	1.5%
Patients with Citations	2%	NA	2.7%

Cataplexy

The sponsor constituted an external adjudication committee to review clinical reports of cataplexy, as well as to review the data captured on a Modified Cataplexy Questionnaire that the subject/patient completed after a possible event.

The committee reviewed 45 cases of suspected cataplexy, and determined that none could be defined as cataplexy.

At least one case that could reasonably be considered to be cataplexy is described below:

A 59 year old man reported leg weakness on Day 46 of treatment with 40 mg of suvorexant. On the same day, he also reported EDS, and discontinued the trial secondary to that event.

About 12 hours after his Day 45 dose, he felt increased tiredness and several episodes of leg weakness (lasting about 5-30 seconds) after laughing with co-workers. He continued feeling weak for about 11 hours. About 5 hours after these episodes, he experienced EDS that lasted until bedtime, and occurred several times while driving.

On the questionnaire, this patient responded positively to the event having occurred “when laughing, when excited, surprised, when required to make a quick verbal response in a playful or funny context, when startled, when telling or hearing a joke”.

Falls

The incidence of falls was essentially the same among all treatment groups in controlled trials. The falls that occurred in the drug-treated patients all appeared to have been related to identifiable, non-drug related, causes.

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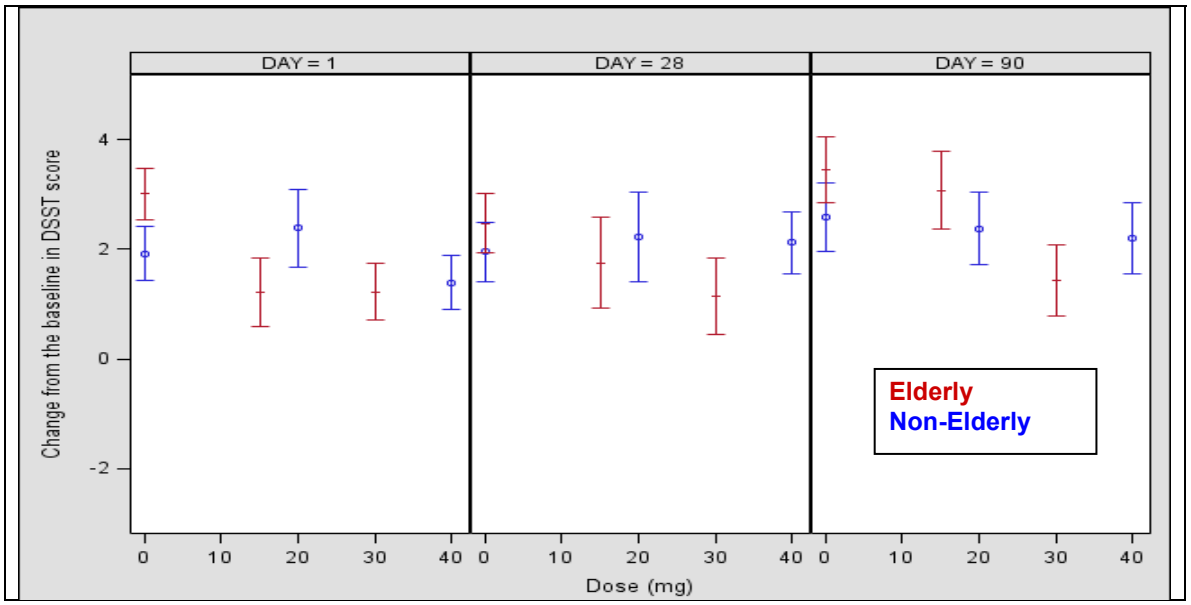
Memory, DSST, Balance

In relatively small studies (the two driving studies, a study in patients with COPD [N=25], a study in patients with Obstructive Sleep Apnea [OSA; N=26]), the sponsor evaluated Delayed Word Recall (IDWR), Digit Symbol Substitution (DSST), and balance (body sway). These studies examined effects at 9 hours after dosing, and included elderly and non-elderly subjects treated up to 9 days; they evaluated various doses: 15 and 30 mg in the elderly, and 20 and 40 mg in non-elderly patients.

Only on the IDWR test in the driving study in non-elderly subjects was a statistically significant worsening on suvorexant (40 mg) seen compared to placebo seen. In no other study were there significant mean effects on memory or balance that differed between the treatment groups.

The sponsor reports no significant between-group differences on the DSST, including in the Phase 3 trials (in which the DSST was performed in the morning after the overnight PSG recordings), except for Night 1 in elderly patients in the Phase 3 trials, and, in the small studies described above, only in the driving study in non-elderly adults at 11 hours after dosing with suvorexant 40 mg on Day 1, but not after 8 days of dosing. The following graph shows the (lack of) relationship between plasma level and DSST results in both elderly and non-elderly patients in the Phase 3 controlled trials:

Figure 5: Dose vs. ΔDSST (top) and C_{9hr} vs. ΔDSST (bottom) relationship by elderly and non-elderly patients



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Clinical Pharmacology

Median peak plasma levels of suvorexant occur about 2 hours after ingestion (range ½ to 6 hours). It is extensively metabolized, primarily by CYP3A4, with some contribution from CYP2C19. The major circulating metabolite, M9, is formed by hydroxylation, and further metabolized to a carboxylic acid derivative, M4. M9 appears in the plasma at about equal concentrations to the parent, but it is a substrate of P-gp, and is not expected to enter the brain.

The primary route of metabolism is through the feces (66% recovered in the feces, 23% recovered in the urine). The mean terminal T1/2 is about 12 hours, and is similar for M9. Accumulation of AUC and Cmax is about 1.2 to 1.6 at steady state.

Suvorexant exposure is higher in women than in men; the female/male ratios of the geometric means for AUC and Cmax were about 1.5 and 1.3, respectively. The apparent oral clearance was about 20% lower in women than in men.

Apparent clearance is inversely related to Body Mass Index (BMI). The concentration of suvorexant at 9 hours after dosing (a critical time point for assessing next day morning effects) is predicted to be about 20% higher in obese patients than in patients with normal BMI. Considering the combination of factors that can affect clearance, some populations may have considerably greater plasma concentrations than others for a given dose. For example, the clearance in obese women is expected to be about 2-3 times lower than in men with a normal BMI.

The concentration at 9 hours post-dose in elderly patients is about 15% greater than that in non-elderly adults.

Based on in vitro studies, suvorexant can inhibit CYP3A4 and intestinal P-gp.

Advisory Committee Meeting

As noted above, this application was discussed at a meeting of the PCNS AC on 5/22/13.

The committee voted that the sponsor had presented substantial evidence of effectiveness for suvorexant in the treatment of sleep maintenance (16 yes, 0 no), and sleep latency (12 yes, 4 no). The committee also voted that the 15 and 20 mg doses were sufficiently safe to be able to be recommended as initial doses (15 yes, 3 no).

However, the committee also clearly endorsed the concept that the lowest effective dose should be recommended in labeling as the initial dose, given

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concerns related to safety issues, primarily next-day effects. In this regard, when asked if the sponsor should be required to perform additional studies to investigate the effectiveness of the 10 mg dose, the committee voted 11 No, 5 Yes (1 abstention). When each member who voted No was specifically questioned about the basis for their vote, most stated that further study was not necessary either because they felt that effectiveness of the 10 mg dose had already been established, or that it was reasonable to conclude that the 10 mg dose was effective, despite the lack of definitive evidence on that point at this time.

Comments

The sponsor has submitted three controlled trials, examining a range of doses, that could contribute to a finding of substantial evidence of effectiveness for suvorexant for patients with insomnia characterized by difficulty falling asleep (latency) and/or staying asleep (maintenance). In Studies 28 and 29, elderly and non-elderly patients were treated with different doses: 15 and 30 mg in the elderly, and 20 and 40 mg in the non-elderly.

In our view, the data clearly demonstrate that suvorexant is effective for both symptoms (latency and maintenance), based primarily on Studies 28 and 29. Study 006 also clearly shows that suvorexant is effective for sleep maintenance (based on WASO); the results in this study are less impressive for sleep latency (based on LPS).

Given that the data, overall, establish effectiveness, we need to examine the response by dose.

Regarding sleep maintenance, it appears that there is some evidence of dose response in Studies 28 and 29, but that all doses are significantly superior to placebo, based on the subjective endpoint, sTST. However, there appears to be little to no dose response for sleep maintenance based on the objective WASO, where, again, all doses are statistically significantly superior to placebo. In addition, all doses (from 10-80 mg) are statistically superior to placebo on WASO in Study 006, with very little evidence of a dose response. As we have also shown, analyses of the combined data from all three studies, show little to no dose or concentration response for sleep maintenance, including at concentrations associated with the 10 mg dose, based on objective WASO.

Regarding sleep latency, there appears to be some evidence of dose response in Studies 28 and 29, with the low dose not shown to be statistically superior to placebo, based on the subjective endpoint, sTSO. On the other hand, in Study 28, all doses are significantly superior to placebo, with no evidence of a real dose response, based on the objective measure, LPS, whereas in Study 29, there appears to be somewhat of a dose response, with the low dose not being

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statistically superior to placebo on LPS. In Study 006, the effects of suvorexant on LPS are unclear; the higher doses (above 20 mg) appear significantly superior to placebo on Night 1, but no doses are significant at Week 4. Some analyses of the first period data suggest that 10 mg may be effective for LPS. However, we have also shown that analyses that combine data from all three studies suggest no dose or concentration response on sleep latency, based on objective LPS. In particular, in those concentration analyses, a median AUC of about 5 microM*hr was shown to be effective, which is equivalent to the median AUC at the 10 mg dose.

These data, taken together, suggest to us that all doses studied (down to, and including, 10 mg) are effective for both endpoints, and that there is little evidence to suggest that the higher doses are substantially superior to 10-15 mg, at least for sleep maintenance, and likely for sleep latency as well. This conclusion is primarily based on the results of the analyses described above of the objective measures, measures we believe more reliably assess the effects of interest than do the subjective measures.

The question of dose response is particularly important, given the safety data.

Suvorexant clearly causes dose related, next day effects, including sedation, which can be of significant concern. For example, as noted above, there is an 8-fold increase in the incidence of next day somnolence between the low and high doses of suvorexant in the 3 Month controlled trial data that led to discontinuation (0.2 and 1.7%, respectively). The incidence of somnolence continues to increase for at least 60 days after initiation of treatment, and the duration of somnolence in suvorexant patients was longer than the duration of somnolence in placebo patients. There was also a dose-related increase in the incidence of somnolence and severe somnolence, and, interestingly, although this was also true in both age groups, elderly patients had a lower incidence of somnolence at each dose (low and high) than did the non-elderly patients.

Perhaps most importantly, the results of a formal driving study demonstrate that suvorexant can cause significant impairment in driving the morning after dosing.

Specifically, in a study (P035) of non-elderly adults, both 20 and 40 mgs were associated with an increase in patients who had excessive deviation in lane position the morning after a single bedtime dose taken the night before. This next-morning effect clearly persisted after 8 days of continuous dosing of 40 mg. Further, and critically, 4 women had to discontinue the testing due to excessive somnolence.

In Study P039, a similar driving study in elderly adults, there were no statistically significant differences between either dose of suvorexant and placebo in the symmetry analysis, though there were ***clear*** numerical increases in the number of subjects who met SDLP criteria for impairment at the 30 mg dose.

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Suvorexant also seems to increase the risk of suicidal ideation/behavior in a dose related fashion. For example, in the 12 Month controlled trial data, there were 0 placebo patients (N=1012) compared to 8 suvorexant patients (N=1268) who were considered to have had suicidal ideation, when these events were classified formally by protocol.

Suvorexant also seems to be associated with adverse events that can be considered to be elements of a narcolepsy-like syndrome.

Specifically, in controlled trials, suvorexant caused an increase in the incidence of excessive daytime sleepiness, sleep paralysis, and hypnogogic/hypnopompic hallucinations. There were also numerous reports (N=45) of suspected cases of cataplexy. Although an adjudication panel did not consider any of these cases to be cataplexy, our independent review suggests that at least one, and perhaps several more, could reasonably have been cases of actual cataplexy.

Pharmacokinetic considerations are also important in the decision about the appropriate dose(s) to be recommended.

In particular, the clearance of suvorexant in women is lower than in men, and increased BMI is also associated with a slower clearance. As described earlier, populations of patients with a combination of factors that decrease clearance (e.g., obese women) would be expected to have a clearance that is 2-3 times lower than men with a normal BMI. Particularly high plasma concentrations would be expected to be associated with an increased incidence of adverse events, in particular (though certainly not only) impaired driving, and dosing recommendations should take this fact into consideration.

It is also worth noting that plasma levels of suvorexant in elderly adults differ little from those of non-elderly adults, for any given dose.

It is also important to note that suvorexant levels are about 3 times greater when taken with a potent CYP3A4 inhibitor, and about 2 times greater when taken with a moderate inhibitor, than when taken without any inhibitor.

The sponsor has proposed that the high dose be recommended (b) (4) In our view, the data taken together (both safety and effectiveness, as well as pharmacokinetics) suggest that a lower dose should be recommended, at least as an initial dose. From the effectiveness point of view, this conclusion is primarily based on our analyses of Studies 28 and 29, as well as on our analyses of Study 006, and the objective measures of both sleep latency and maintenance, as well as our analyses of dose and concentration-response data performed on pooled data by our Clinical Pharmacology team. The lack of significant kinetic differences between elderly and non-elderly patients argues for recommending

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the 10 mg dose, at least as a starting dose, though the lowest dose studied in non-elderly patients was 20 mg.

Safety data demonstrate dose related increases in adverse events, in particular impaired driving. Both doses in non-elderly patients were associated with next-morning impairment, and though neither dose in the elderly driving study was significantly different from placebo, the clear increase in 30 mg dose patients who were impaired, in the context of the data described above, also argues for recommending the 10 mg dose, a dose we believe to be effective.

Finally, as noted above, women and obese patients have higher plasma levels of suvorexant than men and patients with a normal BMI. Clearly, some populations (in addition to these, those taking CYP3A4 inhibitors) would be expected to have considerably higher plasma concentrations than others. In some populations (e.g., obese women, those taking potent and moderate CYP3A4 inhibitors)), we expect the 15 mg dose may be too high, given the risks of high dose suvorexant. In these patients, a lower dose would be necessary. However, the lowest strength proposed for marketing by the sponsor is 15 mg.

The PCNS AC gave, in our view, somewhat conflicting messages regarding an acceptable dose for marketing.

On the one hand, they clearly voted that the 15 and 20 mg doses were acceptably safe to be recommended as starting doses. On the other hand, though, they endorsed the view that the lowest effective dose should be recommended, at least as a starting dose, and, further, they in general concluded that 10 mg was an effective dose.

In our view, the 10 mg dose is an effective dose (though perhaps in fewer patients than higher doses). Given the risks of next day effects at even the 15 and 20 mg dose groups, especially next-day driving impairment, we believe that suvorexant cannot be marketed with an acceptable safety profile without the availability of the 10 mg dose. Given that this dosage strength is not currently available, we believe that the Agency should issue a Complete Response (CR) letter, requiring that the 10 mg dose be available. In addition, because we expect that certain, relatively large, segments of the population for whom the drug will be indicated may have unacceptably high plasma levels even at the 10 mg dose (especially, for example, obese women and patients taking even moderately potent CYP3A4 inhibitors), we recommend that the sponsor also produce a 5 mg dosage strength, a strength that would be expected to yield plasma levels in these populations that are essentially equivalent to the 10 mg dose in other populations.

Finally, because the risks of the high doses (30 and 40 mg) are significantly greater than those of the lower doses, and the effectiveness at these higher

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doses are not importantly different than at the lower doses, we conclude that these higher doses should not be recommended.

Russell Katz, M.D.

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/s/

RUSSELL G KATZ
06/25/2013

CLINICAL REVIEW

Application Type	NDA 505 (b)(1)
Application Number(s)	204569
Priority or Standard	Standard
Submit Date(s)	08/29/2012
Received Date(s)	08/29/2012
PDUFA Goal Date	06/29/2013
Division / Office	DNP/ODE1
Reviewer Name(s)	Kachi Illoh, MD, MPH
Review Completion Date	04/29/2013
Established Name	Suvorexant, MK-4305
(Proposed) Trade Name	
Therapeutic Class	Orexin Receptor Antagonist
Applicant	Merck Sharp & Dohme Corp.
Formulation(s)	40 mg, 30 mg, 20 mg, and 15 mg tablets
Dosing Regimen	30 mg (elderly adults) or 40 mg orally daily at bedtime
Indication(s)	Sleep maintenance insomnia Sleep onset insomnia
Intended Population(s)	Adults with insomnia

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval for this new drug application (NDA). This recommendation is based on my clinical review of Merck's submission to support the proposed indication for suvorexant in the treatment of insomnia, characterized by sleep onset or sleep maintenance difficulties or both sleep onset and sleep maintenance difficulties. The reviewed data suggest that the clinical benefits outweigh the risks of suvorexant treatment. However, appropriate dose adjustments may be needed given the safety assessment and results of the driving studies that suggest some impairment of driving performance with the tested suvorexant doses.

Suvorexant is a new chemical entity that is suggested to act as a highly selective antagonist for orexin receptors OX_1R and OX_2R. It is formulated as an immediate-release tablet for oral administration. The dose proposed for non-elderly adults, younger than 65 years, is 40 mg once daily. For elderly adults, 65 years and older, the proposed dose is 30 mg once daily. In addition, Merck recommends allowing for a lower dose of 20 mg in the non-elderly and 15 mg in the elderly based on individual tolerability.

This clinical review focused on three Phase 3 trials (P028, P029, and P009) for assessing the efficacy and safety of suvorexant. Two of these trials, P028 and P029, provided 3-month treatment data for the primary efficacy assessment. The third Phase 3 trial P009 contributed 12-month treatment data and was included with the other two Phase 3 trials in the safety review. My recommendation on regulatory action is based on my review of the individual trials; the efficacy results; and the combined safety data, primarily from the three Phase 3 trials, with supportive data from the Phase 2 trial (P006) and pooled Phase 1 trials (31 trials).

Three Phase 3 trials provided the primary data for efficacy and safety assessment of suvorexant. In the trials, suvorexant showed clinically significant efficacy on both sleep maintenance and sleep onset in subjects with primary insomnia. Next-day somnolence was the most prominent adverse event (AE), events of clinical interest (ECIs) were of low incidence, and highlighted AEs including EDS and suicidal ideation appeared to occur in a dose-related manner. There was no confirmed case of narcolepsy with or without cataplexy, but there were suggestions of impaired driving performance on assessment of next-day residual effects of suvorexant.

Overall, suvorexant showed convincing evidence of treatment benefit for treating insomnia characterized by both sleep onset and sleep maintenance difficulties. Also, the treatment benefits appear to outweigh the risks.

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1.2 Risk Benefit Assessment

Trials P028 and P029 were similarly designed to provide 3-month treatment data for the primary efficacy assessment in adult subjects with primary insomnia. The trials were to primarily evaluate the efficacy of suvorexant high dose (HD) compared with placebo in improving sleep maintenance and sleep onset at Months 1 and 3, using subjective and objective polysomnographic (PSG) outcomes. In the trials, suvorexant HD signified 30 mg for elderly subjects and 40 mg for non-elderly subjects, suvorexant LD was 15 mg for elderly subjects and 20 mg for non-elderly subjects. The strengths in the trials lie in the large sample size, assessment of both objective and subjective endpoints, and relatively long duration of treatment.

The trials used multiple endpoints to assess efficacy. For sleep maintenance, Merck compared treatment effects of suvorexant HD and placebo on two primary endpoints and at two time points, as follows: change from baseline in mean subjective total sleep time, sTSTm, at Month 1 and Month 3; and change from baseline in the PSG-derived objective wakefulness after persistent sleep onset, WASO, at Month 1 and Month 3. Likewise for sleep onset, suvorexant HD treatment effects were assessed by the following endpoints: change from baseline in mean subjective time to sleep onset, sTSOm, at Month 1 and Month 3; and change from baseline in objective latency to persistent sleep, LPS, at Month 1 and Month 3.

Key secondary endpoints in trial P028 included change from baseline in sTSTm at Week 1 and WASO at Night 1 for suvorexant HD, and an assessment of suvorexant LD on all the above-stated endpoints and time points for suvorexant HD. Trial P029 assessed suvorexant LD as exploratory analyses.

Merck used a multiplicity testing strategy to assess the primary and secondary endpoints. A longitudinal data analysis (LDA) model was used to perform the statistical analyses for efficacy. The model adjusted for the corresponding baseline value of a response variable, age group (non-elderly versus elderly), region, gender, treatment, time, and the interaction of treatment by time.

Suvorexant HD showed statistically significant efficacy effect on both sleep maintenance and sleep onset endpoints. The efficacy effects of suvorexant HD persisted through the entire treatment period and appeared to be clinically meaningful. Suvorexant low dose (LD), which was not primarily evaluated in the trials, appeared to have some efficacy effect on sleep maintenance insomnia. Safety assessments showed a dose-related risk of next-day residual effects, typified by somnolence; and results of the driving trials suggested some impairment of driving performance with the tested suvorexant doses. The risks of severe somnolence and events of clinical interests (ECIs), such as suicidal ideation, excessive daytime sleepiness, sleep paralysis, and hallucinations, from suvorexant treatment were low. However, these risks generally

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occurred more frequently with suvorexant HD treatment. These are some of the issues for discussion at the advisory committee meeting on 22 May 2013.

Benefits of Suvorexant Treatment

Sleep Maintenance Effects
For sleep maintenance, suvorexant HD treatment in both trials P028 and P029 significantly improved both subjective (sTSTm) and objective (WASO) primary endpoints at Month 1 and Month 3. Based on the pooled data, suvorexant HD compared to placebo treatment at Month 3 added about 22 minutes of sTSTm ($p < 0.00001$), and reduced WASO by 26 minutes ($p < 0.00001$). Supporting efficacy assessments using the subjective endpoint sWASO showed similar significant improvements with suvorexant HD compared to placebo at all time points (all p values < 0.006).

Assessment of secondary endpoints provided additional support of efficacy for suvorexant in treating sleep maintenance insomnia. In the secondary analyses of both trials P028 and P029, suvorexant HD significantly improved sTSTm at Week 1 and WASO at Night 1.

Also in trial P028, suvorexant LD significantly improved the sleep maintenance endpoints sTSTm and WASO at all predefined time points. Trial P029 did not include suvorexant LD for secondary endpoint assessment. Based on the pooled data, suvorexant LD compared to placebo treatment added 16 minutes of sTSTm ($p < 0.00001$), and reduced WASO by 23 minutes at Month 3 ($p < 0.00001$). Importantly, suvorexant LD failed to significantly improve sWASOm, a key sleep maintenance endpoint for FDA, at Months 1 and 3 in trial P028.

Overall, suvorexant HD, and to a less extent suvorexant LD, showed significant improvement in sleep maintenance endpoints. The difference between the treatment effect of suvorexant HD and that of suvorexant LD is about 6 minutes on sTSTm, or 3 minutes on WASO. Whether this difference in treatment effects between the suvorexant doses is sufficient to allow approval of the lower dose for sleep maintenance will be a topic of discussion at the advisory committee meeting. Of note, an acceptance of suvorexant LD as an effective treatment for sleep maintenance will fail to consider the inconsistent effect of the dose on sWASO in trial P028.

Sleep Onset Effects
Suvorexant HD improved sleep onset outcomes compared to placebo, though not as consistently as in sleep maintenance. In both trials P028 and P029, suvorexant HD treatment significantly improved the subjective primary endpoint for sleep onset (sTSOm) at Months 1 and 3 (all p values < 0.007). In trial P028, suvorexant HD significantly improved the objective primary endpoint LPS at Months 1 and 3 (p values < 0.0004). However in trial P029, suvorexant HD significantly improved LPS at Month 1

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(p = 0.00004), but it failed to provide significant LPS improvement at Month 3 (p = 0.2651). Based on the pooled data from trials P028 and P029, suvorexant HD compared to placebo treatment decreased sTSOm by about 11 minutes (p <0.00001) and LPS by 6 minutes (p = 0.00235) at Month 3.

The secondary efficacy endpoints assessed for sleep onset, sTSOm at Week 1 and LPS at Night 1, showed significant improvements with suvorexant HD compared to placebo treatment in both trials P028 and P029.

Secondary endpoint assessment for suvorexant LD in trial P028 showed inconsistent improvements on sleep onset endpoints at different time points. Suvorexant LD significantly improved sTSOm at Week 1 and LPS at Night 1. At Month 1, suvorexant LD improved LPS by 10.3 minutes compared to placebo (p = 0.0004), but it did not significantly improve sTSOm compared to placebo despite a 5.4-minute decrease in the endpoint (p = 0.05191).

Overall, suvorexant HD consistently showed significant improvement in the subjective sleep onset endpoint. The dose showed significant improvement in the objective sleep onset endpoint at all time points, except at Month 3 in one of the two trials. In contrast, suvorexant LD showed inconsistent improvements on sleep onset endpoints at different time points. Whether the inability of suvorexant HD to significantly improve LPS at Month 3 is sufficient to deny approval of the dose for sleep onset will be a topic of discussion at the advisory committee meeting.

Clinical Significance of Treatment by Responder Analysis
To further assess the clinical meaningfulness of suvorexant treatment effects, Merck conducted pre-specified responder analyses based on exploratory subjective endpoints. For sleep maintenance, a higher percentage of subjects on suvorexant treatment recorded at least 15% increase from baseline in sTSTm at the different time points. In the pooled data, the percentage of sTSTm responders in the treatment groups at Month 3 was 54.7% (376/688) for suvorexant HD compared to 41.9% (278/664) for placebo, a treatment difference of 12.8% that yielded a number needed to treat to benefit (NNTB) of 8. For sWASO, the percentage of responders in the treatment groups at Month 3 was 77.5% (529/683) for suvorexant HD compared to 69.4% (458/660) for placebo, a treatment difference of 8.1% and NNTB of 12.

On the sleep onset endpoint, there were more responders in the suvorexant-treated groups than placebo. In the pooled data, the percentage of sTSOm responders in the treatment groups at Month 3 was 76.5% (526/688) for suvorexant HD compared to 66.0% (438/664) for placebo, a treatment difference of 10.5% that yielded an NNTB of 10.

The overall data suggest that suvorexant HD has clinically significant efficacy on both sleep maintenance and sleep onset in subjects with primary insomnia. The

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assessments show that the efficacy of suvorexant HD persisted through the entire treatment period. Suvorexant LD, though not primarily evaluated in the trials, appears to have some significant but limited efficacy on sleep maintenance insomnia. In addition, point estimates, shown in review section 4.1.7, for the sleep maintenance and sleep onset endpoints from the pooled data suggest that improvements from suvorexant (HD and LD) treatment were generally consistent across the subgroups.

Risks of Suvorexant Treatment

The most prominent adverse event (AE) from suvorexant treatment was next day sleepiness that occurred at a rate similar to earlier approved insomnia drugs, based on indirect comparison. The suvorexant program also evaluated other known risks associated with sedative hypnotics. Driving trials were conducted to assess post-treatment next-day impairments in driving performance. Further, suvorexant's mechanism of action warranted scrutiny for the risk of developing narcolepsy. The sponsor provided an extensive safety database that meets the requirements of existing guidance documents.

For the safety assessments, Merck summarized data from 35 clinical trials: two Phase 3 confirmatory efficacy trials; and one Phase 3 long-term safety trial; one Phase 2 dose-finding trial; and 31 Phase 1 clinical pharmacology trials, which were conducted in healthy volunteers and special populations. The Phase 3 trials constituted the primary integrated database that Merck used to assess safety in 2,809 subjects with primary insomnia. The number of subjects exposed to the proposed treatment doses, 15 to 40mg daily, was adequate.

Two deaths occurred, both in Phase 3 trials. One subject on suvorexant HD experienced a near-drowning event, was hospitalized, went into cardiac arrest, and became brain dead. The other subject was on placebo when she experienced a stroke with brain swelling before she died.

The most significant AE was somnolence. Suvorexant caused a dose-related increase in somnolence within the initial months of treatment. Somnolence within 0-3 months in the combined Phase 3 population occurred in 10.7% (138/1291) of the suvorexant HD group, 6.7% (33/493) of suvorexant LD, and 3.0% (31/1025) of placebo. The incidence of severe somnolence, which was incapacitating with inability to work or do usual activity, was overall low but higher in the suvorexant HD group at 0.6% (8/1291) compared to suvorexant LD at 0.2% (1/493), and placebo at 0.1% (1/1025). As a result, the risk difference for severe somnolence between each suvorexant dose and placebo was small, though higher in the suvorexant HD group: 0.5% with number needed to treat to cause severe somnolence or harm (NNTH) 200 for suvorexant HD, and 0.1% with NNTH 1000 for suvorexant LD.

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The rates of somnolence in the suvorexant Phase 3 trials appear to be comparable to those of other approved drugs for the sought indication. For example, zolpidem CR 12.5 mg, which is approved for the same indication, recorded somnolence rates of 15% in the active trial arm of 102 subjects compared to 2% in placebo group of 110 subjects in 3-week trial of non-elderly subjects. In another 3-week trial in elderly subjects, the incidence of somnolence was 6% of 99 subjects on zolpidem CR 6.25 mg compared to 5% of 106 subjects on placebo. Other approved insomnia drugs registered similar rates of somnolence. Overall, information gathered on next-day somnolence may serve as a useful guide in assessing dose-response relationships, especially in future clinical dose titrations.

Merck assessed certain adverse events as Events of Clinical Interest (ECIs). These events included the following: suicidal ideation or behavior, complex sleep-related behaviors, hypnagogic and hypnopompic hallucinations, AEs associated with abuse potential, excessive daytime sleepiness (EDS), cataplexy, falls, sleep paralysis, AEs associated with a traffic or motor vehicle accident (MVA), and reports of motor vehicle accidents and violations (MVAV) based on MVAV Questionnaire. An independent committee of experts, blinded to treatment assignment and external to Merck, received ECIs of cataplexy, falls, and sleep onset paralysis for adjudication. Events of falls were adjudicated to determine whether they were suggestive of cataplexy. Overall, the incidences of the individual ECIs were low.

In the Phase 3 Population within 0-3 months of treatment, suicidal Ideation occurred in seven subjects; five of them occurred in the suvorexant HD treatment group, an incidence of 0.4% (5/1291); one subject was in the suvorexant LD group, an incidence of 0.2% (1/493); and one subject was in the placebo group, incidence of 0.15 (1/1025). Beyond three months of treatment, the suvorexant HD group recorded another case of suicidal ideation. The C-SSRS assessment identified three additional cases of suicidal ideation that investigators had not considered as AEs and so did not report them as ECIs. All three subjects were on suvorexant HD.

Only two subjects reported complex sleep-related behaviors (CSRBs) in the Phase 3 Population. Both subjects were on suvorexant HD (0.2%, 2/1291). One case, a 65-year-old male with a history of sleep talking reported an event of sleep talking on Trial Day 85 while on suvorexant HD. The same night he lunged out of bed, and hit his head and face against a wall. On Day 101, he had a different CSRB event, sleep walking, after he had received no trial medication for 2 weeks. The second case was a 58-year-old female who reported somnambulism (sleep walking) and severe sleep paralysis on Trial Day 52 while on suvorexant HD.

EDS was expected to occur suddenly during the day in a subject who had an adequate night sleep. Therefore EDS may portend safety risks during such activities as driving. In the Phase 3 Population, EDS occurred more frequently in the suvorexant HD group. The EDS incidence was 1.1% (14/1291) in suvorexant HD, 0.6% (3/493) in suvorexant

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LD, and 0.2% (2/1025) in placebo groups. The EDS risk difference for suvorexant LD compared to placebo was 0.5% (95% CI: -0.2, 1.7); the risk difference for suvorexant HD, with a 95% confidence interval that excluded zero, was 0.8% (95% CI: 0.1, 1.6), NNTH 125.

Five subjects reported hypnagogic and hypnopompic hallucinations within the first three months of treatment: 0.2% (3/1291) in the suvorexant HD group, 0.4% (2/493) in the suvorexant LD group, and none in the placebo group. The event reported for one (0.2%, 1/493) of the two subjects in the suvorexant LD group was a case of hypnagogic hallucination; the other was a hypnopompic hallucination. In contrast, all three subjects (0.2%, 3/1291) in the suvorexant HD group were cases of hypnagogic hallucinations.

Five subjects reported sleep paralysis within the first 3 months; all five received suvorexant treatment. Numerically more subjects reported this ECI while on suvorexant HD (0.3%, 4/1291) compared to suvorexant LD (0.2%, 1/493), and none on placebo. Three of the four suvorexant HD subjects had confirmed events of sleep onset paralysis on adjudication. One case resulted in treatment discontinuation.

Additional subjects on suvorexant doses of 40 mg and higher reported sleep paralysis in the Phase 2 and Phase 1 trials. In the Phase 2 trial, two subjects on suvorexant 40 mg and 80 mg reported symptoms suggestive of sleep paralysis; these events apparently occurred in the middle of night or on awakening, and not at sleep onset. In the Phase 1 trials, 2% (13/ 662) of subjects on suvorexant alone reported sleep paralysis compared to 0.3% (1/365) on placebo. All 13 subjects in the Phase 1 trial, who reported sleep paralysis on suvorexant, did so while on suvorexant doses of 40 mg to 240 mg; 6 of the 13 subjects were on suvorexant 40 mg.

The suvorexant program had no confirmed cases of narcolepsy with or without cataplexy. The external adjudication committee examined a case of muscle weakness and concluded it was not cataplexy. From the NDA safety submission, no subject among the 2,027 subjects exposed to suvorexant had confirmed cataplexy. If this is accurate, then based on “the rule of threes,” one can be 95% certain that the incidence of cataplexy in suvorexant treated subjects with insomnia is less than 0.0015 (3/2027), or less than 0.0025 (3/1218) for those exposed to at least 3 months of suvorexant treatment. Of note, the external adjudication committee reviewed the fall events, which had comparable incidence across treatment groups, and confirmed that none of the events suggested cataplexy.

Merck assessed the effects of suvorexant treatment on driving performance using AE reports of accident-related injuries, questionnaire responses on motor vehicle accidents or traffic violations (MVAs and MVAVs), and two on-the-road driving trials (P035 and P039). In the Phase 3 trial population within 0-3 months, fewer subjects on suvorexant experienced MVAs while driving than on placebo. The incidence of MVAs among subjects who drove during the trial within each treatment group was: 0.3% (3/891) on

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suvorexant HD, 0.3% (1/342) on suvorexant LD, and 0.6% (4/692) on placebo. However with MVAVs, a numerically higher rate occurred in the suvorexant LD group (2.9%, 10/342) compared to suvorexant HD group (2.3%, 13/569) and placebo (2.3%, 12/531).

In the Phase 1 driving trials (P035 and P039), Merck observed no significant impairment of next-day driving performance based on mean standard deviation of lateral position (SDLP) after one night and eight consecutive nights of suvorexant LD or HD in both elderly and non-elderly subjects. In the driving trials, some subjects who received suvorexant had increased SDLP beyond the pre-defined threshold, resulting in an imbalance in the SDLP symmetry (secondary endpoint) analyses, especially for the non-elderly subjects. Also, four non-elderly subjects felt sleepy enough to prematurely stop their driving tests. These results suggest that a potential for impairment in driving performance exists with suvorexant treatment. The sponsor provided cautionary language in the proposed label, regarding driving and suvorexant treatment, which seems appropriate.

On abrupt cessation of suvorexant treatment, no clear withdrawal effect occurred, however rebound insomnia was suggested. Merck found no obvious withdrawal effect on sudden discontinuation of suvorexant treatment; this was based on analyses of responses on Tyrer Withdrawal Symptom Questionnaire (WSQ) and reports of prespecified AEs associated with potential withdrawal. Regarding rebound effects, more subjects who switched from suvorexant HD to placebo (48.5%, 233/480) showed a decrease in total sleep time sTST on any of the three nights compared to subjects continued on placebo (37.2%, 295/793). Merck suggested that the effects observed for some sleep maintenance measures do not appear to be consistent with clinically meaningful rebound insomnia. However, the sTST findings for both suvorexant doses, and for the elderly subgroup, support the presence of a rebound effect on abrupt cessation of suvorexant treatment.

Laboratory and vital sign data did not show evidence of suvorexant having deleterious effects. However, serum cholesterol levels increased in a dose-related manner following suvorexant treatment in the Phase 2 trial. Mean serum cholesterol levels increased by 3.0 mg/dL at the suvorexant 40 mg dose level, by 2.1 mg/dL at suvorexant 20 mg dose. Merck suggested that the findings were unlikely to be clinically meaningful.

Overall, the safety data show next-day somnolence as the most prominent AE, incidences of ECIs were low, and highlighted AEs including EDS appeared to occur in a dose-related manner. Incidences of risks that are comparable to those of approved drugs for insomnia treatment may be acceptable. Merck conducted an extensive analysis of AEs including ECIs. They found no confirmed case of narcolepsy with or without cataplexy. However, risks associated severe somnolence (NNTH 200 with suvorexant HD), EDS (NNTH 125 with suvorexant HD), suicidal ideation, and suggestions of impaired driving performance on both suvorexant doses, are concerning.

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However, these risks can be addressed using drug labeling and dosing, especially when the overall treatment benefits outweigh the risks.

Benefit-Risk Summary

Suvorexant HD provided statistically significant improvements in objective and subjective endpoints of sleep maintenance and sleep onset insomnia up to 3 months. Further, it showed clinically meaningful benefits based on responder analyses of subjective endpoints of both sleep maintenance and sleep onset insomnia: NNTB of 8 for sTSTm, 12 for sWASOm, and 10 for sTSOm. On the other hand, its NNTH for severe somnolence was 200, and for EDS it was 125. Also, the indirect risks of treatment during activities such as driving while impaired present some concern. Overall, the risks of suvorexant treatment may be comparable to those of approved drugs for insomnia. As a result, the benefit-risk profile for suvorexant in treating insomnia, characterized by sleep onset and maintenance difficulties, appears favorable. Suvorexant LD may be considered in sleep maintenance insomnia, but its benefit for sleep onset insomnia remains uncertain.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no specific recommendations for postmarket risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

There is no recommendation for postmarket requirements and commitments for this drug. However, in the event of an approval of the NDA, Merck may consider examining the association of pharmacogenomic markers, using banked blood samples, and the risk of severe somnolence, EDS, hallucinations, and sleep paralysis.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed drug, suvorexant, is an immediate-release tablet for oral administration. Suvorexant is new molecular entity that is suggested to act as a highly selective antagonist for orexin receptors OX_1R and OX_2R. The proposed indication for suvorexant is for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

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Merck proposes that suvorexant be taken with or without food, immediately before bedtime. The proposed dose in non-elderly adults, younger than 65 years, is 40 mg once daily. Merck suggests that a lower dose of 20 mg once daily may be appropriate for some non-elderly adults based on individual tolerability, but the dose should not exceed 40 mg per day. For elderly adults, 65 years and older, the proposed dose is 30 mg once daily. Again, a lower dose of 15 mg once daily may be appropriate for some elderly adults and the dose should not exceed 30 mg per day.

The suvorexant tablets are film-coated to (b) (4) provide color differentiation: (b) (4) the 20 mg tablets are white and round, and the 15 mg tablets are white and oval.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 below lists currently available drug products that are marketed for the treatment of insomnia. The drug products include benzodiazepine receptor agonists that are approved for the treatment of insomnia. Other classes of products approved for insomnia include sedating antidepressants, melatonin receptor agonist, and anti-histamine agents. Short-acting sedatives are approved for insomnia characterized by sleep-onset difficulties, but not for sleep maintenance. Zolpidem tartrate ER (Ambien CR) and eszopiclone are approved for treatment of insomnia with sleep onset and maintenance difficulties.

Table 1: Marketed Insomnia Drugs

Category	Product Name	Comment
Benzodiazepine		
	Quazepam (Doral)	Treatment of insomnia associated with sleep onset difficulties and nighttime awakenings Maximum concentration of parent drug within 2 hours, but long duration of action Elimination half-life with active metabolite, 39 hours Efficacy assessed in 5-night and 28-night studies
	Temazepam (Restoril)	Short-term insomnia treatment, 7-10 days Half-life of 9 hours Lower dose for the elderly No dose adjustment for liver disease Efficacy assessed in 2-week studies
	Triazolam (Halcion)	Short half-life of parent drug and duration of action Lower dose for the elderly Little residual effects
Non-Benzodiazepine		

	Eszopiclone (Lunesta)	Treatment of sleep onset and maintenance insomnia Up to 6 months use for chronic insomnia Half-life 6 hours, duration of action 8 hours Lower dose for the elderly
	Ramelteon (Rozerem)	Sleep onset insomnia Not to use in severe liver disease Not a controlled substance Lower dose for the elderly
	Zaleplon (Sonata)	Sleep onset insomnia only Half-life 1 hour, duration of action 6 hours Does not increase total sleep time Lower dose for the elderly
	Zolpidem (Ambien)	Sleep onset insomnia No effect on sleep architecture Half-life 2.6 hours, duration of action 6 to 8 hours Lower dose for the elderly
	Zolpidem CR (Ambien CR)	Treatment of sleep onset and maintenance insomnia Half-life 2.6 hours, duration of action 7 to 8 hours Lower dose for the elderly
Sedating Anti-Depressant		
	Doxepine (Silenor)	Sleep maintenance insomnia Clinical trial experience up to 3 month Parent drug half-life 15 hours Not to be taken within 3 hours of a meal Lower dose for the elderly

Available over-the-counter drugs for insomnia treatment include diphenhydramine products. Other products are used off-label to treat insomnia, for example antidepressants, anxiolytics, antihistamines, melatonin, and herbal supplements. Non-pharmacological therapies include: sleep hygiene, stimulus control, relaxation training, and cognitive therapy. The benzodiazepine drugs estazolam (Prosom) and flurazepam (Dalmane) have been discontinued.

2.3 Availability of Proposed Active Ingredient in the United States

Suvorexant is a new chemical entity; it is not currently marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Safety issues associated with approved hypnotic drugs include residual effects such as somnolence, tiredness, psychomotor impairment, and anterograde amnesia; and rebound effects on discontinuation of a hypnotic drug. The rebound effects are more common with the short acting drugs.

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Neuropsychiatric adverse events can be problematic with hypnotic drugs. The events include confusion, amnesia, hallucinations, and worsening of psychiatric symptoms. Labeling is often used to address these issues.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Suvorexant was developed under IND 101847. Below is a summary of the key regulatory milestones:

10 April 2008: Initial IND Submission

26 June 2008: Merck responded to FDA comments on 24 June 2008 regarding IND submission and agreed to the following:

- Add serum magnesium to the clinical safety labs and increase the frequency of ECG assessments.
- Conduct a thorough QTc study, P022

5 November 2009: End-of-phase 2 (EOP2) meeting. Discussion led to the following:

- Design of two Phase 3 confirmatory efficacy trials
- Agreed on a 3-month, double-blind treatment period for both trials and including Month 3 as a key efficacy time point
- Trials to include non-elderly and elderly subjects
- Phase 3 trials testing more than one dose
- Trials to include pertinent subjective and objective efficacy endpoints, time points of measurement for a chronic insomnia indication
- FDA recommended monitoring of specific adverse events to evaluate residual effect and abuse liability potential
- Agreed on nature of driving studies to further assess residual effects
- Agreed on collecting PK samples during phase 3 trials to allow for suvorexant exposure assessment
- FDA requested sponsor to provide rationale for choice of sTST over sWASO endpoints for assessing sleep maintenance effects of suvorexant.
- Subsequently on 2 June 2011, Merck agreed to conduct additional sWASOm analyses to assess the efficacy of suvorexant for sleep maintenance using the multiplicity testing strategy as planned for sTSTm.

18 February 2011: FDA Response to Merck's submission on phase 3 trials including integrated Statistical Analysis Plan (iSAP)

- FDA disagreed on use of sTST as endpoint for sleep maintenance and recommended sWASO use instead
- FDA considered the integrated statistical analysis plan (iSAP) acceptable for exploratory efficacy analysis but not primarily for approval purposes, as each confirmatory efficacy trial needed to be convincing on its own

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2 June 2011: Teleconference on phase 3 trial protocols and Endpoints

- Merck agreed to provide sWASO data in a similar approach as sTST
- Merck related that another regulatory body opposed amending the protocols to allow sWASO use as co-primary endpoint only for FDA
- FDA to consider sWASO as the co-primary endpoint even if sTST was specified in the protocols, without penalizing Merck for this approach.
- FDA to also consider sTST and other efficacy endpoints in its overall efficacy assessments

26 July 2011: [redacted] (b) (4)

31 October 2011: [redacted] (b) (4)

19 March 2012: Pre-NDA Meeting

- Merck's plans included in protocols and iSAP, analyses of subjective wake time after sleep onset (sWASOm) to be provided in the confirmatory efficacy clinical study reports (CSRs) in the same manner as subjective total sleep time (sTSTm), to provide a supportive analysis for evaluation of sleep maintenance efficacy (as agreed to by FDA on June 2, 2011 per FDA Memorandum of Telephone Conference)
- FDA agreed that the planned organization and presentation of the efficacy and safety results appeared adequate for NDA filing
- Also, FDA agreed to Merck's plan to provide analyses of sWASO in a manner that allowed assessment of sWASOm and objective WASO as co-primary endpoints for sleep maintenance efficacy
- FDA relayed expectation of Merck to include in their analyses of adverse experience information on incidence of complex sleep-related behaviors and sleepwalking, as well as abnormalities of vital signs and laboratory testing that are related to the drug treatment
- FDA agreed with the planned format of the phase 3 CSRs
- FDA agreed on plan to provide financial disclosure information for the phase 2 and 3 trials
- FDA reiterated the need for Merck to submit a pediatric development plan in its NDA package
- FDA stated that the extent and timing of the pediatric studies will be determined upon review of the NDA
- FDA was likely to agree to a waiver for children [redacted] (b) (4) although a final decision could not be made at the time. [redacted] (b) (4)

2.6 Other Relevant Background Information

Individuals with insomnia have difficulty initiating or maintaining sleep, early awakening, nonrestorative sleep, or poor quality sleep; these complaints occur despite adequate opportunity and circumstances for sleep, and are associated with impaired daytime functioning. Normal sleep latency is 11 to 12 minutes in young adults and 9 minutes in the elderly. And, the average adult normally sleeps for about 7.5 to 8 hours (Chokroverty and Avidan, 2012).

According to the DSM IV criteria, an individual with primary insomnia takes at least 30 minutes to initiate sleep, wakes up multiple times at night, wakes up too early, or has sleep that is chronically non-restorative or poor in quality. These complaints occur at least three times a week and last a month. In addition to night-time sleep difficulty, chronic insomniacs report at least one of following forms of daytime impairment.

- Fatigue or malaise
- Attention, concentration, or memory impairment
- Social or vocational dysfunction
- Poor school performance
- Mood disturbance or irritability
- Daytime sleepiness
- Reduction in motivation, energy, or initiative
- Proneness for errors and accidents at work or while driving
- Tension headaches, or gastrointestinal symptoms in response to sleep loss
- Concerns or worries about sleep

Primary insomnia is a serious condition because of its chronic course and associated comorbidities. It is associated with decreased quality of life and work output; increased risk of accidents, and higher rates of medical and psychiatric comorbidities; and increased risk of death. Many medical conditions predispose to insomnia to the extent that over 75% of insomniacs have increased risk for comorbid medical conditions (Roth, 2007). But it is often uncertain whether insomnia precedes comorbid disorders, or the disorders cause insomnia.

Although about 30% of the adult population report at least one symptom of insomnia, only 6% have insomnia that lasts at least one month and is associated with daytime impairment (Roth T, 2007; Ohayon and Reynolds III, 2009). The prevalence of chronic insomnia of the primary type will even be lower. Importantly, over 70% of individuals with insomnia report persistence of symptoms beyond a year (Morin et al, 2009).

Multiple medical therapies are approved for insomnia treatment. There is no information to suggest approval of suvorexant in any other country. However, approved therapies provide a perspective on the unmet medical need for primary insomnia. Currently approved therapeutic options have demonstrated efficacy. For example, eszopiclone

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and zolpidem extended release formulation are approved for the treatment of sleep onset and maintenance insomnia.

Based on information from approval labels and review documents, treatment effect for zolpidem ER was examined in pre-approval trials using mean change from baseline. The treatment difference between zolpidem ER 12.5 mg and placebo at 2 weeks was noted on different outcomes, as follows:

- Objective LPS: about 6 minutes
- Subjective Sleep Onset Latency (SOL): -1 to -9 minutes
- Objective WASO (primary outcome): -3 to -11 minutes
- Subjective WASO (sWASO): -11 to -14 minutes
- Subjective Total Sleep Time (sTST): 13 to 15 minutes
- Patient Global Impression (PGI) of treatment aiding sleep: 17% to 48%

Although the approved drugs are fairly well tolerated, there are safety issues of note. For example, somnolence, a next-day residual effect, occurred in 15% of 102 non-elderly adults on zolpidem 12.5 mg, and 2% of 110 adults on placebo, in a 3-week trial. In elderly subjects, somnolence occurred in 6% of 99 subjects on zolpidem 6.25 mg and 5% of 106 subjects on placebo in a 3-week trial. In a 6-month study, next-day somnolence occurred in 6% in the zolpidem group compared to 2% in the placebo group. Note that inter-trial comparisons are difficult because of multiple factors including differences in trial populations, timing, severity of disease, and outcome assessments. Other limitations of some approved insomnia drugs include: lack of trials beyond 6 months, rebound effects, lack of driving study assessments.

Section 2.2 of this review outlines currently available drug products that are marketed for the treatment of insomnia. Without pharmacological therapies, other available treatments include: sleep hygiene, stimulus control, relaxation training, and cognitive therapy.

Despite the availability of multiple therapies, many individuals with insomnia go without pharmacological therapies. The tolerability issues of approved drugs, added to the huge number of individuals with insomnia, suggest that the medical need is currently not well met (Mignot, 2013).

3 Ethics and Good Clinical Practices

No major issues from the Phase 2 and Phase 3 trials presented in the review regarding ethical conduct and compliance with GCP.

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3.1 Submission Quality and Integrity

I found no major issues with the quality and integrity of the overall submission. The overall submission was well organized, with information easy to find.

3.2 Compliance with Good Clinical Practices

The sponsor provided assurance that all trials followed the principles of Good Clinical Practices; investigators obtained informed consent as appropriate from subjects.

Dr. Antoine El-Hage, Office of Scientific Investigations (OSI) provided a report on the clinical inspection conducted for this NDA. OSI inspected four clinical investigator sites, which enrolled subjects in the confirmatory efficacy trial: two sites for trial P028 and two for trial P029. The selection of sites for inspection was based on number of subjects enrolled and contribution to effect size of the primary efficacy outcome by the investigator site.

OSI found no regulatory violations, and gave a final classification for these inspections as No Action Indicated (NAI). The medical records reviewed were verifiable based on the information available at the sites. Further, OSI noted that the field investigator reviewed latency to onset of persistent sleep (LPS) source documents and compared the scores to the data listings provided with the assignment and found no discrepancies.

On 5 April 2013, OSI reported that the inspection of 3 sites revealed no regulatory violations, and the final classification for the inspections was No Action Indicated (NAI). In follow-up report on 26 April 2013, OSI confirmed that the fourth site's classification for the inspection was also No Action Indicated (NAI). The data submitted from all four sites in support of the clinical efficacy and safety were considered reliable. In all, OSI recommended that the data submitted from the four sites be considered as acceptable in supporting the NDA. Please refer to Dr. El-Hage's reports for an extensive discussion of the inspection findings.

3.3 Financial Disclosures

Merck obtained financial disclosure information from clinical investigators and subinvestigators in the Phase 2 and Phase 3 trials (P006, P009, P028, and P029) that certified the absence of financial interests and arrangements. The sponsor was unable to obtain the information from three investigators: one investigator did not return the form and the other two had left their investigation sites, leaving no forwarding address. No investigator held financial interest or arrangements requiring disclosure, as indicated on Form FDA 3454.

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The sponsor appears to have adequately disclosed financial arrangements with the investigators. The financial disclosures raise no obvious questions about the integrity of the data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Dr. Mohan Sapru and Dr. Akm Khairuzzaman reviewed data related to chemistry, manufacturing and controls (CMC) for this NDA. Please refer to their reviews for details of CMC issues.

4.2 Clinical Microbiology

No issue related to clinical microbiology was applicable to this clinical review.

4.3 Preclinical Pharmacology/Toxicology

Dr. Richard Siarey of the Division of Neurology Products (DNP) reviewed the nonclinical data for this NDA. Please refer to his report for details on issues related to nonclinical pharmacology and toxicology issues.

4.4 Clinical Pharmacology

Dr. Hristina Dimova, Dr. Xinning Yang, and Dr. Joo-Yeon Lee reviewed the clinical pharmacology data for the NDA. Please refer to their reviews for details of issues related to clinical pharmacology and pharmacometrics.

4.4.1 Mechanism of Action

Suvorexant is suggested to transiently block the binding of the wake-promoting neurotransmitters orexin A and orexin B to their receptors OX_1R and OX_2R. By doing so, suvorexant inhibits activation of wakefulness-promoting neurons of the arousal system, and facilitates transitions from wake to sleep.

Orexinergic neurons are believed to be less than 80,000 in humans; they are located in the lateral hypothalamic area, from where they project to other brain areas. Through these projections, orexinergic neurons regulate metabolism and sleep and wakefulness.

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4.4.2 Pharmacodynamics

Dual orexin receptor blockers (DORA) have been shown to effectively induce and maintain sleep in non-clinical models. In early Phase 1 trials, Merck used EEG data to show suvorexant's potential to promote sleep. Clinical pharmacology reviews provide details of suvorexant's pharmacodynamic effects in the Phase 1 trials.

Other DORA effects also occur. Classical narcoleptic phenotype occurs with knockout of the orexin receptors; human narcolepsy is associated with CSF orexin deficiency, likely from orexinergic neuron death. This background prompted Merck to closely evaluate for narcolepsy-like adverse events in the suvorexant development program. A potential off-target effect is appetite suppression. In addition, the significance of orexin receptors that have been observed in peripheral tissues including adipose tissue remains largely unclear (Kukkonen, 2012).

Trial P025 showed that suvorexant doses up to 240 mg, that is six times the maximum proposed dose, did not significantly prolong QTc interval.

4.4.3 Pharmacokinetics

Following oral administration under fasted conditions, suvorexant has a T_{max} of 2 hours. Suvorexant 40 mg has mean absolute bioavailability of 47%. Although T_{max} is delayed with a high fat meal, exposure or C_{max} is unaffected. As result, Merck proposes that suvorexant may be taken with or without food.

It is highly bound to human plasma proteins, especially albumin and alpha 1-acid glycoprotein.

Suvorexant is mainly metabolized by CYP3A, with a minor role by CYP2C19. The major metabolite is M9, which is thought to be pharmacologically inactive. The metabolites are the major form through which suvorexant is eliminated. The elimination occurs via feces (66%) and urine (23%).

Suvorexant's mean terminal half-life is 12.2 hours. The drug reaches steady state by 3 days following once-daily dosing. Merck proposes no dose adjustments based on gender, BMI, and race; but higher exposure was observed in obese females. Drug-drug interactions occurred with moderate and strong CYP3A inhibitors and strong CYP3A inducers, prompting Merck to propose dose adjustments with these drugs.

5 Sources of Clinical Data

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5.1 Tables of Studies/Clinical Trials

The table below summarizes the sources of clinical data used in this review.

Table 2: Listing of Clinical Trials

Trial	Objective	Design	Population	Suvorexant Dose	Treatment Duration	Primary Endpoint
Phase 3 Confirmatory Efficacy						
P028	Safety, Efficacy	R, DB, PC, MC	Primary Insomnia N=1022	Suvorexant HD Suvorexant LD Placebo	3-month, 3 more months extension	Onset – sTSO, LPS Maintenance – sTST, WASO
P029	Safety, Efficacy	R, DB, PC, MC	Primary Insomnia N=1019	Suvorexant HD Suvorexant LD Placebo	3-month	Onset – sTSO, LPS Maintenance – sTST, WASO
Phase 3 Long-term Safety						
P009	Safety	R, DB, PC, MC	Primary Insomnia N=781	Suvorexant HD Placebo	12-month	Safety
Phase 2 Dose Finding						
P006	Dose Finding	R, DB, PC, MC, CO	Primary Insomnia, non-elderly N=254	Suvorexant 80 mg Suvorexant 40 mg Suvorexant 20 mg Suvorexant 10 mg Placebo	4-week	Sleep Efficiency

(Source: Modified from Sponsor's submission ISE Page 71 Table 5.3.5.3.2-Insomnia: 1. R=randomized, DB=double-blind, PC=placebo controlled, AC=active controlled, CO=cross-over, MC=multicenter, Suvorexant LD=15 mg in elderly and 20 mg in non-elderly subjects, Suvorexant HD=30 mg in elderly and 40 mg in non-elderly subjects)

5.2 Review Strategy

Overall, this clinical review reflects input from the clinical and other discipline reviewers. Dr. Tristan Massie provided the biometrics review input. Please refer to the biometrics review by Dr. Massie for additional efficacy and statistical details.

The clinical review focused on three Phase 3 trials (P028, P029, and P009) for assessing the efficacy and safety of suvorexant. Two of the three Phase 3 trials, P028 and P029, provided 3-month treatment data for the primary efficacy review. The third Phase 3 trial P009 contributed 12-month treatment data and was included with the other two Phase 3 trials in the safety review. The Phase 2 trial P006 was also reviewed, though it was considered to be supportive in nature. Section 5.3 discusses the individual

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trials. Section 6 Review of Efficacy summarizes the efficacy results of the Phase 3 trials, including an overview of the pooled data for efficacy. Section 7 Review of Safety summarizes the combined safety data, primarily from the three Phase 3 trials. Safety data from the Phase 2 trial (P006) and pooled Phase 1 trials (31 trials) were also reviewed.

5.3 Discussion of Individual Studies/Clinical Trials

This section briefly summarizes the Phase 2 dose finding trial P006, then discusses in more detail the Phase 3 confirmatory efficacy trials and the Phase 3 long-term safety trial P009.

5.3.1 Phase 2 Dose Finding Trial P006

Administrative Information for Trial P006

- **Trial Title:** A Phase IIb, Multicenter, Randomized, Double-Blind Placebo-Controlled, 2-period Adaptive Crossover Polysomnography Study to Evaluate the Safety and Efficacy of MK-4305 in Patients with Primary Insomnia
- **Trial Treatment Dates:** 11/07/2008 to 12/26/2009
- **Trial Sites:** Multicenter (41) in the United States (29) and in Japan (12)
- **Trial Report Date:** 05/09/2011

The primary objectives of P006 were:

- To evaluate the efficacy of suvorexant compared with placebo in improving sleep efficiency (SE) as measured by polysomnography (PSG) on Night 1 and at the end of 4 weeks of treatment, where SE was defined as 100 times total sleep time (minutes) divided by time in bed (minutes).
- To evaluate suvorexant's safety and tolerability.

To achieve the trial's primary objectives, the sponsor tested the hypotheses that at least one dose of suvorexant was superior to placebo in improving SE on Night 1 and at week 4 weeks; and the drug was well tolerated.

The subjects were non-elderly males and females, aged 18 to 64 years, with primary insomnia. They had reported 6.5 hours or less total sleep time on at least 3 out of 7 nights in a week, 30 minutes or more in sleep latency on at least 3 out of 7 nights in a week, 1 hour or more of wakefulness after sleep onset, and spending 6.5 to 9 hours in bed every night. Also, they had more than 20 minutes of latency to persistent sleep (LPS) and more than 45 minutes of wake after sleep onset (WASO) on PSG measurements. They had both sleep onset and maintenance sleep difficulties, which were subjectively and objectively measurable.

P006 randomized 254 subjects with primary insomnia to receive placebo or suvorexant doses 10, 20, 40, or 80 mg. In the crossover trial, each subject received one of the

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suvorexant doses or placebo in each of the two treatment periods. Each treatment period lasted 4 weeks. A single-blind placebo Run-in Phase of 1 to 2-week duration preceded Treatment Period 1; and, a single-blind placebo washout of 1-week duration occurred between the two treatment periods. Then there was a 2-week post-trial follow up.

The primary endpoint was sleep efficiency (SE) as derived from the PSG parameter total sleep time (TST). Secondary endpoints included the PSG parameters of wake after sleep onset (WASO), and latency to persistent sleep (LPS). The trial also assessed exploratory subjective endpoints of sleep, suvorexant's pharmacokinetic (PK) parameters, the Sheehan Disability Scale and the Insomnia Severity Index.

The primary efficacy endpoint (SE) and the secondary efficacy endpoints (WASO and LPS) at Night 1 and at the end of 4 weeks of treatment, were compared between each suvorexant dose and placebo using a mixed effects model with terms for baseline value, region, treatment, sequence, period, time (as a categorical variable), and treatment-by-time and period-by time interactions. Merck used a fixed sequential multiplicity testing strategy for the primary and secondary efficacy hypotheses to provide strong control of Type I error.

Results of Trial P006

On primary endpoint assessment, suvorexant in all tested doses significantly increased sleep efficiency SE compared to placebo at Night 1, with treatment difference in mean SE from placebo of at least 5.2 minutes, and at Week 4, with treatment difference of at least 4.7 minutes (all p values <0.005).

For the secondary endpoint analyses, suvorexant in all tested doses significantly decreased the sleep maintenance measure of WASO compared to placebo at Night 1, with difference in mean WASO from placebo of at least -21.2 minutes, and at Week 4, with difference of at least -21.4 minutes (all p values <0.001).

However, on the secondary endpoint LPS, a measure of sleep onset, no suvorexant dose was statistically significantly better than placebo. Table 3 below is Merck's summary of the efficacy analyses for the primary and secondary endpoints:

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Table 3: Efficacy in Trial P006, Sleep Efficiency (SE), Wakefulness after Persistent Sleep Onset (WASO) and Latency to Onset of Persistent Sleep (LPS)

Endpoint	Timepoint	Treatment	Diff in LS Means versus Placebo (SE)	(95% CI)	p-value
SE	Night 1	Suvorexant 10 mg	5.2 (1.71)	(1.9, 8.6)	0.002
		Suvorexant 20 mg	7.6 (1.72)	(4.2, 11.0)	<0.001
		Suvorexant 40 mg	10.8 (1.72)	(7.4, 14.2)	<0.001
		Suvorexant 80 mg	12.9 (1.73)	(9.5, 16.3)	<0.001
	Week 4	Suvorexant 10 mg	4.7 (1.58)	(1.6, 7.8)	0.003
		Suvorexant 20 mg	10.4 (1.60)	(7.2, 13.6)	<0.001
		Suvorexant 40 mg	7.8 (1.61)	(4.6, 10.9)	<0.001
		Suvorexant 80 mg	7.6 (1.63)	(4.4, 10.9)	<0.001
WASO	Night 1	Suvorexant 10 mg	-21.2 (6.27)	(-33.5, -8.8)	<0.001
		Suvorexant 20 mg	-24.7 (6.31)	(-37.1, -12.3)	<0.001
		Suvorexant 40 mg	-33.9 (6.33)	(-46.4, -21.5)	<0.001
		Suvorexant 80 mg	-36.8 (6.36)	(-49.4, -24.3)	<0.001
	Week 4	Suvorexant 10 mg	-21.4 (6.45)	(-34.2, -8.7)	0.001
		Suvorexant 20 mg	-28.1 (6.58)	(-41.0, -15.1)	<0.001
		Suvorexant 40 mg	-33.2 (6.61)	(-46.3, -20.2)	<0.001
		Suvorexant 80 mg	-28.9 (6.70)	(-42.1, -15.7)	<0.001
LPS	Night 1	Suvorexant 10 mg	-3.4 (6.16)	(-15.6, 8.7)	0.577
		Suvorexant 20 mg	-9.4 (6.17)	(-21.5, 2.8)	0.130
		Suvorexant 40 mg	-23.1 (6.20)	(-35.3, -10.9)	<0.001
		Suvorexant 80 mg	-25.4 (6.23)	(-37.7, -13.1)	<0.001
	Week 4	Suvorexant 10 mg	-2.3 (5.00)	(-12.2, 7.5)	0.644
		Suvorexant 20 mg	-22.3 (5.08)	(-32.3, -12.3)	<0.001
		Suvorexant 40 mg	-3.8 (5.09)	(-13.8, 6.3)	0.459
		Suvorexant 80 mg	-9.5 (5.17)	(-19.7, 0.7)	0.068

(Source: Modified from Sponsor's submission P006 CSR Page 5. Results were based on a mixed effects model with terms for baseline value, region, treatment, sequence, period, time, treatment-by time and period-by-time interactions)

Merck conducted additional post hoc analysis of Period 1 only, on finding evidence of a carryover effect for LPS, and determined the following differences compared to placebo and p-values for Night 1: for suvorexant 10 mg, -19.1 minutes (p-value, 0.020); suvorexant 20 mg, -17.4 minutes (p-value, 0.030); suvorexant 40 mg, -31.0 (p-value, < 0.001); and suvorexant 80 mg, -22.3 minutes (p-value, 0.007). At Week 4 the following differences compared to placebo and p-values were obtained: suvorexant 10 mg, -20.2 minutes (p-value, 0.019); suvorexant 20 mg, -24.6 minutes (p-value, 0.003); suvorexant 40 mg, -15.7 (p-value, 0.063); and suvorexant 80 mg, -19.6 minutes (p-value, 0.024).

Efficacy on Subjective Endpoints

Merck provided analyses for patient-reported outcomes based on morning and evening e-Diary entries: subjective total sleep time, time to sleep onset, wake after sleep onset, number of awakenings, quality of sleep VAS, freshness of sleep VAS, function VAS, tiredness VAS, energy VAS, and relaxation VAS.

At the end of Trial Week 4, subjects on suvorexant 40 mg and 80 mg doses appeared to have improvements with nominal p-values < 0.05 compared to placebo in the following endpoints: total sleep time, time to sleep onset, wake after sleep onset and subjective sleep quality. The subjects on both suvorexant doses reported fewer awakenings than those on placebo at Week 4.

I reviewed the subjective endpoints that were prominently assessed in the subsequent Phase 3 trials: subjective Total Sleep Time (sTST), Time to Sleep Onset (sTSO), and WASO (sWASO). The subjective total sleep time improved on suvorexant 40 mg and 80 mg doses, as shown in the table below.

Table 4: Subjective Total Sleep Time (sTST) at 4 Weeks in Trial P006

Treatment	N	Baseline in minutes (SD)	Mean Change from Baseline in minutes (SD)	Treatment-Placebo Difference in minutes (95% CI)	P value for Difference
Placebo	211	341.4 (60.1)	27.7 (50.31)	-	-
Suvorexant 10 mg	57	338.9 (59.6)	38.6 (50.58)	5.5 (-6.3, 17.3)	0.3578
Suvorexant 20 mg	53	338.4 (55.9)	34.6 (50.23)	-1.8 (-13.9, 10.4)	0.7741
Suvorexant 40 mg	51	349.5 (64.0)	38.1 (55.19)	29.6 (17.1, 42.1)	<.0001

Suvorexant 80 mg	49	342.7 (54.9)	42.3 (42.85)	19.4 (7.1, 31.7)	0.0022

(Source: Modified from Sponsor's submission P006 CSR Page 409 Table 14-72.

Improvements in time to sleep onset with nominal p values less than 0.05 occurred on suvorexant doses of 40 mg and 80 mg as shown in the table below.

Table 5: Subjective Time to Sleep Onset (sTSO) at 4 Weeks in Trial P006

Treatment	N	Baseline in minutes (SD)	Mean Change from Baseline in minutes (SD)	Treatment-Placebo Difference in minutes (95% CI)	P value for Difference
Placebo	211	63.0 (31.0)	-9.8 (29.46)	-	-
Suvorexant 10 mg	57	67.4 (31.4)	-16.7 (24.62)	-3.0 (-9.3, 3.3)	0.3523
Suvorexant 20 mg	53	68.1 (25.7)	-15.6 (25.59)	-4.3 (-10.8, 2.2)	0.1946
Suvorexant 40 mg	51	56.5 (31.7)	-19.2 (24.35)	-17.4 (-24.1, -10.7)	<.0001
Suvorexant 80 mg	49	59.0 (33.0)	-18.4 (20.35)	-7.7 (-14.3, -1.1)	0.0219

(Source: Modified from Sponsor's submission P006 CSR Page 411 Table 14-73)

Based on revised analyses Merck submitted on 28 February 2013, sWASO improvements from baseline with nominal p values less than 0.05 occurred on suvorexant doses of 40 mg and 80 mg as shown in the table below.

Table 6: Subjective WASO (sWASO) at 4 Weeks in Trial P006

Treatment	N	Baseline in minutes (SD)	Mean Change from Baseline in minutes (SD)	Treatment-Placebo Difference in minutes (95% CI)	P value for Difference
Placebo	212	68.8 (41.7)	-16.4 (38.26)	-	-
Suvorexant 10 mg	57	71.2 (39.1)	-23.9 (32.61)	-3.5 (-11.4, 4.4)	0.3838
Suvorexant 20 mg	54	72.3 (47.7)	-18.0 (35.63)	3.2 (-4.9, 11.2)	0.4405
Suvorexant 40 mg	51	75.3 (53.6)	-24.7 (36.26)	-18.3 (-26.7, -10.0)	<.0001
Suvorexant 80 mg	49	56.5 (32.9)	-24.6 (31.77)	-13.9 (-22.1, -5.6)	0.0010

(Source: Modified from Sponsor's submission Efficacy Amendment Submitted on 02/28/13 Page 5 for P006 Revised CSR Table 14-74)

Safety Results Trial P006
The trial reported no serious adverse events and no deaths. Overall, 10% (26/254) of the subjects discontinued the trial. Discontinuations in each trial treatment were as follows: placebo 5.6% (14/249), suvorexant 10 mg 3.2% (2/62), suvorexant 20 mg 6.6% (4/61), suvorexant 40 mg 0.0% (0/59), and suvorexant 80 mg 9.8% (6/61). The most common AEs by SOC were nervous system disorders. The incidence of somnolence was greater at the higher suvorexant doses compared to placebo as follows: placebo 0.4% (1/243), suvorexant 10 mg 0.0% (0/62), suvorexant 20 mg 4.9% (3/61), suvorexant 40 mg 11.9% (7/59), and suvorexant 80 mg 9.8% (6/61). Other adverse event findings are summarized below and in section 7 Review of Safety.

Table 7: Adverse Event Categories in Phase 2 Dose Finding Trial P006

	Placebo		**Suvorexant 10 mg**		**Suvorexant 20 mg**		**Suvorexant 40 mg**		**Suvorexant 80 mg**		**Total Suvorexant**	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	249	(100.0)	62	(100.0)	61	(100.0)	59	(100.0)	61	(100.0)	243	(100.0)
Subjects with one or more adverse events	50	(20.1)	11	(17.7)	12	(19.7)	18	(30.5)	22	(36.1)	63	(25.9)
Subjects with drug- related adverse events, nvestigator determined	17	(6.8)	3	(4.8)	4	(6.6)	12	(20.3)	14	(23.0)	33	(13.6)
Discontinued due to an adverse event	3	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.6)	1	(0.4)
Discontinued due to a drug-related adverse event	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.6)	1	(0.4)

(Source: Modified from Sponsor's submission P006 CSR Page 6)

One subject discontinued trial treatment on suvorexant 80 mg because of the adverse event of visual hallucinations. Three subjects on placebo discontinued because of elevated hepatic enzymes (n=1), tachycardia (n=1), and difficulty thinking with sedation (n=1). These discontinuations occurred in Period 1 of the trial, so carryover effect was unlikely to have played a role in their occurrence.

There were no dose-related suvorexant effects on vital signs, though decreases of 20 mm Hg or more in systolic blood pressure, both sitting and standing, were greater for suvorexant compared to placebo. Also, ECG data did not demonstrate any clear differences in QT prolongation among treatment groups.

Merck suggested that there were no abnormal laboratory values of clinical relevance. However, suvorexant treatment was associated with a dose-related increase in serum

Reference ID: 3301133

cholesterol levels with the maximum mean increase of 6.0 mg/dL at suvorexant 80 mg dose by Week 4.

Reviewer Note: On efficacy at Week 4, all tested suvorexant doses (10 mg, 20 mg, 40 mg and 80 mg) improved the primary efficacy endpoint of sleep efficiency and the objective measure of sleep maintenance, WASO. Only the 40 mg and 80 mg doses appeared to improve the subjective measures of sleep maintenance, sTST and sWASO. None of the doses improved sleep onset that was measured objectively by LPS based on the planned statistical analyses. Suvorexant 40 mg and 80 mg doses appeared to improve the subjective measure of sleep onset, sTSO. There were no deaths and no serious AEs in Trial P006. The most frequent AEs by SOC were nervous system disorders, particularly somnolence. The safety profile and efficacy results at the Phase 2 trial stage suggest that the choice of suvorexant 40 mg for further evaluation in improving both sleep onset and sleep maintenance in the subsequent Phase 3 trials was appropriate.

5.3.2 Phase 3 Confirmatory Efficacy Trial P028

Administrative Information for Trial P028

- **Trial Title:** A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Study to Evaluate the Safety and Efficacy of MK-4305 in Patients with Primary Insomnia – Study A
- **Trial Treatment Dates:** 05/25/2010 to 11/22/2011
- **Trial Sites:** Multicenter with 30 United States (US) and 61 Ex-US centers: Australia (2), Brazil (1), Canada (3), Denmark (1), Finland (2), France (3), Germany (6), Japan (26), Peru (1), Russian Federation (2), South Africa (2), Spain (3), Taiwan (4), Sweden (2), and United Kingdom (3)
- **Trial Report Date:** 07/12/2012

Objectives and Rationale

- To evaluate, in subjects with primary insomnia, efficacy of suvorexant high dose (HD) compared with placebo in improving sleep maintenance and onset at Months 1 and 3, using subjective patient-reported outcomes and objective polysomnographic (PSG) assessments; and to assess the safety and tolerability of suvorexant for up to 3 months of treatment.

Trial Design and Conduct

Trial P028 Overview

This was a multi-center, randomized, double-blind, placebo-controlled, parallel group, questionnaire and PSG trial to assess the safety and efficacy of suvorexant in subjects with primary insomnia. The subjects were males and females 18 years or older, who spent 6.5 to 9 hours nightly in bed but had total sleep time of less than 6.5 hours, sleep latency of 30 minutes or more, and wakefulness after sleep of 1 hour or more. The trial

excluded subjects with narcolepsy, other neurological disorders, and psychiatric disorders requiring ongoing treatment.

The trial had eight visits, V1 to V7 and R2, and two cohorts that had subjects in either the Questionnaire-only cohort (Q-cohort) or the PSG-plus-Questionnaire cohort (PQ-cohort). The screening period commenced at Visit 1. Subjects meeting trial and cohort-specific criteria were evaluated at Visit 2 and commenced on a 2-week single-blind placebo run-in. Subjects in the PQ-cohort underwent PSG assessments during the screening period. At Visit 3, the subjects were randomized in a 3:2:3 ratio to receive suvorexant HD (high dose), suvorexant LD (low dose), or placebo during a 3-month double-blind core treatment period, which ended at Visit 7. During the core treatment period, subjects returned to the clinic after randomization, for Visit 4 at the end of Week 2, and Visits 5-7 end of Months 1, 2, and 3. Overnight PSG assessments occurred at Night 1 and end of Months 1 and 3 visits for PQ cohort subjects, as shown in the figure below.

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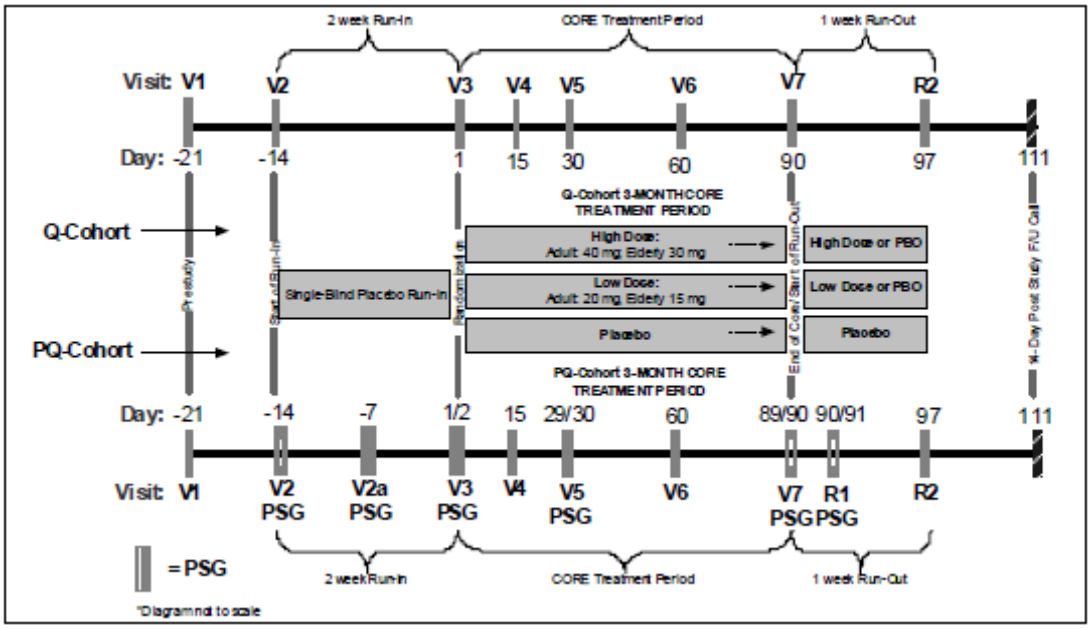
Figure 1: Trial Flow Diagram for P028 Core Period without Extension



(Source: Sponsor's submission SCE Page 138, replicated in P028 Protocol Page 37)

Subjects in both cohorts completed a daily sleep questionnaire via an electronic diary (e-diary). There was an optional 3-month double-blind extension. PQ-cohort subjects who did not enter the extension underwent another PSG assessment at Night 90, the first night of the run-out period, Visit R1-PSG; in effect, these subjects had two consecutive PSG visits, Night 89 (end of Month 3) and Night 90 (beginning of run-out). At the end of core treatment or extension period, there was a 1-week double-blind run-out period.

The table below summarizes the trial schedule and assessments for Q-Cohort.

Table 8: Trial P028 Flow Chart for Q-Cohort Only – Screening, Core Treatment, and Run-out Periods

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QUESTIONNAIRE –Q Cohort	Screening/Placebo Run-In Period		Q-cohort 3-Month Core Treatment Period					Run-Out Period (No extension)		Post-Study Period (No extension)
Treatment Period	Prestudy	Screening/ Run-In	Baseline/ Randomization	End of Week 2	End of Month 1	End of Month 2	End of Month 3	End of Run-Out	Discon Visit[1]	Post-study Follow up Call[2]
Visit Number:	1	2	3	4	5	6	7	R2		
Target Study Day:	-21	-14	1	15	30	60	90	97		111
Visit Window:		-3/+21[17]	-3/+3	-3/+3	-3/+3	-3/+3	-3/+3	-3/+3		-2/+2
Procedures/Assessments[3]					PM[2]					
Informed Consent	X					X[4]	X[4]			
Provide Participant Identification Card	X									
Medical and Psychiatric history	X									
Diagnostic Interview/Sleep History/DSM-IV-TR	X									
MINI International Neuropsychiatric Interview (MINI)	X									
Mini Mental State Examination (MMSE) (elderly only)	X									
Quick Inventory of Depressive Symptomatology (QIDS-SR16)	X									
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X	X	X	X[5]
Inclusion/Exclusion	X	X	X			X	X			
Prior and concomitant therapy	X	X	X	X	X	X	X	X	X	X
Physical examination	X						X		X	
Vital signs	X[6]	X	X	X	X	X	X	X	X	
ECG	X		X	X	X		X		X	
Hematology, chemistry, urinalysis	X[7]		X	X	X		X		X	
Urine drug screen[8]	X		X				X		X	
Urine pregnancy test [9]	X		X		X	X	X		X	
Informed consent for *optional* Specimens for Genetic and Other Biomedical Research analysis[10]	X									
Collection of *Optional* Specimens for genetic and Other Biomedical research[10]			X							
Blood sample for HLA DQB1 allele (DNA) [11]			X							
Pharmacokinetic (PK) Sampling [18]			X	X	X		X		X	
Visit Number:	1	2	3	4	5	6	7	R2		
Target Study Day:	-21	-14	1	15	30	60	90	97		111
Visit Window:		-3/+21[17]	-3/+3	-3/+3	-3/+3	-3/+3	-3/+3	-3/+3		-2/+2
Procedures/Assessments[3]										
Call IVRS	X	X	X		X	X	X	X	X[12]	
Dispense Study Medication to patient		X	X		X	X	X			
Monitor Study Medication Compliance			X	X	X	X	X	X	X	
Evening/Morning e-diary [13]	X[14]----------X									
Tyrer Withdrawal Symptom Questionnaire (evening e-diary) [15]			X[15]				X[15]			
Clinical Global Impressions-Severity (CGI-S)			X	X	X	X	X	X	X	
Clinical Global Impressions- Improvement (CGI-I)				X	X	X	X	X	X	
Patient Global Impressions-Severity (PGI-S)			X	X	X	X	X	X	X	
Patient Global Impressions- Improvement (PGI-I)				X	X	X	X	X	X	
Insomnia Severity Index (ISI)			X		X		X		X[16]	
Motor Vehicle Accidents and Violations		X	X	X	X	X	X	X	X	X
Modified Cataplexy Questionnaire (MCQ)	X----------MCQ will be completed for any report of an adverse experience of cataplexy or falls. ----------X									
Adverse Experiences	X----------X									

1 1) For patients who discontinue during the double-blind treatment period or the double-blind run-out period, a discontinuation visit should be performed. (2) Patients who complete the study or prematurely discontinue during the double-blind treatment period or double-blind run-out period will receive a 14-day (from last dose of study medication) follow-up phone call to assess the potential emergence of any adverse experiences as well as review concomitant medications that may have been taken. If patient discontinues due to an AE, a PK sample should be drawn.

2 Patients will be contacted by telephone 14 days after the end of the run-out or premature discontinuation to assess the potential emergence of any adverse experiences as well as review concomitant medications that may have been taken.

3 Study procedures/assessments should be performed at a consistent time of day if possible.

4 Patients will need to be re-consented at Visit 6 for the optional 3-month extension. It should be noted that at ~ 2 weeks prior to Visit 7, sites should call patients to confirm their consent decision. In the event that a patient changes their consent after Visit 6, consent must be updated at Visit 7. Please see protocol details for more specific information.

5 Patients who at any time during the post-study period spontaneously report AEs of suicidal thoughts or ideation must be assessed by the Primary Investigator using the C-SSRS.

6 Body Mass Index (Appendix 6.2) will be calculated only at the Visit 1 from weight and height. Height will only be measured at Visit 1. Weight will be measured at the specified Vital Sign time points. Please refer to Appendix 6.3 for the measurement of weight and Appendix 6.4 for measurement of blood pressure.

7 Hepatitis/HIV screening are additional Visit 1 procedures to be performed at the discretion of the investigator.

8 At Visit 1, urine drug screen test should be sent into central lab vendor for confirmation. At visits thereafter, patients will undergo an on-site drug test. If a patient has a positive urine drug test, a sample must be sent to the central laboratory for confirmation.

9 All female patients of child-bearing potential (< 65 years old) will undergo a serum pregnancy test at Visit 1 which will be sent into the central lab vendor for confirmation. All other pregnancy tests at other visits will be done on-site. If a female patient has a positive urine pregnancy test, a serum pregnancy test must be performed and sent to the central laboratory for confirmation.

10 Signing of the optional pharmacogenomic sample consent form and obtaining the optional genetic sample can be completed at Visit 3 (randomization). This is not necessary to participate in the study. Sample is only collected if patient is randomized.

11 The allele sample is not optional and will be collected at Visit 3 (randomization). Consent for sample is captured within the main informed study consent.

12 Call IVRS to discontinue the patient from the study.

13 The patient will complete an evening and morning e-diary at home every day after satisfactory completion of Visit 1 and up to Visit 3, pending study criteria is met at each consecutive visit.

14 Morning e-diary should be completed at home by the patient after completion of normal morning routine (e.g., using the bathroom, eating breakfast), and preferably within an hour of awakening for the day. E-diary should also be performed on the morning prior to all treatment period visits. Evening e-diaries should be completed by the patient after completion of normal evening routine, and preferably within 30 minutes prior to Lights-Off. Evening e-diary should be completed prior to drug administration.

15 Tyrer Questionnaire will be part of the e-diary evening questionnaire and will be completed in the evenings ONLY as indicated: Nights 2 and 3-post randomization; first 5 nights of run-out (i.e. Nights 90-94); the Tyrer will be triggered by the Study Coordinator at the following visits: Visit 3 and Visit 7. Please refer to specific instructions in the e-diary procedures manual.

16 The patient will be asked to mail in a completed ISI to the Investigator site 1 month after completion of their discon visit.

17 The +21 day visit window prior to Visit 2, is provided to accommodate a 4-week washout period for certain prohibited medications.

18 Samples can be taken at any time during the study visit and will be collected and archived.

(Source: Sponsor's submission P028 Protocol 1.7 Pages 14-16)

The table below summarizes the trial schedule and assessments for PQ-Cohort.

Table 9: Trial P028 Flow Chart for PQ-Cohort – Screening, Core Treatment, and Run-out Periods

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PSG plus Questionnaire PQ-Cohort	Screening/Placebo Run-In Period					PQ Cohort 3-Month Core Treatment Period								Run-Out Period (No extension)			Post-Study Period (No extension)
Treatment Period	Prestudy	Screening PSG		Baseline PSG		Randomization Night 1 PSG		End of Week 2	End of Month 1 PSG		End of Month 2	End of Month 3 PSG		Run-Out PSG		End of Run-Out	Discon Visit[1]	Post-study Follow up Call[2]
PSGs		PSG 1		PSG 2		PSG 3			PSG 4			PSG 5		PSG 6				
Visit Number:	1	2-PSG		2a-PSG		3-PSG		4	5-PSG		6	7-PSG		R1-PSG		R2		
Target Study Day:	-21	-14/-13		-7/-6		1/2		15	29/30		60	89/90		90/91		97		111
Visit Window:		-3/+21[3]		-3/+3[3]		-3/+3		-3/+3	-3/+3		-3/+3	-3/+3		0		-3/+3		-2/+2
Procedures/Assessments[4]		PM[5]	AM	PM[5]	AM	PM[5]	AM		PM[5]	AM		PM[5]	AM	PM[5]	AM			
Informed Consent	X										X[6]	X[6]						
Provide Participant Identification Card	X																	
Medical and Psychiatric history	X																	
Diagnostic Interview/Sleep History/ DSM-IV-TR	X																	
MINI International Neuropsychiatric Interview (MINI)	X																	
Mini Mental State Examination (MMSE) (elderly only)	X																	
Quick Inventory of Depressive Symptomatology (QIDS-SR16)	X																	
Columbia Suicide Severity Rating Scale (C-SSRS)	X		X		X		X	X		X	X		X			X	X	X[7]
Inclusion/Exclusion	X	X	X	X	X	X					X	X						
Prior and concomitant therapy	X	X		X		X		X	X		X	X		X		X	X	X
Physical examination	X												X				X	
Vital signs	X[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG	X				X			X		X			X				X	
Hematology, chemistry, urinalysis	X[9]				X			X		X			X				X	
Urine drug screen[10]	X	X		X		X			X			X					X	
Urine pregnancy test[11]	X					X			X		X	X					X	
Informed consent for *optional* Specimens for Genetic & Other Biomedical Research[12]	X																	
Collection of *Optional* Specimens for genetic & Other Biomedical research[12]							X											
Blood sample for HLA DQB1 allele (DNA)[13]							X											
Pharmacokinetic (PK) Sampling[14]					X		X	X		X			X				X	
Alcohol breath test[15]	X	X		X		X			X			X		X				
Call IVRS	X	X				X				X	X		X[22]			X	X[16]	
Dispense Study Medication to patient			X				X			X	X			X				
Witnessed Study Medication Dose		X		X		X[17]			X			X		X				
Monitor Study Medication Compliance				X		X		X	X		X	X		X		X	X	
Polysomnography (PSG)		X		X		X			X			X		X				
Evening/Morning e-diary[18]	X[19]----------X																	
Tyrer Withdrawal Symptom Questionnaire (evening e-diary)[20]						X[20]						X[20]		X[20]				
Digit Symbol Substitution Test (DSST)			X		X		X			X			X		X			
Clinical Global Impressions-Severity (CGI-S)					X			X		X	X		X		X	X	X	
Clinical Global Impressions-Improvement (CGI-I)								X		X	X		X		X	X	X	
Patient Global Impressions-Severity (PGI-S)					X			X		X	X		X		X	X	X	
Patient Global Impressions-Improvement (PGI-I)								X		X	X		X		X	X	X	
Insomnia Severity Index (ISI)						X			X			X					X[21]	
Motor Vehicle Accidents and Violations		X		X		X		X	X		X	X				X	X	X
Modified Cataplexy Questionnaire (MCQ)	X----------MCQ will be completed for any report of an adverse experience of cataplexy or falls.----------X																	
Adverse Experiences	X----------X																	

1 1) For patients who discontinue during the double-blind treatment period or the double-blind run-out period, a discontinuation visit should be performed. (2) Patients who complete the study or prematurely discontinue during the double-blind treatment period or double-blind run-out period will receive a 14-day (from last dose of study medication) follow-up phone call to assess the potential emergence of any adverse experiences as well as review concomitant medications that may have been taken. If patient discontinues due to an AE, a PK sample should be drawn.

2 Patients will be contacted by telephone 14 days after the end of the run-out or premature discontinuation to assess the potential emergence of any adverse experiences as well as review concomitant medications that may have been taken.

3 The +21 day visit window prior to Visit 2, is provided to accommodate a 4-week washout period for certain prohibited medications. The interval of time between Visits 2, 2a and 3 should be a minimum of 4 days in order to allow for confirmation of PSG results from the centralized PSG reading center.

4 Study procedures/assessments should be performed around consistent time of day if possible.

5 Measurements that are performed in the PM, with the exception of the PSG, will be conducted prior to study drug administration. This applies to all PSG study visits.

6 Patients will need to be re-consented at Visit 6 for the optional 3-month extension. It should be noted that at ~ 2 weeks prior to Visit 7, sites should call patients to confirm their consent decision. In the event that a patient changes their consent after Visit 6, consent must be updated at Visit 7. Please see protocol details for more specific information.

7 Patients who at any time during the post-study period spontaneously report AEs of suicidal thoughts or ideation must be assessed by the Primary Investigator using the C-SSRS.

8 Body Mass Index (Appendix 6.2) will be calculated only at Visit 1 from weight and height. Height will only be measured at the Visit 1. Weight will be measured at the specified Vital Sign time points (for PSG visits, weight is measured at AM time points). Please refer to Appendix 6.3 for the measurement of weight and Appendix 6.4 for measurement of blood pressure.

9 Hepatitis/HIV screening are additional Visit 1 procedures to be performed at the discretion of the investigator.

10 At Visit 1, urine drug screen test should be sent into central lab vendor for confirmation. At visits thereafter, patients will undergo an on-site drug test. If a patient has a positive urine drug test, a sample must be sent to the central laboratory for confirmation.

11 All female patients of child-bearing potential (< 65 years old) will undergo a serum pregnancy test at Visit 1 which will be sent into the central lab vendor for confirmation. All other pregnancy tests at other visits will be done on-site. If a female patient has a positive urine pregnancy test, a serum pregnancy test must be performed and sent to the central laboratory for confirmation.

12 Signing of the optional pharmacogenomic sample consent form and obtaining the optional genetic sample can be completed at Visit 3 (randomization). This is not necessary to participate in the study. Sample will only be collected if patient is randomized.

13 The allele sample is not optional and will be collected at Visit 3 (randomization). Consent for sample is captured within the main informed study consent.

14 All PK samples taken on PSG in-clinic visits should be drawn 9 hours ±15 minutes post dosing on AM portions of visit and will be archived. All other non-PSG visit samples can be taken at any time during the study visit and will be collected and archived.

15 Patients should have a negative alcohol breath test on the PSG visit nights. Please refer to the Safety Measurements in Section 3.4.1.5 of this protocol for more details.

16 Call IVRS to discontinue the patient from the study.

17 First dose of randomized blinded study medication will be dispensed.

18 The patient will complete an evening and morning e-diary at home every day after satisfactory completion of Visit 1 and up to Visit 3, pending study criteria is met at each consecutive visit, in order to determine the median habitual bedtime of the patient.

19 Morning e-diary should be completed by the patient after completion of normal morning routine (e.g., using the bathroom, eating breakfast), and preferably within an hour of awakening for the day during the at home period or within 1 hour following Lights-On during PSG days. E-diary should also be performed on the morning prior to all treatment period visits. Evening e-diaries should be completed by the patient after completion of normal evening routine, and preferably within 30 minutes prior to Lights-Off. Evening e-diary on PSG nights should be completed prior to drug administration.

20 Tyrer Questionnaire will be part of the e-diary evening questionnaire and will be completed in the evenings ONLY as indicated: Nights 2 and 3-post randomization; Visit 7-PM (Night 89) and for the next 4 nights (i.e. Nights 89-93, cumulative). The Tyrer will be triggered by the Study Coordinator at the following visits: Visit 3-PSG (Night 1) and Visit 7-PSG (Night 89). Please refer to specific instructions in the e-diary procedures manual.

21 The patient will be asked to mail in a completed ISI to the Investigator site 1 month after completion of their discon visit.

22 On the AM portion of Visit 7, for patients not entering the extension, sites will call into IVRS to log the visit and will obtain run-out study medication. Study medication should only be dispensed to the patient the evening of R1-PSG Day 90. For patients who do enter the extension, sites will call into IVRS on the AM of Visit 7 and extension study medication will be dispensed to the patient at that time."

(Source: Sponsor's submission P028 Protocol 1.8 Pages 17-19)

Table 10 below summarizes the trial schedule and assessments for the 3-Month Extension and Run-Out Periods

Table 10: Trial P028 Flow Chart for the 3-Month Extension and Run-Out Periods

	3-Month Extension Period			Run-Out Period		Post-Study Period
Treatment Period	End of Month 4	End of Month 5	End of Month 6	End of Run-out	Discon Visit[1]	Post-study Follow up Call[2]
Visit Number:	8	9	10	11		
Target Study Day:	120	150	180	187		201
Visit Window:	-3/+3	-3/+3	-3/+3	-3/+3		-2/+2
Procedures/Assessments [3]						
Concomitant therapy review	X	X	X	X	X	X
Physical examination			X		X	
Vital signs	X	X	X	X	X	
ECG			X		X	
Hematology, chemistry, urinalysis			X		X	
Urine drug screen[4]					X	
Urine pregnancy test[5]	X	X	X		X	
Pharmacokinetic (PK) Sampling					X	
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X[6]
Call IVRS	X	X	X	X	X[7]	
Dispense Study Medication to patient	X	X	X			
Monitor Study Medication Compliance	X	X	X	X	X	
Evening/Morning e-diary[8]	X	X	X	X		
Tyrer Withdrawal Symptom Questionnaire (evening e-diary)[9]			X[9]			
Clinical Global Impressions-Severity (CGI-S)	X	X	X	X	X	
Clinical Global Impressions- Improvement (CGI-I)	X	X	X	X	X	
Patient Global Impressions-Severity (PGI-S)	X	X	X	X	X	
Patient Global Impressions-Improvement (PGI-I)	X	X	X	X	X	
Insomnia Severity Index (ISI)			X		X[10]	
Motor Vehicle Accidents and Violations	X	X	X	X	X	X
Modified Cataplexy Questionnaire (MCQ)	X-MCQ will be completed for any report of an adverse experience of cataplexy or falls-X					
Adverse Experiences	X----------X					

[1] 1) For patients who discontinue during the double-blind extension period or the double-blind run-out period, a discontinuation visit should be performed. (2) Patients who complete the study or prematurely discontinue during the double-blind treatment period or double-blind run-out period will receive a 14-day (from last dose of study medication) follow-up phone call to assess the potential emergence of any adverse experiences as well as review concomitant medications that may have been taken. If patient discontinues due to an AE, a PK sample should be drawn.

[2] Patients will be contacted by telephone 14 days after the end of the run-out or premature discontinuation to assess the potential emergence of any adverse experiences as well as review concomitant medications that may have been taken.

[3] Study procedures/assessments should be performed around consistent time of day if possible.

[4] All patients will undergo an on-site urine drug test. If any patient has a positive urine drug test, a sample must be sent to the central laboratory for confirmation.

[5] Female patients of child-bearing potential (< 65 years old) will undergo an on-site urine pregnancy test. If a female patient has a positive urine pregnancy test, a serum pregnancy test must be performed and sent to the central laboratory for confirmation.

[6] Patients who at any time during the post-study period spontaneously report AEs of suicidal thoughts or ideation must be assessed by the Primary Investigator using the C-SSRS.

[7] Call IVRS to discontinue the patient from the study.

[8] E-diary will be completed during the last day of Visit 7 and the first 4 days of the extension. It will also be completed during the 5 days prior Visit 8 on the actual day of Visit 8, plus 5 days following Visit 8 (11 days total). Additionally, the e-diary will be completed 5 days prior to Visit 9 and every day thereafter throughout the end of run-out. Evening e-diary should be completed at home by patient at bedtime prior to taking study medication. Morning e-diary should be completed at home by patient after their normal morning routine (e.g., using the bathroom, eating breakfast) and preferably within an hour of waking for the day.

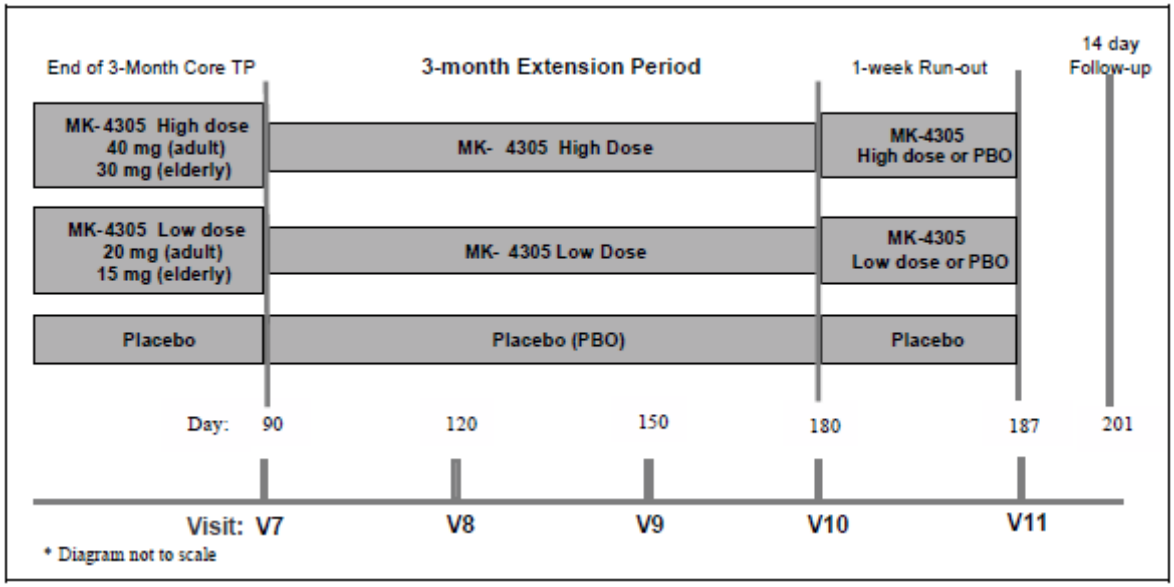
[9] For patients entering the 3-month extension, the Tyrer will be completed on the last day of Visit 7 and the first 4 days of the extension (as noted in Sections 1.7 & 1.8), as well as on the evening of Visit 10 (Night 180) and the following 4 consecutive evenings (i.e Nights 180 to 184, cumulative). The Tyrer will be triggered by the Study Coordinator at Visit 7 and Visit 10.

[10] The patient will be asked to mail in a completed ISI to the Investigator site 1 month after completion of their discon visit.

(Source: Sponsor's submission P028 Protocol 1.9 Page 21)

Trial Population
The trial plan was to enroll 960 subjects, 60% non-elderly and 40% elderly. The sponsor randomized subjects who provided written informed consent and met the trial inclusion and exclusion criteria, using an interactive voice randomization system (IVRS), in a 3:2:3 ratio to suvorexant HD (40 mg for non-elderly; 30 mg for elderly), suvorexant LD (20 mg for non-elderly; 15 mg for elderly), or placebo. Stratifying randomized subjects according to age group (< 65 years; 65 years and older) and cohort (PQ or Q cohort) yielded four distinct strata. Subjects entering the 3-month extension remained on their assigned core treatment during the extension, as shown in the flow diagram below. For the double-blind run-out period, subjects randomized to suvorexant during the core treatment period were simultaneously randomized in a 1:1 ratio to either continue assigned core treatment at the same suvorexant dose or switch to placebo. At completion, the trial had randomized 1,022 subjects.

Figure 2: Trial Flow Diagram for P028 Extension and Run-Out Periods



(Source: Sponsor's submission P028 Protocol Page 37)

Key Inclusion Criteria (From sponsor's submission - Protocol)

Visit 1: Pre-Trial Inclusion
1.a. Male or female subject, 18 years of age on the day of signing informed consent.
1.b. Subject with DSM-IV-TR diagnosis of Primary Insomnia based on the investigator's judgment and the subject's sleep history as assessed on the Sleep Diagnostic Interview/Sleep History.
1.c. For subjects 65 years old: Mini Mental State Examination (MMSE) score of 25.
1.d. Subject is in good physical and mental health in the opinion of the investigator.

1.e. A female subject, who was of reproductive potential, had a serum β-hCG level consistent with the nongravid state, and agreed to use acceptable contraception.
1.f. Subject reported total sleep time of < 6.5 hours on at least 3 out of 7 nights each week during the 4 weeks prior to Visit 1.*
1.g. Subject reported sleep latency of 30 minutes on at least 3 out of 7 nights each week during the 4 weeks prior to Visit 1.*
1.h. Subject reported 1 hour of wakefulness after sleep onset on at least 3 out of 7 nights each week during the 4 weeks prior to Visit 1.*

**Applied to 1.f to 1.h: For subject chronically using a hypnotic or anxiolytic for treatment of insomnia, defined as use of 4 times/week, a 4-week washout (or 5 half lives, whichever was greater) was required prior to assessment of these Visit 1 criteria.*

1.i. Subject reported spending 6.5 to 9 hours nightly in bed on at least 3 out of 7 nights each week during the 4 weeks prior to Visit 1.
1.j. The subject's regular bedtime was between 9 pm (21:00) and 1 AM (01:00).
1.k. During the study, the subject was willing to refrain from napping.
1.l. Subject understood the trial procedures, alternative treatments available, and risks involved with the trial, and voluntarily agreed to participate by giving written informed consent.
1.m. During the trial, subject was willing to limit alcohol to 2 drinks a day and at least 3 hours before going to bed. (A drink was defined as a 12-ounce bottle or can of beer (about14 grams alcohol) or a 4-ounce glass of wine (about 12 grams alcohol) or 1 ounce of liquor (80 proof or 40% alcohol, about 9 grams alcohol)).
1.n. During the trial, the subject was willing to limit caffeine consumption to 5 standard 6-ounce cups of caffeinated beverages a day, or 600 mg caffeine, avoid caffeine after 4 pm (16:00).
1.o. Subject was willing to limit nicotine as required by the protocol.
1.p. Subject was able to read, understand and complete questionnaires and diaries, including operation of the e-diary.

PQ-Cohort Only: Visit 1- Pre-Trial

1.a. Subject was willing to stay overnight at a sleep laboratory for PSG testing visits as specified in Trial Flow Chart.
1.b. Subject was willing to stay in bed for at least 8 hours each night while at the sleep laboratory.
1.c. During the trial, subject was willing to refrain from drinking alcohol on all PSG visit days, and at least 24 hours prior to a PSG visit.
1.d. During the trial, subject was willing to avoid caffeine after 1 pm (13:00) on PSG visit days.

Visit 2, Visit 2a-PSG: Screening Inclusion

2.a. Subject continued to fulfill all of the Pre-Trial Inclusion Criteria.

PQ-Cohort ONLY: Visit 2-PSG-Screening PSG

2.b. Subject had LPS >20 minutes during the Screening PSG at Visit 2. Note: "Persistent sleep" was defined as the first continuous 20 epochs (30 seconds each) of a non-wake state.
2.c. Subject had WASO >45 minutes during the Screening PSG at Visit 2.

PQ-Cohort ONLY: Visit 2a-PSG-Baseline PSG
2.d. Subject continued to fulfill all of the Pre-Trial Inclusion Criteria.
2.e. Subject had LPS >20 minutes on both Screening and Baseline PSG nights.
2.f. Subject had a mean WASO of 60 minutes or higher on the combined Screening and Baseline PSG nights, where neither night can be 45 minutes or less.

Visit 3, Visit 3 PSG Inclusion:
3.a. Subject continued to fulfill all of the Prestudy Inclusion Criteria.
3.b. Subject demonstrated compliance with the morning and evening e-diary for the period between Visit 2 and 3. E-diary compliance was defined as subject having completed at least 70% (for example, 7 out of 10 days and nights) of both the morning and evening e-diaries.

Q-Cohort ONLY: Visit 3- Baseline/Randomization
3.c. During the single-blind placebo run-in, subject had a subjective total sleep time (sTST) < 6.5 hours on at least 4 nights for the week prior to baseline, based on the e-diary.
3.d. During the single-blind placebo run-in, subject had a subjective time to sleep onset (sTSO) 30 minutes on at least 4 nights for the week prior to baseline, based on the e-diary.

Visits 6 and 7: Extension Inclusion
4.a. & 5.a. Subject was compliant with trial procedures.

Key Exclusion Criteria for Trial P028 (From sponsor's submission - Protocol)

Visit 1: Pre-Trial Exclusion
1.a If female, subject was pregnant (positive serum pregnancy test at pretrial), breastfeeding, or expecting to conceive within the projected trial duration.
1.b Subject was expecting to donate egg or sperm during the trial.
1.c Subject had a history or diagnosis of any of the following conditions:
- Narcolepsy
- Cataplexy, familial or idiopathic
- Circadian Rhythm Sleep Disorder
- Parasomnia including nightmare disorder, sleep terror disorder, sleepwalking disorder, and REM behavior disorder
- Sleep-related Breathing Disorder – obstructive or central sleep apnea syndrome or central alveolar hypoventilation syndrome
- Periodic Limb Movement Disorder

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- Restless Legs Syndrome
- Primary Hypersomnia
- Excessive Daytime Sleepiness (EDS), not attributable to primary insomnia

1.d In the opinion of the investigator, subject had difficulty sleeping due to a confounding medical condition such as chronic pain syndromes, chronic migraine, cardiac disease, nocturia (>3 times/night), asthma, gastroesophageal reflux disease (GERD), or hot flashes.

1.e Subject had a history of trans-meridian travel (across >3 time zones or >3 hours time difference) within the previous 2 weeks or expected to travel (across >3 time zones or >3 hours time difference) during the trial. For PQ Cohort only, Transmeridian travel was prohibited 1 week prior to PSG visits.

1.f Subject had history of shift work (defined as permanent night shift or rotating day and night shift work) within the previous 2 weeks or anticipated the need to perform shift work during the trial.

1.g Subject had any history of a neurological disorder, including but not limited to seizure disorder (other than single episodes of childhood febrile seizures), stroke, transient ischemic attack, multiple sclerosis, cognitive impairment, or significant head trauma with sustained loss of consciousness within the last 10 years.

1.h Subject had any of the following:

- Lifetime history of bipolar disorder, a psychotic disorder, or posttraumatic stress disorder
- A psychiatric condition requiring treatment with a prohibited medication
- Other psychiatric condition that, in the investigator's opinion, would interfere with the subject's ability to participate in the trial.

1.i Subject had evidence of ongoing major depression (per MINI), significant depressive symptoms (for example, a score 20 on the Quick Inventory of Depressive Symptomatology-Self Report Scale (QIDS-SR16)) or suicidal ideation (that is, a score 2 or more on the QIDS-SR16 item #12) or, in the investigator's opinion, was unable to complete the trial procedures in a safe and appropriate fashion (regardless of QIDS-SR16 score).

1.j Subject had a history of substance abuse or dependence, except if subject was in sustained full remission for at least one year or met criteria for early full remission, according to DSM-IV-TR. Substances included alcohol, marijuana, hypnotics, other prescription drugs, and drugs of abuse, but exclude nicotine dependence. A subject who fulfilled DSM-IV-TR criteria for sustained remission could be included if he or she, in the investigator's opinion, was at low risk for further drug dependence or abuse.

1.k Subject had either a history within the past 6 months prior to the Pretrial visit or current evidence of an unstable or clinically significant cardiovascular disorder, including but not limited to:

- Acute coronary syndrome
- Unstable angina
- Congestive heart failure
- Cardiogenic syncope

Reference ID: 3301133

- Cardiomyopathy
- Any symptomatic arrhythmia

1.l Subject, in the opinion of the investigator, had a history or current evidence of any condition, therapy, lab or ECG abnormality or other circumstances that might confound the results of the trial, or interfere with the subject's participation for the full duration of the trial, such that it was not in the best interest of the subject to participate. Examples of excluded disorders included, but not limited to: HIV or other relevant infections, history of acute or chronic hepatitis, history of gastric bypass or gastric banding surgery, active endocrine disorders. However, subjects with well-controlled insulin-dependent diabetes, type II diabetes, or hypothyroidism were allowed if on stable doses of appropriate therapy for 1 month or more prior to Screening Visit 2.

1.m Subject at Visit 1-Pretrial had, by ECG, a clinically significant AV conduction disturbance (e.g., second or third degree AV block), sick sinus syndrome, bradycardia (resting pulse <40), or accessory bypass tract (for example, Wolff-Parkinson-White).

1.n Subject had abnormal pre-randomization laboratory values per the guidance below or other clinically significant, unexplained laboratory abnormality in the opinion of the investigator:

- Alanine transaminase (SGPT or ALT) >1.5 x the upper limit of normal (xULN)
- Aspartate transaminase (SGOT or AST) >1.5 x ULN
- Total bilirubin >1.5 x ULN
- Serum Creatinine of >2 mg/dL

1.o Subject had a positive screening urine drug screen to, for example, benzodiazepines, cannabinoids, cocaine, and other drugs.

1.p Subject had a history of hypersensitivity or idiosyncratic reaction to more than two chemical classes of drugs, including prescriptions and over-the-counter medications.

1.q Subject was taking, or planned to take, one or more of the medications shown in table below within the specified washout period prior to Visit 2-Screening and throughout the course of the trial. Section on concomitant treatments below contains a detailed list of the prohibited medications.

Table 11: List of Prohibited Medications and Specified Washout Period

Treatment	Interval*
Investigational compounds	4 weeks or 5 $t_{½}$ lives
Strong CYP3A4 Inhibitors and Inducers	2 weeks or 5 $t_{½}$ lives
Antihistamines (sedating)	2 weeks
Hypnotics	2 weeks or 5 $t_{½}$ lives **
Other Psychotropics:	
Antidepressants (other than fluoxetine) Fluoxetine	2 weeks 4 weeks
Anticonvulsants	2 weeks
Antipsychotics	2 weeks or 5 $t_{½}$ lives
Anxiolytics (benzodiazepines, non-benzodiazepines)	2 weeks or 5 $t_{½}$ lives**
Centrally acting anticholinergics	2 weeks
Any CNS depressants	2 weeks
Mood Stabilizers	2 weeks
Stimulants	2 weeks
Supplements with possible psychotropic effects	2 weeks
Other Medications:	
Anticoagulants, systemic glucocorticoids, isotretinoin, diet pills	2 weeks

* Interval notes minimum washout period. Washout should occur for 5 half lives or the minimum specified period (2 or 4 weeks), which ever is longer to systemically eliminate the compound.

** The indicated hypnotic/anxiolytic washout (prior to Visit 2) applies to intermittent use only (defined as use of < 4 times/week). For those patients chronically using a hypnotic or anxiolytic (defined as use of ≥ 4 times/week) a 4-week washout (or 5 $t_{½}$ lives, whichever is greater) must occur prior to completion of Visit 1. Please see Section 3.2.1 for more information.

(Source: Sponsor's Submission P028 Protocol Page 34 Table 2-1)

1.r Subject consumed the equivalent of >15 cigarettes a day, and the investigator confirmed that the subject's sleep disturbance was in part the result of this consumption.
1.s Subject had donated blood products or had had phlebotomy of >300 mL within 8 weeks of signing informed consent, or intended to donate or receive blood products during trial participation.
1.t Subject had a history of malignancy 5 years or more prior to signing informed consent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.
1.u Subject had a Body Mass Index (BMI) >40 kg/m^2.
1.v Subject was previously randomized in another investigational suvorexant trial.
1.w Subject was at the time participating or had participated in a trial with an investigational compound or device within 30 days of signing informed consent or was not willing to refrain from participating in another trial while participating in this trial.
1.x Subject was unlikely to adhere to the trial procedures and restrictions, keep appointments or was planning to relocate during the trial.

Visit 2, Visit 2a-PSG: Screening Exclusion
2.a. Subject met any of the Pretrial Exclusion Criteria.

PQ-Cohort ONLY: Visit 2-PSG-Screening PSG

2.b. Subject had a positive alcohol breath test as analyzed by a breathalyzer machine.

2.c. Subject had an underlying pathology of sleep identified during the screening PSG as follows:

- Non-elderly (<65 years of age)
  - An Apnea Hypopnea Index >10; or;
  - >10 periodic leg movements associated with an arousal per hour of sleep (PLMAs)
- Elderly (65 years or older)
  - • An Apnea Hypopnea Index >15; or;
  - • >15 periodic leg movements associated with an arousal per hour of sleep (PLMAs)

Visits 6 and 7: Extension Exclusion

- Subject had developed a condition that further puts the subject at risk for continuing in the trial.

Reviewer Comment:
The overall trial design was typical for a Phase 3 insomnia drug assessment. Also, the inclusion and exclusion criteria appear appropriate for a trial of a new molecular entity in subjects with primary insomnia.

Treatments

Treatment Groups

- Suvorexant LD: 15 mg in elderly (65 years and older) and 20 mg in non-elderly subjects (18 to 64 years old)
- Suvorexant HD: 30 mg in elderly and 40 mg in non-elderly subjects
- Placebo

All medications were administered orally, at bedtime or 30 minutes before bedtime during PSG visits.

Concomitant/Restricted Medications:
The trial required the subjects to discontinue prohibited medications at least 2 weeks prior to the Screening Visit 2, except investigational medications and fluoxetine that had to be withdrawn at least 4 weeks prior to Screening Visit 2. Subjects on chronic hypnotic or anxiolytic treatment, defined as use of 4 times/week, needed a 4-week washout (or 5 t½ lives, whichever was greater) before completing Visit 1. The table below is Merck's summary of the medications that were prohibited or limited during the trial.

Table 12: Prohibited or Restricted Concomitant Medications in P028

Medication Category	Examples*/ Notes (*specific medications listed were examples of class	Status

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	compounds and were not limited to those listed)	
Strong CYP3A4 Inhibitors	Included atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, refinavir, ritonavir, saquinavir, telithromycin, and voriconazole	P
Strong CYP3A4 Inducers	Included barbiturates, carbamazepine, efavirenz, modafinil, nevirapine, phenytoin, pioglitazone, primidone, rifabutin, rifampin, rifapentin, St. John's Wort (hypericum), and systemic glucacorticoids (inhaled steroids were permitted)	P
Centrally acting analgesics	Could be taken as needed for pain relief (with the documented approval of the Merck clinical monitor), but use may not exceed 3 consecutive days or > 4 days per any week. Note: Use of narcotics for pain relief was to be avoided if there were effective alternative therapies such as non-steroidal anti-inflammatory agents (NSAIDS). Sponsor was notified of any use exceeding 3 consecutive days or > 4 days per any week.	L
Centrally acting anticholinergics		P
Other Psychotropic Agents		
Antihistamines: Sedating Non-sedating	 Note: Non-sedating antihistamines were not to be taken more than twice a week. Note: Montelukast sodium (Singulair) and inhaled corticosteroids could be used more than twice weekly as needed for allergic symptoms	 P L
Anticonvulsants		P
Antidepressants		P
Antipsychotics		P
Anxiolytics: Benzodiazepines Non-benzodiazepine anxiolytics		 P P
Hypnotics: Prescription hypnotics OTC hypnotics	 Included Tylenol PM, Nytol PM, Unisom	 P P
Mood stabilizers		P
Muscle relaxants (centrally acting with psychotropic effects)	Included methocarbamol Note: Use of centrally acting muscle relaxants were avoided if there were effective alternative therapies such as NSAIDS.	L
Stimulants	Included modafinil, methylphenidate	P

Supplements with possible psychotropic effects	Included melatonin, kava-kava, S-Adenosyl methionine (SAMe), St. Johns Wort, tryptophan, and valerian	P
Other Agents		
Anticoagulants	Included warfarin, heparin, and ticlopidine. Note: baby aspirin was allowed if taken 4 weeks prior to Visit 2	P
Diet Pills (prescription and over-the-counter)		P
Glucocorticoids Systemic glucocorticoids Inhaled corticosteroids	 Included dexamethisone Included beclomethisone Note: Inhaled corticosteroids could be used more than twice weekly as needed for allergic symptoms.	 P L
Isotretinoin	Accutane	P
Over-the-Counter (OTC), combination products containing caffeine for pain relief	Included Excedrin and Anacin Note: Two tablets were equivalent to a caffeinated beverage and were counted as such toward the maximum of 5 beverages per day. As with any caffeinated beverages, subjects were advised to refrain from using these medications after 4 PM. These medications were not to be taken on days when PSGs were conducted.	L
Pseudoephedrine	Note: Only to be used before 2 PM, and no more than twice a week. Dosage was limited to 30 mg of active ingredient in each tablet. Extended release formulations were prohibited. These medications were not to be taken on days when PSGs were conducted.	L
P = Prohibited; L = Limited		

(Source: Modified from Sponsor's Submission P028 Protocol Pages 57-58 Table 3-1)

Primary Endpoints

Overall, Merck performed eight primary endpoints assessments, considering the different endpoints for sleep maintenance and sleep onset, and considering the different time points. The different endpoints for sleep maintenance were sTSTm and WASO, while those for sleep onset were sTSOm and LPS. The time points of assessment for the primary endpoints were Month 1 and Month 3. The endpoints' response at the respective time points was change from baseline.

For sleep maintenance, Merck compared the treatment effects of suvorexant HD and placebo on four primary endpoint assessments, that is, two primary endpoints assessed at two time points, as follows:

Sleep Maintenance

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- Change from baseline in sTSTm at Month 1
- Change from baseline in sTSTm at Month 3
- Change from baseline in WASO at Month 1
- Change from baseline in WASO at Month 3

For sleep onset, Merck also compared suvorexant HD and placebo treatments on four primary endpoint assessments, again, as follows:

Sleep Onset
- Change from baseline in sTSOm at Month 1
- Change from baseline in sTSOm at Month 3
- Change from baseline in LPS at Month 1
- Change from baseline in LPS at Month 3

The table below summarizes the sleep terms Merck used to define the endpoints.

Table 13: Definitions of Sleep Terms for Trial Endpoints

Objective PSG Measures			
A Waking Event	"awakening"; an awakening	A waking event is defined as at least 2 consecutive 30 sec epochs of the PSG scored as waking and bracketed by Stages 1, 2, 3, 4, or REM.	N
LPS	Latency to onset of Persistent Sleep:	The time from the beginning of the recording (lights off) to the onset of the first continuous 20 epochs of a non wake state (i.e., 10 consecutive minutes of sleep in Stages 1, 2, 3, 4, or REM)	Min
SE	Sleep Efficiency:	Total Sleep Time divided by the total duration of the recording period x 100	%
TST	Total Sleep Time:	The duration of REM and non-REM sleep from lights off to lights on.	Min
WASO	Wakefulness After persistent Sleep Onset:	Duration of wakefulness after the onset of persistent sleep to lights on. Wakefulness is defined as any epoch of stage 0. Onset of persistent sleep is defined as the first epoch of 10 consecutive minutes of sleep (REM or non-REM (stage 1, 2, 3 or 4)).	Min
Subjective Measures			
sWASO	Subjective Wakefulness After persistent Sleep Onset:	Patient's reported amount of time spent awake from the time the patient falls asleep to the time the patient wakes up for the day	Min or hours
sTSO	Subjective Time to Sleep Onset:	Patient's report of the time he or she required to fall asleep	Min or hours
sNAW	Subjective Number of Awakenings:	Patient's report of the number of times the patient wakes after falling asleep	N
sTST	Subjective Total Sleep Time:	Patient's report of the total amount of time spent asleep before waking for the day	Min or hours

(Source: Sponsor's Submission P028 Protocol Page 136 Appendix Table 6.6)

A central laboratory performed sleep stage scoring of each 30-second epoch on PSG recordings. Each 30-second epoch received a score of Wake, Stage 1, 2, 3, 4 or REM. The resultant sleep scores were used to derive the PSG parameters for the trial's objective endpoints at Baseline, Night 1 (Day 1), Month 1 (+/-7 days from the target Day 30), and Month 3 (+/-7 days from the target Day 89). Merck defined sleep maintenance parameter WASO as objective or PSG-measured wakefulness after persistent sleep onset. The sleep onset parameter LPS was time to onset of persistent sleep, as defined in the table above. Baseline was defined as PSG parameters obtained at Visit 3 for objective endpoints.

For the subjective endpoints, Merck derived weekly averages, including Months 1 and 3, from the mean of daily measurements that fell within the range of days shown in the table below; the derivation included only the weeks with at least 3 days of data, and excluded PSG nights. Merck defined sTSTm as the mean of the subjective or subjects' daily (morning) e-diary report of total sleep time. The sleep onset endpoint sTSOm was defined as the mean of subjects' daily (morning) e-diary report of time to sleep onset total sleep time. Baseline for subjective endpoint assessments was the mean of the last seven (non-missing) measurements obtained from the placebo-run-in period.

Table 14: Range of Days for Subjective Endpoint Assessments

Week/Month	Day Range
Base Period	
Week 1	2-8
Week 2	9-15
Week 3	16-22
Month 1	23-30
Month 1.5	31-45
Month 2	46-60
Month 2.5	61-75
Month 3	76-90
Extension period	
Month 4	115-125
Month 5	145-155
Month 6	166-180

(Source: Sponsor's Submission P028 Protocol Page 101)

Secondary Endpoints

The secondary endpoints included the following parameters:

Sleep Maintenance:

- Suvorexant HD: Change from baseline sTSTm at Week 1.
- Suvorexant HD: Change from baseline in WASO at Night 1.

- Suvorexant LD: Change from baseline in sTSTm at Week 1, Month 1, and Month 3.
- Suvorexant LD: Change from baseline in WASO at Night 1, Month 1, and Month 3.

Sleep Onset:
- Suvorexant HD: Change from baseline in sTSOm at Week 1.
- Suvorexant HD: Change from baseline in LPS at Night 1.
- Suvorexant LD: Change from baseline in sTSOm at Week 1, Month 1, and Month 3.
- Suvorexant LD: Change from baseline in LPS at Night 1, Month 1, and Month 3.

Exploratory Endpoints
The exploratory endpoints included the following:

- Subjective outcomes evaluated at three time points: Week 1, Month 1, and Month 3
    - Number of awakenings (sNAWm)
    - Wake time after sleep onset (sWASOm) (minutes)
    - Sleep quality (sQUALm)
    - Refreshed upon awakening (sREFRESHEDm)

- Responder analysis endpoints:
    - Percentage of subjects achieving 6-point or higher improvement from baseline in mean Insomnia Severity Index (ISI) total score
    - Percentage of subjects responding to treatment based on the cumulative frequencies of percent change from baseline in mean subjective total sleep time (sTSTm) on the daily sleep diary (for example, 15% response)
    - Percentage of subjects responding to treatment based on the cumulative frequencies of percent change from baseline in mean subjective time to sleep onset (sTSOm) on the daily sleep diary (for example, 15% response)

- PSG exploratory endpoints evaluated at Night 1, end of Month 1, and end of Month 3 are shown below.
    - Sleep architecture endpoints:
        - Stage 1 duration (S1) in minutes from Lights-Off to Lights-On
        - Stage 1 percent (PS1): defined as S1 divided by TST
        - Stage 2 duration (S2) in minutes from Lights-Off to Lights-On
        - Stage 2 percent (PS2): defined as S2 divided by TST
        - Stage 3 duration (S3) in minutes from Lights-Off to Lights-On
        - Stage 3 percent (PS3): defined as S3 divided by TST
        - Stage 4 duration (S4) in minutes from Lights-Off to Lights-On
        - Stage 4 percent (PS4): defined as S4 divided by TST
        - Rapid Eye Movement sleep (REM) duration in minutes from Lights-Off to Lights-On

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        - Rapid Eye Movement sleep (REM) percent: defined as REM divided by TST
        - Power spectra: Each 1 Hz bin from 1 to 128 Hz and traditional bands which include Delta, Theta, Alpha, Slow Beta, and Gamma
    - Other PSG sleep parameters:
        - Total sleep time (TST) in minutes: defined as duration of REM + NREM (Stages 1+2+3+4) from Lights-Off to Lights-On
        - Number of awakenings (NAW): Counted from persistent sleep onset to Lights-On, an awakening was defined as a PSG recording of at least two consecutive wake epochs and was bracketed by an epoch of Stage 1, 2, 3, or 4 non-REM sleep or REM sleep.
        - Slow wave sleep (SWS) in minutes: defined as duration of Stage 3/4 sleep from Lights-Off to Lights-On
        - Sleep onset latency (SOL) in minutes: defined as the duration of time from Lights-Off to the first epoch of any stage of sleep (sleep onset)
        - Non-REM epoch to REM: Number of non-REM epochs to the first epoch of REM sleep
        - Number of Arousals (NOA): Counted from sleep onset to Lights-On, an arousal was defined as a PSG recording of at least one wake epoch and was bracketed by an epoch of Stage 1, 2, 3, or 4 non-REM sleep or REM sleep.
        - Wakefulness After persistent Sleep Onset (WASO) by hour

- Severity and improvement of insomnia exploratory endpoints included:
    - Clinical Global Impressions – Severity of Illness (CGI-S)
    - Patient Global Impressions – Severity of Illness (PGI-S)
    - ISI total score
    - Clinical Global Impressions – Improvement (CGI-I)
    - Patient Global Impressions – Improvement (PGI-I)

- Additional ISI items evaluated in exploratory analyses included the following:
    - ISI difficulty falling asleep score
    - ISI difficulty staying asleep score
    - ISI waking too early score
    - ISI satisfied/dissatisfied with current sleep score
    - ISI sleep problem interfere with daily functioning score
    - ISI sleep problem impair QOL score
    - ISI worried/distressed about sleep problem score

Insomnia Severity Index (ISI) assessed, on a 7-item subject-reported outcome scale, the severity of a subject's insomnia based on the severity of sleep-onset and sleep maintenance difficulties and any insomnia-related interference with daytime functioning. Each item was rated on a 5-point scale (0-4). An ISI total score in the range of 22 to 28

reflected severe insomnia; a score of 15 to 21 reflected moderate insomnia; and scores less than 10 indicated minimal to no insomnia.

The Clinical Global Impressions (CGI) of Severity of Illness (CGI-S) and of Improvement (CGI-I) were clinician-administered instruments used to assess insomnia severity (CGI-S) and change over time (CGI-I). Each scale was rated from 1 to 7, with lower scores reflecting less illness severity and greater improvement. The CGI-I measured global clinical improvement at a certain time point compared to the subject's baseline.

Patient Global Impressions of Severity Scale (PGI-S) assessed the subjects' description of their insomnia severity in the preceding week based on a response to the question: "How would you describe your insomnia over the past week? Each response was rated 0 (none) to 5 (very severe). For Patient Global Impressions of Improvement Scale (PGI-I), the subjects assessed their insomnia improvement from baseline, with the following question: Compared to when I started the trial, my insomnia is now. Each response ranged from 1 (very much better) to 7 (very much worse).

Pharmacokinetic parameters
Investigators collected PK samples at any time during pre-randomization baseline visit 3, Week 2 visit 3, Month 1 visit 4, Month 3 visit 5, and discontinuation visit. PK samples collected during PSG visits were drawn in the mornings at about 9 hours post-dose.

Safety parameters:
Investigators measured the following to monitor safety:

- Physical examination, vital signs, Electrocardiogram (ECG), and clinical labs were performed according to the trial schedule
- Tyrer Withdrawal Symptom Questionnaire via the evening e-diary questionnaire
- Digit Symbol Substitution Test (PQ-cohort only)
- Columbia Suicide Severity Rating Scale
- Motor Vehicle Accidents and Violations
- Subjective adverse experiences including events of clinical interest (ECIs) as follows:
    - Cataplexy
    - Sleep paralysis; sleep-onset paralysis
    - Hypnagogic or hypnopompic hallucinations
    - Excessive Daytime Sleepiness (EDS)
    - Suicidal ideation and/or behaviors
    - Complex sleep-related behaviors
    - Falls
    - Events associated with potential for abuse
    - Adverse experiences associated with traffic or motor vehicle accidents (when a subject was the driver)

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Adjudication Procedures
Investigators identified selected adverse experiences for adjudication by an independent expert committee that was external to Merck and was blinded to the subject's treatment assignment. The selected AEs were ECIs that suggest potential intrusion of REM into either wakefulness or initiation of sleep: cataplexy and sleep onset paralysis.

Medication Compliance
Compliance was monitored and determined at each trial visit by interviewing subjects, reviewing e-diary data, counting pills.

Ethics
This trial was conducted according to the principles of Good Clinical Practice. An institutional review board reviewed and approved the protocol.

Statistical Analysis

Efficacy Analysis
Merck used a longitudinal data analysis (LDA) model on the Full Analysis Set (FAS) population to perform the efficacy analyses. The analysis model adjusted for baseline value of the response variable, age group (non-elderly versus elderly), region, gender, treatment, time, and the interaction of treatment by time. To control for type 1 error, Merck analyzed the primary and secondary endpoints using a multiplicity strategy, as follows:

- Bonferroni approach to evaluate two distinct indications – sleep maintenance and sleep onset effects
- Fixed sequential testing procedure to move from the Month 1 set of primary hypotheses to the Month 3 set of primary hypotheses
- Hochberg approach within each time point to evaluate the objective and subjective endpoints

As shown in the table below, evaluating two indications required a Bonferroni approach to control the overall Type I error among all primary hypotheses at the two-sided 5% significance level. As a result, endpoints for sleep maintenance effect (sTSTm and WASO) were tested at the two-sided 2.5% level and endpoints for sleep onset effect (sTSOm and LPS) were tested at the two-sided 2.5% level.

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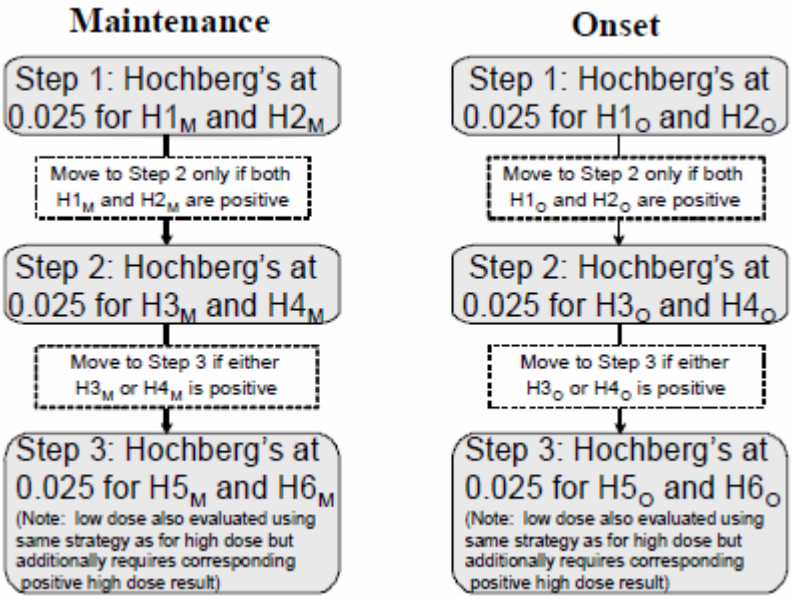
Table 15: Multiplicity Strategy for Testing Primary and Secondary Hypotheses

Dose	Hypotheses	Maintenance (α=0.025 [2-sided])	Onset (α=0.025 [2-sided])
High	Primary	$H1_M$: sTST at Month 1	$H1_O$: sTSO at Month 1
High	Primary	$H2_M$: WASO at Month 1	$H2_O$: LPS at Month 1
High	Primary	$H3_M$: sTST at Month 3	$H3_O$: sTSO at Month 3
High	Primary	$H4_M$: WASO at Month 3	$H4_O$: LPS at Month 3
High	Secondary	$H5_M$: sTST at Week 1	$H5_O$: sTSO at Week 1
High	Secondary	$H6_M$: WASO at Night 1	$H6_O$: LPS at Night 1
Low	Secondary	$H1'_M$: sTST at Month 1	$H1'_O$: sTSO at Month 1
Low	Secondary	$H2'_M$: WASO at Month 1	$H2'_O$: LPS at Month 1
Low	Secondary	$H3'_M$: sTST at Month 3	$H3'_O$: sTSO at Month 3
Low	Secondary	$H4'_M$: WASO at Month 3	$H4'_O$: LPS at Month 3
Low	Secondary	$H5'_M$: sTST at Week 1	$H5'_O$: sTSO at Week 1
Low	Secondary	$H6'_M$: WASO at Night 1	$H6'_O$: LPS at Night 1

(Source: Sponsor's submission P028 Protocol Page 113 Table 3-6)

Within each indication, a fixed sequential testing procedure was used to move from one time point to the next, for example, from the Month 1 set of primary hypotheses to the Month 3 set of primary hypotheses. Then within each time point, a Hochberg approach was used to evaluate the objective and subjective endpoints, as in figure 3 below.

Figure 3: Hochberg approach for Assessment of Objective and Subjective endpoints



(Source: Sponsor's submission P028 Protocol Page 113 Figure 3-1)

Note the following:

1. To move sequentially from Month 1 to Month 3, the testing procedure required both the subjective and objective endpoints to be significant. If only one of the endpoints at Month 1 was significant, then that endpoint is declared positive, but the testing procedure for the indication stopped and no further conclusions was made regarding the suvorexant HD effect at Month 3.

2. Statistical significance for suvorexant HD secondary hypotheses within each indication was based on the following: if according to the multiplicity strategy either Month 3 hypothesis was positive, sTSTm or WASO for maintenance indication and sTSOm or LPS for onset indication, then the set of secondary hypotheses (Week 1/Night 1) was tested using a Hochberg approach at the two-sided 2.5% level.

3. Suvorexant LD was compared to placebo within each indication for the primary and secondary endpoints if at least one of the Month 3 endpoints is positive for suvorexant HD. The same multiplicity strategy noted above was used to assess suvorexant LD dose, with the caveat that suvorexant HD was positive for the particular endpoint before suvorexant LD could be declared positive.

Below is a summary of the analyses of the primary and secondary endpoints

Table 16: Analyses Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	High Dose	Low Dose
Maintenance		
sTSTm – Change from baseline at Month 1	Primary	Secondary
WASO – Change from baseline at Month 1	Primary	Secondary
sTSTm – Change from baseline at Month 3	Primary	Secondary
WASO – Change from baseline at Month 3	Primary	Secondary
Onset		
sTSOm – Change from baseline at Month 1	Primary	Secondary
LPS – Change from baseline at Month 1	Primary	Secondary
sTSOm – Change from baseline at Month 3	Primary	Secondary
LPS – Change from baseline at Month 3	Primary	Secondary
Maintenance		
sTSTm – Change from baseline at Week 1	Secondary	Secondary
WASO – Change from baseline at Night 1	Secondary	Secondary
Onset		
sTSOm – Change from baseline at Week 1	Secondary	Secondary
LPS – Change from baseline at Night 1	Secondary	Secondary

For all analyses above, the plan was to use the following: Statistical Method: Longitudinal data analysis model Analysis Population: Full Analysis set Missing Data Approach: Model-based

(Source: Sponsor's submission P028 Protocol Page 48 Table 2-3)

The LDA model included region as a covariate, which, in turn, consisted of five groups for the subjective endpoints or four groups for the objective PSG endpoints.

The regions for the subjective endpoints included:

- North America: USA, Canada
- Europe: Denmark, Finland, France, Germany, Spain, Sweden, UK
- Asia, Eastern Europe, Africa: Taiwan, Russia, South Africa
- Japan
- Other: Central and South America: Brazil, Peru

The regions for the objective endpoints included:

- North America: USA, Canada
- Europe: Denmark, Finland, France, Germany, Spain, Sweden, UK
- Asia, Eastern Europe, Africa: Taiwan, Russia, South Africa
- Other: Central and South America: Brazil, Peru

Sample Size
Based on the Phase 2 trial P006 experience, Merck determined estimates of standardized effect sizes (SESs), standard deviation, and deltas for suvorexant HD and suvorexant LD, as shown in table below. Suvorexant LD was assumed to have the same underlying estimates as suvorexant HD.

Table 17: Underlying Estimates for Suvorexant Compared to Placebo

Indication	Endpoint	SES†	SD†	Δ†
Maintenance	sTSTm (M1)	0.331	42.4	14.0
	WASO (M1)	0.421	47.9	20.2
	sTSTm (M3)	0.331	42.4	14.0
	WASO (M3)	0.421	47.9	20.2
	sTSTm (W1)	0.334	39.4	13.2
	WASO (N1)	0.757	50.1	37.9
Onset	sTSOm (M1)	0.410	26.9	11.0
	LPS (M1)	0.285	41.5	11.8
	sTSOm (M3)	0.410	26.9	11.0
	LPS (M3)	0.285	41.5	11.8
	sTSOm (W1)	0.376	19.9	7.5
	LPS (N1)	0.501	43.9	22.0

†Standardized Effect Sizes shown are based upon improvement compared to placebo (with respect to change from baseline); SD (adjusted for baseline) and Δ are minutes

(Source: Sponsor's submission Trial P028 Protocol 6.10 Page 141 Table 1)

Merck estimated that a total of 960 subjects, 360 subjects in each of the suvorexant HD and placebo groups and 240 in the suvorexant LD group, provided the trial a 91% power to declare all primary maintenance endpoints significant for suvorexant HD compared to placebo, according to the multiplicity strategy. Also, **the trial had a 62% power to declare all primary onset endpoints significant for suvorexant HD compared to placebo**; and, the probability of declaring both Month 1 onset endpoints significant and at least one Month 3 onset endpoint significant was 81%, as shown in the table below. Further, to support the PSG endpoints, the power calculations estimated that the PQ cohort include a total of 270 subjects in each of the suvorexant HD and placebo groups, and 180 subjects in the suvorexant LD group.

Table 18: Power Analyses for Suvorexant HD Primary and Secondary Analyses

Indication	Endpoint	Standardized effect size†	Marginal power‡	Multiplicity -adjusted power	
				Either§	Both§
Maintenance	sTSTm (M1)	0.331	0.976		
	WASO (M1)	0.421	0.992	0.999	0.969
	sTSTm (M3)	0.331	0.957		
	WASO (M3)	0.421	0.983	0.967	0.910
	sTSTm (W1)	0.334	0.983		
	WASO (N1)	0.757	1.000	0.967	0.950
Onset	sTSOm (M1)	0.410	0.999		
	LPS (M1)	0.285	0.814	0.999	0.813
	sTSOm (M3)	0.410	0.996		
	LPS (M3)	0.285	0.762	0.811	0.618
	sTSOm (W1)	0.376	0.996		
	LPS (N1)	0.502	1.000	0.811	0.808

† SESs shown are based upon improvement compared to placebo (with respect to change from baseline)
‡ Based upon a 2.5% (2-sided) t-test for each endpoint within each indication and assuming N=360/270 per group for Questionnaire/PSG endpoints with dropout rates of 5%/1%, 10% and 20% for Week 1/Night 1, Month 1 and Month 3, respectively
§ For each indication "Either" refers to either endpoint within a time point declared to be significant according to the multiplicity strategy and "Both" refers to both endpoints within a time point declared to be significant according to the multiplicity strategy (see section 3.5.6 Multiplicity)

(Source: Sponsor's submission Trial P028 Protocol Page 115 Table 3-7)

Missing Data

Merck used a model-based approach for missing data. The LDA model allowed for the inclusion of subjects with missing data at certain time points. Merck suggested that the LDA model provided valid statistical inference in the presence of possible missing data when the missing data mechanism was missing at random (MAR) or missing completely at random (MCAR). Prior trial results suggested that other reasons for missing data were uncommon. On trial completion, Merck performed no imputation to estimate missing data for evaluation of the primary, secondary and exploratory efficacy endpoints

using the LDA method. The missing data were assumed to be missing at random (MAR).

Analysis populations
Merck pre-specified three analyses populations: Full Analysis Set (FAS), the Per-Protocol Populations (PPS), and All-Patients as Treated (APaT) population for safety analysis.

The PSG Full Analysis Set (FAS-PSG) population served as the primary population for the analysis of PSG efficacy data. The FAS-PSG population consisted of all randomized subjects who had the following:

- At least one post-randomization PSG observation after receiving at least one dose of trial treatment
- Baseline data for the analyses that required baseline data.

The e-diary Full Analysis Set (FAS–e-diary) population served as the primary population for the analysis of e-diary efficacy data. The FAS–e-diary population consisted of all randomized subjects who had the following:

- At least one post-randomization e-diary observation (that is, weekly mean) after receiving at least one dose of study treatment;
- Baseline data for the analyses that required baseline data

Safety Analyses
The APaT population was used for the analysis of safety data. The population consisted of all randomized subjects who received at least one dose of study treatment. Subjects were included in the treatment group based on the actual treatment received.

Further, Merck proposed to evaluate safety using a tiered approach as follows:

Tier 1 safety endpoints were subject to inferential testing for statistical significance with p-values and 95% confidence intervals (CI) to compare treatment groups. The endpoints included: Cataplexy, sleep onset paralysis, suicidal ideation or behaviors, complex sleep-related behaviors, falls, hypnagogic or hypnopompic hallucinations, selected AEs associated with potential for abuse, withdrawal symptoms, residual effect, and rebound insomnia.

Tier 2 safety endpoints were subject to inferential testing for statistical significance with 95% confidence intervals (CI) to compare treatment groups. The endpoints included: Any AE; any serious AE; any drug-related AE; any serious and drug-related AE; discontinuation due to AE; AEs of sleep paralysis or excessive daytime sleepiness; specific AEs, SOCs, or pre-defined limit of change (PDLCs) with incidence of four or more subjects in one of the treatment groups; and Tier I AEs for the 6 month treatment period.

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Tier 3 safety endpoints were subject to descriptive statistics for analysis. The endpoints included: specific AEs, SOCs, or pre-defined limit of change (PDLCs) with incidence of fewer than four subjects in all of the treatment groups; and change from baseline results in labs, ECGs, and vital signs.

Results:

Protocol Amendments and Changes in Trial Conduct

Protocol amendments were submitted on 3/31/2010 (Japan-specific protocol), 5/5/2010, and 8/1/2011 (Japan-specific clarification). The amendments included corrections of typographical errors; clarification of the timing of some trial assessments; requirement of informed consent from legal representative such as parents, in addition to subject's, for under 20 years olds in Japan; requirement of 240 Japanese subjects to be randomized in Q-cohort; exclusion of subjects with history of antipsychotics use in Japan; allowed inclusion of subjects on supplement with possible psychotropic effects and on diet pills in Japan; and change of medical expert in Japan. Additional changes in the course of the trial are as follows:

Merck changed the scoring of the PSG endpoints from the conventional Rechtschaffen and Kales scale to the sleep scoring guidelines of the AASM. Consequently, sleep stages N1, N2, N3 sleep were replaced with S1, S2, and SWS (S3/S4), respectively.

Merck performed analysis of sWASOm in a similar fashion as sTSTm to further support the evaluation of sleep maintenance efficacy. With this additional sWASOm analysis, a sleep maintenance efficacy was not attributed completely to improvement in sleep onset.

Prior to treatment unmasking, Merck changed the analyses method for Tier 1 AEs, jettisoning the Cox proportional hazards analysis method for the Miettinen & Nurminen method, because of small numbers of AEs.

When the sum of sTSO, sTST, and sWASO was greater than 24 hours, Merck excluded daily e-diary observations from the calculation of weekly averages.

The Per Protocol analysis excluded subjects recording more than seven days of no sleep during the baseline period or during the Treatment Phase. Also, Merck performed a separate sensitivity analysis that excluded these subjects from the FAS analyses of sTST, sTSO, and sWASO.

Prior to treatment unmasking, Merck changed the day ranges for PSG analysis endpoints from the protocol-specified +/-7 days to +/-10 days from the target Day 30 and Day 89. Merck made this change on observing, during blinded data review, that multiple observations needed to be excluded if these tighter day ranges were retained. To evaluate robustness of results, Merck performed additional analyses on the primary

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and secondary hypotheses related to PSG endpoints using the protocol-specified day ranges.

Reviewer Comment: The changes to the protocol do not appear to affect the overall data interpretation.

Protocol Violations
Of 1023 randomized subjects, Merck identified 114 (11.1%) subjects as protocol violators who were subsequently excluded from the per-protocol analysis for efficacy. The protocol violators were identified prior to any treatment unmasking.

Of 1023 subjects randomized to the three treatment groups, one subject, AN 07126, enrolled in more than one suvorexant trial. The subject's data were excluded from all analyses prior to treatment unmasking. Also, the subject reported no AEs.

The most common violation in Trial P028 was from use of prohibited concomitant medication during the core treatment phase (N=33), affecting PSG or e-diary data. In the table below, I summarize information on protocol violations in 110 subjects that Merck provided in Protocol Violators Memo Table 1 for Trial P028. Note that multiple violations may have occurred in a subject.

Table 19: Trial P028 Protocol Violations

Protocol Violation	Action taken for Per Protocol Analysis of efficacy	Number of Subjects	Data/Time point excluded
Incorrect trial medication assignment	Excluded PSG or e-diary data collected during the period that the subject received the incorrect trial medication	N=8	2 subjects: PSG and e-diary at Month 3 excluded. 6 subjects: Required no exclusion, as medication errors were after Visit 5
Subject randomized more than one suvorexant trial or enrolled multiple times within the same trial	In one case with Different-Sequential: "First subject" was included; "Second" subject was excluded. In the other case, Different-Overlapping: "Both subjects" are excluded	N=2	No exclusion for "First" subject All PSG and e-diary entries were excluded.
Exclusion based on high Apnea Hypopnea Index or periodic leg movements associated with an arousal per hour of	Excluded all subject PSG and e-diary data	N=1	All PSG and e-diary entries were excluded

sleep (PLMAs)			
Subjects' e-diary data with >14 consecutive identical e-diary entries based on the morning diary questions related to: sTSO AND sTST	Excluded sTSO, sTST, and sWASO e-diary data corresponding to the primary analysis endpoints Excluded entire subject e-diary data if violation occurred at baseline period	N=15	1 subject: e-diary data at Month 1 excluded. 4 subjects: e-diary data at Months 1 and 3 excluded. 8 subjects: e-diary data at Month 3 excluded 2 subjects: all e-diary data excluded
Alcohol consumption	Excluded based on ≥ 6 drinks per day or > 20 drinks per week, or any alcohol on day of PSG visit Excluded entire subject e-diary data or PSG data if violation occurred at baseline period	N=24	6 subjects: all e-diary data excluded 5 subjects: all PSG data excluded
Any Caffeine after 6 pm on PSG visits	Excluded affected subject PSG visit data. Excluded entire subject PSG data if violations on baseline visit.	N=8	5 subjects: all PSG data excluded
Missed trial medication on PSG visit day	Excluded affected subject PSG visit data	N=1	PSG data at Month 3 excluded.
Positive urine drug screen at PSG visits	Excluded affected subject PSG visit data.	N=1	PSG data at Month 3 excluded
Trial medication compliance of < 75% over the first 3 months	Excluded entire subject PSG and e-diary data	N=6	All PSG and e-diary entries were excluded.
Met exclusionary medical history	Excluded entire subject PSG and e-diary data	N=3	All PSG and e-diary entries were excluded.
Insufficient washout phase of prior therapy that may have had an effect on the relief of sleep symptoms	Excluded entire subject PSG or e-diary data	N=6	All PSG and e-diary entries were excluded. Note: 1 subject, AN 7330, had both PSG and e-diary data excluded
Use of prohibited concomitant medication during the core treatment phase of the trial affecting PSG data	Excluded affected subject PSG visit data for a prohibited concomitant medication taken within 2 days of or on a PSG visit. Excluded entire subject PSG data if violation occurred on baseline visit	N= 14	3 subjects: all PSG data excluded

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Use of prohibited concomitant medication during the core treatment phase of the trial affecting e-diary data	Excluded affected subject e-diary visit data corresponding to the primary analysis endpoints	N=19	No subject had entire e-diary data excluded. 1 subject had Months 1 and 3 data excluded.
No sleep recorded for 7 or more consecutive days	Excluded affected subject e-diary visit data corresponding to the primary analysis endpoints Excluded entire subject e-diary data if violation occurred during baseline period	N=2	1 subject had entire e-diary data excluded.

(Source: Modified from Sponsor's Submission Trial P028 CSR Appendix 16.2.2.1 Protocol Deviations Memo Page 2)

Disposition in Trial P028

Trial P028 had 2879 subjects screened for inclusion. A total of 1856 (64.5%) subjects were not randomized mainly because they (92.5%) failed to meet inclusion or exclusion criteria. Of 1023 subjects randomized, one subject was excluded because of multiple trial enrollments as stated above. Exclusion of the subject yielded an All Patients Randomized (APR) set of 1022 subjects: 254 were randomized to suvorexant LD, 383 subjects to suvorexant HD, and 385 to placebo. One subject, AN 07264, who was randomized into placebo group, did not take the assigned treatment. Therefore, 1021 subjects who received at least one dose of trial treatment were evaluated for safety.

Of the randomized 1022 subjects, 916 (89.6%) completed the trial. More subjects discontinued from the placebo group (11.2%) compared to suvorexant LD (9.4%) and suvorexant HD (9.9%). The most common reason for discontinuation in the Treatment Phase, with a similar pattern in both age groups, was because of an AE. Incidences of AEs ranged from 2.4% to 3.9% for suvorexant and 5.5% for placebo. Also, the discontinuation rate among treatment groups was similar for non-elderly and elderly subjects. The table below summarizes subject disposition in Trial P028.

Table 20: Disposition of Subjects in Trial P028

	Placebo N (%)	**Suvorexant LD N (%)**	**Suvorexant HD N (%)**	**Total N (%)**
Not Randomized				1856
Subjects in population	385	254	383	1022
Trial Disposition				
Not Treated	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Completed Treatment	341 (88.6)	230 (90.6)	345 (90.1)	916 (89.6)

Discontinued during Treatment	43 (11.2)	24 (9.4)	38 (9.9)	105 (10.3)
Adverse Event	21 (5.5)	6 (2.4)	15 (3.9)	42 (4.1)
Withdrawal by Subject	12 (3.1)	6 (2.4)	8 (2.1)	26 (2.5)
Protocol Violation	1(0.3)	5 (2.0)	3 (0.8)	9 (0.9)
Lost to Follow-up	0 (0.0)	1 (0.4)	1 (0.3)	2 (0.2)
Lack of Efficacy	9 (2.3)	1 (0.4)	7 (1.8)	17 (1.7)
Pregnancy	0 (0.0)	1 (0.4)	1 (0.3)	2 (0.2)
Physician Decision	0 (0.0)	4 (1.6)	3 (0.8)	7 (0.7)
Protocol Milestone				
Completed Treatment	341 (88.6)	230 (90.6)	345 (90.1)	916 (89.6)
Continuing Into Extension	151 (39.2)	100 (39.4)	172 (44.9)	423 (41.4)
Continuing Into Run-Out	186 (48.3)	128 (50.4)	172 (44.9)	486 (47.6)
Not Treated in Run-Out	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Not Continuing Into Extension Or Run-Out	4 (1.0)	2 (0.8)	1 (0.3)	7 (0.7)
Discontinued during Treatment	43 (11.2)	24 (9.4)	38 (9.9)	105 (10.3)

(Source: Modified from Sponsor's Submission P028 CSR Page 201 Table 10-3)

Below, I summarize the analysis populations for subjective efficacy endpoints.

Table 21: Efficacy Analyses Populations All Subjects for Subjective Endpoints

Category/Endpoint	Placebo	Suvorexant LD	Suvorexant HD	Total
Multiple Enroller	0	1	0	1
Number Randomized	385	254	383	1022
Number Not Treated	1	0	0	1
All Patients Treated Set (APTS)	384	254	383	1021
sTSTm				
Subjects included in FAS	382	251	381	1014
sWASOm				
Subjects included in FAS	381	251	379	1011
sTSOm				
Subjects included in FAS	382	251	381	1014

(Source: Modified from Sponsor's Submission P028 CSR Page 207 Table 10-6)

Below, I summarize the analysis populations for objective efficacy endpoints.

Table 22: Efficacy Analyses Populations PQ Cohort for Objective Endpoints

Category/Endpoint	Placebo	Suvorexant LD	Suvorexant HD	Total
Multiple Enroller	0	1	0	1
Number Randomized	291	193	291	775
Number Not Treated	1	0	0	1
All Patients Treated Set (APTS)	290	193	291	774

WASO				
Subjects included in FAS	290	193	291	774
LPS				
Subjects included in FAS	290	193	291	774

(Source: Modified from Sponsor's Submission P028 CSR Page 211 Table 10-7)

Reviewer Comment:
Overall, close to 90% of subjects completed the trial treatment. Lack of efficacy may have contributed to the small imbalance in discontinuations between the placebo and suvorexant groups. However, the difference in discontinuations does not appear to be large enough to inflate the suvorexant treatment effect.

Demographics in Trial P028
The subject demographics were similar across treatment groups. The subjects' mean age was 56 years, range 18 to 87 years, with 429 (42%) subjects in the elderly age group. About 62% of all subjects were females. Age and gender distributions were similar across the treatment groups. The subjects were predominantly of white race. Below is a summary of subject characteristics in Trial P028.

Table 23: Subject Characteristics in Trial P028 treatment Phase

Category	Placebo N (%)	Suvorexant LD N (%)	Suvorexant HD N (%)	Total N (%)
Subjects in population	384	254	383	1021
Gender				
Male	139 (36.2)	92 (36.2)	153 (39.9)	384 (37.6)
Female	245 (63.8)	162 (63.8)	230 (60.1)	637 (62.4)
Age in years				
Mean	56	55	56	56
SD	15	16	15	15
Race				
White	244 (63.5)	168 (66.1)	253 (66.1)	665 (65.1)
Black	25 (6.5)	15 (5.9)	18 (4.7)	58 (5.7)
Asian	99 (25.8)	66 (26.0)	98 (25.6)	263 (25.8)
Other	16 (4.2)	5 (2.0)	14 (3.7)	35 (3.4)
Cohort				
Q	94 (24.5)	61 (24.0)	92 (24.0)	247 (24.2)
PQ	290 (75.5)	193 (76.0)	291 (76.0)	774 (75.8)
Region				
Asia Pacific	2 (0.5)	1 (0.4)	2 (0.5)	5 (0.5)
Central and Eastern Europe	0 (0.0)	1 (0.4)	1 (0.3)	2 (0.2)
Central and South America	14 (3.6)	4 (1.6)	15 (3.9)	33 (3.2)
Europe	134 (34.9)	88 (34.6)	135 (35.2)	357 (35.0)

Japan	94 (24.5)	61 (24.0)	92 (24.0)	247 (24.2)
Middle East/Africa	15 (3.9)	7 (2.8)	9 (2.3)	31 (3.0)
North America	125 (32.6)	92 (36.2)	129 (33.7)	346 (33.9)
Body Mass Index (BMI) Category				
Underweight (BMI < 18.5)	11 (2.9)	7 (2.8)	14 (3.7)	32 (3.1)
Normal range (18.5 <= BMI < 25)	190 (49.5)	126 (49.6)	175 (45.7)	491 (48.1)
Overweight (25 <= BMI <= 30)	132 (34.4)	91 (35.8)	153 (39.9)	376 (36.8)
Obese (BMI > 30)	51 (13.3)	30 (11.8)	40 (10.4)	121 (11.9)
Null	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)

(Source: Sponsor's Submission P028 CSR Page 215 Table 10-8)

The baseline values of the efficacy endpoints were comparable across treatment groups. Below is a table summary of the mean values of the efficacy endpoints at baseline.

Table 24: Mean Values of Efficacy Endpoints in Minutes at Baseline

Endpoint	Placebo	Suvorexant LD	Suvorexant HD
sTSTm	315.7	322.4	316.1
sTSOm	66.9	63.3	68.0
sWASOm	78.2	73.9	78.4
WASO	114.9	119.2	117.7
LPS	66.2	68.9	61.8

(Source: Sponsor's Submission P028 CSR Page 231 Table 10-11)

Across treatment groups, subjects had comparable medical history and concomitant medications. Many subjects had history of at least one medical condition: 78.1% (300/384) in placebo, 79.5% (202/254) in suvorexant LD, and 78.6% (301/383) in suvorexant HD groups. Consistent with the medical history, many subjects were on concomitant medications: 60.7% (233/384) in the placebo group, 67.7% (172/254) in the suvorexant LD group, and 64.0% (245/383) in the suvorexant HD group. The most common medications were analgesics, vitamins, and lipid modifying agents.

Reviewer Comment:
Overall, the subjects' demographic and baseline data appear similar across treatment groups. However, there are small numerical differences in baseline values of the efficacy variables across treatment groups. These differences can over time lead to outcome results that give an appearance of meaningful treatment effect.

Treatment Compliance in Trial P028
Measurement of treatment compliance involved pill counts and medication records that were reported in the electronic data capture system (EDC). Compliance was high across treatment groups. About 95% or more of the subjects showed compliance of

between 90% and 100% in the percentage of compliant days on therapy, with a mean compliance rate of at least 98% in all treatment groups. Subjects who showed less than 80% compliance were 0.8 % (3/384) of the placebo group, 0.4% (1/254) of the suvorexant LD group, and 2.1% (8/383) of the suvorexant HD group.

Efficacy
The efficacy results are reviewed under section 6.1.4 of this report.

Safety
The results of safety are reviewed as part of the pooled analyses of safety in section 7.

5.3.3 Phase 3 Confirmatory Efficacy Trial P029

Administrative Information for Trial P029

- **Trial Title:** A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Study to Evaluate the Safety and Efficacy of MK-4305 in Patients with Primary Insomnia – Study B
- **Trial Treatment Dates:** 07/28/2010 to 10/26/2011
- **Trial Sites:** Multicenter with 37 United States (US) and 67 Ex-US centers: Australia (2), Brazil (2), Canada (6), Denmark (2), Finland (2), France (6), Germany (8),India (5), Italy (4), Mexico (3), Peru (5), Poland (5), Republic of Korea (6), Russian Federation (2), South Africa (2), Spain (3), Sweden (3), and United Kingdom (1)
- **Trial Report Date:** 07/10/2012

Objectives and Rationale

- Similar to Trial P028, Trial P029's objective was to evaluate, in subjects with primary insomnia, efficacy of suvorexant HD compared with placebo in improving sleep maintenance and onset at Months 1 and 3, using subjective patient-reported outcomes and objective PSG assessments; and to assess the safety and tolerability of suvorexant for up to 3 months of treatment.

Trial Design and Conduct

Trial P029 Overview
The design of trial P029 was identical to P028, except that P029 reduced its scope of secondary endpoints, and had no extension phase. All secondary endpoints in Trial P029 compared suvorexant HD and placebo, excluding suvorexant LD. Merck compared suvorexant LD and placebo groups, outside the multiplicity strategy, on all efficacy endpoints. Therefore, the secondary endpoints for Trial P029 included the following parameters:

Maintenance:

- Suvorexant HD: Change from baseline sTSTm at Week 1.
- Suvorexant HD: Change from baseline in WASO at Night 1.

Onset:
- Suvorexant HD: Change from baseline in sTSOm at Week 1.
- Suvorexant HD: Change from baseline in LPS at Night 1.

Other aspects of trial P029 that were identical to P028 include trial conduct, inclusion and exclusion criteria, medication restrictions, endpoints, and statistical analysis plan.

Results:
Protocol Amendments and Changes in Trial Conduct
In addition to some of the protocol changes made that were similar to trial P028, two trial sites, #58 and #120, were closed because of GCP noncompliance issues. Site 58 screened five subjects but none of them received trial medication. Site 120 screened 32 subjects and randomized 18 subjects. Among the issues detected with Site 120 included alteration of trial records.

Merck performed efficacy analyses using the Full Analysis Set (FAS) excluding Site 120 as the primary population. They also performed a sensitivity analysis on the FAS with Site 120 included. The primary population was the All Patients as Treated Set (ApaT) with Site 120 included; a sensitivity analysis on the ApaT excluded Site 120.

Protocol Violations in Trial P029
Of 1021 randomized allocations, Merck identified 116 (11.4%) subjects as protocol violators who were subsequently excluded from the per-protocol analysis for efficacy. The protocol violators were identified prior to any treatment unmasking. Two randomized allocations were excluded because one subject had received 2 allocations, AN 12009 and AN 12299; so the second allocation for this subject, AN 12299, was excluded. The other exclusion was for another subject AN 12060 who was simultaneously enrolled in another suvorexant trial. As a result, Trial P029 randomized 1019 subjects.

The most common violations in Trial P029 were related to alcohol use during the core treatment phase (N=31), affecting PSG or e-diary data. Exclusions of all e-diary data of a subject occurred the most when the subject had more than 14 consecutive identical e-diary entries based on the morning diary questions related to sTSO AND sTST (N=15), or when the subject recorded no sleep for 7 or more consecutive days (N=16). In the table below, I summarize information on protocol violations that Merck provided in Protocol Violators Memo Table 1 for Trial P029. Note that multiple violations may have occurred in a subject.

Table 25: Trial P029 Protocol Violations

Protocol Violation	Action taken for Per Protocol Analysis of efficacy	Number of Subjects	Data/Time point excluded

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Incorrect trial medication assignment	Excluded PSG or e-diary data collected during the period that the subject received the incorrect trial medication	N=5	2 subjects: e-diary data at Month 3 excluded. 3 subjects: Required no exclusion, as medication errors were Run-out phase
Subject randomized more than one suvorexant trial or enrolled multiple times within the same trial	In 2 cases, Same-Sequential entries: “Both subjects” were excluded In one case, Different-Sequential: “First subject" was included; "Second" subject was excluded. In another case, Different-Overlapping: "Both subjects" are excluded	N=4	All PSG and e-diary entries were excluded for repeat entries.
The LPS was ≤20 minutes at screening PSG visit 2 or at baseline PSG visit 2a.	Excluded all PSG records	N=2	All PSG entries were excluded
The WASO was ≤ 45 minutes at screening PSG Visit 2 or at baseline PSG visit 2a or the WASO < 60 minutes on the combined screening PGS visits 2 & 2a	Excluded all PSG records	N=1	All PSG entries were excluded
Exclusion based on high Apnea Hypopnea Index or periodic leg movements associated with an arousal per hour of sleep (PLMAs)	Excluded all subject PSG and e-diary data	N=1	All PSG and e-diary entries were excluded
Subject had sTST ≥ 6.5 hours on ≥ 4 nights for the week prior to Visit 3, based on morning e-diary	Excluded all subject e-diary data	N=2	All e-diary entries were excluded
Subject had sTSO < 30 minutes on ≥4 nights for the week prior to visit 3, based on morning e-diary	Excluded all subject e-diary data	N=3	All e-diary entries were excluded
Subjects’ e-diary data with >14 consecutive identical e-diary entries based on the morning diary questions related to: sTSO	Excluded sTSO, sTST, and sWASO e-diary data corresponding to the primary analysis endpoints	N=24	3 subjects: e-diary data at Month 1 excluded. 4 subjects: e-diary data at Month 3 excluded 2 subjects: e-diary data

AND sTST	Excluded entire subject e-diary data if violation occurred at baseline period		at Months 1 and 3 excluded. 15 subjects: all e-diary data excluded
Alcohol consumption	Excluded based on ≥ 6 drinks per day or > 20 drinks per week, or any alcohol on day of PSG visit Excluded entire subject e-diary data or PSG data if violation occurred at baseline period	N=31	6 subjects: all e-diary data excluded 5 subjects: all PSG data excluded
Any Caffeine after 6 pm on PSG visits	Excluded affected subject PSG visit data. Excluded entire subject PSG data if violations on baseline visit.	N=13	7 subjects: all PSG data excluded
Missed trial medication on PSG visit day	Excluded affected subject PSG visit data	N=1	PSG data at Month 3 excluded.
Positive urine drug screen at PSG visits	Excluded affected subject PSG visit data.	N=3	PSG data at Month 3 excluded
Trial medication compliance of < 75% over the first 3 months	Excluded entire subject PSG and e-diary data	N=6	All PSG and e-diary entries were excluded.
Met exclusionary medical history	Excluded entire subject PSG and e-diary data	N=4	All PSG and e-diary entries were excluded.
Insufficient washout phase of prior therapy that may have had an effect on the relief of sleep symptoms	Excluded entire subject PSG or e-diary data	N=2	All PSG or all e-diary entries as appropriate were excluded.
Use of prohibited concomitant medication during the core treatment phase of the trial affecting PSG data	Excluded affected subject PSG visit data for a prohibited concomitant medication taken within 2 days of or on a PSG visit.	N= 2	1 subject: PSG data at Month 1 excluded 1 subject: PSG data at Month 3 excluded
Use of prohibited concomitant medication during the core treatment phase of the trial affecting e-diary data	Excluded affected subject e-diary visit data corresponding to the primary analysis endpoints	N=8	4 subjects had Month 1 data excluded. 4 subjects had Month 3 data excluded.

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No sleep recorded for 7 or more consecutive days	Excluded affected subject e-diary visit data corresponding to the primary analysis endpoints Excluded entire subject e-diary data if violation occurred during baseline period	N=17	1 subject had Month 1 data excluded. 16 subjects had entire e-diary data excluded.

(Source: Modified from Sponsor's Submission Trial P029 CSR Appendix 16.2.2.1 Protocol Deviations Memo Pages 2-8)

Disposition in Trial P029

Trial P029 had 2876 subjects screened for inclusion. A total of 1856 (64.5%) subjects were not randomized mainly because they (89.4%) failed to meet inclusion or exclusion criteria. Of the remaining, one subject was excluded because of a simultaneous enrollment in another suvorexant trial. Another subject had two allocation numbers, prompting exclusion of one. These exclusions resulted in 1019 randomized subjects: 240 were randomized to suvorexant LD, 392 subjects to suvorexant HD, and 387 to placebo. A total of 1009 subjects received at least one dose of trial treatment were evaluated for safety.

Of the randomized 1019 subjects, 881 (86.4%) completed the trial. Subjects who discontinued were 13.7% (53/387) of the placebo group, 14.2% (34/240) of suvorexant LD, and 10.5% (41/392) of suvorexant HD. The most common reason for discontinuation in the Treatment Phase, with a similar pattern in both non-elderly and elderly age groups, was because of an AE. The discontinuation rate was similar across treatment groups. The table below summarizes subject disposition in Trial P029.

Table 26: Disposition of Subjects in Trial P029

	Placebo N (%)	**Suvorexant LD N (%)**	**Suvorexant HD N (%)**	**Total N (%)**
Not Randomized				1856
Subjects in population	387	240	392	1019
Trial Disposition				
Not Treated	4 (1.0)	1 (0.4)	5 (1.3)	10 (1.0)
Completed Treatment	330 (85.3)	205 (85.4)	346 (88.3)	881 (86.5)
Discontinued during Treatment	53 (13.7)	34 (14.2)	41 (10.5)	128 (12.6)
Adverse Event	17 (4.4)	10 (4.2)	19 (4.8)	46 (4.5)
Withdrawal by Subject	19 (4.9)	8 (3.3)	9 (2.3)	36 (3.5)
Protocol Violation	8 (2.1)	5 (2.1)	4 (1.0)	17 (1.7)
Lost to Follow-up	1 (0.3)	2 (0.8)	4 (1.0)	7 (0.7)

Lack of Efficacy	8 (2.1)	7 (2.9)	4 (1.0)	19 (1.9)
Physician Decision	0 (0.0)	2 (0.8)	1 (0.3)	3 (0.3)
Protocol Milestone				
Completed Treatment	330 (85.3)	205 (85.4)	346 (88.3)	881 (86.5)
Continuing Into Run-Out	327 (84.5)	205 (85.4)	344 (87.8)	876 (86.0)
Not Treated in Run-Out	3 (0.8)	0 (0.0)	2 (0.5)	5 (0.5)
Discontinued during Treatment	53 (13.7)	34 (14.2)	41 (10.5)	128 (12.6)

(Source: Modified from Sponsor's Submission P029 CSR Page 159 Table 10-3)

Below, I summarize the analysis populations for subjective efficacy endpoints.

Table 27: Efficacy Analyses Populations All Subjects for Subjective Endpoints

Category/Endpoint	Placebo	Suvorexant LD	Suvorexant HD	Total
Multiple Enroller	2	0	0	2
Number Randomized	387	240	392	1019
Number Not Treated	4	1	5	10
All Patients Treated Set (APTS)	383	239	387	1009
sTSTm				
Subjects included in FAS	369	231	379	979
sWASOm				
Subjects included in FAS	361	226	375	962
sTSOm				
Subjects included in FAS	369	231	379	979

(Source: Modified from Sponsor's Submission P029 CSR Page 164 Table 10-6)

Below, I summarize the analysis populations for objective efficacy endpoints.

Table 28: Efficacy Analyses Populations PQ Cohort for Objective Endpoints

Category/Endpoint	Placebo	Suvorexant LD	Suvorexant HD	Total
Multiple Enroller	2	0	0	2
Number Randomized	299	150	302	751
Number Not Treated	2	0	3	5
All Patients Treated Set (APTS)	290	193	291	774
WASO				
Subjects included in FAS	286	145	294	725
LPS				
Subjects included in FAS	286	145	294	725

(Source: Modified from Sponsor's Submission P029 CSR Page 168 Table 10-7)

Reviewer Comment:
Overall, about 87% of subjects completed the trial treatment. More subjects withdrew from the placebo group compared to the suvorexant groups. The difference in discontinuations is unlikely to inflate the suvorexant treatment effect.

Demographics
Demographics in Trial P029
The subject demographics were similar across treatment groups. The subjects' mean age was 56 years, range 18 to 86 years, with 410 (40.6%) subjects in the elderly age group. About 67% (671/1009) of all subjects were females. Age and gender distributions were similar across the treatment groups. The subjects were predominantly of white race (80.2%, 809/1009). Below is a summary of subject characteristics in Trial P029.

Table 29: Subject Characteristics in Trial P029 treatment Phase

Category	**Placebo N (%)**	**Suvorexant LD N (%)**	**Suvorexant HD N (%)**	**Total N (%)**
Subjects in population	383	239	387	1009
Gender				
Male	136 (35.5)	82 (34.3)	120(31.0)	338 (33.5)
Female	247 (64.5)	157 (65.7)	267(69.0)	671 (66.5)
Age in years				
Mean	57	56	57	56
SD	15	16	15	15
Race				
White	309 (80.7)	190 (79.5)	310 (80.1)	809 (80.2)
Black	21 (5.5)	4 (1.7)	20 (5.2)	45 (4.5)
Asian	25 (6.5)	27 (11.3)	26 (6.7)	78 (7.7)
Other	28 (7.3)	18 (7.5)	31 (8.0)	77 (7.6)
Cohort				
Q	86 (22.5)	89 (37.2)	88 (22.7)	263 (26.1)
PQ	297 (77.5)	150 (62.8)	299 (77.3)	746 (73.9)
Region				
Asia Pacific	25 (6.5)	25 (10.5)	25 (6.5)	75 (7.4)
Central and Eastern Europe	29 (7.6)	16 (6.7)	16 (4.1)	61 (6.0)
Central and South America	28 (7.3)	23 (9.6)	32 (8.3)	83 (8.2)
Europe	113 (29.5)	77 (32.2)	115 (29.7)	305 (30.2)
North America	188 (49.1)	98 (41.0)	199 (51.4)	485 (48.1)
Body Mass Index (BMI) Category				

Underweight (BMI < 18.5)	5(1.3)	4 (1.7)	4(1.0)	13(1.3)
Normal range (18.5 <= BMI < 25)	161(42.0)	106 (44.4)	148(38.2)	415(41.1)
Overweight (25 <= BMI <= 30)	157(41.0)	103 (43.1)	164(42.4)	424(42.0)
Obese (BMI > 30)	59(15.4)	26 (10.9)	71(18.3)	156(15.5)
Null	1(0.3)	0 (0.0)	0(0.0)	1(0.1)

(Source: Sponsor's Submission P029 CSR Page 172 Table 10-8)

The baseline values of the efficacy endpoints were comparable across treatment groups. Below is a summary of the mean values of the efficacy endpoints at baseline.

Table 30: Baseline Mean and Range of Values for Efficacy Endpoints in Minutes

Endpoint	Placebo	Suvorexant LD	Suvorexant HD
sTSTm	309.7 (0.0 - 483.4)	298.3 (0.0 - 512.9)	315.3 (0.0 - 502.6)
sTSOm	81.3 (5.7 - 480.0)	86.0 (10.0 - 480.0)	74.4 (5.7 - 480.0)
sWASOm	83.3 (0.0 - 343.6)	84.8 (0.0 - 303.0)	82.1 (0.0 - 279.1)
WASO	118.4 (45.5 - 317.0)	119.6 (46.0 - 332.5)	119.4 (47.0 - 309.0)
LPS	68.0 (20.5 - 252.0)	65.3 (3.5 - 245.0)	67.3 (20.5 - 386.5)

(Source: Sponsor's Submission P029 CSR Page 182 Table 10-10)

Age group differences in baseline efficacy measures showed mean WASO values at baseline were about 20 minutes longer and mean sTSOm was 10 to 20 minutes shorter for elderly compared to non-elderly subjects. However, the efficacy measures at baseline were generally comparable across treatment groups within each age group.

Also, there were differences between the PQ- and Q-Cohort in baseline subjective efficacy measures: the mean sTST values at baseline were about 60 minutes shorter, and the mean sTSOm values were about 40 to 50 minutes longer in the Q-Cohort compared to the PQ-Cohort.

Across treatment groups, subjects had comparable medical history and concomitant medications. Many subjects had history of at least one medical condition: 79.6% (305/383) in placebo group, 74.1% (177/239) in suvorexant LD group, and 79.8% (309/387) in suvorexant HD group. Subjects on concomitant medications were 64.5% (247/383) in the placebo group, 53.1% (127/239) in suvorexant LD group, and 63.0% (244/387) in suvorexant HD group. The most common medications were analgesics, lipid modifying agents, agents acting on the renin-angiotensin system, anti-inflammatory, and anti-rheumatic products.

Reviewer Comment:
Overall, the subjects' demographic and baseline data appear similar across treatment groups. The small numerical differences in baseline values of the efficacy variables across treatment groups can translate to meaningful effects in the eventual outcome

over time. This further justifies the need to account for baseline values in the final outcome analyses.

Treatment Compliance in Trial P029
Compliance was high across treatment groups. About 97% or more of the subjects showed compliance of between 90% and 100% in the percentage of compliant days on therapy, with a mean compliance rate of at least 98% in all treatment groups. Subjects who showed compliance rates of 80% or less were 1.0 % (4/383) of the placebo group, 0.8% (2/239) of the suvorexant LD group, and 0.8% (3/387) of the suvorexant HD group.

Efficacy
The efficacy results are reviewed under section 6.1.4 of this report.

Safety
The results of safety are reviewed as part of the pooled analyses of safety in section 7.

5.3.4 Phase 3 Long-term Safety Trial P009

Administrative Information for Trial P009

- **Trial Title:** A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Long Term Safety Study of MK-4305 in Patients with Primary Insomnia
- **Trial Treatment Dates:** 12/28/2009 to 08/01/2011
- **Trial Sites:** Multicenter (106) in the United States (48), Australia (3), Belgium (4), Canada (4), Colombia (2), Denmark (5), Finland (3), France (4), Germany (3), Hungary (3), Mexico (1), South Africa (9), Spain (6), Sweden (3), and United Kingdom (8)
- **Trial Report Date:** 06/11/2012

Objectives
The primary objective of P009 was to evaluate safety and tolerability of suvorexant for up to 12 months of treatment.

The secondary objective was to evaluate the efficacy of suvorexant compared with placebo in improving insomnia during the first month of treatment; the improvement was measured by change from baseline in the average of weekly measurements of the subjective variables, sTST and sTSO. To achieve the trial's secondary objectives, the sponsor tested the hypotheses that suvorexant was superior to placebo in improving insomnia during the first month of treatment, using measurements of sTST and sTSO.

Exploratory objectives were to evaluate the following: the efficacy endpoints after 4 to 6 months of trial treatment, other sleep endpoints beyond 1 month of treatment, Clinical Global Impressions-Improvement (CGI-I), Patient Global Impressions-Improvement

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(PGI-I), improving symptoms of depression by assessing the Quick Inventory of Depressive Symptomatology (QIDS-SR16) total score after 6 months of treatment, time to trial treatment discontinuation, and relapse of insomnia during the trial's run-out period.

Trial Design and Conduct

Trial P009 Overview

This was a 12-month, randomized, double-blind, placebo-controlled, parallel group, multi-center trial to assess long-term safety of suvorexant HD in subjects with primary insomnia. The trial had a screening phase preceding the 12-month treatment phase. A 2-month, double-blind run-out phase followed the treatment phase.

About 750 subjects were planned to enter the trial. The subjects were males and females, aged 18 years or older. Elderly subjects older than 65 years were included if they scored 25 or higher on the Mini Mental State Examination (MMSE). Women of reproductive potential needed to have a serum hCG level consistent with the non-gravid state at screening visit 1, and agree to use acceptable contraception during the trial.

The trial excluded subjects with narcolepsy, other neurological disorders, and psychiatric disorders requiring ongoing treatment. Also excluded were subjects with history of malignancy within 5 years of trial screening, except if the malignancy was adequately treated basal cell or squamous cell skin cancer or *in situ* cervical cancer. Other exclusionary criteria were similar to those of the other phase 3 efficacy trials.

The trial had eighteen visits: screening phase Visits 1 to 3, treatment phase visits 4 to16, and run-out phase Visits 17 to 18. The screening phase included a 1-week single-blind placebo run-in that commenced at Visit 2. At Visit 3, the subjects were randomized in a 2:1 ratio to receive either suvorexant HD (high dose) or placebo once daily at bedtime during the 12-month double-blind treatment phase, which ended at Visit 16. The subjects were stratified by age group, elderly and non-elderly, and by region. The goal was to have 50% of the subjects in each age group.

Subjects randomized to suvorexant were, at the same time, randomized in a 1:1 ratio to receive suvorexant HD or placebo during the run-out phase. Those randomized to placebo at trial beginning continued placebo during the run-out phase. As in other phase 3 trials, suvorexant HD was suvorexant 40 mg in non-elderly subjects and suvorexant 30 mg in elderly subjects.

During the treatment phase, subjects returned to the clinic after randomization, at 2-week intervals during the first month, and at Months 3, 6, 9 and 12.
Subjects completed morning and evening questionnaires on e-diary. This was done daily from pre-trial Visit 1 to Visit 5, the end of Month 1. Subsequently, the subjects completed the questionnaire every month for 11 mornings and evenings, that is 5 days before and 5 days after the targeted trial day for a visit or telephone contact, until the

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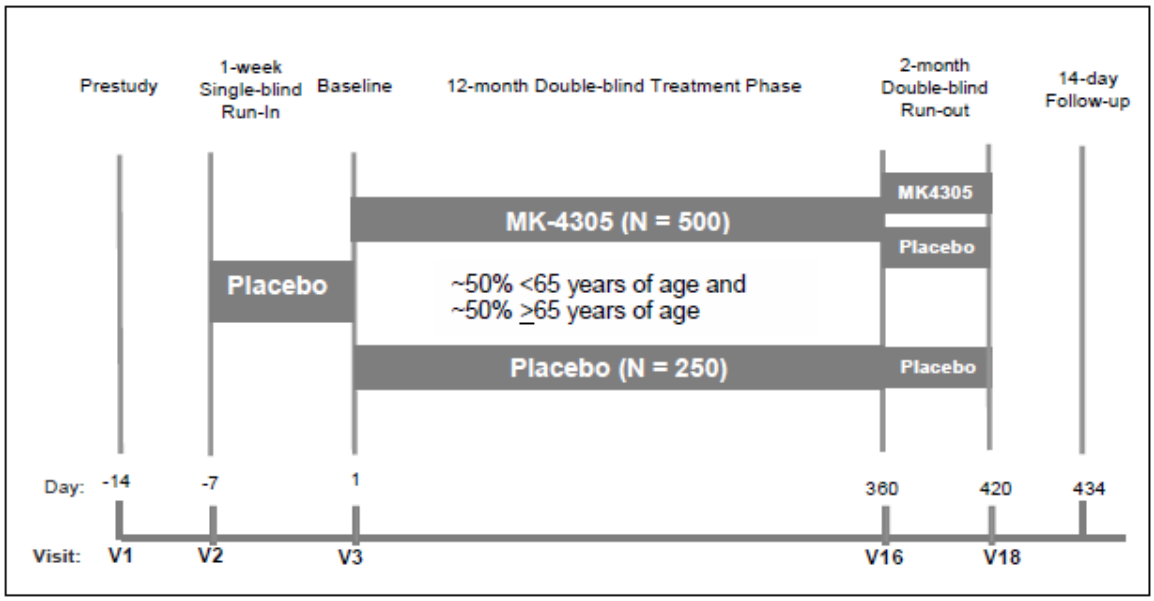
end of month 10 telephone contact. From Month 11, the subjects recommenced daily morning and evening e-diary from 5 days prior to the end of month 11 targeted telephone contact until the end of the trial at Visit 18, the end of run-out phase.

The Tyrer Withdrawal Symptom Questionnaire (WSQ) was administered to subjects, prior to dosing, at Visit 3 and for 3 consecutive evenings. The WSQ was repeated, prior to dosing, for 4 evenings at the targeted end of month 11 telephone contact. Again, it was repeated, prior to dosing, at Visit 16, the evening of the end of Month 12, and for 3 consecutive evenings. Below is the trial flow diagram showing the trial phases and visits.

Figure 4: Trial Flow Diagram for Trial P009



(Source: Sponsor's submission P009 Protocol Page 20)

The table below summarizes the trial schedule and assessments for Trial P009.

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Table 31: Trial P009 Schedule of Assessments

	Screening Phase			Double-Blind Treatment Phase													Run-Out	
Treatment Period	Prestudy	Start Run-in	Baseline[19]/ Randomize	End of Wk 2	End of Mo 1	Phone Call End of Mo2	End of Mo 3	Phone Call End of Mo 4	Phone Call End of Mo 5	End of Mo 6	Phone Call End of Mo 7	Phone Call End of Mo 8	End of Mo 9	Phone Call End of Mo 10	Phone Call End of Mo 11	End of Mo 12	End of Mo 13	End of Mo 14[11]/ **Discon**[11]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Target Study Day[1]	-14	-7	1	15	30	60	90	120	150	180	210	240	270	300	330	360	390	420
Allowed Visit Window[16]		±5	+3/-2	±3	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	+5	+5	±3
Informed consent	X																	
Informed consent for *optional* Specimens for Genetic & Other Biomedical Research analysis[12]			X															
Medical/psychiatric history	X																	
Diagnostic Interview/Sleep History/DSM-IV-TR	X																	
MINI neuropsychiatric interview	X																	
Reading Assessment[2]	X																	
Columbia Suicide Severity Rating Scale (C-SSRS)[21]	X	X	X	X	X		X			X			X			X	X	X
Quick Inventory of Depressive Symptomatology (QIDS-SR16)	X		X		X		X			X			X			X	X	X
Mini Mental State Examination (MMSE)[17]	X																	
Inclusion/exclusion criteria	X	X	X															
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[23]	X				X											X		X
Vital signs[22], height[3], weight[18]	X	X	X	X	X		X			X			X			X	X	X
ECG	X		X	X	X		X			X			X			X		X
Hematology, chemistry and urine pregnancy test[4,10, 25]	X		X[20]	X	X		X			X			X			X	X	X
Urine drug screen	X	X	X															
Optional Specimens for Genetic and Other Biomedical Research[12]			X															
Blood sample for HLA-DQB1 genotyping (DNA)[14]			X															
Pharmacokinetic (PK) Sampling[13]	X			X	X		X											X[13]
CGI-S & CGI-I[15]	X		X		X		X			X						X	X	X
PGI-S & PGI-I[15]	X		X		X		X			X						X	X	X
IVRS call	X	X	X		X		X			X			X			X	X	X
Dispense Study Medication		X	X		X		X			X			X			X	X	
Study Medication Compliance[24]			X	X	X		X			X			X			X	X	X
Insomnia Severity Index (ISI)			X		X		X			X						X[20]	X[20]	X[11]
Motor Vehicle Accidents and Violations (MVAV)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electronic morning diary[6,7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electronic evening diary[6,7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tyrer questionnaire[8]			X												X	X		
Modified Cataplexy Questionnaire (MCQ)	The MCQ will be completed for any report of an adverse experience of cataplexy																	
AE monitoring[9]	X----------X																	
Procedures (related to AEs)	X----------X																	

1 Target Study Day is relative to the first randomized dosing day (Day 1). There is no Day 0; the day before Day 1 is considered to be Day -1.
2 Patients with any secondary education (any formal education beyond 8th grade) do not need to conduct a reading assessment. For patients who have no secondary education, the patients will read the first 2 paragraphs of the informed consent..
3 Body Mass Index will only be calculated at the Prestudy Visit (Visit 1) from weight and height. Height will only be collected at Visit 1 to calculate the BMI. Please refer to appendix 6. 14 for the measurements of weight.
4 Any female patient of child-bearing potential will undergo a urine pregnancy test and a serum pregnancy test (β-hCG) at Visit 1. At other specified time points, if a female patient has a positive urine pregnancy test, a serum pregnancy test must be performed and sent to the central laboratory for confirmation. Serology testing (Hepatitis A and B and HIV 1 and 2) is ***optional*** and is collected at the Investigators discretion.
5 Electronic Morning Diary should be completed at home by patient after their normal morning routine (e.g., using the bathroom, eating breakfast) and preferably within an hour of waking for the day.
6 Electronic Evening Diary should be completed at home by patient at bedtime prior to taking study medication at the times specified below.
7 Electronic diary containing morning and evening questionnaires will be completed every morning and evening starting on the evening of the Prestudy (Visit 1) until the End of Month 1 (Visit 5). The questionnaire will then be completed every month for 11 mornings and evenings (5 days before and 5 days after the targeted study day for a visit or telephone contact) until the End of Month 10 telephone contact. The patient will be asked to complete the morning and evening e-diary daily 5 days prior to the End of Month 11 targeted telephone contact until the end of the study (Visit 18). Patients should be instructed to bring the e-diary to the clinic at each visit. Patient compliance should be monitored via vendor website weekly for the first month of the study and monthly thereafter.
8 The Tyrer Withdrawal Symptom Questionnaire will be administered, prior to dosing, in conjunction with the evening questionnaire on the evening of the Baseline/Randomization Visit (Visit 3) and for 3 consecutive evenings. It will be administered again, prior to dosing, for 4 evenings at the targeted End of Month 11 telephone contact on Day 330 until Day 333. It will also be completed, prior to dosing, on the evening of the End of Month 12 Visit (Visit 16) and for 3 consecutive evenings. Please refer to specific instructions in the e-diary procedures manual.
9 Please refer to Sections 3.4.1.7, 3.4.1.8, and 3.4.5.2 for the pre-specified ECIs.
10 Obtain only if the time between Visit 1 and Visit 3 exceeds 21 days.
11 Patients that complete the study or prematurely discontinue will receive a follow-up phone call 14 days after the last dose of study medication or 14 days after the Discontinuation Visit (whichever time point is later). All adverse events, concomitant medications and motor vehicle accidents and violation (MVAV) since the last study visit will be collected. Patients that discontinue will be asked to complete an ISI at the Discontinuation Visit. Patients that discontinue during the 12 month treatment period will also be sent home with another ISI to complete 1 week after the Discontinuation Visit. The patient will mail the completed ISI to the Investigator site.
12 Signing of the optional pharmacogenomic sample consent form and obtaining the optional genetic sample should be completed any time after Visit 3 (randomization). This is not necessary to participate in the study.
13 PK samples are mandatory sample collections. Consent for these samples is obtained by the patient signing the main study consent. PK samples should be collected if a patient discontinues due to an adverse event.
14 The HLA-DQB1 genotyping sample is a mandatory sample collection. Consent for this sample is obtained by the patient signing the main study consent. This sample should be collected at Visit 3 (randomization).
15 CGI-I and PGI-I should *not* be completed at Visit 1 (Screening Visit) and Visit 3. PGI=Patient Global Impressions (S=Severity, I=Improvement) CGI= Clinical Global Impressions (S=Severity, I=Improvement)
16 The allowed visit window is around the Target Study Day and is not cumulative. If out of window, all subsequent visits should be scheduled according to the original Target Study Day.
17 To be completed at the Prestudy visit for patients ≥65 years of age
18 Please refer to Appendix 6.14 for specific weight measurements.
19 The first dose of double blind study medication will be on the evening of Visit 3, immediately prior to bed (within 5-10 minutes of bedtime).
20 The patient will complete the ISI questionnaire at home at the end of each week after the Month 12 visit, i.e., 1, 2, and 3 weeks after Visit 16, then at the clinic during the Month 1 double-blind run-out visit (Visit 17), and at home during the following 3 weeks (i.e., 1, 2, and 3 weeks after Visit 17), and finally at the clinic during the end of Month 2 double-blind run-out visit (Visit 18).
21 The Baseline CSSRS should only be completed at Visit 1. The Since Last Visit CSSRS should be completed at all visits except Visit 1.
22 Please refer to Appendix 6.7 for measurement of blood pressure. Vital signs include blood pressure, pulse, respiratory rate and temperature.
23 Physical exams **must** be performed by a physician or a physician assistant depending on state laws. The neurological exam should include muscle strength, deep tendon reflexes, romberg, gait and finger to nose.
24 Drug accountability (compliance) will be assessed at each visit by pill count, e-diary data and interview of the patient.
25 Randomized patients with ALT and/or AST values elevated ≥ 3x ULN (Upper Limit of Normal) will require additional follow-up. Please refer to the Neuro Hepatic Guidance and FDA Final Guidance – Drug Induced Liver Injury for details.

(Source: Sponsor's submission P009 Protocol Page 17)

Endpoints and Analyses Trial P009
Trial P009 had no primary efficacy hypotheses. To examine the secondary efficacy hypotheses, Merck examined the average of Weeks 1, 2, 3, and 4 in sTSTm, and sTSOm.

Merck also used exploratory and other endpoints to primarily assess rebound insomnia at the end of 12 months of treatment, and to secondarily examine efficacy. For these purposes, treatment effects on sTSTm, sTSOm, and sWASOm were assessed.

Additional evaluations were performed using the Clinical Global Impressions-Severity (CGI-S) scale, the Clinical Global Impressions-Improvement (CGI-I) scale, the Patient Global Impressions-Severity (PGI-S) scale, the Patient Global Impressions-Improvement (PGI-I) scale, the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR16), the Insomnia Severity Index (ISI), and suvorexant's pharmacokinetic (PK) parameters.

For safety assessments, Merck analyzed data from the following:

- Laboratory evaluations (hematology, chemistry, urine drug screen, and urine pregnancy test
- Physical examination
- Electrocardiogram (ECG)
- Vital Signs
- Motor Vehicle Accident and Violation (MVAV)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Morning questionnaire and Tyrer Withdrawal Symptom Questionnaire via the e-diary

In addition, investigators monitored adverse events (AEs) and the pre-specified ECIs of suicidal ideation or behaviors, events associated with potential for abuse, complex sleep-related behaviors, hypnagogic or hypnopompic hallucinations, excessive daytime sleepiness (EDS), sleep paralysis, cataplexy, falls, and AEs associated with traffic or motor vehicle accidents (when a subject was the driver). The external adjudication committee reviewed events suggestive of cataplexy, falls, and sleep onset paralysis.

Statistical Analyses in Trial P009
Merck analyzed the safety data using a tiered approach as in the other phase 3 trials.

According to the P009 protocol, the trial size was determined by regulatory safety requirements for duration and number of subjects exposed rather than formal statistical considerations. The estimated sample size was of 750 subjects, 500 on suvorexant and 250 on placebo. These estimates expected dropout rates of about 50% by Month 6 and 60% by Month 12 in each treatment group. Also, the estimates needed to ensure that at least 100 subjects in each of the elderly and non-elderly age-groups completed 12-

Reference ID: 3301133

month treatment, and 250 total subjects completed 6-month treatment. The planned sample size presented the power to detect differences in hazard rates for Tier 1 AEs as shown in the table below:

Table 32: Power to Detect Between Treatment Differences in Tier 1 Adverse Events in Trial P009

Study Population	MK-4305 Versus Placebo Hazard Rate	Power[†]
Overall (N=500 for MK-4305 vs. N=250 for Placebo)	0.06 vs. 0.01	81%
	0.10 vs. 0.01	99%
	0.08 vs. 0.02	82%
	0.10 vs. 0.02	94%
	0.15 vs. 0.05	92%
	0.20 vs. 0.05	>99%

[†] Based upon Lachin & Foulkes method (two-sided, 5% level test); 60% dropout rate over 1-year treatment phase.

(Source: Sponsor's submission P009 Protocol Page 33 Table 2-2)

Based on the same sample size estimates and an LDA ANCOVA model with a 2-sided alpha level of 5%, the power to detect differences in sTSTm and sTSOm, averaged over Weeks 1, 2, 3 and 4, between the treatment groups is shown the table below.

Table 33: Power to Detect Between Treatment Differences in Efficacy at Month 1 in Trial P009

Variable	Delta (Improvement)	Power[†]
sTSTm	20	>99%
	15	95%
	12	82%
sTSOm	12	>99%
	10	97%
	8	87%

[†] Based upon N=500 on MK-4305 and N=250 on Placebo; 2-sided, 5%-level test; estimates of covariance matrix and missing data rates based upon prior in-house studies of MK-0928 (Protocols 003, 014, 10403 and 005)

(Source: Sponsor's submission P009 CSR Page 102 Table 9-3)

To monitor safety of subjects, an external Data Monitoring Committee (eDMC) conducted two planned interim analyses. The first occurred when 20% of the

randomized subjects had completed 3 months of the treatment phase; the second was at the time 40% of the subjects completed the 12-month treatment phase.

Results:
Protocol Amendments and Changes in Trial Conduct
Merck made amendments and changes during the trial that included the following:

- Changed the dose for non-elderly subjects, younger than 65 years, from 60 mg to 40 mg
- Revised timing of measurements for PK and other laboratory parameters
- Combined elderly and non-elderly subjects to assess trial hypotheses, thereby making the trial analyses consistent with other phase 3 trials
- Added the form for motor vehicle accidents and violations (MVAV) to the trial assessments; this was done after completing trial enrollment, so no baseline values were obtained
- Allowed use of hormonal contraceptives
- Added gender to efficacy analysis model
- Allowed cognitive behavioral therapy (CBT) during the trial if it was initiated at least 4 weeks before visit 1
- Added falls to events for adjudication

Disposition in Trial P009
Trial P009 had 1076 subjects screened for inclusion. A total of 295 subjects were not randomized. A total of 781 subjects were randomized: 522 subjects to suvorexant HD and 259 subjects to placebo. Two of the randomized subjects, one to each treatment group, received no treatment. Therefore, 779 subjects who received at least one dose of trial treatment were evaluated for safety.

Of the 779 treated subjects, 484 (62%) completed the trial, with similar percentages of completers in each treatment group: 61.7% (322/522) of the suvorexant HD and 62.5% (162/259) of the placebo groups. The most common reason for discontinuation in the Treatment Phase was because of an AE. More subjects discontinued because of an AE in the suvorexant group (11.5%, 60/522) compared to placebo (8.5%, 22/259). Further, in the suvorexant HD group, the discontinuation rate among non-elderly subjects (46.5%, 99/213) was higher than among elderly subjects (32.7%, 101/309). The table below summarizes subject disposition in Trial P009.

Table 34: Disposition of Subjects in Trial P009

	Placebo N (%)	**Suvorexant HD N (%)**	**Total N (%)**
Not Randomized			295
Subjects in population	259	522	781

Study Disposition			
Completed	162 (62.5)	322 (61.7)	484 (62)
Discontinued	97 (37.5)	200 (38.3)	297 (38)
Adverse Events	22 (8.5)	60 (11.5)	82 (10.5)
Lack of Efficacy	28 (10.8)	44 (8.4)	72 (9.2)
Lost to Follow-up	12 (4.6)	14 (2.7)	26 (3.3)
Physician Decision	8 (3.1)	17 (3.3)	25 (3.2)
Pregnancy	0 (0.0)	1 (0.2)	1 (0.1)
Protocol violation	3 (1.2)	4 (0.8)	7 (0.9)
Withdrawal by Subject	24 (9.3)	60 (11.5)	84 (10.8)

(Source: Modified from Sponsor's Submission P009 CSR Page 113 Table 10-1)

Baseline Characteristics
The baseline characteristics were similar across the treatment groups. The subjects' mean age was 61.5 years, range 18 to 90 years, with 459 (58.9%) subjects in the elderly age group. About 56% (436/779) of all subjects were females. Age and gender distributions were similar across the treatment groups. The subjects were predominantly of white race. The treatment groups within the non-elderly and elderly age groups showed similar baseline characteristics. Below is a summary of subject characteristics in Trial P009.

Table 35: Subject Characteristics in Trial P009 Treatment Phase

	Placebo N (%)	**Suvorexant HD N (%)**	**Total N (%)**
Subjects in population	258	521	779
Gender			
Male	109 (42.2)	234 (44.9)	343 (44.0)
Female	149 (57.8)	287 (55.1)	436 (56.0)
Age in years			
Mean	62.0	61.3	61.5
SD	14.6	14.5	14.5
Race			
White	231 (89.5)	476 (91.4)	707 (90.8)
Black	24 (9.3)	33 (6.3)	57 (7.3)
Asian	1 (0.4)	6 (1.2)	7 (0.9)
Multi-Racial	1 (0.4)	4 (0.8)	5 (0.6)
American Indian Or Alaska Native	1 (0.4)	1 (0.2)	2 (0.3)
Native Hawaiian Or Other Pacific Islander	0 (0.0)	1 (0.2)	1 (0.1)

Region			
Asia Pacific	5 (1.9)	11 (2.1)	16 (2.1)
Central and Eastern Europe	6 (2.3)	14 (2.7)	20 (2.6)
Central and South America	4 (1.6)	8 (1.5)	12 (1.5)
Europe	84 (32.6)	169 (32.4)	253 (32.5)
North America	159 (61.6)	319 (61.2)	478 (61.4)
Body Mass Index (BMI) Category			
Underweight (BMI < 18.5)	1 (0.4)	3 (0.6)	4 (0.5)
Normal range (18.5 <= BMI < 25)	81 (31.4)	165 (31.7)	246 (31.6)
Overweight (25 <= BMI <= 30)	116 (45.0)	231 (44.3)	347 (44.5)
Obese (BMI > 30)	60 (23.3)	121 (23.2)	181 (23.2)
Null	0 (0.0)	1 (0.2)	1 (0.1)

(Source: Sponsor's Submission P009 CSR Page 118 Table 10-4)

Below, I summarize the analysis populations for the subjective efficacy endpoints.

Table 36: Efficacy Analyses Populations All Subjects for Subjective Endpoints

Category/Endpoint	**Placebo**	**Suvorexant HD**	**Total**
Number Randomized	259	522	781
Number Not Treated	1	1	2
All Patients Treated Set (APTS)	258	521	779
sTST			
Subjects included in FAS	254	517	771
sWASOm			
Subjects included in FAS	251	512	763
sTSOm			
Subjects included in FAS	254	517	771

(Source: Modified from Sponsor's Submission P009 CSR Page 116 Table 10-3)

Efficacy Results
Efficacy analyses were based on a mixed effects model that included the following covariates: baseline value, age category (<65, ≥65 years), region, gender, treatment, time point, and treatment-by-time point interaction.

Sleep Maintenance
During the first month of treatment, suvorexant HD improved sleep maintenance, as measured by change from baseline in average of weekly sTSTm, compared to placebo. Suvorexant HD showed an increase of 22.7 minutes in average sTSTm from baseline was compared to placebo during the first four weeks of treatment (p-value < 0.0001).

The improvement in sTSTm was observed on each of the first 4 weeks, and continued over the months up to Month 12. Below is a summary of the sTSTm results.

Table 37: Analyses of Subjective Efficacy of Sleep Maintenance Measured by sTSTm in Trial P009

	Placebo			**Suvorexant HD**				
Timepoint	N	Mean Baseline (SD)	LS-MCB	N	Mean Baseline (SD)	LS-MCB	Diff from Placebo (95% CI)	P value
Month 1	254	329.9 (79.4)	16.0	517	320.4 (76.1)	38.7	22.7 (16.4, 29.0)	<0.0001
Month 3	186	333.7 (78.6)	31.9	389	318.9 (73.7)	54.5	22.6 (13.6, 31.6)	<0.0001
Month 6	168	334.8 (77.1)	27.6	347	317.2 (75.0)	54.6	27.0 (17.0, 37.0)	<0.0001
Month 12	147	336.9 (72.3)	33.0	298	320.6 (76.3)	60.5	27.5 (16.2, 38.8)	<0.0001

(Source: Modified from Sponsor's submission P009 CSR Pages 141, 149 Tables 11-3, 11-6; LS=Least Square, MCB=Mean change from Baseline; Measurements from 1 month data at Month 1, 11-14 days' data on other months)

Sleep Maintenance by sWASO
Merck also evaluated suvorexant's effect on sWASOm as a means of measuring the drug's effect on sleep maintenance. During the first month of treatment, suvorexant HD decreased change from baseline in average of weekly sWASOm by 9.3 minutes compared to placebo during the first four weeks of treatment (p-value < 0.0001). Again, the improvement in sWASOm was observed on each of the first 4 weeks, and continued over the months up to Month 12. I present a summary of the sWASOm results below.

Table 38: Analyses of Subjective Efficacy of Sleep Maintenance Measured by sWASOm in Trial P009

	Placebo			**Suvorexant HD**				
Timepoint	N	Mean Baseline (SD)	LS-MCB	N	Mean Baseline (SD)	LS-MCB	Diff from Placebo (95% CI)	P value
Month 1	251	71.5 (56.1)	-12.5	512	80.1 (57.2)	-21.7	-9.3 (-13.5, -5.1)	<.0001

Month 3	184	67.9 (53.7)	-24.3	387	79.3 (55.9)	-33.3	-9.0 (-14.7, -3.4)	0.0018
Month 6	167	69.2 (56.1)	-21.6	344	81.1 (56.7)	-33.5	-11.8 (-18.3, -5.3)	0.0004
Month 12	147	67.7 (55.4)	-23.8	295	80.1 (55.0)	-33.5	-9.7 (-16.5, -3.0)	0.0048

(Source: Modified from Sponsor's submission P009 CSR Pages 143, 153 Tables 11-4, 11-7; LS=Least Square, MCB=Mean change from Baseline; Measurements from 1 month data at Month 1, 11-14 days' data on other months)

Sleep Onset by sTSO

During the first month of treatment, suvorexant HD reduced time to sleep onset, as measured by change from baseline in average of weekly sTSOm, compared to placebo. Suvorexant HD reduced sTSOm from baseline by an average of 9.5 minutes compared to placebo during the first four weeks of treatment (p-value = 0.0002). The improvement in sTSOm was observed on each of the first 4 weeks, and continued over the months up to Month 12. Below is a summary of the sTSTm results.

Table 39: Analyses of Subjective Efficacy of Sleep Onset as Measured by sTSOm in Trial P009

	Placebo			Suvorexant HD				
Timepoint	**N**	**Mean Baseline (SD)**	**LS-MCB**	**N**	**Mean Baseline (SD)**	**LS-MCB**	**Diff from Placebo (95% CI)**	**P value**
Month 1	254	65.0 (60.6)	-8.4	517	65.9 (63.8)	-18.0	-9.5 (-14.6, -4.5)	0.0002
Month 3	186	60.5 (56.0)	-16.7	389	66.9 (63.0)	-25.2	-8.5 (-14.4, -2.6)	0.0048
Month 6	168	59.1 (51.3)	-14.9	347	68.4 (64.9)	-24.8	-9.9 (-16.4, -3.4)	0.0030
Month 12	147	55.6 (42.2)	-17.0	298	64.7 (62.2)	-26.6	-9.7 (-16.5, -2.9)	0.0055

(Source: Modified from Sponsor's submission P009 CSR Pages 146, 157 Tables 11-5, 11-8; LS=Least Square, MCB=Mean change from Baseline; Measurements from 1 month data at Month 1, 11-14 days' data on other months)

Other Endpoints

For most of the 12-month treatment period, the subjective number of awakenings (sNAWm) remained similar between the treatment groups, even increasing slightly at 12 months in the suvorexant group by 0.2 compared to placebo (p=0.0216). Results of other exploratory endpoints shown below include: subjective sleep quality

(sQUALITYm), subjective refreshed upon awakening (sREFRESHm), Insomnia Severity Index (ISI), CGI-S, CGI-I, PGI-S, and PGI-I.

Table 40: Additional Efficacy Endpoints in Trial P009

	Placebo Baseline	Placebo Month 1	Suvorexant HD Month 1		Suvorexant HD Month 3		Suvorexant HD Month 6		Suvorexant HD Month 12	
	Baseline (SD)	Mean Change from Baseline	Difference from Placebo (95% CI)	P value	Difference from Placebo (95% CI)	P value	Difference from Placebo (95% CI)	P value	Difference from Placebo (95% CI)	P value
sNAWm	2.0 (1.1)	-0.2	0.1 (-0.0, 0.2)	0.0765	0.1 (-0.0, 0.3)	0.1287	0.1 (-0.1, 0.3)	0.5522	0.2 (0.0, 0.4)	0.0216
sQUALITYm	2.1 (0.5)	0.1	0.2 (0.1, 0.2)	<.0001	0.1 (0.0, 0.2)	0.0226	0.1 (0.0, 0.2)	0.0170	0.1 (0.0, 0.2)	0.0338
sREFRESHm	1.4 (0.7)	0.2	0.2 (0.1, 0.2)	<.0001	0.1 (0.0, 0.2)	0.0125	0.1 (0.0, 0.3)	0.0137	0.2 (0.0, 0.3)	0.0162
ISI	13.7 (4.6)	-2.2	-1.4 (-2.1, -0.7)	<.0001	-0.9 (-1.7, -0.2)	0.0160	-1.4 (-2.3, -0.6)	0.0007	-0.9 (-1.8, -0.0)	0.0390
CGI-S	4.3 (0.8)	-0.5	-0.3 (-0.5, -0.2)	<.0001	-0.4 (-0.6, -0.2)	<.0001	-0.4 (-0.6, -0.2)	<.0001	-0.4 (-0.6, -0.2)	0.0003
CGI-I	3.3 (1.0) at Month 1	-	-0.4 (-0.6, -0.3)	<.0001	-0.4 (-0.5, -0.2)	<.0001	-0.5 (-0.7, -0.3)	<.0001	-0.5 (-0.7, -0.3)	<.0001
PGI-S	3.1 (0.9)	-0.5	-0.3 (-0.4, -0.1)	0.0026	-0.3 (-0.4, -0.1)	0.0057	-0.4 (-0.6, -0.2)	<.0001	-0.3 (-0.5, -0.1)	0.0110
PGI-I	3.4 (1.2) at Month 1	-	-0.5 (-0.7, -0.3)	<.0001	-0.5 (-0.7, -0.3)	<.0001	-0.5 (-0.7, -0.3)	<.0001	-0.5 (-0.7, -0.3)	<.0001

(Source: Modified from Sponsor's submission P009 CSR Pages 651-663, 670-673; Tables 14-57 to 14-66, 14-73 to 14-76)

Time to study discontinuation from any reason, an adverse event, lack of efficacy, or subject withdrawal was comparable between suvorexant HD and placebo groups; all nominal p-values were > 0.0500 for hazard ratios when the treatment groups were compared by reason of discontinuation. For any reason of discontinuation, the discontinuation rates were 38.2% (199/521) for the suvorexant HD group and 37.2% (96/258) for the placebo group; the hazard ratio for time to discontinuation was 1.014 (P=0.9133).

The change from baseline in QIDS-SR16 total score during the double-blind Treatment Phase was comparable between suvorexant HD and placebo groups. However, components of the QIDS-SR16 related to sleep – falling asleep, sleep during night, and waking up too early – improved with suvorexant treatment.

Randomized Discontinuation Phase
Relapse of Insomnia
The trial categorized subjects with insomnia relapse as those who developed moderate to severe insomnia (ISI total score of 15-28) during the randomized discontinuation phase, but had sub-threshold insomnia or no clinically significant insomnia (ISI total score of 0-14) at the end of Month 12 treatment. More insomnia relapse occurred in

subjects who switched to placebo in the randomized discontinuation phase (MK/PBO group: 27.1%, 38/140) compared to those who remained on suvorexant (MK/MK group: 22.0%, 28/127) or those who remained on placebo (PBO/PBO: 23.2%, 32/138).

When Merck defined insomnia relapse based on sTSTm return to within 5%, 10%, or 20% of baseline, more subjects who switched to placebo developed insomnia relapse. For instance, among subjects with sTSTm returning to within 5% of baseline, insomnia relapse occurred in 38.6% (32/83) of the PBO/PBO group, 32.8% (38/116) of the MK/MK group, and 46.3% (57/123) of the MK/PBO group.

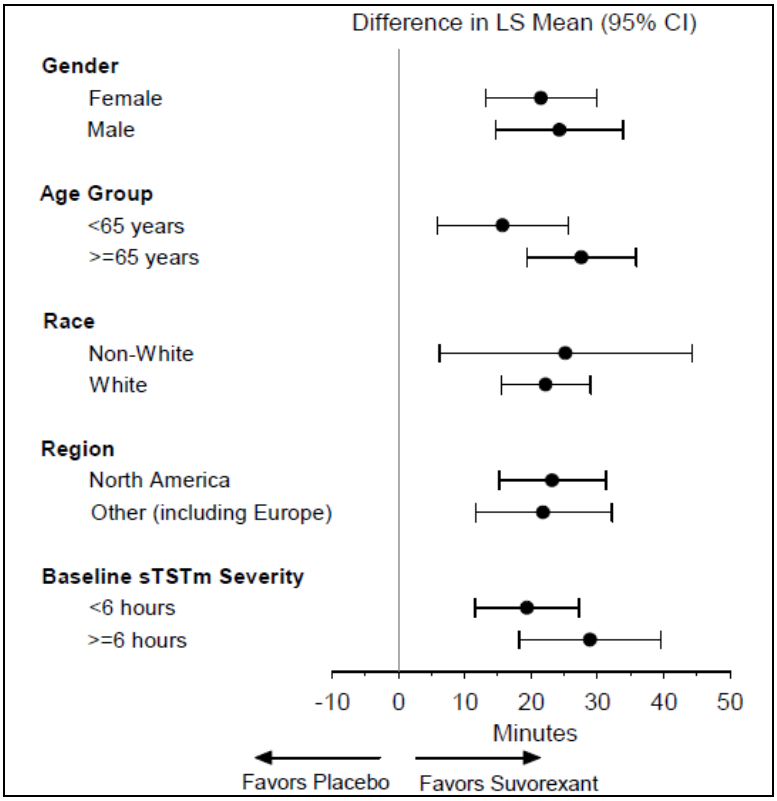
During the randomized discontinuation phase, the average change from Month 12 in sTSTm ranged from 30.3 minutes less per night in the first week to 21.6 minutes less per night in Week 8 for subjects who switched to placebo compared those who remained on suvorexant HD, with nominal p-values < 0.0001. A similar comparison using sWASOm yielded an average change from Month 12 sWASOm ranging from 7.0 minutes to 14.2 minutes more in subjects who switched to placebo compared those who remained on suvorexant HD, with nominal p-values < 0.0200. For sTSOm, the average change ranged from 12.9 minutes to 17.5 minutes more in subjects who switched to placebo compared those who remained on suvorexant HD, with nominal p-values 0.0002 or less.

Further, in the randomized discontinuation phase, subjects who switched to placebo experienced a worsening in their sQUALITYm, sREFRESHm, ISI total score, CGI-S, CGI-I, PGI-S, PGI-I scores compared those who remained on suvorexant HD. There were no notable differences between the groups on sNAWm.

Analyses of Efficacy by Subgroup
Subgroup analyses showed that suvorexant HD improved total sleep time, as measured by sTSTm, with nominal p values <0.0200, in the categories of age group, gender, race, region, and baseline severity. The figure below shows the difference in LS means (95% CI) between suvorexant HD and placebo for sTSTm for each subgroup on average for Month 1.

Reference ID: 3301133

Figure 5: Subgroup Analyses of Difference in LS Means (95% CI) between Suvorexant and Placebo for sTSTm Averaged over Month 1



(Source: Sponsor's submission P009 CSR Page 181 Figure 11-10)

Although the point estimates for sWASOm decreased with suvorexant HD compared to placebo across the subgroups, the effect was less apparent in the non-elderly subjects compared to elderly subjects, with nominal p value of 0.0566 for the non-elderly subjects. Likewise for sleep onset, suvorexant HD decreased sTSOm compared to placebo across the subgroups, but the nominal p values were above 0.05 for the non-elderly age group, non-white race, and baseline sTSOm severity < 45 minutes.

Reviewer Comment
Suvorexant HD showed consistent improvement in sleep onset and sleep maintenance over a treatment period of 12 months. On subgroup analyses, the improvement in sleep onset from suvorexant treatment was less obvious in non-elderly subjects and in subjects with less severe baseline sTSOm.

PK Data
Suvorexant plasma concentration levels were comparable on days 15, 30, and 90 in non-elderly subjects. Similarly, the levels were comparable on same days in the elderly, but on the average about 8% lower than in the non-elderly. Also, suvorexant levels at 24

to 48 hours after last dose were still as high as 70% of the levels at 7 to 13 hour on the different days measured and in each age group.

Safety Results
This section provides a summary of the safety findings in Trial P009. Also, this summary is more detailed than the other phase 3 trials because P009 exposed subjects to a longer 12-month treatment period compared to 3-6 months in Trial P028 and P029. For a more extensive review of suvorexant safety, please see safety analyses of pooled phase 3 data in section 7.

Exposure
Of 521 subjects treated with suvorexant HD in Trial P009, 378 subjects, including 145 non-elderly and 233 elderly subjects, received a dose of suvorexant HD for at least 6 months. Of these, 160 subjects, including 51 non-elderly and 109 elderly subjects, received a dose of suvorexant HD for at least 12 months. The mean duration of treatment with any suvorexant dose was 282 days.

Deaths
Trial P009 recorded no deaths.

Serious AEs
As shown in the table below, the treatment groups had comparable incidence of serious AEs: placebo group with 6.6% (17/258) and suvorexant HD with 5.2% (27/521). Treatment discontinuations due to serious AEs were also comparable between the treatment groups: placebo group with 1.9% (5/258) and suvorexant HD with 1.9% (10/521).

Reference ID: 3301133

Table 41: Adverse Events in Trial P009

	MK-4305		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[†]
Patients in population	521		258		
with one or more adverse events	362	(69.5)	164	(63.6)	5.9 (-1.1, 13.1)
with no adverse events	159	(30.5)	94	(36.4)	-5.9 (-13.1, 1.1)
with drug-related[‡] adverse events	182	(34.9)	53	(20.5)	14.4 (7.8, 20.6)
with serious adverse events	27	(5.2)	17	(6.6)	-1.4 (-5.5, 1.9)
with serious drug-related adverse events	1	(0.2)	3	(1.2)	-1.0 (-3.2, 0.1)
who died	0	(0.0)	0	(0.0)	
discontinued[§] due to an adverse event	61	(11.7)	22	(8.5)	3.2 (-1.5, 7.4)
discontinued due to a drug-related adverse event	43	(8.3)	12	(4.7)	
discontinued due to a serious adverse event	10	(1.9)	5	(1.9)	
discontinued due to a serious drug-related adverse event	0	(0.0)	3	(1.2)	

[†] Based on Miettinen & Nurminen method.
[‡] Determined by the investigator to be related to the drug.
[§] Study medication withdrawn.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
MK-4305 = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥65 years.

(Source: Sponsor's submission P009 CSR Page 195 Table 12-3)

In the treatment phase, similar proportions of serious AEs (SAEs) occurred in the treatment groups: 5.2% (27/521) in the suvorexant HD and 6.6% (17/258) in placebo. The most frequent system organ class (SOC), with higher incidence in the suvorexant HD group, was Nervous System Disorders: 0.8% (4/521) in the suvorexant HD group and 0.4% (1/258) in placebo. Although eleven subjects reported the SOC of Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps), fewer subjects were from the suvorexant group; 7 (1.3%) subjects on suvorexant HD compared to 4 (1.6%) subjects on placebo reported this SOC. The table below shows Merck's summary of SAEs with an incidence >0% in a treatment group.

Table 42: Serious Adverse Events with Incidence >0% in any Treatment Group of Trial P009

Adverse Event Category SOC Preferred Term	Suvorexant HD N (%)	Placebo N (%)
Total Subjects	521 (100)	258 (100)
Subjects with one or more serious adverse events	27 (5.2)	17 (6.6)
Cardiac disorders	**2 (0.4)**	**3 (1.2)**
Atrial fibrillation	1 (0.2)	3 (1.2)
Coronary artery disease	1 (0.2)	0 (0.0)
Ear and labyrinth disorders	**1 (0.2)**	**0 (0.0)**
Vertigo positional	1 (0.2)	0 (0.0)
Gastrointestinal disorders	**1 (0.2)**	**2 (0.8)**
Gastrooesophageal reflux disease	1 (0.2)	0 (0.0)
Ileus	0 (0.0)	1 (0.4)
Pancreatitis	0 (0.0)	1 (0.4)
General disorders and administration site conditions	**1 (0.2)**	**0 (0.0)**
Non-cardiac chest pain	1 (0.2)	0 (0.0)
Infections and infestations	**4 (0.8)**	**2 (0.8)**
Abdominal infection	0 (0.0)	1 (0.4)
Diverticulitis	2 (0.4)	1 (0.4)
Erysipelas	0 (0.0)	1 (0.4)
Pneumonia	1 (0.2)	0 (0.0)
Urinary tract infection	1 (0.2)	1 (0.4)
Injury, poisoning and procedural complications	**3 (0.6)**	**1 (0.4)**
Clavicle fracture	1 (0.2)	0 (0.0)
Concussion	1 (0.2)	0 (0.0)
Joint dislocation	0 (0.0)	1 (0.4)
Tendon rupture	1 (0.2)	0 (0.0)
Musculoskeletal and connective tissue disorders	**3 (0.6)**	**2 (0.8)**
Arthralgia	1 (0.2)	0 (0.0)
Back pain	0 (0.0)	1 (0.4)
Meniscal degeneration	0 (0.0)	1 (0.4)
Spinal column stenosis	1 (0.2)	0 (0.0)
Spondylitis	1 (0.2)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**7 (1.3)**	**4 (1.6)**
B-cell lymphoma	1 (0.2)	0 (0.0)
Basal cell carcinoma	2 (0.4)	2 (0.8)
Hodgkin's disease	1 (0.2)	0 (0.0)
Malignant melanoma	0 (0.0)	1 (0.4)
Neoplasm skin	1 (0.2)	0 (0.0)
Squamous cell carcinoma	1 (0.2)	1 (0.4)
Uterine cancer	1 (0.2)	0 (0.0)
Nervous system disorders	**4 (0.8)**	**1 (0.4)**
Cerebral infarction	0 (0.0)	1 (0.4)
Cervicobrachial syndrome	1 (0.2)	0 (0.0)
Headache	1 (0.2)	0 (0.0)
Migraine	1 (0.2)	0 (0.0)
Transient ischemic attack	1 (0.2)	0 (0.0)
Psychiatric disorders	**1 (0.2)**	**0 (0.0)**
Suicidal ideation	1 (0.2)	0 (0.0)
Renal and urinary disorders	**0 (0.0)**	**2 (0.8)**
Calculus ureteric	0 (0.0)	1 (0.4)
Renal failure acute	0 (0.0)	1 (0.4)
Reproductive system and breast disorders	**0 (0.0)**	**1 (0.4)**
Vaginal prolapse	0 (0.0)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	**1 (0.2)**	**0 (0.0)**
Lung disorder	1 (0.2)	0 (0.0)

(Source: Sponsor's submission P009 CSR Page 208 Table 12-8)

Although more elderly subjects reported SAEs, the incidence of SAEs was comparable between the treatment groups in each of the age groups. In elderly subjects, the incidence of SAEs was 6.8% (21/308) for the suvorexant HD group and 7.9% (12/151) in the placebo group. In the non-elderly subjects, the incidence of SAEs was 2.8% (6/213) for the suvorexant HD group and 4.7% (5/107) in the placebo group. The most frequently reported SOC was Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps), in five elderly subjects.

During the randomized discontinuation phase, SAEs occurred in five subjects: three subjects (1.9%) who continued suvorexant HD reported one event each of positional vertigo (0.6%), cellulitis (0.6%), and squamous cell carcinoma (0.6%); one subject who switched from suvorexant HD to placebo reported breast cancer in situ; and on subject who remained on placebo reported basal cell carcinoma.

Drug-related AEs
In the treatment phase, suvorexant treatment resulted in a higher incidence of drug-related AEs compared to placebo. The incidences of drug-related AEs were 34.9% (182/521) in the suvorexant HD and 20.5% (53/258) in the placebo groups. The most frequent SOC was Nervous System Disorders: 20.3% (106/521) in the suvorexant HD group and 9.7% (25/258) in placebo. Specifically, somnolence occurred most frequently with incidences of 11.7% (61/521) in the suvorexant HD and 1.6% (4/258) in the placebo groups. The table below shows Merck's summary of drug-related AEs with an incidence >2% in a treatment group. Note that the specific AEs (PTs) in the table, except dizziness, occurred more frequently in suvorexant-treated subjects.

Reference ID: 3301133

Table 43: Drug-Related Adverse Events with Incidence >2% in any Treatment Group of Trial P009

Adverse Event Category **SOC** Preferred Term	**Suvorexant HD N (%)**	**Placebo N (%)**
Total Subjects	521 (100)	258 (100)
Subjects with one or more drug-related adverse events	182 (34.9)	53 (20.5)
Gastrointestinal disorders Dry mouth	**43 (8.3)** 23 (4.4)	**14 (5.4)** 4 (1.6)
General disorders and administration site conditions Fatigue	**30 (5.8)** 22 (4.2)	**7 (2.7)** 3 (1.2)
Investigations	**13 (2.5)**	**8 (3.1)**
Musculoskeletal and connective tissue disorders	**11 (2.1)**	**2 (0.8)**
Nervous system disorders Dizziness Headache Somnolence	**106 (20.3)** 15 (2.9) 18 (3.5) 61 (11.7)	**25 (9.7)** 10 (3.9) 8 (3.1) 4 (1.6)
Psychiatric disorders Abnormal dreams	**40 (7.7)** 17 (3.3)	**8 (3.1)** 5 (1.9)

(Source: Sponsor's submission P009 CSR Page 206 Table 12-7)

Age group analyses of trial P009's treatment phase showed a greater proportion of subjects on suvorexant reported drug-related AEs in both elderly and non-elderly subjects. In elderly subjects, the incidence of drug-related AEs was 30.5% (94/308) for the suvorexant HD group and 20.5% (31/151) in the placebo group. In the non-elderly subjects, the incidence of drug-related AEs was 41.3% (88/213) for the suvorexant HD group and 20.6% (22/107) in the placebo group. In both age groups, the most frequently reported SOC was Nervous System Disorders, which in elderly subjects, occurred at an incidence of 16.2% (50/308) in suvorexant HD subjects compared to 11.3% (17/151) in placebo subjects. In non-elderly subjects, Nervous System Disorders SOC occurred at an incidence of 26.3% (56/213) in suvorexant HD subjects compared to 7.5% (8/107) in placebo subjects.

During the randomized discontinuation phase, drug-related AEs occurred in 3.8% (6/156) of subjects who continued suvorexant treatment, 3.7% (6/162) of subjects who remained on placebo, and 1.8% (3/166) of subjects who switched to placebo. Merck reported the following statement on page 206 of trial P009 CSR: "The only specific drug-related AE with incidence ≥2% that occurred during the Randomized Discontinuation Phase was nightmares in the elderly age group (2.0% in MK/MK 0% MK/PBO and PBO/PBO groups)." However, the statement may have been referring to

non-elderly subjects instead, as Table 14-223 on pages 974 to 977 lists nightmares with an incidence of 2% (1/51) under non-elderly subjects who remained on suvorexant HD (MK/MK). The table reported no elderly MK/MK subject with nightmares.

Discontinuations Because of AEs
AEs leading to treatment discontinuation occurred in 83 subjects and was more frequent in suvorexant-treated subjects with an incidence of 11.7% (61/521) compared to placebo subjects with an incidence of 8.5% (22/258). Also, more subjects discontinued due to a drug-related AE in the suvorexant group compared to the placebo group: 8.3% (43/521) of suvorexant HD group and 4.7% (12/258) of the placebo group.

The most frequent event SOC leading to discontinuation was Nervous System Disorders: 6.5% (34/521) in the suvorexant HD group and 1.9% (5/258) in placebo. Events due to somnolence occurred most frequently with incidences of 3.8% (20/521) in the suvorexant HD and 0.8% (2/258) in the placebo groups. Two (0.4%) additional subjects on suvorexant HD and none (0.0%) on placebo discontinued because of sedation. Discontinuations due to memory impairment occurred in 4 subjects (0.8%) on suvorexant HD and none (0.0%) on placebo. Further, under the SOC of General disorders and administration site conditions, fatigue led to discontinuations in 1.3% (7/521) of suvorexant HD subjects on and 0.4% (1/258) of placebo subjects.

Table 44: Discontinuations due to Adverse Events with Incidence >0% in any Treatment Group of Trial P009

Adverse Event Category **SOC** Preferred Term	**Suvorexant HD** **N (%)**	**Placebo** **N (%)**
Total Subjects	521 (100)	258 (100)
Subjects with one or more adverse events for discontinuation	61 (11.7)	22 (8.5)
Cardiac disorders	**2 (0.4)**	**2 (0.8)**
Atrial fibrillation	1 (0.2)	2 (0.8)
Coronary artery disease	1 (0.2)	0 (0.0)
Gastrointestinal disorders	**0 (0.0)**	**2 (0.8)**
Ileus	0 (0.0)	1 (0.4)
Nausea	0 (0.0)	1 (0.4)
General disorders and administration site conditions	**8 (1.5)**	**3 (1.2)**
Chest pain	1 (0.2)	0 (0.0)
Fatigue	7 (1.3)	1 (0.4)
Feeling abnormal	0 (0.0)	1 (0.4)
Gait disturbance	0 (0.0)	1 (0.4)

Infections and infestations	**1 (0.2)**	**0 (0.0)**
Diverticulitis	1 (0.2)	0 (0.0)
Injury, poisoning and procedural complications	**1 (0.2)**	**2 (0.8)**
Ankle fracture	0 (0.0)	1 (0.4)
Clavicle fracture	1 (0.2)	0 (0.0)
Joint dislocation	0 (0.0)	1 (0.4)
Investigations	**2 (0.4)**	**3 (1.2)**
Blood amylase increased	1 (0.2)	0 (0.0)
Blood calcium increased	1 (0.2)	0 (0.0)
Blood creatine phosphokinase increase	0 (0.0)	2 (0.8)
Blood lactate dehydrogenase decrease	1 (0.2)	0 (0.0)
Blood magnesium increased	1 (0.2)	0 (0.0)
Lipase increased	1 (0.2)	1 (0.4)
Musculoskeletal and connective tissue disorders	**3 (0.6)**	**0 (0.0)**
Myalgia	1 (0.2)	0 (0.0)
Pain in extremity	1 (0.2)	0 (0.0)
Spinal column stenosis	1 (0.2)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3 (0.6)**	**0 (0.0)**
B-cell lymphoma	1 (0.2)	0 (0.0)
Hodgkin's disease	1 (0.2)	0 (0.0)
Uterine cancer	1 (0.2)	0 (0.0)
Nervous system disorders	**34 (6.5)**	**5 (1.9)**
Balance disorder	1 (0.2)	0 (0.0)
Dizziness	1 (0.2)	2 (0.8)
Lethargy	1 (0.2)	0 (0.0)
Memory impairment	4 (0.8)	0 (0.0)
Migraine	1 (0.2)	0 (0.0)
Paraesthesia	1 (0.2)	1 (0.4)
Parkinson's disease	1 (0.2)	0 (0.0)
Poor quality sleep	1 (0.2)	0 (0.0)
Sedation	2 (0.4)	0 (0.0)
Sleep paralysis	1 (0.2)	0 (0.0)
Somnolence	20 (3.8)	2 (0.8)

Psychiatric disorders	**9 (1.7)**	**4 (1.6)**
Abnormal dreams	1 (0.2)	0 (0.0)
Affective disorder	1 (0.2)	0 (0.0)
Anxiety	0 (0.0)	2 (0.8)
Bradyphrenia	1 (0.2)	0 (0.0)
Depressed mood	1 (0.2)	0 (0.0)
Depression	2 (0.4)	0 (0.0)
Hallucination, auditory	1 (0.2)	0 (0.0)
Hallucination, visual	1 (0.2)	0 (0.0)
Hypnagogic hallucination	1 (0.2)	0 (0.0)
Insomnia	0 (0.0)	2 (0.8)
Somnambulism	1 (0.2)	0 (0.0)
Suicidal ideation	1 (0.2)	0 (0.0)
Renal and urinary disorders	**0 (0.0)**	**1 (0.4)**
Renal failure acute	0 (0.0)	1 (0.4)

(Source: Sponsor's submission P009 CSR Page 212 Table 12-10)

In age group analyses of the trial's treatment phase, discontinuations because of AEs were similar between the treatment groups in elderly subjects: 12.0% (37/308) on suvorexant HD and 11.9% (18/151) on placebo. However, in the non-elderly subjects, a greater proportion of subjects on suvorexant discontinued because of AEs: 11.3% (24/213) on suvorexant HD compared to 3.7% (4/107) on placebo. Specifically somnolence led to discontinuations in non-elderly subjects in 3.8% (8/213) on suvorexant HD compared to 0.9% (1/107) on placebo. Similarly in elderly subjects, somnolence led to discontinuations in 3.9% (12/308) on suvorexant HD compared to 0.7% (1/151) on placebo.

During the randomized discontinuation phase, only one subject, a 69 year old female who switched to placebo (MK/PBO group), discontinued because of an AE of breast cancer.

Common AEs
The percentage of subjects who reported one or more adverse events on suvorexant HD (69.5%, 362/521) was comparable to placebo (63.6 %, 164/258) during the treatment phase. Similarly, the percentages of elderly and non-elderly subjects who reported one or more adverse events were comparable.

Merck evaluated for AE system organ classes (SOCs) in which suvorexant subjects reported more AEs than placebo subjects, and in which the 95% confidence intervals of the risk difference between treatment groups excluded zero. As show on table below, four SOCs met these conditions: General Disorders and Administration Site Conditions, Immune System Disorders, Nervous System Disorders, and Psychiatric Disorders. The most frequent AEs were nervous system disorders, with incidence in the suvorexant group 29.2% (152/521) compared to placebo 21.3% (55/258).

Table 45: Adverse Events by System Organ Classes (SOCs) with Higher Incidence in Suvorexant Group and with Significant Risk Difference

Dictionary-Derived Term (SOC)	Suvorexant HD N=521 n (%)	Placebo N=258 n (%)	Risk Difference (95% CI)
General Disorders and Administration Site Conditions	64 (12.3)	16 (6.2)	6.1 (1.7, 10.0)
Immune System Disorders	10 (1.9)	0 (0.0)	1.9 (0.4, 3.5)
Nervous System Disorders	152 (29.2)	55 (21.3)	7.9 (1.3, 14.0)
Psychiatric Disorders	58 (11.1)	15 (5.8)	5.3 (1.1, 9.1)

(Source: Modified from Sponsor's submission P009 CSR Page 198 Table 12-5)

The AE with the highest incidence during the treatment period was somnolence, which occurred in 13.2% (69/521) of the suvorexant HD group and 2.7% (7/258) of the placebo group. Four other **AEs were more prevalent on suvorexant HD and the 95% confidence interval of the risk difference from placebo excluded zero**. The risk difference (95% CI) for the four AEs were as follows: dry mouth, 3.4 (95% CI: 0.7, 5.9); dyspepsia, 1.9 (95% CI: 0.4, 3.5); fatigue, 4.6 (95% CI: 1.6, 7.4); and peripheral edema, 1.7 (95% CI: 0.3, 3.3). Below I summarize the adverse events by preferred terms (PTs) that occurred at an incidence of at least 2% in a treatment group.

Table 46: Subjects with Adverse Event Preferred Terms of Incidence >2% in a Treatment Group in Trial P009

Dictionary-Derived Term (PT)	Suvorexant HD N=521	Placebo N=258	Total Subjects N=779
Somnolence	69 (13.24%)	7 (2.71%)	76 (9.73%)
Headache	44 (8.45%)	22 (8.53%)	66 (8.45%)
Nasopharyngitis	42 (8.06%)	20 (7.75%)	62 (7.94%)
Dizziness	24 (4.61%)	16 (6.20%)	40 (5.12%)
Upper respiratory tract infection	28 (5.37%)	11 (4.26%)	39 (4.99%)
Fatigue	34 (6.53%)	5 (1.94%)	39 (4.99%)
Dry mouth	26 (4.99%)	4 (1.55%)	30 (3.84%)
Diarrhoea	17 (3.26%)	9 (3.49%)	26 (3.33%)
Nausea	18 (3.45%)	7 (2.71%)	25 (3.20%)
Abnormal dreams	19 (3.65%)	6 (2.33%)	25 (3.20%)
Drug administration error	13 (2.50%)	12 (4.65%)	25 (3.20%)
Arthralgia	16 (3.07%)	8 (3.10%)	24 (3.07%)
Back pain	15 (2.88%)	7 (2.71%)	22 (2.82%)
Fall	12 (2.30%)	8 (3.10%)	20 (2.56%)
Cough	14 (2.69%)	5 (1.94%)	19 (2.43%)

Urinary tract infection	12 (2.30%)	6 (2.33%)	18 (2.30%)
Influenza	14 (2.69%)	4 (1.55%)	18 (2.30%)
Sinusitis	9 (1.73%)	7 (2.71%)	16 (2.05%)
Pain in extremity	10 (1.92%)	6 (2.33%)	16 (2.05%)
Nightmare	13 (2.50%)	2 (0.78%)	15 (1.92%)
Hypertension	8 (1.54%)	7 (2.71%)	15 (1.92%)
Oropharyngeal pain	5 (0.96%)	6 (2.33%)	11 (1.41%)
Lipase increased	5 (0.96%)	6 (2.33%)	11 (1.41%)
Constipation	3 (0.58%)	7 (2.71%)	10 (1.28%)
Oropharyngeal pain	5 (0.96%)	6 (2.33%)	11 (1.41%)
Lipase increased	5 (0.96%)	6 (2.33%)	11 (1.41%)
Constipation	3 (0.58%)	7 (2.71%)	10 (1.28%)

(Source: Reviewer Analyses; Shaded portions show AEs more prevalent in suvorexant group)

Reviewer Comment:
The common AEs observed in trial P009 appear typical for an insomnia drug development program.

Adverse Events of Special Interests

Although the incidences of ECIs were low in Trial P009, most of them occurred more frequently in subjects on suvorexant HD. Merck reported no statistically significant difference in the proportion of subjects with any ECI between the treatment groups during the treatment phase. No event of cataplexy was confirmed by the adjudication committee. One subject reported both visual and auditory hallucinations on Day 324 of suvorexant HD treatment. The adjudication committee confirmed one case of sleep onset paralysis. Below I summarize the incidences of the ECIs. Section 7 of this review contains additional assessments of ECIs.

Table 47: Events of Clinical Interest (ECI) in Trial P009 Treatment Phase

Events of Clinical Interest (ECIs)	**Suvorexant HD % (n/N)**	**Placebo % (n/N)**	**Risk Difference (95% CI)**	**P value**
Total Subjects	521	258		
Suicidal ideation or behaviors	**0.8% (4/521)**	**0.0% (0/258)**	**0.8 (-0.7, 2.0)**	**0.159**
Events associated with potential for abuse	**3.5% (18/521)**	**3.9% (10/258)**	**-0.4 (-3.8, 2.2)**	**0.767**
Drug maladministration	2.3% (12/521)	3.9% (10/258)	-1.6 (-4.8, 0.8)	0.213
Derealisation	0.2% (1/521)	0.0% (0/258)	0.2 (-1.3, 1.1)	0.482
Hallucination, auditory and visual	0.2% (1/521)	0.0% (0/258)	0.2 (-1.3, 1.1)	0.482
Hypnagogic hallucination	0.6% (3/521)	0.0% (0/258)	0.6 (-0.9, 1.7)	0.222

Hypnopompic hallucination	0.2% (1/521)	0.0% (0/258)	0.2 (-1.3, 1.1)	0.482
Complex sleep-related behaviors (Somnambulism)	**0.2% (1/521)**	**0.0% (0/258)**	**0.2 (-1.3, 1.1)**	**0.482**
Hypnagogic or hypnopompic hallucinations Hypnagogic hallucination Hypnopompic hallucination	**0.8% (4/521)** 0.6% (3/521) 0.2% (1/521)	**0.0% (0/258)** 0.0% (0/258) 0.0% (0/258)	**0.8 (-0.7, 2.0)** 0.6 (-0.9, 1.7) 0.2 (-1.3, 1.1)	**0.159** 0.222 0.482
Excessive daytime sleepiness	**2.5% (13/521)**	**0.8% (2/258)**	**1.7 (-0.5, 3.6)**	**>0.05**
Sleep paralysis Sleep onset paralysis	**0.4% (2/521)** 0.2% (1/521)	**0.0% (0/258)** 0.0% (0/258)	**0.4 (-1.1, 1.4)** 0.2 (-1.3, 1.1)	**>0.05** 0.482
Cataplexy	**0.0% (0/521)**	**0.0% (0/258)**	**0.0 (no event)**	**>0.05**
Falls	**2.3% (12/521)**	**3.1% (8/258)**	**-0.8 (-3.9, 1.5)**	**0.508**
AEs associated with traffic or motor vehicle accidents, with subject as the driver	**0.4% (2/521)**	**0.0% (0/258)**	**0.4 (95% CI, not stated)**	**>0.05**

(Source: Modified from Sponsor's submission P009 CSR Pages 217, 224, 226 to 232; Tables 12-11, 12-14 to 12-21)

Merck provided additional information on events that were related to ECIs but not reported as ECIs. Four cases of suicidal ideation were reported as ECIs during the treatment phase, as noted in the table above. A fifth case was determined on C-CASA assessment. During the follow-up period, one additional subject, who had been on suvorexant, reported suicidal ideation.

Using the Motor Vehicle Accidents and Violations (MVAV) Questionnaire, Merck assessed for occurrence of traffic or MVA since the subject's last visit and any related injuries. Although Merck suggests that no association was found between suvorexant administration and occurrence of MVAs, **numerically more subjects on suvorexant HD (5.5%, 22/397) compared to placebo (4.1%, 8/196) had at least one MVAV event.** A similar pattern was observed for number of subjects with accidents. The table below summarizes the MVAV events in Trial P009.

Table 48: Subjects with Motor Vehicle Accidents or Violations (MVAV) in Trial P009 Treatment Phase

MVAV Category	Suvorexant HD N (%)	Placebo N (%)
Total Subjects	397	196

Subjects with one or more MVAV events Number of MVAV events	22 (5.5) 24	8 (4.1) 11
Subjects with Accidents Number of Accidents	7 (1.8) 7	3 (1.5) 3
Subjects with violations Number of violations	15 (3.8) 17	6 (3.1) 8

(Source: Modified from Sponsor's submission P009 CSR Page 233 Table 12-22)

No reports of suicidal ideation, complex sleep-related behaviors, hallucinations, or sleep paralysis occurred during the randomized discontinuation phase.

Rebound and Withdrawal
Merck compared the sleep parameters of sTST, sTSO, and sWASO between the MK/PBO and PBO/PBO groups on the first 3 nights of run-out to the last baseline values, and determined that no statistically significant differences indicative of clinically meaningful rebound were observed in Trial P009. However, the proportion of subjects with rebound, based on sTST on nights 1, 2, or 3, was numerically higher in subjects who switched to placebo (MK/PBO: 51.0%, 80/157) compared to those who remained on placebo (PBO/PBO: 40.1%, 61/152) with a treatment difference of 10.8 (95% CI, -0.3, 21.7; p value=0.057). The incidence in the MK/MK group was 28.9% (44/152). With regards to withdrawal, the treatment groups were similar in proportion of subjects who reported withdrawal symptoms across nights 1, 2, and 3.

Laboratory Values over Time
Merck assessed laboratory measurements using mean values at baseline, treatment period, and change-from-baseline values. Based on the values, no remarkable changes in lab values were noted. During the randomized discontinuation phase, elderly subjects showed increases in creatine kinase mean (SD) values at Month 13 for MK/PBO subjects: MK/PBO, 12.3 (62.8); MK/MK, -2.7 (46.8); and PBO/PBO, 11.7 (48.4). A similar pattern occurred at Month 14: MK/PBO, 7.6 (58.2); MK/MK, -2.4 (61.5); and PBO/PBO, 20.2 (56.9).

Reviewer Comment:
The changes in creatine kinase are unlikely to be clinically significant, especially with a comparable change in subjects who remained on placebo (PBO/PBO).

Laboratory Values meeting Pre-defined Limits of Change
Also, Merck assessed laboratory measurements using pre-defined limits of change to show changes in laboratory values that are likely to be clinically significant. Based on the pre-defined Tier 2 safety assessment plan, there were no significant differences between the treatment groups in all laboratory parameters, as the 95% confidence intervals for the treatment differences included zero. Although elevated potassium levels (≥111.1% ULN) occurred more frequently in subjects on suvorexant HD (3.1%, 16/515)

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compared to placebo (2.0%, 2/254), the confidence interval for the risk difference of 1.1 included zero (-1.6 to 3.4).

Vital Signs
Based on change in mean values, no significant differences occurred between the groups in SBP, DBP, pulse rate, temperature, and weight. Also, no clinically significant differences between the treatment groups, overall or in either age group, were observed based on proportion of subjects meeting the pre-defined limits of change in the vital signs.

ECG
Based on change in mean values or proportion of subjects exceeding pre-defined limits of change from baseline in QTc Interval (Bazett), no significant differences occurred between the treatment groups.

Reviewer Comment:
Trial P009 showed no significant imbalances in laboratory values, vital signs, and ECG data. Further, Trial P009 contributes to the pooled analyses of overall safety of suvorexant that I discuss extensively in Section 7 of this review. Rebound effect and withdrawal of suvorexant are also discussed more extensively in Section 7.

6 Review of Efficacy

Efficacy Summary

The overall data from two confirmatory efficacy trials showed that suvorexant high dose (HD) had statistically significant efficacy effect on both sleep maintenance and sleep onset endpoints in adult subjects with primary insomnia. The efficacy effects of suvorexant HD persisted through the entire treatment period and appeared clinically meaningful. Suvorexant low dose (LD), which was not primarily evaluated in the trials, appeared to have some efficacy effect on sleep maintenance insomnia. In the trials, suvorexant HD signified 30 mg for elderly subjects and 40 mg for non-elderly subjects, suvorexant LD was 15 mg for elderly subjects and 20 mg for non-elderly subjects.

Two parallel-group 3-month Phase 3 trials, P028 and P029, provide the primary support of efficacy for suvorexant treatment of primary insomnia. The two similarly designed trials were conducted in the US and non-US sites. Both trials shared the same primary objective: to evaluate the efficacy of suvorexant HD compared with placebo in improving sleep maintenance and sleep onset at Months 1 and 3, using subjective patient-reported outcomes and objective polysomnographic (PSG) assessments. Suvorexant HD consisted of 30 mg in elderly subjects (65 years and older) and 40 mg in non-elderly subjects (younger than 65 years).

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The trials used multiple endpoints to assess the efficacy of suvorexant. For sleep maintenance, Merck compared the treatment effects of suvorexant HD and placebo on two primary endpoints that were assessed at two time points, as follows: change from baseline in mean subjective total sleep time, sTSTm, at Month 1 and Month 3; and change from baseline in the PSG-derived objective wakefulness after persistent sleep onset, WASO, at Month 1 and Month 3. Likewise for sleep onset, suvorexant HD treatment effects were assessed by the following endpoints: change from baseline in mean subjective time to sleep onset, sTSOm, at Month 1 and Month 3; and change from baseline in objective latency to persistent sleep, LPS, at Month 1 and Month 3.

Key secondary endpoints in trial P028 included change from baseline in sTSTm at Week 1 and WASO at Night 1 for suvorexant HD, and an assessment of suvorexant LD on all the above-stated endpoints and time points for suvorexant HD. Trial P029 assessed suvorexant LD as exploratory analyses.

Merck used a multiplicity testing strategy to assess the primary and secondary endpoints. A longitudinal data analysis (LDA) model was used to perform the statistical analyses for efficacy. The analysis model adjusted for baseline values of the response variable, age group (non-elderly versus elderly), region, gender, treatment, time, and the interaction of treatment by time. To control for type 1 error, Merck analyzed the primary and secondary endpoints using a multiplicity testing strategy that included a Bonferroni approach to evaluate two distinct indications – sleep maintenance and sleep onset effects. The strategy also encompassed a fixed sequential testing procedure to move from Month 1 to Month 3 sets of primary hypotheses, and a Hochberg approach within each time point to evaluate the objective and subjective endpoints. As a result, endpoints for sleep maintenance effect (sTSTm and WASO) were tested at the two-sided 2.5% alpha level, while endpoints for sleep onset effect (sTSOm and LPS) were also tested at the two-sided 2.5% level. Overall, the trial's choice of endpoints, blinding procedure, duration, conduct, and statistical analyses appear adequate.

An earlier phase 2 dose finding trial P006 that evaluated multiple suvorexant doses from 10 mg to 80 mg in non-elderly subjects informed on the choice of dose to study in the phase 3 trials. The 40 mg dose chosen for further assessment appears appropriate based on the 4-week treatment effect on both objective and subjective endpoints. Using drug exposure data from prior clinical pharmacology studies, Merck chose a 30 mg dose to treat elderly subjects in the Phase 3 trials; this dose was considered comparable to the 40 mg dose in non-elderly subjects. Both doses for the two age groups are referred to as suvorexant HD. Based on feedback from regulatory interaction with FDA during the drug development, Merck included a lower dose in the phase 3 program, suvorexant LD, which consisted of 15 mg for elderly subjects and 20 mg for non-elderly subjects.

<u>Sleep Maintenance Effects</u>

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For sleep maintenance, suvorexant HD treatment, in both confirmatory efficacy trials P028 and P029, resulted in statistically significant improvements on both subjective (sTSTm) and objective (WASO) primary endpoints at Month 1 and Month 3. Based on the pooled data, suvorexant HD compared to placebo treatment added about 22 minutes of subjective total sleep time, and reduced objective wakefulness after persistent sleep by 26 minutes at Month 3. Supporting efficacy assessments using the subjective endpoint sWASO showed similar improvements with suvorexant HD compared to placebo at all time points.

Assessment of secondary endpoints provided additional support for efficacy of suvorexant in treating sleep maintenance insomnia. In the secondary analyses for both trials P028 and P029, suvorexant HD significantly improved sTSTm and WASO at all pre-defined time points.

Also in trial P028, suvorexant LD significantly improved the sleep maintenance endpoints sTSTm and WASO at all predefined time. Trial P029 did not include suvorexant LD for secondary endpoint assessment. Based on the pooled data, suvorexant LD compared to placebo treatment added 16 minutes of sTSTm ($p < 0.00001$), and reduced WASO by 23 minutes at Month 3 ($p < 0.00001$). Importantly, suvorexant LD failed to significantly improve sWASOm at Months 1 and 3 in trial P028. Of note, FDA had previously requested sWASO as a key sleep maintenance endpoint.

Overall, suvorexant HD, and to a less extent suvorexant LD, showed significant improvement in sleep maintenance endpoints. The difference between the treatment effect of suvorexant HD and that of suvorexant LD is about 6 minutes on sTSTm and 3 minutes on WASO. Whether this difference in treatment effects between the suvorexant doses is sufficient to allow approval of the lower dose for sleep maintenance will be a topic of discussion at the advisory committee meeting. Of note, an acceptance of suvorexant LD as an effective treatment for sleep maintenance will ignore the inconsistent effect of the dose on sWASO in trial P028.

Sleep Onset Effects

Suvorexant HD treatment improved sleep onset compared to placebo, though not as consistently as in sleep maintenance. In both confirmatory efficacy trials P028 and P029, suvorexant HD treatment resulted in statistically significant improvements on the subjective (sTSOm) primary endpoint for sleep onset at Month 1 and Month 3. In trial P028, suvorexant HD significantly improved the objective primary endpoint LPS at Month 1 and Month 3. However in trial P029, suvorexant HD significantly improved LPS at Month 1 but failed to provide similar LPS improvement at Month 3. Based on the pooled data from trials P028 and P029, suvorexant HD compared to placebo treatment decreased subjective time to sleep onset by about 11 minutes ($p < 0.00001$) and objective LPS by 6 minutes ($p = 0.00235$) at Month 3.

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The secondary efficacy endpoints assessed for sleep onset, sTSOm at Week 1 and LPS at Night 1, showed significant improvements with suvorexant HD compared to placebo treatment in both trials P028 and P029.

Secondary endpoint assessment for suvorexant LD in trial P028 showed inconsistent improvements on sleep onset endpoints at different time points. Suvorexant LD significantly improved sTSOm at Week 1 and LPS at Night 1. The dose improved LPS at Month 1 by 10.3 minutes compared to placebo ($p = 0.0004$), but it did not significantly improve sTSO compared to placebo despite a 5.4-minute decrease in the endpoint ($p = 0.05191$).

Overall, suvorexant HD consistently showed significant improvement in the subjective sleep onset endpoint. The dose showed significant improvement in the objective sleep onset endpoint at all time points, except at Month 3 in one of the two trials. In contrast, suvorexant LD showed inconsistent improvements on sleep onset endpoints at different time points. Whether the inability of suvorexant HD to significantly improve LPS at Month 3 is sufficient to deny approval of the dose for sleep onset will be a topic of discussion at the advisory committee meeting.

Clinical Significance of Efficacy Based on Responder Analysis

Merck conducted analyses on pre-specified responder analyses based on exploratory subjective endpoints to further assess the clinical meaningfulness of suvorexant treatment effects. For sleep maintenance, a higher percentage of subjects on suvorexant treatment recorded at least 15% increase from baseline in sTSTm at the different time points in the pooled data. The percentage of sTST responders in the treatment groups at Month 3 was 54.7% (376/688) for suvorexant HD compared to 41.9% (278/664) for placebo, a treatment difference of 12.8% that yielded a number needed to treat to benefit (NNTB) of 8. For sWASO, the percentage of responders in the treatment groups at Month 3 was 77.5% (529/683) for suvorexant HD compared to 69.4% (458/660) for placebo, a treatment difference of 8.1% and NNTB of 12.

For sleep onset, the pooled data from P028 and P029 trials showed that a higher percentage of subjects recorded improvement in subjective sleep onset based on at least 15% decrease from baseline in sTSOm at the different time points with suvorexant treatment. The percentage of sTSO responders in the treatment groups at Month 3 was 76.5% (526/688) for suvorexant HD compared to 66.0% (438/664) for placebo, a treatment difference of 10.5% that yielded an NNTB of 10.

The overall data suggest that suvorexant HD has clinically significant efficacy on both sleep maintenance and sleep onset in subjects with primary insomnia. The assessments showed that the efficacy of suvorexant HD persisted through the entire treatment period. Suvorexant LD, though not primarily evaluated in the trials, appears to have some significant but limited efficacy on sleep maintenance insomnia. In addition, point estimates, shown in review section 6.1.7, for the sleep maintenance and sleep

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onset endpoints from the pooled data suggest that improvements from suvorexant (HD and LD) treatment were generally consistent across the subgroups.

6.1 Indication

Suvorexant is proposed for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. The proposed dose is 40 mg in non-elderly adults, or 30 mg in elderly adults, once daily immediately before bedtime.

6.1.1 Methods

The two similarly designed trials provide primary support for efficacy of suvorexant in treating insomnia for at least three months. The two trials, P028 and P029, had similar primary endpoints to assess improvements in sleep onset, sTSO and LPS, and sleep maintenance, sTST and WASO. In addition, the two 3-arm trials primarily assessed the superiority of suvorexant HD over placebo in improving the sleep parameters during 3 months of treatment. Secondarily, the trials assessed benefit of suvorexant LD in treating the sleep parameters. The trials also evaluated the effect of the suvorexant doses on sWASO, an endpoint traditionally used to assess sleep maintenance. Trial P028 further added a 3-month extension phase to evaluate longer treatment effects.

Both trials were adequately designed to evaluate efficacy of suvorexant HD in subjects with primary insomnia. Section 5 provided extensive discussion on the individual trials. Statistical analysis plans showed that the trials were adequately powered to detect a treatment difference between suvorexant HD and placebo for both sleep maintenance primary endpoints and for at least one sleep onset primary endpoint.

To support the label claims for possible use of lower doses, Merck evaluated the trials, individually and pooled, for efficacy of suvorexant LD. The two confirmatory efficacy trials, P028 and P029, provided pooled data to assess suvorexant LD for efficacy. Merck pooled data from the two trials to provide more precise estimates for treatment differences between suvorexant HD and placebo, and between suvorexant LD and placebo, for the primary and secondary efficacy endpoints. Also, the pooled data enabled Merck to further assess the treatment effects across the subgroups of age, gender, and race.

Merck used similar statistical methods as described in Section 5 of this review for the individual phase 3 trials, and additionally adjusted for the individual trials to analyze the pooled data. Phase 2 trial P006 provided data for suvorexant dose assessment in non-elderly subjects with insomnia treated for four weeks. Section 5 of this review provided additional information on the dose-finding, crossover trial P006.

The primary analyses included all subjects in the full analysis set (FAS) trial population. To be included in the FAS population for any efficacy endpoint, a subject needed to

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have at least one post-randomization efficacy observation after receiving at least one dose of trial treatment, and if needed, appropriate baseline data. Subjects were analyzed according to the treatment to which they were randomized, suggestive of a modified intention-to-treat approach.

Merck conducted the analyses for the primary, secondary and exploratory efficacy endpoints using the longitudinal data analysis (LDA) method that allowed for an approach of no imputation for missing data. This approach assumed that the missing data were missing at random (MAR) and was used across the trials and pooled (P028 and P029) analyses.

The efficacy assessments for suvorexant HD included non-elderly subjects treated with suvorexant 40 mg and elderly subjects treated with suvorexant 30 mg, while suvorexant LD included non-elderly subjects treated with suvorexant 20 mg and elderly subjects treated with suvorexant 15 mg. Combining the separate doses in each category was based on Merck's earlier studies that matched the respective suvorexant doses with the PK exposures for the age groups.

Merck analyzed the pooled P028 and P029 data to determine consistency of treatment effects across categories of subgroups. A category of Baseline Entry Criteria for subjective endpoints was also included in the subgroup analyses. This subgroup enabled Merck to analyze consistency of response for the key subjective endpoints in the PQ-cohort that included subjects who were enrolled based on PSG criteria. The analysis compared subjects who met Q-Cohort entrance criteria, by having at least four out of seven pre-randomization nights (excluding PSG nights) where sTST <6.5 hours and sTSO ≥30 minutes, with those who did not meet Q-Cohort entrance criteria. The subgroups analyzed with the pooled P028 and P029 data included the following:

- Age: elderly and non-elderly
- Gender: females and males
- Race: white and other;
- Regions: North America, Europe, and Other
- Cohort: Q-Cohort vs. PQ-Cohort
- Baseline severity of insomnia: dichotomized at median severity for trial population
- Baseline Entry Criteria for subjective endpoints in PQ-cohort: sTSTm<6.5 and sTSOm>=30 compared to sTSTm>=6.5 and sTSOm<30

Also, Merck evaluated efficacy of long-term treatment with suvorexant HD. Phase 3 trial P009 assessed the persistence of suvorexant HD's efficacy in adults with insomnia beyond 3 months and up to 12 months of treatment. The long-term trial was reviewed in detail in Section 5.

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6.1.2 Demographics

Pooled Subject Demographics P028 and P029 Trials
The subject demographics were similar across treatment groups. The subjects' mean age was 56 years (SD, 15 years) with 839 (41.3%) subjects in the elderly age group. About 64% (1308/2030) of all subjects were females. Age and gender distributions were similar across the treatment groups. The subjects were predominantly of white race (72.6%, 1474/2030). Section 5.3 Discussion of Individual Studies/Clinical Trials described subject demographics for the individual trials contributing to efficacy assessments. Trial P028 enrolled more Asian subjects after the Q-cohort enrolled only Japanese subjects. Otherwise, the demographic data from the individual component trials, P028 and P029, were generally similar. Below is a summary of pooled subject characteristics from Trials P028 and P029.

Table 49: Pooled Subject Characteristics Treatment Phase of Trials P028 and P029

Category	Placebo N (%)	Suvorexant LD N (%)	Suvorexant HD N (%)	Total N (%)
Subjects in population	767	493	770	2,030
Gender				
Male	275 (35.9)	174 (35.3)	273 (35.5)	722 (35.6)
Female	492 (64.1)	319 (64.7)	497 (64.5)	1,308 (64.4)
Age in years				
Mean	56	55	56	56
SD	15	16	15	15
Age Categories				
<65 years	449 (58.5)	291 (59.0)	451 (58.6)	1,191 (58.7)
>=65 years	318 (41.5)	202 (41.0)	319 (41.4)	839 (41.3)
Race				
White	553 (72.1)	358 (72.6)	563 (73.1)	1,474 (72.6)
Black	46 (6.0)	19 (3.9)	38 (4.9)	103 (5.1)
Asian	124 (16.2)	93 (18.9)	124 (16.1)	341 (16.8)
Other	44 (5.7)	23 (4.7)	45 (5.8)	112 (5.5)
Ethnicity				
Hispanic or Latino	123 (16.0)	90 (18.3)	133 (17.3)	346 (17.0)
Not Hispanic or Latino	644 (84.0)	403 (81.7)	637 (82.7)	1,684 (83.0)
Cohort				
Q	180 (23.5)	150 (30.4)	180 (23.4)	510 (25.1)
PQ	587 (76.5)	343 (69.6)	590 (76.6)	1,520 (74.9)
Region				
Asia Pacific	27 (3.5)	26 (5.3)	27 (3.5)	80 (3.9)
Central and Eastern Europe	29 (3.8)	17 (3.4)	17 (2.2)	63 (3.1)
Central and South America	42 (5.5)	27 (5.5)	47 (6.1)	116 (5.7)

Europe	247 (32.2)	165 (33.5)	250 (32.5)	662 (32.6)
Japan	94 (12.3)	61 (12.4)	92 (11.9)	247 (12.2)
Middle East/Africa	15 (2.0)	7 (1.4)	9 (1.2)	31 (1.5)
North America	313 (40.8)	190 (38.5)	328 (42.6)	831 (40.9)
Body Mass Index (BMI) in kg/m^2				
Mean	25.6	25.4	25.7	25.6
SD	4.2	4.1	4.3	4.2
BMI Category				
Underweight (BMI < 18.5)	16 (2.1)	11 (2.2)	18 (2.3)	45 (2.2)
Normal range (18.5 <= BMI < 25)	351 (45.8)	232 (47.1)	323 (41.9)	906 (44.6)
Overweight (25 <= BMI <= 30)	289 (37.7)	194 (39.4)	317 (41.2)	800 (39.4)
Obese (BMI > 30)	110 (14.3)	56 (11.4)	111 (14.4)	277 (13.6)
Null	1 (0.1)	0 (0.0)	1 (0.1)	2 (0.1)

(Source: Modified from Sponsor's Submission ISE Page 281 Table Appendix 5.3.5.3.2-Insomnia: 19)

The mean age for the non-elderly adults was 46 years (SD, 12 years) and for the elderly subjects 71 years (4 years). The pattern of other demographic characteristics was similar between the non-elderly and non-elderly age groups.

As shown in Section 5.3 Discussion of Individual Studies/Clinical Trials, the baseline values of the subjective efficacy endpoints suggested that trial P029 had more severe insomnia symptoms than subjects in P028. However, generally there was remarkable overlap in the ranges of the baseline efficacy endpoint values, particularly with the objectives endpoint values, WASO and LPS. Below is a summary of the mean values of the efficacy endpoints at baseline for the pooled P028 and P029 trials.

Table 50: Pooled Subject Baseline Mean and Range of Values for Efficacy Endpoints in Minutes Treatment Phase of Trials P028 and P029

Endpoint	Placebo	Suvorexant LD	Suvorexant HD
sTSTm	312.7 (0.0 - 548.4)	310.7 (0.0 - 512.9)	315.7 (0.0 - 502.6)
sTSOm	74.1 (5.7 - 480.0)	74.3 (10.0 - 480.0)	71.2 (5.7 - 480.0)
sWASOm	80.7 (0.0 - 365.0)	79.1 (0.0 - 303.0)	80.3 (0.0 - 335.1)
WASO	116.7 (45.5 - 317.0)	119.4 (46.0 - 332.5)	118.6 (46.0 - 343.0)
LPS	67.1 (20.5 - 347.5)	67.3 (3.5 - 335.0)	64.6 (20.5 - 386.5)

(Source: Modified from Sponsor's Submission ISE Page 303 Table Appendix 5.3.5.3.2-Insomnia: 26)

6.1.3 Subject Disposition

Section 5.3 Discussion of Individual Studies/Clinical Trials described subject disposition for the individual trials. For the pooled P028 and P029 trials, 2041 subjects were randomized; of these, 11 subjects received no treatment, leaving 2030 randomized subjects who received treatment. A total of 1797 (88%) subjects completed 3-month treatment. Discontinuation rates were comparable across treatment groups. More

subjects withdrew from the placebo group, in part from lack of efficacy, compared to the suvorexant groups. The table below summarizes the subject disposition during the treatment phase for the pooled trials P028 and P029.

Table 51: Disposition for Pooled P028 and P029 Trials Treatment Phase

	Placebo N (%)	Suvorexant LD N (%)	Suvorexant HD N (%)	Total N (%)
Not Randomized				3712
Total Subjects	772	494	775	2041
Study Disposition				
Not Treated	5 (0.6)	1 (0.2)	5 (0.6)	11 (0.5)
Completed Treatment	671 (86.9)	435 (88.1)	691 (89.2)	1797 (88.0)
Discontinued during Treatment	96 (12.4)	58 (11.7)	79 (10.2)	233 (11.4)
Adverse Event	38 (4.9)	16 (3.2)	34 (4.4)	88 (4.3)
Withdrawal by Subject	31 (4.0)	14 (2.8)	17 (2.2)	62 (3.0)
Protocol Violation	9 (1.2)	10 (2.0)	7 (0.9)	26 (1.3)
Lost to Follow-up	1 (0.1)	3 (0.6)	5 (0.6)	9 (0.4)
Lack of Efficacy	17 (2.2)	8 (1.6)	11 (1.4)	36 (1.8)
Pregnancy	0 (0.0)	1 (0.2)	1 (0.1)	2 (0.1)
Physician Decision	0 (0.0)	6 (1.2)	4 (0.5)	10 (0.5)
Protocol Milestone				
Completed Treatment	671 (86.9)	435 (88.1)	691 (89.2)	1797 (88.0)
Continuing Into Extension	151 (19.6)	100 (20.2)	172 (22.2)	423 (20.7)
Continuing Into Run-Out	513 (66.5)	333 (67.4)	516 (66.6)	1362 (66.7)
Not Treated in Run-Out	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)
Not Continuing Into Extension Or Run-Out	7 (0.9)	2 (0.4)	3 (0.4)	12 (0.6)
Discontinued during Treatment (not cont into Ext or RO)	96 (12.4)	58 (11.7)	79 (10.2)	233 (11.4)

(Source: Modified from Sponsor's submission ISE Page 265 Table Appendix 5.3.5.3.2-Insomnia: 4)

Reviewer Comment:
Screen failure and subject withdrawal were the most common reasons for non-randomization of subjects. Overall, about 88% of the randomized subjects completed the trial treatment. More subjects withdrew from the placebo group compared to the suvorexant groups. Also, more subjects withdrew from the placebo group because of

lack of efficacy. The difference in discontinuations is unlikely to inflate the suvorexant treatment effect.

6.1.4 Analysis of Primary Endpoint(s)

A primary objective of trials P028 and P029 was to evaluate, in subjects with primary insomnia, efficacy of suvorexant high dose (HD) compared with placebo in improving sleep maintenance and onset at Months 1 and 3, using subjective patient-reported outcomes and objective polysomnographic (PSG) assessments. This section reviews the results of the primary endpoints for sleep maintenance and sleep onset.

Sleep Maintenance

For sleep maintenance, Merck compared the treatment effects of suvorexant HD and placebo on four primary endpoint assessments: two primary endpoints, sTSTm and WASO, assessed at two time points, Months 1 and 3, as follows:

- Change from baseline in sTSTm at Month 1
- Change from baseline in sTSTm at Month 3
- Change from baseline in WASO at Month 1
- Change from baseline in WASO at Month 3

Sleep Maintenance by sTSTm
In trial P028, following a multiplicity testing strategy, suvorexant HD significantly increased total sleep time, as measured by sTSTm, compared to placebo, with a treatment difference in mean change from baseline of 19.6 minutes ($p < 0.00001$) at Month 1, and 19.7 minutes ($p < 0.00001$) at Month 3. Although the primary endpoint analysis did not include Week 1, similar improvements in sTST with suvorexant HD occurred at that time point.

Similarly in trial P029, suvorexant HD significantly increased total sleep time, as measured by sTSTm, compared to placebo, with a treatment difference in mean change from baseline of 26.3 minutes ($p < 0.00001$) at Month 1, and 25.1 minutes ($p < 0.00001$) at Month 3. It is not surprising that the same pattern was observed in the pooled P028 and P029 data.

Below I summarize the results for sTSTm at the different time points in the individual trials and pooled data, including results at Week 1 and for suvorexant LD for comparisons.

Table 52: Primary Efficacy Endpoint for Sleep Maintenance by sTSTm in Trials P028, P029, Pooled P028 and P029

	Placebo	Suvorexant LD	Suvorexant HD

Time point	LS Mean change from baseline	LS Mean change from baseline	Diff. from placebo	P value	LS Mean change from baseline	Diff. from placebo	P value
P028							
Week 1	14.6	28.2	13.6	0.00007	36.0	21.4	<0.00001
Month 1	23.1	39.4	16.3	0.00016	42.6	19.6	<0.00001
Month 3	40.6	51.2	10.7	0.01711	60.3	19.7	<0.00001
P029							
Week 1	14.0	30.8	16.8	0.00002	40.4	26.4	<0.00001
Month 1	22.4	43.4	20.9	<0.00001	48.7	26.3	<0.00001
Month 3	37.7	59.8	22.1	0.00004	62.8	25.1	<0.00001
Pooled P028+P029							
Week 1	14.4	29.4	15.0	<0.00001	38.1	23.7	<0.00001
Month 1	22.9	41.3	18.4	<0.00001	45.6	22.7	<0.00001
Month 3	39.3	55.3	16.0	<0.00001	61.4	22.1	<0.00001

(Source: Modified from Sponsor's submission ISE Page 315 Table Appendix 5.3.5.3.2-Insomnia: 33; P028 CSR Page 259 Table 11-5; P029 CSR Page 204 Table 11-5; Shaded portions represent primary efficacy analyses)

Sleep Maintenance by WASO

In both trials P028 and P029, suvorexant HD significantly decreased wakefulness after persistent sleep onset WASO, as shown in the table below. The pooled data also mirrored the findings of the individual trials.

Table 53: Primary Efficacy Endpoint for Sleep Maintenance by WASO in Trials P028, P029, Pooled P028 and P029

	PBO	**Suvorexant LD**			**Suvorexant HD**		
Time point	LS Mean change from baseline	LS Mean change from baseline	Diff. from placebo	P value	LS Mean change from baseline	Diff. from placebo	P value
P028							
Night 1	-19.6	-52.1	-32.5	<.00001	-58.0	-38.4	<.00001
Month 1	-18.7	-45.0	-26.4	<.00001	-45.0	-26.3	<.00001
Month 3	-25.0	-41.6	-16.6	0.00009	-47.9	-22.9	<.00001
P029							
Night 1	-21.3	-58.3	-37.0	<.00001	-63.3	-42.0	<.00001
Month 1	-22.5	-46.6	-24.1	<.00001	-51.9	-29.4	<.00001
Month 3	-24.8	-56.0	-31.1	<.00001	-54.2	-29.4	<.00001
Pooled P028+P029							
Night 1	-20.5	-55.1	-34.6	<.00001	-60.4	-39.9	<.00001

Month 1	-20.6	-46.1	-25.4	<.00001	-48.3	-27.6	<.00001
Month 3	-25.0	-48.0	-23.1	<.00001	-50.9	-25.9	<.00001

(Source: Modified from Sponsor's submission ISE Page 323 Table Appendix 5.3.5.3.2-Insomnia: 39; P028 CSR Page 265 Table 11-7; P029 CSR Page 210 Table 11-7; Shaded portions represent primary efficacy analyses)

Sleep Maintenance by sWASOm
To support the results for sleep maintenance, the trials evaluated the effect of suvorexant on the subjective endpoint sWASOm. As with other sleep maintenance endpoints above, suvorexant HD decreased sWASOm at all time points and in both trials, as shown in the table below.

Table 54: Supporting Efficacy Endpoint for Sleep Maintenance by sWASOm in Trials P028, P029, and Pooled P028 and P029

	Placebo	**Suvorexant LD**			**Suvorexant HD**		
Time point	LS Mean change from baseline	LS Mean change from baseline	Diff. from placebo	P value	LS Mean change from baseline	Diff. from placebo	P value
P028							
Week 1	-10.6	-17.3	-6.8	0.0033	-21.1	-10.5	<0.00001
Month 1	-17.9	-23.3	-5.4	0.06168	-27.4	-9.5	0.00025
Month 3	-29.6	-32.0	-2.4	0.38819	-36.5	-6.9	0.00565
P029							
Week 1	-13.6	-17.8	-4.2	0.1268	-22.0	-8.4	0.00046
Month 1	-20.8	-29.2	-8.4	0.00626	-29.5	-8.7	0.00099
Month 3	-29.8	-37.5	-7.7	0.01885	-38.7	-8.9	0.00167
Pooled P028+P029							
Week 1	-12.1	-17.4	-5.3	0.00281	-21.5	-9.5	<0.00001
Month 1	-19.4	-26.0	-6.6	0.00159	-28.5	-9.1	<0.00001
Month 3	-29.8	-34.5	-4.7	0.02680	-37.6	-7.8	0.00003

(Source: Modified from Sponsor's submission ISE Page 319 Table Appendix 5.3.5.3.2-Insomnia: 36; P028 CSR Page 262 Table 11-6; P029 CSR Page 207 Table 11-6)

Sleep Onset
For sleep onset, the treatment effects of suvorexant HD and placebo were compared on the two primary endpoints, sTSOm and WASO, with both assessed at Months 1 and 3, as follows:

- Change from baseline in sTSOm at Month 1
- Change from baseline in sTSOm at Month 3
- Change from baseline in LPS at Month 1
- Change from baseline in LPS at Month 3

Sleep Onset by sTSOm
In trial P028, following the multiplicity testing strategy, suvorexant HD significantly decreased time to sleep onset, as measured by sTSOm, compared to placebo, with a treatment difference in mean change from baseline of 7.4 minutes (p = 0.00298) at Month 1, and 8.4 minutes (p = 0.00019) at Month 3. Similar improvements in sTSOm with suvorexant HD treatment occurred at Week 1, with a treatment difference of 5.7 minutes (p = 0.00609).

In trial P029, improvements in sleep onset with suvorexant HD were more remarkable than in trial P028, as suvorexant HD in trial P029 significantly decreased sTSOm compared to placebo, with a treatment difference in mean change from baseline of 12.8 minutes (p = 0.00003) at Month 1, and 13.2 minutes (p = 0.00003) at Month 3. At Week 1, suvorexant HD decreased sTSOm compared to placebo by 13.1 minutes (p <0.00001). The pooled P028 and P029 data showed suvorexant HD decreased sTSOm by 9 to 11 minutes at the different time points.

The table below summarizes the results for sTSOm at the different time points in the individual trials and pooled data, including results at Week 1 and for suvorexant LD for comparisons.

Table 55: Primary Efficacy Endpoint for Sleep Onset by sTSOm in Trials P028, P029, and Pooled P028 and P029

	PBO	Suvorexant LD			Suvorexant HD		
Time point	LS Mean change from baseline	LS Mean change from baseline	Diff. from placebo	P value	LS Mean change from baseline	Diff. from placebo	P value
P028							
Week 1	-9.6	-15.2	-5.6	0.01564	-15.3	-5.7	0.00609
Month 1	-11.7	-17.1	-5.4	0.05191	-19.1	-7.4	0.00298
Month 3	-17.3	-22.5	-5.2	0.03771	-25.7	-8.4	0.00019
P029							
Week 1	-6.7	-14.2	-7.5	0.00593	-19.7	-13.1	<0.00001
Month 1	-14.1	-21.0	-6.9	0.04975	-26.9	-12.8	0.00003
Month 3	-20.5	-28.1	-7.6	0.03894	-33.7	-13.2	0.00003
Pooled P028+P029							
Week 1	-8.3	-14.4	-6.1	0.00081	-17.6	-9.4	<0.00001
Month 1	-13.0	-18.6	-5.6	0.01209	-23.2	-10.1	<0.00001
Month 3	-19.0	-24.9	-5.9	0.00675	-29.8	-10.8	<0.00001

(Source: Modified from Sponsor's submission ISE Page 325 Table Appendix 5.3.5.3.2-Insomnia: 41; P028 CSR Page 268 Table 11-8; P029 CSR Page 213 Table 11-8; Shaded portions represent primary efficacy analyses)

Sleep Onset by LPS
In trial P028, suvorexant HD significantly decreased the objective endpoint of latency to persistent sleep LPS compared to placebo, with a treatment difference in mean change from baseline of 11.2 minutes (p = 0.00002) at Month 1, and 9.4 minutes (p = 0.00037) at Month 3. Similar improvements in LPS with suvorexant HD treatment occurred at Week 1, with a treatment difference of 10.3 minutes (p = 0.00002).

However, in trial P029 suvorexant HD failed to significantly decrease LPS at all time points. At Month 1, suvorexant HD significantly decreased LPS, with a treatment difference of 12.1 minutes in mean change from baseline (p = 0.00004); but **at Month 3, suvorexant HD treatment produced a non-significant decrease of 3.6 minutes in LPS mean change from baseline compared to placebo (p = 0.2651).** In the pooled data, suvorexant HD decreased the LPS endpoint by 6.4 minutes compared to placebo, with a nominal p value of 0.0024. The table below summarizes the LPS results at the different time points and suvorexant doses.

Table 56: Primary Efficacy Endpoint for Sleep Onset by LPS in Trials P028, P029, and Pooled P028 and P029

	Placebo	**Suvorexant LD**			**Suvorexant HD**		
Time point	LS Mean change from baseline	LS Mean change from baseline	Diff. from placebo	P value	LS Mean change from baseline	Diff. from placebo	P value
P028							
Night 1	-20.3	-29.9	-9.6	0.00041	-30.6	-10.3	0.00002
Month 1	-23.3	-33.6	-10.3	0.0004	-34.5	-11.2	0.00002
Month 3	-26.6	-34.7	-8.1	0.00606	-36.0	-9.4	0.00037
P029							
Night 1	-13.0	-25.3	-12.4	0.00392	-34.7	-21.7	<.00001
Month 1	-24.6	-32.5	-7.8	0.03063	-36.7	-12.1	0.00004
Month 3	-28.6	-28.9	-0.3	0.93219	-32.2	-3.6	0.2651
Pooled P028+P029							
Night 1	-16.8	-28.0	-11.2	<.00001	-32.5	-15.8	<.00001
Month 1	-24.1	-33.2	-9.1	0.00007	-35.5	-11.4	<.00001
Month 3	-27.6	-32.2	-4.6	0.06205	-34.0	-6.4	0.00235

(Source: Modified from Sponsor's submission ISE Page 329 Table Appendix 5.3.5.3.2-Insomnia: 44; P028 CSR Page 271 Table 11-9; P029 CSR Page 216 Table 11-9; Shaded portions represent primary efficacy analyses, with additional color for non-significant result for primary endpoint)

Sensitivity analyses using nonparametric procedures yielded results that were consistent with the primary analyses for the change from baseline of the endpoints during the treatment phase.

Reviewer Comment:
For sleep maintenance, suvorexant HD treatment resulted in a statistically significant improvement on both subjective (sTSTm) and objective (WASO) primary endpoints at Month 1 and Month 3, and in both confirmatory efficacy trials P028 and P029. Based on the pooled data, treatment with suvorexant HD compared to placebo added about 22 minutes of subjective total sleep time, and reduced objective wakefulness after persistent sleep by 26 minutes at Month 3. Supporting efficacy assessments showed similar improvements with suvorexant HD compared to placebo at Week 1, and on the subjective endpoint sWASO at all time points.

For sleep onset, suvorexant HD compared to placebo treatment provided improvements, though not as consistently as in sleep maintenance. In both confirmatory efficacy trials P028 and P029, suvorexant HD treatment resulted in a statistically significant improvement on the subjective (sTSOm) primary endpoint for sleep onset at Month 1 and Month 3. Suvorexant HD significantly improved the objective primary endpoint LPS at all time points only in trial P028. Based on the pooled data, suvorexant HD reduced subjective time to sleep onset (sTSOm) by11 minutes and the objective endpoint counterpart, LPS, by 6 minutes compared to placebo at Month 3.

Of note, suvorexant HD failed to significantly improve LPS response at Month 3 in trial P029. The pre-trial sample size calculations provided for at least 81% power for either of the primary endpoints for sleep onset to be positive at the Month 3 based on the calculated standardized effect size. In Trial P029, sTSOm was positive at Month 3. That LPS is a more clinically relevant endpoint than sTSOm is debatable. Within the limits of recall bias, sTSOm may appear to be more clinically relevant because it is based on the subject's experience rather than on objectively determined biomarker as LPS. Morin and Benca provide the following assessments on these endpoints (Reference: Morin CM, Benca R. Chronic insomnia. Lancet. 2012 Mar 24;379:1129-41):
"Polysomnographic assessment can show objective sleep impairments (e.g., longer sleep latencies, reduced sleep time), but severity does not always match the patient's complaint of poor sleep. The patient's appraisal of sleep and daytime functioning is crucial since a diagnosis of insomnia is based on clinical symptoms rather than on objective laboratory findings."

Although it could be argued that LPS provides a reasonably valid estimate of the time to definitive sleep, the large difference between Month 1 and Month 3 values in trial P029, which was not seen in P028 or with other endpoints, calls into question the reliability of LPS adequately or more completely measuring a subject's feelings of sleep onset changes. Therefore, sTSOm response, which is based on the subject's perception of time to sleep onset, at Month 3 may be adequate in itself to assess improvements in

Reference ID: 3301133

sleep onset. As a result, Suvorexant HD appears to have improved sleep onset at Months 1 and 3 as suggested by the sponsor.

6.1.5 Analysis of Secondary Endpoints(s)

Sleep Maintenance
For sleep maintenance, the secondary endpoints in trial P028 were to further assess the effects of suvorexant HD using change from baseline in sTSTm at Week 1 and in WASO at Night 1; and to assess suvorexant LD effects using the endpoints at the time points as follows:

- Suvorexant LD: Change from baseline in sTSTm at Week 1, Month 1, and Month 3.
- Suvorexant LD: Change from baseline in WASO at Night 1, Month 1, and Month 3.

Trial P029 had secondary endpoints to only assess the effects of suvorexant HD and not suvorexant LD.

Suvorexant HD on Sleep Maintenance
Based on the multiplicity strategy for testing endpoints, suvorexant HD significantly improved sTSTm at Week 1 and WASO at Night 1 in both trials P028 and P029, as shown in review section 6.1.4 Primary Endpoint analysis tables.

Suvorexant LD on Sleep Maintenance
Again based on the multiplicity strategy for testing endpoints in trial P028, suvorexant LD significantly improved sTSTm at Week 1, Month 1, and Month 3; the dose also significantly improved WASO at Night 1, Month 1, and Month 3 (all p values <0.025). The estimates are summarized in review section 6.1.4 Primary Endpoint analyses tables. Trial P029 showed similar results for the endpoints, though they were not tested as secondary endpoints in that trial. Note that suvorexant LD did not consistently improve sWASO at all time points in both trials.

Sleep Onset

Suvorexant HD significantly improved sTSOm at Week 1 and LPS at Night 1 in both trials P028 and P029, as shown in review section 6.1.4 Primary Endpoint analysis tables.

Secondary endpoint assessment for suvorexant LD in trial P028 showed inconsistent improvements on sleep onset endpoints at different time points. Suvorexant LD significantly improved sTSOm at Week 1 and LPS at Night 1. The dose improved LPS at Month 1 by 10.3 minutes compared to placebo (p = 0.0004), but it did not significantly improve sTSO despite a 5.4-minute decrease in the endpoint compared to placebo (p = 0.05191).

Reviewer Comment:

Reference ID: 3301133

The results of the secondary endpoints provide support for the efficacy of suvorexant HD in improving sleep maintenance and sleep onset times in subjects with primary insomnia. Suvorexant HD showed the efficacy effect (all p values <0.025) on subjective endpoints at Week 1 and objective endpoints at Night 1, on both sleep maintenance and sleep onset endpoints, and in both trials P028 and P029. In the pooled P028 and P029 data, endpoint values of mean change from baseline compared to placebo for Week 1 and Night 1 were, in general, comparable or numerically higher than Month 1 and Month 3 values.

Suvorexant LD treatment effects provide further support for efficacy of suvorexant on sleep maintenance. The lower suvorexant dose was assessed with secondary endpoints in trial P028. It improved sleep maintenance endpoints sTSTm and WASO at all three time points (all p values <0.025). However, it failed to show similar consistency on sWASOm, a key supporting endpoint for sleep maintenance assessment, in trial P028: 5-minute improvement with suvorexant LD compared to placebo (p = 0.06168) at Month 1 and 2-minute improvement (p = 0.38819) at Month 3.

In trial P028, suvorexant LD improved sTSOm and LPS at Week 1; but it did not improve sleep onset endpoints beyond Month 1, when only change from baseline in LPS was positive based on Merck's pre-defined multiplicity testing strategy. As a result, ***the efficacy of suvorexant LD in treating sleep onset difficulties in primary insomnia subjects remains uncertain based on the NDA data****.*

6.1.6 Other Endpoints

In both trials P028 and P029, suvorexant HD and suvorexant LD appeared to improve the following endpoints at Month 1 and Month 3: sQUALm, ISI total score, CGI-S and CGI-I, and PGI-S and PGI-I. The endpoint sREFRESHEDm did not appear to be consistently improved in both trials at Month 3. No improvement in sNAWm occurred with either dose of suvorexant at any time point. The table below summarizes the analyses of the additional endpoints from the pooled P028 and P029 data.

Table 57: Additional Subjective Efficacy Endpoints in Pooled P028 and P029 Population

	Placebo	Suvorexant LD		Suvorexant HD	
Endpoints at Different Time Points	LS Mean Change from Baseline	Difference from Placebo in LS Mean Change from Baseline	P value	Difference from Placebo in LS Mean Change from Baseline	P value
sNAWm					
Week 1	-0.17	0.02	0.53667	-0.01	0.70530
Month 1	-0.32	0.01	0.89316	-0.01	0.70759
Month 3	-0.48	0.02	0.67356	0.03	0.46903

sQUALITYm					
Week 1	0.15	0.10	0.00008	0.14	<0.00001
Month 1	0.21	0.14	<0.00001	0.16	<0.00001
Month 3	0.34	0.10	0.00090	0.11	0.00005
sREFRESHEDm					
Week 1	0.17	0.10	0.00076	0.13	<0.00001
Month 1	0.28	0.16	0.00003	0.16	<0.00001
Month 3	0.46	0.13	0.00205	0.12	0.00161
ISI					
Month 1	-3.0	-1.4	<0.00001	-1.8	<0.00001
Month 3	-4.9	-1.3	0.00004	-1.8	<0.00001
CGI-S					
Month 1	-0.6	-0.4	<.00001	-0.5	<0.00001
Month 3	-1.0	-0.3	<.00001	-0.5	<0.00001
CGI-I					
Month 1	3.3	-0.4	<.00001	-0.5	<0.00001
Month 3	3.0	-0.4	<.00001	-0.5	<0.00001
PGI-S					
Month 1	-0.5	-0.4	<.00001	-0.5	<0.00001
Month 3	-0.8	-0.3	<.00001	-0.4	<0.00001
PGI-I					
Month 1	3.2	-0.4	<.00001	-0.5	<0.00001
Month 3	2.9	-0.4	<.00001	-0.5	<0.00001

(Source: Modified from Sponsor's submission ISE Pages 331-336, 389, 397, 398, 399, 400 Section 5.3.5.3.2.7.3.4.3 Tables Appendix 5.3.5.3.2-Insomnia: 46, 47, 48, 101, 109, 110, 111, and 112)

Responder Analyses

Merck conducted analyses on pre-specified responder analyses based on exploratory subjective endpoints to further assess the clinical meaningfulness of suvorexant treatment effects. Based on 6-point or greater improvement at Month 3 from baseline in the ISI total score, the proportion of responders was higher with either suvorexant HD (51.1%, 168/329) or suvorexant LD (52.0%, 115/221)) treatment compared to placebo (39.3%, 129/328) in trial P028. Similarly in trial P029, the proportion of responders was higher with either suvorexant HD (58.7%, 192/327) or suvorexant LD (59.5%, 113/190) treatment compared to placebo (45.2%, 140/310).

From the pooled P028 and P029 analyses, the proportion of ISI total score responders at Month 3, was higher with either suvorexant HD or suvorexant LD. The proportions of responders in the treatment were as follows: 42.2% (269/638) for placebo; 54.9% (360/656) for suvorexant HD, with a treatment difference from placebo of 12.7%; and 55.5% (228/411) for suvorexant HD, with a treatment difference from placebo of 13.3%. The table below summarizes the responder analysis based on ISI total score in the pooled data from trials P028 and P029.

Table 58: Responder Analyses by ≥6 point improvement in Insomnia Severity Index (ISI) Total Score in Pooled Trials P028 and P029

Treatment	N	n	(%)	Treatment vs. Placebo at Time Point: Estimated odds ratio (95% CI)[†]	Treatment vs. Placebo at Time Point: p-Value [†]
Month 1					
MK-4305 LD	440	149	(33.9)	1.8 (1.4, 2.4)	0.00004
MK-4305 HD	699	279	(39.9)	2.4 (1.9, 3.1)	<0.00001
Placebo	685	157	(22.9)		
Month 3					
MK-4305 LD	411	228	(55.5)	1.8 (1.4, 2.3)	0.00002
MK-4305 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.
MK-4305 LD = MK-4305 20 mg for patients <65 years and MK-4305 15 mg for patients ≥65 years.
MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years.

(Source: Sponsor's submission Reference 636 Results for Pooled Efficacy Analyses Page 278 Table 5.3.5.3.4.7:211)

Suvorexant treatment also resulted in higher proportion of responders based on 15% or greater improvement in sTSTm or sWASOm at different time points in both trials P028 and P029. For the sleep onset endpoint sTSOm, suvorexant treatment had more responders than placebo at various time points, except for suvorexant LD at Month 3 in trial P028.

In the pooled data from P028 and P029 trials, a higher percentage of subjects recorded improvement in subjective sleep onset based on at least 15% decrease from baseline in sTSOm at the different time points with suvorexant treatment. **The percentage of responders in the treatment groups at Month 3 was 76.5% (526/688) for suvorexant HD compared to 66.0% (438/664) for placebo, a treatment difference of 10.5%** (OR, 1.6; 95% CI: 1.3, 2.1; p value = 0.00004). Below is a summary of the responder analysis based on sTSOm in the pooled data from trials P028 and P029.

Table 59: Responder Analyses by ≥15% improvement in sTSOm in Pooled Trials P028 and P029

Treatment	N	n	(%)	Treatment vs. Placebo at Time Point: Estimated odds ratio (95% CI)[†]	Treatment vs. Placebo at Time Point: p-Value [†]
Week 1					
MK-4305 LD	479	267	(55.7)	1.7 (1.4, 2.2)	<0.00001
MK-4305 HD	752	451	(60.0)	2.0 (1.7, 2.5)	<0.00001
Placebo	740	316	(42.7)		
Month 1					
MK-4305 LD	463	289	(62.4)	1.5 (1.1, 1.9)	0.00210
MK-4305 HD	728	508	(69.8)	2.0 (1.6, 2.5)	<0.00001
Placebo	715	384	(53.7)		
Month 3					
MK-4305 LD	425	297	(69.9)	1.2 (0.9, 1.5)	0.19823
MK-4305 HD	688	526	(76.5)	1.6 (1.3, 2.1)	0.00004
Placebo	664	438	(66.0)		

[†] 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.
MK-4305 LD = MK-4305 20 mg for patients <65 years and MK-4305 15 mg for patients ≥65 years.
MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years.

(Source: Sponsor's submission Reference 636 Results for Pooled Efficacy Analyses Page 279 Table 5.3.5.3.4.7:212)

Similarly for sleep maintenance, a higher percentage of subjects on suvorexant treatment recorded at least 15% increase from baseline in sTSTm at the different time points in the pooled data. **The percentage of responders in the treatment groups at Month 3 was 54.7% (376/688) for suvorexant HD compared to 41.9% (278/664) for placebo, a treatment difference of 12.8%** (OR, 1.8; 95% CI: 1.4, 2.3; p value <0.00001). Below is a summary of the responder analysis based on sTSTm in the pooled data from trials P028 and P029.

Table 60: Responder Analyses by ≥15% improvement in sTSTm in Pooled Trials P028 and P029

Treatment	N	n	(%)	Treatment vs. Placebo at Time Point	
				Estimated odds ratio (95% CI)†	p-Value †
Week 1					
MK-4305 LD	479	150	(31.3)	2.1 (1.6, 2.8)	<0.00001
MK-4305 HD	752	262	(34.8)	2.5 (2.0, 3.3)	<0.00001
Placebo	740	145	(19.6)		
Month 1					
MK-4305 LD	463	197	(42.5)	2.0 (1.5, 2.5)	<0.00001
MK-4305 HD	728	316	(43.4)	2.1 (1.6, 2.6)	<0.00001
Placebo	715	210	(29.4)		
Month 3					
MK-4305 LD	425	213	(50.1)	1.5 (1.2, 2.0)	0.00158
MK-4305 HD	688	376	(54.7)	1.8 (1.4, 2.3)	<0.00001
Placebo	664	278	(41.9)		

† 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.
MK-4305 LD = MK-4305 20 mg for patients <65 years and MK-4305 15 mg for patients ≥65 years.
MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years.

(Source: Sponsor's submission Reference 636 Results for Pooled Efficacy Analyses Page 280 Table 5.3.5.3.4.7:213)

Similar results were obtained for responders based on sWASOm improvement. As shown in the table below for the pooled data, the percentage of responders in the treatment groups at Month 3 was 77.5% (529/683) for suvorexant HD compared to 69.4% (458/660) for placebo, a treatment difference of 8.1% (OR, 1.5; 95% CI: 1.2, 1.9; p value <0.00077).

Table 61: Responder Analyses by ≥15% improvement in sWASOm in Pooled Trials P028 and P029

Treatment	N	n	(%)	Treatment vs. Placebo at Time Point: Estimated odds ratio (95% CI)[†]	Treatment vs. Placebo at Time Point: p-Value [†]
Week 1					
MK-4305 LD	474	267	(56.3)	1.5 (1.1, 1.8)	0.00179
MK-4305 HD	746	486	(65.1)	2.0 (1.6, 2.5)	<0.00001
Placebo	729	350	(48.0)		
Month 1					
MK-4305 LD	457	307	(67.2)	1.5 (1.2, 1.9)	0.00193
MK-4305 HD	723	512	(70.8)	1.7 (1.4, 2.1)	<0.00001
Placebo	704	414	(58.8)		
Month 3					
MK-4305 LD	425	322	(75.8)	1.4 (1.1, 1.9)	0.00923
MK-4305 HD	683	529	(77.5)	1.5 (1.2, 1.9)	0.00077
Placebo	660	458	(69.4)		

[†] 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.
MK-4305 LD = MK-4305 20 mg for patients <65 years and MK-4305 15 mg for patients ≥65 years.
MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years.

(Source: Sponsor's submission Reference 636 Results for Pooled Efficacy Analyses Page 281 Table 5.3.5.3.4.7:214)

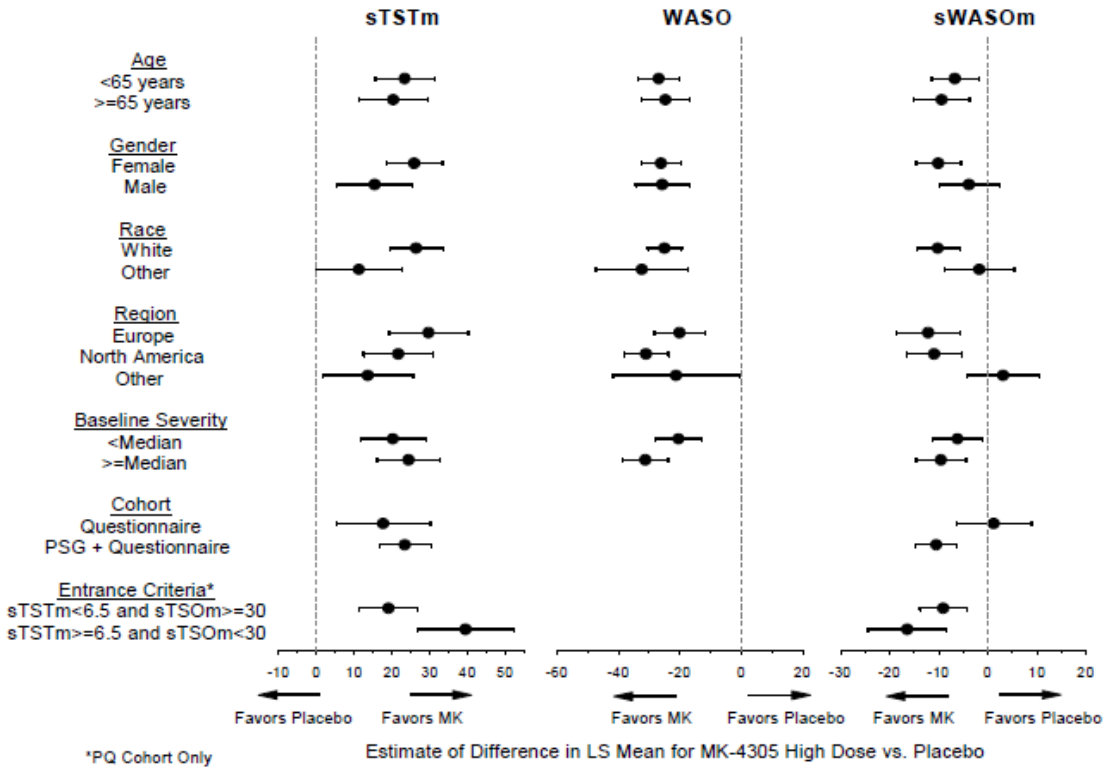
In all the responder analyses from the pooled data, there appeared to be a dose-related improvement of the insomnia endpoints from suvorexant treatment.

6.1.7 Subpopulations

Subgroup Analyses
Merck analyzed the pooled P028 and P029 data to determine consistency of treatment effects across categories of subgroups: age; gender; race; regions; cohort; baseline severity; and for the PQ-cohort, base entry criteria.

Subgroup Analyses for Sleep Maintenance
Point estimates from the pooled data that suggest improvements from suvorexant (HD and LD) treatment in sleep maintenance endpoints, sTSTm and WASO, were consistent across the subgroups. However for sWASOm, "Other" race, "Other" region, and Q-Cohort did not appear to have such improvements as other subgroups. The figure below summarizes the subgroup analyses of endpoint estimates with 95% confidence intervals at Month 3 for suvorexant HD treatment.

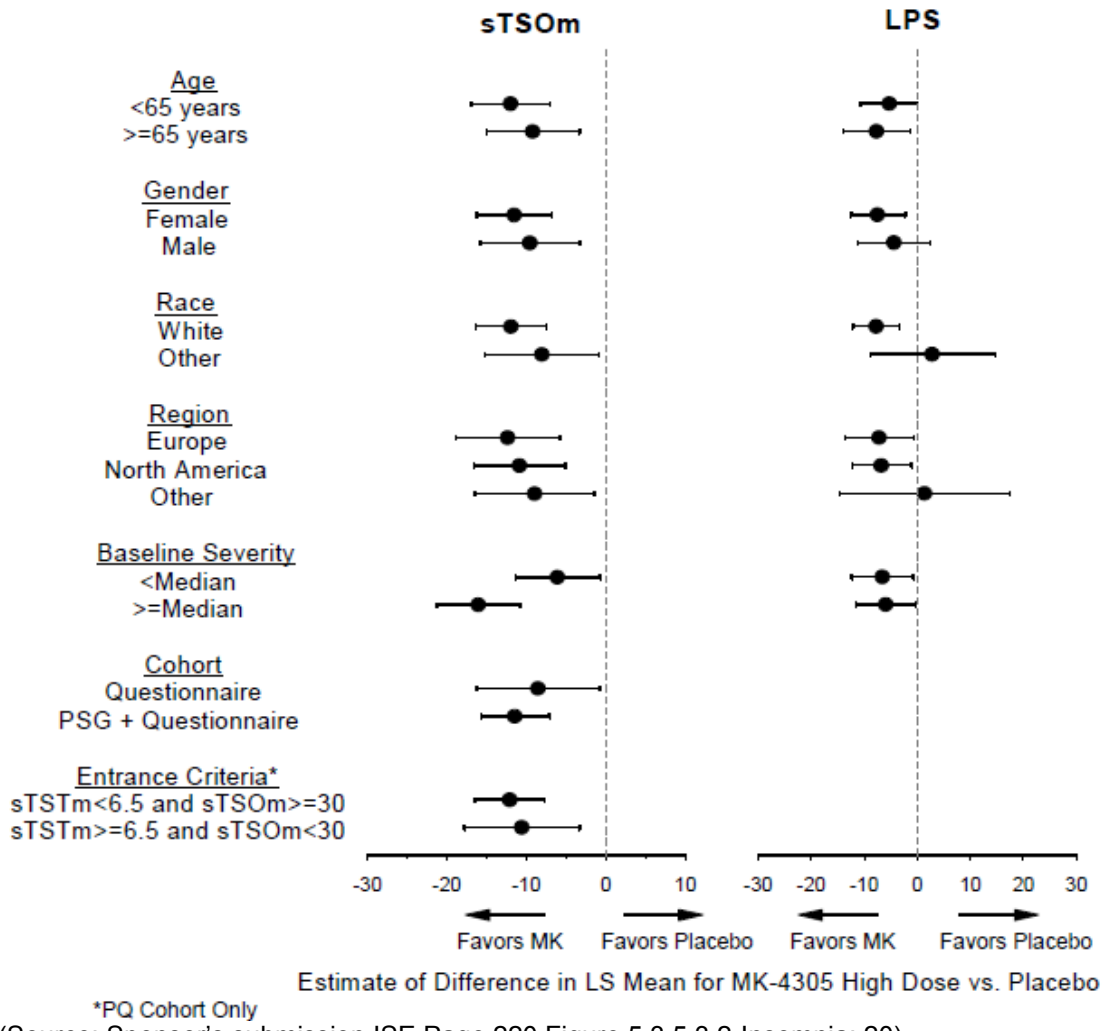
Figure 6: Subgroup Analyses of Change from Baseline in Sleep Maintenance Efficacy Endpoints at Month 3 for Suvorexant HD Compared to Placebo in Pooled P028 and P029 Data



(Source: Sponsor's submission ISE Page 215 Figure 5.3.5.3.2-Insomnia: 26)

Subgroup Analyses for Sleep Onset
Point estimates from the pooled data that suggest treatment improvements from suvorexant HD and suvorexant LD were consistent across the subgroups in the sleep onset endpoint sTSOm. However for LPS, the subgroups of "Other" race and "Other" region did not appear to be similarly improved with either suvorexant LD or suvorexant HD at Month 3. The confidence intervals for these subgroup point estimates were wide, suggesting sample size may have played a role in the results. The figure below summarizes the subgroup analyses of endpoint estimates with 95% confidence intervals at Month 3 for suvorexant HD treatment.

Figure 7: Subgroup Analyses of Change from Baseline in Sleep Onset Efficacy Endpoints at Month 3 for Suvorexant HD Compared to Placebo in Pooled P028 and P029 Data



(Source: Sponsor's submission ISE Page 220 Figure 5.3.5.3.2-Insomnia: 20)

FDA Biometrics review team conducted extensive subgroup analyses on the individual and pooled data from trials P028 and P029. Please see Dr. Massie's review for details, including tables of analyses. I note the following observations from Dr. Massie's review:

Gender:

- With suvorexant LD or suvorexant HD treatment, there was no compelling evidence of differential efficacy by gender based on LPS, WASO, sTST, or sTSO results from trials P028 and P029 pooled data.

Race:

- The subgroup assessment of suvorexant HD treatment effects on sTSO showed no evidence suggestive of an interaction in either trial P028 or P029.
- However for sTST in trial P028, the differential efficacy of suvorexant HD between "Whites" and "Others" (p =0.0162) at Month 1 suggested an interaction. Trial P029 had no such interaction for sTST.
- For LPS in trial P028, again the differential efficacy of suvorexant HD between "Whites" and "Others" (p =0.0016) at Month 1 suggested an interaction. Trial P029 had no such interaction for LPS.
- For suvorexant HD treatment effects on WASO in both trials P028 and P029, no remarkable interaction was evident.

Age:
- With suvorexant LD or suvorexant HD treatment, there was no compelling evidence of differential efficacy by age group, based on WASO, sTST, or sTSO results from trials P028 and P029 pooled data.
- Suvorexant HD treatment showed lower effects on LPS for the elderly compared to the non-elderly at 1 month in the pooled analysis. However, the LPS effect on in the elderly subgroup was still numerically in the right direction.

Regions (North America compared to Non-North America):
- With suvorexant LD or suvorexant HD treatment, there was no compelling evidence of differential efficacy by region based on LPS, WASO, sTST, or sTSO results from either trial P028 or trial P029.

Site:
- In trial P028, excluding any site had no effect on the significance of suvorexant HD treatment effects compared to placebo for the LPS endpoint at Month 1, Month 3, or Night 1. In trial P029, excluding any site had no effect on the significance of suvorexant HD treatment effects compared to placebo for the LPS endpoint at Month 1. However, exclusion of site 0004 resulted in a loss of nominal significance for suvorexant LD treatment effects compared to placebo for the LPS endpoint at Month 1.

Cohort:
- With suvorexant HD treatment, there was no compelling evidence of substantial differential efficacy by cohort based on sTST or sTSO results from either trial P028 or trial P029.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Merck proposes to market multiple dose strengths for suvorexant to enable non-elderly subjects to be treated with a dose of 40 mg once daily and elderly subjects with a dose of 30 mg once daily. (b) (4)

(b) (4)

A dose-finding phase 2 trial, P006, evaluated multiple suvorexant doses from 10 mg to 80 mg in non-elderly subjects. This trial was reviewed in section 5.3 Discussion of Individual Clinical Trials, and FDA Biometrics report by Dr. Massie. In trial P006, suvorexant in all tested doses significantly improved sleep efficiency sleep efficiency (SE) and WASO compared to placebo at Night 1 and at Week 4. However, only the 40 mg and 80 mg doses appeared to improve the subjective measures of sleep maintenance and onset, sTST, sWASO, and sTSO.

Merck chose to further evaluate the suvorexant 40 mg dose in the subsequent Phase 3 trials. This dose improved sleep onset and sleep maintenance insomnia, as measured by objective and subjective endpoints after 4 weeks of suvorexant treatment. The dose choice for further Phase 3 trial evaluation appears appropriate. Based on drug exposure data from clinical pharmacology studies, Merck chose the suvorexant 30 mg dose for elderly subjects as being comparable to the 40 mg dose in the non-elderly. This decision also appears appropriate. Of note, it appears that limiting the indication to only sleep maintenance insomnia, suvorexant doses from 10 mg to 40 mg were appropriate for subsequent Phase 3 trial evaluation.

In the phase 3 trials, the sponsor evaluated primarily suvorexant HD, consisting of 30 mg in elderly subjects and 40 mg dose in the non-elderly. The trials evaluated suvorexant LD, which consisted of 15 mg in elderly subjects and 20 mg in the non-elderly, in secondary or exploratory analysis. The estimates from the pooled analyses suggest that suvorexant produced dose-related treatment effects on all endpoints, subjective and objective, at all time points (Week 1 or Night 1, Month 1, and Month 3). Further, suvorexant LD appeared to have significantly improved sleep maintenance endpoints at the different time points. However, only the suvorexant HD appeared to provide better assurance of improving sleep onset endpoints at the different time points, especially with the subjective sTSO endpoint. As a result, the proposed dose of suvorexant HD for sleep onset and sleep maintenance insomnia appears appropriate. Merck did not explore dose titration, based on efficacy or tolerability, in individual subjects during the phase 3 trials.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Suvorexant HD treatment showed persistent efficacy during the 3-month treatment phase of trials P028 and P029. As reviewed in section 5, trial P009 showed suvorexant HD's persisting efficacy up to 12 months of treatment.

Persistence of Effects during 3-month Treatment

Reference ID: 3301133

For almost all endpoints, the estimates for suvorexant HD's treatment difference from placebo at Month 1 were similar to those of Month 3 in trials P028 and P029. Except for LPS endpoints at Month 3 in trial P029, suvorexant HD showed significant positive effects on all endpoints tested in the primary analyses at Months 1 and 3. The pooled data results shown on section 6.1.4 support the evidence for persistence of efficacy for suvorexant HD. Below is a summary of the efficacy results for suvorexant HD during the treatment phase of trials P028 and P029.

Table 62: Efficacy of Suvorexant HD compared to Placebo in Trials P028 and P029 - Summary of LS Mean Differences in Change from Baseline of Endpoints

	Maintenance			Onset	
Timepoint	sTSTm	sWASOm	WASO	sTSOm	LPS
			P028		
Week 1/Night 1	21.4*	-10.5*	-38.4*	-5.7*	-10.3*
Week 2	19.3	-9.7		-6.5	
Week 3	19.1	-7.9		-7.3	
Month 1	19.6*	-9.5*	-26.3*	-7.4*	-11.2*
Month 1.5	17.5	-7.3		-7.5	
Month 2	18.9	-6.4		-7.2	
Month 2.5	18.4	-7.5		-8.5	
Month 3	19.7*	-6.9*	-22.9*	-8.4*	-9.4*
			P029		
Week 1/Night 1	26.4*	-8.4*	-42.0*	-13.1*	-21.7*
Week 2	23.5	-7.4		-13.6	
Week 3	28.1	-8.3		-14.2	
Month 1	26.3*	-8.7*	-29.4*	-12.8*	-12.1*
Month 1.5	26.5	-11.0		-14.1	
Month 2	25.6	-11.3		-13.9	
Month 2.5	23.3	-9.3		-12.3	
Month 3	25.1*	-8.9*	-29.4*	-13.2*	-3.6

Note: All timepoints' results are included in this table; however, shaded cells represent primary or secondary time points that were included as part of the multiplicity strategy, and thus assessed for statistical significance (*)
*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)

(Source: Sponsor's submission ISE Page 241 Table 5.3.5.3.2-Insomnia: 51)

For suvorexant LD, the pooled data results shown in review section 6.1.4 support the evidence for persistence of the magnitude of suvorexant LD effects during the 3 months of treatment. Below is a summary of the efficacy results for suvorexant LD during the treatment phase of trials P028 and P029.

Table 63: Efficacy of Suvorexant LD compared to Placebo in Trials P028 and P029 - Summary of LS Mean Differences in Change from Baseline of Endpoints

	Maintenance			Onset	
Timepoint	sTSTm	sWASOm	WASO†	sTSOm	LPS
P028					
Week 1/Night 1	13.6*	-6.8	-32.5*	-5.6	-9.6
Week 2	12.7	-5.5		-2.7	
Week 3	12.1	-3.2		-3.8	
Month 1	16.3*	-5.4	-26.4*	-5.4	-10.3*
Month 1.5	13.6	-2.6		-5.1	
Month 2	15.9	-4.2		-4.3	
Month 2.5	12.3	-2.8		-6.0	
Month 3	10.7*	-2.4	-16.6*	-5.2	-8.1
P029‡					
Week 1/Night 1	16.8	-4.2	-37.0	-7.5	-12.4
Week 2	18.9	-8.8		-9.7	
Week 3	18.1	-7.0		-5.8	
Month 1	20.9	-8.4	-24.1	-6.9	-7.8
Month 1.5	18.6	-7.5		-8.6	
Month 2	21.9	-11.7		-8.7	
Month 2.5	20.1	-8.5		-6.5	
Month 3	22.1	-7.7	-31.1	-7.6	-0.3

Note: All timepoints' results are included in this table; however, shaded cells represent primary or secondary time points that were included as part of the multiplicity strategy, and thus assessed for statistical significance (*)

*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

†Asterisks represent statistical significance based on protocol-specified primary analysis (i.e. sTSTm and WASO as primary variables for assessment of efficacy on sleep maintenance)

(Source: Sponsor's submission ISE Page 242 Table 5.3.5.3.2-Insomnia: 52)

Persistence of Effects during 12-month Treatment

The efficacy of suvorexant persisting through 12 months of treatment was demonstrated by the results of trial P009. The figure below shows the trend of the change from baseline in mean sTSTm, sTSOm, and sWASOm for the suvorexant HD and placebo groups during the 12 months of treatment.

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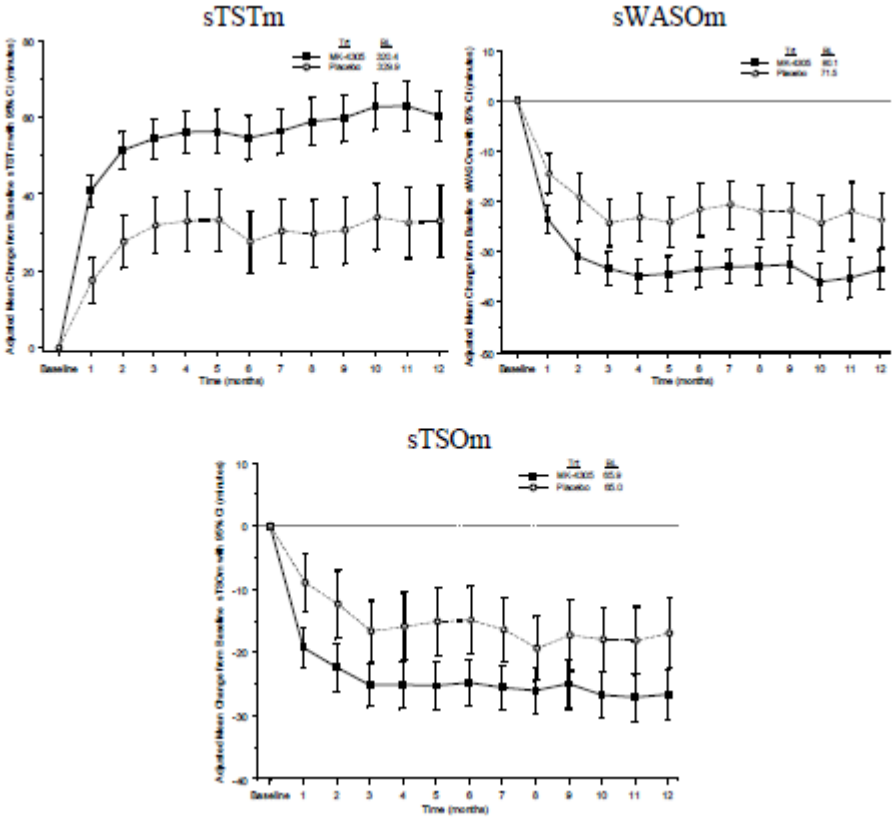
Figure 8: Adjusted Means and 95% Confidence Intervals for Change from Baseline in Mean sTSTm, sTSOm, and sWASOm (minutes) during 12-Month Treatment of Suvorexant HD and Placebo in Trial P009



Source: Sponsor's submission ISE Page 245 Figure 5.3.5.3.2-Insomnia: 32)

Reviewer Comment:
In general, the magnitude of suvorexant treatment effects appears to be sustained in the 3-month or 12-month treatment period.

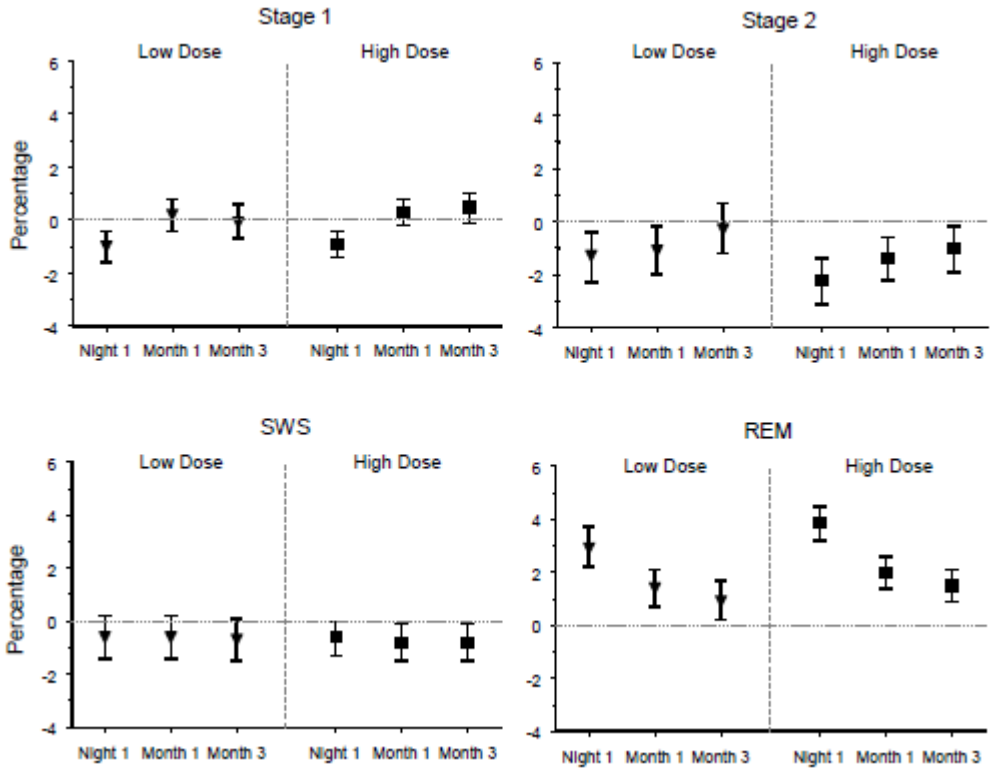
6.1.10 Additional Efficacy Issues/Analyses

Additional Endpoints
Sleep Architecture Endpoints

In trials P028 and P029, suvorexant HD and suvorexant LD caused an increase in the duration of all sleep stages. However, when the duration of the sleep stages were corrected for the overall increase in TST, only stage REM was increased in the suvorexant dose groups compared to placebo. Consistent, with the mechanism of action of orexin receptor antagonists (ORAs), the REM stage increase from suvorexant treatment appears to account for most increase in total sleep time. The figure below

shows results of the differences in LS Means for the sleep architecture endpoints, expressed as percentages of TST, from the pooled P028 and P029 data.

Figure 9: Differences from Placebo in Least Squares Means (95% CI) for Sleep Architecture Endpoints: Stages 1, 2, SWS and REM (percent of TST) from Pooled P028 and P029 Data



Source: Sponsor's submission ISE Page 346 Figure Appendix 5.3.5.3.2-Insomnia: 58)

REM Sleep Latency
In the pooled P028 and P029 analysis, suvorexant treatment reduced REM Sleep Latency. Compared to placebo, suvorexant HD reduced REM sleep latency by 46.1 minutes at Night 1 (p <0.00001) and by 21.4 minutes at Month 3 (<0.00001). Similarly, suvorexant LD reduced the REM sleep latency by 40.3 minutes at Night 1 (<0.00001) and by 15.9 minutes at Month 3 (p = 0.00123).

Other Polysomnographic Sleep Endpoints

TST
In the pooled P028 and P029 analysis, suvorexant HD increased TST by 54.4 minutes more than placebo at Night 1 (<0.00001) and 33.3 minutes more at Month 3 (<0.00001).

Similarly, suvorexant LD increased TST by 44.8 minutes more than placebo at Night 1 (<0.00001) and 27.5 minutes more at Month 3 ((<0.00001).

NAW as a Ratio of TST
To account for the longer sleep duration of suvorexant-treated subjects, the results of NAW after persistent sleep (NAWPS2E) were adjusted for TST duration. In the pooled analysis of trials P028 and P029, with NAWPS2E adjusted for TST, both doses of suvorexant showed lower rates of awakenings on Night 1 (all p-values <0.002). At Month 1 and Month 3 both suvorexant doses showed comparable rates of awakenings as placebo.

Sleep Onset Latency

Analysis of change from baseline in SOL provides additional insight on the effect of suvorexant treatment on objective sleep onset. While LPS is duration from lights off to the first epoch of the first twenty consecutive epochs of non-wake, SOL is the duration of time in minutes from lights off to the first epoch of three consecutive epochs of Stage S1 or any single epoch of Stage S2, SWS, or Stage R. As shown in the table below, suvorexant HD and suvorexant LD decreased SOL change from baseline in a dose-dependent manner at Night 1, Month 1 and Month 3.

Reference ID: 3301133

Table 64: Sleep Onset Latency (SOL 1; minutes) Change from Baseline at All Time Points during the Treatment Phase of Pooled P028 and P029 data

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					
MK-4305 LD	336	50.8 (40.7)	28.2 (24.6)	-22.6 (36.6)	-20.0 (-22.7, -17.3)
MK-4305 HD	576	46.1 (38.0)	23.2 (19.4)	-22.9 (36.3)	-24.0 (-26.1, -21.9)
Placebo	570	46.6 (35.7)	33.1 (34.8)	-13.5 (37.9)	-14.2 (-16.3, -12.1)
Month 1					
MK-4305 LD	317	50.3 (38.0)	22.5 (21.4)	-27.8 (37.1)	-25.6 (-28.3, -22.9)
MK-4305 HD	550	46.5 (38.5)	19.1 (19.3)	-27.4 (38.0)	-28.2 (-30.2, -26.1)
Placebo	542	47.1 (36.0)	28.8 (32.8)	-18.3 (40.3)	-18.7 (-20.7, -16.6)
Month 3					
MK-4305 LD	299	49.2 (36.8)	22.7 (23.3)	-26.4 (35.2)	-25.1 (-27.7, -22.5)
MK-4305 HD	511	46.3 (38.9)	18.3 (17.9)	-27.9 (37.5)	-28.8 (-30.8, -26.9)
Placebo	503	47.6 (35.6)	26.2 (29.7)	-21.4 (38.7)	-21.3 (-23.3, -19.3)

Pairwise Comparison	Difference in LS Means (95% CI)†	p-Value†
Night 1		
MK-4305 HD vs. Placebo	-9.8 (-12.7, -6.9)	<.00001
MK-4305 LD vs. Placebo	-5.8 (-9.3, -2.4)	0.00082
Month 1		
MK-4305 HD vs. Placebo	-9.5 (-12.4, -6.6)	<.00001
MK-4305 LD vs. Placebo	-7.0 (-10.4, -3.6)	0.00006
Month 3		
MK-4305 HD vs. Placebo	-7.6 (-10.4, -4.8)	<.00001
MK-4305 LD vs. Placebo	-3.8 (-7.1, -0.5)	0.02306

†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, and treatment-by-time point interaction as covariates.

MK-4305 LD = MK-4305 20 mg for patients <65 years and MK-4305 15 mg for patients ≥65 years.

MK-4305 HD = MK-4305 40 mg for patients <65 years and MK-4305 30 mg for patients ≥65 years.

(Source: Sponsor's submission ISE Page 373 Table Appendix 5.3.5.3.2-Insomnia: 85)

Number of Arousals (NOAs)
Arousals were defined as a shift from deeper stages of sleep to S1 or Wake. Suvorexant HD and suvorexant LD treatments increased number of arousals compared with placebo in trials P006, P028, and P029, at all time points. In the pooled P028 and P029 analysis, suvorexant HD increased LS Mean change from baseline in NOAs by 3.8 compared to placebo at Night 1 and Month 3 (each p<0.00001). Similarly, suvorexant LD increased the endpoint by 3.9 at Night 1 (p<0.00001) and by 2.4 at Month 3 (p = 0.00050).

WASO by Segments of the Night
Merck analyzed WASO by hour of the night and showed that suvorexant HD and suvorexant LD had greater WASO reductions from baseline compared to placebo in the

pooled P028 and P029 data. The reductions appeared from the second hour of Night 1 through Hour 8.

Power Spectra
Merck analyzed treatment to baseline ratio of spectral power (microvolts2/Hz) for the gamma, beta, sigma, alpha, theta, and delta bands, during NREM all night.

In the pooled P028 and P029 analysis, suvorexant HD and suvorexant LD treatment was associated with a 3%-6% decrease in power in the Gamma, Beta, and Alpha bands at Night 1 only. Simultaneously, the suvorexant treatments compared to placebo were associated with 4%-8% increase in power in the Delta band and =<3% increase in power in the Theta band also at Night 1.

7 Review of Safety

Safety Summary

This review considers the safety data for suvorexant (MK-4305) as presented in Merck's NDA 204569. Merck's overall goal with this submission is to gain approval for suvorexant for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. In the NDA submission, suvorexant is associated with next day sleepiness at a rate that appears similar, by indirect comparison, to the earlier approved insomnia drugs. The suvorexant program also evaluated other known risks associated with sedative hypnotics. Further, suvorexant's mechanism of action warranted scrutiny for the risk of developing narcolepsy. The sponsor provided an extensive safety database that meets the requirements of existing guidance documents.

Suvorexant is an orally administered selective antagonist for orexin receptors OX_1R and OX_2R. It blocks the binding of orexin A and orexin B to orexin receptors OX1R and OX_2R, thereby inhibiting wakefulness and promoting sleep. Suvorexant has no pharmacological affinity for receptors that bind to gamma-aminobutyric acid (GABA), serotonin, dopamine, noradrenaline, melatonin, histamine, acetylcholine, or opiates. No drug of this pharmacologic class has been approved for clinical use.

For this NDA, Merck summarized data from 35 clinical trials: two Phase 3 confirmatory efficacy trials; and one Phase 3 long-term safety trial; one Phase 2b dose-finding trial; and 31 Phase 1 clinical pharmacology trials, which were conducted in healthy volunteers and special populations. The Phase 3 trials constituted the primary integrated database that Merck used to assess safety in 2,809 subjects with primary insomnia. On 7 December 2012, Merck provided a Safety Update that included information on the 32nd Phase 1 trial, which compared bioavailability of four doses of suvorexant under fasting condition in 120 subjects.

Reference ID: 3301133

This safety review summary depended on analyses of the Phase 3 safety database to characterize overall risk estimates of adverse events (AEs). I examined the safety pools from the Phase 2 and Phase 1 trials to further characterize the AE risks.

The number of subjects exposed to suvorexant exceeds the target recommended in the ICH guidelines. Adequate numbers of subjects were exposed to the proposed treatment doses, 15 to 40mg daily. A total of 2,027 subjects with chronic insomnia received any suvorexant dose: 1,198 non-elderly and 829 elderly subjects. The Phase 3 trials exposed 1,784 subjects to suvorexant 15 to 40 mg doses, of which 1,218 subjects received treatment for at least 3 months, 507 subjects for at least 6 months, and 160 subjects for at least 12 months.

My review revealed no major deficiencies in the safety aspects of the NDA. I found all necessary summaries and supporting data for the major risk events that the sponsor had identified. Also, I observed no major inconsistencies between the data sources. The routine safety assessments appeared capable of detecting major safety signals from suvorexant treatment.

As stated earlier, in the Phase 3 trials, suvorexant 15 mg in elderly subjects and suvorexant 20 in non-elderly subjects constituted suvorexant LD, while suvorexant 30 mg in elderly subjects and suvorexant 40 mg in the non-elderly constituted suvorexant HD.

Deaths were infrequent in the suvorexant development program. Two deaths occurred, both in Phase 3 trials. One subject, a 40-year old female on suvorexant HD, was on a leisure ocean swim when she was caught in a rip current. She nearly drowned but was rescued and then hospitalized. Later she went into cardiac arrest, and developed a serious adverse event (SAE), hypoxic-ischemic encephalopathy, before she was declared brain dead. The other subject, a 58-year-old white female with a history of coronary artery disease, status post myocardial infarction and coronary stent placement, was on placebo when she experienced a stroke with brain swelling before she died.

SAEs occurred less frequently in suvorexant treated subjects than in placebo. Over 12 months, SAEs occurred in 2.8% (36/1291) of the subjects who received suvorexant HD and 3.2% (33/1025) who received placebo. Likewise, fewer subjects on suvorexant LD reported SAEs (0.6%, 3/493) compared to placebo (2.1%, 16/767) in the 0-6 months safety population. SAEs in the post-treatment phase included three events of spontaneous abortions, all three received suvorexant treatment: suvorexant HD had two subjects, and suvorexant LD one subject. Two of the three cases had confounding concomitant medications.

Numerically more subjects on suvorexant HD discontinued treatment because of an adverse event compared to those on suvorexant LD or placebo. Discontinuation of

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treatment because of adverse event in all subjects treated occurred in 5.4% (70/1291) of the HD suvorexant group and 3.2% (16/493) of the LD suvorexant group, compared to 4.7% (48/1025) of the placebo group. Adverse events most commonly associated with treatment discontinuation were somnolence and fatigue in the HD suvorexant group.

Merck reported a higher incidence of any AEs in suvorexant HD subjects with 51.0% (658/1291) compared to suvorexant LD with 46.5% (229/493) or placebo 46.6% (478/1025). Also, subjects on suvorexant HD reported more adverse events in the Nervous system disorders SOC with 21.4% (276/1291) compared to suvorexant LD 16.8% (83/493) or placebo13.2% (135/1025). The most common AEs that had incidences of 2% or more and occurred more frequently, in dose-related manner, in the suvorexant group than placebo were somnolence and fatigue.

The most significant AE was somnolence. Suvorexant caused a dose-related increase in somnolence within the initial months of treatment. Somnolence within 0-3 months in the combined Phase 3 population occurred in 10.7% (138/1291) of the suvorexant HD group, 6.7% (33/493) of suvorexant LD, and 3.0% (31/1025) of placebo. Severe somnolence was incapacitating sleepiness that made an affected subject unable to work or do usual activity. The incidence of severe somnolence was overall low but higher in the suvorexant HD group at 0.6% (8/1291) compared to suvorexant LD at 0.2% (1/493), and placebo at 0.1% (1/1025). As a result, the risk difference for severe somnolence between each suvorexant dose and placebo was small, though higher in the suvorexant HD group: 0.5% with number needed to treat to cause severe somnolence or harm (NNTH) 200 for suvorexant HD, and 0.1% with NNTH 1000 for suvorexant LD. If harm is considered as moderate or severe somnolence, the risk difference will be 3.0% (NNTH 33) for suvorexant HD, and 0.8% (NNTH 125) for suvorexant LD.

More subjects on either suvorexant dose reported somnolence within one week of starting treatment compared to any other period in the first 3 months of treatment. Assessing adverse events by age showed that fewer elderly subjects on suvorexant treatment reported somnolence compared to non-elderly subjects. For example, among 1291 subjects treated with suvorexant HD, somnolence occurred in 12.5% (83/664) of the elderly subjects and 8.8% (55/627) of the non-elderly subjects. Likewise among the subjects on suvorexant LD, elderly subjects reported lower somnolence rates than the non-elderly. This pattern of lower somnolence reports in elderly subjects compared to non-elderly adults was consistent across treatment periods. This may be attributed to the lower dose that the elderly subjects received at each suvorexant dose level.

The rates of somnolence in the suvorexant Phase 3 trials appear to be comparable to those of other approved drugs for the sought indication. For example, zolpidem CR 12.5 mg, which is approved for the same sought indication, recorded somnolence rates of 15% in the active trial arm of 102 subjects compared to 2% in placebo group of 110

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subjects in 3-week trial of non-elderly subjects. In another 3-week trial in elderly subjects, the incidence of somnolence was 6% of 99 subjects on zolpidem CR 6.25 mg compared to 5% of 106 subjects on placebo. Other approved insomnia drugs registered similar rates of somnolence. Overall, information gathered on next-day somnolence may serve as a useful guide in assessing dose-response relationships, especially in future clinical dose titrations.

Merck assessed certain adverse events as Events of Clinical Interest (ECIs), selected based on safety concerns associated with other marketed sedative hypnotic drugs, and on safety concerns related to suvorexant's mechanism of action. These events included the following: suicidal Ideation or behavior, complex sleep-related behaviors, hypnagogic and hypnopompic hallucinations, AEs associated with abuse potential, excessive daytime sleepiness (EDS), cataplexy, falls, sleep paralysis, AEs associated with a traffic or motor vehicle accident (MVA), and reports of motor vehicle accidents and violations (MVAV) based on MVAV Questionnaire. An independent committee of experts, blinded to treatment assignment and external to Merck, received ECIs of cataplexy, falls, and sleep onset paralysis for adjudication. Adjudication for events of fall was to determine whether falls were suggestive of cataplexy. Overall, the incidences of the individual ECIs were low.

In the Phase 3 Population within 0-3 months, suicidal Ideation occurred in seven subjects; five of them occurred in the suvorexant HD treatment group, an incidence of 0.4% (5/1291); one subject was in the suvorexant LD group, an incidence of 0.2% (1/493); and one subject was in the placebo group, incidence of 0.15 (1/1025). Beyond three months of treatment, the suvorexant HD group recorded another case of suicidal ideation. The C-SSRS assessment identified three additional cases of suicidal ideation that investigators had not considered as AEs and so did not report them as ECIs. All three subjects were on suvorexant HD.

Only two subjects reported complex sleep-related behaviors (CSRBs) in the Phase 3 Population. Both subjects were on suvorexant HD (0.2%, 2/1291). One case, a 65-year-old male with a history of sleep talking reported an event of sleep talking on Trial Day 85 while on suvorexant HD. The same night he lunged out of bed, and hit his head and face against a wall. On Day 101, he had a different CSRB event, sleep walking, after he had received no trial medication for 2 weeks. The second case was a 58-year-old female who reported somnambulism (sleep walking) and severe sleep paralysis on Trial Day 52 while on suvorexant HD. No additional CSRBs were reported in the Phase 1 and Phase 2 trials.

EDS, as defined in the suvorexant development program, was expected to occur with a sudden onset during the day, in a subject who had adequate night sleep. EDS occurrence has safety implications, especially when it occurs while individuals are going about their usual duties such as driving. In the Phase 3 Population, EDS occurred more frequently in the suvorexant HD group. The EDS incidence in each treatment group was

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as follows: 1.1% (14/1291) suvorexant HD, 0.6% (3/493) suvorexant LD, and 0.2% (2/1025) placebo. The EDS risk difference for suvorexant LD compared to placebo was 0.5% (95% CI: -0.2, 1.7); the risk difference for suvorexant HD, with a 95% confidence interval that excluded zero, was 0.8% (95% CI: 0.1, 1.6), NNTH 125.

Five subjects reported hypnagogic and hypnopompic hallucinations within the first three months of treatment: 0.2% (3/1291) in the suvorexant HD group, 0.4% (2/493) in the suvorexant LD group, and none in the placebo group. The event reported for one (0.2%, 1/493) of the two subjects in the suvorexant LD group was a case of hypnagogic hallucination; the other was a hypnopompic hallucination. In contrast, all three subjects (0.2%, 3/1291) in the suvorexant HD group were cases of hypnagogic hallucinations.

Published literature estimate the lifetime prevalence of sleep paralysis at 7.6% of the general population. In the suvorexant Phase 3 trial population, the incidence of sleep paralysis was low as only five subjects reported the event within the first 3 months; all five received suvorexant treatment. Numerically more subjects reported this ECI while on suvorexant HD (0.3%, 4/1291) compared to suvorexant LD (0.2%, 1/493), and none on placebo. All cases occurred 2-3 months of starting trial treatment. Investigators deemed the sleep paralysis events in the suvorexant LD subject as not of sleep onset because the events occurred in the middle of the night. Three of the four suvorexant HD subjects had confirmed events of sleep onset paralysis on adjudication. One case resulted in treatment discontinuation.

Additional subjects on suvorexant doses of 40 mg and higher reported sleep paralysis in the Phase 2 and Phase 1 trials. In the Phase 2 trial, two subjects on suvorexant 40 mg and 80 mg reported symptoms suggestive of sleep paralysis; these events apparently occurred in the middle of night or on awakening, and not at sleep onset. In the Phase 1 trials, 2% (13/ 662) of subjects on suvorexant alone reported sleep paralysis compared to 0.3% (1/365) on placebo. All 13 subjects in the Phase 1 trial, who reported sleep paralysis on suvorexant, did so while on suvorexant doses of 40 mg to 240 mg; 6 of the 13 subjects were on suvorexant 40 mg.

The suvorexant program had no confirmed cases of narcolepsy with or without cataplexy. The external adjudication committee examined a case of muscle weakness and concluded it was not cataplexy. From the NDA safety submission, no subject among the 2,027 subjects exposed to suvorexant had confirmed cataplexy. If this is accurate, then based on “the rule of threes,” one can be 95% certain that the incidence of cataplexy in suvorexant treated subjects with insomnia is less than 0.0015 (3/2027), or less than 0.0025 (3/1218) for those exposed to at least 3 months of suvorexant treatment.

The incidence of falls in the Phase 3 trials within the first 3 months of treatment was 0.8% (22/2809), and the fall risks across treatment groups were comparable. Falls occurred in less than 1% in each of the treatment groups: 0.7 % (9/1291) with

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suvorexant HD, 0.8% (4/493) with suvorexant LD, and 0.9 % (9/1025) with placebo. The external adjudication committee reviewed the fall events and confirmed that none of the events suggested cataplexy.

Merck assessed the effects of suvorexant treatment on driving performance using AE reports of accident-related injuries, questionnaire responses on motor vehicle accidents or traffic violations (MVAs and MVAVs), and two on-the-road driving studies (P035 and P039). In the Phase 3 trial population within 0-3 months, fewer subjects on suvorexant experienced MVAs while driving than on placebo. The incidence of MVAs among subjects who drove during the trial within each treatment group was: 0.3% (3/891) on suvorexant HD, 0.3% (1/342) on suvorexant LD, and 0.6% (4/692) on placebo. However with MVAVs, a numerically higher rate occurred in the suvorexant LD group (2.9%, 10/342) compared to suvorexant HD group (2.3%, 13/569) and placebo (2.3%, 12/531).

In the Phase 1 driving trials (P035 and P039), Merck observed no significant impairment of next-day driving performance based on mean standard deviation of lateral position (SDLP) after one night and eight consecutive nights of suvorexant LD or HD in both elderly and non-elderly subjects. In the driving trials some subjects who received suvorexant had increased SDLP beyond the pre-defined threshold, resulting in an imbalance in the SDLP symmetry (secondary endpoint) analyses, especially for the non-elderly subjects. Also, four non-elderly subjects felt sleepy enough to prematurely stop their driving tests. These results suggest that a potential for impairment in driving performance exists with suvorexant treatment. The sponsor provided cautionary language in the proposed label, regarding driving and suvorexant treatment, which seems appropriate.

The incidence of any ECI potentially relevant to abuse potential was comparable across treatment groups: suvorexant HD 2.0% (26/1291), suvorexant LD 3.2% (16/493), and placebo 2.2% (23/1025). One event of derealization occurred in the suvorexant HD group. Other events were of drug maladministration, with an incidence of 1.9% (25/1291) in the suvorexant HD group.

Merck evaluated, in Trial P025, abuse potential of single doses of suvorexant compared to placebo and two doses of zolpidem in healthy male and female recreational polydrug users. Based on the primary outcome, “Drug Liking visual analog score, VAS,” suvorexant in all tested doses (40 mg, 80 mg, and 150 mg) showed greater abuse potential than placebo in recreational polydrug users. The mean peak effect difference from placebo for each group was 22.84 for suvorexant 40 mg, 21.99 for suvorexant 80 mg, and 20.44 for suvorexant 100 mg. The suvorexant treatment effect appeared to be similar to, or slightly better than, that of zolpidem 15 mg (24.86) or zolpidem 30 mg (28.08).

A major concern with the use of hypnotic sedatives is next-day residual effects. Merck evaluated AEs associated with residual effects and observed the highest incidence with

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somnolence, discussed above. Fatigue occurred less frequently, and like somnolence, it also occurred in a dose-related manner: suvorexant HD 3.8% (49/1291); suvorexant LD 2.2% (11/493); and placebo 1.8% (18/1025.

Merck evaluated another next-day residual effect, impaired psychomotor performance, using the Digit Symbol Substitution Test (DSST) values from 1,493 subjects in the Phase 3 trials, P028 and P029. They found no clinically meaningful differences between each of the suvorexant groups and placebo. Four Phase 1 trials (P002, P032, P036, and P039) evaluated next-day residual effects at 9-10 hours after suvorexant doses between 10 mg and 100 mg; these trials also failed to show significant treatment effects on DSST (number of correct responses) with suvorexant compared to placebo; a fifth Phase 1 trial P035, which assessed driving in healthy non-elderly subjects, suggested suvorexant 40 mg impairing psychomotor performance after a single dose but not after multiple doses.

Trial P035 also evaluated balance and memory, and showed a statistically significant decrease in word recall 11 hours after single dose of suvorexant 40 mg, and increase in body sway area 11 hrs after single dose of either suvorexant 20 or suvorexant 40 mg. Three other Phase 1 trials (P032, P036, and P039) evaluated balance and memory and found no significant next-day effects following suvorexant treatment.

On abrupt cessation of suvorexant treatment, no clear withdrawal effect occurred, however rebound insomnia was suggested. Merck found no obvious withdrawal effect on sudden discontinuation of suvorexant treatment; this was based on analyses of responses on Tyrer Withdrawal Symptom Questionnaire (WSQ) and reports of prespecified AEs associated with potential withdrawal. Regarding rebound effects, more subjects who switched from suvorexant HD to placebo (48.5%, 233/480) showed a decrease in total sleep time sTST on any of the three nights compared to subjects continued on placebo (37.2%, 295/793). Merck suggested that the effects observed for some sleep maintenance measures do not appear to be consistent with clinically meaningful rebound insomnia. However, the sTST findings for both suvorexant doses, and for the elderly subgroup, support the presence of a rebound effect on abrupt cessation of suvorexant treatment.

Laboratory and vital sign data did not show evidence of suvorexant having deleterious effects. Serum cholesterol levels increased in a dose-related manner following suvorexant treatment in the Phase 2 trial. Mean serum cholesterol levels increased by 3.0 mg/dL at the suvorexant 40 mg dose level, by 2.1 mg/dL at suvorexant 20 mg dose. It is not clear that cholesterol levels were measured in the Phase 3 trials; but the sponsor suggested that the Phase 2 trial finding was not replicated in the Phase 3 population, and that the small sample size in the Phase 2 trials may have contributed to the finding. Also, the sponsor stated that the findings are unlikely to be clinically meaningful.

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Problem List and Recommendations for Labeling
Labeling should describe risks of ECI events that occurred with suvorexant treatment: it should include dose-related findings and a suggestion to discontinue suvorexant treatment on emergence of such events.

Avoid suvorexant use in individuals with narcolepsy-like events and suicidal ideation.

Consider periodic monitoring of serum cholesterol levels especially in individuals with cardiovascular risk factors.

Individuals taking suvorexant should be cautioned against driving or operating heavy machinery.

Consider use of lower suvorexant dose as appropriate for an individual's situation.

For Pediatric development, waiver for children (b) (4) appears reasonable. Deferral until additional postmarketing data available is also reasonable given theoretical risk of narcoleptic events that are yet to be clearly defined in the adult population.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review for this NDA is based on the principles outlined in the Agency's GRP with a view of addressing two specific goals: First, assess the adequacy of the sponsor's safety evaluation; and second, identify and assess the significance of the adverse events observed in the safety database. The sponsor reported 35 clinical trials: two Phase 3 confirmatory efficacy trials, and one Phase 3 long-term safety trial, one Phase 2b dose-finding trial, and 31 Phase 1 clinical pharmacology trials conducted in healthy volunteers and special populations.

Suvorexant integrated safety database included 2,809 subjects with primary insomnia in the three Phase 3 trials (P028, P029, and P009), in which subjects received the proposed doses of suvorexant (15 mg to 40 mg). The sponsor also provided separate safety data from the Phase 2b and Phase 1 trials to further characterize suvorexant's safety profile. The safety data were summarized separately due to differences in trial populations, trial design, drug doses, and duration of treatment. The Phase 2 trial was analyzed separately because of its different trial design: a crossover trial that evaluated multiple suvorexant doses (10 mg to 80 mg) over a shorter duration of four weeks compared to at least 3 months of the Phase 3 trials.

The Phase 3 and Phase 2 trials assessed safety in subjects with primary insomnia. A total of 2,027 subjects with chronic insomnia received any suvorexant dose: 1,198 non-elderly and 829 elderly subjects. The Phase 3 trials exposed 1,784 subjects to suvorexant 15 mg to 40 mg doses, of which 1218 subjects received treatment for at least 3 months, 507 subjects for at least 6 months, and 160 subjects for at least 12 months.

Table 65: Number of Primary Insomnia Subjects in the Phase 2 and Phase 3 Trials

Trial	Trial Design	Placebo	Suvorexant LD	Suvorexant HD	Suvorexant Total
P006	Phase 2 Dose-Finding, 2-period crossover (4-week treatment phase in each period), multicenter trial in **non-elderly** adults with primary insomnia.	249	Suvorexant 10 mg: 62 Suvorexant 20 mg: 61	Suvorexant 40 mg: 59 Suvorexant 80 mg: 61	243
P028	Phase 3, multicenter, RCT, DB, 3-month with 3-month DB Extension treatment in adults with primary insomnia	385	254	383	637
P029	Phase 3, multicenter, RCT, DB, 3- month treatment	387	240	392	632
P009	Phase 3, RCT, DB, 12-month treatment for Long-Term Safety in adults with primary insomnia	259	None administered	522	522
					2034

(Source: Modified from Sponsor's submission ISS Page 76 Table 5.3.5.3.3:2. Except for suvorexant doses specified for P006, Suvorexant LD = 15 mg in elderly and 20 mg in the non-elderly subjects, Suvorexant HD = 30 mg in elderly and 40 mg in non-elderly subjects. RCT = randomized controlled trial; DB = double-blind)

In examining the apparent discrepancy between the total number of subjects in the suvorexant group in the table above for the Phase 2 and Phase 3 trials (N = 2,034) and the stated drug exposure of 2,027 subjects, I noticed that the sponsor excluded some subjects as follow: In Trial P009, two randomized subjects did not receive treatment, one from each treatment group; therefore, the total number of subjects evaluated for safety was 779 (P009 CSR Page 112). Further, the sponsor excluded 6 cases of

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transient treatment errors; these were identified after database lock for P028 and P009, as cases of medication dispensing or assignment errors at the site (ISS Page 123).

The Phase 1 trials assessed healthy subjects; and subjects with renal insufficiency, hepatic impairment, chronic obstructive pulmonary disease (COPD), and obstructive sleep apnea (OSA). The trials enrolled a total of 922 subjects. Below is a summary of the initially submitted 31 Phase 1 trials.

Table 66: Number of Subjects Enrolled in Suvorexant Clinical Pharmacology Studies in the Safety Database

Study Type	Trial Number	Protocol Short Title	Dosing	Number of Subjects
Comparative BA/BE	P007	Biocomparison Study	AM	18
	P041	Biocomparison Study	AM	12
Bioavailability	P020	FMI Food Effect	AM	14
	P042	Japanese Food Effects	AM	12
Healthy Subject PK and Initial Tolerability	P001	FIM SD Young	AM (two panels have PM)	40
	P003	MD Young	PM	40
	P011	SD Young Extension	AM	17
	P012	ADME	AM	6
	P018	Dose Proportionality	AM	Part 1: 32 Part 2: 16
Intrinsic Factors	P004	SD Elderly	AM	20
	P005	Japanese SD PK	AM/PM	32 (n = 16 in only Part II data)
	P017	Hepatic Insufficiency	AM	8 moderate; 8 healthy
	P023	Renal Insufficiency	AM	8 severe; 8 healthy
	P027	MD Elderly	PM	75
Extrinsic Factors	P008	Ketoconazole DDI	AM	10
	P013	OCP DDI	PM	20
	P015	Midazolam DDI	AM	12
	P016	Digoxin DDI	AM	20
	P024	Warfarin DDI	AM	14
	P026	Paroxetine DDI	PM	24

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	P038	Rifampin and Diltiazem DDI	AM	Part I: 10 Part II: 20
Healthy Subject PD and PK/PD	P002	Healthy Subject PSG	PM	22
	P010	Alcohol Interaction	AM	31
	P021	Elderly PM Safety	PM	12
	P022	Thorough QTc	AM	53
	P025	Human Abuse Liability Part I – Qualifying Phase Part II – Treatment Phase	AM	73
	P035	Car Driving Study (Non-Elderly)	PM	28
	P039	Car Driving Study (Elderly)	PM	24
	P040	Healthy Subject Respiratory Safety	PM	12
Patient PD and PK/PD	P032	Respiratory Safety Study in COPD Patients	PM	25
	P036	Respiratory Safety Study in OSA Patients	PM	26
Total N in suvorexant safety database = 802				

(Source: Modified from Sponsor's submission ISS Page 74 Table 5.3.5.3.3:1)

The sponsor's Safety Update on 7 December 2012 provided additional suvorexant exposure data from a Phase 1 trial, the 32nd trial, which compared bioavailability of four doses of suvorexant under fasting condition in 120 subjects.

7.1.2 Categorization of Adverse Events

The sponsor defined an adverse experience or event (AE) as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the trial product, whether or not considered related to the use of the product. An adverse experience also included any worsening of a preexisting condition which is temporally associated with the use of the trial product. AEs reported by investigators were coded using the Medical Dictionary for Regulatory Activities (MedDRA). The sponsor used MedDRA Version 14.1 for the pooled analyses in the ISS.

To evaluate safety concerns related to marketed sedative hypnotic medications or to suvorexant's mechanism of action, the sponsor identified specific AEs for close monitoring in the Phase 2 and Phase 3 trials. These selected AEs, termed Events of Clinical Interest (ECIs), were updated over time during the suvorexant development program. Therefore, the sponsor conducted a retrospective review of all Phase 1 trials for ECIs. Pre-specified ECIs for the Phase 3 trials included suicidal ideation or behavior, complex sleep-related behaviors, hypnagogic and hypnopompic hallucinations, excessive daytime sleepiness, sleep paralysis, cataplexy, falls, and AEs associated with

traffic or motor vehicle accidents. For the Phase 2 trial, the prespecified ECIs were narcolepsy-like events, including cataplexy-like events; suicidal thoughts or ideation; and complex sleep related behaviors.

Investigators collected AEs by open-ended questioning at each visit and recorded spontaneously reported events. At the subjects' trial visits, investigators recorded adverse events and provided additional information based on the sponsor's list of specific terms and guidance for ECIs. An independent committee of experts, blinded to treatment assignment and external to the sponsor, completed an adjudication of selected ECIs. The adjudicated ECIs were cataplexy; falls, to determine occurrence of cataplexy; and sleep onset paralysis. A summary of safety parameters that the sponsor evaluated in the Phase 3 trial is presented in the table below.

Table 67: Safety Parameters for Phase 3 Trials in ISS

Safety Parameter	Description	Protocol	Time Points for Data Collection	Comment
AEs	- Spontaneously reported by the subject - Based on investigator's review of physical examination and vital sign findings and lab/ECG results - Collected up to 14 days after the last dose of study medication according to protocols, although AEs reported after this time frame were also included	P028 P029 P009	Each visit	- Selected terms identified for abuse potential, residual effects, and withdrawal - Selected events designated as Events of Clinical Interest (ECIs)
Laboratory safety tests	- Hematology and blood chemistry - Change from baseline - Values exceeding predefined limits of change	P028 P029 P009	BL, week 2, months 1, 3, and 6* BL, week 2, months 1 and 3 BL, week 2, months 1, 3, 6, 9, and 12	
ECGs	- Change from baseline - Values exceeding predefined limits of change	P028 P029 P009	BL, week 2, months 1, 3, and 6* BL, week 2, months 1 and 3 BL, week 2, months 1, 3, 6, 9, and 12	
Vital signs	- Change from baseline - Values exceeding predefined limits of change	P028 P029 P009	Each visit	- PSG visits: performed in PM prior to and AM following PSG assessment - Non-PSG visits: at any time during visit

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Sleep architecture	- Minutes and percent of time in sleep Stages 1, 2, 3 and REM	P028 P029	PSG visits	
Suicidal ideation and/or behavior	- Responses provided on the Columbia Suicidalitiy Severity Rating Scale are mapped to corresponding categories on the Columbia Classification Algorithm for Suicidality Assessment (C-CASA)	P028 P029 P009	Each visit	
Residual effects	- DSST: Change from baseline in number attempted, number correct	P028 P029	For Treatment Phase: BL, night 1, months 1 and 3 For Run-out Phase: End of Treatment Phase (BL), night 1 (of Run-out Phase)	- For P028, includes subjects not continuing into the extension phase only
	- Selected AE terms - Motor Vehicle Accident and Traffic Violation summary	P028 P029 P009	Each visit	
Withdrawal	- Tyrer Withdrawal Symptom Questionnaire (WSQ)	P028 P029 P009	The first 3 days of the Run-out Phase with the last value from the double-blind treatment serving as the baseline	
	- Selected AE terms	P028 P029	1-week Run-out Phase	
Rebound	- LPS, WASO	P028 P029	At the 3-month PSG visit and after the first night of the Run-out Phase with the last value from the baseline period (pre-randomization) serving as the baseline	- For P028, includes subjects not continuing into the extension phase only
	- sTSO, sTST, sWASO	P028 P029 P009	The first three nights of the Run-out Phase with the last value from the baseline period (pre-randomization) serving as the baseline	
BL = baseline * for Subjects completing the extension phase				

(Source: Sponsor's submission ISS Page 86 Table 5.3.5.3.3:3)

Also, the investigators reported intensity of adverse events as follows:

- Mild: Awareness of sign or symptom, but easily tolerated
- Moderate: Discomfort enough to cause interference with usual activity
- Severe: Incapacitating with inability to work or do usual activity

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The sponsor provided multiple data pools to summarize the suvorexant safety experience. Although the major safety data included information from Phase 3 trials, Phase 2, and Phase 1 trials, this review depended largely on analyses of the safety population from the three Phase 3 trials (P028, P029, and P009). To gain further insight of risks associated with the trial treatment, the safety pools of the Phase 2 and Phase 1 trials were examined.

The Safety Analysis Populations included subjects in the sponsor's All Patients as Treated (APaT) population. The APaT population included all randomized subjects who received at least one dose of trial treatment. A subject's treatment group was based on actual treatment received, not randomized.

The Combined Phase 3 Population was the primary data pool for safety analyses. The Phase 3 trials had subjects treated over different intervals: Trial P028 treated subjects for up to 6 months in the treatment and extension phases, including placebo, suvorexant LD, and suvorexant HD; Trial P029 treated subjects for up to 3 months, including all three dose groups; and Trial P009 treated subjects for at least 12 months with only suvorexant HD or placebo. As a result, the sponsor created three data pools to describe the safety of suvorexant within the combined Phase 3 population as follows:

- 0-3 months: This data pool, for the Combined Phase 3 Population, provided all key safety analyses to support suvorexant LD and suvorexant HD, including subgroup analyses by age.
- 0-6 months: This data pool contained Treatment and Extension Phase data for Phase 3 trials P028 and P029. It provided safety analyses of the long-term use of suvorexant LD.
- 0-12 months: This pool, from the Combined Phase 3 Population, provided data for the safety analyses of the long-term use of suvorexant HD

The sponsor's populations for safety assessments are shown in the table below:

Table 68: Phase 3 Trial Populations for Safety Assessment

Safety Populations	Placebo	Suvorexant LD	Suvorexant HD	Total	Completers
0-3 months (Trials: P028+P029+P009)	1025 (36%)	493 (18%)	1291 (46%)	2809 (100%)	86%
0-6 months (Trials: P028+P029)	767 (61%)	493 (39%)	N/A	1260 (100%)	86%

0-12 months (Trials: P028+P029+P009)	1025 (44%)	N/A	1291 (56%)	2316 (100%)	78%

Using data pooled from the 1-week Run-out Phase of Trials P028 and P029, the sponsor characterized suvorexant next-day residual effects, as well as rebound and withdrawal effects over the first 3 days of treatment cessation. Further, the sponsor summarized AEs related to suvorexant discontinuation.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall, the number of subjects exposed to suvorexant in the development program appears adequate, as it exceeds the recommended subject exposure in the ICH guidance document. The Phase 2 and Phase 3 trials exposed 2,027 subjects with primary insomnia to suvorexant as shown in the table below.

Table 69: Chronic Insomnia Subjects Ever Exposed to Suvorexant in the Phase 2 and Phase 3 Trials

Cumulative Duration of Exposure	N	%
Ever Exposed	2027	100
3 months or more	1218	60
6 months or more	507	25
12 months or more	160	8

The Phase 1 trials enrolled 802 subjects, of which 722 were exposed to suvorexant. Maximum single dose exposure was up to 240 mg.

Demographics
Of the 2,027 subjects with primary insomnia who were exposed to suvorexant Phase 2 and Phase 3 trials, 1,198 (59.1%) were non-elderly adults and 829 (40.9%) elderly adults 65 years or older. The mean duration of treatment for elderly subjects with any dose of suvorexant was 177 days; most of them received treatment for between 3 and 6 months in the Phase 3 trials. In the Combined Phase 3 Population the mean age of subjects was 58 years, with a range from 18 to 90 years. The population had more

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females (62%) compared to males (38%). The table below summarize the demographic characteristics of the Combined Phase 3 Population.

Table 70: Demographic Characteristics for Subjects in Combined Phase 3 Population (P028, P029, and P009)

Demographic Variable	Placebo	Suvorexant LD	Suvorexant HD	Total
Subjects with data	1025	493	1291	2809
Age (years)				
Mean	58	55	58	58
SD	15	16	15	15
Median	62	59	64	62
Range	18 to 90	18 to 86	18 to 88	18 to 90
Gender N (%)				
Male	384 (37.5)	174 (35.3)	507 (39.3)	1,065 (37.9)
Female	641 (62.5)	319 (64.7)	784 (60.7)	1,744 (62.1)
Race N (%)				
American Indian or Alaska Native	3 (0.3)	0 (0.0)	2 (0.2)	5 (0.2)
Asian	125 (12.2)	93 (18.9)	130 (10.1)	348 (12.4)
Black	70 (6.8)	19 (3.9)	71 (5.5)	160 (5.7)
Multiple	42 (4.1)	23 (4.7)	48 (3.7)	113 (4.0)
Native Hawaiian or Other Pacific Islander	1 (0.1)	0 (0.0)	1 (0.1)	2 (0.1)
White	784 (76.5)	358 (72.6)	1,039 (80.5)	2,181 (77.6)
Body Mass Index (BMI) Category N (%)				
Underweight (BMI <18.5)	17 (1.7)	11 (2.2)	21 (1.6)	49 (1.7)
Normal range (18.5 ≤ BMI <25)	432 (42.1)	232 (47.1)	488 (37.8)	1,152 (41.0)
Overweight (25 ≤ BMI ≤30)	405 (39.5)	194 (39.4)	548 (42.4)	1,147 (40.8)
Obese (BMI > 30)	170 (16.6)	56 (11.4)	232 (18.0)	458 (16.3)
Null	1 (0.1)	0 (0.0)	2 (0.2)	3 (0.1)

(Source: Sponsor's submission ISS Page 134 Table 5.3.5.3.3: 12)

7.2.2 Explorations for Dose Response

The Phase 2 and Phase 3 trials included 2,027 subjects with primary insomnia who were exposed to suvorexant doses of 10 mg to 80 mg. Majority of the subjects received three to six months treatment, as shown in the table below.

Table 71: Exposure to Suvorexant by Dose and Duration in the Phase 2 and Phase 3 Trials (P006, 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 Subjects	Duration Range	Mean Duration
Any Dose	33	318	458	711	170	177	160	2,027	1 to 434 days	139.9 days
10 mg	19	60	2	0	0	0	0	81	1 to 31 days	21.5 days
15 mg	3	10	71	96	22	0	0	202	1 to 189 days	104.9 days
20 mg	9	67	105	152	20	0	0	353	1 to 191 days	85.7 days
30 mg	22	34	123	196	54	107	109	645	1 to 434 days	194.1 days
40 mg	19	97	154	267	73	70	51	731	1 to 426 days	141.6 days
60 mg	11	0	0	0	0	0	0	11	1 to 3 days	1.7 days
80 mg	13	54	4	0	0	0	0	71	1 to 31 days	22.3 days

(Source: Sponsor's submission ISS Page 125 Table 5.3.5.3.3:6)

The phase 3 trials (P028, P029, and P009) exposed 1,784 subjects with primary insomnia to suvorexant. Apart from a few subjects who mistakenly took lower or higher doses, most of the subjects received suvorexant doses between 15 mg and 40 mg, as shown in the table below. The mean duration of treatment with suvorexant doses between 15 mg and 40 mg ranged from 98 to 152 days.

Table 72: Exposure to Suvorexant by Dose in 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 Subjects	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

(Source: Sponsor's submission ISS Page 126 Table 5.3.5.3.3:7)

7.2.3 Special Animal and/or In Vitro Testing

The sponsor assessed the risk of narcoleptic-like events in non-clinical studies, which appeared lacking of cataplexy-like events. FDA non-clinical reviewer, Dr. Siarey, reviewed the data and is of the opinion that narcoleptic events cannot be excluded in the dog studies. Please refer to Dr. Siarey's review for details.

7.2.4 Routine Clinical Testing

The routine clinical testing for safety appears appropriate and capable of identifying major adverse signal. The assessment for ECIs appears rigorous enough to identify and characterize a frequent occurrence of narcoleptic-like events. The Phase 3 trials evaluated subjects for safety using physical examination, body system review, electrocardiography, vital sign assessment, blood chemistry, hematology, urinalysis, concomitant medication monitoring, and adverse event reporting. Also, investigators assessed the subjects during the trials' discontinuation phase for rebound and withdrawal events, and late-occurring AEs. Further, investigators conducted routine safety assessments that appear adequate for the long-term trial P009.

7.2.5 Metabolic, Clearance, and Interaction Workup

The sponsor performed specific studies examining suvorexant metabolism, clearance, and potential for interaction. The *in vitro* and *in vivo* testing appears appropriate. Please refer to Clinical Pharmacology review for details of the specific assessments.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Suvorexant is a new molecular entity and an orexin receptor antagonist (ORA). No drug in this ORA class has previously received approval. The Phase 3 trials incorporated monitoring for toxicities associated with sedative hypnotics and narcolepsy-like events, which have been associated with brain orexin deficiency.

7.3 Major Safety Results

7.3.1 Deaths

Two deaths occurred in the suvorexant clinical development program. Both occurred in Phase 3 trials; one of the subjects received suvorexant HD, the other received placebo.

One of the subjects was a 40-year old female who was enrolled in Trial P029 at a US site in Florida. She had no known active medical history and no concomitant medications. She received suvorexant HD starting (b) (6) (Day 1) until Trial Day 34. The exact time of her last suvorexant dose was unknown. On Day 35, she was on a recreational ocean swim at about 08:00 h, when she was caught in a rip current and experienced a near drowning event. Following her rescue, she was admitted to an intensive care unit (ICU). Later she developed cardiac arrest, hypoxic-ischemic encephalopathy (a serious AE); and, on Trial Day 38 she was declared brain dead and removed from life support.

Another fatal case was a 58-year-old white female with a history of coronary artery disease, status post myocardial infarction and coronary stent placement, who received placebo in Trial P028. She received her last dose of trial medication on Day 70. On Trial Day 71, she experienced a stroke that was documented on computed axial tomography scan as a blood clot and swelling of her brain. She died on Trial Day 72.

Although both deaths were deemed unrelated to treatment, it remains uncertain whether a residual effect of suvorexant HD contributed to the near drowning event of the subject on active treatment. Even so, mortality between suvorexant and placebo groups was similar with one subject in each of the suvorexant HD and placebo groups. No deaths occurred in the suvorexant LD group. No deaths occurred in the Phase 1 and Phase 2 trials.

7.3.2 Nonfatal Serious Adverse Events

Nonfatal serious AEs (SAEs) were uncommon in the suvorexant trials. The SAEs occurred less frequently in suvorexant treated subjects than in placebo. Over 12 months, SAEs occurred in 2.8% (36/1291) of the subjects who received suvorexant HD and 3.2% (33/1025) who received placebo. Likewise, fewer subjects on suvorexant LD reported SAEs (0.6%, 3/493) compared to placebo (2.1%, 16/767) in the 0-6 months safety population. Because SAEs occurred infrequently in the Phase 3 trials, the sponsor used a 0% tables to summarize the events in the Combined Phase 3 Population over 0-6 months for suvorexant LD and over 0-12 months for suvorexant HD. The table below is a summary of the SAEs with incidence > 0% in at least one treatment group in the Combined Phase 3 Population over 0-12 months.

Table 73: SAEs in the Combined Phase 3 Population (P028, P029, and P009) over 0-12 months for Suvorexant HD

System Organ Class (SOC) AE Preferred Term (PT)	**Placebo** **N = 1,025** n (%)	**Suvorexant HD** **N = 1,291** n (%)
Subjects with one or more adverse events	33 (3.2)	36 (2.8)

Cardiac disorders	**4 (0.4)**	**2 (0.2)**
Atrial fibrillation	3 (0.3)	1 (0.1)
Coronary artery disease	0 (0.0)	1 (0.1)
Myocardial infarction	1 (0.1)	0 (0.0)
Ear and labyrinth disorders	**0 (0.0)**	**2 (0.2)**
Meniere's disease	0 (0.0)	1 (0.1)
Vertigo positional	0 (0.0)	1 (0.1)
Endocrine disorders	**0 (0.0)**	**1 (0.1)**
Autoimmune thyroiditis	0 (0.0)	1 (0.1)
Gastrointestinal disorders	**3 (0.3)**	**2 (0.2)**
Colitis	1 (0.1)	0 (0.0)
Duodenal ulcer	0 (0.0)	1 (0.1)
Gastrooesophageal reflux disease	0 (0.0)	1 (0.1)
Ileus	1 (0.1)	0 (0.0)
Pancreatitis	1 (0.1)	0 (0.0)
General disorders and administration site conditions	**0 (0.0)**	**1 (0.1)**
Non-cardiac chest pain	0 (0.0)	1 (0.1)
Infections and infestations	**5 (0.5)**	**4 (0.3)**
Abdominal infection	1 (0.1)	0 (0.0)
Diverticulitis	1 (0.1)	2 (0.2)
Endometritis	1 (0.1)	0 (0.0)
Erysipelas	1 (0.1)	0 (0.0)
Gastroenteritis	2 (0.2)	0 (0.0)
Pneumonia	0 (0.0)	1 (0.1)
Urinary tract infection	1 (0.1)	1 (0.1)
Injury, poisoning and procedural complications	**3 (0.3)**	**5 (0.4)**
Clavicle fracture	0 (0.0)	1 (0.1)
Compression fracture	0 (0.0)	1 (0.1)
Concussion	0 (0.0)	1 (0.1)
Fall	2 (0.2)	1 (0.1)

Fibula fracture	1(0.1)	0 (0.0)
Joint dislocation	1 (0.1)	0 (0.0)
Rib fracture	1 (0.1)	0 (0.0)
Tendon rupture	0 (0.0)	1 (0.1)
Tibia fracture	1 (0.1)	0 (0.0)
Ulna fracture	0 (0.0)	1 (0.1)
Musculoskeletal and connective tissue disorders	**3 (0.3)**	**4 (0.3)**
Arthralgia	0 (0.0)	1 (0.1)
Back pain	1 (0.1)	0 (0.0)
ntervertebral disc protrusion	1 (0.1)	0 (0.0)
Meniscal degeneration	1 (0.1)	0 (0.0)
Musculoskeletal chest pain	0 (0.0)	1 (0.1)
Spinal column stenosis	0 (0.0)	1 (0.1)
Spondylitis	0 (0.0)	1 (0.1)
Neoplasms benign, malignant and unspecified (inclu cysts and polyps)	**10 (1.0)**	**8 (0.6)**
B-cell lymphoma	0 (0.0)	1 (0.1)
Basal cell carcinoma	3 (0.3)	3 (0.2)
Bladder neoplasm	1 (0.1)	0 (0.0)
Borderline ovarian tumor	1 (0.1)	0 (0.0)
Breast cancer	1 (0.1)	0 (0.0)
Hodgkin's disease	0 (0.0)	1 (0.1)
Malignant melanoma	2 (0.2)	0 (0.0)
Neoplasm skin	0 (0.0)	1 (0.1)
Squamous cell carcinoma	1 (0.1)	1 (0.1)
Uterine cancer	0 (0.0)	1 (0.1)
Uterine leiomyoma	1 (0.1)	0 (0.0)
Nervous system disorders	**3 (0.3)**	**6 (0.5)**
Cerebral Infarction	2 (0.2)	0 (0.0)
Cerebrovascular accident	1 (0.1)	0 (0.0)
Cervicobrachial syndrome	0 (0.0)	1 (0.1)
Headache	0 (0.0)	1 (0.1)

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Hypoxic-ischemic encephalopathy	0 (0.0)	1 (0.1)
Migraine	0 (0.0)	1 (0.1)
Subarachnoid hemorrhage	0 (0.0)	1 (0.1)
Transient ischemic attack	0 (0.0)	1 (0.1)
Psychiatric disorders	**1 (0.1)**	**1 (0.1)**
Depressed mood	1 (0.1)	0 (0.0)
Suicidal ideation	1 (0.1)	1 (0.1)
Renal and urinary disorders	**2 (0.2)**	**0 (0.0)**
Calculus ureteric	1 (0.1)	0 (0.0)
Renal failure acute	1 (0.1)	0 (0.0)
Reproductive system and breast disorders	**1 (0.1)**	**0 (0.0)**
Vaginal prolapse	1 (0.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**1 (0.1)**	**1 (0.1)**
Lung disorder	0 (0.0)	1 (0.1)
Pneumothorax	1 (0.1)	0 (0.0)

(Source: Sponsor's submission ISS Page 167 Table 5.3.5.3.3:20)

Below is a summary of the SAEs with incidence > 0% in at least one treatment group in the Combined Phase 3 Population over 0-6 months.

Table 74: SAEs in the Combined Phase 3 Population (P028 and P029) over 0-6 months for Suvorexant LD

System Organ Class (SOC) AE Preferred Term (PT)	**Placebo N=767 n (%)**	**Suvorexant LD N=493 n (%)**
Subjects with one or more adverse events	16 (2.1)	3 (0.6)
Cardiac disorders	**1 (0.1)**	**1 (0.2)**
Atrial fibrillation	0 (0.0)	1 (0.2)
Myocardial infarction	1 (0.1)	0 (0.0)
Gastrointestinal disorders	**1 (0.1)**	**0 (0.0)**
Colitis	1 (0.1)	0 (0.0)
Infections and infestations	**3 (0.4)**	**1 (0.2)**
Endometritis	1 (0.1)	0 (0.0)
Gastroenteritis	2 (0.3)	0 (0.0)

Pneumonia	0 (0.0)	1 (0.2)
Injury, poisoning and procedural complications	**2 (0.3)**	**1 (0.2)**
Ankle fracture	0 (0.0)	1 (0.2)
Fall	2 (0.3)	0 (0.0)
Fibula fracture	1 (0.1)	0 (0.0)
Rib fracture	1 (0.1)	0 (0.0)
Tibia fracture	1 (0.1)	0 (0.0)
Musculoskeletal and connective tissue disorders	**1 (0.1)**	**0 (0.0)**
Intervertebral disc protrusion	1 (0.1)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**6 (0.8)**	**0 (0.0)**
Basal cell carcinoma	1 (0.1)	0 (0.0)
Bladder neoplasm	1 (0.1)	0 (0.0)
Borderline ovarian tumor	1 (0.1)	0 (0.0)
Breast cancer	1 (0.1)	0 (0.0)
Malignant melanoma	1 (0.1)	0 (0.0)
Uterine leiomyoma	1 (0.1)	0 (0.0)
Nervous system disorders	**2 (0.3)**	**0 (0.0)**
Cerebrovascular accident	2 (0.3)	0 (0.0)
Psychiatric disorders	**1 (0.1)**	**0 (0.0)**
Depressed mood	1 (0.1)	0 (0.0)
Suicidal ideation	1 (0.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**1 (0.1)**	**0 (0.0)**
Pneumothorax	1 (0.1)	0 (0.0)

(Source: Sponsor's submission ISS Page 170 Table 5.3.5.3.3:21)

SAEs in the Run-out (P028 and P029) and Discontinuation (P009) Periods of the Phase 3 Trials

The Run-out (P028 and P029) and Discontinuation (P009) Phases, which followed the treatment phases in the Phase 3 trials, recorded seven SAEs. As reported by the sponsor, the SAEs included the following: meningitis in a subject on MK-LD/PBO; cellulitis, positional vertigo, and squamous cell carcinoma in subjects on MK-HD/MK-HD; breast cancer and atrial fibrillation in subjects on MK-HD/PBO; and basal cell carcinoma in one subject on PBO/PBO.

SAEs in the Post-Treatment Follow-up and Post-Trial Period

In the Combined Phase 3 Population, ten SAEs occurred during the Post-Treatment Follow-up and Post-Study Phase. The SAEs included the following: gestational diabetes and spontaneous abortion in subjects who received suvorexant LD during the trial's treatment phase; ovarian cancer, spontaneous abortion in two subjects, and alcohol withdrawal syndrome in one subject who had received suvorexant HD; and cartilage injury, device-related infection, post-operative wound infection, and hypertension in subjects earlier treated with placebo. The sponsor stated that at the time of SAE onset, subjects had been off trial medication from 4 days to up to 4 months.

The spontaneous abortions pose some concern because all three cases occurred in subjects treated with suvorexant. The sponsor addresses the issue with the following statement: "Regarding the three events of spontaneous abortion, these AEs occurred in young adult females approximately 2 to 6 weeks after the last dose of study medication. In one instance, a subject had taken misoprostol to terminate the pregnancy. When she was found to have a blighted ovum by ultrasound and a non-viable pregnancy, the investigator determined the event as spontaneous abortion rather than therapeutic abortion. None of these three subjects had history of failed pregnancies." Below, I summarized the SAEs that occurred during the Post-Treatment Follow-Up and Post-Trial Periods of the three Phase 3 trials (P028, P029, and P009).

Table 75: Serious Adverse Events in the Combined Phase 3 Population during Post-Treatment Follow-Up and Post-Trial Period (P028, P029, and P009)

Trial Treatment	Trial	Trial Epoch	Adverse Event	Outcome	Last trial dose to onset	Comment
Suvorexant LD	P028	Post Study	Gestational diabetes	Resolved	3.45 Months	Subject AN 06111, 36 year old, Asian female
	P029	Post Study	Spontaneous abortion		13 days	AN 12110, 25 year old white female
Suvorexant HD	P009	Post Study	Ovarian cancer	Not Resolved	2 months 4 days	AN 02629, 61 year old white female
	P009	Treatment Follow Up	Spontaneous abortion	Resolved	15 days	AN 02609, 19 year old white female
	P028	Core Treatment Follow Up	Spontaneous abortion	Resolved	14 days	AN 07423, 30 year old, multiracial female

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	P029	Core Treatment Follow Up	Alcohol withdrawal syndrome	Resolved	4 days	AN 12115, 41 year old white male
Placebo	P009	Post Study	Cartilage injury	Unresolved	22 days	AN 03791, 51 year old white male
	P009	Post Study	Device related infection	Resolved	1 month 19 days	AN 04083, 70 year old white female
	P009	Treatment Follow Up	Hypertension	Resolved	4 days	AN 04650, 77 year old white male
	P009	Treatment Follow Up	Postoperative wound infection	Resolved	11 days	AN 04617, 66 year old white female

(Source: Modified from Sponsor's submission ISS Page 176 Table 5.3.5.3.3:23)

The Phase 2 trial recorded no SAEs.

SAEs in Phase 1 Trials
The Phase 1 trials recorded four SAEs. In one case, Subject AN 0024, a 27 year old healthy female subject in the Thorough QTc study, after a single dose of suvorexant 240 mg, reported chest pain, was hospitalized, and had an evaluation for myocardial infarction, which was negative. At the same setting, the subject had myoclonus and sleep paralysis confirmed by a neurologist.

In the second case, Subject AN 0006, a 65 year old healthy elderly male in a Multiple Dose Elderly Subjects, reported pyrexia (febrile illness) requiring hospitalization about 24 days after his last suvorexant 40 mg dose. The subject had fever, chills, nausea, vomiting, abdominal pain and confusion, elevated liver enzymes, increased lymphocytes and decreased platelet counts. He also had a slightly elevated titer for Epstein-Barr virus capsid IgG antigen. All symptoms resolved over days. While the liver function tests returned to within normal limits, the subject continued to be anemic. No final diagnosis was made.

The third case was Subject AN0016, a 34 year old black female in the Oral Contraceptive DDI study, who reported an episode of appendicitis about 9 hours after her sixth daily dose of suvorexant 40 mg. Subsequently, she was treated with a laparoscopic appendectomy without surgical complications.

The fourth case was a 32 yr old white female in the Young Driving Study. She reported an SAE of therapeutically induced abortion about 77 days after her last trial treatment of suvorexant 40 mg. In the table below, I summarize the SAEs in the Phase 1 trials.

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Table 76: SAEs in the Phase 1 Trials

AN	Gender	Race	Age	Suvorexant Dose	Time Since Last Dose (d-h:m)	Onset Day Relative To Study	Onset Day Relative to Period	Adverse Experience	Duration of Adverse Experience	Action Taken	Outcome
Protocol Number : 013											
16	F	black	34 yr	Suvorexant 40 mg	0-9:29	20	7	Appendicitis	11.43 hr	discontinued treatment	recovered
Protocol Number : 022											
24	F	white	27 yr	Suvorexant 240 mg	0-4:34	12	1	Chest pain	0.03 hr	discontinued treatment	recovered
Protocol Number : 027											
6	M	white	65 yr	Post study	16-2:35	24	4	Pyrexia	1.91 mo	no action with test drug	recovered
Protocol Number : 035											
7	F	white	32 yr	Post study	26-15:5	77	14	Abortion induced	0.08 hr	no action with test drug	recovered

(Source: Modified from Sponsor's submission Summary of Pooled Safety Data for Clinical Pharmacology Page 44 Table 5.3.5.3.1: 10)

7.3.3 Dropouts and/or Discontinuations

In the table below, the sponsor summarized disposition of subjects in the Phase 3 trials, including reasons for subject discontinuations. Numerically more subjects on suvorexant HD discontinued treatment because of an adverse event compared to those on suvorexant LD or placebo. In the combined Phase 3 population (P028, P029, and P009) within 0-3 months, discontinuation of treatment because of adverse event in all subjects treated were 5.4% (70/1291) in the HD suvorexant group and 3.2% (16/493) the LD suvorexant group, compared to 4.7% (48/1025) in the placebo group. Adverse events most commonly associated with treatment discontinuation were somnolence and fatigue in the HD suvorexant group.

Table 77: Disposition of Subjects Combined Phase 3 Population 0-3 months (P028, P029, and P009)

	Protocols 028+029+009							
	MK-4305 LD		MK-4305 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.
MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.
MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.

(Source: Sponsor's submission ISS Page 128 Table 5.3.5.3.3:8)

In the 0-6 month's period, 4.4% (56/1260) of the population discontinued because of adverse events: 3.2% (16/493) of the LD suvorexant group, and 5.2% (40/767) of the placebo group. The sponsor summarized disposition of subjects in the Phase 3 trials P028 and P029) in the table below.

Table 78: Disposition of Subjects Combined Phase 3 Population 0-6 months (P028 and P029)

	Protocols 028+029					
	MK-4305 LD		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	493		767		1260	
Trial Disposition						
Completed	420	(85.2)	661	(86.2)	1081	(85.8)
Discontinued	73	(14.8)	106	(13.8)	179	(14.2)
Adverse Event	16	(3.2)	40	(5.2)	56	(4.4)
Lack of Efficacy	9	(1.8)	18	(2.3)	27	(2.1)
Lost to Follow-up	4	(0.8)	2	(0.3)	6	(0.5)
Physician Decision	7	(1.4)	0	(0.0)	7	(0.6)
Pregnancy	1	(0.2)	0	(0.0)	1	(0.1)
Protocol Violation	10	(2.0)	12	(1.6)	22	(1.7)
Withdrawal by Subject	26	(5.3)	34	(4.4)	60	(4.8)

Each patient is counted once for Study Disposition based on the latest corresponding disposition record.
MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.

(Source: Sponsor's submission ISS Page 130 Table 5.3.5.3.3:10)

Again, during 0-12 months, discontinuations from adverse events were more frequent among suvorexant-treated subjects compared to placebo as shown in the table below.

Table 79: Disposition of Subjects Combined Phase 3 Population 0-12 months (P028, P029, and P009)

	Protocols 028+029+009					
	MK-4305 HD		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	1291		1025		2316	
Trial Disposition						
Completed	992	(76.8)	823	(80.3)	1815	(78.4)
Discontinued	299	(23.2)	202	(19.7)	501	(21.6)
Adverse Event	101	(7.8)	62	(6.0)	163	(7.0)
Lack of Efficacy	56	(4.3)	46	(4.5)	102	(4.4)
Lost to Follow-up	24	(1.9)	14	(1.4)	38	(1.6)
Physician Decision	21	(1.6)	8	(0.8)	29	(1.3)
Pregnancy	2	(0.2)	0	(0.0)	2	(0.1)
Protocol Violation	12	(0.9)	14	(1.4)	26	(1.1)
Withdrawal by Subject	83	(6.4)	58	(5.7)	141	(6.1)

Each patient is counted once for Study Disposition based on the latest corresponding disposition record.
MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.

(Source: Sponsor's submission ISS Page 129 Table 5.3.5.3.3:9)

Disposition in the Run-out Period of the Combined Phase 3 Population from Trials P028 and P029
There were 1,738 subjects in the Run-out Phase of the combined P028 and P029 trials. Of these, 418 had received suvorexant LD in the Treatment Phase, including 199 subjects who continued the same suvorexant LD in the Run out Phase (MK-LD/MK-LD) and 219 subjects who switched to placebo (MK-LD/PBO). Of the 666 subjects on suvorexant HD during the treatment phase, 333 subjects continued the same suvorexant HD in the Run out Phase (MK-HD/MK-HD), while 333 switched to placebo (MK-HD/PBO). Further, 654 subjects received placebo in the treatment phase and continued the same placebo in the Run out Phase (PBO/PBO). Only 0.6% (11/1738) discontinued trial participation during the Run-out Phase. One subject discontinued because of an adverse event: Subject AN 08169, a 74-year old male, randomized to MK-HD/PBO, had received suvorexant HD in the treatment phase of P028. He experienced atrial fibrillation while on placebo after the first night of the Run-Out phase.

Disposition of Subjects in the Phase 2 Trial
The Phase 2 Dose Finding trial P006 randomized 254 subjects; of these, 243 subjects received at least one dose of suvorexant and 249 received at least one dose of placebo. Trial completers were 228 of 254 subjects (89.8%). Among occurred with 26 subjects

(10.2%) with trial discontinuations, four subjects (1.6%) discontinued because of an adverse event. The sponsor noted that the proportion of subjects in each group who discontinued during the treatment periods were similar between placebo (5.6%; n=14) and the suvorexant total group (4.9%; n=12). However, more subjects in the suvorexant 80 mg group discontinued compared to the other groups as shown in the table below that summarizes the disposition of subjects in the Phase 2 trial.

Table 80: Disposition of Subjects by Treatment in the Phase 2 Dose-Finding Trial (P006)

Treatment Periods 1 And 2	Placebo N=249	Suvorexant 10 mg N=62	Suvorexant 20 mg N=61	Suvorexant 40 mg N=59	Suvorexant 80 mg N=61	Suvorexant Total N=243
Completed	235 (94.4)	60 (96.8)	57 (93.4)	59 (100.0)	55 (90.2)	231 (95.1)
Discontinued	14 (5.6)	2 (3.2)	4 (6.6)	0 (0.0)	6 (9.8)	12 (4.9)
Adverse Event	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.4)
Lack Of Efficacy	1 (0.4)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.4)
Lost To Follow-Up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.4)
Physician Decision	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.4)
Pregnancy	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol Violation	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal By Subject	6 (2.4)	2 (3.2)	3 (4.9)	0 (0.0)	3 (4.9)	8 (3.3)

(Source: Modified from Sponsor's submission ISS Page 672 Table Appendix 5.3.5.3.3:1)

Disposition of Subjects in the Phase 1 Trials
Of 802 subjects enrolled in the Phase 1 trials, 70 (8.7%) subjects discontinued the trials, and 15 (1.9%) of the all subjects discontinued because of adverse events.

Discontinuations Because of AEs
In the combined Phase 3 population 0-3 months, the rate of discontinuation because of AEs was highest with suvorexant HD. The percentages of discontinuation because of AEs in the groups are follows: 6.2% (80/1291) for suvorexant HD, 3.0% (15/493) for suvorexant LD, and 4.9% (50/1025) for placebo. The most frequent SOC category leading to discontinuation was Nervous System Disorders that occurred at the following proportions: 3.3% (42/1291) in the suvorexant HD group, 1.0% (5/493) for suvorexant LD, and 1.4% (14/1205) in placebo. The specific AE somnolence occurred most frequently with incidences of 1.7% (22/1291) in the suvorexant HD, 0.2% (1/493) for suvorexant LD, and 0.3% (3/1025) in the placebo groups.

Psychiatric disorders category, the next most frequent AE category that led to discontinuation, occurred in the treatment groups as follows: 1.0% (13/1291) suvorexant

HD, 0.4% (2/493) suvorexant LD, and 0.8% (8/1025) placebo. Within this category, insomnia was the most frequent specific AE, and it occurred most frequently in the placebo group.

AEs in the General Disorders SOC led to discontinuations in 0.8% (10/1291) suvorexant HD, 0.4% (2/493) suvorexant LD, and 0.3% (3/1025) placebo groups. In this category, fatigue most frequently led to discontinuations; it occurred in the treatment groups as follows: 0.7% (9/1291) suvorexant HD, 0.2% (1/493) suvorexant LD, and 0.0% (0/1205) placebo. The table below is a summary of AEs that led to discontinuations within 0-3 months in the combined Phase 3 population.

Table 81: Discontinuations due to Adverse Events with Incidence >0% in any Treatment Group within 0-3 Months in Combined Phase 3 Trials (P028, P029, and P009)

Adverse Event Category **SOC** Preferred Term	**Placebo** **N (%)**	**Suvorexant LD** **N (%)**	**Suvorexant HD** **N (%)**
Total Subjects	1,025 (100.0)	493 (100.0)	1,291 (100.0)
Subjects with one or more adverse events for discontinuation	50 (4.9)	15 (3.0)	80 (6.2)
Cardiac disorders	**2 (0.2)**	**1 (0.2)**	**3 (0.2)**
Atrial fibrillation	1 (0.1)	0 (0.0)	1 (0.1)
Atrial flutter	1 (0.1)	0 (0.0)	0 (0.0)
Coronary artery disease	0 (0.0)	0 (0.0)	1 (0.1)
Palpitations	0 (0.0)	0 (0.0)	1 (0.1)
Tachycardia	1 (0.1)	1 (0.2)	0 (0.0)
Ear and labyrinth disorders	**1 (0.1)**	**0 (0.0)**	**1 (0.1)**
Vertigo	1 (0.1)	0 (0.0)	1 (0.1)
Endocrine disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**
Autoimmune thyroiditis	0 (0.0)	0 (0.0)	1 (0.1)
Eye disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.1)**
Diplopia	0 (0.0)	0 (0.0)	1 (0.1)
Vision blurred	0 (0.0)	0 (0.0)	1 (0.1)
Visual acuity reduced	0 (0.0)	0 (0.0)	1 (0.1)

Gastrointestinal disorders	**4 (0.4)**	**2 (0.4)**	**3 (0.2)**
Abdominal pain	1 (0.1)	0 (0.0)	0 (0.0)
Aphthous stomatitis	0 (0.0)	0 (0.0)	1 (0.1)
Colitis	1 (0.1)	0 (0.0)	0 (0.0)
Constipation	0 (0.0)	2 (0.4)	0 (0.0)
Dyspepsia	0 (0.0)	1 (0.2)	0 (0.0)
Ileus	1 (0.1)	0 (0.0)	0 (0.0)
Nausea	1 (0.1)	0 (0.0)	1 (0.1)
Paraesthesia oral	0 (0.0)	0 (0.0)	1 (0.1)
General disorders and administration site conditions	**3 (0.3)**	**2 (0.4)**	**10 (0.8)**
Asthenia	0 (0.0)	1 (0.2)	0 (0.0)
Chest pain	0 (0.0)	0 (0.0)	1 (0.1)
Discomfort	1 (0.1)	0 (0.0)	0 (0.0)
Fatigue	0 (0.0)	1 (0.2)	9 (0.7)
Feeling abnormal	1 (0.1)	0 (0.0)	0 (0.0)
Gait disturbance	1 (0.1)	0 (0.0)	0 (0.0)
Infections and infestations	**3 (0.3)**	**0 (0.0)**	**2 (0.2)**
Body tinea	1 (0.1)	0 (0.0)	0 (0.0)
Bronchitis	0 (0.0)	0 (0.0)	1 (0.1)
Cystitis	0 (0.0)	0 (0.0)	1 (0.1)
Gastroenteritis	1 (0.1)	0 (0.0)	0 (0.0)
Nasopharyngitis	1 (0.1)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	**3 (0.3)**	**1 (0.2)**	**2 (0.2)**
Ankle fracture	1 (0.1)	1 (0.2)	0 (0.0)
Clavicle fracture	0 (0.0)	0 (0.0)	1 (0.1)
Fall	0 (0.0)	0 (0.0)	1 (0.1)
Fibula fracture	1 (0.1)	0 (0.0)	0 (0.0)
Rib fracture	1 (0.1)	0 (0.0)	0 (0.0)
Tibia fracture	1 (0.1)	0 (0.0)	0 (0.0)
Investigations	**0 (0.0)**	**1 (0.2)**	**2 (0.2)**
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	1 (0.1)
Blood calcium increased	0 (0.0)	0 (0.0)	1 (0.1)
Blood creatine phosphokinase increased	0 (0.0)	1 (0.2)	0 (0.0)
Blood lactate dehydrogenase decreased	0 (0.0)	0 (0.0)	1 (0.1)
Blood magnesium increased	0 (0.0)	0 (0.0)	1 (0.1)

Musculoskeletal and connective tissue disorders	**4 (0.4)**	**0 (0.0)**	**4 (0.3)**
Back pain	1 (0.1)	0 (0.0)	0 (0.0)
Muscular weakness	0 (0.0)	0 (0.0)	1 (0.1)
Neck pain	1 (0.1)	0 (0.0)	0 (0.0)
Osteoarthritis	1 (0.1)	0 (0.0)	0 (0.0)
Pain in extremity	1 (0.1)	0 (0.0)	3 (0.2)
Neoplasms benign, malignant & unspecified (incl cysts & polyps)	**4 (0.4)**	**0 (0.0)**	**1 (0.1)**
B-cell lymphoma	0 (0.0)	0 (0.0)	1 (0.1)
Bladder neoplasm	1 (0.1)	0 (0.0)	0 (0.0)
Borderline ovarian tumour	1 (0.1)	0 (0.0)	0 (0.0)
Breast cancer	1 (0.1)	0 (0.0)	0 (0.0)
Malignant melanoma	1 (0.1)	0 (0.0)	0 (0.0)
Nervous system disorders	**14 (1.4)**	**5 (1.0)**	**42 (3.3)**
Cerebrovascular accident	2 (0.2)	0 (0.0)	0 (0.0)
Depressed level of consciousness	0 (0.0)	1 (0.2)	0 (0.0)
Dizziness	4 (0.4)	1 (0.2)	2 (0.2)
Dysaesthesia	1 (0.1)	0 (0.0)	0 (0.0)
Headache	3 (0.3)	2 (0.4)	0 (0.0)
Hypoxic-ischaemic encephalopathy	0 (0.0)	0 (0.0)	1 (0.1)
Lethargy	0 (0.0)	0 (0.0)	3 (0.2)
Memory impairment	0 (0.0)	0 (0.0)	3 (0.2)
Migraine	0 (0.0)	1 (0.2)	1 (0.1)
Paraesthesia	1 (0.1)	0 (0.0)	2 (0.2)
Parkinson's disease	0 (0.0)	0 (0.0)	1 (0.1)
Poor quality sleep	0 (0.0)	0 (0.0)	1 (0.1)
Sedation	0 (0.0)	0 (0.0)	3 (0.2)
Sleep paralysis	0 (0.0)	0 (0.0)	2 (0.2)
Somnolence	3 (0.3)	1 (0.2)	22 (1.7)
Tension headache	1 (0.1)	0 (0.0)	0 (0.0)
Tremor	0 (0.0)	0 (0.0)	1 (0.1)
Psychiatric disorders	**8 (0.8)**	**2 (0.4)**	**13 (1.0)**
Abnormal dreams	0 (0.0)	0 (0.0)	1 (0.1)
Affective disorder	0 (0.0)	0 (0.0)	1 (0.1)
Alcohol abuse	0 (0.0)	0 (0.0)	1 (0.1)
Bradyphrenia	0 (0.0)	0 (0.0)	1 (0.1)
Depressed mood	1 (0.1)	0 (0.0)	1 (0.1)
Depression	1 (0.1)	0 (0.0)	2 (0.2)
Insomnia	4 (0.4)	0 (0.0)	2 (0.2)
Libido decreased	1 (0.1)	0 (0.0)	1 (0.1)
Nightmare	0 (0.0)	1 (0.2)	2 (0.2)
Post-traumatic stress disorder	1 (0.1)	0 (0.0)	0 (0.0)
Somnambulism	0 (0.0)	0 (0.0)	1 (0.1)
Suicidal ideation	0 (0.0)	1 (0.2)	1 (0.1)

Skin and subcutaneous tissue disorders	**2 (0.2)**	**3 (0.6)**	**0 (0.0)**
Eczema	1 (0.1)	1 (0.2)	0 (0.0)
Rash	0 (0.0)	1 (0.2)	0 (0.0)
Rash macular	0 (0.0)	1 (0.2)	0 (0.0)
Urticaria	1 (0.1)	0 (0.0)	0 (0.0)
Vascular disorders	**3 (0.3)**	**0 (0.0)**	**1 (0.1)**
Hypertension	1 (0.1)	0 (0.0)	0 (0.0)
Hypertensive crisis	1 (0.1)	0 (0.0)	0 (0.0)
Ischaemia	0 (0.0)	0 (0.0)	1 (0.1)
Orthostatic hypotension	1 (0.1)	0 (0.0)	0 (0.0)

(Source: Sponsor's submission ISS Page 188 Table 5.3.5.3.3: 26)

In the age group analyses, discontinuations because of AEs during the trial's treatment phase followed the pattern of the overall population. In elderly subjects, AEs leading to discontinuations occurred in 6.4% (40/627) of suvorexant HD, 3.5% (7/202) suvorexant LD, and 5.5% (26/469) placebo groups. In the non-elderly, AEs led to discontinuations in 6.0% (40/664) of the suvorexant HD, 2.7% (8/291) of the suvorexant LD, and 4.3% (24/556) of the placebo groups. As in the overall population, the SOC categories of Nervous System Disorders, Psychiatric disorders, and General Disorders were the most frequent AEs that led to discontinuations in the age groups. Specifically, somnolence was the most frequent AE leading to discontinuation.

Discontinuations because of AEs in 0-6 months
In the 0-6 month population, the rates of discontinuation because of AEs were similar between suvorexant LD and placebo groups: 3.0% (15/493) in the suvorexant group and 5.2% (40/767) in the placebo group. The SOC category of Nervous System Disorders was the most frequent in leading to discontinuations: 1.0% (5/493) for suvorexant LD compared to 1.4% (11/767) for placebo. Within this SOC category, the most frequent specific AE leading to discontinuation was headache that occurred in 0.4% in each treatment group, suvorexant LD (2/493) and placebo (3/767). One case of migraine caused a discontinuation in the suvorexant LD group and a case of tension headache caused a discontinuation in the placebo group.

Discontinuations because of AEs in 0-12 months
Over 0-12 months, there was a small increase in the rate of discontinuation because of AEs, and it remained slightly higher with suvorexant HD treatment at 7.8% (101/1291) compared to placebo at 6.0% (62/1025). The specific AEs that led to discontinuations were similar to those in the 0-3 month population. The SOC categories of Nervous System Disorders, Psychiatric disorders, and General Disorders were the most frequent AEs that led to discontinuations. Again as in the overall population, somnolence, insomnia, and fatigue were the most frequent specific AEs that led to discontinuation. Generally, they occurred at low rates. For example, somnolence leading to

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discontinuation occurred in 2.2% (28/1291) of suvorexant HD group and 0.4% (4/1025) of the placebo group.

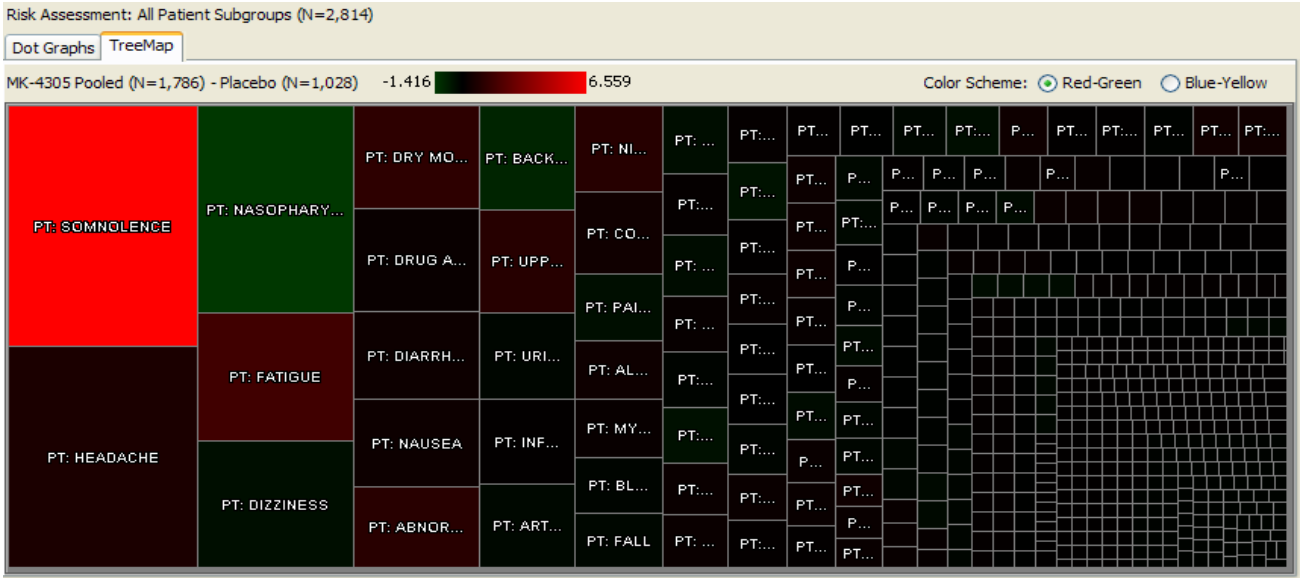
Reviewer Comment: The incidence of discontinuation because of AEs was generally highest with suvorexant HD compared to suvorexant LD and placebo, but the differences between the treatment groups were small. Somnolence was the AE most frequently associated with discontinuations. I examined dropouts and disposition of subjects by individual dose groups from the datasets for trials P028 and P029; the results of my analyses yielded similar findings, including dropouts because of AEs.

7.3.4 Significant Adverse Events

Somnolence

Next day sleepiness, reported as the preferred term Somnolence and shown in the figure below, was the most frequent AE during the first three months in the suvorexant safety database. Somnolence as an AE preferred term included the following lower level terms: daytime sleepiness, drowsiness, drowsy on awakening, excessive daytime sleepiness, feeling of residual sleepiness, groggy, groggy on awakening, hard to awaken, and somnolence. This review section examines characteristics of the somnolence events and influence of treatment dose, treatment duration, and demographic factors on somnolence occurrence.

Figure 10: Somnolence shown as the most Prominent Risk on Map based on Risk Difference Comparing Pooled Suvorexant (LD+HD) and Placebo Groups over 0-3 Months



(Source: Clinical Reviewer Analyses; Risk Difference (RD) Heat Map in Combined P009+P028+P029, ITT population 0-3 months; Somnolence in bright red has highest RD of 6.559)

Suvorexant caused a dose-related increase in somnolence within the initial months of treatment. As shown in the table below, somnolence within 0-3 months in the combined Phase 3 population occurred in 10.7% (138/1291) suvorexant HD, 6.7% (33/493) suvorexant LD, and 3.0% (31/1025) placebo. With regards to severity of sleepiness, the incidence of severe somnolence was higher in the suvorexant HD at 0.6% (8/1291) compared to suvorexant LD at 0.2% (1/493), and placebo at 0.1% (1/1025). A separately reported event was sedation; it included lower level terms of oversedation and sedation, and occurred in more suvorexant HD subjects, eight (0.6%), compared to none (0%) in suvorexant LD, and four (0.4%) in placebo. The incidence of somnolence including sedation events remained 11% in the suvorexant HD group and 3% in placebo. Also, discontinuation of treatment because of somnolence was highest in the HD suvorexant group as shown in the table below.

Table 82: Somnolence Within 0-3 months in Combined Phase 3 Populations (P028, P029, and P009)

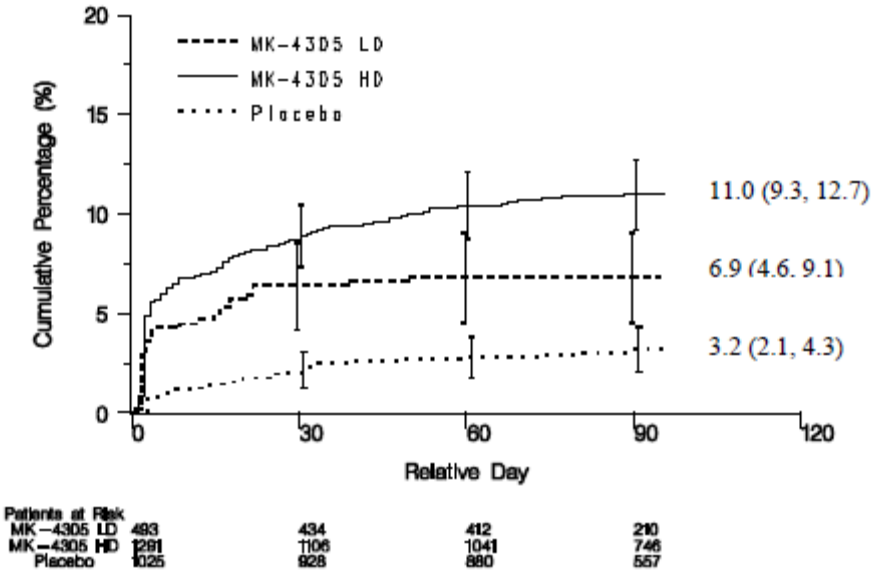
Variable Category	Placebo (N=1025)	Suvorexant LD (N=493)	Suvorexant HD (N=1291)
Somnolence	31 (3.0%)	33 (6.7%)	138 (10.7%)
Severe Somnolence	1 (0.1%)	1 (0.2%)	8 (0.6%)
Somnolence-Trial discontinuation	3 (0.3%)	1 (0.2%)	22 (1.7%)
Somnolence by Age >=65 years <65 years	 3.2% (15/469) 2.9% (16/556)	 5.4% (11/202) 7.6% (22/291)	 8.8% (55/627) 12.5% (83/664)
Somnolence by sex Female Male	 2.3% (15/641) 4.2% (16/384)	 8.5% (27/319) 3.4% (6/174)	 11.1% (87/784) 10.1% (51/507)

(Source: Modified from Sponsor's submission ISS Pages 427, 429, 649, 661 and 663; Tables 5.3.5.3.3: 149, 150, 257, 260, and 261)

Time to Onset of Somnolence

More subjects on either dose of suvorexant reported somnolence within one week of starting treatment compared to any other period in the first 3 months of treatment. Cumulative somnolence reports reached near peak within one month of treatment in the suvorexant LD group; the suvorexant HD group, which was yet to peak at one month, added another 2.5% reports beyond the first month. As shown in the figure below, the cumulative percentages of subjects who reported somnolence over the 3 months occurred in a dose-related fashion: 11.0% suvorexant HD, 6.9% suvorexant LD, and 3.2% placebo.

Figure 11: Cumulative Percentage of Subjects Who Reported Somnolence of over 0-3 Months among all Subjects in the Combined Phase 3 Population (P028, P029, and P009)



(Source: Sponsor's submission ISS Page 650 Figure 5.3.5.3.3.:5)

The different somnolence **intensities** were more frequent with suvorexant HD. A dose-related increase in the different somnolence intensities – mild, moderate, and severe – occurred with treatment as shown in the table below.

Table 83: Intensity of Somnolence by Dose Group Treated over 0-3 Months among all Subjects in the Combined Phase 3 Population (P028, P029, and P009)

	Intensity Grading	Placebo N (%)	MK-4305 LD N (%)	MK-4305 HD N (%)
Subjects in Population		1,025	493	1,291
Somnolence	All Grades	31 (3.0)	33 (6.7)	138 (10.7)
	Mild	21 (2.0)	24 (4.9)	86 (6.7)
	Moderate	9 (0.9)	8 (1.6)	44 (3.4)
	Severe	**1 (0.1)**	**1 (0.2)**	**8 (0.6)**

(Source: Sponsor's submission ISS Page 649 Table 5.3.5.3.3.:257)

Reviewer Note: The risk difference for severe somnolence reflected a dose-response relationship. The trials categorized somnolence severity as follows:

- *Mild: Awareness of sign or symptom, but easily tolerated*
- *Moderate: Discomfort enough to cause interference with usual activity*
- *Severe: Incapacitating with inability to work or do usual activity*

The risk difference for severe somnolence between each suvorexant dose and placebo was small, though higher in the suvorexant HD group; 0.5 with number needed to treat to cause severe somnolence or harm (NNTH) 200 for suvorexant HD, and 0.1 with NNTH 1000 for suvorexant LD. If harm is considered as moderate or severe somnolence, the risk difference is 3 (NNTH 33) for suvorexant HD, and 0.8 (NNTH 125) for suvorexant LD.

Demographics – Somnolence by Age, by Gender, by BMI, by Age and Gender, and by Gender and BMI
Fewer elderly subjects reported somnolence while on suvorexant treatment as shown in table below and in earlier table on Somnolence Within 0-3 months in Combined Phase 3 Populations. The lower somnolence reports in elderly subjects compared to non-elderly adults were consistent across dose groups and treatment periods. This may be attributed to the lower dose received by the elderly subjects at each suvorexant dose level: 15 mg and 30 mg compared to 20 and 40 mg in non-elderly subjects for suvorexant LD and HD respectively.

Table 84: Somnolence Events by Age Groups across Treatment Periods in Phase 3 Trials

Variable Category	Placebo	Suvorexant LD	Suvorexant HD
Somnolence 0-3 Months, Trials P028, P029, & P009			
>=65 years	3.2% (15/469)	5.4% (11/202)	8.8% (55/627)
<65 years	2.9% (16/556)	7.6% (22/291)	12.5% (83/664)
Somnolence 0-6 Months, Trials P028 & P029			
>=65 years	3.8% (12/318)	5.9% (12/202)	Not Applicable
<65 years	3.1% (14/449)	7.6% (22/291)	Not Applicable
Somnolence 0-12 Months, Trials P028, P029, & P009			
>=65 years	3.4% (16/469)	Not Applicable	10.0% (63/627)
<65 years	3.1% (17/556)	Not Applicable	13.3% (88/664)

(Source: Modified from Sponsor's submission ISS Pages 661, 663, 1745, 1748, 1767, 1769 Tables 5.3.5.3.3: 260, 261, Appendix 5.3.5.3.3: 200, 201, 210 and 211)

Interpreting the analyses of somnolence by Age and Gender, and by Gender and BMI may be limited by the small number of events. However, the table below and earlier table on Somnolence Within 0-3 months in Combined Phase 3 Populations suggest that

females reported more somnolence events than males, particularly at suvorexant LD level.

Table 85: Somnolence Events in Elderly and Non-Elderly Subjects by Gender in the Combined 0-3 Months Populations (P028, P029, and P009)

Age Group and Gender Category	Placebo	Suvorexant LD	Suvorexant HD
Somnolence in Age >=65 years			
Females	2.3% (7/299)	7.5% (10/133)	9.4% (35/372)
Males	4.7% (8/170)	1.4% (1/69)	7.8% (20/255)
Somnolence in Age <65 years			
Females	2.3% (8/342)	9.1% (17/186)	12.6% (52/412)
Males	3.7% (8/214)	4.8% (5/105)	12.3% (31/252)

(Source: Modified from Sponsor's submission ISS Pages 439, 441, 443, 445 Tables 5.3.5.3.3: 153 to 156)

Regarding BMI effect on incidence of somnolence, non-obese subjects showed a dose-related increase in somnolence events; this pattern was not apparent in obese subjects, as shown in the table below, probably because of small numbers of events.

Table 86: Somnolence Events in Non-Obese, Over-Weight, and Obese Subjects in the Combined 0-3 Months Population (P028, P029, and P009)

Variable Category	Placebo	Suvorexant LD	Suvorexant HD
Somnolence in Non-Obese Subjects (BMI <25)	2.2% (10/449)	7.4% (18/243)	11.0% (56/509)
Somnolence in Over-weight Subjects (BMI 25-30)	3.0% (12/405)	7.2% (14/194)	8.9% (49/548)
Somnolence in Obese Subjects (BMI >30)	5.3% (9/170)	1.8% (1/56)	13.4% (31/232)

(Source: Modified from Sponsor's submission ISS Pages 511, 513, and 515 Tables 5.3.5.3.3: 187, to 189)

Long-Term Somnolence Events
In long–term treatment evaluations covering 0–6 months, combined P028 and P029 population, somnolence remained higher with suvorexant LD at 6.9% (34/493) compared to placebo 3.4% (26/767). The incidence of severe somnolence remained unchanged from the 0-3 month's population with suvorexant LD at 0.2% (1/493) compared to placebo at 0.1% (1/767). The cumulative percent of subjects who reported

somnolence increased slightly in the treatment groups from Month 3 end to Month 6 end: 6.9% to 7.9% in the suvorexant LD group compared to 3.4% to 4.1% in the placebo group. Generally, subjects on suvorexant LD experienced longer somnolence duration compared to those on placebo as shown in the somnolence plots for individual subjects below.

Figure 12: Somnolence Time Course for Individual Subjects over 0–6 Months of Placebo or Suvorexant Low Dose in Combined Phase 3 Population (P028 and P029)

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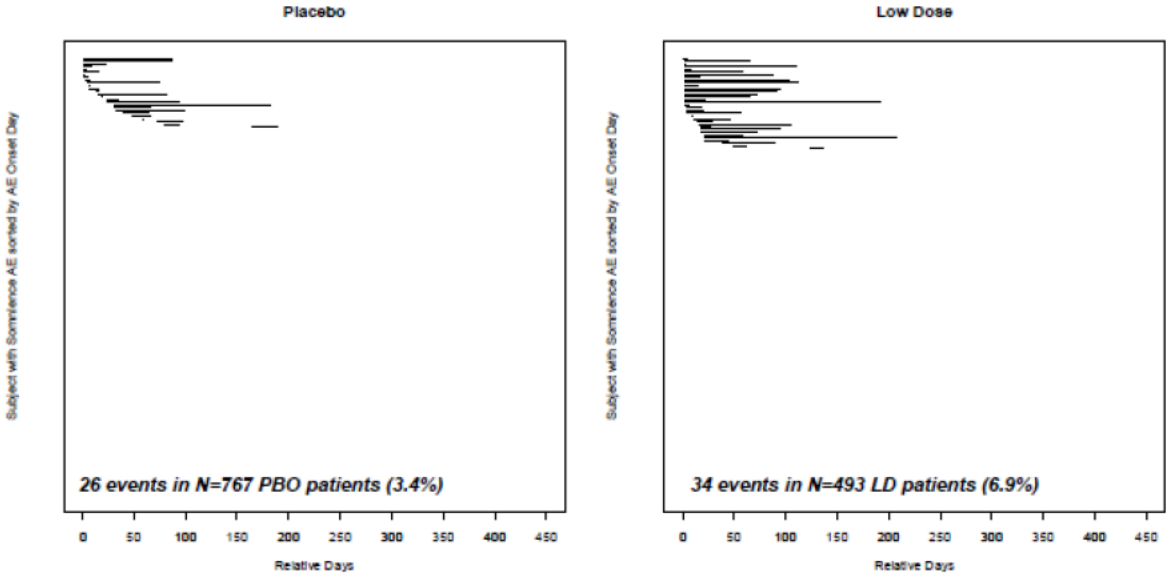

(Source: Sponsor's submission ISS Page 658 Figure 5.3.5.3.3:9)

In the 12-month period evaluations of the combined Phase 3 population (P028, P029, and P009), somnolence remained higher in the suvorexant HD group at 11.7% (151/1291) compared to placebo at 3.2% (33/1025). The incidence of severe somnolence from suvorexant HD treatment was 0.6% (8/1291) compared to placebo 0.1% (1/1025); these rates were unchanged from those of the 0-3 month's evaluations. The cumulative percent of subjects who reported somnolence, based on the sponsor's Kaplan-Meier's estimates, increased in the treatment groups from Month 3 end to Month 12 end: in the suvorexant HD group 11.0% to 13.6% compared to placebo 3.2% to 3.8%. Subjects on suvorexant HD experienced longer somnolence duration compared to those on placebo as shown on the individual subject's plots below. Of note, in the 12-month assessment, 28 suvorexant HD events (2.2%) led to study discontinuation compared to 4 (0.4%) on placebo. The plots suggest that subjects who received suvorexant HD experienced somnolence events of longer duration than those treated with suvorexant LD or placebo.

Figure 13: Subject Plots of Somnolence Events over 0-12 Months among all Subjects in the Combined Phase 3 Population (P028, P029, and P009)

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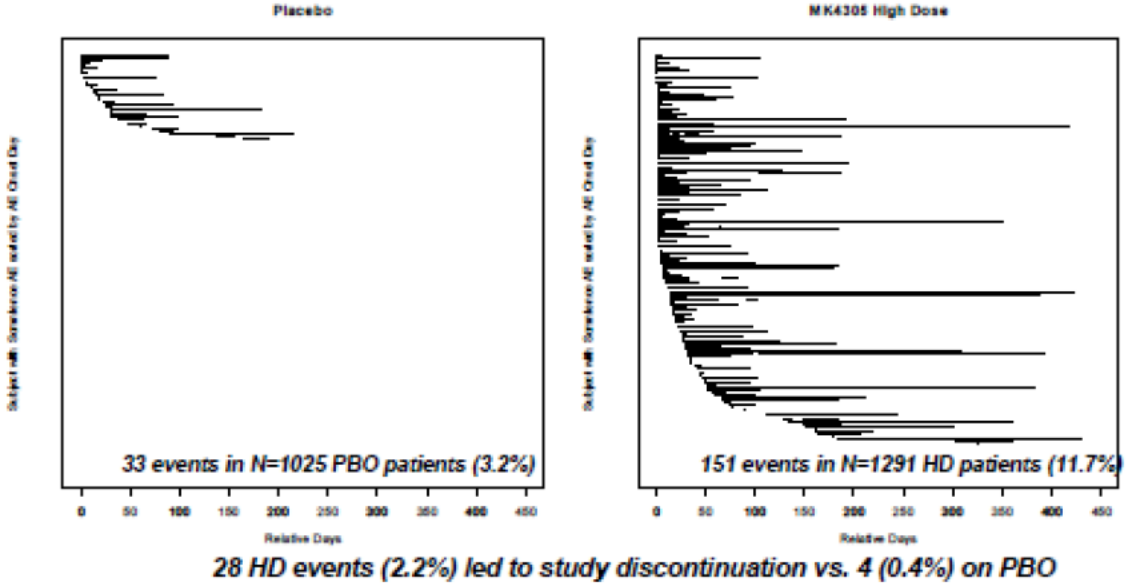

(Source: Sponsor's submission ISS Page 654 Figure 5.3.5.3.3:7)

Somnolence in Individual Phase 3 Trials
Across the individual component Phase 3 trials, as shown in the table below, the incidence of somnolence appeared consistent with those of the combined Phase 3 population of P028, P029, and P009 trials.

Table 87: Incidence of Somnolence in Individual Phase 3 Trials

Trial	Placebo %	Suvorexant LD %	Suvorexant HD %
P028 (0-3 months)	3.4 (13/384)	5.1 (13/254)	10.7 (41/383)
P029 (0-3 months)	3.1 (12/383)	8.4 (20/239)	10.3 (40/387)
P009 (0-12 months)	2.7 (7/258)	Not applicable	13.2 (69/521)

(Source: Modified from Sponsor's submission CSR P028 Page 339 Table 12-7, CSR P029 Page 273 Table 12-6, and CSR P009 Page 198 Table 12-5)

Somnolence in Earlier Phase Trials
The early phase trials showed dose-related increases in somnolence with suvorexant treatment. In the Phase 2 trial P006 that included non-elderly subjects, somnolence occurred at a similar rate and in dose-related manner as observed in the Phase 3 trials:

0.4% (1/249) in Placebo, 0% (0/62) in suvorexant 10 mg, 4.9% (3/61) in suvorexant 20 mg, 11.9% (7/5)9 in suvorexant 40 mg, and 9.8% (6/61) in suvorexant 80 mg groups. A combination of five Phase 1 trials (P026, P032, P035, P036, and P039), in which subjects received night-time trial treatment and had next-day assessment for residual effects, somnolence occurred in 22.4% (28/125) after suvorexant treatment compared to 0.8% (5/105) after placebo. In these studies, suvorexant was administered at the clinical doses (15 or 30 mg in elderly, 20 or 40 mg in non-elderly). It remains unclear why the somnolence rate was remarkably higher in the collection of Phase 1 trials compared to the Phase 3 experience, though closer monitoring in the early phase trials may have played a role.

Somnolence in Marketed Drugs for the Proposed Indication
The rates of somnolence in the suvorexant Phase 3 trials appear to be comparable to those of other approved drugs for the sought indication. The table below shows the somnolence rates from a review of the prescribing information and available approval packages for some of the long-acting drugs approved for insomnia. In general, the marketed drugs were evaluated over a shorter duration of treatment thereby limiting the inter-drug comparisons of somnolence rates or other adverse events.

Table 88: Somnolence in Some Marketed Insomnia Drugs

Treatment	N for Group	Percent of Subjects with Somnolence	Duration of studies, Other Comments
Zolpidem CR 12.5 mg Placebo	102 110	15% 2%	3-week trial Non-elderly adults
Zolpidem CR 6.25 mg Placebo	99 106	6% 5%	3-week trial in elderly subjects
Eszopiclone 3 mg Eszopiclone 2 mg Placebo	105 104 99	8% 10% 3%	6-week trial in non-elderly adults.
Quazepam 7.5-15 mg Placebo	267 268	12% 3%	Short duration trials over less than a month
Temazepam 7.5-30 mg Placebo	1076 783	9% 6%	Adverse event reported as Drowsiness
Doxepin 6 mg Doxepin 3 mg Placebo	203 157 278	9% 6% 4%	4 weeks, Approved for maintenance only

(Source: Prescribing Information for Respective Drugs)

7.3.5 Submission Specific Primary Safety Concerns

In this section, I address the safety concerns related to the specific adverse events termed Events of Clinical Interest (ECIs) that the sponsor identified for close evaluation: suicidal ideation, complex sleep related behaviors, hallucinations, excessive day time sleepiness, sleep paralysis, cataplexy, falls, abuse, motor vehicle accidents and violations (MVAVs).

Suicidal Ideation or Behavior

The sponsor followed recommendations in an FDA draft guidance issued in 2010, "Guidance for Industry - Suicidality: Prospective Assessment of Occurrence in Clinical Trials," and prospectively assessed suicidal ideation and behavior in the Phase 2 and Phase 3 trials using the Columbia Suicidality Severity Rating Scale (C-SSRS). Each suicidal ideation or behavior event was categorized according to the Columbia Classification Algorithm for Suicide Assessment (C-CASA).

The incidence of suicidal ideation (including "death wish") or behavior reported for the Combined Phase 3 Population over 0-3 Months was very low overall at < 0.4% (7 subjects) but **numerically higher with suvorexant HD treatment**: Suvorexant LD, 0.2% (1 subject), suvorexant HD 0.4% (5 subjects), and placebo 0.1% (1 subject). The subjects on placebo and suvorexant LD had prior history of suicidal ideation. The suvorexant LD subject, a 34-year old male, had two events, the first on Day 25 when he reported feeling depressed about his job, which he quit on Day 28. Despite starting a new job, he reported another suicidal thought Day31. This subject discontinued the trial because of the AE on Day 30.

Among the 5 subjects on suvorexant HD who reported suicidal ideation or behavior, one subject, a 61-year old male (AN 02637), had prior history of depression and suicide attempt. He reported 3 events of suicidal ideation on Days 20, 21, and 25. He discontinued trial treatment on Day 29 because of the AE. Another subject, a 70-year old male (AN 04559) reported mild suicidal ideation on Day 81 and discontinued trial treatment on Day 111 after he was diagnosed with depression. A 42-year old female (AN 11361) reported mild suicidal ideation on Day 66; she thought of taking medications as a means to end her life. However, her month-long suicidal ideation ended after she started a new social relationship; all the while she continued the trial treatment.

A 54-year old female (AN 12362) reported suicidal ideation on Day 91; she had missed Day 90 dose and had been on suvorexant HD. After an argument with her daughter, she felt like she wanted to die but had no intention of acting on the thought.

The fifth subject AN 03053 was a 38-year old male on suvorexant HD who reported suicidal ideation on Trial Day 9. He reported, "wishing to be dead", with "thoughts of not

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waking up anymore felt easy, but I could control the thoughts" and subsequently discontinued from the trial because of to lack of efficacy.

Following longer treatment duration, a 21-year old male on suvorexant HD in Trial P009 reported suicidal ideation on Day 269. He was the sixth case of suicidal ideation on suvorexant HD. He had a prior history of suicidal ideation in 2004. On C-SSRS assessment at the Month 9 visit, he reported unemployment difficulties and ideation lasting 4 days. He subsequently completed the trial treatment.

Table 89: Suicidal Ideation or Behavior with Suvorexant High Dose Compared to Placebo in Combined Phase 3 Population 0-12 Months in Trials P028, P029, and P009

Protocols 028+029+009	MK-4305 HD		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[†]
Patients in population	1,291		1,025		
with one or more Suicidal Ideation and/or Behaviors Adverse Events	6	(0.5)	1	(0.1)	0.3 (-0.2, 0.9)
with no Suicidal Ideation and/or Behaviors Adverse Events	1,285	(99.5)	1,024	(99.9)	-0.3 (-0.9, 0.2)
Psychiatric disorders					
Death wishes	1	(0.1)	0	(0.0)	0.1 (-0.3, 0.5)
Suicidal ideation	5	(0.4)	1	(0.1)	0.3 (-0.2, 0.8)

[†] 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.

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.

Lower Level Term is displayed for the specific adverse events.

MK-4305 HD=MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.

(Source: Sponsor's submission ISS Page 210 Table 5.3.5.3.3.:31)

The C-SSRS assessment identified three additional cases of suicidal ideation as shown in Table below. The investigators did not consider these as adverse events and so did not report them as ECIs. All three subjects were on suvorexant HD. One 68-year old female had a history of thyroid disease and experienced suicidal ideation from the placebo-run in period. Another, a 54-year old male had a history of depression and anxiety and reported suicidal ideation at Month 3 before withdrawing from the trial for unclear reasons. The third had no history of psychiatric illness but reported suicidal ideation at Months 1 and 3. Subsequently, he discontinued trial treatment because of lack of treatment efficacy. The sponsor added that, based on the Columbia Classification Algorithm for Suicide Assessment (C-CASA) analysis, only 3 subjects had suicidal ideation among subjects with no prior history of suicidal ideation, all three were on suvorexant HD.

Table 90: Suicidal Events Based on Columbia Classification Algorithm for Suicide Assessment (C-CASA) with Suvorexant High Dose Compared to Placebo in Combined Phase 3 Population 0-12 Months in Trials P028, P029, and P009

C-CASA Category†	Protocols 028+029+009	
	MK-4305 HD n (%)	Placebo n (%)
Patients in population	1268	1012
with one or more events	8 (0.6)	0 (0.0)
with no event	1260 (99.4)	1012 (100.0)
Suicide completed	0 (0.0)	0 (0.0)
Suicide attempt	0 (0.0)	0 (0.0)
Preparatory acts toward imminent suicidal behavior	0 (0.0)	0 (0.0)
Suicidal ideation	8 (0.6)	0 (0.0)
Self-injurious behavior, no suicidal intent	0 (0.0)	0 (0.0)

† C-CASA categories are derived from the Columbia Suicide Severity Rating Scale (C-SSRS).

Patients who were treated and had at least one post-treatment C-SSRS evaluation during the indicated phase of study period were included in the table.

MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.

(Source: Sponsor's submission ISS Page 214 Table 5.3.5.3.3.:33)

The sponsor reported no suicidal ideation or behavior events in the Phase 2 dose-finding trial. However, in a Phase I drug interaction trial (P026), a 21-year-old female without a prior history of suicidal ideation, reported suicidal ideation 4 days after the final dose of trial treatment, suvorexant 40 mg plus paroxetine 20 mg. The event lasted 10 days and was designated mild in intensity.

Reviewer Comment: In all, suicidal ideation appeared more frequent in the suvorexant HD group in the phase 3 trials, though the events occurred in very low numbers. One subject in each dose group discontinued trial treatment because the suicidal ideation event. No additional subject on suvorexant LD reported suicidal ideation based on the CSSRS assessment.

Complex Sleep-Related Behaviors

Only 2 subjects on suvorexant HD reported complex sleep-related behaviors in the Combined Phase 3 Population over 0-3 Months.

First case, a 65-year-old male with a history of sleep talking reported an event of sleep talking on Trial Day 85 while on suvorexant HD. The event started about 2.5 hours his last trial medication, during PSG recording. About 90 minutes after sleep talking, he lunged out of bed, and hit his head and face against a wall. A second event of complex sleep-related behavior, described as sleep walking, occurred on Day 101 after he had received no trial medication for 2 weeks (last dose given on Day 87).

The second case was a 58-year-old female who reported mild somnambulism (sleep walking) and severe sleep paralysis on Trial Day 52 while on suvorexant HD. She awoke after a dream, and during subsequent repeated arousals she felt unable to move her extremities or speak. Hours later, she was unaware when she walked to a window. No additional events occurred afterwards. She had no prior history of somnambulism. Trial medication was discontinued after the event.

No events of a complex sleep-related behavior were reported for the Combined Phase 3 Population from 0-6 months for suvorexant LD. They were not observed during the Run-out Phase in Trials P028 and P029, or in the Phase 1 and Phase 2 trials.

Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS) in the suvorexant development program was defined as: uncharacteristic chronic and persistent sleepiness during the day, possibly starting as sudden involuntary sleep episodes and occurring throughout the day or over multiple consecutive days. The sleepiness was often associated with impairment in daytime function. The persistence of the sleepiness differentiated EDS from the short-lasting adverse event of somnolence. To be considered an ECI, the EDS needed to occur in a subject who had adequate sleep during the preceding night. As a result, daytime sleepiness from being awake the previous night did not qualify as an ECI of EDS.

The incidence of EDS was low in the suvorexant program. However, it occurred more frequently from suvorexant treatment in a dose-related manner in the first 3 months in the combined phase 3 population: 1.1% (14/1291) of suvorexant HD group, 0.6% (3/493) suvorexant LD, and 0.2% (2/1025) placebo. As shown in the table below, the EDS risk difference for suvorexant LD compared to placebo was 0.5% (95% CI: -0.2, 1.7); the risk difference for suvorexant HD, with a 95% confidence interval that excluded zero, was 0.8% (95% CI: 0.1, 1.6).

Table 91: Excessive Daytime Sleepiness By Dose Group Treated over 0-3 Months among all Subjects in the Combined Phase 3 Population (P028, P029, and P009)

Protocols 028+029+009	n	(%)	Difference in % vs Placebo Estimate (95% CI)[†]
Patients in population			
MK-4305 LD	493		
MK-4305 HD	1,291		
Placebo	1,025		
with one or more Excessive Daytime Sleepiness Adverse Events			
MK-4305 LD	3	(0.6)	0.5 (-0.2, 1.7)
MK-4305 HD	14	(1.1)	0.8 (0.1, 1.6)
Placebo	2	(0.2)	
with no Excessive Daytime Sleepiness Adverse Events			
MK-4305 LD	490	(99.4)	-0.5 (-1.7, 0.2)
MK-4305 HD	1,277	(98.9)	-0.8 (-1.6, -0.1)
Placebo	1,023	(99.8)	
Nervous system disorders			
Excessive daytime sleepiness			
MK-4305 LD	3	(0.6)	0.5 (-0.2, 1.7)
MK-4305 HD	14	(1.1)	0.8 (0.1, 1.6)
Placebo	2	(0.2)	

[†] 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.

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

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

Lower Level Term is displayed for the specific adverse events.

MK-4305 LD=MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.

MK-4305 HD=MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.

(Source: Sponsor's submission ISS Page 238 Table 5.3.5.3.3.:43)

Apart from severity of EDS, there was considerable overlap in other characteristics of the EDS among the treatment groups. Among the suvorexant HD subjects, 35.7% (5/14) reported their EDS as severe, 50.0% (7/14) as moderate, and 14.3% (2/14) as mild. The suvorexant LD reported 33.3% (1/3) as moderate EDS and 66.7% (2/3) as mild EDS. The placebo group reported one case each of mild and moderate EDS. None of the suvorexant LD and placebo cases were regarded as severe. Time to EDS onset from treatment initiation and EDS duration were not noticeably different among the treatment groups: Across the three dose groups, EDS onset after commencing treatment ranged from 7 hours to 64 days and EDS duration from 3 to 127 days (the longest duration occurred in a placebo subject). EDS resulted in treatment discontinuation in 33.3% (1/3) of the suvorexant LD group and in 71.4% (10/14) of the suvorexant HD group. Both subjects with EDS in the placebo group discontinued treatment because of the EDS event.

Over extended treatment, the suvorexant HD group recorded six additional EDS cases. In the Combined Phase 3 Population, treated over 0-12 months, EDS occurred in 1.5% (20/1291) suvorexant HD and 0.3% (3/1025). Of the 15 subjects who reported EDS during Trial P009 treatment period, 13 subjects were on suvorexant HD and 2 subjects on placebo. In that 12-month trial, EDS led to trial discontinuations in 11 (5 non-elderly, 6 elderly) of the 13 subjects on suvorexant HD and both subjects on placebo. Also, no additional EDS cases occurred in the suvorexant LD group beyond three months of treatment.

Table 92: Excessive Daytime Sleepiness and Suvorexant High Dose over 0-12 Months among all Subjects Treated in the Combined Phase 3 Population (P028, P029, and P009)

Protocols 028+029+009	MK-4305 HD		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[†]
Patients in population	1,291		1,025		
with one or more Excessive Daytime Sleepiness Adverse Events	20	(1.5)	3	(0.3)	1.1 (0.3, 2.0)
with no Excessive Daytime Sleepiness Adverse Events	1,271	(98.5)	1,022	(99.7)	-1.1 (-2.0, -0.3)
Nervous system disorders					
Excessive daytime sleepiness	20	(1.5)	3	(0.3)	1.1 (0.3, 2.0)

[†] 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.

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.

Lower Level Term is displayed for the specific adverse events.

MK-4305 HD=MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.

(Source: Sponsor's submission ISS Page 241 Table 5.3.5.3.3.:44)

Other Trials

The sponsor reported two additional EDS cases in the suvorexant development program: one event occurred in a 63-year old female in the Phase 2 trial P006, who developed severe EDS of 4 hours duration after two days on suvorexant 80 mg. She completed the trial as planned. The other EDS event occurred in the Phase 1 COPD trial P032 in a 63-year old female with COPD, who developed EDS after a day of suvorexant 40mg treatment; the EDS event lasted five days.

Reviewer note: The sponsor states, "EDS occurred more frequently with suvorexant HD. Taken together with the low overall somnolence rates reported in the program, these data indicate that for the vast majority of subjects taking suvorexant HD, clinically important next-day somnolence is not an issue." I agree that the EDS occurred more with suvorexant HD, risk difference from placebo 0.8% NNTH 125, and that the overall

EDS incidence in the program was low. However, its occurrence has safety implications especially when individuals taking the HD have to go about their usual duties such as driving. For such individuals, EDS will be a major issue. It is not clear that switching to a lower dose will resolve the EDS issue as the clinical trials did not explore such strategy. The EDS problem appears to be less of a problem with suvorexant LD, though the sample size did not allow for a more precise EDS estimate for the dose.

Hypnagogic and Hypnopompic Hallucinations

In the Phase 3 population, only subjects treated with suvorexant reported hypnagogic and hypnopompic hallucinations, though the incidence of this ECI in the overall suvorexant development program was low. In the suvorexant development program, hypnagogic hallucinations referred to vivid dreamlike experiences that occur during sleep onset; hypnopompic hallucinations were experiences occurring upon waking. The subjects reported what they saw, heard, felt, or smelled about things that were not actually there. The Combined Phase 3 Population had five subjects who reported hypnagogic and hypnopompic hallucinations within the first three months of treatment: 0.4% (2/493) in the suvorexant LD group and 0.2% (3/1291) in the suvorexant HD group; none of this ECI occurred in the placebo group of the population. The event reported for one (0.2%, 1/493) of the two subjects in the suvorexant LD group was a case of hypnagogic hallucination; the other was a hypnopompic hallucination. In contrast, all three subjects (0.2%, 3/1291) in the suvorexant HD group were cases of hypnagogic hallucinations.

The two subjects on suvorexant LD reported their hallucinations as mild; despite the hallucinations, the subjects completed the trial as planned. The first, Subject AN 07058, a 28-year old female in Trial P028 reported hypnagogic hallucinations on Trial Day 2 starting 1 hour after suvorexant LD. The “sensation of an inability to move and feeling the presence of an individual in bed with her” lasted 15 minutes at sleep onset. The experiences resolved by Day 15. The second subject, AN 12873, a 76-year-old male in Trial P029, reported hypnopompic hallucination starting 8.5 hours after taking suvorexant LD on Trial Day 90 and while undergoing PSG evaluation. The “out of body experience, as if subject were floating” lasted 2 minutes on awakening. He had no additional events.

The hallucinations reported by the three subjects on suvorexant HD were termed mild, moderate, and severe; one subject discontinued trial treatment because of hypnagogic hallucinations. Subject AN 12896, a 68-year old female in Trial P029, reported hypnagogic hallucinations termed severe on Trial Day 46 and mild on Day 67. The initial event, which occurred at sleep onset about the same time she received her trial treatment, was described as “a sensation in her brain of flashing lights and, as if she was being shocked in her brain by a taser. Her body became paralyzed and she began to hear vivid sounds of people coming up the stairs with a sense of violent intent on their part.” She reported having a similar event many years before the trial. Her second

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hypnagogic hallucination on Day 67 was described as mild, when she heard faint murmurs of people speaking. A second subject, AN 03039, on suvorexant HD, a 58-year old male in Trial P009, had mild hypnagogic hallucination on Day 21 about 1 hour after trial treatment. This was described as "a feeling of a shadow falling over his body, being physically hunted by enemies in hospital environment, and hearing extremely loud screams." The feelings occurred within an hour of trial treatment and lasted 39 days. The third subject, AN 04557, on suvorexant HD who experienced hypnagogic hallucination within 3 months of treatment was a 73 year-old male in Trial P009. The events, described as moderate, occurred on Days 40, 96, and 97: "A frightening feeling of being chased and reported feeling disoriented and confused. During another event, he felt like he was being dragged up the wall." He discontinued from the trial because of the experience.

With extended treatment up to 12 months, the suvorexant HD group recorded two additional subjects who reported hallucinations. In the Combined Phase 3 Population treated over 0-12 months, as shown in the table below, a moderate event of hypnagogic hallucination associated with sleep paralysis occurred at 8 months. Another subject reported two mild episodes of hypnopompic hallucinations after 3 and 6 months of trial treatment. No cases occurred in the placebo group. No additional cases occurred in the suvorexant LD group beyond three months of treatment in the Phase 3 population.

Table 93: Hypnagogic and Hypnopompic Hallucinations and Suvorexant High Dose over 0-12 Months among all Subjects Treated in the Combined Phase 3 Population (P028, P029, and P009)

Protocols 028+029+009	MK-4305 HD		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[†]
Patients in population	1,291		1,025		
with one or more Hypnagogic/Hypnopompic Hallucinations Adverse Events	5	(0.4)	0	(0.0)	0.3 (-0.1, 0.8)
with no Hypnagogic/Hypnopompic Hallucinations Adverse Events	1,286	(99.6)	1,025	(100.0)	-0.3 (-0.8, 0.1)
Psychiatric disorders					
Hypnagogic hallucination	4	(0.3)	0	(0.0)	0.3 (-0.1, 0.8)
Hypnopompic hallucination	1	(0.1)	0	(0.0)	0.1 (-0.3, 0.4)

[†] 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.

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.

Lower Level Term is displayed for the specific adverse events.

MK-4305 HD=MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.

(Source: Sponsor's submission ISS Page 229 Table 5.3.5.3.3.:41)

The Phase 2 trial P006 recorded no cases of hypnagogic and hypnopompic hallucinations. However, three subjects in Phase 1 trials reported the events, two hypnagogic and one hypnopompic hallucination, 60 to 75 minutes after taking suvorexant 40 mg to 60 mg doses. Also, three additional subjects in the Phase 1 population reported hypnagogic experiences, as abnormal sleep related events, while on suvorexant 40 mg. No hypnagogic and hypnopompic hallucinations or related events occurred with placebo treatment in the Phase 1 and Phase 2 trials.

Reviewer Note: The incidence of hallucinations in this program was small. As the sponsor mentioned, referencing published literature, even though such hallucinations are frequent in narcolepsy, their prevalence can be as high as 12.5% in the general population. The small numbers of cases in this program make it difficult to determine the relationship of hallucinations and potential narcoleptic risk with suvorexant. Despite the small numbers, the following observations suggest a need for cautious evaluation of the drug's dose response: the severity of cases in the suvorexant HD group compared to suvorexant LD, a subject on suvorexant HD discontinued treatment because of the hallucinations, incidence of the events in subjects on suvorexant HD increased from 0.2% within 3 months to 0.4% within 12 months of treatment, association of the hallucinations and sleep paralysis, and the absence of events in the placebo group.

Sleep paralysis

Sleep paralysis is characterized by complete muscle atonia or weakness and has been theorized to occur from inappropriate overlap of sleep stages such as intrusion of REM activity into normal sleep transitions. The sponsor provided literature reference that estimated the lifetime prevalence of sleep paralysis at 7.6% of the general population. Higher prevalence occurs in some medical conditions such as narcolepsy, hypertension, seizure disorders, migraine, anxiety disorders, and obstructive sleep apnea; and other situations that are associated with insomnia or other sleep disturbances such as jet lag and shift work, student status, and African decent.

Narcoleptic cataplexy closely resembles true sleep paralysis; however, narcoleptic attacks are more common at sleep onset and true sleep paralysis on awakening. In the suvorexant clinical development program, sleep paralysis referred to the temporary inability to talk or move at sleep onset, during sleep, or upon awakening. Events of sleep paralysis that occurred at sleep onset in the Phase 3 trials were adjudicated to further evaluate the timing of the events in relation to sleep onset.

Only five subjects reported sleep paralysis within the first 3 months in the Phase 3 population; all of them received suvorexant treatment. Despite the low incidence of sleep paralysis, numerically more subjects reported the ECI while on suvorexant HD compared to suvorexant LD: 0.3% (4/1291) in the suvorexant HD group and 0.2% (1/493) in the suvorexant LD group; no placebo subject reported sleep paralysis in this population. All cases occurred 2-3 months of starting trial treatment. Investigators

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deemed the sleep paralysis events in the suvorexant LD subject as not of sleep onset because the events occurred in the middle of the night. The subject had three episodes of 5-minute long sleep paralysis, each starting two to fours after trial treatment and on return from the bathroom, on Trial Days 59, 62 and 64. In the past, he had experienced similar events up until junior high school; then, the events were at sleep onset and without any medication. **Three of the four suvorexant HD subjects were confirmed events of sleep onset paralysis** on adjudication. One case resulted in treatment discontinuation.

On extended treatment for up to 12 months, the suvorexant HD group added one more subject from Trial P009 who reported sleep onset paralysis associated with hypnagogic hallucinations on Trial Day 245. This event was also confirmed by adjudication to be sleep onset paralysis. The events of sleep onset paralysis in the Combined Phase 3 Population treated over 0-12 months are shown in the table below. No cases occurred in the placebo group. Also, the suvorexant LD subjects reported no cases of sleep onset paralysis in the Phase 3 population.

Table 94: Sleep Onset Paralysis and Suvorexant High Dose over 0-12 Months among all Subjects Treated in the Combined Phase 3 Population (P028, P029, and P009)

Protocols 028+029+009	MK-4305 HD		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[†]
Patients in population	1,291		1,025		
with one or more Sleep Onset Paralysis Adverse Events (confirmed by adjudication)	4	(0.3)	0	(0.0)	0.3 (-0.0, 0.8)
with no Sleep Onset Paralysis Adverse Events	1,287	(99.7)	1,025	(100.0)	-0.3 (-0.8, 0.0)
Nervous system disorders					
Sleep paralysis	4	(0.3)	0	(0.0)	0.3 (-0.0, 0.8)

[†] 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.
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.
Lower Level Term is displayed for the specific adverse events.
Note: although the lower level term displays "Sleep paralysis", the verbatim term indicates occurrence during sleep onset.
MK-4305 HD=MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.

(Source: Sponsor's submission ISS Page 249 Table 5.3.5.3.3.:49)

Additional subjects on suvorexant doses of 40 mg and higher reported sleep paralysis in the Phase 2 and Phase 1 studies. The sponsor's review of the Phase 2 trial data revealed two subjects on suvorexant 40 mg and 80 mg who reported symptoms suggestive of sleep paralysis; these events apparently occurred in the middle of the night or on awakening, and not at sleep onset. The first subject, a 24 year-old male, was on suvorexant 80 mg when on Day 8 he developed the symptom that lasted 2-3 minutes and occurred once a week over 16 days. The second subject, a 45-year-old male on 40

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mg suvorexant, reported the symptom that lasted 10 minutes starting from Trial Day 3 and occurring once a week over 29 days.

Phase 1 Trials
In the Phase 1 trials, 2% (13/ 662) of subjects on suvorexant alone reported sleep paralysis compared to 0.3% (1/365) on placebo. The placebo subject experienced sleep paralysis that the sponsor described in Trial P011, a dose-escalation clinical pharmacology trial, as follows: "A female subject AN 0012 experienced sleep paralysis lasting 5 minutes following placebo upon waking. The onset of sleep paralysis was 20 minutes following the placebo dose. The investigator rated this event as mild in intensity and probably related to study drug. During this time, the subject also experienced somnolence which lasted 3 hours and 15 minutes."

All 13 subjects who reported sleep paralysis on suvorexant did so while on suvorexant doses of 40 mg to 240 mg; 6 of the 13 subjects were on suvorexant 40 mg.
Below, I summarized information on sleep paralysis events that occurred in six subjects from the Phase 1 trial P025, a trial that assessed abuse potential in subjects with polydrug use.

#1: One subject, a 33-year old male, experienced an episode of sleep paralysis that lasted 6 minutes starting at 1 hour 25 minutes after he received suvorexant 150 mg. He reported "an inability to speak and was only able to move his legs slightly during the episode, which occurred as he was starting to fall asleep."

#2: A 35 year old white female reported an episode of sleep onset paralysis 52 minutes after receiving suvorexant 150 mg dose. The event lasted about 2 minutes and was described as inability to move her extremities, open her eyes or speak.

#3: A 26 year old Asian male reported two events of sleep paralysis in Trial P025. The first event consisted of three episodes, each of which lasted 5 seconds and started 1 hour and 30 minutes, 2 hours, and 4 hours after he received suvorexant 40 mg dose. These episodes occurred when the subject, on being awoken by study staff, reported an inability or great difficulty in initiating movements. The second event occurred in another treatment period after he received suvorexant 80 mg; this was an episode of the subject being unable to speak or move, starting 39 minutes (34 minutes calculated from the CSR narrative) and lasting for 20 seconds.

#4: A 48 year old white male experienced two events of intermittent sleep paralysis. In the first treatment period, he reported intermittent episodes of sleep paralysis starting from 3 hours and 32 minutes after receiving suvorexant 150 mg dose. The episodes were described as inability to talk and initiate voluntary movements except for the eyes. The event lasted 13 minutes. The second event of sleep paralysis occurred in the fourth treatment period 1 hour and 38 minutes after receiving suvorexant 40 mg. This event included three episodes of sleep paralysis at sleep onset; each episode lasted about 10

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seconds, consisted of inability to move or speak. The whole event lasted about 7 minutes, and was associated with fearful episodes of inability to take deep breaths and auditory hypnagogic hallucinations.

#5: A 29 year old female of mixed race, white and African descent, reported intermittent sleep paralysis that started 1 hour and 33 minutes after receiving suvorexant 150 mg. The event consisted of five intermittent episodes of inability to move or speak that lasted about 2 minutes; the whole event lasted 1 hour. The subject was unable to tell whether the event occurred at sleep onset but recalled having similar episodes in the past.

#6: A 47 year old white female with life-long history of sleep paralysis reported three events of sleep paralysis in study P025. The first event started 3 hours after receiving suvorexant 150 mg dose and lasted 1 hour and 20 minutes. This event consisted of intermittent episodes sleep paralysis that lasted 5-10 seconds; described as inability to move, speak, or breathe; associated with visual hallucinations; appeared to occur with sleep onset. The episodes were similar to her earlier pre-study occurrences. The second event occurred 1 hour and 10 minutes after she received suvorexant 80 mg in another treatment period; the event lasted for lasted 15 minutes. The third event of sleep paralysis occurred 1 hour and 35 minutes after she received suvorexant 40 mg and lasted 5 minutes.

Further, I summarized the narratives in the following table:

Table 95: Sleep Paralysis in Subjects on Suvorexant in Phase 1 Trials

Study	Age, Gender	Treatment	Onset after Treatment	Sleep Paralysis Experience
P025	33-year old male	Suvorexant 150 mg	85 minutes	Sleep onset, 6 minutes of inability to speak with slight mobility of legs
P025	35-year old female	Suvorexant 150 mg	52 minutes	Sleep onset, unable to open eyes, speak and move arms and leg
P025	26 year old Asian male	Suvorexant 40 mg Suvorexant 80 mg	90, 120, & 240 minutes 34 minutes	On awakening, 3 episodes, each 5 seconds Sleep onset, 20 seconds, unable to speak or move
P025	48 year old white male	Suvorexant 150 mg Suvorexant 40 mg	212 minutes 98 minutes	3 episodes, each 1-2 minutes, unable to speak or initiate movements Sleep onset, 3 episodes, each lasted 10 seconds, inability to move or speak. Whole event lasted about 7 minutes Associated fearful episodes of inability to take deep breaths and auditory hypnagogic hallucinations.

P025	29 year old female of mixed race	Suvorexant 150 mg	93 minutes	5 episodes, each lasted 2 minutes, inability to move or speak.
P025	47 year old white female	Suvorexant 150 mg Suvorexant 80 mg Suvorexant 40 mg	180 minutes 70 minutes 95 minutes	Episodes lasted 5-10 seconds; inability to move, speak, or breathe; associated with visual hallucinations Similar pre-study episodes may be not as frequent Occurred during sleep, unclear if any are sleep onset

(Source: Modified from Sponsor's submission)

Reviewer Note: The sponsor summarized the sleep paralysis experience as follows: "few self-limited AEs of sleep paralysis were reported with suvorexant. Of five events potentially associated with sleep onset, 4 were confirmed to be events of sleep onset paralysis. These AEs generally occurred within 2-3 months of treatment initiation, with no pattern of increasing incidence associated with continued treatment, and were not suggestive of any safety concern." However from my review, the sleep paralysis data from the Phase 1 trials do not appear as reassuring as the sponsor suggests, given the number of events at suvorexant doses of 40 mg and above. This may facilitate adequate dose evaluation weighing the benefits against the risks.

Effects on Driving and Operating Machinery

The sponsor assessed the effects of suvorexant treatment on driving performance using AE reports of accident-related injuries, questionnaire responses on motor vehicle accidents or traffic violations, and two on-the-road driving studies (P035 and P039). Please see Review Section 7.4.5 for additional review of the driving studies.

Adverse Events Associated with Motor Vehicle Accidents
ECIs included adverse events that occurred from traffic or motor vehicle accident (MVA) in which a trial subject was a vehicle driver.

Fewer subjects on suvorexant experienced MVAs while driving than on placebo. The incidence of MVAs among subjects who drove during the trial was low within the treatment groups: 0.3% (1/342) on suvorexant LD, 0.3% (3/891) on suvorexant HD, and 0.6% (4/692) on placebo. None of the events was considered drug-related by the investigators. One subject a 33-year-old female, said to be upset with marital problems, had experienced concentration problem and weakness before the MVA on Trial Day 7, in which she drove into a curb and a parked car. She was on placebo treatment. The other subjects had either swerved to avoid an accident or their vehicles were hit by other drivers.

Treatment effects did not appear to be related to the MVAs in subjects on suvorexant. A 36-year-old male on suvorexant LD was driving his moped on Trial Day 49 when a car hit him and he fell on his right leg. He recovered on Trial Day 52 and subsequently completed the trial.

Among the three subjects who experienced MVAs while on suvorexant HD, a 32-year old female in Trial P009 was struck from behind by another car when she stopped at a light on Trial Day 50. She recovered from neck pain and whiplash by Trial Day 198 but subsequently withdraw from the trial. The second subject, a 46-year old male, also in Trial P009, was driving on a rainy day on Trial Day 284 when he ran into another car that was reported to have suddenly changed lanes. By Trial Day 376, he had recovered from his injuries: neck pain, external contusion, and pectoral muscle strain. He completed the trial as planned. The third subject, a 50-year old female in Trial P028 experienced an MVA, reportedly caused by another vehicle driver, at about 8.5 hours after taking trial medication on Trial Day 53. She sustained moderate cervical vertebra dislocation, pelvic contusions, and a right knee contusion. She recovered by Trial Day 78.

The Phase 1 trials reported no MVAs, but review of the Phase 2 trial P006 yielded one MVA in a subject on placebo.

Questionnaire-based assessment of motor vehicle accidents or traffic violations

Following an FDA recommendation at the End of Phase 2 meeting, the sponsor obtained responses to a Motor Vehicle Accidents and Violations (MVAV) Questionnaire in the Phase 3 trials. The questionnaire, in the sponsor's ISS Appendix 5.3.5.3.3: 47, collected information on subjects' driving performance preceding the trial visit. Subject involved in MVAs provided information on time and date of accident, and injuries as a result of the accident. The sponsor used the responses to assess occurrence of traffic or motor vehicle accidents and related injuries.

In the Combined Phase 3 Population, 0-3 Months, the differences in incidence of Motor Vehicle Accidents and Violations (MVAV) among the dose groups were small, although, as shown in the Table below, a numerically higher rate occurred in the suvorexant LD group (2.9%, 10/342) compared to suvorexant HD group (2.3%, 13/569) and placebo (2.3%, 12/531).

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Table 96: Motor Vehicle Accidents and Violations (MVAV) By Dose Group Treated over 0-3 Months among all Subjects Who Drove in the Combined Phase 3 Population (P028, P029, and P009)

	MK-4305 LD n (%)	MK-4305 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.

MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.

MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.

(Source: Sponsor's submission ISS Page 275 Table 5.3.5.3.3.:59)

The two tables below show that over extended treatment periods of 6 to 12 months with suvorexant, the incidence of MVAV was marginally increased by suvorexant LD (3.5%, 12/342) compared to placebo (2.6%, 14/532), and by suvorexant HD (4.0%, 36/891) compared to placebo (3.2%, 26/692).

Table 97: Motor Vehicle Accidents and Violations (MVAV) and Suvorexant Low Dose over 0-6 Months among all Subjects Who Drove and Were Treated in the Combined Phase 3 Population (P028, P029, and P009)

	MK-4305 LD n (%)	Placebo n (%)
Patients in population	342	532
with one or more MVAV events	12 (3.5)	14 (2.6)
with no MVAV event	330 (96.5)	518 (97.4)
Number of MVAV events	13	16
Number of Patients with Accidents	4 (1.2)	7 (1.3)
Number of Accidents	4	7
Number of Patients with citations†	8 (2.3)	8 (1.5)
Number of citations†	9	9

Only patients who were treated and drove during the indicated phase of the study period were included in the table.

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

† Citation = violation.

MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.

(Source: Sponsor's submission ISS Page 277 Table 5.3.5.3.3.:61)

Table 98: Motor Vehicle Accidents and Violations (MVAV) and Suvorexant High Dose over 0-12 Months among all Subjects Who Drove and Were Treated in the Combined Phase 3 Population (P028, P029, and P009)

	MK-4305 HD n (%)	Placebo n (%)
Patients in population	891	692
with one or more MVAV events	36 (4.0)	22 (3.2)
with no MVAV event	855 (96.0)	670 (96.8)
Number of MVAV events	39	27
Number of Patients with Accidents	13 (1.5)	10 (1.4)
Number of Accidents	13	10
Number of Patients with citations†	24 (2.7)	14 (2.0)
Number of citations†	26	17

Only patients who were treated and drove during the indicated phase of the study period were included in the table.
Percents of sub-category levels calculated using the total number of patients in that sub-category as the denominator.
† Citation = violation.
MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.

(Source: Sponsor's submission ISS Page 276 Table 5.3.5.3.3.:60)

Reviewer note: The MVAV questionnaire was introduced after Trial P009 had commenced. Within limits of indirect comparison among treatment groups, the incidence trend over the extended treatment periods may suggest a suvorexant dose effect on the occurrence of MVAVs. This suggestion is contrary to the sponsor's position in a statement on Page 628 of the ISS (Section 5.3.5.3.3.5.8.3 Summary: Effects on Ability to Drive or Operate Machinery), "The incidence of accidents and citations were generally comparable between the treatment arms (~3%), without evidence of an increased occurrence with suvorexant, based on suvorexant dose or with continued treatment over time."

Despite comparable reports of accidents and traffic violations, and driving performance in the driving studies, the overall assessment suggests that suvorexant-treated individuals need to avoid driving, operating machinery, or engaging in activities that require full mental alertness until they become fully awake. In the Phase 3 trials, the incidence of motor vehicle accidents and traffic violations were comparable between suvorexant and placebo treatments. In Phase 1 driving trials, the sponsor observed no significant impairment of next-day driving performance that tested mean SDLP after one night and eight consecutive nights of suvorexant LD or HD in both elderly and non-elderly subjects. However, the trials showed that some subjects who received suvorexant had increased SDLP and four non-elderly subjects felt sleepy enough to prematurely stop their driving tests. As a result, a potential for impaired driving performance exists with suvorexant treatment. The sponsor provided cautionary language in the proposed label, which seems appropriate.

Cataplexy

The sponsor recorded no cases of cataplexy in the entire suvorexant development program. For the suvorexant development program, the sponsor defined cataplexy as characterized by sudden, unexpected, and fleeting muscle weakness ranging from slight weakness to complete body collapse. The cataplexy event had to be preceded by an emotional trigger or stimulus, localized to a specific muscle group or part of the body, and had to occur in a subject who was fully awake, lucid, and aware. An external adjudication committee reviewed the ECI reports and the Modified Cataplexy Questionnaire that the subject completed after the event. After reviewing 45 cases of falls and an event of muscle weakness, the committee determined none of the events in the Phase 3 trials was suggestive of cataplexy. Similarly, the Phase 2 and Phase 1 trials recorded no cataplexy events.

Cataplexy is a symptom of narcolepsy and a result of intrusion of muscle atonia, which typically occur in REM sleep, into wakefulness. Published literature suggests that narcolepsy subjects with cataplexy have low cerebrospinal fluid (CSF) orexin levels, likely from progressive orexinergic neuronal death (Nishono et al, 2000; Kukkonen, 2012). The concern that orexin receptor antagonists (ORAs) including suvorexant may increase the risk of narcolepsy led the sponsor to specifically evaluate for symptoms such as cataplexy. Occurrence of cataplexy may cause falls, accidents, and injuries, and so pose a major safety concern.

An investigator in one of the Phase 3 trials referred one case of muscle weakness while on suvorexant HD treatment to the adjudication committee as an event suggestive of potential cataplexy. This case highlights two events of clinical interest (ECIs) from a subject: Excessive Daytime Sleepiness (EDS) and Muscle Weakness in Legs (Muscular Weakness). I summarize the narrative below.

Event Suggestive of Cataplexy with EDS and Elevated Amylase Level – Summary of Narrative
Subject AN 02642, a 59 year old male, in the 12-month, double-blind, Trial P009, reported an event of muscle weakness in legs on Day 46, while on suvorexant HD. Later that day, he reported EDS that led to discontinuation from the trial. The external adjudication committee concluded upon review of the case that the Muscle Weakness event was not cataplexy.

Muscle weakness event was suggestive of potential cataplexy. The subject had a pre-trial elevation of amylase levels that apparently increased further during the first month of trial treatment. He remained asymptomatic and his amylase levels were 58 U/L at baseline, 503 U/L, and 80 U/L before trial medication was interrupted from Day 38 to Day 42. On Day 46, about 12 hours after his Day 45 treatment with suvorexant HD, he developed muscle weakness in legs that lasted 5-30 seconds. At the time of the event, he was at work, fully awake, and laughing with his co-workers when he developed

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increased tiredness and, in total, three brief episodes of weakness of lower extremities. Also, he continued to feel weak for another 11 hours, and had a headache that started about 4 hours after onset of muscle weakness and lasted 2 hours.

Still on Day 46 at about 5 hours after onset of muscle weakness, the subject developed excessive daytime sleepiness that lasted up to bedtime. The daytime sleepiness episodes occurred variously at work. One episode occurred at a traffic stop; another episode of microsleep, which was witnessed by his wife, occurred while he was driving. The EDS resolved after he discontinued the trial medication. There were no reports of associated seizures, seep paralyses, or hallucinations.

The subject's past medical history was significant for hypertension, dyslipidemia and osteoarthritis. His concomitant medications included ezetimibe, amlodipine besylate, irbesartan, vitamin B complex, vitamins (unspecified), ubidecarenone, potassium (unspecified), glucosamine, sildenafil citrate, simvastatin. He denied use of alcohol or non-prescribed drugs within 24 hours prior to the events and denied a history of substance abuse. He drank about 2 beers a night, but not every night.

According to the sponsor's narrative concerning the muscle weakness event, the subject's responses in the Modified Cataplexy Questionnaire were positive to the following questions about situations in which the leg weakness or knee buckling occurred: when laughing, when excited, surprised, when required to make a quick verbal response in a playful or funny context, when startled, when telling or hearing a joke. The investigator was concerned the event was potentially cataplexy. Subsequently, the external adjudication committee reviewed the case and concluded that the muscle weakness event was not cataplexy.

Merck evaluated their non-clinical and clinical data, including up to 12 months suvorexant treatment, and concluded that no identified risk of cataplexy exists in the setting of clinical insomnia treatment using ORAs. The sponsor further supported its conclusion by noting that progressive neuronal loss led to narcolepsy, in contrast to the intermittent or transient cyclical exposure from ORAs for clinical insomnia in which the orexin receptor is exposed to a drug such as suvorexant only during the sleep period part of a day.

Reviewer Note: So far there are no confirmed cases of narcolepsy in earlier trials of orexin antagonists. The dual orexin receptor antagonist almorexant was in an earlier development for insomnia, which was stopped for unclear reasons; the development program recorded no cases of narcolepsy or cataplexy in an early proof of concept trial. In the trial, investigators reported that almorexant treatment decreased latency to REM sleep. They added that shortened REM latency may suggest narcolepsy-like changes in sleep architecture or potential direct effects of dual orexin receptor antagonists on sleep; alternatively, it may indicate REM rebound in individuals susceptible to chronic partial REM deprivation (Hoever et al, 2012).

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The absence of cataplexy in the development programs does not necessarily exclude the risk of drug-induced narcolepsy from exposure to ORAs. Although, the external adjudication committee concluded that the muscle weakness event summarized above was not cataplexy, features of the event present concerns for a narcoleptic process that may be associated with trial treatment. Even discounting the event, a small risk of narcoleptic events cannot be ruled out during suvorexant or other ORAs treatment, especially if the risk is so small that it will need a larger safety database to detect it. The limited experience with ORAs, especially beyond 14 months of treatment, suggests the continued need to carefully assess this drug class for the risk of cataplexy.

Also, the HLA status of subjects in the development program remains largely unknown. It may be that HLA interaction with ORA drug exposure is required to manifest narcoleptic symptoms such as cataplexy. The sponsor has stored blood samples from the trials that may be useful for future genomic studies. A potential evaluation is to determine the subjects HLA genotype and compare subjects with and without features of the narcolepsy components such as sleep paralysis, hypnopompic hallucinations, EDS, and muscle weakness suggestive of cataplexy.

Falls

The sponsor examined the Phase 3 trials for the risk of falls, which were treated as ECIs and adjudicated to determine whether the events suggested cataplexy or were associated with suvorexant treatment.

The trials defined a fall as a loss of posture or balance. An external adjudication committee reviewed the ECI report and the subject-completed Modified Cataplexy Questionnaire, and adjudicated the events to assess whether they were suggestive of cataplexy.

The incidence of falls in the Phase 3 trials within the first 3 months of treatment was low at 0.8% (22/2809), and the fall risks across treatment groups were comparable as shown in the table below. Falls occurred in less than 1% in each of the treatment groups: 0.7 % (9/1291) with suvorexant HD, 0.8% (4/493) with suvorexant LD, and 0.9 % (9/1025) with placebo. Further, each treatment group recorded at least one severe fall: 0.2 % (3/1291) with suvorexant HD, 0.2% (1/493) with suvorexant LD, and 0.1 % (1/1025) with placebo.

Table 99: Events of Falls in the Phase 3 Trials at 0-3, 0-6s, and 0-12 months

Variable Category	Placebo	Suvorexant LD	Suvorexant HD
Falls in 0-3 Months	0.9 % (9/1025)	0.8% (4/493)	0.7 % (9/1291)
Falls in 0-6 Months	0.9% (7/767)	1.0% (5/493)	Not applicable

Falls in 0-12 Months	1.5% (15/1025)	Not applicable	1.6% (21/1291)

(Source: Modified from Sponsor's submission ISS Pages 261, 267, and 268 Tables 5.3.5.3.3: 55, 56, and 57)

Based on the sponsor's assessment, the falls appeared not related to residual somnolence or impaired coordination, but they were associated with circumstances that led to fall such as faulty ladder or other unstable footing, icy or other slippery conditions. Brief summaries of the narratives for falls in 0-3 months are as follows:

Suvorexant HD
Subject AN 12253 in Trial P029, a 42-year-old female who was on suvorexant HD and reported a fall on Trial Day 40 about 22 hours after taking trial medication. She fell on an icy surface while walking to her car, sustained moderate swelling of her left knee and right foot. She recovered the same day and continued the trial treatment.

Subject AN 12288 in Trial P029, a 46-year-old male who received suvorexant HD and reported a severe fall on Trial Day 65 at about 19 hours after taking trial medication. While at work, the subject slipped on olive oil and fell down a staircase. He lost consciousness and sustained multiple non-serious musculoskeletal injuries including contusions, shoulder dislocation, and nasal fracture. He completed the trial per protocol.

Subject AN 12324 in Trial P029, a 39-year-old female was on suvorexant HD when she reported a mild fall on Trial Day 12 at about 15 hours after taking trial medication. She was hiking when she tripped and fell; afterwards she reported moderate left foot pain, from which she recovered that same day. She completed the trial per protocol.

Subject AN 07229 in Trial P028, a 61-year-old female was receiving suvorexant HD when he reported a mild fall on Trial Day 43 at about 17 hours after taking trial medication. While on a walk, she slipped on the snow and fell. She reported mild coccydynia. She completed the trial per protocol.

Subject AN 07959 in Trial P028, a 73-year-old male was on suvorexant HD treatment when he reported a mild fall on Trial Day 44 at about 11 hours after taking trial medication. He slipped on ice, fell, and sustained a mild knee contusion. He completed the trial per protocol.

Subject AN 12214 in Trial P029, a 58-year-old female assigned to suvorexant HD, reported a severe fall on Trial Day 46 at about 24 hours after taking trial medication. She slipped on the ice while walking her dog. She fell and sustained an ankle fracture but completed the trial treatment per protocol.

Subject AN 13003 in Trial P029, a 67-year-old female assigned to suvorexant HD. She had a history of multiple medical conditions including dizziness and orthostatic hypotension, and required concomitant medications. She reported two events of fall and

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a vertebral (T12) compression fracture. On Trial Day 45 at about 10 hours after taking trial medication, she tripped on a comforter, had a severe fall, and sustained moderate musculoskeletal injuries including neck and lumber sprain/strain and a right foot fracture. Although the investigator considered this event to be related to study medication, she continued trial medication. On Trial Day 47 at about 9 hours after taking trial medication, she had a second fall. She awoke in the morning, felt dizzy, and fell. She was hospitalized, and diagnosed with a T12 compression fracture (serious and severe) and pneumonia. She discontinued trial medication on Trial Day 48 because of the second fall. Comorbid conditions included COPD, gastroesophageal reflux disease, hypercholesterolemia, hypothyroidism, osteoporosis, and back pain. Concomitant medications included ibandronate sodium, levothyroxine sodium, omeprazole, simvastatin, aspirin, calcium, beclomethasone dipropionate, albuterol, vitamins, acetaminophen, and dicyclomine hydrochloride.

Subject AN 04168 in Trial P009, a 75-year old female on suvorexant HD who reported a moderate fall on Trial Day 87. While taking out trash, she tripped over netting covering newly laid sod, and sustained mild knee and elbow injuries. She completed the trial per protocol.

Subject AN 07971 in Trial P028, a 68-year-old male on suvorexant HD who reported a mild fall on Trial Day 92, a day after his last trial medication. At 04:00 hours on Day 92, he awakened and fell on attempting to roll out of bed. Subsequently, he completed the trial per protocol.

Suvorexant LD
Subject AN 12149 in Trial P029, a 57-year-old female on suvorexant LD who reported a mild fall on Trial Day 25 at about 11 hours after taking trial medication. She was getting dressed in the morning, then felt dizzy and fell on her knee, sustaining a mild hematoma. She completed the trial per protocol.

Subject AN 07878 in Trial P028, a 75-year-old female on suvorexant LD reported a mild fall on Trial Day 32 at about 3 hours after taking trial medication. She had received laxative treatment for a colonoscopy planned for the next day and was making frequent trips to the bathroom, when she tripped over a folding door. She fell and sustained a mild skin laceration near her left eye. Subsequently, she missed two doses of trial medication on Trial Days 32 and 33. Afterwards, she completed the trial per protocol.

Subject AN 08170 in Trial P028, a 68-year-old female was receiving suvorexant LD when she reported a moderate fall on Trial Day 61 at a time unspecified relative to the earlier dose of trial medication. She fell while trying to lift a table and sustained moderate right flank bruising and pain. Subsequently, she discontinued from the trial after withdrawing consent because of family commitments.

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Subject AN 12953 in Trial P029, a 73-year-old female was receiving suvorexant LD when she reported a severe fall on Trial Day 29 at about 14 hours after taking trial medication. She fell from a ladder while putting away items in the attic, fractured her right ankle, and was hospitalized. Subsequently, she discontinued from the trial on Trial Day 36.

Placebo
Subject AN 12814 in Trial P029, a 74-year-old female was on placebo when she reported a fall of moderate intensity on Study Day 10 at about 2 hours after taking trial medication. . She awoke to use the bathroom at 00:30, slipped on the wet kitchen floor from, a roof leak, and struck her head on the floor. She apparently lost consciousness because when she awoke on the floor the time was 02:00. She completed the trial per protocol.

Subject AN 12970 in Trial P029, a 70-year-old male was on placebo when he reported two separate events of mild falls. He reported the first fall on Trial Day 44 about 17 hours after taking trial medication when the subject fell while running with his grandson. He sustained a thigh muscle tear and a moderate rib contusion. He reported the second fall on Trial Day 78 about 12 hours after taking trial medication, when he slipped in the snow, fell, and sustained a mild right shoulder contusion. Subsequently, he completed the trial per protocol.

Subject AN 07912 in Trial P028, a 74-year-old female treated with placebo reported a mild fall on Trial Day 6 at about 19 hours after taking trial medication. She tripped on a door mat, fell, and sustained a mild hematoma on her right thigh. She completed the trial per protocol.

Subject AN 08023 in Trial P028, an 85-year-old female on placebo reported a mild fall on Trial Day 28 at about 12 hours after taking trial medication. She accidentally tripped on the edge of the rug and fell, sustaining a mild toe injury. She completed the trial per protocol.

Subject AN 08100 in Trial P028, a 66-year-old female on placebo reported a moderate fall on Trial Day 28 at about 22 hours after taking trial medication. While at work she slipped on a sanded floor, fell, and sustained a foot fracture reported to be of moderate intensity. She completed the trial per protocol.

Subject AN 07245 in Trial P028, a 51-year-old female on placebo reported a severe fall on Trial Day 49 at about 19 hours after taking trial medication. She slipped on ice while walking, and sustained severe fractures of left fibula and tibia. Later she discontinued trial medication on Day 58 because of the fractures.

Subject AN 07889 in Trial P028, a 67-year-old female on placebo reported moderate fall on Trial Day 45 (P028). She was thrown from an apparently frightened horse that she

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was riding. On falling, she sustained severe rib fractures and a moderate pneumothorax. She discontinued trial medication on Trial Day 45 because of the rib fracture.

Subject AN 04294 in Trial P009, an 87-year old female on placebo reported two ECIs, **fall** and **excessive daytime sleepiness (EDS)**, in addition to the adverse events of morning dizziness and lethargy. From Day 37, she developed intermittent dizziness and lethargy that occurred in the mornings. The dizziness lasted eight days and lethargy continued to the end of the trial. On Trial Day 85, she reported a mild fall at about 19 hours after taking trial medication. She was placing two bags of groceries on a table when she lost her balance and fell. An evaluation at the Emergency Department on the same day confirmed she had chest wall contusion and upper arm strain, though the fall was reported as mild in intensity. She interrupted her trial medication for four days. About 7 weeks later, on Trial Day 136, she reported excessive daytime sleepiness of moderate intensity, which lasted 20 days. She described the events as feeling weak after lunch and sleepy for about an hour, resulting in daily naps despite having adequate night's sleep. She discontinued trial medication on Day 154 and recovered from EDS next day. Comorbid conditions included history of drug hypersensitivity, gastrooesophageal reflux disease, hypothyroidism, osteoarthritis, deafness bilateral, hearing aid use and hypertension. Concomitant medications included furosemide, levothyroxine sodium, potassium (unspecified), ibandronate sodium, celecoxib, calcium (unspecified), vitamins (unspecified), omeprazole, ranibizumab, bevacizumab, nebivolol hydrochloride and hydrocodone. She denied use of alcohol within 24 hours prior to the events, or any history of substance abuse. Her discontinuation from the trial was because of EDS.

Subject AN 03061 in Trial P009, a 56-year old female on placebo reported a moderate fall on Trial Day 74 at about 12 hours after taking trial medication. She fell on being accidentally pushed by another person, lost consciousness, and sustained moderate fractures of the ulna and radius. She completed the trial per protocol.

Long-Term Events of Falls
At 0-6 months and at 0-12 months, the fall risks were comparable across treatment groups as shown on table above. In 0-12 months, increases in events of falls were noted in both suvorexant HD and placebo groups, with a risk difference of 0.1%. Also, falls reported as serious adverse events in the sponsor's CSS Table 2.7.4:7 were comparable between treatment groups: suvorexant HD group at 0.1% (1/1291) compared to placebo subjects at 0.2% (2/1025). In addition to the falls within 0-3 months, the assessments for 0-12 months recorded 11 more subjects with falls in the suvorexant HD group, including one of severe intensity and another with EDS; there were 6 more subjects for placebo, none was severe. I summarize the narratives of the severe falls and falls associated with EDS below:

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Subject AN 04646 in Trial P009, a 67-year old female on suvorexant HD reported a severe fall on the morning of Trial Day 356 about 7.5 hours after taking trial medication. She awoke with nausea, went to the bathroom, and sat on the toilet. She lost consciousness and was found on floor by her husband about 30 minutes later. Also she reported associated severe malaise, which she experienced in the past after previous petit mal seizures. She recovered on the day, and subsequently completed the trial per protocol.

Subject AN 02674 in Trial P009, a 43-year old white female reported a fall and excessive daytime sleepiness. She was on suvorexant HD when she reported excessive daytime sleepiness (EDS) in the morning of Trial Day 2, at about 12 hours after taking trial drug. The EDS started while she was at work and lasted four days before it subsided. During the event she had to walk about her office to stay awake. However, the EDS was of moderate intensity and required no intervention. On Trial Day 347, the subject reported a fall that occurred at about 15 hours after she took trial drug. She was carrying gifts, not seeing where she was going, she slipped on the wet floor and fell. She reported no muscle weakness, loss of consciousness, or emotional events. She had a history of slipping and falling prior to the trial, although she had none of such falls in the preceding 6 months. During this event she sustained a 5 cm contusion of the left knee, which apparently resolved by Trial Day 358. Her comorbid conditions included a history of temporomandibular joint syndrome, hypercholesterolemia, endometriosis, and seasonal allergy. Concomitant medications included estradiol, medroxyprogesterone acetate, atorvastatin calcium, sertraline hydrochloride, calcium (unspecified), vitamin D (unspecified), vitamins (unspecified). She denied use of alcohol within 24 hours prior to the event and or a history of substance abuse. She completed the trial per protocol.

Falls in the Phase 1 and Phase 2 Trials
There were no reports of falls in the earlier phase trials.

Reviewer Note: The incidence of falls in the suvorexant development program was low and the fall risks across treatment groups were comparable. An external adjudication committee of experts reviewed the fall events to assess whether they were suggestive of cataplexy. None of the cases suggested cataplexy.

Adjudicated ECIs
AEs were collected from the time of consent through the 14-day postdose follow-up telephone call. Classification of AE terms was based on the Medical Dictionary for Regulatory Activities (MedDRA) version 14.1. ECIs, which were selected non-serious AEs, were identified through spontaneous reports by the subject or upon review of subjects' data. Investigators recorded the ECIs and collected additional information to include in the trial database.

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In addition, AE data were monitored for other events that potentially suggested eligible ECIs. Such potentially eligible terms include: muscular weakness of different body areas, shoulder slumping, generalized weakness, syncope, loss of balance, and falls identified with associated AEs such fracture from a fall.

For adjudication, the trial database was periodically queried for events of cataplexy, sleep onset paralysis, and falls (to rule out cataplexy). The suvorexant adjudication charter described the standard operating procedure (SOP) used by an external Adjudication Committee to monitor for ECIs in the Phase 2 and Phase 3 trials. The committee included three experienced academic physicians, who are experts in the diagnosis and treatment of sleep disorders, as well as conduct of clinical trials.

On review of the adjudication package, the adjudicators, who were blinded to the treatment, determined whether an event met the criteria that included the following:

- Cataplexy was defined as an episode of sudden and transient loss of motor tone triggered by emotion.
- Falls were evaluated based on their potential to represent an episode of cataplexy.
- Sleep onset paralysis was defined as an episode of sleep paralysis that occurred during the transition to sleep or within the first 15 minutes of sleep.

If the event did not meet the criteria but the clinical picture was strongly suggestive of an event, the adjudicators used clinical judgment to confirm the event.

Reviewer Comment:
The procedure to identify ECIs for analysis appeared appropriate. However, the process may be limited by the extent to which the investigators were able to elicit AEs from subjects or refer potential cases for adjudication. In my analyses of the pooled suvorexant group compared to placebo, more subjects on suvorexant reported the PT of muscular weakness, which occurred in 0.6% (10/1786) in the suvorexant group compared to 0.2% (2/1028) within 0-3 months in the combined Phase 3 trials (risk difference, 0.4%; 95%CI: -0.07, 0.80). Also, I identified 5 subjects (0.3%) with sleep paralysis, which included the verbatim term sleep onset paralysis, in pooled suvorexant group and none in the placebo group. It is possible that the ECI analysis may have been strengthened by referring more events for adjudication.

Next-day Residual Effects
A major concern with the use of hypnotic sedatives is residual effects the following day. These effects may influence the ability to operate heavy machinery or drive. The sponsor assessed next day residual effects in Phase 1, Phase 2, and Phase 3 trials as shown in the table below.

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Table 100: Trials with Objective Evaluations of Next Day Residual Effects Following Night Time Dosing of Suvorexant.

Trials	Doses	Timepoints	Measurements
Phase 1 (N=125)			
Elderly driving (P039)	15 and 30 mg, MD (N=24)	Day 1 and 8 at 9hr post dose.	Driving endpoints: Standard Deviation of Lane Position Memory: Immediate and Delayed Word Recall (IDWR) Balance: body sway (A95) Psychomotor: Digit Symbol Substitution Test (DSST)
Non-elderly driving (P035)	20 and 40 mg, MD (N=28)		
COPD Study (P032)	40mg (non-elderly) 30mg (elderly), MD, (N=25)	Days 1 & 4 at 9hr post dose	Memory: IDWR Balance: body sway (A95) Psychomotor: DSST
OSA study (P036)	40mg, MD, N=26	Days 1 & 4 at 9hr post dose	Memory: IDWR Balance: body sway (A95) Psychomotor: DSST
Healthy PSG (P002)	10, 50 and 100mg, SD (N=22)	10 hr post dose	Psychomotor: Simple Reaction Time (SRT), Choice Reaction Time (CRT), DSST
Phase 2b			
Dose-Finding Trial (P006)	MK-4305 10 mg (N=62) MK-4305 20 mg (N=61) MK-4305 40 mg (N=59) MK-4305 80 mg (N=61) nightly for 4 weeks	am portion of PSG visits (Day -14, Day -7, Day 1 and Day 28 (Period 1), Day 1 and Day 28 (Period 2))	Psychomotor: DSST, Digit Symbol Copy Test
Phase 3			
Confirmatory Efficacy Trials (PQ cohorts, P028 and P029)	High dose (30 and 40 mg), N=1291; low dose (15 and 20 mg), N=493 nightly for 3 months	am portion of PSG visits (Day -14, Day-7, Day 1, Day 30, Day 90, Day 91(runout))	Psychomotor: DSST

(Source: Sponsor's submission ISS Page 629 Table 5.3.5.3.3:243)

In the trials, the sponsor examined suvorexant effects on balance and memory, psychomotor performance, and AEs identified as associated with next day residual effects. I reviewed somnolence AE, a viable measure of next day residual effects, in Section 7.3.4.

Balance and Memory Effects
In four Phase 1 trials (P032, P036, P035, P039), the sponsor used a word learning test and body sway test (Accusway) to examine the effects of suvorexant on next-day memory and balance. The driving trial P035 with healthy non-elderly subjects showed a statistically significant decrease in word recall after the words were presented to subjects in the morning 11 hours after a single dose of suvorexant 40 mg. Also a statistically significant increase on body sway area occurred in the morning 11 hours

after a single dose of either suvorexant 20 or suvorexant 40 mg. The other three trials (P032, P036, and P039) showed no significant effects on next-day memory and balance.

Psychomotor Performance
The Phase 3 trials, P028 and P029, assessed residual effects of trial medication on psychomotor performance using the Digit Symbol Substitution Test (DSST). This widely used test was performed in the mornings of the PSG visits to evaluate coordination and attention processes. DSST scores, obtained from 1,493 subjects in the phase 3 trials, were based on the number of items completed correctly, incorrectly, and the number attempted.

Analysis of psychomotor performance using DSST, and assessing number of correct responses in combined Phase 3 trial population, is shown in table below. The sponsor reported no clinically meaningful differences between each of the suvorexant groups and placebo group in the baseline-adjusted number correct responses at any time point. For example, differences in LS mean at month 3 for the suvorexant doses compared to placebo were as follows: suvorexant HD -0.8 (95% CI: -1.9, 0.3), suvorexant LD -0.5 (95% CI: -1.9, 0.8). Further, the analysis of the attempted responses by time point for the Treatment Phase also yielded similar results to those for correct responses.

Table 101: Analysis of Digit Symbol Substitution Test Number of Correct Responses by Time Point Combined Phase 3 Population: 0-3 Months

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					
MK-4305 LD	338	50.8 (14.7)	52.7 (15.4)	1.9 (8.9)	1.6 (0.8, 2.5)
MK-4305 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					
MK-4305 LD	321	51.1 (14.4)	53.1 (16.2)	2.0 (10.5)	1.8 (0.8, 2.8)
MK-4305 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					
MK-4305 LD	307	50.8 (14.1)	53.5 (14.7)	2.7 (8.6)	2.4 (1.3, 3.4)
MK-4305 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	
MK-4305 HD vs. Placebo	-0.9 (-1.8, 0.1)
MK-4305 LD vs. Placebo	-0.7 (-1.8, 0.4)
Month 1	
MK-4305 HD vs. Placebo	-0.3 (-1.4, 0.8)
MK-4305 LD vs. Placebo	-0.4 (-1.7, 0.9)
Month 3	
MK-4305 HD vs. Placebo	-0.8 (-1.9, 0.3)
MK-4305 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.

MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.

MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.

(Source: Sponsor's submission ISS Page 632 Table 5.3.5.3.3:244)

DSST by Age

The mean DSST correct responses improved from baseline at all time points among non-elderly subjects treated with either suvorexant or placebo. No significant differences were observed among the treatment groups, as shown in the table below.

Table 102: Digit Symbol Substitution Test Number of Correct Responses by Time Point Combined Phase 3 Population: 0-3 Months, Non-Elderly Subjects

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					
MK-4305 LD	193	55.3 (13.8)	57.7 (14.9)	2.4 (9.9)	2.1 (0.8, 3.3)
MK-4305 HD	335	57.4 (15.8)	58.8 (15.6)	1.4 (9.1)	1.5 (0.5, 2.4)
Placebo	332	56.5 (16.3)	58.5 (16.4)	1.9 (8.9)	2.0 (1.0, 2.9)
Month 1					
MK-4305 LD	186	55.6 (13.2)	57.8 (15.6)	2.2 (11.1)	1.9 (0.5, 3.3)
MK-4305 HD	323	57.1 (14.8)	59.2 (15.1)	2.1 (10.0)	2.2 (1.2, 3.2)
Placebo	312	56.7 (16.2)	58.7 (15.6)	2.0 (9.5)	2.0 (1.0, 3.1)
Month 3					
MK-4305 LD	175	55.5 (12.8)	57.9 (14.0)	2.4 (8.9)	2.2 (0.7, 3.6)
MK-4305 HD	304	57.4 (14.9)	59.6 (15.4)	2.2 (11.3)	2.3 (1.2, 3.4)
Placebo	292	56.5 (16.2)	59.1 (15.9)	2.6 (10.6)	2.6 (1.5, 3.8)

Pairwise Comparison	Difference in LS Means (95% CI)†
Night 1	
MK-4305 HD vs. Placebo	-0.5 (-1.8, 0.8)
MK-4305 LD vs. Placebo	0.1 (-1.5, 1.7)
Month 1	
MK-4305 HD vs. Placebo	0.2 (-1.3, 1.7)
MK-4305 LD vs. Placebo	-0.1 (-1.9, 1.6)
Month 3	
MK-4305 HD vs. Placebo	-0.3 (-1.9, 1.2)
MK-4305 LD vs. Placebo	-0.5 (-2.3, 1.4)

† 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.

MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.

MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.

(Source: Sponsor's submission ISS Page 636 Table 5.3.5.3.3:248)

In elderly subjects, mean DSST correct responses also improved from baseline at all time points, which the sponsor attributed to the learning effect generally observed with this assessment. However, On Night 1, placebo subjects showed greater performance than suvorexant-treated subjects as shown in table below.

Table 103: Digit Symbol Substitution Test Number of Correct Responses by Time Point Combined Phase 3 Population: 0-3 Months, Elderly Subjects

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					
MK-4305 LD	145	44.7 (13.7)	46.0 (13.4)	1.2 (7.5)	1.1 (-0.1, 2.3)
MK-4305 HD	242	46.3 (17.2)	47.5 (16.2)	1.2 (8.0)	1.4 (0.5, 2.3)
Placebo	246	45.2 (12.7)	48.2 (12.4)	3.0 (7.4)	2.9 (2.0, 3.8)
Month 1					
MK-4305 LD	135	44.9 (13.7)	46.6 (14.6)	1.8 (9.7)	1.6 (0.1, 3.2)
MK-4305 HD	237	46.7 (17.3)	47.9 (16.3)	1.1 (10.9)	1.4 (0.2, 2.5)
Placebo	239	45.4 (13.1)	47.9 (13.1)	2.5 (8.4)	2.4 (1.3, 3.5)
Month 3					
MK-4305 LD	132	44.6 (13.3)	47.7 (13.7)	3.1 (8.2)	2.7 (1.2, 4.1)
MK-4305 HD	222	47.0 (17.5)	48.5 (16.8)	1.4 (9.7)	1.9 (0.8, 3.0)
Placebo	224	45.4 (12.8)	48.9 (13.9)	3.5 (9.0)	3.3 (2.2, 4.5)

Pairwise Comparison	Difference in LS Means (95% CI)†
Night 1	
MK-4305 HD vs. Placebo	-1.5 (-2.8, -0.2)
MK-4305 LD vs. Placebo	-1.8 (-3.3, -0.3)
Month 1	
MK-4305 HD vs. Placebo	-1.0 (-2.6, 0.6)
MK-4305 LD vs. Placebo	-0.8 (-2.7, 1.2)
Month 3	
MK-4305 HD vs. Placebo	-1.5 (-3.1, 0.1)
MK-4305 LD vs. Placebo	-0.7 (-2.5, 1.2)

† 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.

MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.

MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.

(Source: Sponsor's submission ISS Page 637 Table 5.3.5.3.3:249)

In the Phase 2 trial P006, the sponsor reported that the baseline-adjusted number correct on DSST assessment was generally not different between suvorexant doses and placebo, and that the confidence intervals for comparisons between suvorexant and placebo all included 0, except for an isolated case on Day 1 for suvorexant 20 mg. The results for DSST attempted responses by time point were similar to those of the correct responses.

In five Phase 1 trials (P002, P035, P039, P032, P036), the sponsor used DSST, simple reaction time (SRT), and choice reaction time (CRT) to evaluate psychomotor performance 9 to 11 hours post nighttime dose of suvorexant in 125 subjects. Trial P002 tested single doses of suvorexant 10 mg to 100 mg in 22 males aged 18 to 44 years. P035 and P039 were driving trials in non-elderly and elderly subjects, respectively; each trials tested suvorexant LD (15 mg or 20 mg) and suvorexant HD (30

mg or 40 mg). Trials P032 and P036 assessed respiratory safety in subjects with COPD and OSA, respectively; both trials evaluated the suvorexant HD dose. Only the driving trial (PN035) in healthy non-elderly subjects showed a statistically significant decrease in number of correct for DSST (3 item decrease) at 11 hr after a single dose of suvorexant 40 mg compared to placebo. However, the same study failed to show such significant effects on DSST following 8-day consecutive doses of suvorexant.

Reviewer Note: Although four of five trials failed to show significant treatment effects on DSST (# of correct) with suvorexant compared to placebo, the results of the driving trial PN035 in healthy non-elderly subjects suggests suvorexant 40 mg can impair psychomotor performance after a single dose. Also in the Phase 3 trials, the point estimates of the DSST correct responses suggest that subjects on suvorexant LD or HD have reduced number of correct responses, though not statistically significant, compared to placebo. Despite, the clinical significance of the differences observed is unclear.

Specific AEs Associated with Residual Effects
The sponsor's ISS Table 5.3.5.3.3:256 showed the AEs associated with residual effects. Somnolence had the highest incidence: suvorexant HD 10.7% (138/1291); suvorexant LD 6.7% (33/493); and placebo 3.0% (31/1025). Fatigue occurred less frequently: suvorexant HD 3.8% (49/1291); suvorexant LD 2.2% (11/493); and placebo 1.8% (18/1025.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The sponsor reported a higher incidence of any AEs in suvorexant HD subjects with 51.0% (658/1291) compared to suvorexant LD with 46.5% (229/493) or placebo 46.6% (478/1025). Similarly, in subjects treated for up to 12 months in the combined phase 3 population, more AEs occurred in the suvorexant HD group (59.9%) than in placebo (52.7%). As shown in the table below, suvorexant HD also had more subjects who discontinued the trial because of AEs within 0-3 months.

Table 104: Adverse Event Categories in Combined Phase 3 Trial Populations

Category	Placebo (N=1025)	Suvorexant LD (N=493)	Suvorexant HD (N=1291)
Any Adverse Event (AEs)	478 (46.6%)	229 (46.5%)	658 (51.0%)
AEs with trial discontinuation	50 (4.9%)	15 (3.0%)	80 (6.2%)

Deaths	1 (0.0%)	0 (0.0%)	1 (0.0%)
Serious AEs	23 (2.2%)	3 (0.6%)	18 (1.4%)

(Source: Modified from Sponsor's submission ISS Page 138 Table 5.3.5.3.3:13)

The table below summarizes the common AEs, which occurred at an incidence of at least 2% in one or more treatment groups, by system organ class (SOC) and treatment group in the Combined Phase 3 Population within 0-3 Months. In that first 3 months of treatment, subjects on suvorexant HD reported more adverse events in the Nervous system disorders SOC with 21.4% (276/1291) compared to suvorexant LD 16.8% (83/493) or placebo13.2% (135/1025). Infections and infestations SOC had similar incidences among the treatment groups.

The most common AEs, having incidence 2% or more that occurred more frequently in the suvorexant group than placebo were somnolence and fatigue. Other AEs were slightly more frequent in the suvorexant group: headache, abnormal dreams, dry mouth, and upper respiratory tract infection. Headache events in the first 3 months in the combined Phase 3 population was more frequent from suvorexant treatment, but without a dose-response relationship: 6.6% (85/1291) of suvorexant HD group, 7.3% (36/493) suvorexant LD, and 6.0% (61/1025) placebo. Falls and AEs related to motor vehicle accidents were infrequent and appeared not related to treatment.

Table 105: Adverse Events (AEs) by System Organ Class (SOC) and AE Preferred Term (PT) ≥ 2% in One or More Treatment Groups in Combined Phase 3 Population 0-3 Months (P028, P029, and P009)

System Organ Class (SOC) AE Preferred Term (PT)	**Placebo (N=1025)** n (%)	**Suvorexant LD (N=493)** n (%)	**Suvorexant HD (N=1291)** n (%)
Eye disorders	**18 (1.8)**	**11 (2.2)**	**23 (1.8)**
Gastrointestinal disorders	**82 (8.0)**	**39 (7.9)**	**121 (9.4)**
Diarrhea	15 (1.5)	12 (2.4)	21 (1.6)
Dry mouth	14 (1.4)	9 (1.8)	36 (2.8)
Nausea	16 (1.6)	7 (1.4)	27 (2.1)
General disorders and administration site conditions	**46 (4.5)**	**31 (6.3)**	**92 (7.1)**
Fatigue	18 (1.8)	11(2.2)	49 (3.8)
Infections and infestations	**147 (14.3)**	**70 (14.2)**	**161 (12.5)**
Nasopharyngitis	56 (5.5)	26 (5.3)	49 (3.8)
Upper respiratory tract infection	12 (1.2)	8 (1.6)	28 (2.2)
Urinary tract infection	20 (2.0)	8 (1.6)	15 (1.2)
Injury, poisoning and procedural complications	**57 (5.6)**	**31 (6.3)**	**62 (4.8)**
Drug administration error	23 (2.2)	16 (3.2)	25 (1.9)

Investigations	**39 (3.8)**	**22 (4.5)**	**57 (4.4)**
Metabolism and nutrition disorders	**9 (0.9)**	**4 (0.8)**	**31 (2.4)**
Musculoskeletal and connective tissue disorders	**80 (7.8)**	**25 (5.1)**	**107 (8.3)**
Back pain	23 (2.2)	7 (1.4)	16 (1.2)
Nervous system disorders	**135 (13.2)**	**83 (16.8)**	**276 (21.4)**
Dizziness	29 (2.8)	15 (3.0)	32 (2.5)
Headache	61 (6.0)	36 (7.3)	85 (6.6)
Somnolence	31 (3.0)	33 (6.7)	138 (10.7)
Psychiatric disorders	**32 (3.1)**	**28 (5.7)**	**85 (6.6)**
Abnormal dreams	10 (1.0)	9 (1.8)	27 (2.1)
Respiratory, thoracic and mediastinal disorders	**28 (2.7)**	**18 (3.7)**	**48 (3.7)**
Skin and subcutaneous tissue disorders	**29 (2.8)**	**18 (3.7)**	**34 (2.6)**

(Source: Sponsor's submission ISS Page 146 Table 5.3.5.3.3.:15)

Common AEs in 0-6 months
In the 0-6 months Phase 3 trial population (P028 and P029), 49.3% (243/493) of the subjects who received suvorexant LD reported one or more AE; this incidence was comparable to 49.0% (376/767) in the placebo group. Below I summarize the common AEs that occurred with an incidence ≥2% in a treatment group in the 6 months treatment period.

Table 106: Adverse Events ≥ 2% of Subjects in Suvorexant Low Dose or Placebo Group in the Combined Phase 3 Population 0-6 Months (P028 and P029)

System Organ Class (SOC) AE Preferred Term (PT)	**Placebo** (N = 767) n (%)	**Suvorexant LD** (N = 493) n (%)
Cardiac disorders	**16 (2.1)**	**9 (1.8)**
Eye disorders	**14 (1.8)**	**11 (2.2)**
Gastrointestinal disorders	**63 (8.2)**	**40 (8.1)**
Diarrhea	11(1.4)	12 (2.4)
General disorders and administration site conditions	**37 (4.8)**	**32 (6.5)**
Fatigue	14 (1.8)	11 (2.2)
Infections and infestations	**128 (16.7)**	**77 (15.6)**
Nasopharyngitis	47 (6.1)	29 (5.9)
Urinary tract infection	20 (2.6)	8 (1.6)
Injury, poisoning and procedural complications	**47 (6.1)**	**38 (7.7)**
Drug administration error	19 (2.5)	20 (4.1)
Investigations	**30 (3.9)**	**23 (4.7)**

Musculoskeletal and connective tissue disorders Back pain	**62 (8.1)** 22 (2.9)	**30 (6.1)** 8 (1.6)
Nervous system disorders Dizziness Headache Somnolence	**102 (13.3)** 19 (2.5) 46 (6.0) 26 (3.4)	**85 (17.2)** 15 (3.0) 37 (7.5) 34 (6.9)
Psychiatric disorders Abnormal dreams	**21(2.7)** 5 (0.7)	**30 (6.1)** 10 (2.0)
Respiratory, thoracic and mediastinal disorders Cough	**21 (2.7)** 8 (1.0)	**19 (3.9)** 10 (2.0)
Skin and subcutaneous tissue disorders	**28 (3.7)**	**21 (4.3)**

(Source: Sponsor's submission ISS Page 740 Table Appendix 5.3.5.3.3:16)

Common Adverse Events 0-12months

In the period of 0-12 months, subjects in the suvorexant HD group had a higher incidence of AEs (59.9%, 773/1291) compared to placebo (52.7%, 540/1025). AEs in the Nervous system disorders SOC occurred most frequently and at a higher rate in the suvorexant HD group (24.9%, 322/1291) compared to placebo (15.3%, 157/1025). Somnolence was more frequently reported in subjects treated with suvorexant HD (11.7%, 151/1291) than placebo (3.2%, 33/1025). Fatigue occurred in 4.7% (61/1291) in the suvorexant group compared to 1.9% (19/1025) in placebo. Abnormal dreams in subjects treated for over 3 months occurred in 2.6% (34/1291) of the suvorexant group compared to 1.1% (11/1025) of placebo.

Below I summarize the common AEs that occurred with an incidence ≥2% in a treatment group in the 6 months treatment period.

Table 107: Adverse Events ≥ 2% of Subjects in Suvorexant High Dose or Placebo Group in the Combined Phase 3 Population 0-12 Months (P028, P029 and P009)

System Organ Class (SOC) AE Preferred Term (PT)	**Placebo** (N = 1025) n (%)	**Suvorexant HD** (N = 1291) n (%)
Cardiac disorders	**24 (2.3)**	**26 (2.0)**
Eye disorders	**25 (2.4)**	**35 (2.7)**
Gastrointestinal disorders Diarrhea Dry mouth Nausea	**98 (9.6)** 20 (2.0) 15 (1.5) 20 (2.0)	**160 (12.4)** 26 (2.0) 43 (3.3) 33 (2.6)
General disorders and administration site conditions Fatigue	**53 (5.2)** 19 (1.9)	**120 (9.3)** 61 (4.7)

Infections and infestations	**194 (18.9)**	**257 (19.9)**
Influenza	16 (1.6)	30 (2.3)
Nasopharyngitis	67 (6.5)	95 (7.4)
Upper respiratory tract infection	19 (1.9)	37 (2.9)
Urinary tract infection	26 (2.5)	21 (1.6)
Injury, poisoning and procedural complications	**78 (7.6)**	**99 (7.7)**
Drug administration error	31 (3.0)	32 (2.5)
Investigations	**57 (5.6)**	**85 (6.6)**
Metabolism and nutrition disorders	**15 (1.5)**	**38 (2.9)**
Musculoskeletal and connective tissue disorders	**104 (10.1)**	**163 (12.6)**
Arthralgia	18 (1.8)	29 (2.2)
Musculoskeletal and connective tissue disorders	**104 (10.1)**	**163 (12.6)**
Back pain	29 (2.8)	25 (1.9)
Nervous system disorders	**157 (15.3)**	**322 (24.9)**
Dizziness	35 (3.4)	41 (3.2)
Headache	68 (6.6)	101 (7.8)
Somnolence	33 (3.2)	151 (11.7)
Psychiatric disorders	**36 (3.5)**	**107 (8.3)**
Abnormal dreams	11 (1.1)	34 (2.6)
Nightmare	7 (0.7)	27 (2.1)
Respiratory, thoracic and mediastinal disorders	**39 (3.8)**	**72 (5.6)**
Skin and subcutaneous tissue disorders	**37 (3.6)**	**42 (3.3)**
Vascular disorders	**17 (1.7)**	**29 (2.2)**

(Source: Sponsor's submission ISS Page 714 Table Appendix 5.3.5.3.3:13)

Common AEs in Phase 2 Dose-Finding Trial

In the Phase 2 trial, more subjects who received suvorexant reported AEs (25.9%, 63/243) compared to placebo (20.1%, 50/249). The increase in the frequency of AEs was particularly evident at suvorexant doses of 40 mg and 80 mg as shown in the table below. Consistent with the Phase 3 trial experience, AEs in the Nervous system disorders SOC occurred most frequently than other categories. AEs were more frequent at higher suvorexant doses. Somnolence was more frequently reported in subjects treated with suvorexant in a dose-related manner. Below I summarize the common AEs that occurred with an incidence ≥2% in one or more treatments group in the Phase 2 trial P006.

Table 108: Adverse Events ≥ 2% of Subjects by Treatment Group in Phase 2 Population (P006)

System Organ Class (SOC) AE Preferred Term	Placebo n (%)	Suvorexant 10 mg n (%)	Suvorexant 20 mg n (%)	Suvorexant 40 mg n (%)	Suvorexant 80 mg n (%)	Total Suvorexant n (%)
Subjects in population	249	62	61	59	61	243
Subjects with one or more adverse events	50 (20.1)	11 (17.7)	12 (19.7)	18 (30.5)	22 (36.1)	63 (25.9)
Gastrointestinal disorders	**8 (3.2)**	**1 (1.6)**	**1 (1.6)**	**1 (1.7)**	**3 (4.9)**	**6 (2.5)**
General disorders and administration site conditions	**4 (1.6)**	**0 (0.0)**	**1 (1.6)**	**3 (5.1)**	**2 (3.3)**	**6 (2.5)**
Infections and infestations	**7 (2.8)**	**2 (3.2)**	**3 (4.9)**	**3 (5.1)**	**4 (6.6)**	**12 (4.9)**
Upper respiratory tract infection	1 (0.4)	1 (1.6)	2 (3.3)	0 (0.0)	2 (3.3)	5 (2.1)
Urinary tract infection	2 (0.8)	0 (0.0)	0 (0.0)	3 (5.1)	2 (3.3)	5 (2.1)
Investigations	**6 (2.4)**	**5 (8.1)**	**1 (1.6)**	**3 (5.1)**	**2 (3.3)**	**11 (4.5)**
Alanine aminotransferase increased	1 (0.4)	1 (1.6)	0 (0.0)	2 (3.4)	1 (1.6)	4 (1.6)
Blood creatine phosphokinase increased	2 (0.8)	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)	2 (0.8)
Musculoskeletal and connective tissue disorders	**5 (2.0)**	**1 (1.6)**	**0 (0.0)**	**4 (6.8)**	**1 (1.6)**	**6 2.5)**
Muscular weakness	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.4)	1 (1.6)	3 (1.2)
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)
Respiratory, thoracic and mediastinal disorders	**5 (2.0)**	**0 (0.0)**	**0 (0.0)**	**2 (3.4)**	**2 (3.3)**	**4 (1.6)**
Oropharyngeal pain	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)	2 (0.8)

(Source: Sponsor's submission ISS Page 787 Table Appendix 5.3.5.3.3:24)

Drug-Related Adverse Events

In the Phase 3 trials 0-3 months, a higher incidence of drug-related AEs occurred in subjects who received suvorexant HD (25.5%, 329/1291) compared to those who received suvorexant LD (22.1%, 109/493) or placebo (15.0%, 154/1025). Below I summarize occurrence of the dose-related AEs.

Table 109: Drug-related AEs ≥ 2% in One or More Treatment Groups in the Combined Phase 3 Population 0-3 Months (P028, P029, and P009)

System Organ Class (SOC) AE Preferred Term (PT)	**Placebo** **(N = 1,025)** **n (%)**	**Suvorexant LD** **(N = 493)** **n (%)**	**Suvorexant HD** **(N = 1,291)** **n (%)**
Gastrointestinal disorders	**31 (3.0)**	**17 (3.4)**	**65 (5.0)**
Dry mouth	11 (1.1)	8 (1.6)	32 (2.5)
General disorders and administration site conditions	**24 (2.3)**	**20 (4.1)**	**64 (5.0)**
Fatigue	13 (1.3)	11 (2.2)	40 (3.1)
Investigations	**14 (1.4)**	**12 (2.4)**	**22 (1.7)**
Nervous system disorders	**82 (8.0)**	**58 (11.8)**	**200 (15.5)**
Headache	31 (3.0)	21 (4.3)	36 (2.8)
Somnolence	26 (2.5)	30 (6.1)	126 (9.8)
Psychiatric disorders	**25 (2.4)**	**19 (3.9)**	**60 (4.6)**

(Source: Sponsor's submission ISS Page 156 Table 5.3.5.3.3.:17)

Drug-related AEs during Long-term Treatment
In the 0-6 months Phase 3 trial population (P028 and P029), AEs with incidence ≥1% in a treatment group occurred more frequently in subjects who received suvorexant LD (22.5%, 111/493) compared to those who received placebo (15.6%, 120/767). Below I summarize the analyses of drug-related AEs covering 6 months treatment

Table 110: Drug-related AEs ≥ 1% in One or More Treatment Groups in the Combined Phase 3 Population 0-6 Months (P028 and P029)

System Organ Class (SOC) AE Preferred Term (PT)	**Placebo** (N = 767) n (%)	**Suvorexant LD** (N = 493) n (%)	**Suvorexant-Placebo Difference in %**
			Estimate (95% CI)

Gastrointestinal disorders Dry mouth Nausea	**19 (2.5)** 8 (1.0) 8 (1.0)	**17 (3.4)** 8 (1.6) 6 (1.2)	**1.0 (-0.9, 3.2)** 0.6 (-0.7, 2.2) 0.2 (-1.0, 1.7)
General disorders and administration site conditions Fatigue	**19 (2.5)** 11 (1.4)	**20 (4.1)** 11 (2.2)	**1.6 (-0.4, 3.9)** 0.8 (-0.7, 2.6)
Investigations	**11 (1.4)**	**12 (2.4)**	**1.0 (-0.5, 2.9)**
Musculoskeletal and connective tissue disorders	**8 (1.0)**	**5 (1.0)**	**-0.0 (-1.2, 1.4)**
Nervous system disorders Dizziness Headache Somnolence	**65 (8.5)** 10 (1.3) 24 (3.1) 24 (3.1)	**59 (12.0)** 8 (1.6) 21 (4.3) 31 (6.3)	**3.5 (0.1, 7.1)** 0.3 (-1.0, 2.0) 1.1 (-0.9, 3.5) 3.2 (0.8, 5.9)
Psychiatric disorders Abnormal dreams Nightmare	**19 (2.5)** 5 (0.7) 4 (0.5)	**20 (4.1)** 8 (1.6) 6 (1.2)	**1.6 (-0.4, 3.9)** 1.0 (-0.2, 2.6) 0.7 (-0.3, 2.2)
Skin and subcutaneous tissue disorders	**6 (0.8)**	**8 (1.6)**	**0.8 (-0.3, 2.5)**

(Source: Sponsor's submission ISS Page 822 Table 5.3.5.3.3.:33)

In the 12 months Combined Phase 3 Trial Population (P028, P029 and P009), subjects who received suvorexant HD reported more drug-related AEs with an incidence ≥1% in at least one of the treatment groups compared to subjects who received placebo: 28.5% (368/1291) in suvorexant HD compared to 16.9% (173/1025) in placebo. Again, nervous system disorders accounted for the most frequent drug-related AEs, as shown in the table below. Dizziness, headache, and somnolence occurred at incidences of over 2%; and, somnolence occurred more frequently in the suvorexant HD group (10.5%, 136/1291) than in the placebo group (2.7%, 28/1025).

Table 111: Drug-related AEs ≥ 1% in One or More Treatment Groups in the Combined Phase 3 Population 0-12 Months (P028, P029 and P009)

System Organ Class (SOC) AE Preferred Term (PT)	**Placebo** (N = 1025) n (%)	**Suvorexant HD** (N = 1291) n (%)	**Suvorexant-Placebo Difference in %** Estimate (95% CI)
Gastrointestinal disorders Dry mouth Nausea	**33 (3.2)** 12 (1.2) 11 (1.1)	**73 (5.7)** 37 (2.9) 18 (1.4)	**1.9 (0.1, 3.6)** 1.5 (0.3, 2.7) 0.3 (-0.7, 1.2)
General disorders and administration site conditions Fatigue	**26 (2.5)** 14 (1.4)	**72 (5.6)** 45 (3.5)	**3.0 (1.4, 4.6)** 2.1 (0.8, 3.4)
Investigations	**19 (1.9)**	**30 (2.3)**	**0.3 (-1.0, 1.5)**

Metabolism and nutrition disorders	**5 (0.5)**	**16 (1.2)**	**0.8 (-0.0, 1.6)**
Musculoskeletal and connective tissue disorders	**10 (1.0)**	**22 (1.7)**	**0.7 (-0.3, 1.7)**
Nervous system disorders	**90 (8.8)**	**222 (17.2)**	**8.0 (5.2, 10.7)**
Dizziness	20 (2.0)	24 (1.9)	-0.4 (-1.7, 0.7)
Headache	32 (3.1)	42 (3.3)	0.1 (-1.4, 1.6)
Somnolence	28 (2.7)	136 (10.5)	7.8 (5.9, 9.8)
Psychiatric disorders	**27 (2.6)**	**71 (5.5)**	**2.6 (0.9, 4.2)**
Abnormal dreams	10 (1.0)	28 (2.2)	1.0 (-0.1, 2.1)
Nightmare	6 (0.6)	21 (1.6)	1.0 (0.1, 1.9)
Skin and subcutaneous tissue disorders	**8 (0.8)**	**13 (1.0)**	**0.2 (-0.7, 1.0)**

(Source: Sponsor's submission ISS Page 811 Table 5.3.5.3.3.:30)

Drug-Related Adverse Events in Phase 2 Dose-Finding Trial P006
The Phase 2 trial reported drug-related AEs in the Nervous system disorders SOC more frequently than other systems. Below I summarize dose-related occurrence of the AEs from the Phase 2 trial P006.

Table 112: Suvorexant-Related Adverse Events with Incidence > 2% for One or More Treatments among All Treated Subjects in Treatment Periods 1 and 2 of Trial P006

Category	**Placebo N (%)**	**Suvorexant 10 mg N (%)**	**Suvorexant 20 mg N (%)**	**Suvorexant 40 mg N (%)**	**Suvorexant 80 mg N (%)**	**Total Suvorexant N (%)**
Subjects	249	62	61	59	61	243
Subjects with one or more adverse events	17 (6.8)	3 (4.8)	4 (6.6)	13 (22.0)	14 (23.0)	34 (14.0)
General disorders and administration site conditions	**1 (0.4)**	**0 (0.0)**	**0 (0.0)**	**2 (3.4)**	**2 (3.3)**	**4 (1.6)**
Musculoskeletal and connective tissue disorders	**3 (1.2)**	**0 (0.0)**	**0 (0.0)**	**3 (5.1)**	**1 (1.6)**	**4 (1.6)**
Muscular weakness	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.4)	1 (1.6)	3 (1.2)
Nervous system disorders	**5 (2.0)**	**1 (1.6)**	**3 (4.9)**	**10 (16.9)**	**10 (16.4)**	**24 (9.9)**
Headache	3 (1.2)	0 (0.0)	0 (0.0)	3 (5.1)	1 (1.6)	4 (1.6)
Sedation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)	2 (0.8)
Somnolence	1 (0.4)	0 (0.0)	3 (4.9)	7 (11.9)	6 (9.8)	16 (6.6)

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)

(Source: Modified from Sponsor's submission CSR P006 Page 158 Table 12-8)

Reviewer Comments: Although the above analyses on drug-relatedness of AEs were presented by Merck, the procedures used to determine and analyze the drug-relatedness of AEs appear appropriate. In assessing the relationship between AEs and treatment, a physician investigator determined the likelihood that the test drug caused the adverse experience. The sponsor provided reference guidelines to aid the investigator in determining the drug-relatedness of the AE. The components that were used to assess the relationship between the test drug and the AE include: evidence of drug exposure, reasonable temporal sequence from drug administration to AE occurrence, absence of competing etiology, AE resolved on dechallenge, AE recurs or worsens on approved rechallenge, and AE consistent with known drug profile. These guidelines appear reasonable. I further examined the drug-relatedness of AEs in section 7.5.1 Dose Dependency for AEs.

7.4.2 Laboratory Findings

The sponsor evaluated laboratory results using mean changes from baseline over time and values that met predetermined criteria for change relative to normal range. The laboratory results in hematology and chemistry categories are summarized as follows:

Hematology

The mean changes in hematological parameters from baseline to Month 3 were generally comparable among the treatment groups. The table below shows a summary of the results.

Table 113: Hematology Mean Changes from Baseline to Month 3 in Combined Phase 3 Population 0-3 months (P028, P029, and P009)

		n	Baseline		Value		Change from Baseline	
Visit	**Treatment**		**Mean (SD)**	**[Min, Max]**	**Mean (SD)**	**[Min, Max]**	**Mean (SD)**	**[Min, Max]**
Basophils (10^3/microL)								
Month 3	Suvorexant LD	424	0.00 (0.02)	[0.0, 0.2]	0.00 (0.02)	[0.0, 0.1]	-0.00 (0.03)	[-0.2, 0.1]
	Suvorexant HD	1118	0.01 (0.02)	[0.0, 0.2]	0.01 (0.03)	[0.0, 0.2]	0.00 (0.03)	[-0.2, 0.1]
	Placebo	875	0.01 (0.02)	[0.0, 0.1]	0.01 (0.02)	[0.0, 0.2]	-0.00 (0.03)	[-0.1, 0.2]
Eosinophils (10^3/microL)								
Month 3	Suvorexant LD	424	0.17 (0.14)	[0.0, 1.4]	0.18 (0.14)	[0.0, 1.3]	0.01 (0.12)	[-1.2, 0.5]
	Suvorexant HD	1118	0.17 (0.14)	[0.0, 1.2]	0.18 (0.17)	[0.0, 2.5]	0.01 (0.13)	[-0.5, 2.4]
	Placebo	875	0.19 (0.18)	[0.0, 2.9]	0.19 (0.17)	[0.0, 1.8]	0.00 (0.13)	[-1.1, 1.1]

Hematocrit (%)								
Month 3	Suvorexant LD	424	41.73 (4.33)	[27.3, 80.3]	41.31 (4.01)	[25.6, 54.7]	-0.42 (3.06)	[-43.7, 6.1]
	Suvorexant HD	1119	41.61 (3.88)	[29.3, 60.9]	41.45 (3.92)	[27.5, 55.5]	-0.16 (2.25)	[-15.8, 13.6]
	Placebo	878	41.64 (3.80)	[31.1, 56.5]	41.57 (3.98)	[23.4, 57.5]	-0.07 (2.50)	[-13.2, 20.3]
Hemoglobin (g/L)								
Month 3	Suvorexant LD	424	13.96 (1.52)	[7.7, 26.4]	13.78 (1.42)	[7.1, 18.1]	-0.18 (0.96)	[-13.7, 2.1]
	Suvorexant HD	1119	13.98 (1.33)	[9.0, 20.1]	13.86 (1.33)	[8.4, 18.0]	-0.12 (0.70)	[-5.1, 4.8]
	Placebo	878	13.95 (1.30)	[10.1, 18.0]	13.88 (1.36)	[8.0, 19.3]	-0.07 (0.77)	[-3.4, 6.5]
Lymphocytes (10^3/microL)								
Month 3	Suvorexant LD	424	2.11 (0.67)	[0.7, 4.5]	2.09 (0.67)	[0.5, 4.2]	-0.02 (0.46)	[-2.2, 1.9]
	Suvorexant HD	1118	1.99 (0.65)	[0.7, 6.3]	1.98 (0.65)	[0.6, 6.9]	-0.02 (0.48)	[-2.4, 3.0]
	Placebo	875	2.09 (0.70)	[0.7, 5.5]	2.08 (0.70)	[0.5, 6.3]	-0.02 (0.54)	[-2.9, 4.4]
Monocytes (10^3/microL)								
Month 3	Suvorexant LD	424	0.40 (0.24)	[0.0, 3.2]	0.40 (0.21)	[0.0, 3.1]	0.01 (0.24)	[-2.6, 2.5]
	Suvorexant HD	1118	0.41 (0.18)	[0.0, 1.5]	0.39 (0.16)	[0.0, 1.2]	-0.02 (0.16)	[-0.8, 0.9]
	Placebo	875	0.40 (0.17)	[0.0, 1.5]	0.40 (0.17)	[0.0, 1.3]	0.00 (0.16)	[-0.6, 0.8]
Neutrophils (10^3/microL)								
Month 3	Suvorexant LD	424	3.50 (1.27)	[0.2, 8.1]	3.47 (1.39)	[0.4,10.8]	-0.04 (1.23)	[-6.2, 6.8]
	Suvorexant HD	1118	3.66 (1.34)	[0.4, 11.6]	3.54 (1.31)	[0.4, 12.4]	-0.12 (1.20)	[-7.0, 6.2]
	Placebo	875	3.58 (1.37)	[0.4, 9.3]	3.58 (1.39)	[0.1, 11.1]	-0.00 (1.18)	[-6.5, 7.6]
Platelets (10^3/microL)								
Month 3	Suvorexant LD	419	232.2 (58.1)	[67, 551]	230.9 (59.5)	[41, 571]	-1.2 (33.6)	[-224, 222]
	Suvorexant HD	1085	228.8 (54.4)	[111, 621]	226.3 (54.6)	[98, 795]	-2.5 (27.9)	[-128, 174]
	Placebo	850	233.9 (54.0)	[101, 586]	233.5 (55.0)	[101, 571]	-0.4 (31.3)	[-204, 162]
Leukocytes (10^3/microL)								
Month 3	Suvorexant LD	424	6.21 (1.63)	[2.3, 11.5]	6.17 (1.72)	[2.4, 13.3]	-0.04 (1.33)	[-5.6, 6.3]
	Suvorexant HD	1119	6.26 (1.62)	[2.8, 15.7]	6.12 (1.62)	[2.5, 17.0]	-0.14 (1.28)	[-6.3, 5.6]
	Placebo	878	6.30 (1.75)	[2.2, 14.4]	6.28 (1.78)	[2.3, 16.1]	-0.02 (1.27)	[-6.3, 7.4]

(Source: Sponsor's submission ISS Page 942 Table Appendix 5.3.5.3.3:48)

Chemistry

The sponsor observed no clinically significant mean changes for the chemistry parameters in the different treatment groups from baseline to Month 3. The table below shows a summary of the results.

Table 114: Chemistry Mean Changes from Baseline to Month 3 in Combined Phase 3 Population 0-3 months (P028, P029, and P009)

			Baseline		Value		Change from Baseline	
Visit	**Treatment**	**n**	**Mean (SD)**	**[Min, Max]**	**Mean (SD)**	**[Min, Max]**	**Mean (SD)**	**[Min, Max]**
Albumin (g/dL)								

Month 3	Suvorexant LD	437	4.40 (0.28)	[3.5, 5.3]	4.36 (0.30)	[3.3, 5.2]	-0.04 (0.28)	[-0.8, 0.8]
	Suvorexant HD	1140	4.42 (0.27)	[3.3, 5.6]	4.36 (0.27)	[3.4, 5.3]	-0.06 (0.26)	[-1.1, 0.9]
	Placebo	900	4.41 (0.27)	[3.4, 5.4]	4.37 (0.28)	[3.2, 5.6]	-0.04 (0.26)	[-1.2, 1.2]
Alkaline Phosphatase (U/L)								
Month 3	Suvorexant LD	436	69.4 (21.9)	[15, 239]	70.4 (23.2)	[25, 282]	1.0 (11.5)	[-47, 108]
	Suvorexant HD	1134	70.7 (21.7)	[11, 309]	69.6 (20.1)	[12, 190]	-1.2 (11.9)	[-248, 73]
	Placebo	899	71.0 (21.0)	[26, 166]	71.2 (22.0)	[25, 238]	0.1 (10.8)	[-64, 90]
ALT (U/L)								
Month 3	Suvorexant LD	436	19.6 (9.7)	[6, 66]	19.1 (10.5)	[4, 88]	-0.5 (8.7)	[-38, 62]
	Suvorexant HD	1139	20.6 (10.3)	[4, 95]	20.0 (13.5)	[4, 246]	-0.6 (11.9)	[-78, 216]
	Placebo	900	20.3 (10.1)	[4, 88]	20.8 (11.5)	[4, 100]	0.5 (8.7)	[-51, 65]
Amylase (U/L)								
Month 1	Suvorexant HD	421	73.4 (30.4)	[25, 243]	72.5 (36.5)	[14, 503]	-0.9 (26.0)	[-67, 445]
	Placebo	207	71.4 (34.0)	[21, 349]	68.1 (37.4)	[7, 416]	-3.3 (16.3)	[-73, 67]
AST (U/L)								
Month 3	Suvorexant LD	437	21.5 (6.9)	[9, 64]	21.3 (7.5)	[10, 63]	-0.3 (6.4)	[-23, 38]
	Suvorexant HD	1140	21.7 (6.6)	[8, 78]	21.6 (8.8)	[9, 191]	-0.1 (8.4)	[-54, 167]
	Placebo	900	21.7 (6.4)	[7, 55]	22.1 (7.5)	[7, 74]	0.3 (6.3)	[-30, 53]
Bilirubin (mg/dL)								
Month 3	Suvorexant LD	437	0.536 (0.263)	[0.16, 2.53]	0.513 (0.254)	[0.14, 2.03]	-0.022 (0.193)	[-1.09, 1.10]
	Suvorexant HD	1140	0.518 (0.253)	[0.11, 1.99]	0.506 (0.247)	[0.12, 2.35]	-0.012 (0.197)	[-1.21, 1.57]
	Placebo	900	0.519 (0.251)	[0.12, 1.92]	0.507 (0.251)	[0.14, 1.94]	-0.012 (0.185)	[-0.94, 0.80]
Blood Urea Nitrogen (mg/dL)								
Month 3	Suvorexant LD	437	14.8 (4.3)	[6, 32]	15.1 (4.6)	[6, 42]	0.3 (3.7)	[-14, 20]
	Suvorexant HD	1140	15.8 (4.6)	[4, 35]	16.0 (4.7)	[4, 48]	0.2 (3.6)	[-14, 21]
	Placebo	900	15.3 (4.7)	[3, 40]	15.7 (5.2)	[4, 59]	0.4 (3.9)	[-14, 39]
Calcium (mg/dL)								
Month 3	Suvorexant LD	436	9.47 (0.41)	[8.1, 11.2]	9.38 (0.41)	[8.4, 11.8]	-0.08 (0.41)	[-1.4, 2.4]
	Suvorexant HD	1133	9.56 (0.45)	[5.4, 11.7]	9.44 (0.45)	[6.2,12.6]	-0.12 (0.40)	[-2.1, 2.4]
	Placebo	899	9.53 (0.42)	[7.4, 11.3]	9.47 (0.44)	[6.8, 12.1]	-0.06 (0.41)	[-3.1, 1.8]
Creatine Kinase (U/L)								
Month 3	Suvorexant LD	437	109.8 (83.7)	[6, 672]	107.4 (109.6)	[19, 1921]	-2.4 (105.7)	[-510, 1673]
	Suvorexant HD	1140	115.8 (128.2)	[20, 3395]	112.8 (88.8)	[13, 1383]	-3.0 (95.9)	[-2012, 753]
	Placebo	900	114.0 (111.7)	[19, 1576]	113.5 (86.4)	[18, 863]	-0.5 (85.1)	[-1184, 772]
Chloride (mmol/L)								
Month 3	Suvorexant LD	436	103.6 (2.4)	[95, 112]	103.7 (2.5)	[95, 111]	0.1 (2.4)	[-6, 7]
	Suvorexant HD	1136	103.4 (2.5)	[90, 111]	103.6 (2.4)	[88, 111]	0.2 (2.3)	[-9, 9]
	Placebo	899	103.2 (2.5)	[92, 110]	103.5 (2.4)	[94, 112]	0.3 (2.4)	[-8, 12]
Creatinine Clearance Estimation (mL/min)								

Month 3	Suvorexant LD	437	82.3 (25.0)	[27, 201]	82.9 (25.9)	[23, 201]	0.6 (9.6)	[-40, 44]
	Suvorexant HD	1140	82.8 (26.5)	[33, 242]	82.4 (26.9)	[31, 218]	-0.4 (10.3)	[-46, 56]
	Placebo	899	82.2 (25.8)	[31, 214]	81.9 (26.3)	20, 224]	-0.4 (10.4)	[-79, 100]
Creatinine (mg/dL)								
Month 3	Suvorexant LD	437	0.92 (0.18)	[0.6, 1.7]	0.92 (0.19)	[0.6, 1.7]	0.00 (0.10)	[-0.3, 0.6]
	Suvorexant HD	1140	0.94 (0.19)	[0.5, 1.9]	0.95 (0.19)	[0.5, 1.8]	0.01 (0.10)	[-0.4, 0.6]
	Placebo	899	0.93 (0.18)	[0.5, 2.0]	0.94 (0.21)	[0.4, 3.0]	0.01 (0.13)	[-0.4, 2.0]
Glucose (mg/dL)								
Month 3	Suvorexant LD	437	98.2 (19.3)	[45, 199]	97.9 (21.1)	[46, 225]	-0.3 (17.8)	[-79, 80]
	Suvorexant HD	1140	98.6 (24.0)	[47, 374]	99.6 (26.7)	[43, 402]	1.0 (21.3)	[-189, 170]
	Placebo	897	97.5 (19.4)	[50, 293]	99.6 (24.4)	[20, 355]	2.1 (22.3)	[-119, 275]
Bicarbonate (mEq/L)								
Month 3	Suvorexant LD	437	26.2 (2.5)	[16, 33]	26.6 (2.7)	[15, 34]	0.5 (2.7)	[-16, 8]
	Suvorexant HD	1138	26.2 (2.4)	[16, 34]	26.4 (2.4)	[17, 37]	0.2 (2.6)	[-10, 18]
	Placebo	899	26.3 (2.4)	[17, 35]	26.5 (2.5)	[18, 33]	0.2 (2.5)	[-11, 9]
Potassium (mEq/L)								
Month 3	Suvorexant LD	436	4.22 (0.42)	[2.9, 5.9]	4.24 (0.40)	[2.5, 5.5]	0.02 (0.42)	[-1.5, 1.8]
	Suvorexant HD	1132	4.26 (0.41)	[2.7, 5.9]	4.27 (0.40)	[3.1, 6.1]	0.00 (0.40)	[-1.5, 1.4]
	Placebo	899	4.23 (0.41)	[2.6, 6.1]	4.26 (0.40)	[3.0, 6.0]	0.02 (0.43)	[-2.2, 1.6]
Lactose Dehydrogenase (U/L)								
Month 3	Suvorexant LD	436	165.1 (34.9)	[65, 357]	162.2 (41.4)	[62, 563]	-2.9 (33.2)	[-165, 300]
	Suvorexant HD	1139	167.0 (34.3)	[72, 447]	165.2 (34.5)	[62, 423]	-1.8 (25.3)	[-136, 166]
	Placebo	898	165.5 (34.3)	[64, 382]	165.0 (33.9)	[68, 400]	-0.5 (28.7)	[-264, 251]
Triacylglycerol Lipase (U/L)								
Month 1	Suvorexant HD	421	41.8 (18.2)	[15, 160]	40.6 (21.6)	[13, 223]	-1.1 (19.1)	[-122, 137]
	Placebo	207	41.9 (21.5)	[14, 211]	39.8 (18.9)	[8, 142]	-2.1 (18.2)	[-152, 97]
Magnesium (mEq/L)								
Month 3	Suvorexant LD	436	1.74 (0.13)	[1.2, 2.3]	1.73 (0.13)	[1.4, 2.1]	-0.01 (0.12)	[-0.5, 0.4]
	Suvorexant HD	1133	1.78 (0.15)	[1.1, 2.3]	1.73 (0.15)	[1.1, 2.2]	-0.05 (0.13)	[-0.6, 0.6]
	Placebo	899	1.76 (0.15)	[1.1, 2.3]	1.73 (0.14)	[1.1, 2.2]	-0.03 (0.13)	[-0.9, 0.6]
Phosphate (mg/dL)								
Month 3	Suvorexant LD	437	3.73 (0.58)	[2.2, 7.4]	3.74 (0.52)	[2.0, 6.7]	0.01 (0.51)	[-3.1, 2.6]
	Suvorexant HD	1140	3.70 (0.54)	[1.4, 6.9]	3.71 (0.55)	[2.1, 7.3]	0.01 (0.52)	[-2.6, 3.8]
	Placebo	898	3.70 (0.52)	[1.8, 5.5]	3.71 (0.54)	[1.2, 7.0]	0.01 (0.51)	[-2.6, 3.7]
Sodium (mEq/L)								
Month 3	Suvorexant LD	436	140.6 (2.2)	[32, 147]	140.8 (2.6)	[132, 169]	0.2 (2.6)	[-10, 27]
	Suvorexant HD	1136	140.6 (2.3)	[130, 149]	140.5 (2.2)	[125, 147]	-0.1 (2.3)	[-10, 7]
	Placebo	898	140.5 (2.3)	[128, 149]	140.6 (2.2)	[130, 147]	0.1 (2.2)	[-9, 7]
Urate (mg/dL)								
Month 3	Suvorexant LD	437	5.18 (1.36)	[1.9, 10.4]	5.22 (1.39)	[1.9, 10.7]	0.04 (0.75)	[-2.9, 2.1]

	Suvorexant HD	1140	5.30 (1.38)	[0.8, 10.0]	5.40 (1.41)	[0.8, 12.6]	0.10 (0.71)	[-3.7, 3.5]
	Placebo	900	5.23 (1.34)	[1.6, 10.3]	5.29 (1.36)	[1.8, 11.6]	0.06 (0.71)	[-3.2, 3.4]

(Source: Sponsor's submission ISS Page 942 Table Appendix 5.3.5.3.3:48. Note: Sampling for amylase and lipase levels was interrupted during development program, so table includes values for only suvorexant HD and placebo groups at Month 1, which had the largest sample size.)

Urinalysis

The sponsor's analyses showed no meaningful differences in the mean changes from baseline of the urinalysis measurements among the treatment groups.

Phase 2 Dose-Finding Trial Laboratory Experience - Mean Change from Baseline to Week 4 in Phase 2 Trial (P006)

Suvorexant increased serum cholesterol levels in a dose-related manner with the maximum mean increase of 6.0 mg/dL at suvorexant 80 mg dose, as shown in the table below. The sponsor suggested that this finding was not replicated in the Phase 3 population, and that the small sample size in the Phase 2 trials may have contributed to the finding. Also, the sponsor stated that the findings are unlikely to be clinically meaningful.

Table 115: Serum Cholesterol Levels Mean Change from Baseline to Week 4 in Phase 2 Trial (P006)

Treatment	N	Baseline Mean (mg/dL)	Treatment Mean (g/dL)	Change from Baseline (g/dL)
Placebo	228	202.3 (40.37)	198.6 (38.99)	-3.7 (25.59)
Suvorexant 10 mg	56	204.8 (40.58)	206.0 (47.30)	1.2 (27.67)
Suvorexant 20 mg	58	199.9 (42.69)	202.2 (40.65)	2.3 (25.94)
Suvorexant 40 mg	59	201.9 (43.88)	205.0 (48.50)	3.1 (22.60)
Suvorexant 80 mg	55	199.3 (32.52)	205.3 (32.30)	6.0 (19.65)
Total Suvorexant	228	201.5 (40.06)	204.6 (42.53)	3.1 (24.08)

(Source: Modified from Sponsor's submission ISS Page 974 Table Appendix 5.3.5.3.3:49).

Reviewer Note: The sponsor stated that these observations on cholesterol levels are not likely to be clinically meaningful given the small sample size within each treatment group in the trial, about 60 in each dose arm, and the absence of changes in the combined Phase 3 population. I was unable to locate the sponsor's analyses on serum cholesterol levels from the Phase 3 trials in either the ISS or laboratory result dataset. From the lists of laboratory tests in the Phase 3 trial protocols, I did not find lipid panel or cholesterol tests. For potential long-term users of suvorexant, knowledge of the effect on cholesterol levels will be important. A rise in serum cholesterol levels to the extent

found in the Phase 2 trial, up to 6 g/dL difference from placebo, may not be trivial especially if maintained over a longer period.

Subjects Who Met Predefined Criteria for Change Relative to Normal Range in Laboratory Measurements

The sponsor summarized the count of subjects who met predefined criteria for change relative to normal range of laboratory measurements. As shown in table below, more subjects met the criterion for raised levels of potassium in the suvorexant HD group (2.4%, 31/1284) compared to suvorexant LD group (1.0%, 5/ 485) or placebo (1.0%, 10/1011). One subject's value increased to a maximum of 6.8 mEq/L and was reported as an AE, though not considered related to suvorexant. The subject completed the trial with a potassium level of 4.1 mEq/L. In the 0-12 month's assessments, suvorexant HD continued to maintain higher frequency of subjects who met the criterion for raised potassium levels.

Table 116: Laboratory Measurements by Count of Subjects Who Met Predefined Criteria for Change Relative to Normal Range in Combined Phase 3 Population 0-3 Months (P028, P029, and P009)

Protocols 028+029+009		Suvorexant LD (N=493) n/m (%)	Suvorexant HD (N=1291) n/m (%)	Placebo (N=1025) n/m (%)
Laboratory Parameter	**Predefined Limit**			
Hematology				
Hematocrit (%) (Male) Hematocrit (%) (Female)	≤94.9% LLN ≤94.1% LLN	1/ 169 (0.6) 6/ 315 (1.9)	16/ 505 (3.2) 13/ 777 (1.7)	7/ 375 (1.9) 10/ 635 (1.6)
Hemoglobin (gm/dL) (Male) Hemoglobin (gm/dL) (Female)	≤90.5% LLN ≤81.9% LLN	1/ 169 (0.6) 4/ 315 (1.3)	9/ 505 (1.8) 2/ 777 (0.3)	5/ 375 (1.3) 2/ 635 (0.3)
Leukocytes (10[3]/microL)	≤64.2% LLN ≥149.0% ULN	2/ 484 (0.4) 2/ 484 (0.4)	3/1282 (0.2) 3/1282 (0.2)	1/1010 (0.1) 0/1010 (0.0)
Neutrophils (10[3]/microL)	≤37.0% LLN	5/ 484 (1.0)	6/1282 (0.5)	1/1009 (0.1)
Eosinophils (10[3]/microL)	≥147.0% ULN	3/ 484 (0.6)	4/1282 (0.3)	8/1009 (0.8)
Platelet (10[3]/microL)	≤57.7% LLN ≥177.7% ULN	1/ 484 (0.2) 0/ 484 (0.0)	0/1277 (0.0) 1/1277 (0.1)	0/1006 (0.0) 0/1006 (0.0)
Hepatic Function				
Bilirubin (mg/dL)	≥166.7% ULN	2/ 485 (0.4)	7/1285 (0.5)	7/1011 (0.7)
Alkaline Phosphatase (IU/L)	≥300.0% ULN	0/ 485 (0.0)	0/1284 (0.0)	0/1011 (0.0)
Aspartate Aminotransferase (IU/L)	≥300.0% ULN	1/ 485 (0.2)	3/1285 (0.2)	1/1011 (0.1)
Alanine Aminotransferase (IU/L)	≥300.0% ULN	2/ 485 (0.4)	7/1284 (0.5)	3/1011 (0.3)
Renal Function				
Creatinine (mg/dL)	≥142.9% ULN	1/ 485 (0.2)	1/1285 (0.1)	5/1011 (0.5)
Clinical Chemistry				

Sodium (mEq/L)	≤94.7% LLN ≥105.4% ULN	0/ 485 (0.0) 1/ 485 (0.2)	2/1285 (0.2) 1/1285 (0.1)	0/1011 (0.0) 0/1011 (0.0)
Potassium (mEq/L)	≤88.2% LLN ≥111.1% ULN	1/ 485 (0.2) 5/ 485 (1.0)	2/1284 (0.2) 31/1284 (2.4)	4/1011 (0.4) 10/1011 (1.0)

N = Number of subjects treated by trial medication (took at least one tablet of study drug) during the indicated phase.
m = Number of treated subjects with valid post-treatment value of the parameter.
n = Number of subjects meeting the predefined limit criteria.
ULN = Upper limit of normal range; LLN = Lower limit of normal range.
Suvorexant LD= Suvorexant 20 mg for subjects <65 years and Suvorexant 15 mg for subjects ≥65 years.
Suvorexant HD= Suvorexant 40 mg for subjects <65 years and Suvorexant 30 mg for subjects ≥65 years.

(Source: Sponsor's submission ISS Page 286 Table 5.3.5.3.3:62)

Hepatic Enzymes

The frequency of subjects identified with increased ALT or AST in the suvorexant development program was similar across dose groups. Subjects who achieved >3 times upper limit of normal range (ULN) for ALT within 0-3 months were as follows: suvorexant HD 0.5% (7/1284), suvorexant LD 0.4% (2/485), and placebo 0.3% (3/1011). AST findings were similarly comparable. The sponsor found no cases of Hy's Law in the development program. CDER analyzed the long-term Phase trial (P009) for cases of Hy's Law and found none as shown in the figure below.

Figure 14: Analysis Showing Absence of Hy's Law Cases in the Long-term Phase 3 Trial P009

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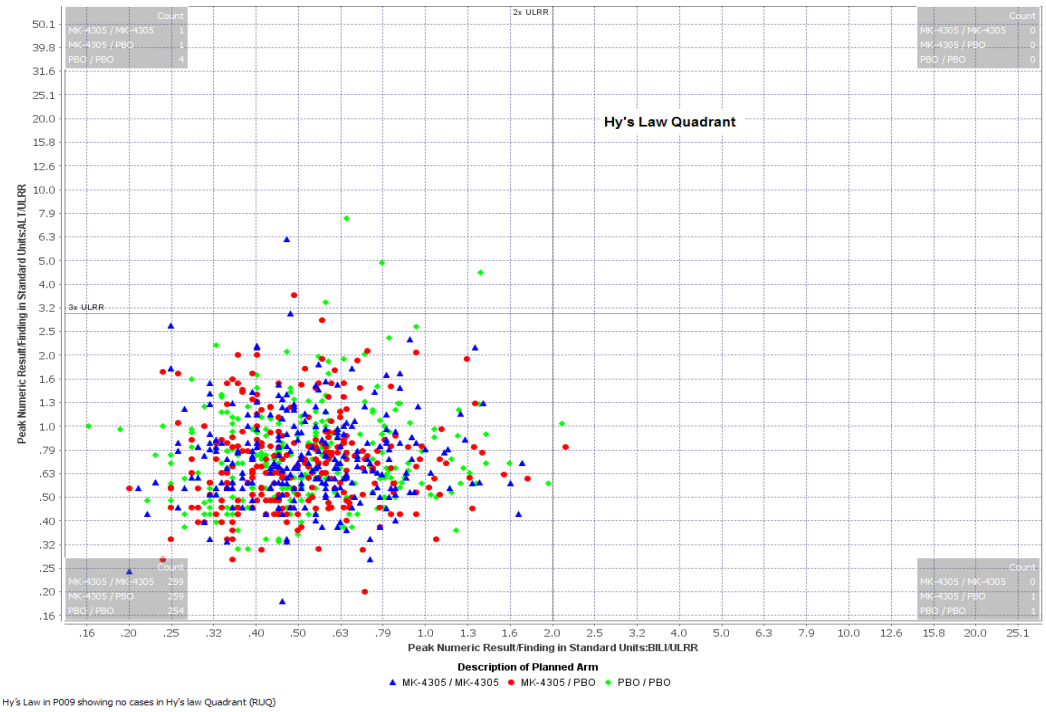

(Source: CDER Review Team and Clinical Reviewer Analyses)

7.4.3 Vital Signs

Merck summarized the vital sign measurements in terms of mean change from baseline; they noted no clinically meaningful changes or trends in the vital sign parameters with suvorexant treatment. The table below summarizes the mean change in vital signs from baseline at Week 2 and Month 3 for the different treatment groups in the combined phase 3 population.

Table 117: Vital Sign Change from Baseline at Week 2 and Month 3 in Combined Phase 3 Population (P028, P029, and P009)

Vital Sign Parameter	Placebo	Suvorexant LD	Suvorexant HD
Diastolic BP (mmHg)			
Week 2	-1.4 (n=1001)	-1.1 (n=479)	-1.5 (n=1272)
Month 3	-0.5 (n=375)	-0.1 (n=129)	-0.9 (n=623)
Systolic Blood Pressure (mmHg)			
Week 2	-2.4 (n=1001)	-2.2 (n=479)	-2.2 (n=1272)
Month 3	-1.3 (n=375)	0.2 (n=129)	-1.3 (n=623)
Pulse Rate (beats/min)			
Week 2	1.7 (n=1001)	1.6 (n=479)	0.2 (n=1273)
Month 3	-0.5 (n=375)	-0.2 (n=129)	-1.2 (n=623)
Respiratory Rate (breaths/min)			
Week 2	0.0 (n=995)	0.1 (n=477)	-0.1 (n=1263)
Month 3	0.0 (n=372)	-0.4 (n=129)	-0.3 (n=616)
Temperature (°C)			
Week 2	-0.01 (n=996)	0.00 (n=478)	-0.05 (n=1263)
Month 3	0.01 (n=370)	-0.04 (n=129)	-0.02 (n=615)
Weight (kg)			
Week 2	0.2 (n=998)	0.1 (n=476)	0.1 (n=1267)
Month 3	0.0 (n=373)	0.1 (n=129)	0.2 (n=623)

(Source: Modified from Sponsor's submission ISS Page 984 Table Appendix 5.3.5.3.3:51).

In the assessments by percentage of subjects who met predefined criteria for change from baseline, no meaningful differences occurred among the treatment groups for blood pressure, pulse rate, respiratory rate, or temperature. However, weight reductions and increases of 7% or more from baseline occurred more in the suvorexant LD group compared to suvorexant HD, or placebo.

7.4.4 Electrocardiograms (ECGs)

The sponsor observed no clinically meaningful mean changes or trends in changes in ECG parameters. In the Phase 3 trials, P028 and P029, ECG measurements occurred at baseline, ends of Week 2, Months 1 and 3, and on trial discontinuation. Suvorexant did not appear to have remarkable effects on the ECG measurements in terms of mean

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changes in intervals from baseline over time and QTc values that met predetermined criteria for change from baseline. The table below is a summary of the mean change from baseline in ECG parameters at 3 months.

Table 118: ECG Mean Change from Baseline at 3 Months in Combined Phase 3 Population (P028, P029, and P009)

ECG Parameter	Placebo		Suvorexant LD		Suvorexant HD	
	Baseline	MCB	Baseline	MCB	Baseline	MCB
Ventricular Heart Rate (mean BPM)	64.7	0.1 (n= 898)	64.7	-0.5 (n= 437)	65.1	-1.1 (n=1152)
PR Interval (msec)	166.0	-0.1 (n= 882)	164.8	0.2 (n= 432)	166.8	1.0 (n=1132)
QRS Interval (msec)	90.9	0.2 (n= 895)	90.7	0.2 (n= 436)	92.3	0.1 (n=1146)
QT interval (msec)	404.6	0.4 (n= 877)	406.3	3.1 (n= 432)	404.1	2.7 (n=1125)
QTcB	416.9	0.4 (n= 877)	418.9	1.2 (n= 432)	417.7	-0.5 (n=1125)
RR Interval	950.4	0.3 (n= 898)	948.9	7.4 (n= 437)	942.9	17.0 (n=1152)

MCB = Mean Change from Baseline; BPM = Beats per minute; n = No of subjects evaluated
(Source: Modified from Sponsor's submission ISS Page 1003 Table Appendix 5.3.5.3.3:56)

Also, evaluation of the age subgroups for ECG changes from baseline showed no remarkable changes with suvorexant treatment. For example, the sponsor's ISS Appendix 5.3.5.3.3: 132 and Appendix 5.3.5.3.3: 133 tables show the mean changes in QTc (Bazett's) from baseline to 3 months in elderly subjects were -0.8 for suvorexant HD, 0.4 for suvorexant LD, and -1.9 for Placebo. For non-elderly subjects, the QTc changes were -0.2 for suvorexant HD, 1.7 for suvorexant LD, and 2.3 for placebo.

ECG Findings, Subjects that Met Predefined Criteria for Change from Baseline

The incidence of subjects who met predefined criteria for QTc Interval change from baseline was comparable across the treatment groups in the 0-3 Months period. For QTc Interval change from baseline between 30 and 60 msec the incidence for each treatment group was: suvorexant HD, 10.2% (130/1276); suvorexant LD, 10.0% (48/482); and placebo, 10.6% (107/1005). For QTc Interval change from baseline more than 60 msec, incidence for each group was: suvorexant HD, 0.2% (2/1276); suvorexant LD, 0.2% (2/482); and placebo, 0.7% (7/1005). The table below summarizes the proportion of subjects who met the QTc Interval change from baseline of more than 500 msec at different periods: 0-3, 0-6, and 0-12 Months.

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Table 119: Subjects with QTc Interval >500 msec as ECG Measurements that Met Predefined Criterion for Change from Baseline in the Phase 3 Trials over Time

Treatment Period	Placebo (N=1025)	Suvorexant LD (N=493)	Suvorexant HD (N=1291)
0-3 Months QTc interval Bazett >500 msec (Trials P028, P029, P009)	0.1 % (1/1008)	0.0 % (0/483)	0.2 % (2/1280)
0-6 Months QTc interval Bazett >500 msec (Trials P028, P029)	0.0% (0/755)	0.0% (0/483)	Not applicable
0-12 Months QTc interval Bazett >500 msec (Trials P028, P029, P009)	0.1% (1/1010)	Not applicable	0.2% (2/1281)

(Source: Modified from Sponsor's ISS Pages 307-312 Tables 5.3.5.3.3:76- 80)

In the Phase 2 trial, no subject achieved a treatment-emergent QTc value of 500 msec or more.

Sleep Architecture on Polysomnography

The sponsor provided a summary of time to REM sleep onset that I reproduce in the table below. From Night 1 through Month 3, subjects on suvorexant entered REM sleep about 20 to 35 minutes faster than those on placebo. The percentage of subjects on suvorexant who enter REM sleep within 15 minutes does not increase from Night 1 to Month 3, as shown in the table below. On page 314 of the sponsor's ISS, Merck states that based on the data there was no evidence to suggest that subjects treated with suvorexant who experienced shorter REM onset (<15 minutes), increased REM duration, or REM percent, were more likely to experience adverse events of clinical concern, including EDS.

Table 120: Time to REM from Sleep Onset and Subjects with REM Onset Less Than 15 Minutes by Treatment Group and Time Point in Combined Phase 3 Population 0-3 Months (P028 and P029, PQ Cohort)

Summary REM Onset Measure	MK-4305 LD	MK-4305 HD	Placebo
Night 1	**N = 339**	**N = 580**	**N = 576**
Mean time to onset of first epoch of REM (minutes)	69.2	63.7	101
Number (%) of subjects with REM onset < 15 minutes	14 (4.1%)	38 (6.6%)	6 (1.0%)
Month 1	**N = 321**	**N = 554**	**N = 550**

Mean time to onset of first epoch of REM (minutes) Number (%) of subjects with REM onset < 15 minutes	80.1 9 (2.8%)	80.2 21 (3.8%)	100.9 5 (0.9%)
Month 3	**N = 304**	**N = 517**	**N = 518**
Mean time to onset of first epoch of REM (minutes) Number (%) of subjects with REM onset < 15 minutes	81.5 8 (2.6%)	76.9 27 (5.2%)	96 12 (2.3%)

(Source: Modified from Sponsor's ISS Page 315 Table 5.3.5.3.3:82)

Reviewer Comment: There are subjects with missing values after Night 1, thereby limiting comparisons between time points. If it is verifiable that subjects with missing values were unlikely to have shortened their REM sleep latency at a rate lower than the subjects with values at 3 months, then it is reasonable to suggest that suvorexant treatment over 3 months does not appear to be associated with narcoleptic changes in these Phase 3 trial population.

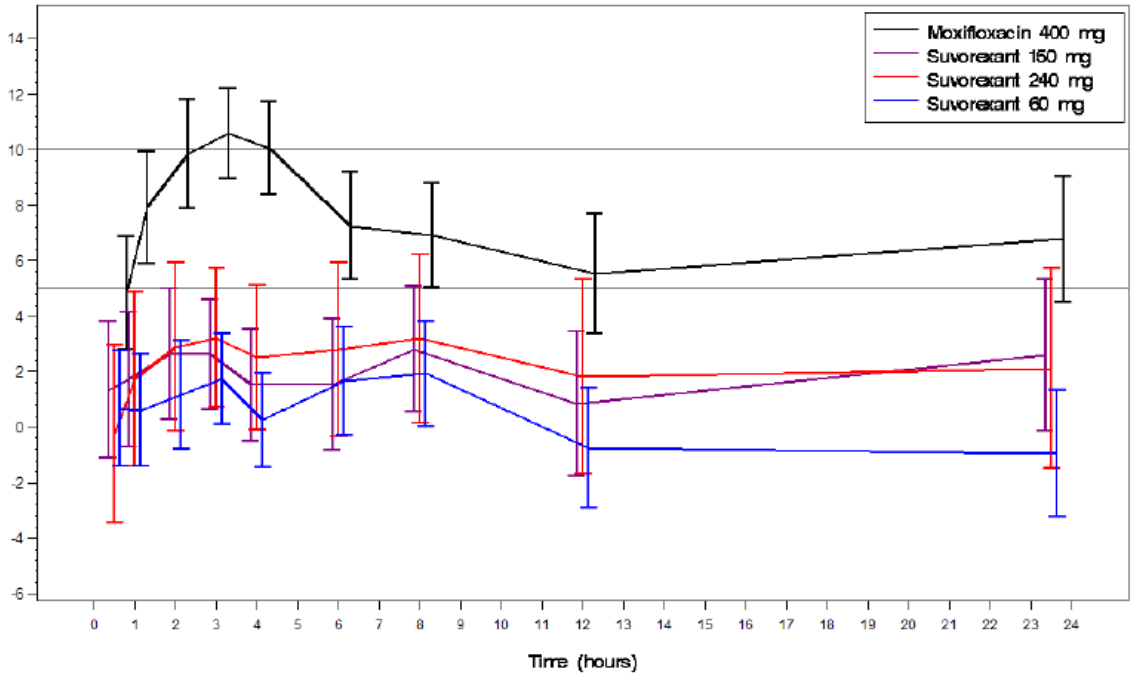
7.4.5 Special Safety Studies/Clinical Trials

The studies reviewed in this section are mainly Phase 1 trials. Please refer to Clinical Pharmacology review for additional details of the trials.

Thorough QT Trial (P022)

Merck conducted a Thorough QTc Trial (P022) in Healthy Subjects to examine the effect of suvorexant on the QTc interval. CDER's interdisciplinary review (IR) team for QT Studies evaluated the sponsor's Thorough QT Study and detected no significant QTc prolongation effect of suvorexant. Further, the IR team remarked that the largest upper bounds of the 2-sided 90% CI for the mean difference between suvorexant and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. Assay sensitivity was established, as the largest lower bound of the two-sided 90% CI (unadjusted) for the ΔΔQTcF for moxifloxacin was greater than 5 ms, as shown in the figure below.

Figure 15: Mean and 90% CI ΔΔQTcF Time Course for Suvorexant and Moxifloxacin



All CIs are unadjusted, including moxifloxacin.

(Source: CDER Interdisciplinary Review Team for TQT studies Consult Report Page 13 Figure 5)

Please see IR team consult report for additional details. Below is a summary of my safety review of the thorough QT trial P022.

The randomized, placebo-controlled, double-blind, 4-period, crossover Thorough QTc (TQT) trial enrolled 53 healthy male (n=28) and female (n=25) volunteers, aged 20 to 45 years. The subjects received single doses of suvorexant 240 mg, 150 mg or 60 mg, matching placebo, and moxifloxacin 400 mg as the positive control. The 240 mg and 150 mg dose data were pooled for analysis. The sponsor reported that the maximum mean difference between suvorexant up to supratherapeutic doses had 90% confidence interval below 10 ms, the threshold for regulatory concern as recommended in the ICH E14 guidance. As stated by the sponsor, “The maximum mean difference in the QT interval prolongation was 4.13 msec with a 90% CI of 2.03 and 6.23 msec and was recorded at 8 hours in the 240/150 mg Suvorexant treatment. For both the therapeutic and supratherapeutic doses, all confidence intervals lay completely below 10 msec.” The positive result from moxifloxacin group showed assay sensitivity with a maximum mean QTcF change from baseline difference from placebo of 11.06 msec with a 90% CI of 8.99 and 13.16, recorded at 3 hours postdose.

Two subjects on suvorexant 240 mg developed SAEs, prompting the sponsor to decrease the maximum trial dose from 240 mg to 150 mg during the trial. One subject, AN 0024, a 27-year old female reported a serious adverse experience of chest pain, requiring hospitalization. She had a negative work-up for myocardial infarction. She also had myoclonus and sleep paralysis during the evaluation. The second subject, AN 0014, developed a non-serious adverse experience of respiratory depression, described as shallow respiration and transiently decreased O2 saturation (from between 96% and 98% to 90%), about 1 hour 19 minutes after receiving suvorexant 240 mg. She discontinued from the trial.

In the trial, the most frequent AEs (>10%) overall were somnolence (18 subjects, 34%), dizziness (9 subjects, 17%), headache (9 subjects, 17%), fatigue (9 subjects, 17%), application site pruritus at electrode sites (6 subjects, 11.3%), and abnormal dreams (6 subjects, 11.3%).

Renal Insufficiency (Trial P023)
In a Phase 1 PK trial (P023), Merck evaluated safety of suvorexant in subjects aged 18 to 70 years with renal impairment, as part of the clinical development program. The aim of the trial was to determine whether suvorexant exposures were similar in subjects with renal impairment and healthy subjects. In the open-label PK trial, eight subjects with severe renal impairment, with 24-hour urinary creatinine clearance of 30 ml/min or less, and eight healthy controls received a single dose suvorexant 20 mg. The controls were matched by age, gender, race, and BMI to the renal impairment subjects. All subjects completed the trial.

The sponsor reported that total and unbound suvorexant plasma level was similar between subjects with severe renal impairment and healthy matched control subjects. Suvorexant had a median Tmax of 2 hours in severe renal impairment subjects and 1 hour in the matched control subjects. The mean apparent terminal half life was 13.5 hours for both populations. The trial recorded no SAEs, deaths, or subject discontinuations because of an adverse experience. Four healthy subjects reported 5 adverse experiences: three headache and two dry mouth events. Further, two subjects with severe renal impairment reported a total of 2 adverse events, somnolence and oligomenorrhoea. As result, Merck recommended no dose adjustment with renal impairment. Of note, this trial did not evaluate the suvorexant 40 mg dose.

Hepatic impairment (Trial P017)
In a Phase 1 PK trial (P017), the sponsor evaluated safety and PK characteristics of suvorexant in male and female subjects aged 18 to 65 years with hepatic impairment. In the open-label PK trial, eight subjects with moderate hepatic impairment, defined by Child-Pugh scale score of 7 to 9, and eight healthy controls received a single dose suvorexant 20 mg. The controls were matched to hepatic impairment subjects by age, gender, race, and BMI. All subjects completed the trial.

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On completion, the result showed similar suvorexant exposure in the controls and hepatic impairment subjects. Apparent half life was longer in the hepatic impairment subjects at 19.1 hours compared to the healthy subjects at 14.7 hours. With regards to safety, the trial reported no deaths, no SAEs, and no discontinuations resulting from AEs. Somnolence occurred in 75% (6/8) of the hepatic impairment subjects and 63% (5/8) of the control healthy subjects.

Respiratory Safety

The sponsor conducted three studies to assess respiratory safety – P032 in COPD subjects, P036 in OSA subjects, and P040 in healthy adults. CDER's pulmonary review team is reviewing the results of the trials. Below is a brief overview of the trial reports.

Respiratory Safety – Healthy Subjects (Trial P040)
In a Phase 1, placebo-controlled, double-blind, 3-period crossover trial design, the sponsor evaluated the effect of a single dose of suvorexant on mean oxygen saturation (SaO2), using pulse oximetry, during total sleep time (TST) in healthy subjects. The trial also assessed safety, apnea-hypopnea index (AHI), and PK characteristics of suvorexant in the 12 male (n=8) and female (n=4) subjects, aged 18 to 55 years, and with body mass index (BMI) 30 kg/m^2 or less. There was a 5-day washout between the trial treatment periods. After a 4-hour fast, subjects received, in each treatment period, a single evening dose of suvorexant 150 mg, suvorexant 40 mg, or matching placebo. Then the subjects were evaluated overnight in the sleep laboratory using 8-hour PSG recording and SaO2 monitoring. PSG sleep was scored based on the American Academy of Sleep Medicine (AASM) Manual for Scoring of Sleep and Associated Events criteria into the 4 stages of sleep. The sponsor obtained PSG scoring, SaO2, and AHI parameter derivation at a central PSG laboratory that was blinded to treatment, period, and time postdose.

The results as summarized by the sponsor in the table below showed no statistically significant difference in mean SaO2 during TST between each suvorexant dose and placebo. Also, the mean SaO2 during wake, NREM, and REM sleep stages and AHI did not appear to be statistically significantly different.

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Table 121: Suvorexant Effects on Pharmacodynamic (PD) Endpoints of Respiratory Function in Trial P040

Endpoint	Suvorexant 150 mg LSmean (95% CI)	Suvorexant 40 mg LSmean (95% CI)	Placebo LSmean (95% CI)	Difference (150 mg Suvorexant - Placebo) of LSmean (90% CI)	Difference (40 mg Suvorexant - Placebo) of LSmean (90% CI)	MSE‡
Mean SaO_2 during TST (%)	96.67 (95.79, 97.55)	96.33 (95.45, 97.21)	96.67 (95.79, 97.55)	-0.00 (-0.90, 0.90)	-0.33 (-1.23, 0.57)	1.64
Mean SaO_2 during Wake (%)	96.83 (96.09, 97.58)	96.75 (96.00, 97.50)	97.25 (96.50, 98.00)	-0.42 (-1.22, 0.38)	-0.50 (-1.30, 0.30)	1.29
Mean SaO_2 during NREM (%)	96.75 (95.89, 97.61)	96.17 (95.31, 97.02)	96.75 (95.89, 97.61)	-0.00 (-0.87, 0.87)	-0.58 (-1.45, 0.29)	1.53
Mean SaO_2 during REM (%)	96.67 (95.79, 97.55)	96.33 (95.45, 97.21)	96.83 (95.95, 97.71)	-0.17 (-1.07, 0.73)	-0.50 (-1.40, 0.40)	1.64
Apnea-hypopnea index §	-0.82 (-2.62, 0.99)	0.15 (-1.65, 1.95)	-0.63 (-2.44, 1.17)	-0.18 (-1.68, 1.31)	0.78 (-0.71, 2.28)	4.49

‡ Estimate of within subject variance.
§ For AHI test, change from baseline is analyzed where screening PSG visit serves as baseline, mean =3.62, SD=3.26, (N=12).
SaO_2 = Oxygen Saturation, TST = Total Sleep Time.

(Source: Sponsor's submission Clinical Study Report Trial P040 Page 51 Table 11-1)

With regards to safety, the trial reported no deaths, no SAEs, and no discontinuations resulting from AEs. More AEs occurred with suvorexant 150 mg compared to other treatments. Five of the 12 subjects in the 150 mg suvorexant treatment reported 1 or more adverse experiences. With the suvorexant 150 mg dose treatment, the most frequently reported adverse experiences were dizziness in 3 subjects (25%), headache in 2 subjects (17%), and somnolence in 2 subjects (17%). The suvorexant 40 mg and placebo groups recorded no incidence of somnolence. No suicidal ideation or suicidal behavior was recorded based on the Columbia-Classification Algorithm for Suicide Assessment (C-CASA).

Respiratory Safety – COPD (Trial P032)
In trial P032, Merck used a randomized, placebo-controlled, double-blind, 2-period crossover trial design to evaluate subjects with COPD for safety and oxygen saturation (SaO2) during multiple doses of suvorexant treatment.

The trial enrolled 25 male and female subjects, aged 18 to 85 years, with mild or moderate COPD according to the modified GOLD criteria, and with a BMI 40 kg/m^2 or less. Subjects received a suvorexant 40 mg (non-elderly) or 30 mg (elderly) or matching placebo once daily, about 30 minutes before nighttime PSG recording time, for 4 consecutive days, with a 7-day washout between each treatment period. Overnight PSG recording occurred on Days 1 and 4. One subject discontinued the trial, though not because of an adverse event.

Although single and multiple doses of suvorexant did not appear to reduce mean SaO2 during total sleep time compared to placebo, slight increases occurred in Percentage of Total Sleep Time that SaO2 was less than 85% with multiple dose suvorexant treatment – treatment difference of 0.32% (90% CI; 0.00, 0.63) compared to placebo. Likewise, Apnea-hypopnea index (AHI) increased by with multiple dose suvorexant treatment 2.05 (90% CI; 0.33, 3.77) compared to placebo.

With regards to safety, overall, somnolence and headache occurred most frequently each in 12% (3/25) of the subjects. The trial reported no deaths, no SAEs, and no discontinuations resulting from AEs. However, an ECI of sleep paralysis occurred in Subject AN0046, reported event at about 8.5 hours after suvorexant 40 mg treatment on Trial Day 1.

Respiratory Safety – OSA (Trial P036)
The sponsor conducted Trial P036 in subjects with mild to moderate obstructive sleep apnea (OSA); this trial was similar to Trial P032 that I described above. Trial P036 enrolled 26 subjects, 19 males and 7 females, aged 18 to 65 years. The subjects received a suvorexant 40 mg or matching placebo once every evening for 4 consecutive days, with a 5-day washout between each treatment period. One subject discontinued from the trial, not from an AE. On completion, multiple doses of suvorexant 40 mg produced a small increase in mean AHI; the observed mean AHI treatment difference, suvorexant minus placebo, on Day 4 was 2.66 (90% CI; 0.22, 5.09). Overall, somnolence occurred in 19.2% (5/26) of the subjects and nausea in 8% of the subjects; these were the most frequently reported AEs. No somnolence event occurred with placebo. There were no deaths, no SAEs, and no discontinuations resulting from AEs.

Middle of the Night Safety in Elderly Subjects (Trial P021)

Merck conducted a randomized, double-blind, placebo-controlled 3-period crossover trial (P021) to evaluate middle of the night safety after suvorexant treatment in elderly subjects. The trial evaluated effects of single nighttime doses of suvorexant 30 mg, zolpidem 5 mg, and placebo on safety, PK, and nighttime psychomotor performance in 12 healthy elderly male (n=7) and female (n=5) subjects, aged 65 to 80 years. The investigators awakened the subjects at 1.5 hours, 4 hours, and 8 hours post-dose. At each time-point, the investigators assessed the subjects on postural stability (equilibrium and ataxia) using Accusway stabilometric platform, cognitive performance (attention and concentration) using Choice Reaction Time (CRT) and Immediate and Delayed Word Recall (IDWR). Accusway platform analyzed stability as a 95% confidence interval area of ellipse around center of positional trajectory (A95), as a measure of body sway or equilibrium and ataxia. On trial completion, **Suvorexant 30 mg at 1.5 hours post-dose, increased A95 by 49% at eyes-open condition.** No statistically significant difference from placebo in A95 occurred at eyes-closed condition. In contrast, zolpidem 5mg, at 1.5 hour post-dose, increased A95 body sway by 97% at eyes-open and 113% at eyes-closed conditions. These increases in body sway

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indicated some impaired balance at 1.5 hour post-dose for both drugs, worse on zolpidem. For both drugs, there were no statistically significant differences from placebo in body sway at 4 or 8 hours postdose, and no impaired episodic memory at 4 hour post dose. The trial report further showed that **suvorexant 30 mg significantly prolonged reaction time indicating slowed information processing and impaired attention at 1.5 hour**, but not at 4 and 8 hour post dose.

Eight subjects reported 14 clinical adverse events while on suvorexant 30 mg; fatigue and somnolence were the most frequent of these events. Six subjects on zolpidem 5 mg reported nine clinical adverse events, dizziness was the most frequent. On placebo, one subject reported severe eye pain two days after the placebo treatment. Also, one subject on placebo in period 1 discontinued after developing an erythematous rash 1.5 hours after treatment. The trial recorded no SAEs and no deaths.

Driving Trial in Non-elderly Subjects (Trial P035)

Highway Car Driving Assessment of Next-day Residual Effects of Suvorexant
Trial Title: A Multiple Dose Study to Evaluate Next Day Effects of MK-4305 (Suvorexant) on Driving Performance in Healthy Non-Elderly Subjects

The trial's primary objective was to evaluate the next day residual effects of suvorexant as assessed by highway driving performance after single dose administration in healthy non-elderly male and female subjects.

To achieve trial objectives, the sponsor stated the following hypotheses:

Primary: At least 1 dose of suvorexant (20 or 40 mg) does not produce next-day residual effects as compared to placebo as assessed by mean SDLP (standard deviation of lateral position) on highway driving after single dose administration in healthy non-elderly subjects. Specifically, the true mean treatment difference between suvorexant and placebo (suvorexant minus placebo) on SDLP (on Day 2) is less than 2.4 cm.

Secondary:

1. Single doses of zopiclone produce next-day residual effects as compared to placebo as assessed by SDLP on highway driving in healthy non-elderly subjects. Specifically, a true mean treatment difference between zopiclone and placebo (zopiclone – PBO) on SDLP of 2.5 cm is expected.
2. At least 1 dose of suvorexant (20 or 40 mg) does not produce next-day residual effects as compared to placebo as assessed by SDLP on highway driving after repeated dose administration (8 days) in healthy non-elderly subjects. Specifically, the true mean treatment difference between suvorexant and placebo (suvorexant – PBO) on SDLP is less than 2.4 cm.

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3. At least 1 dose of suvorexant (20 or 40 mg) does not result in next day driving impairment as measured by SDLP after single-dose and repeated-dose administration. Specifically, the distribution of changes in SDLP (suvorexant – PBO) above +2.4 cm and below -2.4 cm is symmetric around zero.
4. Single doses of 7.5 mg zopiclone result in next day driving impairment as measured by SDLP. Specifically, the distribution of changes in SDLP (zopiclone – PBO) above +2.4 cm and below -2.4 cm is not symmetric around zero. There are more subjects with increases in SDLP than those with decreases in SDLP.
5. Estimation: The effects of suvorexant (20 and 40 mg) on mean standard deviation of speed (SDS) of highway driving as compared to placebo after single and repeated dose (8 days) administration will be estimated.
6. Estimation: The effects of suvorexant (20 and 40 mg) on word learning tests and Body Sway as compared to placebo after single and repeated dose (8 days) administration will be estimated.
7. Suvorexant is safe and well tolerated after single and repeated dose administration of 20 and 40 mg in healthy non-elderly subjects.

Trial P035 was a randomized, double-blind, placebo and active controlled, multiple oral dose, 4-period crossover trial to evaluate highway car driving performance the day after bedtime treatment with suvorexant 20 mg, suvorexant 40 mg, zopiclone (active control), or placebo. The PD, PK, and safety trial enrolled 28 non-elderly male and female subjects, aged 21 to 64 years to receive each treatment for 8 days per period with a 7-day washout between periods. Following overnight stays on Days 1 and 8, the subjects underwent an hour long driving test on the highway on Days 2 and 9 at about 9 hours from trial treatment. They were evaluated on the following tests at about 11 hours from trial treatment: Body Sway Test, Bond-Lader VAS, Word Learning Test, and DSST. Investigators also collected PK samples during the trial.

Key Trial Assessments
Pharmacodynamics: the primary PD variable was SDLP for car driving performance, with emphasis on both the mean between-treatment differences and the percentage of subjects whose individual difference from placebo were beyond specific cut points of positive and negative 1.5, 2, 2.4, 3, 3.5, and 4. The secondary endpoints were: standard deviation of speed (SDS) of highway driving, Word Learning Tests, DSST, Bond-Lader VAS, Driving Instructor VAS, and A95 in the eyes closed position for Body Sway assessment.

The sponsor analyzed mean SDLP using a linear mixed model that was applied to individual values of SDLP, with fixed factors for treatment, day (2 and 9), period, treatment by day interaction, and random factor for subject. Multiple hypotheses for treatment effect were tested in a step-wise manner. The suvorexant 20 mg dose on Day 2 was tested first. The mean treatment difference (suvorexant minus placebo) of SDLP on Day 2 based on the model results was calculated. If the 90% confidence interval of the treatment difference was below 2.4 cm, then the hypothesis was supported for 20

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mg suvorexant, allowing the hypothesis for the higher dose suvorexant 40 mg to be tested. If one of the two doses was supported, the hypothesis was supported for suvorexant. The sponsor performed a similar hypothesis testing for Day 9 as a secondary hypothesis.

In the other key PD assessment, Symmetry Analyses for SDLP, the sponsor used a generalized sign test to determine whether the distribution of differences (suvorexant minus placebo) above 2.4 and below -2.4 was symmetric about zero. The percentage of subjects lying above 2.4 was compared to 50% using the binomial distribution. A non-significant result (one-sided, alpha=0.05) supported the hypothesis for a particular day and dose. The active control zopiclone was similarly evaluated.

The results showed that the 90% confidence intervals for suvorexant 20 mg and 40 mg were below the pre-specified clinical bound of 2.4 cm on both Days 2 and 9, suggesting a lack of next-day residual effects by either of the tested suvorexant doses. In contrast, the 90% confidence intervals around the SDLP treatment difference for zopiclone on Days 2 and 9 both lay above 0 cm, suggesting next-day residual effects and demonstrating assay sensitivity. The sponsor summarized the results in the following table:

Table 122: Standard Deviation of Lateral Position (SDLP) on Driving Assessment after Treatment with Suvorexant 20 mg, Suvorexant 40 mg and Zopiclone 7.5 mg in Non-elderly Subjects from Trial P035

Day	Treatment	N	LS Mean SDLP (cm)		Difference From Placebo (cm)	
			Mean	95% CI	Mean	90% CI
2	Placebo	28	15.53	(14.53,16.53)		
	Zopiclone 7.5 mg	28	17.66	(16.66,18.66)	2.14	(1.49,2.79)
	Suvorexant 20 mg	28	16.54	(15.54,17.54)	1.01	(0.36,1.66)
	Suvorexant 40 mg	28	17.19	(16.19,18.19)	1.66	(1.01,2.31)
9	Placebo	27	15.47	(14.46,16.47)		
	Zopiclone 7.5 mg	28	16.91	(15.91,17.91)	1.45	(0.79,2.10)
	Suvorexant 20 mg	28	15.94	(14.94,16.94)	0.48	(-0.18,1.13)
	Suvorexant 40 mg	28	16.77	(15.77,17.77)	1.31	(0.65,1.96)

(Source: Sponsor's submission Clinical Study Report P035 Page 60 Table 11-1)

On symmetry analysis of SDLP, the percentage of subjects with SDLP treatment difference (suvorexant minus placebo) above 2.4 cm was significantly greater than that

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below -2.4 cm on both Day 2 and Day 9 for suvorexant 40 mg, and on Day 2 only for suvorexant20 mg. The sponsor summarized the symmetry analysis in the table below.

Table 123: Symmetry Analysis for Individual Differences in Standard Deviation of Lateral Position (SDLP) on Driving Assessment after Treatment with Suvorexant 20 mg, Suvorexant 40 mg and Zopiclone 7.5 mg in Non-elderly Subjects from Trial P035

	Day=2			Day=9		
Treatment	Suvorexant 20 mg	Suvorexant 40 mg	Zopiclone 7.5 mg	Suvorexant 20 mg	Suvorexant 40 mg	Zopiclone 7.5 mg
n+1 †	6	10	14	2	6	8
n-1 ‡	0	2	1	1	0	0
m = n+1 + n-1	6	12	15	3	6	8
Test Statistic §	2.45	2.31	3.36	0.58	2.45	2.83
Reject Null Hypothesis? ‖	Yes	Yes	Yes	No	Yes	Yes

† n+1 = number of subjects with treatment difference (from placebo) ≥ 2.4 cm.
‡ n-1 = number of subjects with treatment difference (from placebo) ≤ -2.4 cm.
§ Test Statistic = (n+1 - n-1)/sqrt(m).
‖ Reject Null hypothesis if test statistic > 1.74, which is the critical value for general sign test with exact unconditional approach for sample size N=28 and N=27.
Null Hypothesis: the percentage of subjects falling above the positive cut point and falling below the negative cut point is symmetric about zero.

(Source: Sponsor's submission Clinical Study Report P035 Page 61 Table 11-2)

Other trial results as summarized by the sponsor include:

- There was a statistically significant increase in SDS following single and multiple doses of suvorexant 40 mg, and following a single dose of suvorexant 20 mg (at 9 hours postdose).
- There was no statistically significant effect on memory following single and multiple doses of suvorexant 20 mg (at 11 hours postdose). But a statistically significant decrease in delayed word recall was found following a single dose of suvorexant 40 mg.
- There was no statistically significant effect on balance as assessed by Body Sway Test following multiple doses of suvorexant 20 mg or suvorexant 40 mg (at 11 hours postdose). But a statistically significant increase on Body Sway Area (A95) was observed following a single dose of suvorexant 20 mg or suvorexant 40 mg.

Safety Assessment in Driving Trial P035
Regarding safety, the trial reported one serious clinical adverse experience of induced abortion in Subject AN 0007 who became pregnant during the trial and subsequently had an elective abortion after the trial. The trial recorded no deaths. Twenty-five (25) subjects reported a total of 132 clinical adverse experiences.

Safety Assessment for Suvorexant 40 mg in Driving Trial P035
While on suvorexant 40 mg, 17 (60.7%) subjects reported at least one AE. The most frequently reported AEs in subjects on suvorexant 40 mg were somnolence (25.0%,

7/28) headache (17.9%, 5/28), and fatigue (14.3%, 4/28). Three subjects (AN 0006, AN 0007, and AN 0016) stopped driving test early on Day 2.

Safety Assessment for Suvorexant 20 mg in Driving Trial P035
While on suvorexant 20 mg, 10 (35.7%) subjects reported at least one AE. The most frequently reported AEs in subjects on suvorexant 20 mg were headache (25.0%, 7/28) and somnolence (14.3%, 4/28. Two subjects (AN 0007, and AN 0021) stopped driving test early, one subject on Day 2 and the other on Day 9 (AN 0007).

Safety Assessment for Zopiclone 7.5 mg in Driving Trial P035
While on Zopiclone 7.5 mg, 10 (35.7%) subjects reported at least one AE. The most frequently reported AE was dysgeusia (25%, 7/28). No subject stopped driving test early.

Placebo
The adverse events reported for placebo treatment included experience from the zopiclone treatment period between Days 2 to 7 when the subjects received placebo between Day 1 and Day 8 zopiclone treatment. While on placebo, 21 (75.0%) subjects reported at least one AE. The most frequently reported AEs were headache (39.3%, 11/28), fatigue (17.9%, 5/28), and dyssomnia (10.7%, 3/28). No subject stopped driving test early.

Reviewer Note: Assessing the trial results beyond the primary hypothesis is problematic because of the sheer number of comparisons. Regulatory decisions based on results of secondary hypotheses can be difficult, especially with the background of multiple hypotheses tested in a small sized trial. Based on the primary hypothesis, suvorexant showed no significant impairment in driving. But there are other issues. Premature stopping of driving, seen with suvorexant 40 mg and 20 mg treatment, suggests impairment in driving that may not be captured on SDLP analysis. Symmetry of SDLP analysis is another suggestion of driving impairment with suvorexant 40 mg and 20 mg treatment. Interpretation of all these analyses is limited by the fact that this trial's sample size was small. However, the gravity of the consequences of impaired driving, such as in accidents, demand that cautionary language be in place in the label for individuals taking suvorexant to avoid driving or operating heavy machinery.

Driving Trial in Elderly Subjects (P039)

Trial P039 was similarly designed as Trial P035. However, Trial P039 enrolled 24 elderly male and female subjects, aged 65 to 80 years. The key findings as summarized by the sponsor are as follows:

Suvorexant at 15 mg and 30 mg did not produce next-day residual effects (RE) on highway driving assessed at 9-hr postdose by SDLP (mean and symmetry analysis),

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following single dose and multiple doses (8 consecutive days) administration. The table below shows the mean SDLP analyses.

Table 124: SDLP on Driving Assessment after Treatment with Suvorexant 15 mg, Suvorexant 30 mg and Zopiclone 7.5 mg in Elderly Subjects from Trial P039

Day	Treatment	N	LS Mean		Difference from PBO	
			Mean	95% CI	Mean	90% CI
2	Placebo	24	16.67	(15.48,17.86)		
	Zopiclone 7.5 mg	24	18.56	(17.37,19.75)	1.89	(1.22,2.55)
	MK-4305 15 mg	24	16.24	(15.05,17.43)	-0.43	(-1.10,0.23)
	MK-4305 30 mg	24	17.04	(15.85,18.23)	0.37	(-0.30,1.03)
9	Placebo	24	15.41	(14.22,16.60)		
	Zopiclone 7.5 mg	24	16.58	(15.39,17.78)	1.17	(0.51,1.84)
	MK-4305 15 mg	24	15.50	(14.31,16.69)	0.09	(-0.58,0.76)
	MK-4305 30 mg	24	16.01	(14.82,17.20)	0.60	(-0.06,1.27)

(Source: Sponsor's submission Clinical Study Report P039 Page 59 Table 11-1)

Further SDLP symmetry analysis is shown in the table below. Note that more subjects treated with suvorexant 30 mg had treatment difference from placebo above 2.4 cm compared to below -2.4 cm at Days 2 and 9; however, the apparent asymmetry was not statistically significant.

Table 125: SDLP Symmetry Analysis on Driving Assessment after Treatment with Suvorexant 15 mg, Suvorexant 30 mg and Zopiclone 7.5 mg in Elderly Subjects from Trial P039

Treatment	Day=2			Day=9		
	MK-4305 15 mg	MK-4305 30 mg	Zopiclone 7.5 mg	MK-4305 15 mg	MK-4305 30 mg	Zopiclone 7.5 mg
n+1 †	0	3	8	0	5	6
n-1 ‡	3	1	0	0	1	1
m = n+1 + n-1	3	4	8	0	6	7
Test Statistic §	-1.73	1	2.83	N.D.	1.63	1.89
Reject Null Hypothesis? ‖	No	No	Yes	No	No	Yes

† n+1 = number of subjects with treatment difference from placebo ≥ 2.4 cm.
‡ n-1 = number of subjects with treatment difference from placebo ≤ -2.4 cm.
§ Test Statistic = (n+1 - n-1)/sqrt(m).
‖ Reject Null hypothesis if test statistic > 1.74, which is the critical value for general sign test with exact unconditional approach for sample size N=24.
Null Hypothesis: the percentage of subjects falling above the positive cut point and falling below the negative cut point is symmetric about zero.

(Source: Sponsor's submission Clinical Study Report P039 Page 60 Table 11-2)

Other trial findings as summarized by the sponsor include the following:

- Single doses of zopiclone (7.5 mg) demonstrated assay sensitivity on highway driving as assessed by SDLP (mean and symmetry analysis) at 9-hr postdose.
- Based on the standard deviation of speed of highway driving test, suvorexant (15 mg and 30 mg) did not show any statistically significant next-day residual effect following single and multiple dose administration.
- Based on the word learning and body sway tests, suvorexant (15 mg and 30 mg) did not show any statistically significant next-day effect on memory and balance assessed at 11-hr postdose following single and multiple doses administration.
- Based on digital symbol substitution test, Bond and Lader VAS and Driving Instructor VAS, suvorexant (15 mg and 30 mg) did not show any statistically significant next-day effects assessed at 11-hr postdose following single and multiple dose administration.

Safety Assessment in Driving Trial P039
Regarding safety, no SAEs, deaths, or trial discontinuations because of AEs occurred in the trial. The most frequently reported AEs were somnolence, poor sleep quality, headache, nightmare and dysgeusia. Twenty-four subjects reported a total of 102 clinical AEs.

Safety Assessment for Suvorexant 30 mg in Driving Trial P039
While on suvorexant 30 mg, 13 (54.2%) subjects reported at least one AE. The most frequently reported AEs in subjects on suvorexant 30 mg were headache (20.8%, 5/24) and somnolence (29.2%, 7/24). No subject stopped driving test early.

Safety Assessment for Suvorexant 15 mg in Driving Trial P039
While on suvorexant 15 mg, 14 (58.3%) subjects reported at least one AE. The most frequently reported AEs in subjects on suvorexant 15 mg was poor quality sleep (25.0%, 6/24).

Safety Assessment for Zopiclone 7.5 mg in Driving Trial P039
While on Zopiclone 7.5 mg, 11 (45.8%) subjects reported at least one AE. The most frequently reported AEs were dysgeusia (12.5%, 3/24), headache (12.5%, 3/24) and somnolence (12.5%, 3/24).

Placebo in Driving Trial P039
The adverse events reported for placebo treatment included experience from the zopiclone treatment period between Days 2 to 7 when the subjects received placebo between Day 1 and Day 8 zopiclone treatment. While on placebo, 13 (54.2%) subjects reported at least one AE. The most frequently reported AEs were headache (29.2%, 7/24), somnolence (16.7%, 4/24), poor quality sleep (12.5%, 3/24), and (12.5%, 3/24).

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Reviewer Note: Based on the primary hypothesis of Trial P039, suvorexant shows no significant impairment in driving by elderly subjects at both suvorexant 15 mg and suvorexant 30 mg doses. No premature stopping of driving occurred with either dose. However, the SDLP symmetry analysis, though without statistical significance support, hints at possible driving impairment with suvorexant 30 mg on Days 2 and 9. Again, interpretation of these analyses is limited by the trial's small sample size.

7.4.6 Immunogenicity

No immunogenicity studies were required.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The sponsor recommends suvorexant 40 mg for non-elderly adults and 30 mg for the elderly for insomnia treatment (b) (4) Also, the sponsor leaves room for use of lower doses depending on a subject's dose tolerance. The information presented on dose dependency for AEs may serve as a useful guide for physicians in making the dose changes. Somnolence, as reviewed in section 7.3.4., appears to be the most appropriate AE for assessment of suvorexant dose response. Below I summarize other AEs that occurred in a dose-related manner in the Phase 3 trials.

Fatigue in the first 3 months in the combined phase 3 population was observed more frequently from suvorexant treatment in a dose-related manner: 3.8% (49/1291) of suvorexant HD group, 2.2% (11/493) suvorexant LD, and 1.8% (18/1025) placebo.

Abnormal dreams (nightmares) in the first 3 months in the combined phase 3 population were more frequent from suvorexant treatment (2%, 36/1784), in an apparent a dose-response relationship: 2.1% (27/1291) of suvorexant HD group, 1.8% (9/493) suvorexant LD, and 1.0% (10/1025) placebo. This finding is of uncertain clinical significance.

In the combined phase 3 population 0-3 months, dry mouth was more frequent from suvorexant treatment (2.5%, 45/1784), in an apparent a dose-related manner: 2.8% (36/1291) of suvorexant HD group, 1.8% (9/493) of suvorexant LD, and 1.4% (14/1025) of placebo. This finding is also of uncertain clinical significance.

Infections and Infestations, as an AE group (in the first 3 months in the combined phase 3 population), were comparable among treatment groups: 12.5% (161/1291) of suvorexant HD group, 14.2% (70/493) of suvorexant LD, and 14.3% (147/1025) of placebo. Similarly, nasopharyngitis rates were comparable between suvorexant treatment and placebo. In contrast, AEs specifically termed "Upper respiratory tract

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infection (URI)" appeared slightly higher with suvorexant treatment, in a dose-response relationship: 2.2% (28/1291) of suvorexant HD group, 1.6% (8/493) of suvorexant LD, and 1.2% (12/1025) of placebo.

Dose Dependency for AEs in the Phase 2 Trial P006
The Phase 2 trial experience concerning suvorexant-related AEs that show dose response, in which suvorexant HD showed higher risk than suvorexant LD, were summarized in review section 7.4.1 under Drug-Related Adverse Events in Phase 2 Dose-Finding Trial P006. Briefly, the most frequent dose-related AE in the Phase 2 trial was somnolence with incidence: 0.4% (1/249) from placebo, 4.9% (3/62) suvorexant 20 mg, 11.9% (7/59) suvorexant 40 mg, and 9.8% (6/61) suvorexant 80 mg. No somnolence event occurred while 62 subjects received suvorexant 10 mg. Muscular weakness, under musculoskeletal and connective tissue disorders SOC, occurred in suvorexant 40 mg (3.4%, 2/59), and suvorexant 80 mg (1/61) treatment periods. The incidence of abnormal dreams, under psychiatric disorders SOC, was highest at the maximum suvorexant dose: placebo (0.8%, 2/249), suvorexant 10 mg (1.6%, 1/62), and suvorexant 80 mg (4.9%, 3/61).

7.5.2 Time Dependency for Adverse Events

I reviewed the time dependency for select AEs above in section 7.3.4, section 7.3.5, and section 7.4.1.

7.5.3 Drug-Demographic Interactions

Age
The sponsor analyzed AEs by age group in the Combined Phase 3 Population 0-3 Months (Trials P028, P029, and P009). The incidence of any AE in non-elderly subjects was increased on suvorexant HD treatment (51.5%, 342/664) compared to suvorexant LD (44.7%, 130/291) or placebo (44.2%, 246/556). However, the incidence of any AE in elderly subjects was similar among the treatment groups: suvorexant HD (50.4%, 316/627), suvorexant LD (49.0%, 99/202) or placebo (49.5%, 232/469). Two deaths occurred among the non-elderly subjects, one on placebo and the other on suvorexant 40 mg. Below, I summarize AE categories by the demographic factor Age. In review section 7.3.4, I summarized the AE somnolence by demographic factors, including age.

Table 126: Summary of Adverse Events by Demographic Factor Age in Combined Phase 3 Population 0-3 Months (P028, P029, and P009)

Demographic Variable	Placebo N (%)	Suvorexant LD N (%)	Suvorexant HD N (%)	Total
Subjects in Overall Population	1025	493	1291	2809

Age – Non-elderly (<65years)				
Subjects with data	556	291	664	1511
At least one AE	246 (44.2)	130 (44.7)	342 (51.5)	718
Drug-related AE, investigator determined	85 (15.3)	67 (23.0	180 (27.1)	332
SAE	12 (2.2)	0 (0.0)	6 (0.9)	18
Discontinued because of AE	24 (4.3)	8 (2.7)	40 (6.0)	72
Discontinued because of SAE	8 (1.4)	0 (0.0)	4 (0.6)	12
Deaths	1 (0.2)	0 (0.0)	1 (0.2)	2
Age – Elderly (>=65years)				
Subjects with data	469	202	627	1298
At least one AE	232 (49.5)	99 (49.0)	316 (50.4)	647
Drug-related AE, investigator determined	69 (14.7)	42 (20.8)	149 (23.8)	260
SAE	11 (2.3)	3 (1.5)	12 (1.9)	26
Discontinued because of AE	26 (5.5)	7 (3.5)	40 (6.4)	73
Discontinued because of SAE	4 (0.9)	5 (0.8)	1 (0.5)	10
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0

(Source: Modified from Sponsor's ISS Pages 331-334 Tables 5.3.5.3.3:90-91)

Gender

The incidence of any AE in males was higher on suvorexant HD treatment (48.7%, 2472/507) compared to suvorexant LD (40.8%, 71/174) or placebo (43.0%, 165/384). In females, the incidence of any AE was mildly increased on suvorexant HD (52.4%, 411/784), compared to suvorexant LD (49.5%, 158/319) or placebo (48.8%, 313/641). Among females, the placebo and suvorexant 40 mg groups each recorded one death. Below, I summarize AE categories by gender. In review section 7.3.4, I summarized the AE somnolence by demographic factors, including gender.

Table 127: Summary of Adverse Events by Demographic Factor Gender in Combined Phase 3 Population 0-3 Months (P028, P029, and P009)

Demographic Variable	Placebo N (%)	Suvorexant LD N (%)	Suvorexant HD N (%)	Total
Subjects in Overall Population	1025	493	1291	2809
Male				
Subjects with data	384	174	507	1065
At least one AE	165 (43.0)	71 (40.8)	247 (48.7)	483

Drug-related AE, investigator determined	52 (13.5)	36 (20.7)	125 (24.7)	213
SAE	8 (2.1)	0 (0.0)	7 (1.4)	15
Discontinued because of AE	16 (4.2)	7 (4.0)	35 (6.9)	58
Discontinued because of SAE	2 (0.5)	0 (0.0)	5 (1.0)	7
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0
Female				
Subjects with data	641	319	784	1744
At least one AE	313 (48.8)	158 (49.5)	411 (52.4)	882
Drug-related AE, investigator determined	102 (15.9)	73 (22.9)	204 (26.0)	379
SAE	15 (2.3)	3 (0.9)	11 (1.4)	29
Discontinued because of AE	34 (5.3)	8 (2.5)	45 (5.7)	87
Discontinued because of SAE	10 (1.6)	1 (0.3)	4 (0.5)	15
Deaths	1 (0.1)	0 (0.0)	1 (0.1)	2

(Source: Modified from Sponsor's ISS Page 425 Tables 5.3.5.3.3:148)

In ISS Tables 5.3.5.3.3:149-150, the sponsor showed that the incidence of somnolence was higher with suvorexant LD in females (8.5%, 27/319) than in males (3.4%, 6/174), but it was similar with suvorexant HD between males (10.1%, 51/507) and females (11.1% (87/784). For placebo, the incidence of somnolence was 4.2% (16/384) for males and 2.3% (15/641) for females. Some other AEs such as headache, abnormal dreams, nightmares, and dry mouth were more frequent in females.

Race
The Combined Phase 3 Population 0-3 Months consisted mainly of Caucasian subjects. The population was 77.6% (2181/2809) White race and 12.4% (348/2809) Asian. The small number of subjects in other race subgroups limits the ability to detect risk differences by race.

BMI
Obese subjects showed a dose-related increase in frequency of any AEs: 48.2% (82/170) with placebo, 53.6% (30/56) with suvorexant LD, and 56.9% (132/232) with suvorexant HD. In the other weight categories, the frequency of AEs was similar and lower than in obese subjects. The rates of the AE somnolence by BMI category was summarized in review section 7.3.4. Below, I summarize the AE categories by BMI subgroups.

Table 128: Summary of Adverse Events by Demographic Factor BMI in Combined Phase 3 Population 0-3 Months (P028, P029, and P009)

Demographic Variable	Placebo N (%)	Suvorexant LD N (%)	Suvorexant HD N (%)	Total
Subjects in Overall Population	1025	493	1291	2809
Underweight (BMI <18.5) and Normal range (18.5 ≤ BMI < 25)				
Subjects with data	449	243	509	1201
At least one AE	198 (44.1)	107 (44.0)	251 (49.3)	556
Drug-related AE, investigator determined	65 (14.5)	55 (22.6)	134 (26.3)	254
SAE	9 (2.0)	1 (0.4)	6 (1.2)	16
Discontinued because of AE	25 (5.6)	9 (3.7)	32 (6.3)	66
Discontinued because of SAE	8 (1.8)	1 (0.4)	4 (0.8)	13
Deaths	1 (0.2)	0 (0.0)	1 (0.2)	2
Overweight (25 ≤ BMI ≤30)				
Subjects with data	405	194	548	1147
At least one AE	197 (48.6)	92 (47.4)	273 (49.8)	562
Drug-related AE, investigator determined	61 (15.1)	44 (22.7)	131 (23.9)	236
SAE	8 (2.0)	0 (0.0)	8 (1.5)	16
Discontinued because of AE	15 (3.7)	6 (3.1)	29 (5.3)	50
Discontinued because of SAE	2 (0.5)	0 (0.0)	3 (0.5)	5
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0
Obese (BMI > 30)				
Subjects with data	170	56	232	458
At least one AE	82 (48.2)	30 (53.6)	132 (56.9)	244
Drug-related AE, investigator determined	28 (16.5)	10 (17.9)	64 (27.6)	102
SAE	6 (3.5)	2 (3.6)	4 (1.7)	12
Discontinued because of AE	10 (5.9)	0 (0.0)	18 (7.8)	28
Discontinued because of SAE	2 (1.2)	0 (0.0)	2 (0.9)	4
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0

(Source: Modified from Sponsor's ISS Pages 508-510 Tables 5.3.5.3.3:184-186)

7.5.4 Drug-Disease Interactions

Diseases associated with respiratory compromise – COPD, and OSA are discussed in review section 7.4.5 Special Studies. Also discussed in section 7.4.5 are the safety of suvorexant in subjects with hepatic impairment and renal impairment.

Suvorexant-Depression Interaction
Among the three Phase 3 trials, only the long-term safety Trial P009 included subjects with major depression. P009 assessed subjects for depressive features based on the 16-item Quick Inventory of Depressive Symptomatology (QIDS-SR16). At baseline, most subjects had no depression, QIDS mean total score for suvorexant HD was 4.5 and placebo 4.3. The sponsor reported in the P009 CSR that there were no significant differences between suvorexant HD and placebo for the change from baseline in QIDS-SR16 total score during the 12-month treatment, but improvements appeared to occur on individual QIDS items related to sleep in favor of suvorexant HD: Item 1, Falling Asleep; and Item 2, Sleep During Night. Other items showed no consistent differences between treatment groups. Further, the sponsor conducted subgroup analyses by QIDS severity at baseline (<10 and ≥10) to determine whether baseline depressive symptoms posed any safety risk. These analyses yielded no evidence of an interaction between baseline depression severity and treatment, suggesting no worsening depression features.

7.5.5 Drug-Drug Interactions

The Phase 2 (P006) and Phase 3 trials (P028 and P029) excluded concomitant use of psychotropic and other CNS active drugs, except as needed brief use of centrally-acting analgesics and muscle relaxants, pseudoephedrine, and sedating antihistamines. The long-term Phase 3 trial P009 allowed use of sedating antihistamines, concomitant use of antidepressant medications, except monoamine oxidase inhibitors and tricyclic antidepressants. Despite the measures, concomitant use of the drugs was uncommon; this limits the ability to draw useful conclusion on drug interactions from the Phase 3 trials. The sponsor conducted Phase 1 drug interaction trials that were reviewed under Clinical Pharmacology.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The sponsor's ISS contained no formal assessment of any association of suvorexant with neoplastic disease in the clinical development program. In the combined Phase 3 population, 14 cases of the SOC category of "Neoplasms benign, malignant and unspecified (incl cysts and polyps)" occurred within 0-3 months. More subjects who received placebo treatment reported neoplastic disease in the combined Phase 3

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population 0-3 months. The incidence of SOC category was 0.5% (6/1291) in the suvorexant HD group and 0.8% (8/1025) in the placebo group. Suvorexant LD recorded no case. Neoplasms found in subjects on suvorexant HD but not in the placebo group include B-cell lymphoma (0.1%, 1/1291), Bowen's disease (0.1%, 1/1291), Haemangioma of liver (0.1%, 1/1291), Morton's neuroma (0.1%, 1/1291), and skin neoplasm (0.1%, 1/1291). Likewise, in the 0-12 months assessments, the incidence of neoplastic disease was higher in the placebo group (1.1% (11/1291) compared to suvorexant HD (0.9%, 12/1025). These results, added to the relatively short exposure period to suvorexant, prevent a reasonable assessment of any relationship between suvorexant and neoplastic disease.

7.6.2 Human Reproduction and Pregnancy Data

The sponsor identified five pregnancies during the suvorexant development program. One case resulted in the birth of a healthy baby. Another had elective abortion. One of the three cases of spontaneous abortion was not confounded by concomitant medications. Although the incidence of spontaneous abortion may be low in the clinical development program, this may be an issue for surveillance. Below, I summarize the pregnancy cases in the suvorexant development program.

Subject AN 02609 in Trial P009, a 19-year-old female on suvorexant HD for 18 days and on Day 19 she had a positive urine pregnancy test. She stopped trial medications, but on Day 32 she had a spontaneous abortion. The estimated gestation of the pregnancy was 32 days at the time of the miscarriage, as she had a negative pregnancy at trial randomization.

Subject AN 02609 in Trial P028, a 36-year-old female on suvorexant LD had a positive pregnancy test on Trial Day 49, about 27 days after her last menstrual period. Her last trial medication was on Day 48. She discontinued from the trial on Day 53; 124 days later she reported gestational diabetes. The subject delivered a healthy female baby by caesarean section 220 days after she discontinued the trial. Afterwards, her gestational diabetes was reported as resolved.

Subject AN 07423 in Trial P028, a 30-year-old female on suvorexant HD reported being pregnant on Trial Day 61. Her last trial medication was on Day 60. She discontinued from the trial on Day 61. She had a spontaneous abortion on Day 72, but she had taken 4 tablets of misoprostol on Days 59 and 60. Ultrasound examination on Day 61 revealed gestational sac without a heartbeat. A second ultrasound 11 days later confirmed an anembryonic gestation and a non-serious AE of blighted ovum. The subject discontinued the trial because of the pregnancy. Concomitant medications include medroxyprogesterone acetate.

Subject AN 12110 in Trial P029, a 25-year-old female on suvorexant LD reported a positive pregnancy test on Trial Day 56 (October 7). Her last menstrual period was on

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August 30. Her last trial medication was reported as Day 54 and she discontinued from the trial because of allergic dermatitis. On Day 97, she had a spontaneous abortion. At the time of the miscarriage, her estimated gestation of the pregnancy was about 10 weeks. Concomitant medications included desogestrel and almotriptan malate.

Subject AN 0007 in a Phase 1 car driving trial P035, a 32-year-old female had a positive pregnancy test during a post trial evaluation 12 days after her last dose of eight consecutive days of suvorexant 40 mg. She had elective abortion afterwards.

There were no reports of lactation in any of the clinical trials.

7.6.3 Pediatrics and Assessment of Effects on Growth

The sponsor has not tested suvorexant in the pediatric population.

Under the Pediatric Research Equity Act (PREA), Merck was required to provide in the NDA an assessment of the safety and effectiveness of suvorexant for the claimed indication insomnia in pediatric subjects unless this requirement was waived, deferred, or inapplicable.

(b) (4)

The sponsor's pediatric plan includes (b) (4) a proposal for a full waiver for pediatric subjects (b) (4)

(b) (4)

(b) (4)

[redacted]

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose
None of the subjects who reported overdose in the Phase 3 and Phase 2 trials had other AEs associated with the overdose event.

The sponsor reported that during the Phase 3 trials (P028, P029, P009), 9 (0.7%) on suvorexant HD, 2 (0.4%) on suvorexant LD (total of 11 subjects on suvorexant), and 10 on placebo reported overdose. Yet no other concurrent AEs were observed.

The Thorough QT trial (P022) had two subjects who developed AEs on receiving suvorexant 240 mg. As described above, one subject developed chest pain, myoclonus, and sleep paralysis, with a negative work up for myocardial infarction. The other subject had excessive somnolence and respiratory depression. A third subject AN0024 in the COPD trial P024, a 59–year-old male with moderate COPD was accidentally overdosed at the trial site with suvorexant 280 mg in a day. He reported no AEs.

Drug Abuse Potential

Please refer to the report from FDA's Controlled Substance Staff (CSS) review team for details of the assessment of suvorexant's abuse potential. The sponsor suggests that the potential for abuse of suvorexant appears to be low, considering the lack of nonclinical evidence of abuse potential and the overall clinical data, which showed no consistent patterns of intentional suvorexant misuse and no obvious withdrawal syndrome.

To examine the abuse potential for suvorexant, the sponsor conducted a Human Abuse Liability trial in recreational polydrug users, Trial P025, and analyzed ECIs potentially relevant to abuse potential in the Phase 1 and Phase 3 trials. The ECIs of interest include: depersonalization, derealization, dissociation, euphoric mood, hallucination, mania, and potential trial medication misuse.

In the Combined Phase 3 Population 0-3 months, the incidence of any ECI potentially relevant to abuse potential was comparable across treatment groups: suvorexant HD 2.0% (26/1291), suvorexant LD 3.2% (16/493), and placebo 2.2% (23/1025). One event of derealization occurred in the suvorexant HD group. Other events were of drug maladministration, yielding an incidence of 1.9% (25/1291) in the suvorexant HD group.

In the 0-6 months' evaluation, the incidence of abuse potential events was higher in the suvorexant group compared to placebo: suvorexant LD 4.1% (20/493) and placebo 2.5% (19/767). All events were cases of drug maladministration.

In 0-12 months' evaluation, the events were similar between treatment groups: suvorexant HD 2.6% (34/1291), and placebo 3.0% (31/1025). Among the eight additional events in the suvorexant HD group, one event of auditory hallucination and one of visual hallucination were observed in the 0-12 months. Other events were drug maladministration. The sponsor explained that the majority of drug maladministration events (96.8%) were accidental where subjects lost trial medication (pills or bottles) or denied taking additional trial medication.

For the Phase 2 trial, ECIs of abuse potential were not prespecified, but a retrospective data review yielded two cases of hallucinations: One visual hallucination occurred in a 62 year-old female on suvorexant 80 mg (Day 14 of treatment); the other occurred in a 45 year-old male on Day 1 of the placebo washout following suvorexant 40 mg treatment.

Trial in Recreational Polydrug Users to Evaluate Abuse Potential of Suvorexant (Trial P025)

P0025 was a randomized, double-blind, balanced, placebo- and active comparator-controlled, 6-way crossover study to evaluate the abuse potential of single doses of suvorexant compared to placebo and two doses of zolpidem in healthy male and female recreational polydrug users, aged 20 to 53 years. The subjects received one of the

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following six treatments per treatment period in a randomized, double-blinded, and balanced fashion: Placebo, Zolpidem 15 mg, Zolpidem 30 mg, Suvorexant 40 mg, Suvorexant 80 mg, and Suvorexant 150 mg. The treatment periods were separated by washout periods of at least 10 days to avoid carry-over effects. The subjects needed to have a negative urine drug screen to enter a dosing period. The primary endpoint was "Drug Liking" visual analog scale (VAS), based on a scores ranging from 0 for "Strong Disliking" to 100 for "Strong Liking" in response to a question: "At this moment, my liking for this drug is … "

Trial P025 Results Summary
Based on the primary outcome, "Drug Liking VAS," suvorexant in all tested doses (40 mg, 80 mg, and 150 mg) showed greater abuse potential than placebo in recreational polydrug users. The mean peak effect difference from placebo for each group was 22.84 for suvorexant 40 mg, 21.99 for suvorexant 80 mg, and 20.44 for suvorexant 100 mg. The treatment effect appeared to be similar to that of zolpidem. Below is the sponsor's summary of the primary endpoint analyses.

Table 129: Peak Effect for Drug Liking Visual Analog Scale (VAS), Following Single-Dose Treatment with Suvorexant, Zolpidem, or Placebo in Healthy Recreational Polydrug Users (Trial P025)

	Suvorexant 40 mg	Suvorexant 80 mg	Suvorexant 150 mg	Zolpidem 15 mg	Zolpidem 30 mg	Placebo
N	34	35	34	33	33	34
Time (hr) to Peak Effect-max						
Mean (SD)	2.13 (2.24)	3.03 (2.93)	2.94 (3.11)	2.15 (1.67)	3.09 (2.74)	1.85 (2.48)
Peak Effect-max						
Mean 95% CI	76.38 (70.3, 82.5)	75.53 (69.5, 81.5)	73.98 (67.9, 80.1)	78.40 (72.3, 84.5)	81.62 (75.5, 87.8)	53.54 (47.5, 59.6)
Difference vs Placebo						
Mean 95% CI† P-value	22.84 (15.9, 29.7) <.0001	21.99 (15.1, 28.9) <.0001	20.44 (13.5, 27.3) <.0001	24.86 (17.9, 31.9) <.0001	28.08 (21.1, 35.1) <.0001	
Difference vs Zolpidem 15 mg						
Mean 95% CI‡ P-value	-2.02 (-9.0, 5.0) 0.5691	-2.87 (-9.8, 4.1) 0.4176	-4.43 (-11.4, 2.6) 0.2137			
Difference vs Zolpidem 30 mg						
Mean 95% CI‡ P-value	-5.24 (-12.2, 1.7) 0.1395	-6.09 (-13.0, 0.9) 0.0853	-7.64 (-14.6, -0.7) 0.0318			

† For suvorexant vs placebo, CI below 15 supports the first primary hypothesis. For zolpidem vs. placebo, CI above zero supports the second primary hypothesis.
‡ For suvorexant vs. zolpidem, CI below zero supports the secondary hypothesis.

(Source: Sponsor's submission P025 Clinical Study Report Page 83 Table 11-1)

The incidence of abuse potential AEs was lower in suvorexant dose groups compared to zolpidem: 17.6% (6/34) for suvorexant 150mg, 20.0% (7/35) suvorexant 80mg, 17.1% (6/35) suvorexant 40mg, 54.3% (19/35) zolpidem 30mg, 38.2% (13/34) zolpidem 15mg, 0.0% (0/36) placebo. When the dose groups were combined for each drug, the incidences of abuse potential AEs were 30.6% for suvorexant and 58.3% for zolpidem. The incidence of euphoric mood was lower in suvorexant dose groups compared to zolpidem: 5.9% (2/34) for suvorexant 150mg, 2.9% (1/35) suvorexant 80mg, 5.7% (2/35) suvorexant 40mg, 8.6% (3/35) zolpidem 30mg, 11.8% (4/34) zolpidem 15mg, 0.0% (0/36) placebo. Hallucination occurred in 0.0% of the suvorexant, zolpidem 15 mg, and placebo groups, but occurred in 8.6% (3/35) of zolpidem 30 mg group.

Tolerance

Merck stated that, with the efficacy results of the Phase 3 trials, there was no evidence to suggest tolerance to drug effect during treatment duration ranging from 3 months to 1 year.

Withdrawal

In the Phase 3 trials, Merck defined withdrawal as emergence or worsening on three or more items on the Tyrer Withdrawal Symptom Questionnaire (WSQ) on a night of the first three nights of the Run-out Phase. The proportion of subjects with the positive WSQ responses after switching from suvorexant to placebo was compared to those who continued on suvorexant. Merck noted no significant differences at any timepoint or by suvorexant dose between subjects switched from suvorexant to placebo compared to those who continued suvorexant. The results summarized below, from the sponsor's ISS table, provide information on withdrawal effects based on "Yes" responses on 3 or more emergent or worsening withdrawal symptom out of 20 WSQ Items, and obtained in the Combined Phase 3 Population Run-out Phase following trial treatment.

Table 130: Analysis of Withdrawal Based on Response to Withdrawal Symptom Questionnaire Items in the Combined Phase 3 Population Run-out Phase Following Treatment Phase (P028, P029, and P009)

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 (%)
MK LD / MK LD	157	6 (3.8)	160	5 (3.1)	151	7 (4.6)	172	11 (6.4)
MK LD / PBO	184	7 (3.8)	186	13 (7.0)	182	9 (4.9)	197	17 (8.6)
MK HD / MK HD	398	6 (1.5)	396	16 (4.0)	387	9 (2.3)	424	23 (5.4)
MK 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		
MK HD / MK HD versus MK HD / PBO	-1.6	(-4.0, 0.5)
MK LD / MK LD versus MK LD / PBO	0.1	(-4.3, 4.8)
Night 2		
MK HD / MK HD versus MK HD / PBO	0.6	(-2.2, 3.4)
MK LD / MK LD versus MK LD / PBO	-3.9	(-8.9, 0.9)
Night 3		
MK HD / MK HD versus MK HD / PBO	-0.7	(-4.0, 2.4)
MK LD / MK LD versus MK LD / PBO	-0.2	(-5.0, 5.1)
Night 1, 2, or 3		
MK HD / MK HD versus MK HD / PBO	0.2	(-3.0, 3.3)
MK LD / MK LD versus MK 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 sampel size as weight).

MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.

MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.

PBO = Placebo.

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

n = Number of patients with withdrawal.

(Source: Sponsor's submission ISS Page 582 Table 5.3.5.3.3:208)

Subgroup analyses were limited by the small number of events. On Night 1, elderly subjects switched from suvorexant HD to placebo reported significantly more responses to the WSQ (4.4% [n=9]) compared to subjects continuing on suvorexant HD (0.9% [n=2]). The intergroup difference in WSQ responses for "suvorexant HD continued on suvorexant HD" versus "suvorexant HD switched to placebo" was -5.3 (95% CI, -11.0, -1.0). Merck suggests that this difference does not appear to be clinically important because of the low incidence of withdrawal symptoms overall, the absence of patterns observed in individual WSQ item responses, and lack of subjective report of AEs associated with potential withdrawal.

Also, Merck found no reports of AEs associated with potential withdrawal, based on predefined terms, during the Run-out Phase of Trials P028 and P029, Randomized

Discontinuation Phase of Trial P009, and placebo-washout period of the Phase 2 trial P006. The sponsor summarized the overall withdrawal assessment as suggesting the absence of withdrawal phenomenon associated with abrupt discontinuation of suvorexant.

Rebound Effects

The sponsor evaluated rebound insomnia objectively with PSG measurements of WASO and LPS, and subjectively with sTST, sTSO, and sWASO values. Both types of parameters had their values at each time point on any of the three days after treatment discontinuation, the Run-out Phase after core trial treatment, compared to pretreatment baseline values. Then the sponsor analyzed percentage of subjects who developed worsening of each parameter and the mean change from baseline in the parameter values. Specific analysis of interest was to compare each suvorexant dose group switched to placebo and group of placebo subjects continued on placebo in the Run-out Phase of the trials.

Subjective Parameters

Rebound Effects by sTST
In the combined Phase 3 population (Trials P028, P029, and P009), more subjects who switched from suvorexant HD to placebo (48.5%, 233/480) showed a decrease in total sleep time sTST on any of the three nights compared to subjects continued on placebo (37.2%, 295/793). The treatment difference between the groups was 10.8% (95% CI; 5.2, 16.5); note that the confidence interval excludes 1. For subjects switching from suvorexant LD to placebo, the treatment difference from the continued placebo group was a smaller 4.8% (95% CI; -2.7, 12.4). The sponsor's table below shows the sTST values on the different nights. In other analyses, the mean sTST did not decrease from baseline in any treatment group at any timepoint.

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Table 131: sTST Rebound Effects in Combined Phase 3 Population Run-out Phase Following Treatment Phase (P028, P029, and P009)

Protocols 028+029+009	Night of Run-out							
	Night 1		Night 2		Night 3		Night 1, 2, or 3	
Treatment	N	n (%)	N	n (%)	N	n (%)	N	n (%)
MK LD / MK LD	184	44 (23.9)	181	38 (21.0)	184	39 (21.2)	194	76 (39.2)
MK LD / PBO	206	55 (26.7)	195	39 (20.0)	201	53 (26.4)	213	88 (41.3)
MK HD / MK HD	451	90 (20.0)	441	78 (17.7)	431	71 (16.5)	477	148 (31.0)
MK HD / PBO	448	157 (35.0)	449	132 (29.4)	453	136 (30.0)	480	233 (48.5)
PBO / PBO	744	201 (27.0)	755	164 (21.7)	733	165 (22.5)	793	295 (37.2)

Pairwise Comparison	Point Differences (%)†	95% CI‡
Night 1		
MK HD / PBO versus PBO / PBO	8.1	(2.6, 13.6)
MK LD / PBO versus PBO / PBO	-0.1	(-6.8, 7.2)
Night 2		
MK HD / PBO versus PBO / PBO	6.6	(1.5, 11.9)
MK LD / PBO versus PBO / PBO	-0.4	(-6.5, 6.4)
Night 3		
MK HD / PBO versus PBO / PBO	6.0	(0.9, 11.3)
MK LD / PBO versus PBO / PBO	6.0	(-0.6, 13.2)
Night 1, 2, or 3		
MK HD / PBO versus PBO / PBO	10.8	(5.2, 16.5)
MK LD / PBO versus PBO / PBO	4.8	(-2.7, 12.4)

† Percentage Point Difference.

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

MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.

MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.

PBO = Placebo.

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

N = Number of randomized patients who took at least one dose of Run-out phase study medication and has a value at baseline and during Run-out phase.

n = Number of patients with rebound.

(Source: Sponsor's submission ISS Page 594 Table 5.3.5.3.3.:216)

Because the sTST pattern was suggestive of rebound effect, I examined the sTST results in the Age subgroups. In ISS Table 5.3.5.3.3.:231, the sponsor showed that more elderly subjects who switched from suvorexant HD to placebo (59.2%, 138/233) registered a decrease in sTST on any of the three nights compared to subjects continued on placebo (38.4%, 138/359). The treatment difference between the groups was 21.1% (95% CI; 12.7, 29.1). Similar treatment differences occurred on each of the individual three nights of the Run-out Phase. Likewise, more elderly subjects who switched from suvorexant LD to placebo (51.1%, 45/88) recorded an sTST decrease on any of the three nights compared to subjects continued on placebo (38.4%, 138/359), with a treatment difference of 14.4% (95% CI; 2.5, 26.1). In the elderly subjects on Night

1, sTST increased in the continued placebo group with the mean change in sTST from baseline of 39.3 minutes. In contrast, the mean change was 4.3 minutes for suvorexant HD to placebo and 12.1 minutes for suvorexant LD to placebo transitions. In non-elderly subjects, the percentage of subjects with a decrease in sTST on any night from baseline was comparable across all treatment groups: suvorexant HD to placebo 38.5%, suvorexant LD to placebo 34.4%, and continued placebo 36.2%,

Rebound Effects by sTSO
Neither the percentage of subjects showing an increase in time to sleep onset sTSO nor the mean change from baseline analyses suggested suvorexant rebound effects. Percentage of subjects who reported an increase in sTSO on any of the three nights was similar across treatment groups: suvorexant HD/placebo, 37.7% (181/480); suvorexant LD/placebo, 36.2% (77/213); and placebo/placebo, 34.0% (270/793).

Rebound Effects by sWASO
Again, neither the percentage of subjects showing an increase in awakenings after sleep onset sWASO nor the mean change from baseline analyses suggested suvorexant rebound effects. Percentage of subjects who reported an increase in sWASO on any of the three nights was similar across treatment groups: suvorexant HD/placebo, 42.1% (201/478); suvorexant LD/placebo, 40.8% (87/213); and placebo/placebo, 37.1% (293/790). The mean change in sWASO did not increase in any of the treatment groups.

Objective Parameters

Rebound Effects by WASO
More subjects who switched from suvorexant HD to placebo (33.6%, 71/211) showed an increase in PSG-measured WASO on any of the three nights compared to subjects continued on placebo (24.1%, 105/436). The sponsor's table below shows the difference in percentage of subjects with WASO increases between suvorexant HD to placebo and placebo continued treatment transitions, a treatment difference of 9.6% (95% CI, 2.2, 17.2). However, no mean increases in WASO relative to baseline were observed in any treatment group.

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Table 132: Rebound Effects Assessment by Proportion of Subjects with WASO Increases after Suvorexant Discontinuation in Trials P028 and P029

Protocols 028+029 Treatment	First Night of Run-out	
	N	n (%)
MK LD / MK LD	121	11 (9.1)
MK LD / PBO	129	43 (33.3)
MK HD / MK HD	210	18 (8.6)
MK HD / PBO	211	71 (33.6)
PBO / PBO	436	105 (24.1)
Pairwise Comparison	**Point Differences (%)†**	**95% CI‡**
MK HD / PBO versus PBO / PBO	9.6	(2.2, 17.2)
MK LD / PBO versus PBO / PBO	8.6	(-0.0, 18.0)

† Percentage Point Difference.

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

MK-4305 LD = MK-4305 20 mg for patients < 65 years and MK-4305 15 mg for patients ≥ 65 years.

MK-4305 HD = MK-4305 40 mg for patients < 65 years and MK-4305 30 mg for patients ≥ 65 years.

PBO = Placebo.

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

N = Number of randomized patients who took at least one dose of Run-out phase study medication and has a value at baseline and during Run-out phase.

n = Number of patients with rebound.

(Source: Sponsor's submission ISS Page 590 Table 5.3.5.3.3.:212)

Rebound Effects by LPS

Neither the percentage of subjects showing an increase LPS nor the mean change from baseline analyses suggested suvorexant rebound effects. Percentage of subjects who reported an increase in LPS on any of the three nights was similar across treatment groups: suvorexant HD/placebo, 16.8% (36/214); suvorexant LD/placebo, 18.3% (24/131); and placebo/placebo, 16.4.0% (72/439). No group recorded worsening of mean LPS change from baseline. All treatment groups showed similar mean LPS decreases from baseline: suvorexant HD/placebo, -33.6 minutes; suvorexant LD/placebo, -34.5 minutes; and placebo/placebo, -32.7 minutes.

Rebound Effects in the Phase 2 Trial P006

The sponsor summarized the Phase 2 trial experience on suvorexant by stating that the results from the Phase 2 trial did not show evidence of clinically meaningful return of insomnia symptoms based on assessment of sleep onset and maintenance. Below, I present some of the findings of the Phase 2 trial from the sponsor's ISS regarding rebound effects.

Rebound Effects by sTST

- The percentage of subjects with an sTST decrease from baseline was higher with suvorexant 40 mg on Night 2 and with suvorexant 20 mg on any night compared to placebo.

- The mean change in sTST from baseline in minutes significantly decreased on Night 2 with suvorexant 40 mg only.

Rebound Effects by sWASO
- The percentage of subjects with a significant increase in sWASO from baseline was seen with suvorexant 10 mg on Night 1, suvorexant 80 mg on Nights 1 and 3, and suvorexant 40 mg on any night.
- The mean change in sWASO from baseline in minutes significantly increased with suvorexant 10 mg on Night 1 only.

Rebound Effects by sTSO
- The percentage of subjects with a significant increase in sTSO from baseline was seen with suvorexant 10 mg on any night.

Reviewer Note: The sponsor summarized the rebound effects as showing no clinically meaningful differences between suvorexant and placebo, based on mean change from baseline on either sleep onset or maintenance measures. Further, no rebound effects were observed on measures of sleep onset based on the percentage of subjects with any worsening compared to baseline. Interestingly, the sponsor suggests that rebound effects observed for some sleep maintenance measures do not appear to be consistent with clinically meaningful rebound insomnia. However, I believe that sTST findings for suvorexant, in both doses and in the elderly subgroup, are suggestive of a rebound effect.

7.7 Additional Submissions / Safety Issues

4-Month Safety Update Report
On 7 December 2012 the sponsor submitted a 4-month safety update report (SUR) that included the clinical study report for a Phase 1 trial: Protocol 051: A Two-Part, Single-Dose, Comparative Bioavailability Study of Four Dose Strengths of MK-4305 Tablets under Fasting Conditions.

This non-IND trial was conducted between 29 April 2012 and 11 May 2012 in Canada to meet Japanese requirements. All other suvorexant studies were submitted to the NDA and there are no ongoing trials.

This trial was a Phase 1, randomized, open-label, 2-part, 2-period, single dose, 2-treatment, 2-sequence, crossover trial conducted in a single center. The trial compared bioavailability of different drug strengths that achieved the same dose: two 15 mg tablets compared to one 30 mg tablet, and two 20 mg tablets compared to one 40 mg tablet. Healthy young adults (N=120), aged 20-55 years, and including 63 males and 57 females were enrolled.

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In Part 1, subjects (N=60) were randomized to dosing sequence AB or BA, where A = 2 x 15 mg dose and B =1 x 30 mg dose. Each treatment was a total single dose of 30 mg. Part 2 subjects (N=60) were randomized to dosing sequence CD or DC, where C = 2 x 20 mg dose and B =1 x 40 mg dose. Each Part 2 treatment was a total single dose of 40 mg.

Over a 2-week period, each subject under fasting conditions received a single dose of the trial treatment in each period. The two single-dose treatments of a sequence were separated by a 7-day interval. The outcomes were PK and safety assessments.

On completion of the trial, two 15 mg tablets were found bioequivalent to one 30 mg tablet. Also, two 20 mg tablets and one 40 mg tablet were bioequivalent. With regards to safety, the trial reported no deaths, no SAEs, no ECIs, and no discontinuations resulting from AEs.

Reviewer Note: I agree with the sponsor's opinion that this 4-month SUR data do not impact the sections 4-6 of the proposed draft labeling. Also, the data from the 32 Clinical Pharmacology studies revealed no reports of cataplexy, motor vehicle accidents, falls or complex sleep related behaviors..

8 Postmarket Experience

Suvorexant is not approved in any country. As a result, there is no postmarketing experience with the drug.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

The following are recommended for labeling:

- Labeling should describe risks of ECI events that occurred with suvorexant treatment, including dose-related findings and direction to discontinue suvorexant treatment on emergence of such events.
- Avoid suvorexant use in individuals with narcolepsy-like events and suicidal ideation.
- Consider periodic monitoring of serum cholesterol levels especially in individuals with cardiovascular risk factors.
- Caution individuals taking suvorexant to avoid driving or operating heavy machinery.
- Consider use of lower suvorexant dose as appropriate for an individual's situation.

9.3 Advisory Committee Meeting

An advisory committee meeting is scheduled for 22 May 2013 to discuss issues related to this NDA.

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/s/

KACHIKWU O ILLOH
04/29/2013

RONALD H FARKAS
06/25/2013

For additional safety and efficacy findings, and differing conclusions and recommendations, please see the Team Leader review filed by Ronald Farkas

Office of Drug Evaluation-I: Decisional Memo

Date	June 28, 2013
From	Ellis F. Unger, M.D., Director Office of Drug Evaluation-I, Office of New Drugs, CDER
Subject	Office Director Decisional Memo
NDA #	204569
Applicant Name	Merck & Company, Inc.
Date of Submission	August 30, 2012
PDUA Goal Date	June 29, 2013
Proprietary Name/	not yet established
Established (USAN) Name	suvorexant
Dosage Forms/ Strengths	Oral tablets: 15, 20, 30, and 40 mg
Indication	Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance
Action:	Complete response

Material Reviewed/Consulted - Action Package, including:	
Project Manager	Cathleen Michaloski
Medical Officer Clinical Review	Kachikwu Illoh
Clinical Pharmacology Review	Hristina Dimova, Joo-Yeon Lee, Satjit Brar, Xinning Yang, Angela Men, Atul Bhattaram
Statistical Review	Tristen Massie, Kun Jin
Pharmacology Toxicology	Richard Siarey, Lois Freed, Paul Brown
Executive Carcinogenicity Assessment Committee	David Jacobson-Kram, Abby Jacobs, Paul Brown, Karen Davis Bruno, Adele Seifried
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Director, Division of Neurology Products	Russell G Katz

Action:

Reference ID: 3334017

The Division of Neurology Products is recommending a Complete Response of suvorexant, 15-, 20-, 30-, and 40-mg Tablets for oral administration for insomnia, and I concur with the Division's recommendation.

Introduction:

Orexins are neuropeptides that bind to specific receptors (orexin 1 and orexin 2) that are thought to promote wakefulness. In the late 1990s, it was discovered that a mutation of an orexin receptor caused narcolepsy in dogs, and knockout mice lacking the orexin gene were found to have narcolepsy. Thus, the orexin system became an attractive target for drug development – to promote both sleep and wakefulness. Suvorexant, the subject of this NDA, antagonizes the orexin 1 and 2 receptors, and has been developed as a sleep drug. Suvorexant is both a new molecular entity and first-in-class.

Indication Sought: [Tradename] is an orexin receptor antagonist indicated for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

Regulatory Background:

The IND for suvorexant was submitted on 4/10/08 by Merck. Development proceeded with an end-of-phase 2 meeting on 11/5/09, discussions of the phase 3 trial designs in 2011, and a pre-NDA meeting on 3/19/12. The history is well-summarized in Dr. Illoh's review.

Chemistry Manufacturing and Controls (CMC):

The drug substance and product were found to be acceptable. The NDA was acceptable from a biopharmaceutics perspective.

The Office of Compliance issued an acceptable recommendation for all the establishments that were listed in the application for the manufacture, testing, and quality control of the drug substance and the drug product.

Pharmacology/Toxicology:

The Pharmacology/Toxicology review team recommended approval, with some concern regarding cataplexy-like behavior in dogs. Cataplexy-like behavior occurred near T_{max}, however, and the review team concluded that patients would typically be in bed at this time, such that the importance of this is uncertain. The findings of cataplexy-like behavior in dogs will be described in labeling, and no additional studies will be needed to characterize this issue further.

Site Inspections:

Four sites were inspected from the phase 3 trials in support of this NDA. Selection was based on the numbers of subjects enrolled and the contribution to effect size of the 1° efficacy outcome. OSI found no regulatory violations, and gave a final classification for these inspections as No Action Indicated.

Clinical Pharmacology:

In the fasted state, peak plasma levels of suvorexant occur at a median T_{max} of 2 hours (range 0.5 to 6 hours); a high-fat meal delays T_{max} by 1.5 hours, leading to a recommendation to take suvorexant 30 minutes before going to bed.

Suvorexant is eliminated primarily through metabolism by CYP3A4, with a minor contribution from CYP2C19. The major circulating metabolite, M9, is formed by hydroxylation, and further metabolized to a carboxylic acid derivative, M4. M9 appears in the plasma at about equal concentrations to the parent, but is not expected to enter the brain.

The primary route of elimination is fecal (66%); 23% of elimination is through the urine. The mean terminal half-life is about 12 hours, and is similar for M9.

The oral clearance of suvorexant is 20.5% lower in females than males; therefore, suvorexant exposure is higher in women than in men. The female/male ratios of the geometric means for AUC and C_{max} are about 1.2 and 1.1, respectively.

Clearance is inversely related to body mass index (BMI). The suvorexant concentration 9 hours after dosing (a critical time point for assessing next day effects) is 19% higher in obese patients (BMI > 30 kg/m^2) than in patients with normal BMI.

The concentration at 9 hours post-dose in elderly patients is about 15% greater than that in non-elderly adults.

Based on *in vitro* studies, suvorexant can inhibit CYP3A4 and intestinal P-gp.

Thorough QT Study:

Suvorexant was evaluated in a thorough QT study at doses up to 240 mg. The study demonstrated appropriate assay sensitivity, and the baseline-corrected QTc interval was <10 msec, the threshold of clinical concern.

Evidence of Effectiveness:

The applicant submitted 3 trials relevant to establishing evidence of effectiveness for suvorexant for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. There were two similarly designed randomized, double-blind, placebo-controlled parallel-group studies of 3 months duration (studies 28 and 29), and a randomized, double-blind, placebo-controlled crossover study of 1 month duration (Study 6). These studies are summarized, below (from review of Dr. Massie).

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Principal Suvorexant Efficacy Studies

Study	Subjects per group	Follow-up Period	Completed N (%)	1° Efficacy Endpoint	Study Population
28	Placebo: 385 LD: 255 HD: 383	3 months	341 (89) 230 (91) 345 (90)	Latency Maintenance LPS WASO sTSO sTST at months 1 and 3 PSG and diary-based measures	42% Elderly 34% North American 62% Female
29	Placebo: 389 LD: 240 HD: 392	3 months	330 (85) 205 (85) 346 (88)	Latency Maintenance LPS WASO sTSO sTST at months 1 and 3 PSG and diary based measures	41% Elderly 48% North American 67% Female
6	2-Period Crossover Placebo: 10 mg 10 mg: Placebo Placebo: 20 mg 20 mg: Placebo Placebo: 40 mg 40 mg: Placebo Placebo: 80 mg 80 mg: Placebo	1 month for each Period plus 1 week washout	31 (94) 32 (94) 33 (91) 32 (81) 32 (94) 32 (84) 31 (90) 31 (90)	Sleep Efficiency at Night 1 and 28 Secondary Endpoints WASO and LPS	100% Non-Elderly 87% North American 58% Female

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Study 28

This was a parallel-group, fixed-dose study in which patients with insomnia were randomized to higher or lower fixed doses of suvorexant or placebo for 3 months.

Non-elderly (age <65) adult patients were randomized to suvorexant 40 mg, 20 mg, or placebo in a 2:3:3 ratio. Elderly patients were randomized to suvorexant 30 mg, 15 mg, or placebo in the same ratio. The higher 40-mg and 30-mg doses (HD) in adults were expected to result in similar exposure to the lower 20- and 15-mg doses (LD) in elderly patients. The higher and lower doses were separately pooled for the efficacy analyses.

Patients were assessed either with questionnaires only (Q-cohort) or polysomnography (PSG) and questionnaires (PQ-cohort). Test drugs were to be taken right before bedtime.

Patients were assessed at baseline and Night 1, the end of Week 1, and Months 1, 2, and 3. In the PQ-cohort, PSG was performed on Night 1, Month 1, and Month 3.

As described by Dr. Massie, the 1° hypotheses were to be evaluated by comparing the high-dose suvorexant group to placebo for maintenance endpoints: change from baseline in mean subjective total sleep time (sTST) and change from baseline in wakefulness after persistent sleep onset (WASO) at Months 1 and 3; and for onset endpoints: change from baseline in mean subjective time to sleep onset (sTSO) and change from baseline in latency to onset of persistent sleep (LPS) at Months 1 and 3

The high-dose 2° hypotheses were evaluated for the same endpoints at Week 1 (sTST and sTSO) or Night 1 (WASO and LPS). The following multiplicity strategy was used to control the overall Type I error at the two-sided 5% significance level for the 1° hypotheses: a Bonferroni approach was used to account for the evaluation of 2 distinct indications; within each indication, a fixed sequential testing procedure was used to move from the first set of 1° hypotheses (Month 1) to the next set of 1° hypotheses (Month 3). Within each time point, a Hochberg approach was used to evaluate the objective and subjective endpoints.

Low Dose:

A similar approach was taken for the low-dose-placebo comparisons, if the Month 3 outcome was positive for that particular endpoint at the high dose.

Results: A total of 1022 patients were randomized at 79 centers in North America (34%), Europe (35%), Japan (24%), Asia/Eastern Europe/Africa (4%), and Central and South America (3%). The disposition of patients is shown below:

	Placebo	LD	HD
Randomized	385	254	383
Completed treatment	341 (89%)	230 (91%)	345 (90%)
Discontinued 2°:			
adverse event	21 (5%)	6 (2%)	15 (4%)
withdrawal	12 (3%)	6 (2%)	8 (2%)
lack of efficacy	9 (2%)	1 (0%)	7 (2%)

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Patients were 18 to 87 years old, with 42% >65 years old. A total of 776 were randomized to the PQ-cohort, and 247 to the Q cohort; the latter were all enrolled in Japan.

The following chart displays the results for sTST and WASO, left (measures of sleep maintenance), and results for sTSO and LPS, right (measures of sleep latency):

Study 28: sTST and WASO (sleep maintenance):

	Difference in LS Means (minutes)	*p* -value
sTST		
Week 1		
HD vs placebo	21.4*	<0.00001
LD vs placebo	13.6*	0.00007
Month 1		
HD vs placebo	19.6*	<0.00001
LD vs placebo	16.3*	0.00016
Month 3		
HD vs placebo	19.7*	<0.00001
LD vs placebo	10.7*	0.017
WASO		
Night 1		
HD vs placebo	-38.4*	<0.00001
LD vs placebo	-32.5*	<0.00001
Month 1		
HD vs placebo	-26.3*	<0.00001
LD vs placebo	-26.4*	<0.00001
Month 3		
HD vs placebo	-22.9*	<0.00001
LD vs placebo	-16.6*	0.000009

Study 28: sTSO and LPS (sleep latency):

	Difference in LS Means (minutes)	*p* -value
sTSO		
Week 1		
HD vs placebo	-5.7*	0.006
LD vs placebo	-5.6	0.016
Month 1		
HD vs placebo	-7.4*	0.003
LD vs placebo	-5.4	0.052
Month 3		
HD vs placebo	-8.4*	0.0002
LD vs placebo	-5.2	0.04
LPS		
Night 1		
HD vs placebo	-10.3*	0.00002
LD vs placebo	-9.6*	0.0004
Month 1		
HD vs placebo	-11.2*	0.00002
LD vs placebo	-10.3*	0.0004
Month 3		
HD vs placebo	-9.4*	0.0004
LD vs placebo	-8.1*	0.0061

* statistically significant

Study 29

The design was similar to that of Study 28. A total of 1019 patients were randomized at 90 centers in North America (48%), Europe (30%), and Asia/Central and Eastern Europe (14%).

The disposition of patients is shown below:

	Placebo	LD	HD
Randomized	387	240	392
Completed treatment	330 (85%)	205 (85%)	346 (88%)
Discontinued 2°:			
adverse event	17 (5%)	10 (4%)	19 (5%)
withdrawal	19 (5%)	8 (3%)	9 (2%)
lack of efficacy	8 (2%)	7 (3%)	4 (1%)

Patients were 18 to 86 years old. A total of 41% (N=410) were greater than 65 years old. There were 753 patients randomized to the PQ cohort, and 268 to the Q cohort.

The following chart displays the results for sTST and WASO, left (measures of sleep maintenance), and sTSO and LPS, right (measures of sleep latency):

Study 29: sTST and WASO (sleep maintenance):

	Difference in LS Means (minutes)	*p* -value
sTST		
Week 1		
HD vs placebo	26.4*	<0.00001
LD vs placebo	16.8*	0.00002
Month 1		
HD vs placebo	26.3*	<0.00001
LD vs placebo	20.9*	<0.00001
Month 3		
HD vs placebo	25.1*	<0.00001
LD vs placebo	22.1*	0.00004
WASO		
Night 1		
HD vs placebo	-42.0*	<0.00001
LD vs placebo	-37.0*	<0.00001
Month 1		
HD vs placebo	-29.4*	<0.00001
LD vs placebo	-24.1*	<0.00001
Month 3		
HD vs placebo	-29.4*	<0.00001
LD vs placebo	-31.1*	0.000009

Study 29: sTSO and LPS (sleep latency):

	Difference in LS Means (minutes)	*p* -value
sTSO		
Week 1		
HD vs placebo	-13.1*	<0.00001
LD vs placebo	-7.5	0.006
Month 1		
HD vs placebo	-12.8*	0.00003
LD vs placebo	-6.9	0.05
Month 3		
HD vs placebo	-13.2*	0.00003
LD vs placebo	-7.6	0.04
LPS		
Night 1		
HD vs placebo	-21.7*	<0.00001
LD vs placebo	-12.4	0.004
Month 1		
HD vs placebo	-12.1*	0.00004
LD vs placebo	-7.8	0.03
Month 3		
HD vs placebo	-3.6	0.27
LD vs placebo	-0.3	0.93

* statistically significant

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Study 6

This was a two-period cross-over study in which patients received one of 4 doses of suvorexant (10, 20, 40, or 80 mg) and placebo. Each treatment period was 4 weeks, with a single-blind placebo washout period of at least 1 week between periods. Patients were assessed with a PSG on Night 1 and Week 4 of each period. The primary outcome was Sleep Efficiency (SE), defined as 100% X total sleep time/time in bed (in minutes). The time in bed was fixed at 8 hours. WASO and LPS were the 2° outcomes measures.

A hierarchical approach was used to maintain the study-wide Type I error at 5%: the highest dose was compared to placebo, and needed to be significant (p=0.05) at both time points (Night 1 and Week 4) in order to test the next highest dose in the same way. Doses significant at both time points for SE were then tested for WASO; doses significant for SE and WASO were tested for LPS.

A total of 254 subjects were randomized at 41 centers; approximately 60 subjects in each arm. Patients ranged in age from 18 to 64 years; mean age was 44 years.

Results of the primary and secondary outcomes are as follows:

Sleep Efficiency - LS Mean Change From Placebo

Night 1		*p* -value
10 mg	5.2	<0.002
20 mg	7.6	<0.002
40 mg	10.8	<0.002
80 mg	12.9	<0.002
Week 4		
10 mg	4.7	<0.003
20 mg	10.4	<0.003
40 mg	7.8	<0.003
80 mg	7.6	<0.003

LPS - Difference in LS Means

Night 1		*p* -value
10 mg vs placebo	-3.4	0.6
20 mg vs placebo	-9.4	0.13
40 mg vs placebo	-23.1	<0.001
80 mg vs placebo	-25.4	<0.001
Week 4		
10 mg vs placebo	-2.3	0.6
20 mg vs placebo	-22.3	<0.001
40 mg vs placebo	-3.8	0.46
80 mg vs placebo	-9.5	0.07

WASO - Difference in LS Means

Night 1		
10 mg vs placebo	-21.2	<0.001
20 mg vs placebo	-24.7	<0.001
40 mg vs placebo	-33.9	<0.001
80 mg vs placebo	-36.8	<0.001
Week 4		
10 mg vs placebo	-21.4	0.001
20 mg vs placebo	-28.1	<0.001
40 mg vs placebo	-33.2	<0.001
80 mg vs placebo	-28.9	<0.001

All 4 doses of suvorexant (i.e., 10, 20, 40, and 80 mg) were more effective than placebo in improving insomnia as measured by the 1° efficacy endpoint, sleep efficiency (SE), at Night 1 and Week 4 (table above, left). All were more effective than placebo in improving sleep maintenance as measured by the 2° efficacy endpoint, wakefulness after persistent sleep onset (WASO), at Night 1 and at Week 4.

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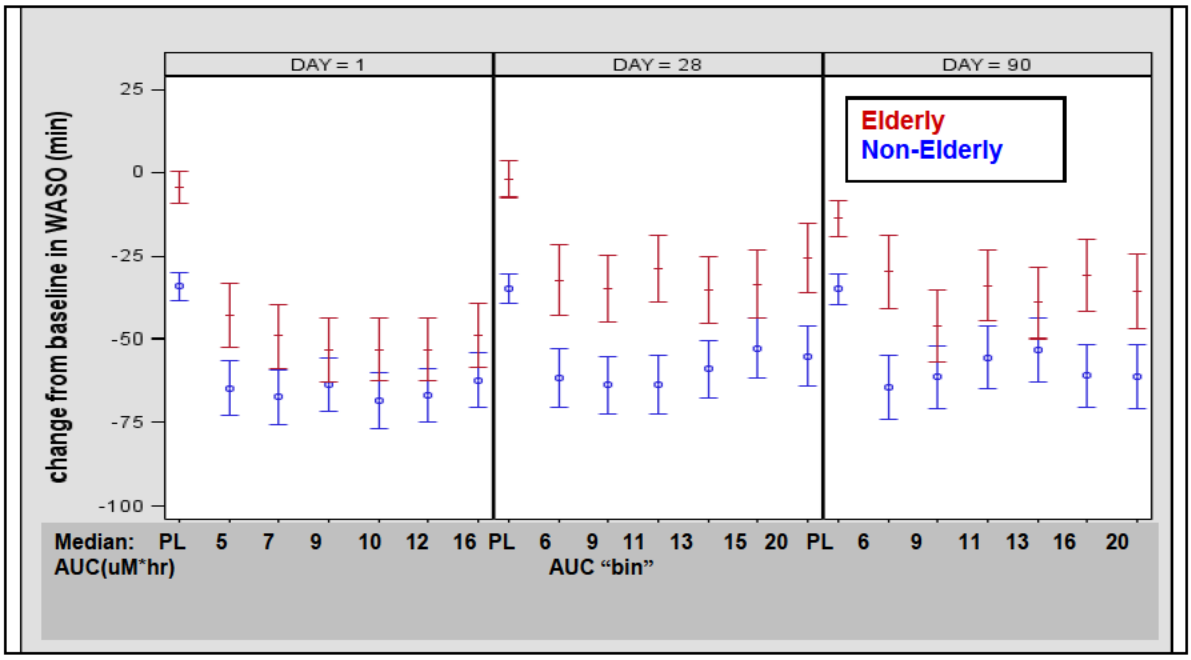
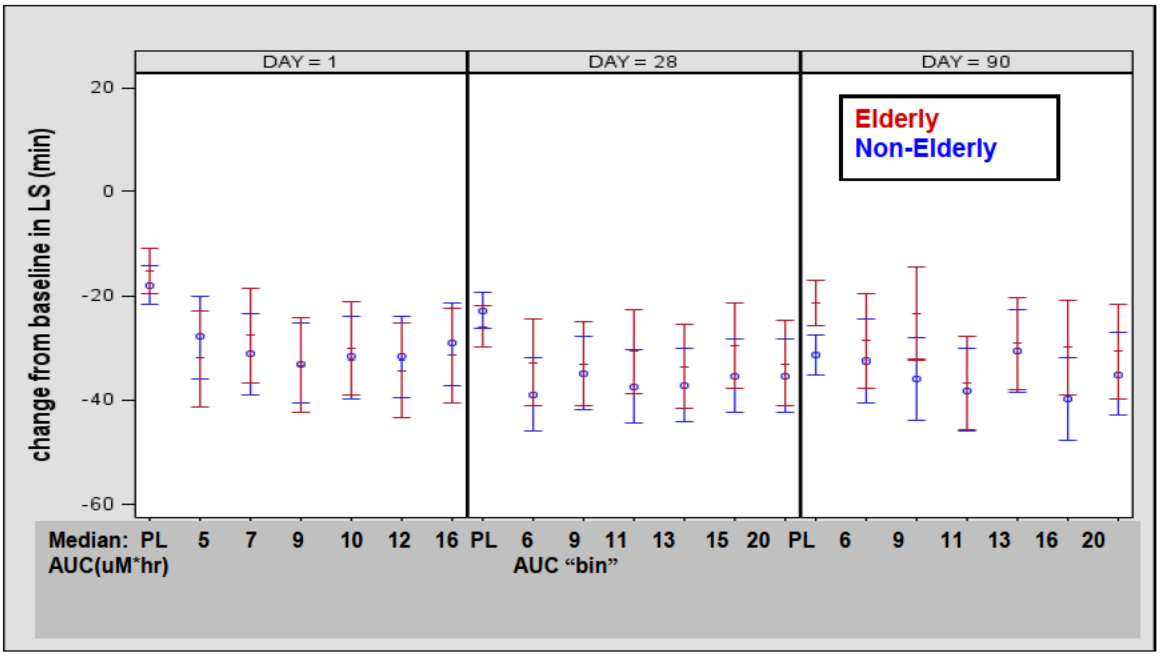
According to the testing strategy, none of the doses of suvorexant was more effective than placebo in improving sleep onset as measured by the 2° efficacy endpoint, latency to onset of persistent sleep (LPS), at either Night 1 or Week 4. Nominal p-values were significant for the 40-and 80-mg doses (vs. placebo) at Night 1, and for the 20-mg dose at Week 4 (table above, right), but were not statistically significant given the multiple testing strategy.

Study 6 provides the sole evidence of efficacy for the 10 mg dose. As above, there are statistically significant effects on reducing sleep latency and increasing sleep maintenance, based on objective measures, but subjective measures, subjective total sleep time (TST) and subjective time to sleep onset (TSO), were not statistically significantly different from placebo (data not shown).

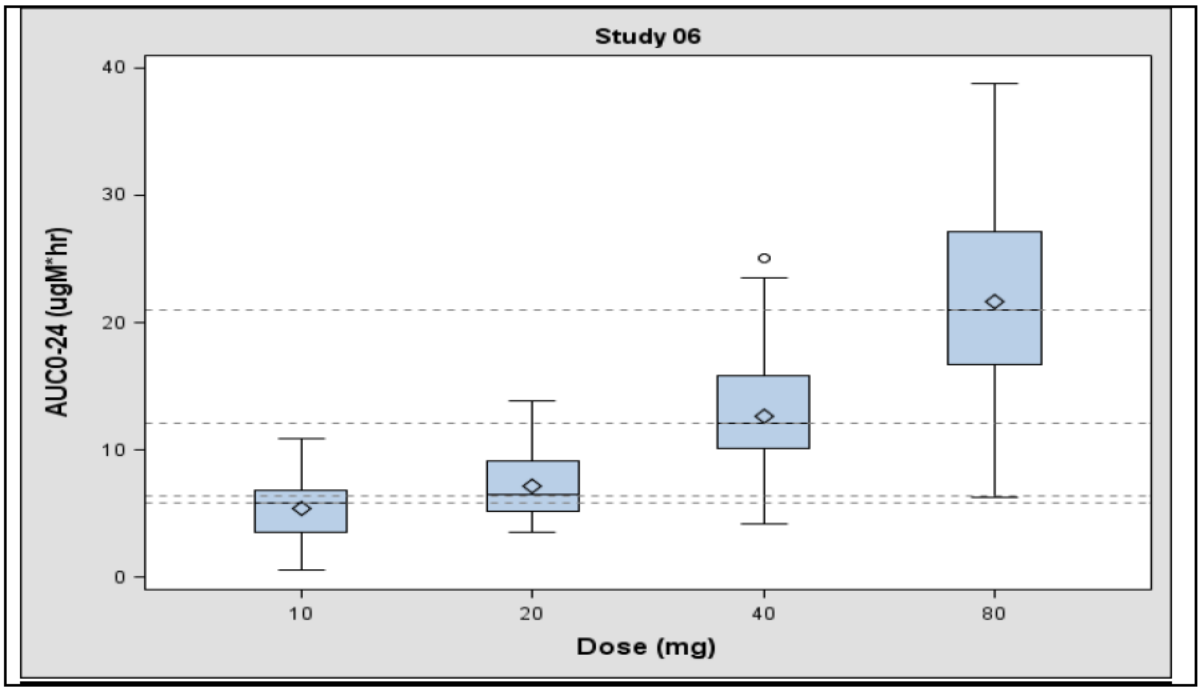
The clinical pharmacology reviewers combined data from Studies 28 and 29 and performed analyses of the objective measures (WASO, LPS) by dose and by plasma levels, the latter divided into "bins" on the basis of median AUC. The subjects were divided by age (elderly, non-elderly). The following graphs, extracted from the Clinical Pharmacology review, show these analyses.

Here, the LS mean with 95% CI for Δ WASO (below) and Δ LPS (next page) are shown vs. exposure (AUC_{0-24}) and by time (Days 1, 28, and 90), for elderly (red) and non-elderly (blue) patients. LS means were adjusted by baseline value, age group, region and gender, to be consistent with dose-response analysis.





The figure, below, shows the dose-proportionality of suvorexant over the dose range of 20 mg to 80 mg. The median AUC_{0-24} for the 10-mg dose was 5.3 μM*hr. The median AUC_{0-24} was 6.3 μM*hr for the 20-mg dose, which is little different (data from 1st period of Study 6). The dotted horizontal lines indicate the median AUC_{0-24} for each dose. The median AUC_{0-24} for the 40- and 80-mg doses are 12 μM*hr and 21 μM*hr, respectively.



The important point is that the median AUC for the 10-mg dose is close to that of the 20-mg dose, and similar to the lowest AUC examined in the previous two graphs and AUC for which effectiveness was demonstrated.

The overall conclusion is that for the range of plasma levels achieved at doses from 10 to 80 mg, there is little difference in efficacy measured by objective sleep maintenance and sleep latency, and, at least for some patients, 10 mg is an effective dose.

Overall Efficacy:

Primarily on the basis of Studies 28 and 29, suvorexant is effective for both sleep latency and maintenance. Study 6 also shows that suvorexant is effective for sleep maintenance (based on WASO); the results in this study are less persuasive for sleep latency (based on LPS).

In Study 6, the effects of suvorexant on LPS are unclear; the higher doses (above 20 mg) appear significantly superior to placebo on Night 1, but no doses are significant at Week 4. Some analyses of the first period data suggest that 10 mg may be effective for LPS.

Analyses that combine data from all three studies do not suggest a dose- or concentration-response for sleep latency, based on objective LPS. In particular, a median AUC of about 5 μM*hr was shown to be effective, which is equivalent to the median AUC for the 10-mg dose.

Taken together, these data suggest that all doses studied (≥ 10-mg) are effective for both endpoints, and there is little evidence to suggest that the higher doses are substantially superior to 10 to 15 mg, at least for sleep maintenance, and probably for sleep latency as well. This conclusion is based primarily on the results of the analyses described above of the objective measures, measures we believe more reliably assess the effects of interest than do the subjective measures.

Safety:

Exposure: A total of 2027 subjects with insomnia were exposed to suvorexant in the phase 2 and phase 3 trials, including 1218 for ≥ 3 months, 507 for ≥ 6 months, and 160 for ≥ 1 year, of whom 41% were age 65 and older. It is noteworthy that 41% of subjects were overweight (BMI ≥ 25 to < 30) and 16% were obese (BMI ≥ 30).

Deaths: There were 2 deaths in the development program (1 suvorexant; 1 placebo). Drug-relatedness was not really interpretable.

Serious Adverse Events: These were relatively healthy subjects, and there were only 99 subjects with 1 or more serious adverse events in the entire program. With randomization approximately 1.3:1 (suvorexant:placebo), not a single serious adverse event was reported in an excess of 2 subjects in the suvorexant group (relative to placebo), and there were no particular patterns within organ systems that suggested causality.

Adverse Events of Importance:

Somnolence/ Impairment: The main non-serious adverse event that stood out was somnolence, which was reported in 3.0%, 6.7%, and 10.7% of subjects in the placebo, low-dose, and high-dose groups, respectively. Severe somnolence was reported in 0.1%, 0.2%, and 0.6% of subjects in these respective groups. Approximately half of all somnolence was initially reported

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within the first week; with approximately half reported later. The duration of somnolence was longer in suvorexant subjects than in placebo subjects. There were no consistent patterns in somnolence in terms of age, sex, or BMI.

Related to somnolence, excessive daytime sleepiness was reported in 0.2%, 0.6%, and 1.1% of subjects in the placebo, low-dose, and high-dose groups, respectively.

Driving: The results of a formal driving study demonstrated that suvorexant can cause significant impairment in driving the morning after dosing. In study P035, a study of non-elderly adults, both 20- and 40-mg doses caused an increased fraction of patients with excessive deviation in lane position the morning after a single bedtime dose taken the night before. This next-morning effect clearly persisted after 8 days of continuous dosing of 40 mg. Furthermore, 4 women had to discontinue the testing due to excessive somnolence.

In Study P039, a similar driving study in elderly adults, there were no statistically significant differences between either dose of suvorexant and placebo in the symmetry analysis, though at the 30-mg dose there were clear numerical increases in the number of subjects who met SDLP criteria for impairment.

Suicidal Ideation/Behavior: Suvorexant increased the risk of suicidal ideation/behavior. In the 12-month controlled trial data, there were 0 placebo subjects (0%, N=1012) vs. 8 suvorexant subjects (0.6%, N=1268) who were considered to have had suicidal ideation, based on the Columbia Classification Algorithm for Suicide Assessment (C-CASA).

Narcolepsy-like Syndrome: Suvorexant was also associated with adverse events that can be considered to be elements of a narcolepsy-like syndrome. Suvorexant caused an increase in the incidence of sleep paralysis and hypnogogic/hypnopompic hallucinations.

In the 3-month phase 3 population, 3 high dose (0.4%) and 2 low dose (0.2%) suvorexant patients experienced hypnogogic or hypnopompic hallucinations, versus no placebo patients (N = 1,025 placebo patients). In some cases, hallucinations were frightening to patients, with the sense that another person was in bed with them, or intended to harm them.

There were 45 suspected cases of cataplexy adjudicated. Although the adjudication panel did not consider any of these cases to be cataplexy, our independent review suggests that at least one, and perhaps several more, could reasonably have been cases of actual cataplexy.

Cholesterol: Dr Illoh's review notes that in Study 6, suvorexant increased serum cholesterol levels in a dose-related manner with the maximum mean increase of 6.0 mg/dL at a suvorexant dose of 80 mg, versus 3.7 mg/dL decrease in placebo (table below). Cholesterol was not measured in phase 3 studies.

	placebo	suvorexant			
		10 mg	20 mg	40 mg	80 mg
Δ cholesterol	-3.7	1.2	2.3	3.1	6

Dr. Illoh suggested that including this effect in labeling would be appropriate.

Advisory Committee: This application was discussed by the Peripheral and Central Nervous System Advisory Committee on May 22, 2013.

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- Most Committee members agreed that there was substantial evidence of efficacy for suvorexant at the doses studied, for both sleep onset (12 'yes'/4 'no') and sleep maintenance (16 'yes'/0 'no').
- Most Committee members agreed that doses of 15 mg and 20 mg were acceptably safe to be recommended as starting doses, by a vote of 15 'yes'/ 3 'no.'
- Most Committee members endorsed the view that the lowest effective dose of suvorexant should be recommended, at least as a starting dose. Some Committee members voiced concern that starting with a dose too low could lead to middle of the night use, as well as premature discontinuations.
- Most Committee members agreed that an additional study of 10 mg was not necessary to establish efficacy of that dose, by a vote of 11 'no', 5 'yes' and 1 abstention, but reasons for this recommendation differed. About one-third of members voted no because they thought existing evidence was adequate to support efficacy of the 10 mg dose, whereas approximately one-third voted yes because they thought inadequate evidence of efficacy had been presented, although several of these members expressed the view that, with more study, the 10-mg dose seemed likely to be found effective. The remaining one-third expressed the general opinion that the 10-mg dose was either not effective, or not of sufficient efficacy to merit further study.
- The Committee was divided on whether safety had been adequately demonstrated for the 30- and 40- mg doses, with 7 voting 'yes', and 8 voting 'no.'

Pediatric Assessments: The applicant (b) (4) requested a full waiver for pediatric studies (b) (4)

The Division discussed the issue with the Pediatric Review Committee (PeRC) on May 1, 2013, and concluded that an appropriate pediatric population had not been identified. The PeRC agreed that a full waiver of pediatric studies was appropriate because studies were impossible or highly impractical given lack of an appropriate identified pediatric population.

Risk Evaluation and Mitigation Strategy (REMS): The review team did not see the need for a REMS.

Conclusions:

The applicant originally proposed suvorexant doses of 20 or 40 mg for non-elderly adults, and 15 or 30 mg for elderly adults, with the higher doses recommended. On May 14, 2013, in response to the Division's concerns enumerated in the FDA Briefing Package in advance of the Peripheral and Central Nervous System Advisory Committee Meeting, the applicant proposed a new, lower dosing recommendation: 20 mg for non-elderly adult patients and 15 mg for elderly patients.

Given that next-morning somnolence and other side effects were dose-related, it is important to identify the lowest effective dose. For the objective endpoints, suvorexant's efficacy was reasonably consistent at all doses tested.

There was recognition that the 10 mg dose was not statistically significantly different from placebo for the subjective endpoints. But given that relatively few subjects were tested at this dose, statistical significance was not expected. Moreover, the exposure-response data showed that exposure to 10 and 15 mg was not importantly different.

These data, and the growing recognition that patients are individuals who may respond differently to a given dose, provided the impetus to approve a 10-mg dose, acknowledging that dose will need to be individualized, and will need to be higher for some patients. The 10-mg dose provides additional safety for special populations – patients taking moderate CY3A4 inhibitors and patients with moderate hepatic impairment – as well as women, obese patients, and obese women in particular, where clearance that is 2-3 times lower than men with a normal BMI. High plasma concentrations would be expected to be associated with an increased incidence of adverse events, in particular impaired next-day driving, and dosing recommendations should take this into consideration.

The lack of significant pharmacokinetic differences between non-elderly and elderly subjects argues for recommending the 10-mg dose for both elderly and non-elderly patients, at least as a starting dose, though the lowest dose studied in non-elderly patients was 20 mg.

The Peripheral and Central Nervous System Advisory Committee provided somewhat conflicting advice regarding an acceptable dose for marketing. The majority believed that 10-mg suvorexant was efficacious, and that this dose should be available for marketing. The countervailing view was similar to the view of the Clinical Reviewer, who took the position that the 15-, 20-, 30-, and 40-mg doses sought by the applicant showed efficacy, and that the risks of suvorexant would be comparable to those of approved drugs for insomnia. This conclusion seems defensible; however, I would argue that risks comparable to those of approved drugs for insomnia are higher than necessary, which is why I agree with others in the Division who have argued for the availability of a 10-mg dose.

In summary, the 10 mg dose appears to be an effective dose (though perhaps in fewer patients than higher doses). Given that other risks, especially the risk of next-day driving impairment, seem dose-related, I agree with most in the Division who believe that suvorexant cannot be marketed with an acceptable safety profile without the availability of the 10-mg dose. Given that this dosage strength is not currently available, we will issue a Complete Response (CR) letter, requiring that the 10 mg dose be available. In addition, because we expect that certain relatively large segments of the population may have unacceptably high plasma levels, even at the 10-mg dose (for example, obese women and patients taking moderate CYP3A4 inhibitors), we recommend that the applicant also produce a 5-mg dosage strength, a strength that would be expected to yield plasma levels in these populations that are essentially equivalent to the 10-mg dose in other populations.

Finally, because the risks of the highest doses (30 and 40 mg) are significantly greater than those of the lower doses, and effectiveness is not importantly better, we conclude that these higher doses should not be marketed.

Reference ID: 3334017

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/s/

ELLIS F UNGER
06/28/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Neurology Products (HFD-120)

Memo to File

Date: June 21, 2013

From: Kachi Illoh, MD, MPH, Reviewer, CDER/OND/ODE1/DNP

Subject: Addendum to Primary Clinical Review

NDA#: 204,569
Application Drug: Suvorexant (MK-4305), Antagonist to Orexin Receptors
Proposed Use: Treatment of Insomnia, sleep onset and maintenance difficulties
Sponsor: Merck Sharp & Dohme Corp.

Submission: 08/30/2013 (Original NDA)
05/22/13 (SD#29, eCTD 027 Response to Information Request)

Advisory Committee Meeting: 05/22/2013
Pediatric Review Committee (PeRC) Meeting: 06/05/13
CDER Pulmonary Consult Team Review: 06/12/13

Summary: This is an addendum to the primary clinical review of NDA 204569, suvorexant for the treatment of insomnia, dated April 29, 2013. This addendum updates the primary review of the original NDA with the following information:

- Advisory committee meeting discussions and votes
- Editorial changes to the primary review
- Pediatric Review Committee (PeRC) assessment of Waiver Request
- CDER Pulmonary Consult Team review
- Sponsor's response to Information Request from FDA
- Updated dosing recommendations

This document does not discuss issues covered in the primary review such as regulatory background, CMC, Pharmacology-Toxicology, Clinical Pharmacology, or clinical development.

The discussions outlined in this document are consistent with the results of the original NDA analyses. No new or different safety issues were identified to significantly change the overall risk benefit assessment from the primary review.

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of this NDA for suvorexant initiated at the 15 mg dose and not exceeding 40 mg once daily at bedtime for the treatment of insomnia that is characterized by sleep onset and sleep maintenance difficulties.

1.2 Risk Benefit Assessment

Merck submitted the NDA to support approval of suvorexant for the treatment of insomnia, characterized by sleep onset or sleep maintenance difficulties or both sleep onset and sleep maintenance difficulties. Previously the recommended initial suvorexant doses were the high doses (suvorexant HD), 30 mg in elderly and 40 mg in non-elderly individuals, to be taken once daily at bedtime. Merck revised the dosing recommendations, proposing to initiate treatment at the low doses (suvorexant LD) tested in the Phase 3 confirmatory efficacy trials, which were 15 mg in elderly and 20 mg in non-elderly subjects.

To support this NDA, Merck submitted data from three Phase 3 clinical trials (P028, P029, and P009), one Phase 2 trial (P006), and a pool of Phase 1 trials (32 trials). Two of the Phase 3 trials, P028 and P029, provided 3-month treatment data for the primary efficacy assessment of suvorexant LD and HD. The dose-finding trial P006 provided supportive efficacy data on doses including 10 mg and 80 mg. Trial P009 provided long-term safety and efficacy data for suvorexant HD. Additional details of these trials with risk benefit assessments of the tested doses are provided in the primary clinical review.

My recommendation on regulatory action, consistent with the primary review, is based on the review of the efficacy trials and combined safety data that are primarily from the three Phase 3 trials with supportive data from the Phase 2 trial and pooled Phase 1 trials. This addendum provides no new safety issues to significantly change the overall risk benefit assessment from the primary clinical review. Therefore, my earlier recommendation for approval based on the clinical review remains unchanged.

1.3 Recommendations for Postmarket Requirements and Commitments

There are no new recommendations for postmarket requirements and commitments for this drug. Merck requested a waiver of pediatric studies (b) (4) ; the Agency's Pediatric Review Committee (PeRC) considered the request as follows.

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Pediatric Review Committee (PeRC) Review

To fulfill the Pediatric Research Equity Act (PREA) requirements, Merck needed to include in the NDA a pediatric development plan for the treatment of insomnia. In the NDA, Merck requested a waiver of studies [redacted] (b) (4) For this plan, Merck requested a waiver of studies for children [redacted] (b) (4) Please see primary clinical review Section 7.6.3 for additional information on Merck's proposed pediatric plan.

During NDA review, the Division concluded that PREA studies were impossible or highly impractical in pediatric patients with insomnia and co-morbid ADHD, or in any other pediatric population. [redacted] (b) (4) Absence of a well characterized population in the pediatric population would make it impossible or highly impracticable to enroll subjects for a trial. Also, the Division previously waived pediatric studies for another hypnotic-sedative drug partly because of neuropsychiatric adverse events including hallucinations in children. Suvorexant has a potential to cause similar adverse events in children, given the experience of a small increase in the incidence of hallucinations in the adult population trials. Other neuropsychiatric adverse events of concern with suvorexant include excessive daytime sleepiness, sleep paralysis, and suicidal ideation. The Division noted that these events may not be acceptable in children.

PeRC reviewed the waiver request on 6/05/13 and agreed with the Division for a waiver of suvorexant studies in all pediatric populations.

2 Editorial Changes to the Primary Review

Corrections and clarifications for the Primary Clinical Review include the following:

1. Pages 16, 138, and 186 Corrections: "Fewer subjects on suvorexant experienced MVAs while driving than on placebo. The incidence of MVAs among subjects …" should read "Fewer subjects on suvorexant experienced MVA-associated AEs while driving than on placebo. The incidence of MVA-associated AEs among subjects …"
2. Page 173 Correction: In a combination of five Phase 1 trials, somnolence occurred in 22.4% (28/125) after suvorexant treatment compared to 4.8% (5/105) after placebo. The original text had "0.8% (5/105) after placebo."
3. Page 174 Addition: The sponsor noted that Subject AN 04559, one of the five subjects on suvorexant HD who reported suicidal ideation or behavior, had a prior history of suicidal ideation reported on the C-SSRS.

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4. Page 207 Correction: The sentence introducing Table 107 should read: Below I summarize the common AEs that occurred with an incidence ≥2% in a treatment group in the 12 months treatment period, not 6 months treatment period as stated in the original text.
5. Page 236 Addition: Reviewer Comment should include "One subject displayed cognitive impairment on zolpidem in Period 1 and on suvorexant 30 mg in Period 2, and stopped driving test early on Day 2 of placebo (9 hours after Day 1 treatment) in Period 4."
6. Page 242 Correction: Subject AN 06111 in Trial P028 is the 36-year-old female on suvorexant LD who had a positive pregnancy test, not Subject AN 02609.
7. Page 247 Addition: When considering both terms of euphoria and feeling high, the incidence of euphoric mood was 8.8% (3/34) for the suvorexant 150 mg group and 14.7% (5/34) for the zolpidem 15 mg group.

3 Additional Review of Safety

3.1 Supportive Safety Results – Respiratory Safety

Pulmonary Consult Team Review of Special Safety Clinical Trials

CDER Pulmonary Consult Team reviewed the results of the clinical trials in which Merck evaluated suvorexant for respiratory safety. Please see their consult review of 6/12/13 for details. Below I summarize their findings.

In Trial P036, subjects with mild to moderate obstructive sleep apnea (OSA) who were treated with multiple suvorexant doses recorded a small increase in apnea-hypopnea index (AHI). The small AHI increase (mean 2.66) was unlikely to be clinically significant, and was not associated with any clinically meaningful decrease in oxygen saturation.

In Trial P032, no deleterious respiratory effects were noted in subjects with mild to moderate chronic obstructive pulmonary disease (COPD) who were treated with suvorexant for four days.

In Trial P040, healthy subjects received a single supra-therapeutic dose of suvorexant. The treatment did not have a deleterious effect on oxygen saturation or the AHI.

Please refer to the primary clinical review for additional details of the Supportive Safety Results, including those of other special safety studies.

3.2 Additional Submissions / Safety Issues

Response to Information Request from FDA on 15 May 2013

Reference ID: 3330009

On 5/22/13, Merck submitted a response to the Division's clinical questions on certain adverse events in Trials P006, P009, P028, and P029. Below is a summary of the response.

FDA Question #1: Did patient AN00857 in study 006 experience 'muscular weakness' events that were different than the sleep paralysis events? Please describe what is known about the patient's adverse events, and how you evaluated them as possible cataplexy.

Sponsor's Response: The muscular weakness event was inconsistent with a diagnosis of cataplexy as outlined in the sponsor's guidance to clinical trial investigators on Events of Clinical Interest (ECIs). The event occurred in the absence of an emotional trigger, and occurred in a consistent and predictable way. Therefore it was not submitted for adjudication.

FDA Question #2: Are the patients below different from AN02642 or AN00857? Please describe what is known about the adverse events experienced by these patients, and how you evaluated if the events were cataplexy.

a. 4305-006-000700001, study 006, attack of muscle weakness (right knee)
b. 4305-006-00900002, study 006 weakness of legs
c. 5305-009-009900001, study 009 weak feeling in both legs
d. 001600001, study 29, 10 second muscle weakness
e. 28-009400005, study 28 feeling of weakness both knees

Sponsor's Response: AN00857 and 4305-006-000700001 represent the Allocation and screening numbers for the same subject. The five listed subjects were different from AN 02642. Below is a tabular summary of the six cases cited in FDA Question #2.

Table: Cases of Muscular Weakness Cited in Question #2

Study ID – (Allocation)	AE Description	Intensity	Duration	Other details – dose, age, gender, comments
006 – 000900002 (AN 00856)	Weakness of legs	Mild	28 days	40 mg: 60 year old male. Persists throughout
006 – 000700001 (AN 0857)	Muscle weakness	Mild	22 days	80 mg: 24 year old male. Unilateral weakness in the middle of the night, ~3 hrs post-dose, when getting out of bed
009 – 009900001 (AN 03053)	Weak feeling both legs	Mild	10 days	40 mg: 38 year old male. Reported in association with a fever and viral illness
009 – 004800008 (AN 02642)	Muscular weakness	Moderate	11 hours	40 mg: 59 year old male
028 – 009400005 (AN 06058)	Feeling of weakness both knees	Moderate	1 min	40 mg: 60 year old female. Occurred ~3 hrs after taking study drug when patient got out of car when taking husband to the hospital

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029 – 001600001 (AN 12108)	10 sec muscle weakness	Mild	10 sec	20 mg: 60 year old female. Unilateral. Occurred while walking ~15 hrs post-dose. No emotional triggers reported

(Source: Sponsor's submission on 6/22/13 Module 1.11.3 Information Amendment: Response to FDA Questions Page 3 Table 1)

Merck noted that the five cases (a-e) had events atypical of cataplexy based on the duration of the weakness, inconsistent elements of focality, and occurrence without emotional triggers. For these reasons, none of these cases were submitted for adjudication as potential cataplexy. Two of the cases, summarized below, had the Modified Cataplexy Questionnaire completed but were not sent for adjudication.

Subject AN 06058 in Trial P028, a 60 year old female on suvorexant HD (40 mg) experienced muscular weakness, described as feeling weak in both knees, of moderate intensity and lasting 1 minute on Trial Day 13. The event occurred about 3 hours after she took trial medication. She reported "feeling strange" (as though her body was not her body) for 20 minutes while driving. Subsequently, when she got out of the car at her destination, she had feelings of weakness in her knees that lasted about 1 minute. She reported no emotional triggers as confirmed on the Modified Cataplexy Questionnaire completed on Day 15. Her medical history included uveitis and hysterectomy, and concomitant medications included dexamentasone (for stomatitis) and loxoprofen and serrapeptase (for common cold). She completed the trial per protocol.

Subject AN 12108 in Trial P029, a 60 year old female on suvorexant LD (20 mg) experienced two brief episodes of muscle weakness, described as brief weakness in her right leg, a sensation that her leg was giving out, while she was walking on Trial Day 11 at about 15 hours after taking trial medication. The two events occurred 30 minutes apart, each lasting 5-30 seconds. There was no emotional trigger. The Modified Cataplexy Questionnaire completed on Day 17 confirmed the report of unilateral leg weakness. As shown in the graphical patient profile below, other AEs reported during the core treatment period included memory impairment, dry mouth, leg cramps, and somnolence. Her laboratory test results showed a brief rise from baseline in liver enzymes during the month she reported the weakness. Her medical history included the following: Osler Webber Rendu Syndrome; collapsed vertebrae; kyphoplasty; Grave's Disease; epistaxis; anemia; post-menopause; and oral surgery. The sponsor's audit trail showed the event was briefly coded as cataplexy based on Merck's guidance document, but it was later recoded as muscle weakness during revision of the guidance document. According Merck, "the site noted that they would not have described the event as 'cataplexy' but rather as 'brief muscle weakness' because of the lack of emotional context; and, they did not send the case for adjudication." The subject completed the trial per protocol, as dosage exposure shows in the graphical profile below.

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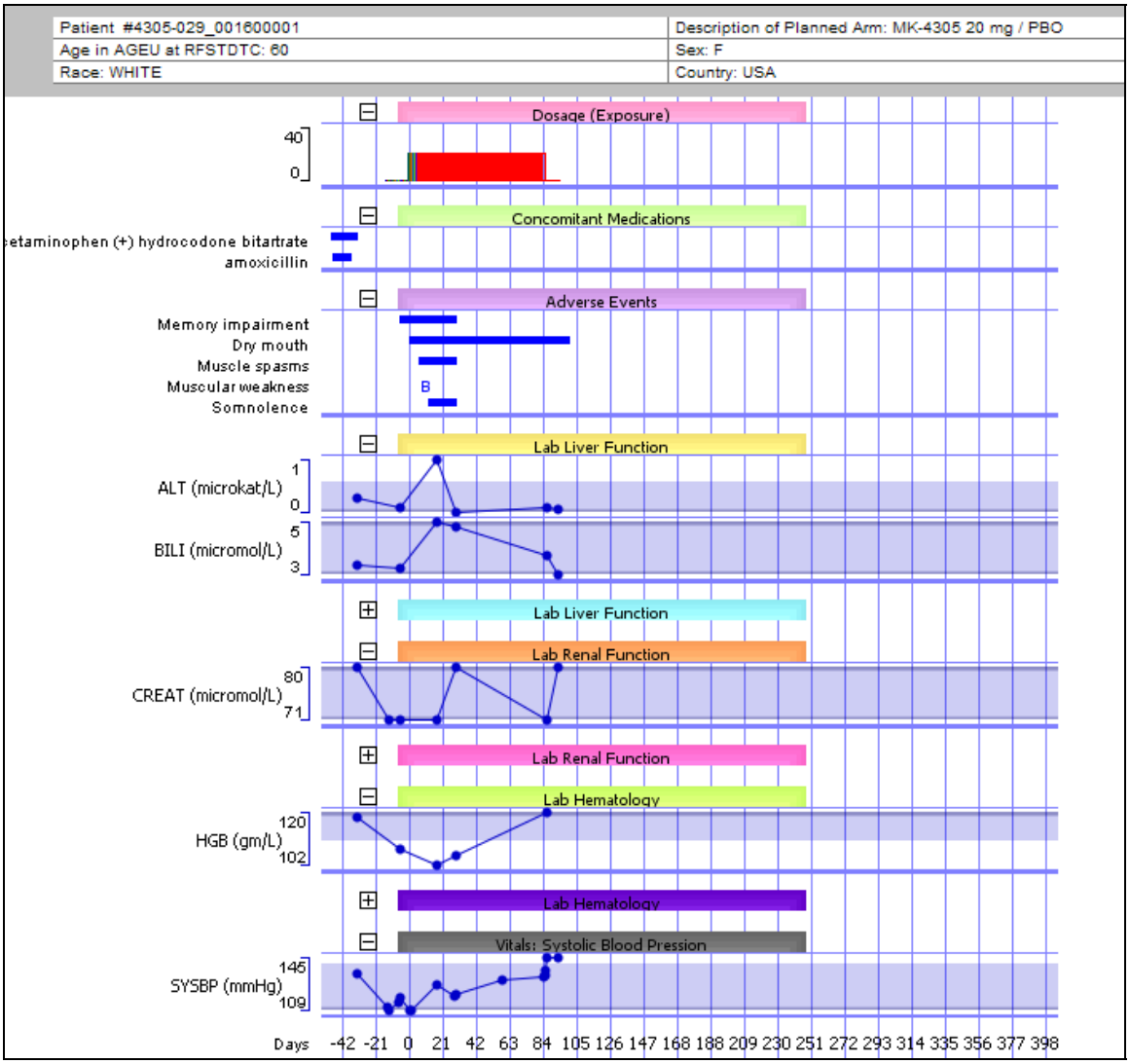
Figure: Subject AN 12108 Graphical Patient Profile



***Reviewer Comments**: The available information is insufficient to support a diagnosis of cataplexy in any of the cases. Subject AN 12108 reported somnolence, however none of the five cases reported excessive daytime as classified in Merck's ECI. None of the events were precipitated by emotional triggers.*

4 Advisory Committee Meeting

This section discusses the advisory committee meeting questions.

Efficacy

1. For suvorexant, the applicant seeks an indication for the treatment of insomnia characterized by difficulties with sleep onset and/or maintenance. The proposed dosing algorithm includes higher and lower doses for non-elderly and elderly patient populations:
    - Starting dose: 20 mg in the non-elderly, less than 65 years of age; 15 mg in the elderly, aged 65 years and older
    - High Dose: 40 mg in the non-elderly and 30 mg in the elderly

    a. **DISCUSSION:** Please discuss whether separate doses are necessary for non-elderly and elderly patient populations.

    Committee Discussion: The committee did not give a definitive answer regarding whether separate doses were needed for non-elderly and elderly patients. Some members suggested that lower doses may be considered for elderly patients who are often on multiple concomitant medications. However, others suggested that additional factors beyond age, such as comorbidities, may be more important in determining the need to offer lower doses. Further, members noted that an assessment of the 10 mg dose in the elderly population data was lacking.

    b. **DISCUSSION:** Please discuss separately the evidence of effectiveness in improving sleep onset and sleep maintenance.

    Committee Discussion: The committee generally agreed that there was evidence of effectiveness in improving sleep in insomnia patients. For sleep onset, some committee members felt that the evidence of effectiveness was weak; but for sleep maintenance, the majority of the committee agreed that there was evidence of effectiveness for suvorexant.

    The sleep experts on the committee stressed that subjective outcome measures were clearly more important than the objective measures. And insomnia relief was important for next day functioning.

    c. **VOTE:** Are these dose ranges effective for the treatment of insomnia characterized by difficulties with sleep onset?

    Vote: Yes = 12 No = 4 Abstain = 1

    Committee Discussion: The majority of the committee members agreed that the dose ranges stated above were effective for the treatment of insomnia characterized by difficulties with sleep onset. Those who disagreed voted “NO” because of their concerns that the low dose lacked efficacy for sleep onset insomnia.

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d. **VOTE:** Are these dose ranges effective for the treatment of insomnia characterized by difficulties with sleep maintenance?

Vote: Yes = 16 No = 0 Abstain = 1

Committee Discussion: The committee members agreed that the dose ranges were effective for the treatment of insomnia characterized by difficulties with sleep maintenance.

2. The applicant has submitted data supporting the conclusion that 10 mg is an effective dose. If 10 mg were the recommended initial dose, labeling would include a recommendation to increase the dose, if necessary, to achieve efficacy for an individual patient (if safety of higher doses were considered acceptable). Such labeling could reduce side effects and would be consistent with recent labeling changes for zolpidem products.

a. **DISCUSSION:** Please discuss the pros and cons of the general approach of starting sleep-aid drugs at the lowest dose with a reasonable effect, even if not the full effect.

Committee Discussion: The committee agreed that starting suvorexant at a low dose and escalating to a higher dose was reasonable. However, the sleep experts on the committee were concerned that if the low dose was not effective, the patients were more likely to permanently discontinue the medication or take a second dose in the middle of the night to relieve their insomnia. Either of these results would be undesirable.

b. **DISCUSSION:** Please discuss whether the applicant has established that 10 mg is an effective dose.

Committee Discussion: The committee did not agree on whether the applicant had established that 10 mg was an effective dose. Committee members noted that it was interesting that the applicant never established 10 mg as an effective dose and it was FDA that performed the post hoc analysis of an underpowered Phase 2 trial to suggest effectiveness for the dose. They further noted that if the patient's feeling was considered, the answer was "No" to whether 10 mg was an effective dose. A member expressed concern about how the patient and the doctor would know when to increase the dose.

c. **DISCUSSION:** Please discuss whether 10 mg would be an appropriate recommendation as a starting dose, with labeling that suggests increasing the dose for patients in whom 10 mg is not effective.

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Committee Discussion: The committee did not agree on whether 10 mg would be an appropriate recommendation as a starting dose, with labeling that suggests increasing the dose for patients in whom 10 mg is not effective. Some members noted that the data were inadequate to show the 10 mg dose as effective and that additional efficacy trials were needed. Others noted that having the 10 mg dose would allow for individualized therapy for patients who could benefit from such a low dose.

d. **VOTE:** Should the applicant be required to perform additional efficacy studies of the 10 mg dose prior to approval?

Vote: Yes = 5 No = 11 Abstain = 1

Committee Discussion: The majority of the committee agreed that the applicant should not be required to perform additional efficacy trials of the 10 mg dose prior to approval because an additional trial would not provide new information. Those who voted "Yes" suggested that the 10 mg dose may not be an effective dose and that efficacy trials were needed to sufficiently support its efficacy. One member voted "Yes" because he thought the 10 mg dose appeared effective in the Phase 2 trial, but he would like more data on the 10 mg dose or even 5 mg dose. Some members who voted "No" observed that the 10 mg dose showed no evidence of efficacy and there was no reason to further evaluate the dose. Others voted "No" because they believed the FDA analysis suggesting the dose to be effective, so there was no need for additional trials before its approval.

3. **DISCUSSION:** The Agency believes that the safe use of hypnotic drugs should incorporate the concept that the lowest effective dose should be used. The exposure-response data suggests doses even lower than 10 mg might be effective in some patients. Please discuss whether the applicant should study safety and efficacy of doses lower than 10 mg.

   Committee Discussion: The committee did not address this question.

Safety

4. **VOTE:** The applicant has recommended starting doses of 15 mg and 20 mg in elderly and non-elderly patients, respectively. Is the safety of these doses acceptable?

   Vote: Yes = 13 No = 3 Abstain = 1

Reference ID: 3330009

Committee Discussion: The majority of the committee agreed that the safety of the proposed starting doses—15 mg in elderly patients and 20 mg in non-elderly patients—was acceptable. Members who voted "Yes" noted that the observed adverse events at these doses showed a better safety profile for the drug than currently marketed insomnia drug products. A member noted that he voted "Yes" but wished he had more safety information for the stated doses. Another member, a sleep expert, expressed that the adverse events observed with drug such as parasomnias were not new for insomnia drugs. Further, he thought the case of muscle weakness that was referred for adjudication from the clinical trials was unlikely to be cataplexy, especially with weakness event lasting up to 11 hours. The members who voted "No" expressed concerns about the drug's safety profile, potential drug interactions, and the potential for harm with titration to higher doses. They thought these doses were not safe for initiating treatment but were reasonable to titrate to, after starting from even lower doses. The committee member who abstained expressed concerns about non-neurologists prescribing the drug without adequately assessing for co-morbidities. Also, the committee members clarified that dose escalation would be based on efficacy and tolerability of the dose.

5. **VOTE:** The applicant has recommended doses up to 30 and 40 mg in elderly and non-elderly patients, respectively, who have not responded to lower does. Is the safety of these doses acceptable, if recommended only for patients who do not respond adequately to lower doses?

   Vote: Yes = 7 No = 8 Abstain = 2

   Committee Discussion: The committee members did not reach a consensus on whether the safety of the doses, 30 mg in elderly and 40 mg in non-elderly patients who had not responded to lower doses, was acceptable. Members who voted "Yes" were concerned about the lack of efficacy at lower doses and noted that it would be appropriate to start low and monitor for adverse events as the dose was titrated. A committee member noted that the safety profile was not different from approved insomnia drugs. Members also noted that rates of somnolence and suicidal ideation with these suvorexant doses were not so high when compared with those for antidepressants. Those who voted "No" expressed that the higher doses showed no evidence of increased efficacy but caused more adverse events, such as somnolence and driving impairment. A member noted that the titration strategy was not tested in the clinical trials. A committee member who abstained noted that it was uncertain whether the drug at these doses was less safe that currently marketed drugs.

6. **DISCUSSION:** The Agency believes that in some populations (e.g., obese women; patients taking metabolic inhibitors) the 15 mg dose results in excessive suvorexant exposure. Please discuss if you agree.

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Committee Discussion: The committee members noted that some populations, including obese women and patients on concomitant medications, warranted special attention. Many of the committee members expressed that the 15 mg dose did not result in excessive suvorexant exposure in obese women. The modest increase in exposure (drug concentration) in the obese women did not appear clinically meaningful, so it did not pose a huge concern.

7. **DISCUSSION:** If you deem the safety of suvorexant to be acceptable at some dose(s), please discuss whether labeling could be adequate to protect patients who drive, and to protect the public? If so, what would need to be included in labeling?

   Committee Discussion: Some of the labeling suggestions offered by some committee members included the following:

   - Use plain language that is clear and easy to understand
   - Recommend a 1-week follow up with the prescribing physician to assess safety and efficacy
   - Request driving assessment self-reports or simulator tests from the patient
   - Include statement for patients on suvorexant to avoid driving or use of heavy machinery, and avoid use with alcohol
   - Include a warning particularly for the high doses about somnolence that can occur even when the patient is not feeling sleepy and pose a danger to the driving patient and others
   - A committee member suggested halting advertisement and promotion for one year until more dosing and safety data were available.

5 Update on Dosing Recommendations

Merck changed the suvorexant dosing recommendations in an addendum to the briefing documents for the 22 May 2013 advisory committee meeting. The new proposal is for initiating treatment at suvorexant LD levels, the lowest doses tested in the Phase 3 confirmatory efficacy trials—15 mg in elderly and 20 mg in non-elderly individuals. Previously, the recommended initiating doses were at the high dose levels—30 mg in elderly and 40 mg in non-elderly individuals.

Lower doses than those tested in the Phase 3 trials have limited efficacy and safety data to determine their benefit-risk profile. However, safety issues at the proposed doses and PK/PD data may support further explorations for clear evidence of effectiveness for even lower doses. The results of the Phase 3 trials suggest that the lower doses may not provide adequate cover for both sleep onset and sleep maintenance insomnia, especially when considering both subjective perception of benefit and objective evidence of efficacy in individuals with insomnia. Indeed suvorexant 10 mg effects in Trial P006 do not provide convincing evidence of effectiveness based on endpoints frequently used to approve insomnia drugs. At the 10

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mg dose, suvorexant compared to placebo did not significantly improve any subjective insomnia endpoints for sleep onset and sleep maintenance. This suggests that individuals initiated on this dose may not expect benefits beyond the placebo effect, based on Trial P006 experience. Establishing this dose as truly efficacious over placebo may require an independent clinical investigation, but the advisory committee members objected to this option.

The absence of somnolence events (0%, 0/62) with suvorexant 10 mg in the Phase 2 trial does not give an assurance of the drug's safety at that dose because of the small sample size. Moreover, this dose was not evaluated in the driving studies. The relative absence of safety data limits the ability to provide meaningful risk-benefit assessments for suvorexant 10 mg or lower doses.

The advisory committee was supportive of initiating treatment at suvorexant LD levels (15 mg in elderly and 20 mg in non-elderly individuals). Also the sleep experts on the advisory committee were supportive of the sponsor's dosing recommendations. Granted that the vote was about evenly split on the safety of suvorexant HD, the sleep experts on the committee noted that the safety of suvorexant HD was acceptable if recommended for individuals who do not respond to lower doses. Considering these observations and data from the Phase 3 trials, the sponsor's recent dosing recommendation appears reasonable. On subgroups, there is insufficient data to suggest that obese females have better risk-benefit profiles at suvorexant doses below those tested in the Phase 3 trials. In all, I recommend initiating suvorexant at the 15 mg dose and to not exceed 40 mg once daily, with dosing at bedtime as in the Phase 3 trials, for the treatment of insomnia that is characterized by sleep onset and sleep maintenance difficulties.

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/s/

KACHIKWU O ILLOH
06/25/2013

RONALD H FARKAS
06/26/2013
For additional safety and efficacy findings, and differing conclusions and recommendations, please see the Team Leader review filed by Ronald Farkas

DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS
MEDICAL OFFICER CONSULTATION

Date:	June 12, 2013
To:	Russell Katz, Division of Neurology Products
From:	Lydia Gilbert-McClain, MD, Deputy Division Director Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Through	Badrul Chowdhury, MD PhD, Director, Division of Pulmonary Allergy, and Rheumatology Products
Subject:	Consult re NDA 204-569

General Information

NDA	204-569
Sponsor:	Merck Sharp & Dohme, Whitehouse Station, NJ
Drug Product:	Suvorexant (MK-4305)
Request From:	Russell Katz, Division Director, Division of Neurology Products
Date of Request:	December 18, 2012: **NOTE: division was not aware of this consult until several months later**
Desired completion date	April 30, 13
Materials Reviewed:	Consult request, NDA study reports

Introduction

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) was consulted by the Division of Neurology Products (DNP) for assistance in interpreting the results of studies done to assess safety of suvorexant (MK-4305), a new molecular entity (NME) under NDA review for insomnia. DNP requests review of the pulmonary studies P032 (conducted in COPD patients), P036 (conducted in patients with obstructive sleep apnea), and study P040 (in healthy subjects).

Suvorexant is a selective antagonist for orexin receptors OX_1R and OX_2R. The drug inhibits activation of wakefulness by blocking the binding of orexin A and orexin B to their orexin receptors thereby dampening the wake-promoting effects of these two neurotransmitters. It has been shown that selective inhibition of orexin receptors by orexin receptor antagonists facilitate the physiological process by which the brain transitions from wake to sleep by transiently blocking binding of the wake-promoting neurotransmitters orexin A and orexin B to receptors OX_1R and OX_2R. Suvorexant is formulated as an immediate-release tablet for oral administration in 15 mg, 20 mg, and 30mg and 40 mg strengths. The proposed indication is for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. The proposed dose is 40 mg once daily for non-elderly adults (<65 years) and 30 mg once daily for elderly adults (> 65 years) immediately before bedtime.

The purported advantage of this product is that unlike other products with hypnotic effects that are used to treat insomnia (benzodiazepines, non-benzodiazepines, barbiturates) suvorexant does not possess the intrinsic neuro-relaxant or anxiolytic properties that accompany interaction with the GABA system. The approach to facilitating sleep with suvorexant is specifically selective through antagonism of the wake-inducing output of a relatively limited and discreet pool of orexin neurons as opposed to activation of the more widely distributed inhibitory GABAergic neurons.

As part of the safety aspect of the drug development program, the sponsor evaluated the effects of suvorexant on respiratory function in patients with mild to moderate chronic obstructive pulmonary disease (study 032) and in patients with obstructive sleep apnea (study 036). A single dose study in healthy subjects (study 40) was also conducted. A brief summary of these studies and results are described below. Results for the respiratory effects evaluated (i.e. oxygen saturation [SaO_2] and the apnea-hypopnea index [AHI]) are presented. Results for study endpoints relating to sleep and wakefulness are not reviewed and are referred to the neurology reviewer.

REVIEW of STUDIES

Study 032 – At study to evaluate the Effects of MK-4305 (Suvorexant) in patients with chronic obstructive pulmonary disease

Design/objectives

The study was designed as a multicenter, randomized, double-blind, placebo-controlled, 2-period crossover study. The primary objectives of the study were to evaluate the safety and tolerability of multiple oral doses of suvorexant in patients with COPD and to evaluate the effect of multiple doses of suvorexant on oxygen saturation (SaO2) during total sleep time as measured by pulse oximetry. Secondary objectives included evaluation of several parameters following multiple dose administration of suvorexant: 1) The proportion of the night in which SaO2 was < 90%, < 85%, and < 80%; 2) Comparison of the mean SaO2 during different sleep stages; 3) the effect on AHI as measured by polysomnography. A number of exploratory objective sleep parameters were also assessed.

Inclusion Criteria

Patients eligible for enrollment in the study could be male and female patients with a diagnosis of COPD ages 18-85 by medical history and pulmonary function tests (i.e. with evidence of fixed obstruction on spirometry with $FEV_1/FVC < 70\%$). Patients with mild to moderate COPD were eligible for enrollment.

Reviewer comment: The sponsor used a modification of the GOLD criteria for moderate COPD to allow for enrollment of patients with more severe airflow obstruction. According to the GOLD criteria mild COPD is classified as having a Post-bronchodilator $FEV_1 \geq 80\%$, and moderate COPD as having a post-bronchodilator FEV_1 of $\geq 50\%$ (with $FEV_1/FVC < 70\%$ predicted). For this study, the sponsor defined moderate COPD as patients with $FEV_1 \geq 40\%$.

Note that this degree of obstruction would fit the definition of severe COPD by the GOLD criterion. This modification allowed for enrollment of COPD patients with more severe degrees of airflow obstruction. This patient population allows for evaluation of a "worse case scenario" and is acceptable since patients were being monitored continuously on Day 1 and Day 4.

Patients with a history of insomnia could be enrolled, but patients should not have clinically significant abnormalities on the screening polysomnogram (PSG) including no evidence of obstructive sleep apnea (OSA), restless leg syndrome, periodic limb movement disorder, parasomnia including nightmare disorder, sleep terror disorder, and sleepwalking disorder. Also, patients should sleep for 4 hours or more/night, must be able to complete a sleep diary for at least 5 consecutive days any time prior to the screening PSG; must be a nonsmoker, or if a smoker must be smoking ≤ 20 cigarettes or equivalent/day without the urge to wake up to smoke during the night, and must be able to follow the smoking restrictions by the clinical research unit and sleep laboratory. Patients must have a usual bedtime between 8:00 PM and 12:30 AM and should not have any unusual changes in sleeping routine during the study. Patients must be in stable physical health for at least 2 weeks prior to study entry. Patients enrolled in the study had to have a body mass index of ≤ 40 Kg/m^2.

Exclusion Criteria

Exclusion criteria included the presence of lung diseases other than COPD, major cardiovascular disease within the last 6 months, neurological disorders; patients hospitalized within the last 2 months because of COPD; patients on long term oxygen for COPD (i.e. > 16 hours/day), patients with positive screening tests for alcohol or illicit drugs and benzodiazepines, malignancies except for non-melanoma skin cancer that has been treated and carcinoma *in situ* of the cervix; or nursing mothers. In addition, patients with ALT and AST and bilirubin > 1.5 x the upper limit of normal and serum creatinine > 2 mg/dL, or hematocrit > 55% were to be excluded. Patients with SaO_2 < 90% while awake (both supine and sitting) at the screening visit were excluded. Female patients could not be pregnant or breast-feeding and females of child-bearing potential were required to use specified birth control measures. Exclusion criteria based on the screening PSG included: SaO_2 < 80% for ≥ 5 consecutive minutes; ii) for patients < 65 an AHI > 10 or 5 – 10 with symptoms of excessive daytime sleepiness, impaired cognition, mood disorders, insomnia, hypertension, ischemic heart disease of history of stroke; iii) for patients > 65 an AHI > 15 or an AHI of 5 - 15 with symptoms.

Study conduct

Following the screening PSG, eligible patients were to report to the sleep laboratory for overnight PSG on Study Day 1 and Day 4 for overnight PSG after single dose (Day 1) and multiple doses (Day 4) of suvorexant. In each treatment period, patients < 65 years of age were assigned to suvorexant 40 mg, and patients ≥ 65 years were assigned to suvorexant 30 mg, or matching placebo for 4 consecutive days. Study drug was administered in the evening approximately half hour before PSG recording. In each treatment period patients remained in

the study unit overnight on days 1 and 4 for PSG recording and SaO_2 monitoring. There was a minimum washout period of 7 days between treatment periods.

The next day effects of suvorexant were evaluated by IDWR, DSST, Bond-Lader VAS, and Body sway. This review will not focus on these assessments as these are best evaluated by the DNP reviewers. Blood samples for plasma suvorexant concentrations were collected predose, and at 9 hours postdose on days 1 and 4 in both periods 1 and 2. Throughout the study, safety evaluations included physical exams, 12-lead ECG, and laboratory evaluations (hematology, blood chemistry, and urinalysis).

Results

A total of 25 patients entered the study. There were 9 men (age range 47 – 70 years) and 16 women (39 – 72 years). One patient (AN2124) was deemed a protocol violator and should not have entered into the study because the patient's AHI enrollment value was significantly higher than what was defined as study entry criteria. Therefore, this patient was excluded from the primary evaluation of SaO_2 and AHI data but was included in the evaluation of safety.

Five patients were considered elderly (age > 65 years) and received 30 mg suvorexant. The other patients received 40 mg suvorexant. The mean age was 58.2 years. A total of 21 patients were of white race and 4 were of black race. Four patients were obese (BMI 30 Kg/m^2 or greater).

Mean O_2 saturations

The individual listings of mean SaO_2 during Total Sleep Time (TST) showed no clinically meaningful change in Mean SaO_2 for any patients on day 1 or day 4. One patient had a mean SaO_2 of 87% on suvorexant compared to a SaO2 of 89% on placebo on Day 1 and one patient had a SaO_2 of 89 % on suvorexant compared to 90% on placebo on Day 4. The individual listings of Mean SaO_2 are shown below copied from the sponsor's submission.

Individual Listings of Mean SaO_2 During Total Sleep Time Results Following Multiple Dose Administration of Suvorexant: Source – Sponsor's table 11-4

	Day 1 SaO_2 During Total Sleep Time (%)			Day 4 SaO_2 During Total Sleep Time (%)		
AN	**Suvorexant**	**Placebo**	**Suvorexant -Placebo**	**Suvorexant**	**Placebo**	**Suvorexant -Placebo**
0001	96.00	95.00	1.00	97.00	96.00	1.00
0024	95.00	95.00	0.00	93.00	94.00	-1.00
0046	90.00	91.00	-1.00	89.00	Discon	Discon
0047	93.00	92.00	1.00	94.00	94.00	0.00
0048	91.00	92.00	-1.00	92.00	92.00	0.00
0049	93.00	91.00	2.00	93.00	90.00	3.00
0050	94.00	93.00	1.00	93.00	91.00	2.00
0051	94.00	93.00	1.00	92.00	93.00	-1.00
0071	92.00	94.00	-2.00	92.00	94.00	-2.00
0072	96.00	95.00	1.00	96.00	96.00	0.00
0094	95.00	94.00	1.00	96.00	94.00	2.00
0095	94.00	95.00	-1.00	94.00	94.00	0.00
0096	95.00	95.00	0.00	95.00	95.00	0.00
0172	94.00	93.00	1.00	94.00	93.00	1.00
0347	93.00	93.00	0.00	93.00	93.00	0.00
0348†	96.00	95.00	1.00	97.00	Missing	Missing
2023	93.00	95.00	-2.00	94.00	94.00	0.00
2024	90.00	90.00	0.00	90.00	91.00	-1.00
2046	95.00	96.00	-1.00	95.00	93.00	2.00
2047	92.00	92.00	0.00	92.00	93.00	-1.00
2048	87.00	89.00	-2.00	89.00	90.00	-1.00
2072	94.00	94.00	0.00	94.00	93.00	1.00
2073	91.00	92.00	-1.00	92.00	89.00	3.00
2124‡	93.00	92.00	1.00	91.00	90.00	1.00
2196	93.00	94.00	-1.00	96.00	95.00	1.00

† For AN0348, Period 2 (Placebo) Day 4 SaO_2 data are missing due to an unreadable SaO_2 channel.
‡ AN2124 was not included in the statistical analysis since this patient was a protocol violator.
Lower SaO_2 values are associated with impairment.

Data Source: [16.4]

Apnea-Hypopnea Index

Similarly, evaluation of the Apnea-Hypopnea index (AHI) did not reveal any clinically meaningful differences between Day 1 and Day 4 results following multiple dose administration of Suvorexant or placebo in patients with COPD.

Safety

There were no deaths or serious adverse events in this study. The listing of adverse events by System Organ Class (SOC) is shown in the table below

Adverse events by System Organ Class (Source: Sponsor table 12-1 from clinical study report)

	Suvorexant 40 mg (N=20)		Suvorexant 30 mg (N=5)		Placebo (N=25)	
	n	(%)	n	(%)	n	(%)
Patients with one or more adverse experiences	6	(30.0)	2	(40.0)	5	(20.0)
Patients with no adverse experience	14	(70.0)	3	(60.0)	20	(80.0)
Cardiac Disorders	0	(0.0)	1	(20.0)	2	(8.0)
Atrioventricular block second degree	0	(0.0)	1	(20.0)	0	(0.0)
Supraventricular tachycardia	0	(0.0)	1	(20.0)	0	(0.0)
Ventricular extrasystoles	0	(0.0)	0	(0.0)	2	(8.0)
Gastrointestinal Disorders	2	(10.0)	0	(0.0)	1	(4.0)
Abdominal pain	1	(5.0)	0	(0.0)	0	(0.0)
Crohn's disease	1	(5.0)	0	(0.0)	0	(0.0)
Dry mouth	0	(0.0)	0	(0.0)	1	(4.0)
General Disorders and Administration Site Conditions	1	(5.0)	0	(0.0)	0	(0.0)
Fatigue	1	(5.0)	0	(0.0)	0	(0.0)
Infections and Infestations	1	(5.0)	0	(0.0)	0	(0.0)
Urinary tract infection	1	(5.0)	0	(0.0)	0	(0.0)
Injury, Poisoning, and Procedural Complications	1	(5.0)	0	(0.0)	0	(0.0)
Accidental overdose	1	(5.0)	0	(0.0)	0	(0.0)
Investigations	0	(0.0)	0	(0.0)	1	(4.0)
Positive rombergism	0	(0.0)	0	(0.0)	1	(4.0)
Musculoskeletal and Connective Tissue Disorders	0	(0.0)	1	(20.0)	0	(0.0)
Muscle tightness	0	(0.0)	1	(20.0)	0	(0.0)
Nervous System Disorders	3	(15.0)	1	(20.0)	2	(8.0)
Headache	1	(5.0)	0	(0.0)	2	(8.0)
Sleep paralysis	1	(5.0)	0	(0.0)	0	(0.0)
Somnolence	2	(10.0)	1	(20.0)	0	(0.0)
Psychiatric Disorders	0	(0.0)	0	(0.0)	1	(4.0)
Abnormal dreams	0	(0.0)	0	(0.0)	1	(4.0)

Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category.
The same patient may appear in different categories.
Adverse experience terms are from MedDRA® Version 14.1 as modified by Merck & Co., Inc.

Conclusion

The administration of suvorexant to patients with mild to moderate COPD did not have any clinically meaningful change in oxygen saturation or the apnea-hypopnea Index (API)

Study 36: A Study to Evaluate Effects of Suvorexant (MK-4305) in Patients with Obstructive Sleep Apnea

This study was of similar design to Study 32 as a randomized double-blind cross-cover study with 2 treatment periods. A single oral dose of suvorexant or matching placebo was administered on consecutive evenings on Day 1 to Day 4 in each of 2 treatment periods with a minimum of 5 days between the last dose in Period 1 and the first dose in Period 2. The primary objectives of the study were to evaluate the safety and tolerability of multiple doses of suvorexant in patients with mild to moderate obstructive sleep apnea (OSA), and to

evaluate the effect of multiple doses of suvorexant on the mean Apnea-Hypopnea Index (AHI) overnight as measured by polysomnogram (PSG). As secondary objectives, the SaO_2 (as measured by pulse oximetry) during total sleep time, as well as the proportion of the night in which SaO_2 was < 90%, < 85%, and < 80% ; comparison of the mean SaO_2 during different sleep stages and a number of exploratory objective sleep parameters were also assessed.

Entry Criteria

Adults aged 18 years of age and older with a diagnosis of OSA could be enrolled. Patients needed to have mild to moderate OSA with AHI ranging from AHI ≥ 5 and < 15 (for mild OSA) and AHI between ≥ 15 and < 30 (for moderate OSA)

Results

A total of 26 patients (19 males and 7 females) participated. The mean age was 49 years (range 30 – 64). One patient discontinued because of withdrawal of consent after Period 1, and 24 patients had complete evaluable SaO_2 data from both treatment periods. Six of the patients were black and the rest were white race. The mean weight in kg was 92.1 and the mean height was 174.3 cm (mean BMI 30.3 mg/m^2).

Pharmacodynamic results

Compared to placebo, there was an increase in the mean AHI following multiple doses of suvorexant in patients with mild to moderate OSA. This increase was small (mean difference 2.66 [CI 0.22, 5.09] on Day 4. However, multiple doses of suvorexant did not produce a clinically significant reduction of mean SaO2 (there was no clinical desaturations: i.e. O_2 saturations < 90%) during total sleep time in patients with mild to moderate OSA on suvorexant or placebo. These results are depicted in the table below copied from the sponsor's submission.

Respiratory Safety following multiple dose administration of 40 mg suvorexant or placebo in patients with mild to moderate OSA (table source: sponsor's clinical study report study 36 page 8)

Endpoint	Suvorexant		Placebo		Difference of Least Squares Means (90% CI)
	N	Least Square Mean (95% CI)	N	Least Square Mean (95% CI)	
Apnea and Hypopnea Index †	26	17.07 (13.30, 20.84)	25	14.41 (10.61, 18.22)	2.66 (0.22, 5.09)
Mean SaO_2 during TST (%)	26	94.15 (93.53, 94.78)	25	94.21 (93.59, 94.84)	-0.06 (-0.45, 0.33)
Mean SaO_2 during NREM (%)	26	94.27 (93.64, 94.90)	25	94.25 (93.62, 94.89)	0.02 (-0.40, 0.43)
Mean SaO_2 during REM (%)	26	93.96 (93.17, 94.76)	25	93.83 (93.03, 94.63)	0.13 (-0.24, 0.50)
Mean SaO_2 during Wake (%)	26	94.73 (94.11, 95.36)	25	94.91 (94.28, 95.54)	-0.18 (-0.61, 0.25)
Percentage of Total Sleep Time that SaO_2 is less than 90%	26	2.16 (0.88, 3.45)	25	1.95 (0.66, 3.25)	0.21 (-0.59, 1.01)
Percentage of Total Sleep Time that SaO_2 is less than 85%	26	0.69 (0.16, 1.23)	25	0.41 (-0.13, 0.95)	0.28 (-0.09, 0.65)

† AHI at screening, mean = 15.18, SD=6.11 (N=26)

SaO_2 = Oxygen Saturation; TST = Total Sleep Time

Higher AHI values and lower SaO_2 values associated with impairment

Safety

There were no deaths or serious adverse events and no subjects discontinued because of adverse events. Somnolence (19% of subjects) and nausea (8% of subjects) were the most common events reported.

Study 40: A study to evaluate the respiratory Safety of suvorexant following a single dose administration in healthy subjects

This was a single dose study in which healthy subjects were administered a supra-therapeutic dose of suvorexant (150 mg) , a therapeutic dose of suvorexant (40 mg), or placebo in a double-blind, 3-period crossover study. A total of 12 healthy subjects were evaluated.

There was a minimum of 5 days between treatments in each treatment period for any given subject. The primary objective was to evaluate the effect of a single dose of suvorexant on mean oxygen saturation (SaO_2) as measured by pulse oximetry during total sleep time (TST). A number of secondary endpoints including the proportion of the night in which SaO_2 is les than 90%, SaO_2 during different sleep stages, and the effect of a single dose administration of suvorexant on the AHI index as measured by PSG.

Results

A total of 8 males and 4 females participated and the age range was 25 – 50 years. There were no discontinuations.

Respiratory safety

There were no desaturations during the study. The mean SaO_2 saturation was within the normal range. There was no clinically meaningful increase (> 5) in the AHI as shown in the table below from the sponsor's submission (source study 40 clinical study report).

Endpoint	Suvorexant 150 mg LSmean (95% CI)	Suvorexant 40 mg LSmean (95% CI)	Placebo LSmean (95% CI)	Difference (150 mg Suvorexant - Placebo) of LSmean (90% CI)	Difference (40 mg Suvorexant - Placebo) of LSmean (90% CI)	MSE‡
Mean SaO_2 during TST (%)	96.67 (95.79, 97.55)	96.33 (95.45, 97.21)	96.67 (95.79, 97.55)	-0.00 (-0.90, 0.90)	-0 33 (-1.23, 0.57)	1.64
Mean SaO_2 during Wake (%)	96.83 (96.09, 97.58)	96.75 (96.00, 97.50)	97.25 (96.50, 98.00)	-0.42 (-1.22, 0.38)	-0 50 (-1.30, 0.30)	1.29
Mean SaO_2 during NREM (%)	96.75 (95.89, 97.61)	96.17 (95.31, 97.02)	96.75 (95.89, 97.61)	-0.00 (-0.87, 0.87)	-0 58 (-1.45, 0.29)	1.53
Mean SaO_2 during REM (%)	96.67 (95.79, 97.55)	96.33 (95.45, 97.21)	96.83 (95.95, 97.71)	-0.17 (-1.07, 0.73)	-0 50 (-1.40, 0.40)	1.64
Apnea-hypopnea index §	-0.82 (-2.62, 0.99)	0.15 (-1.65, 1.95)	-0.63 (-2.44, 1.17)	-0.18 (-1.68, 1.31)	0.78 (-0.71, 2.28)	4.49

‡ Estimate of within subject variance.
§ For AHI test, change from baseline is analyzed where screening PSG visit serves as baseline, mean =3.62, SD=3.26, (N=12).
SaO_2 = Oxygen Saturation, TST = Total Sleep Time.

Conclusion

This single dose study showed that a single supra-therapeutic dose of suvorexant did not have a deleterious effect on oxygen saturation or the AHI in healthy subjects.

Conclusions

Study 32 and 36 assessed the respiratory safety of suvorexant in patients with mild to moderate COPD (study 32) and OSA (study 36). There was a small increase in the AHI index following multiple doses of suvorexant in patients with mild to moderate OSA but this increase was small (mean 2.66) and is not likely to be clinically significant and was not associated with any clinically meaningful decreases in Oxygen saturation. The study is however limited by its short duration (4 days). It is unknown if long term continued use of this product would have more profound effects on respiratory parameters in patients with OSA. There were no deleterious respiratory effects noted after 4 days of treatment with suvorexant in patients with mild to moderate COPD. A single supra- therapeutic dose of suvorexant did not have a deleterious effect on oxygen saturation or the AHI.

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/s/

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06/13/2013

BADRUL A CHOWDHURY
06/13/2013
I concur