FDA Peripheral and Central Nervous System Advisory Committee Meeting
May 22, 2013

Suvorexant
MK-4305

Nadine Margaretten, Ph.D.

Merck Research Laboratories

Agenda

• Introductions	Nadine Margaretten, Ph.D., Senior Principal Liaison, Global Regulatory Group, Merck Research Laboratories
• Insomnia Background and Scientific Rationale • Clinical Program Overview • Suvorexant Efficacy Methods and Results • Suvorexant Safety Methods and Results	Wm. Joseph Herring, M.D., Ph.D., Executive Director, Clinical Research, Neuroscience and Ophthalmology, Merck Research Laboratories
• Benefit-Risk Assessment and Dosing	David Michelson, M.D., Vice President, Clinical Research, Neuroscience and Ophthalmology, Merck Research Laboratories

Consultant Introductions

• Thomas Roth, Ph.D.	
Director, Sleep Disorders and Research Center and Professor, Dept. of Psychiatry	Henry Ford Hospital and Wayne State University School of Medicine Detroit, MI
• Thomas Scammell, M.D.	
Professor of Neurology Department of Neurology	Harvard Medical School Beth Israel Deaconess Medical Center Boston, MA
• Eric Nestler, M.D., Ph.D.	
Chair, Nash Family Professor of Neuroscience Director	Department of Neuroscience, Mount Sinai School of Medicine, NY Mount Sinai Brain Institute
• Gary Koch, Ph.D.	
Professor of Biostatistics and Head, Biostatistics Consulting Lab	University of North Carolina Chapel Hill, NC

Introduction to Suvorexant

- New chemical entity with novel mechanism of action
- Highly selective antagonist for orexin receptors OX1R and OX2R
- Transiently blocks wake signaling, allowing sleep to occur
- Provides alternative treatment option for patients with insomnia:
  - Improved sleep onset and maintenance that is sustained during the night
  - Efficacy demonstrated after the first night of therapy and after chronic use, with no evidence of tolerance, or withdrawal after treatment cessation
  - Well-tolerated acutely and with long term use, and with acceptable residual effect profile

Regulatory History

- Agency guidance incorporated into program included feedback at End of Phase 2 (November, 2009), PreNDA (March, 2012), and CSS (March, 2010) meetings:
  - Phase 1 trials and assessments
  - Phase 3 combined age and endpoint trials allowed thorough assessments:
    - Efficacy and safety of elderly and non-elderly
    - Onset and maintenance, with objective and subjective efficacy endpoints including multiple patient reported outcomes
  - NDA accepted for review November, 2012

NDA=New Drug Application; CSS=Controlled Substance Staff of the FDA.

Suvorexant Clinical Program Overview

- 36 trials, 2869 subjects/patients treated with suvorexant, 1784 in Phase 3
- Comprehensive efficacy and safety assessment
  - Replicate 3 month objective and subjective efficacy trials in elderly and non-elderly patients
  - Unique 12-month placebo-controlled safety trial in patients with DSM-IV-TR primary insomnia without insomnia severity inclusion criteria
    - Supportive monthly efficacy assessments
    - Randomized discontinuation phase to assess relapse of insomnia
- Thorough assessment of safety included:
  - Prospective evaluation based on adverse events associated with
    - Marketed sedative hypnotics including residual effects
    - Mechanism of action
    - CNS activity (e.g. suicidality, withdrawal, rebound, and abuse potential)
  - Special safety studies/populations

DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorder-4th Edition-Text Revision.

Proposed Indication and Dose Considerations

Indication: treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance

Revised Dose Considerations:

- Use the lowest effective dose for the patient. The usual starting dose should be 20 mg (15 mg in elderly). For patients whose symptoms persist and who demonstrate acceptable tolerability, a dose increase to 40 mg (30 mg in elderly) may be considered.

Suvorexant Efficacy and Safety

W. Joseph Herring, M.D., Ph.D.
Merck Research Laboratories

Presentation Outline

- Sleep and Insomnia Background
- Scientific Rationale for Orexin Antagonism
- Clinical Program Overview
- Suvorexant Efficacy
  - Overview of efficacy
  - Supportive exploratory endpoints
- Suvorexant Safety
  - Overview of safety
  - Residual effects profile
  - Assessment of other important factors, including rebound and withdrawal
- Benefit-Risk Assessment and Dosing Considerations

Sleep and Insomnia Background

Everyone Needs Sleep…

- The impact of sleep loss and sleep deprivation are well-established[1]
- Insomnia affects up to a third of the adult population
- Insomnia incurs significant societal costs due to accidents, health care costs, lost productivity and absenteeism
  - Based on the American Insomnia Survey[2], annualized costs attributed to insomnia-related diminished productivity in the workforce are approximately $63 billion USD[2]

[1] Van Dongen, et al. *Sleep*. 2003;2:117-126; Goel and Dinges. *J. Clin. Sleep Med*. 2011;7:S19-S21.
[2] Kessler, et al. *Sleep*. 2011;34:1161-1171.

Insomnia Symptoms and Diagnosis

- The DSM-IV-TR diagnosis of primary insomnia requires:
  - Difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month
  - Distress or perceived impaired functioning
  - Symptoms do not stem from another sleep disorder, another psychiatric problem, a medical illness, or use of a substance

- Insomnia symptoms can be measured…
  - Objectively, by polysomnography (PSG) in a sleep laboratory
  - Subjectively, by patient-report diary

DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorder-4th Edition-Text Revision.

How Insomnia Is Assessed: Key Efficacy Measures in Sleep Research[1,2]

Sleep Disturbance	Variable		How Assessed	
	Full Term	Abbrev. Term	Objective vs. Subjective	Instrument
Sleep Onset	Latency to the onset of persistent sleep	LPS	Objective	PSG
	Subjective time to sleep onset	sTSO	Subjective	Sleep diary
Sleep Maintenance	Wake after persistent sleep onset	WASO	Objective	PSG
	Subjective total sleep time	sTST	Subjective	Sleep diary
	Subjective wake after sleep onset	sWASO	Subjective	Sleep diary
Global	Sleep Efficiency = total sleep time/time in bed (8 hrs) x 100	SE	Objective	PSG

[1] Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 5th ed. St Louis, MO: Elsevier; 2011.
[2] Lankford DA, et al. *Sleep*. 2008;31:1359-1370.
PSG=polysomnography.

Scientific Rationale for Orexin Antagonism and Unmet Medical Need

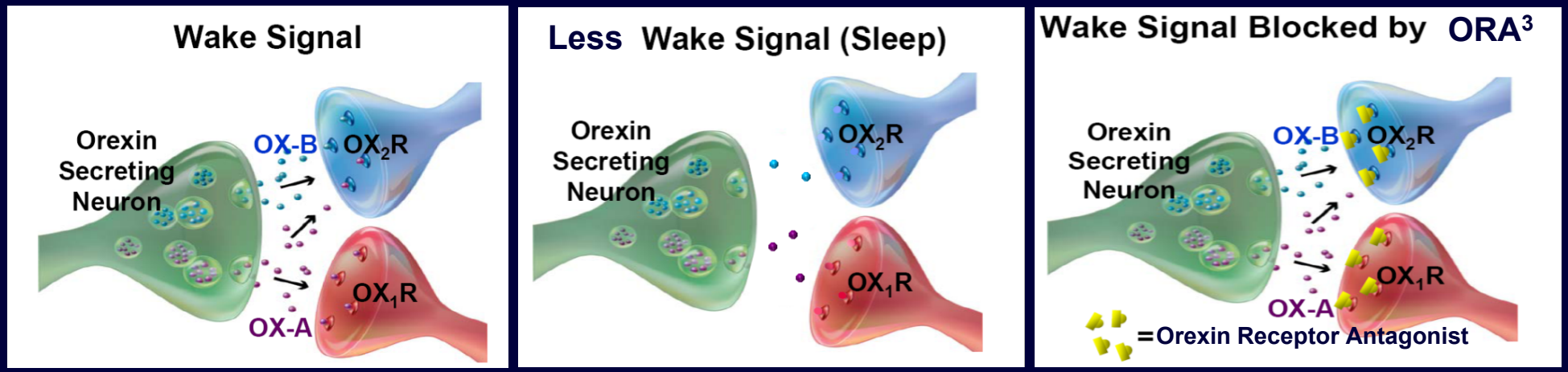
New Treatments Are Needed

- The most widely used treatments for insomnia induce sleep by increasing the action of GABA, a global CNS inhibitory neurotransmitter
- Shorter acting benzodiazepines and 'z-drugs' induce sleep well, but most maintain sleep less effectively, or not at all[1]
- Older benzodiazepines (e.g. quazepam) induce and maintain sleep well, but at the cost of increased risk (e.g. falls, next day effects)[2]
- Few treatment options improve sleep induction and have efficacy for sleep maintenance that is sustained through the entire night while having limited, generally tolerable residual effects

[1] Silber, MH. *N Engl J Med*. 2005;353:803-10.
[2] Riemann, D. *Sleep Med*. Rev. 2009;13:205-14.

Orexin Antagonists Offer a New Approach to the Treatment of Insomnia

- Genetic and clinical studies demonstrate orexin neuron activity promotes wake[1,2]
- Orexin receptor antagonists (ORAs) selectively block this wake promoting system, facilitating transition to sleep



[1] Nishino S, et al. *Lancet*. 2000;355:39-40.
[2] Hagan JJ, et al. *PNAS*. 1999;96:10911-6.
[3] Derived from Winrow CJ, et al. *Drug Discovery for Psychiatric Disorders*. 2012;28:416-442.

Orexin Antagonists Target Sleep Physiology Differently from GABA Agonists

System	GABA[1,2]	Orexin[3,4]
CNS distribution	Widespread: ~40% of all neurons	Highly localized: <90,000 neurons in hypothalamus
Neurotransmitter	Gamma-amino butyric acid (GABA)	Orexin A and B neuropeptide
Function	Primary inhibitory neurotransmitter of many neuronal circuits	Highly selective, promotes wakefulness
Sleep therapeutic pharmacology	$GABA_A$ modulators: e.g. zolpidem, eszopiclone	Competitive reversible antagonist: suvorexant
Physiology	Broad CNS suppression reduces consciousness to induce sleep	Mechanism specifically promotes sleep by blocking peptide wake signaling

[1] Rudolph and Knoflach. *Nat Rev Drug Discov*. 2011;10:685-97. [2] Roehrs and Roth. *Neurotherapeutics*. 2012;9:728-738.
[3] Mieda and Sakurai. *CNS Drugs*. 2013;27:83-90. [4] Thannickal TC, et al. *Neuron*. 2000;27:469-474.

Suvorexant Clinical Program Overview

Comprehensive Clinical Development Program

Phase 1

- 32 studies
- N=922; 842 with suvorexant
- Special safety studies assessed respiratory safety, residual effects, and abuse potential

Phase 2b

- P006 dose-finding in non-elderly patients
- N=254; 243 with suvorexant
- 10, 20, 40, 80 mg doses vs. placebo
- 4-week x-over treatment design

Phase 3

- **3 trials: 1 long-term safety and 2 confirmatory efficacy**
- **2809 patients; 1784 with suvorexant (160 treated for ≥12 months) = 758.2 person years (>275,000 patient nights) exposure**
- **Diverse population: 46% elderly; patients from 24 countries**

Long-Term Safety (P009)	Confirmatory Efficacy (P028 & P029)
• N=779; 521 with suvorexant HD	• N=2030; 1263 with suvorexant
• 12-month treatment; 2-month rand. discon. (RD) phase	• 3-month treatment; 3-month extension in P028
• Suvorexant HD	• Suvorexant HD and LD

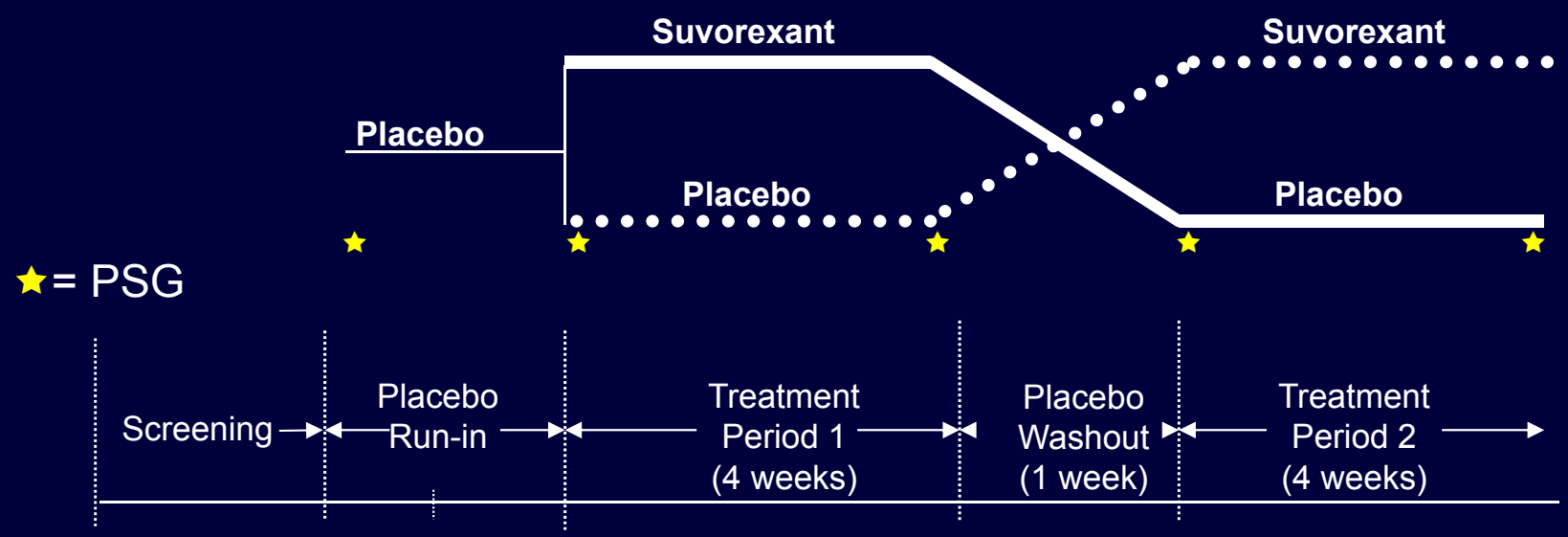
HD=high dose; LD=low dose.

Clinical Pharmacology of Suvorexant

- Single doses up to 240 mg and multiple doses up to 100 mg were studied
- Suvorexant PK supports dosing without regard to food:
  - Oral absorption is relatively rapid with a T_{max} of ~2 hours
  - Plasma $t_{1/2}$ of ~12 hours
- Eliminated primarily via CYP3A-mediated metabolism with manageable drug-drug interactions via labeling recommendations
- Low potential to be a perpetrator of clinically meaningful pharmacokinetic drug interactions
- Intrinsic factors (e.g., gender, BMI) effects on suvorexant PK generally modest (<25%)

PK=pharmacokinetic; BMI=body mass index.

Phase 2b Trial Study Design

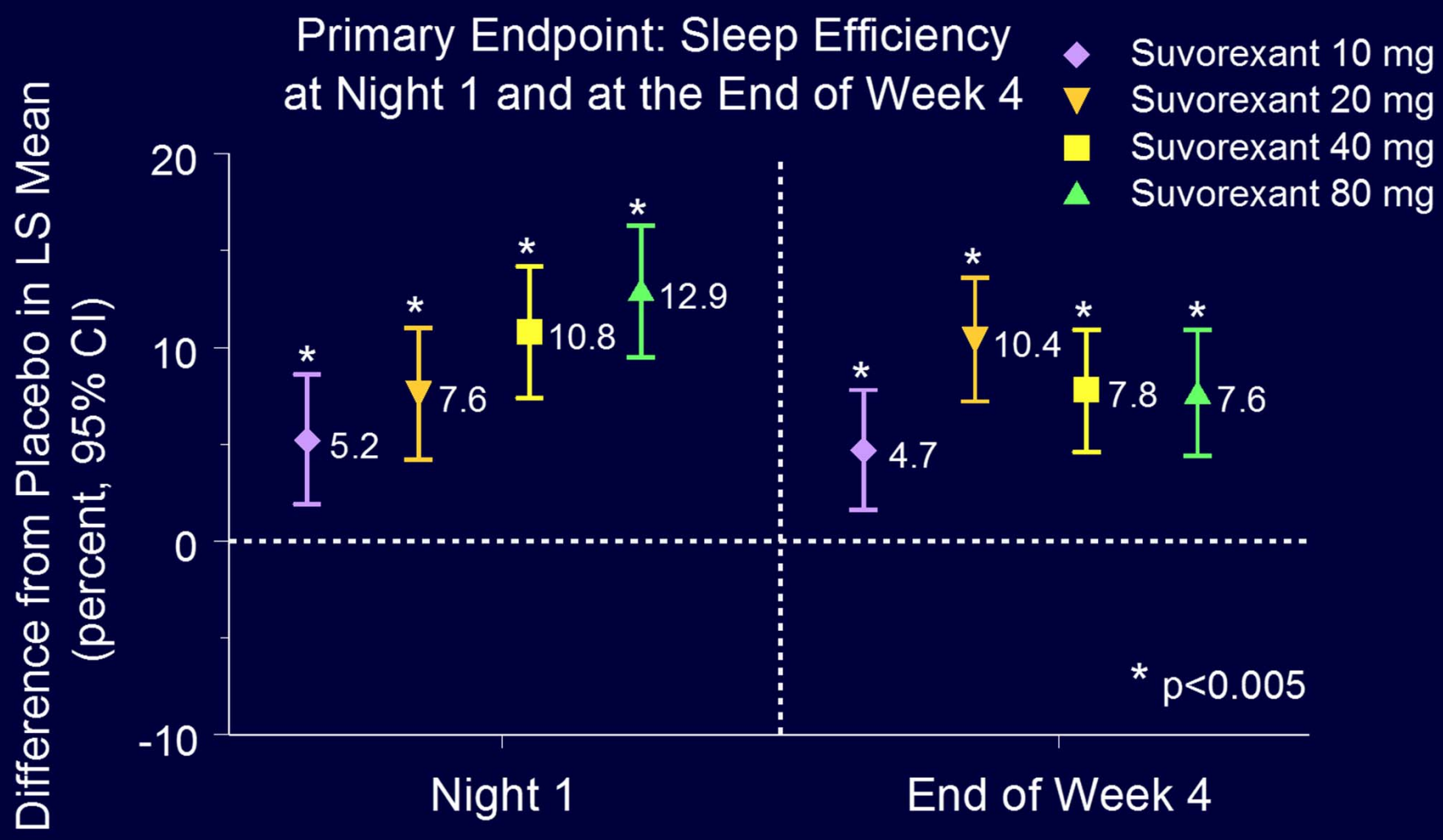


- Design: double-blind crossover polysomnography (PSG) trial with two 4-week treatment periods separated by 1-week placebo washout
- N=254 non-elderly primary insomnia patients
- PSG at Night 1 (N1) and Week 4 (W4) of each treatment period
- Endpoints (vs. placebo, baseline-adjusted):
  - Primary – Sleep efficiency (SE) at N1 & W4
  - Secondary – WASO and LPS at N1 & W4

Dose	N
10 mg	62
20 mg	61
40 mg	59
80 mg	61
Placebo	249

WASO=wake after onset to persistent sleep; LPS=latency to the onset of persistent sleep.

Efficacy Demonstrated in Phase 2b

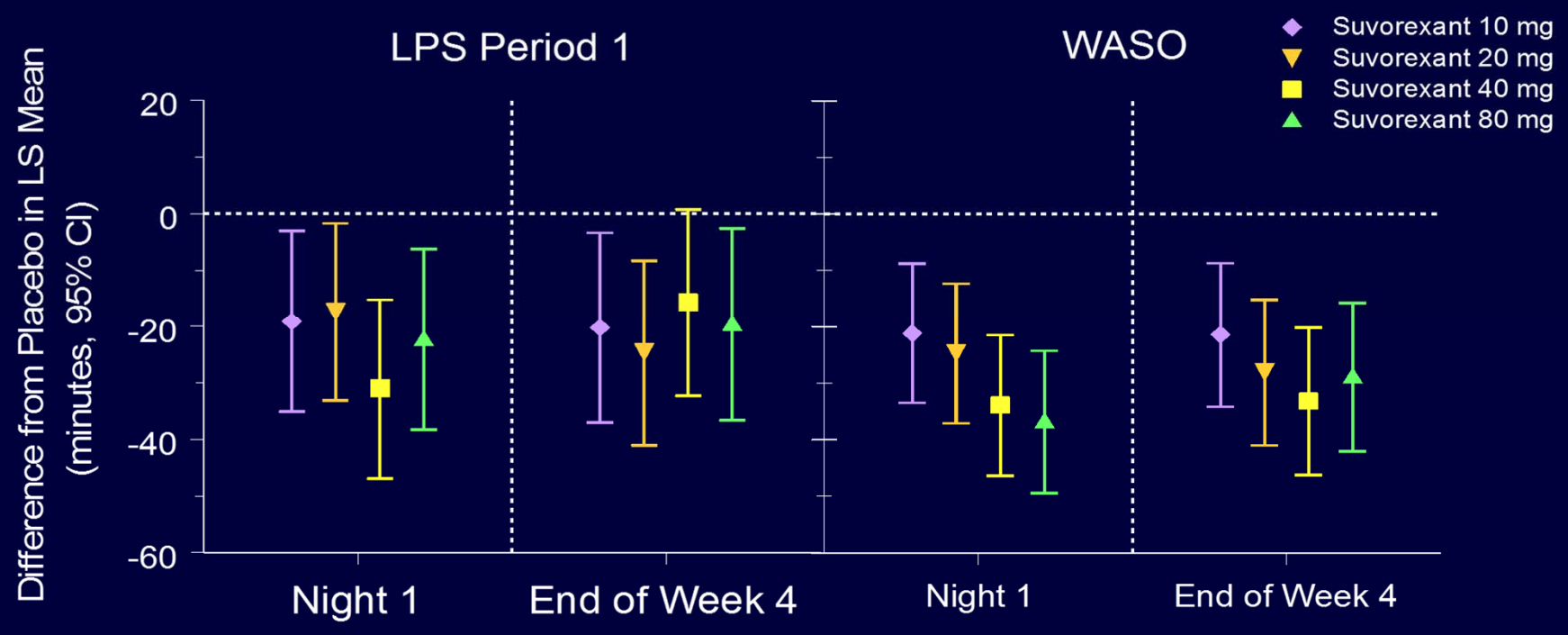


- Suvorexant efficacious with dose trend at Night 1
- 10 mg was the least efficacious dose at both timepoints

LS=Least-Squares.

Objective Sleep Maintenance and Induction Shown in Phase 2b

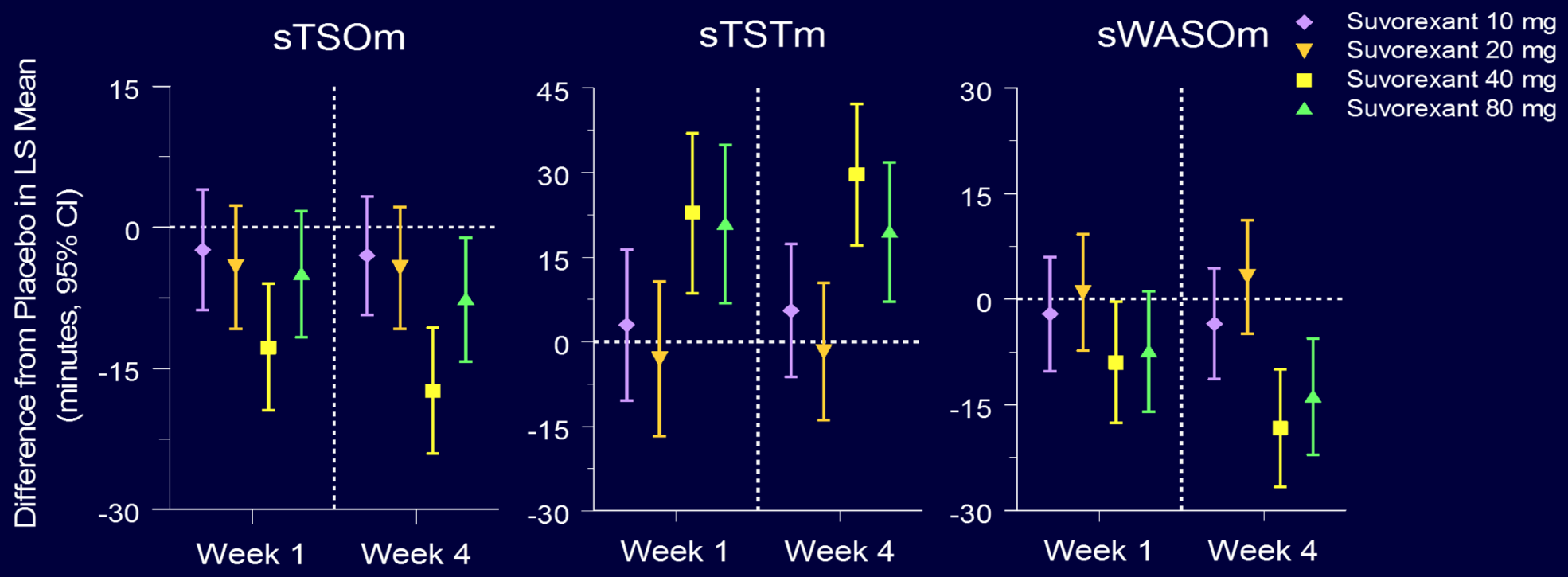
- Dose response demonstrated for WASO
  - 10 mg least effective, and 40 and 80 mg maximally effective
- No dose response for LPS
  - Carryover observed complicates interpretation of data



WASO=wake after onset to persistent sleep; LPS=latency to the onset of persistent sleep; LS=Least-Squares.

Patients Reported More Consistent Sleep Effects at Higher Doses

- 40 and 80 mg improved subjective sleep onset and maintenance
- 10 and 20 mg were ineffective for all subjective endpoints



sTSOm=subjective Time to Sleep Onset mean; sTSTm=subjective Total Sleep Time mean; sWASOm=subjective Wake After Sleep Onset mean; LS=Least-Squares.

Suvorexant Generally Well-Tolerated in Phase 2b

Adverse Events of the Nervous System Disorders and Psychiatric Disorder Categories (Incidence ≥2% for One or More Treatments) – Treatment Periods 1 and 2 (All Patients as Treated)

	Placebo		Suvorexant 10 mg		Suvorexant 20 mg		Suvorexant 40 mg		Suvorexant 80 mg	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	**249**		**62**		**61**		59		61	
with ≥ 1 AE	**50**	**(20.1)**	**11**	**(17.7)**	**12**	**(19.7)**	18	(30.5)	22	(36.1)
Nervous system disorders	***9***	***(3.6)***	***2***	***(3.2)***	***5***	***(8.2)***	***9***	***(15.3)***	***12***	***(19.7)***
Dizziness	0	(0.0)	0	(0.0)	1	(1.6)	0	(0.0)	3	(4.9)
Headache	6	(2.4)	0	(0.0)	1	(1.6)	3	(5.1)	3	(4.9)
Sedation	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	2	(3.3)
Somnolence	1	(0.4)	1	(1.6)	3	(4.9)	6	(10.2)	7	(11.5)
Psychiatric disorders	***3***	***(1.2)***	***1***	***(1.6)***	***0***	***(0.0)***	***2***	***(3.4)***	***5***	***(8.2)***
Abnormal dreams	2	(0.8)	1	(1.6)	0	(0.0)	0	(0.0)	3	(4.9)

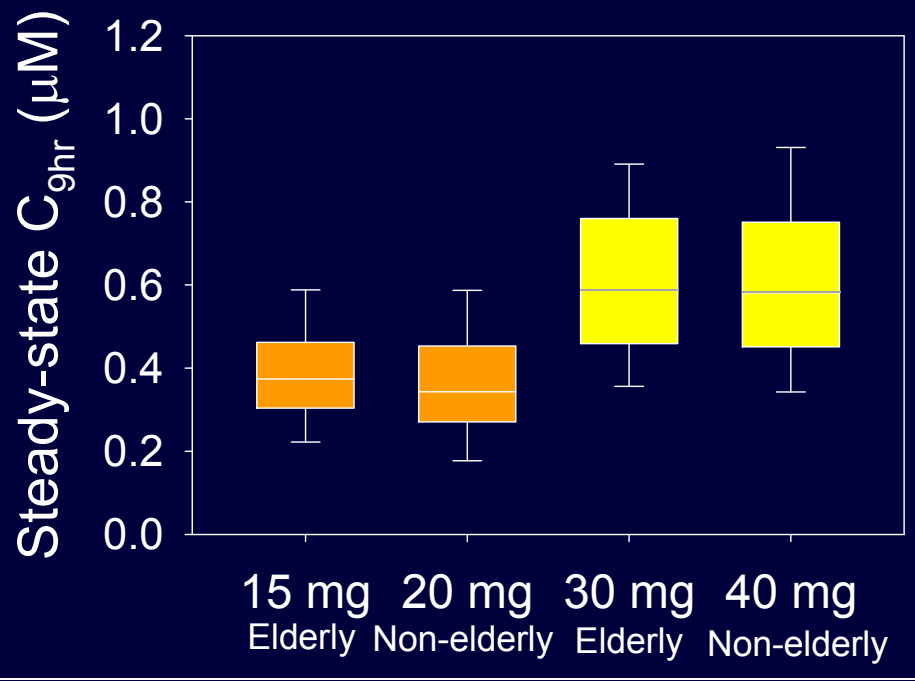
Every patient is counted a single time for each applicable specific adverse event and treatment. A patient with multiple adverse events within a system organ class is counted a single time for that system organ class. A system organ class or specific adverse event appears on this report only if its incidence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

Phase 3 Dose Selection

- Based on the totality of objective and subjective efficacy and tolerability profile:
  - 40 mg: showed maximum and most consistent efficacy, chosen as primary dose
  - 20 mg: chosen as secondary dose due to mixed efficacy in the clinical data and agency feedback to test multiple doses in Phase 3
- Doses not selected:
  - 10 mg: inconsistent efficacy and lower efficacy than 20 mg for sleep efficiency and WASO
  - 80 mg: no additional benefit over 40 mg

Dose Adjustment for Elderly in Phase 3

Confirmed by Phase 3 Data



Nomenclature for Phase 3 Suvorexant Doses		
Dose	Non-elderly (<65 years)	Elderly (≥65 years)
High Dose (HD)	40 mg	30 mg
Low Dose (LD)	20 mg	15 mg

† Box and line represent inter quartile and median; whiskers extend to the 10th and 90th percentiles.
C_{9hr}=suvorexant plasma concentration the morning after bedtime dosing at ~9 hours postdose.

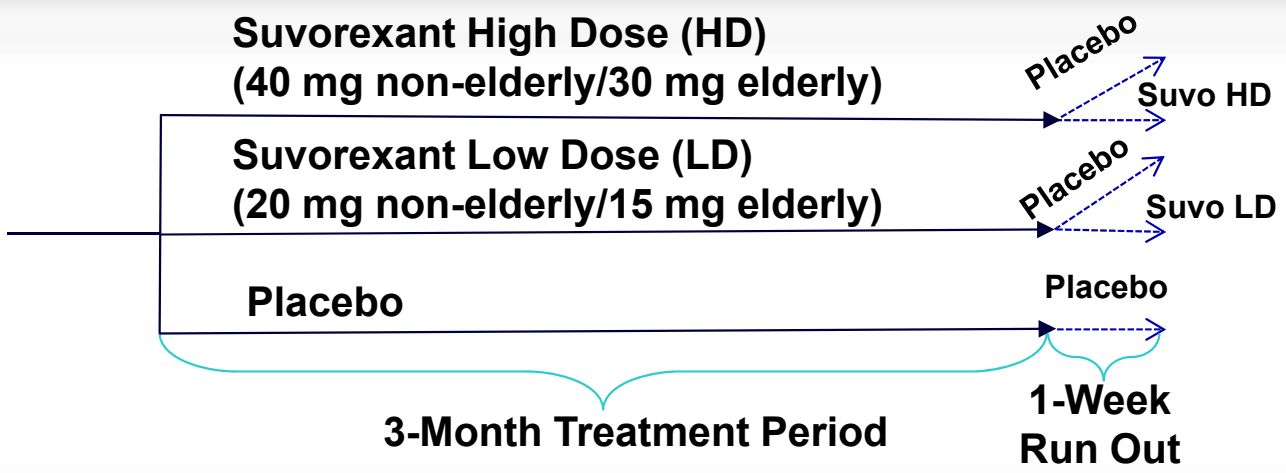
Clinical Program Objectives

- The clinical development program was designed to assess whether:
  - Suvorexant improves sleep induction
    - Objective latency to persistent sleep onset, subjective time to sleep onset
  - Suvorexant improves sleep maintenance
    - Objective wake after persistent sleep onset, subjective total sleep time
  - Suvorexant is effective in the short- and long-term
    - Efficacy assessed at 1 week, 1 month, 3 months, 1 year
    - Relapse prevention after 1 year
  - Suvorexant is generally safe and well-tolerated
    - Evaluate rebound, withdrawal, and residual effects
    - Address mechanism specific questions

Suvorexant Phase 3 Efficacy

Efficacy and Results

Confirmatory Phase 3 Studies Design



3-month core treatment period with polysomnography and subjective efficacy in both trials

- Two similarly designed combined-age and combined subjective and objective efficacy trials with core 3-month treatment period (P028 & P029)
  - Subjective efficacy collected from <u>all</u> patients by daily electronic diary (e-diary)
  - Objective efficacy measured by nighttime polysomnography (PSG) after dosing on Night 1, Month 1, and Month 3 of the treatment period in the majority of patients (PSG & Questionnaire “PQ-Cohort”)
- One of the two trials included an optional 3-month safety extension (P028)

Statistical Methods

- Full Analysis Set (FAS) population used for primary and secondary analyses of efficacy
  - Included all randomized patients with at least 1 change from baseline value subsequent to administration of at least 1 dose
- Longitudinal data analysis model used to compare treatments at each time point
  - Included terms for baseline value, age group, region, gender, cohort, treatment, time, and the interaction of time by treatment
- Multiplicity strategy used to control Type I error for primary efficacy hypotheses at 2-sided 5% level
- All Patients-as-Treated (APaT) population used to analyze safety data
  - Included all randomized patients receiving at least 1 dose

Patient Disposition – Pivotal Trials (P028 and P029 - Treatment Phase)

	P028			P029		
Screened (N)	2879			2876		
	PBO	LD	HD	PBO	LD	HD
Randomized (N)	385	254	383	387	240	392
Not Treated (%)	0.3	0.0	0.0	1.0	0.4	1.3
Discontinued (%)	11.2	9.4	9.9	13.7	14.2	10.5
Adverse Event (%)	5.5	2.4	3.9	4.4	4.2	4.8
Withdrawal (%)	3.1	2.4	2.1	4.9	3.3	2.3
Lack of Efficacy (%)	2.3	0.4	1.8	2.1	2.9	1.0
Lost to Follow-up (%)	0.0	0.4	0.3	0.3	0.8	1.0
Other† (%)	0.3	3.9	1.8	2.1	2.9	1.3
Completed (%)	88.6	90.6	90.1	85.3	85.4	88.3

† Other=protocol violation, pregnancy, and/or physician decision.

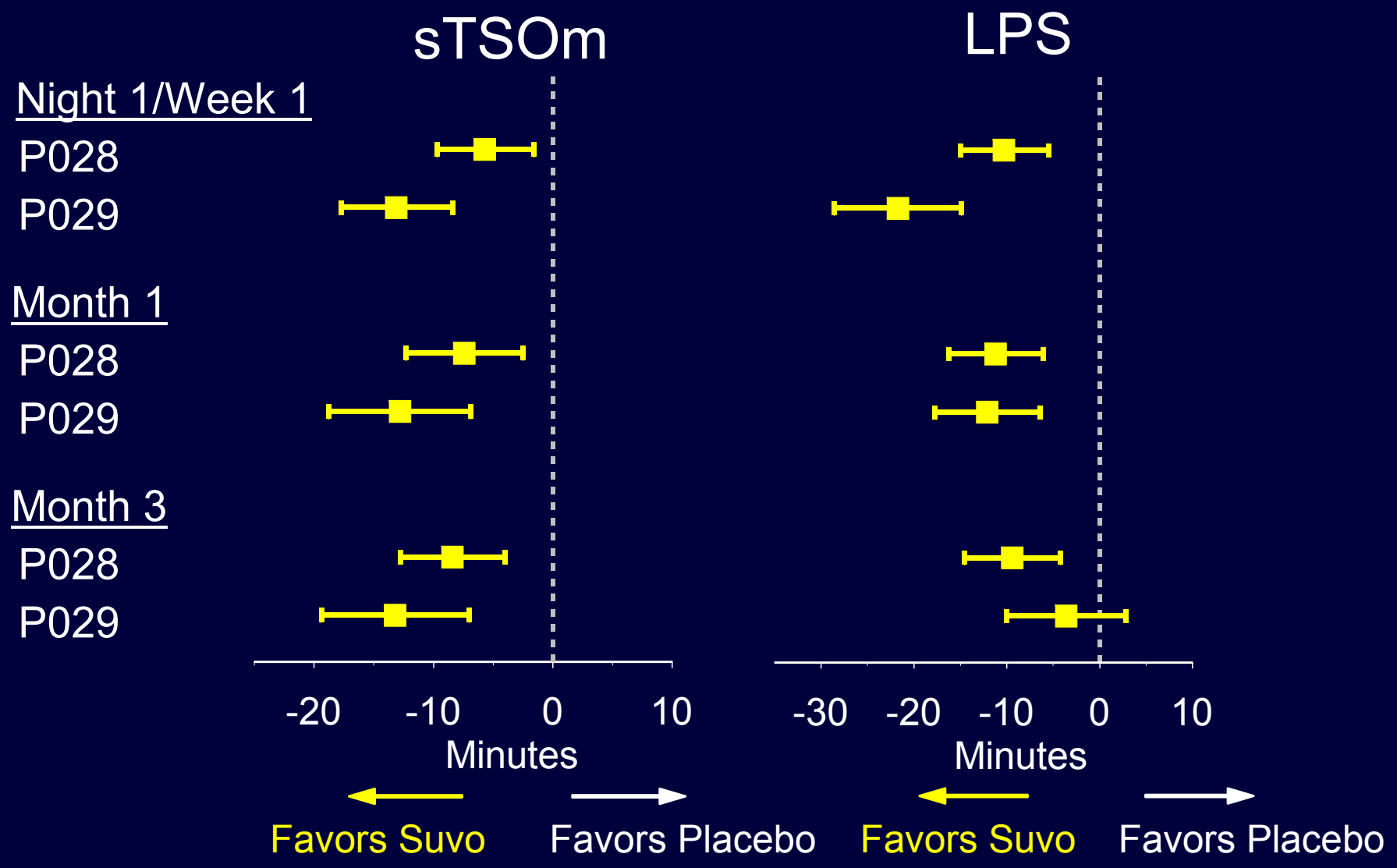
Confirmatory Studies Patient Demographics for Pooled Data (P028+P029)

	Placebo (N†=767) %	Suvorexant LD (N†=493) %	Suvorexant HD (N†=770) %	Total (N†=2030) %
Gender				
Male	35.9	35.3	35.5	35.6
Female	64.1	64.7	64.5	64.4
Age Category (years)				
<65 (non-elderly)	58.5	59.0	58.6	58.7
≥65‡ (elderly)	41.5	41.0	41.4	41.3
Race				
White	72.1	72.6	73.1	72.6
Black or African American	6.0	3.9	4.9	5.1
Asian	16.2	18.9	16.1	16.8
Other	5.7	4.7	5.8	5.5

† All Patients Treated.
‡ Patients ≥75 years represent 7.4% of the total population.
HD=high dose (40 mg for non-elderly, 30 mg for elderly); LD=low dose (20 mg for non-elderly, 15 mg for elderly).

Suvorexant HD Improves Sleep Onset

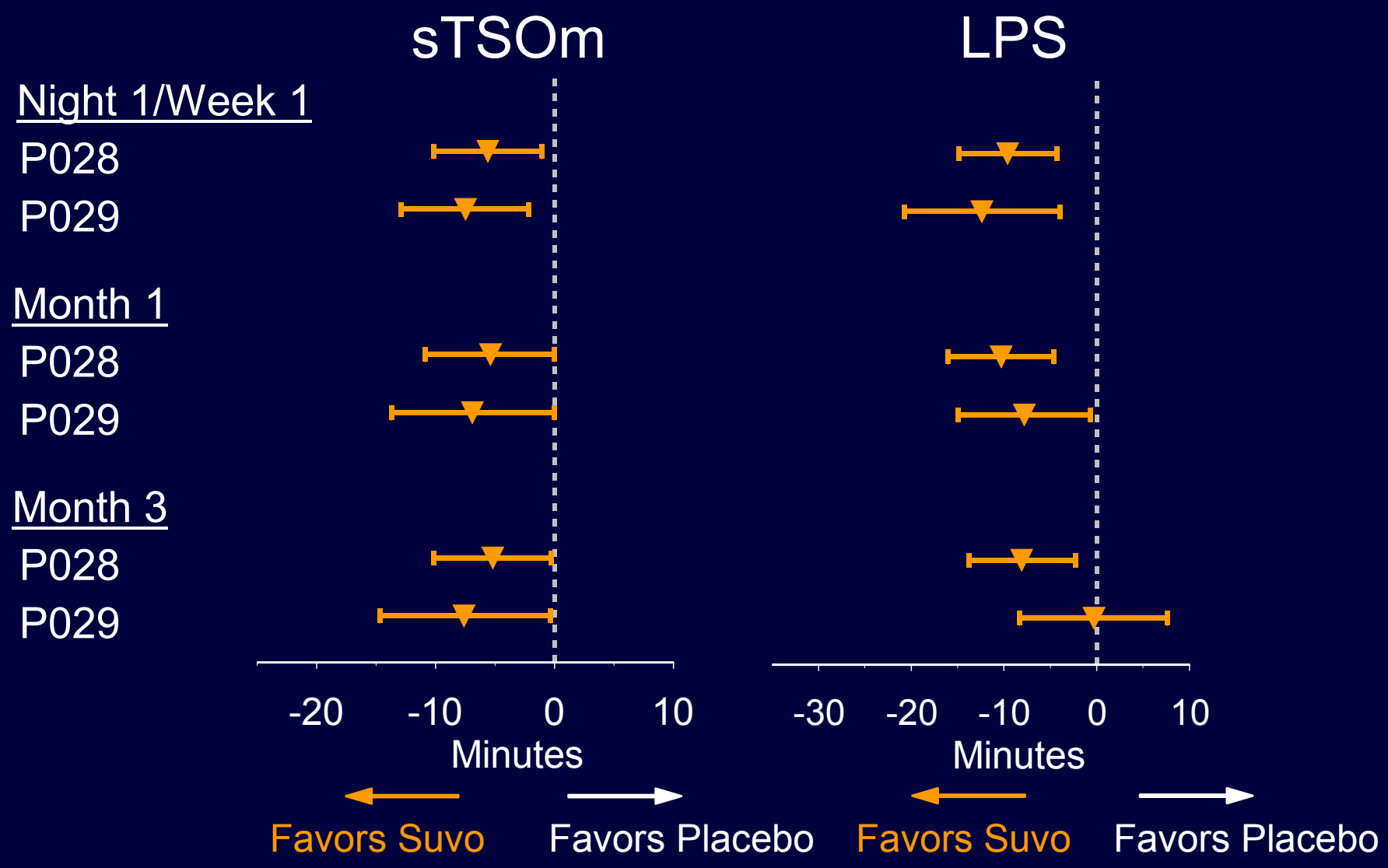
Estimate (95% CI) of Difference in LS Mean for Suvorexant High Dose vs. Placebo*



* All results statistically significant (p<0.007) except for P029 LPS at Month 3.
LS=Least-Squares; sTSOm=subjective Time to Sleep Onset mean; LPS=Latency to onset of Persistent Sleep.

Suvorexant LD Improves Sleep Onset

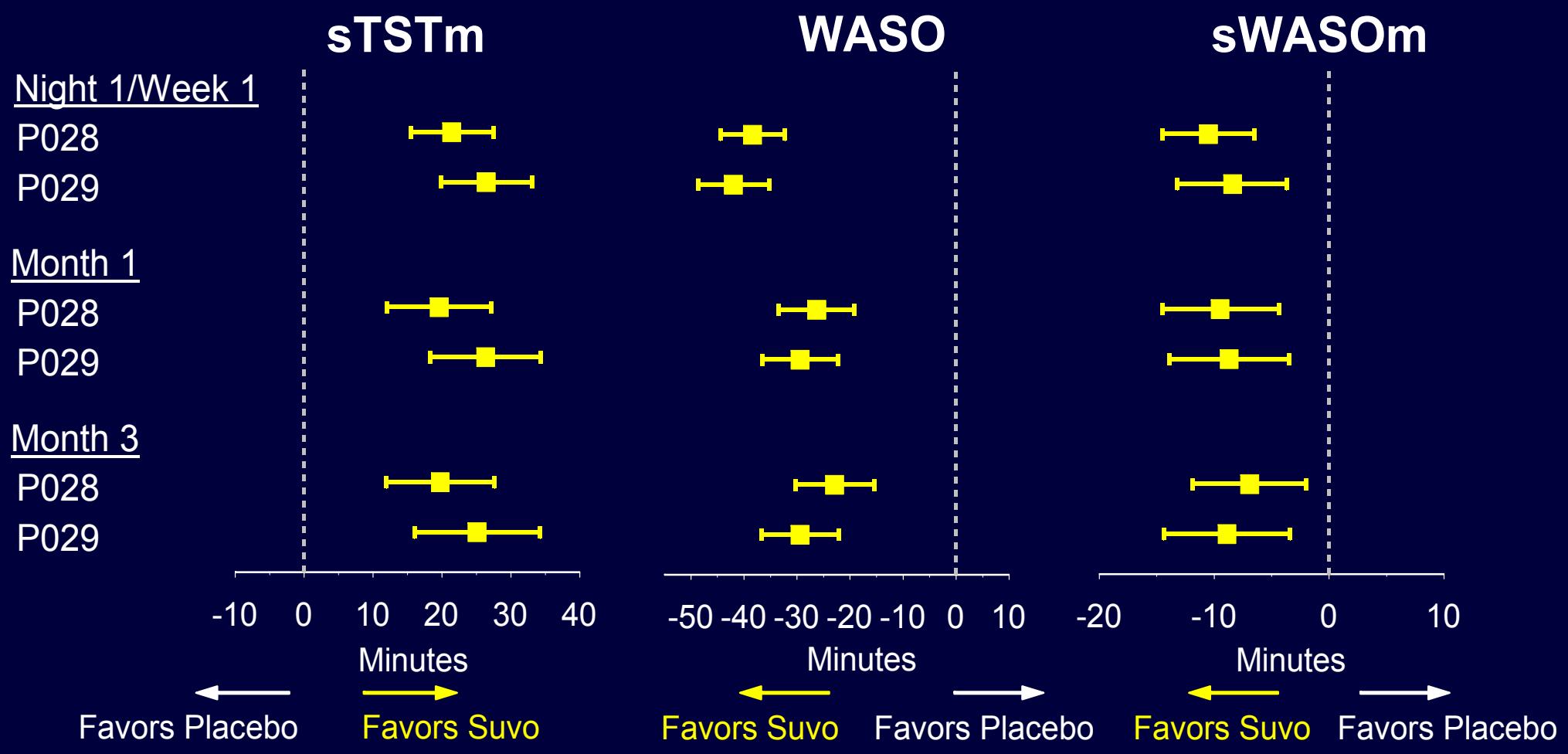
Estimate (95% CI) of Difference in LS Mean for Suvorexant Low Dose vs. Placebo



LS=Least-Squares; sTSOm=subjective Time to Sleep Onset mean; LPS=Latency to onset of Persistent Sleep.

Suvorexant HD Improves Sleep Maintenance

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

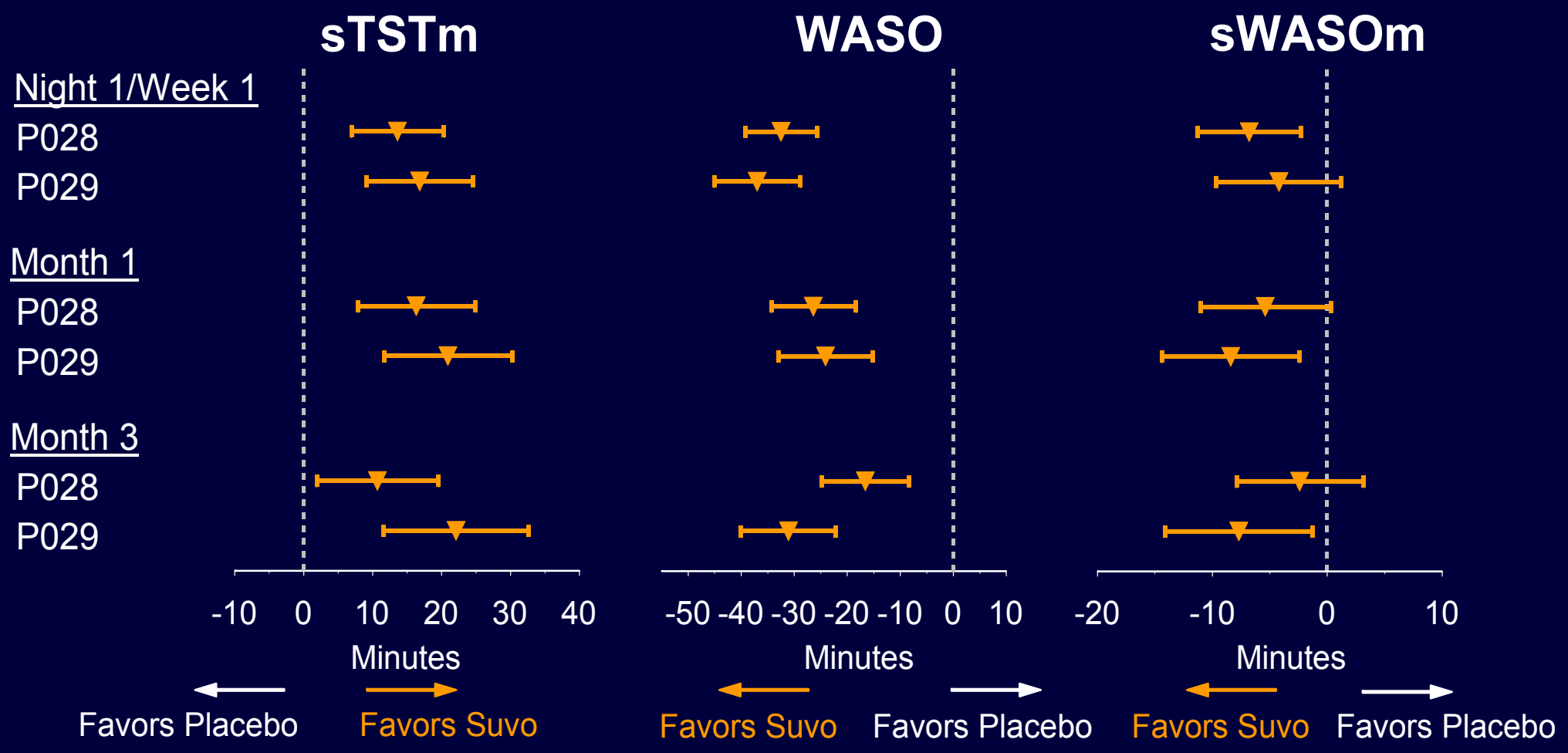


* All results statistically significant (p<0.006).

LS=Least-Squares; sTSTm=subjective Total Sleep Time mean; sWASOm=subjective Wake After Sleep Onset mean; WASO=objective Wake After persistent Sleep Onset.

Suvorexant LD Improves Sleep Maintenance

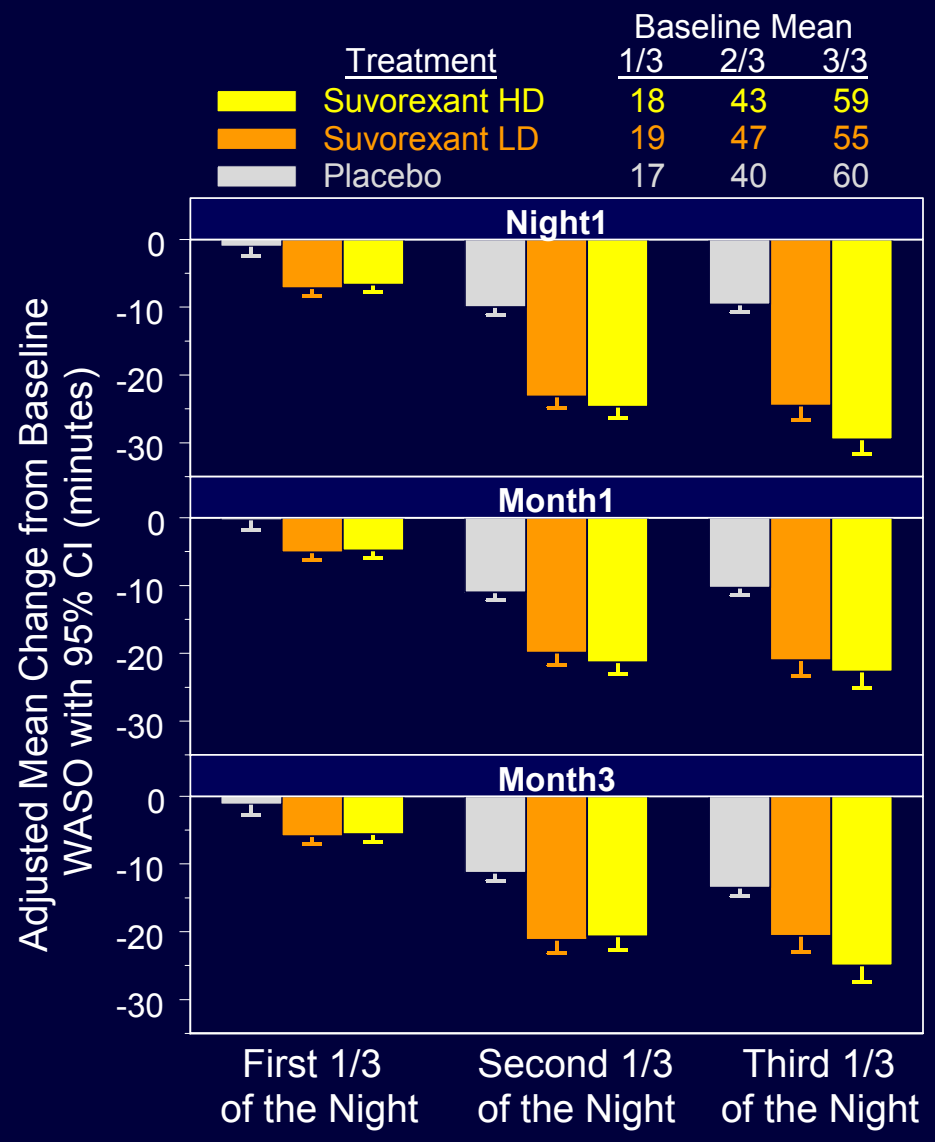
Estimate (95% CI) of Difference in LS Mean for Suvorexant Low Dose vs. Placebo



LS=Least-Squares; sTSTm=subjective Total Sleep Time mean; sWASOm=subjective Wake After Sleep Onset mean; WASO=objective Wake After persistent Sleep Onset.

Suvorexant Maintains Sleep Throughout the Night

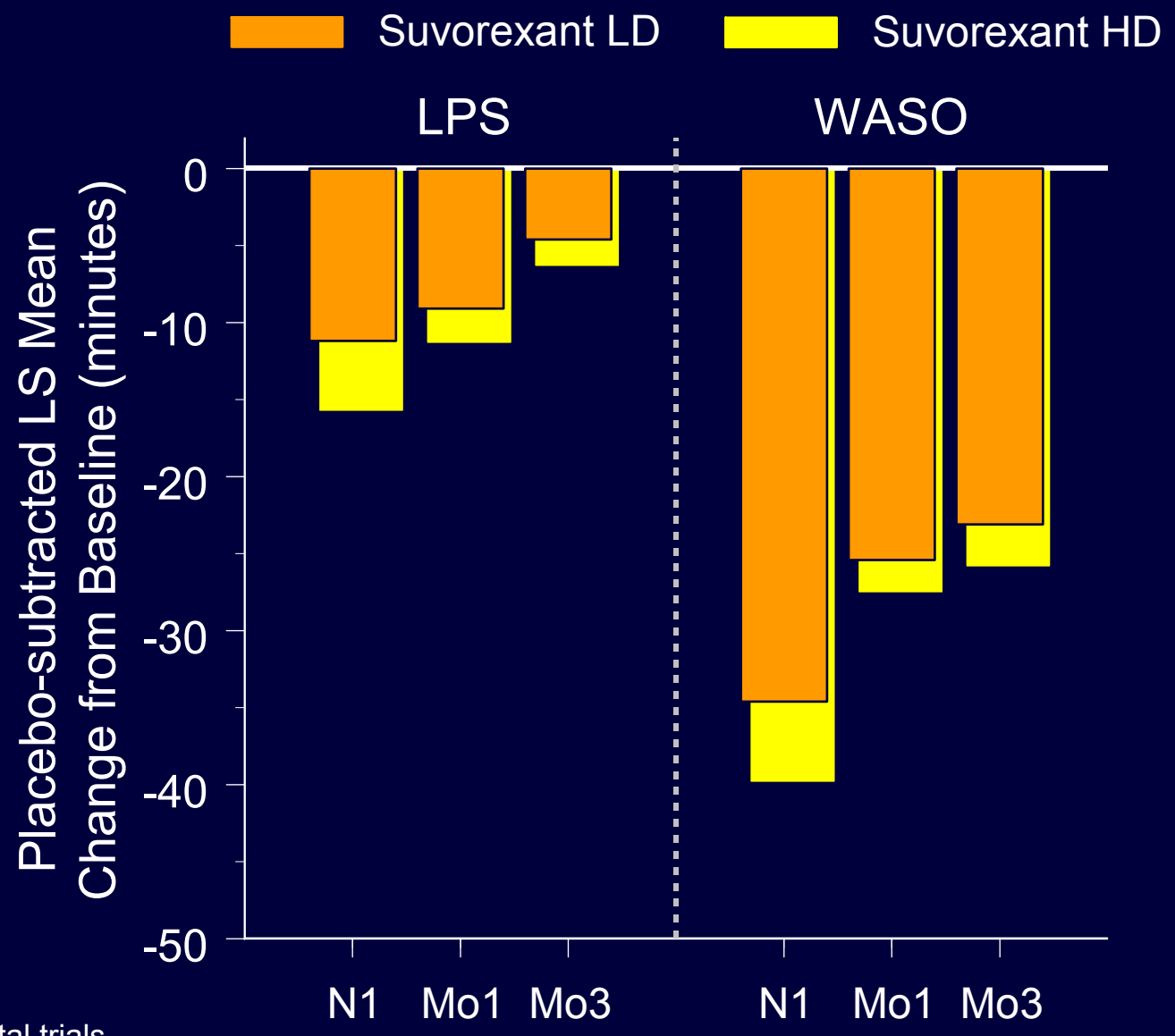
LS Mean Change from Baseline in WASO During Thirds of the Night



Note: Data from pooled pivotal trials. Nominal p-values <0.05 for suvorexant vs. placebo during each third of the night in each trial (P028 and P029) except in P028 at Month 3 for first 1/3 of the night (LD and HD) and third 1/3 of the night (LD).

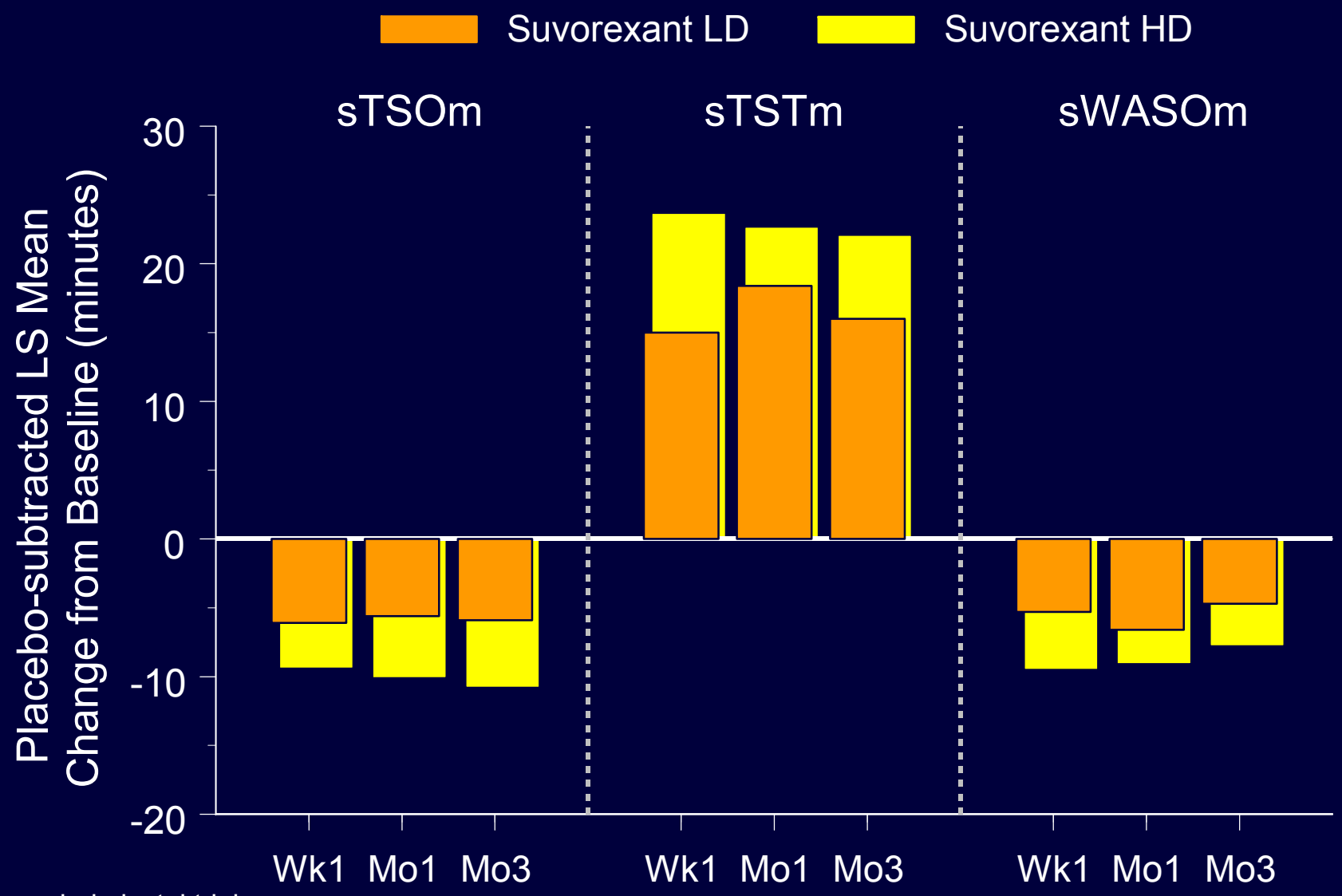
LS=Least-Squares; WASO=objective Wake After persistent Sleep Onset.

High Dose Provides Consistently Greater Objective Improvement than Low Dose



Data from pooled pivotal trials.
LPS=latency to the onset of persistent sleep; WASO=wake after persistent sleep onset; LS=Least-Squares.

High Dose Provides Consistently Greater Subjective Improvement than Low Dose



Data from pooled pivotal trials.

sTSOm=subjective Time to Sleep Onset mean; sTSTm=subjective Total Sleep Time mean; sWASOm=subjective Wake After Sleep Onset mean; LS=Least-Squares.

Patient Perception of Clinical Benefit: Insomnia Severity Index (ISI)

- 7-item composite measure[1] of a patient's perception of their insomnia:

1. Difficulty initiating sleep
2. Difficulty staying asleep
3. Waking too early
4. Satisfied/dissatisfied with current sleep
5. Sleep problems interference w/daily functioning
6. Sleep problems impair quality of life
7. Worry/distress about sleep problems

- ≥6 point improvement from baseline in ISI total score is a clinically meaningful improvement (i.e., responder)[2]

[1] Bastien CH, Vallieres A, Morin CM. *Sleep Med*. 2001;2:297-307.
[2] Yang M, et al. *Current Med Research and Opinion*. 2009;10:2487-2494.

More Patients on Suvorexant Achieve Clinically Meaningful Response by ISI

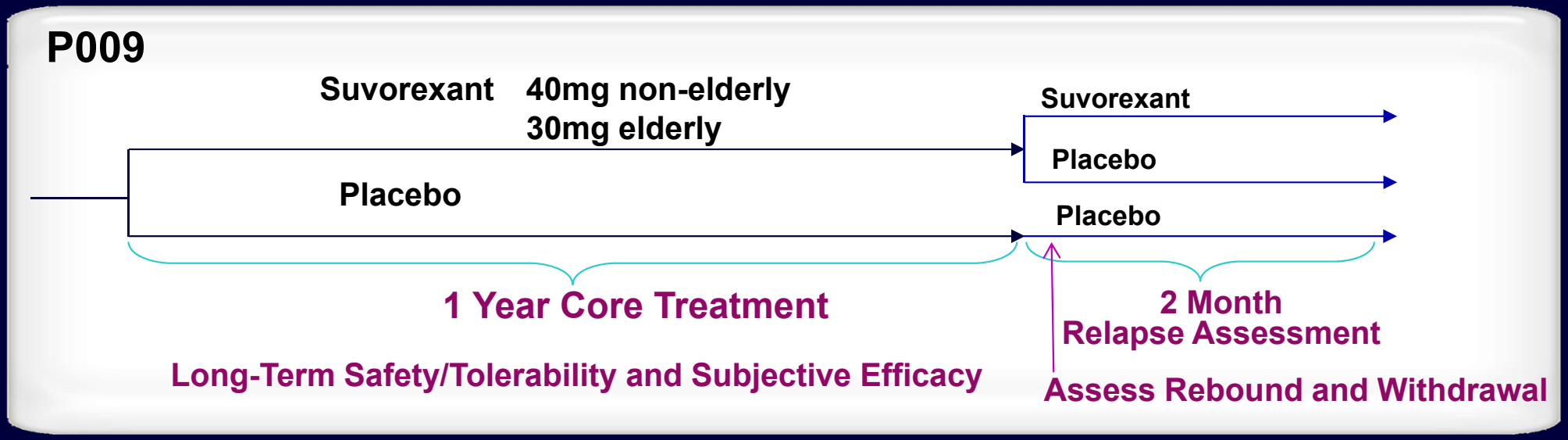
Analysis of Response (≥6 point improvement)
in Insomnia Severity Index Total Score (Pooled P028+P029)

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

Note: nominal $p<0.05$ for comparisons of HD and LD to placebo at both time points in each trial

† 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.

Phase 3 Long-Term Safety Study Design (P009)



Patient Disposition (P009)

	PBO	HD	
Screened (N)	1076		
Randomized (N)	259	522	
Not Treated (%)	0.4	0.2	
Discontinued Treatment Phase (%)	37.1	38.1	
Adverse Event (%)	8.5	11.5	
Withdrawal (%)	9.3	11.5	
Lack of Efficacy (%)	10.8	8.4	
Lost to Follow-up (%)	4.6	2.7	
Other† (%)	4.2	4.2	
Completed Treatment Phase (%)	62.5	61.7	
	PBO	HD	PBO
Entered Randomized Discontinuation Phase (N)	162	156	166
Completed Randomized Discontinuation Phase (%)	96.9	97.4	97.0

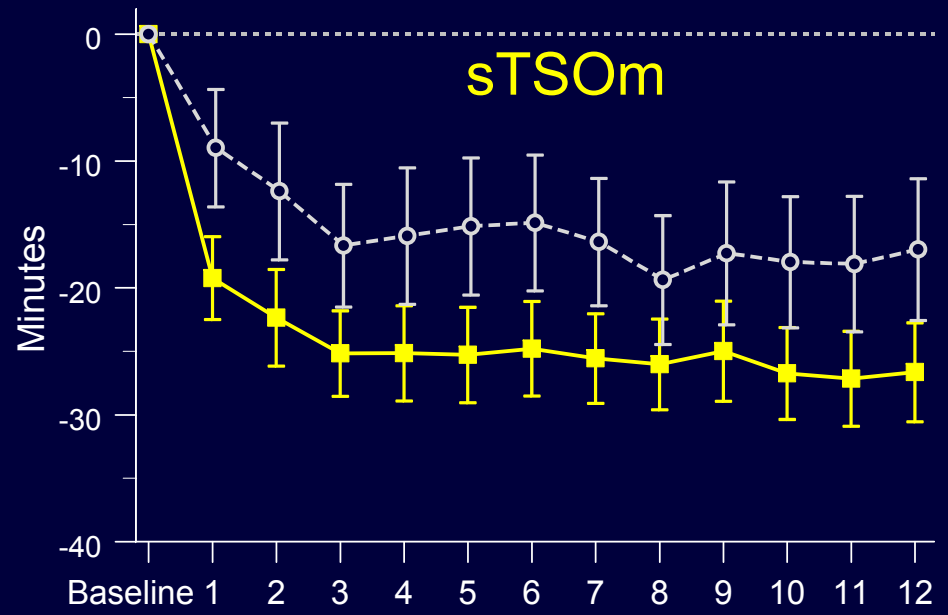
† Other=protocol violation, pregnancy and physician decision.

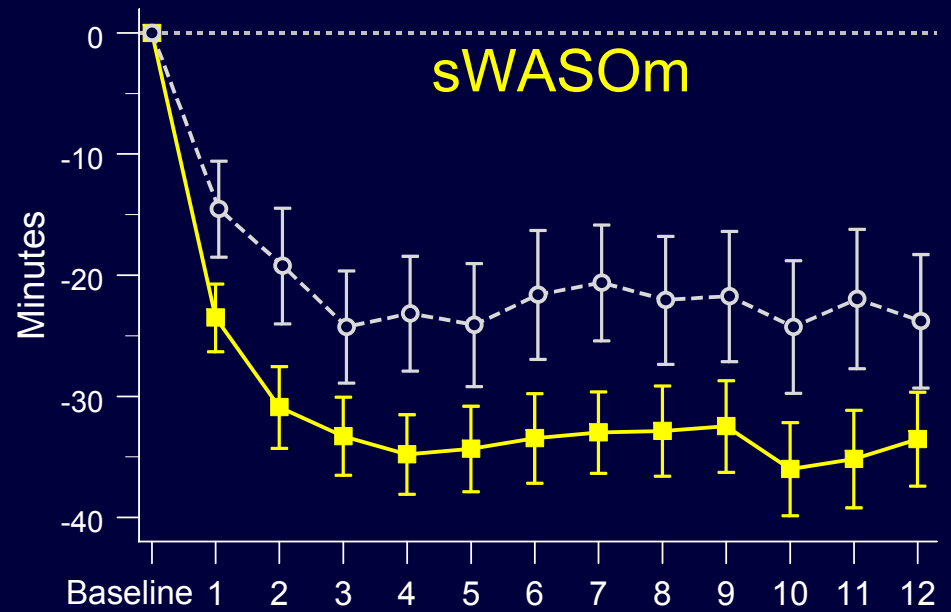
P009 Baseline Characteristics Treatment Phase

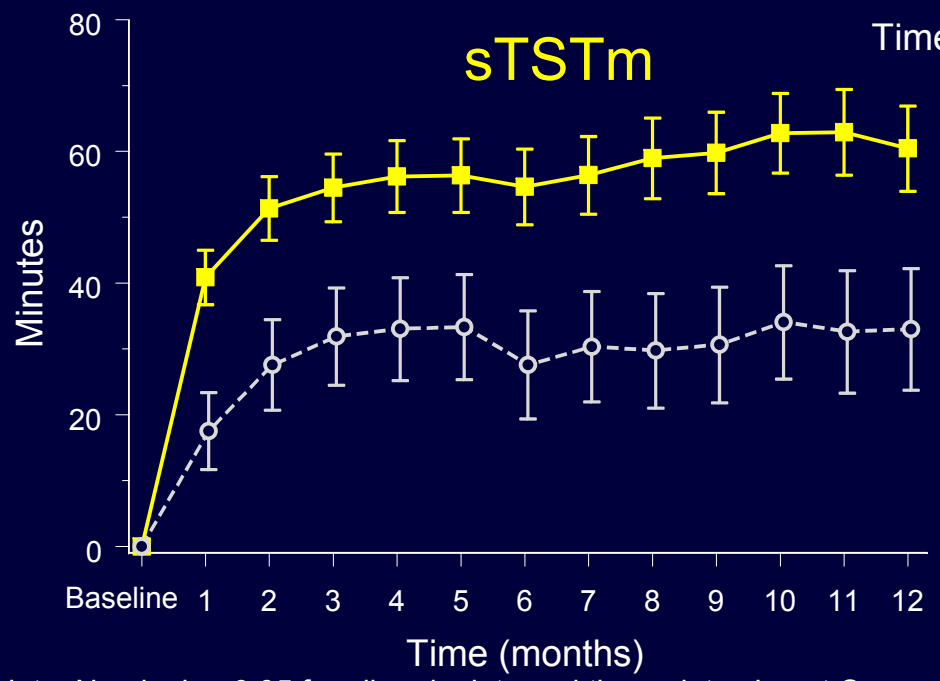
All Patients as Treated

	Placebo N=258 n (%)	Suvorexant N=521 n (%)
Gender		
Male	109 (42.2)	234 (44.9)
Female	149 (57.8)	287 (55.1)
Age (years)		
<65	107 (41.5)	213 (40.8)
≥65	151 (58.5)	308 (59.2)
≥75	47 (18.2)	72 (13.8)
Race		
White	231 (89.5)	476 (91.4)
Black or African American	24 (9.3)	33 (6.3)
Asian	1 (0.4)	6 (1.2)
Other	2 (0.8)	6(1.2)

Suvorexant HD Efficacy Persists for 12 Months







	Treatment	Baseline Mean
sTSOm	Suvorexant	65.9
	Placebo	65.0
sWASOm	Suvorexant	80.1
	Placebo	71.5
sTSTm	Suvorexant	320.4
	Placebo	329.9

Note: Nominal $p<0.05$ for all endpoints and timepoints. Least-Squares mean changes from baseline and 95% confidence intervals shown in plots. sTSOm=subjective Time to Sleep Onset mean; sWASOm=subjective Wake After Sleep Onset mean; sTSTm=subjective Total Sleep Time mean.

Efficacy Conclusions

- Efficacy was demonstrated objectively and subjectively for sleep onset and sleep maintenance in replicate 3 month pivotal trials
- Efficacy was sustained over the course of a full year
- Both high (40/30 mg) and low (20/15 mg) suvorexant doses were efficacious, with consistent results in elderly and non-elderly
- HD consistently delivered more efficacy across endpoints than LD, particularly for subjective measures
- Sleep maintenance effects were sustained throughout the night
- Suvorexant's efficacy is perceived as meaningful by patients

Suvorexant Safety

Methods & Results

Timeframes for Phase 3 Safety Analyses

Key Time Intervals of Interest

- Analyses performed on data pooled across all Phase 3 trials
- 0-3 months
  - Time frame corresponds to primary efficacy evaluation
  - Key safety database for chronic treatment of insomnia
- 0-12 months (high dose) and 0-6 months (low dose)
  - Overall suvorexant exposure
  - AE summary and specific AEs
  - Uncommon AEs
    - Serious Adverse Events (SAEs)
    - Events of Clinical Interest (ECIs)
    - Discontinuations due to AEs
    - Selected AEs associated with residual effects and abuse potential

Special Safety Assessments: Events of Clinical Interest (ECI)

- Adverse events (AE) prospectively identified as potentially important to the safety profile of suvorexant:

Safety considerations pertinent to:	ECI
• Sleep medications	Complex sleep-related behaviors, sleep paralysis, hypnagogic/ hypnopompic hallucinations, excessive daytime sleepiness, falls, AEs associated with traffic or motor vehicle accidents
• Novel CNS-active compounds	Suicidal ideation and/or behavior, abuse potential
• Theoretical considerations related to the novel mechanism of action	Cataplexy

- AE/ECIs reported as potential cataplexy, falls (to rule out cataplexy), and sleep onset paralysis were adjudicated by a committee external to Merck

Suvorexant Well-Tolerated in Phase 3: AE Summary 0-3 Months

Patients	Placebo N=1025		Suvorexant LD N=493		Suvorexant HD N=1291	
	n	%	n	%	n	%
With one or more AEs	478	(46.6)	229	(46.5)	658	(51.0)†
With drug-related AEs	154	(15.0)	109	(22.1)†	329	(25.5)†
With serious AEs	23	(2.2)	3	(0.6)	18	(1.4)
With serious drug-related AEs	1	(0.1)	0	(0.0)	0	(0.0)
Who died	1	(0.1)	0	(0.0)	1	(0.1)
Discontinued due to an AE	50	(4.9)	15	(3.0)	80	(6.2)
Discontinued due to a drug-related AE	25	(2.4)	13	(2.6)	53	(4.1)

† 95% CI of comparison to placebo excluded zero.

Phase 3 Common AEs (≥2%) and Greater than Placebo: 0-3 Months

Protocols 028+029+009	Placebo		Suvorexant LD		Suvorexant HD	
	n	(%)	n	(%)	n	(%)
Patients in population	1025		493		1291	
Somnolence	31	(3.0)	33	(6.7)	138	(10.7)
Headache	61	(6.0)	36	(7.3)	85	(6.6)
Fatigue	18	(1.8)	11	(2.2)	49	(3.8)
Dry mouth	14	(1.4)	9	(1.8)	36	(2.8)
Dizziness	29	(2.8)	15	(3.0)	32	(2.5)
Upper respiratory tract infection	12	(1.2)	8	(1.6)	28	(2.2)
Nausea	16	(1.6)	7	(1.4)	27	(2.1)
Abnormal dreams	10	(1.0)	9	(1.8)	27	(2.1)
Drug administration error	23	(2.2)	16	(3.2)	25	(1.9)
Diarrhea	15	(1.5)	12	(2.4)	21	(1.6)

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

Consistent safety profile seen with longer term treatment with LD up to 6 months and HD up to 12 months

Phase 3 General Safety

- Serious adverse events (SAE) uncommon, with similar frequency between suvorexant and placebo
  - No specific SAE occurred at >0.2%
  - Drug-related SAEs: 1 with suvorexant HD and 3 with placebo
  - 2 deaths, neither drug-related: suvorexant HD (hypoxic-ischemic encephalopathy), placebo (subarachnoid hemorrhage)
- Discontinuation due to AEs were uncommon, with comparable frequency between suvorexant and placebo
  - Somnolence most common reason for discontinuation (suvorexant HD)
- Safety profile over 12 months of treatment similar to 3 months
  - No new types of AEs or increase in AE incidence to suggest emerging safety concern
- No clinically meaningful differences in safety for age or gender

Suvorexant Residual Effects Profile

Adverse Event Reports

Digit Symbol Substitution Test

On-the-Road Driving Model

Phase 3 Motor Vehicle Accidents and Violations

Program Assessments of Residual Effects

	Phase 1	Phase 2	Phase 3
Adverse events	√	√	√
Memory and balance			
Word learning test	√		
Body sway test	√		
Adverse events of falls	√	√	√
Next-day performance			
Psychomotor performance			
Digit symbol substitution test	√	√	√
Digit symbol copy test		√	
Simple reaction time	√		
Choice reaction time	√		
Driving performance			
Highway driving studies	√		
Motor vehicle accidents and violations			√

A Minority of Patients Experienced Next-Day Somnolence in Phase 3

Pooled 0-3 Month Data	Placebo N=1025 n (%)	Suvorexant LD N=493 n (%)	Suvorexant HD N=1291 n (%)
Total reporting somnolence	31 (3.0)	33 (6.7)	138 (10.7)
By age <65†	16 (2.9)	22 (7.6)	83 (12.5)
By age ≥65†	15 (3.2)	11 (5.4)	55 (8.8)
Intensity			
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)
% Discontinuation	3 (0.3)	1 (0.2)	22 (1.7)

- Somnolence = a feeling of sleepiness or drowsiness
- Somnolence was the most common AE and was dose related
- Generally mild to moderate
- Majority of somnolence reported within first month of treatment
- Discontinuation due to somnolence was uncommon

† Treatment group percentages based upon number of patients within each age subgroup.

Few Patients Reported EDS in Phase 3

- Excessive daytime sleepiness (EDS) as defined for this program was reported as higher severity (duration or intensity) somnolence
- EDS cases are a subset of the somnolence AEs discussed

Pooled 0-3 Month Data	Placebo N=1025	Suvorexant LD N=493	Suvorexant HD N=1291
	n (%)	n (%)	n (%)
EDS	2 (0.2)	3 (0.6)	14 (1.1)
Intensity			
Mild	1 (0.1)	2 (0.4)	2 (0.2)
Moderate	1 (0.1)	1 (0.2)	7 (0.5)
Severe	0 (0.0)	0 (0.0)	5 (0.4)
% Discontinuation	2 (0.2)	1 (0.2)	10 (0.8)

No Consistent Objective Evidence of Next Day Effects in Phase 3 as Assessed by the DSST

- DSST (Digital Symbol Substitution Test) is a validated, standard measure of psychomotor performance used in sleep research[1,2,3]
  - Completed on mornings following polysomnography (PSG), at ~8.5-9 hours post suvorexant dose at Night 1, Month 1 and Month 3
- Results
  - No differences were observed between suvorexant and placebo in the combined age data

[1] Stone B. *Br J Clin Pharmacol.* 1984;18:15S-20S.
[2] Erman, et al. *Human Psychopharmacology*. 2001;16:169-176.
[3] Banks, et al. *Sleep*. 2010;33:1013-1026.

Phase 1 On-the-Road Driving Studies

- Two similarly designed randomized, 4-period, placebo- and active-controlled driving studies were conducted using a model road driving test[1]:
  - One study each in non-elderly (N=28) and elderly (N=24) healthy subjects
  - Suvorexant HD (40/30 mg) and LD (20/15 mg) evaluated
  - One-hour long highway driving tests were conducted on the morning after a single evening dose (Day 2) and after multiple (8) nightly doses of suvorexant (Day 9)
  - Positive control was single dose zopiclone 7.5 mg, administered in the evening of Day 1 and Day 8

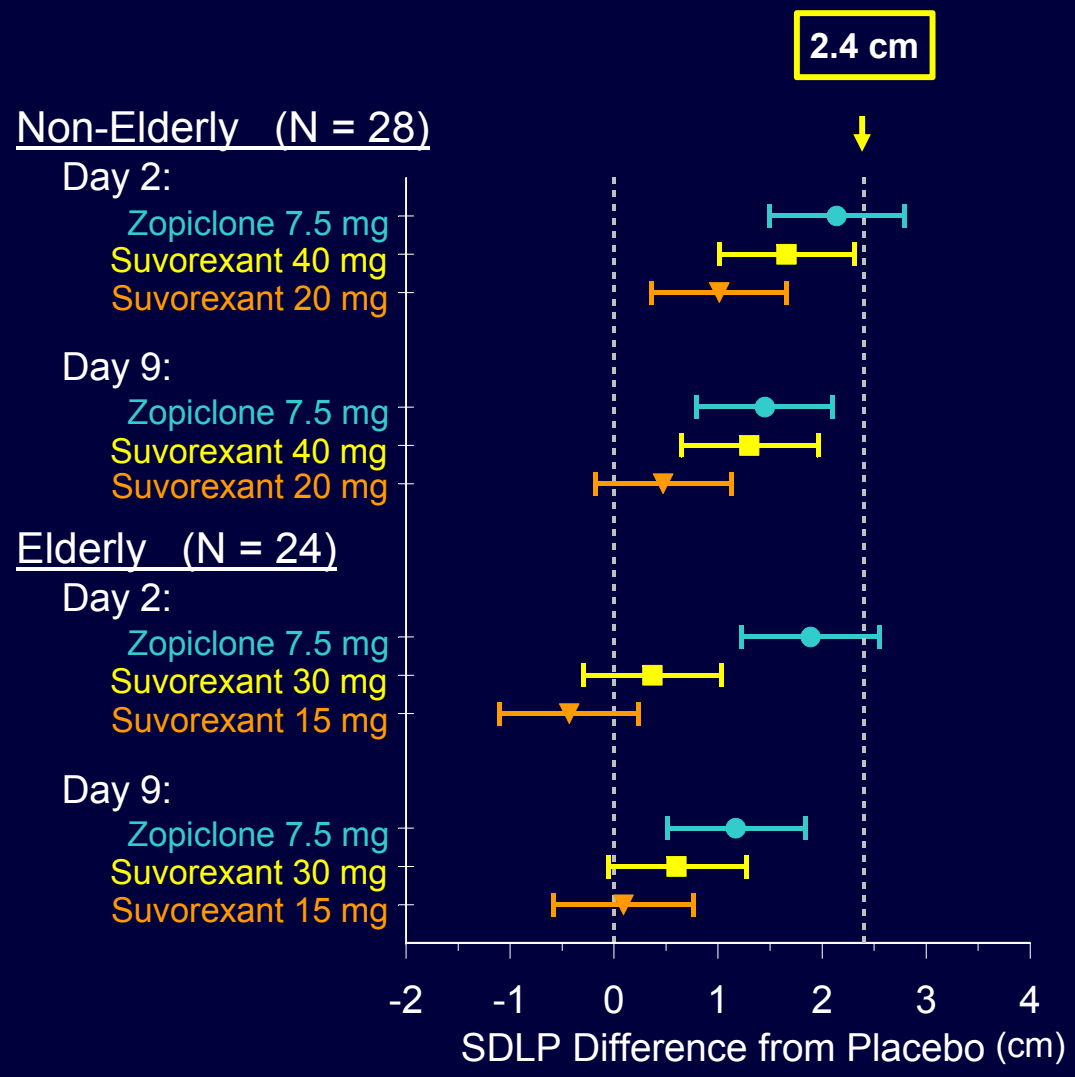
[1] Verster, JC and Roth, T. *International Journal of General Medicine*. 2011:4 359-371.

Phase 1 On-the-Road Driving Studies

- Primary endpoint for driving studies was mean SDLP
  - SDLP=Standard Deviation of Lane Position
    - A measure of “weaving”
  - Primary hypothesis was that the true mean ΔSDLP (difference from placebo) would not exceed the standard threshold in the literature
    - Hypothesis supported if 90% CI lies below 2.4 cm
- Secondary analyses included Symmetry Analysis of ΔSDLP

Suvorexant Driving Studies: Results

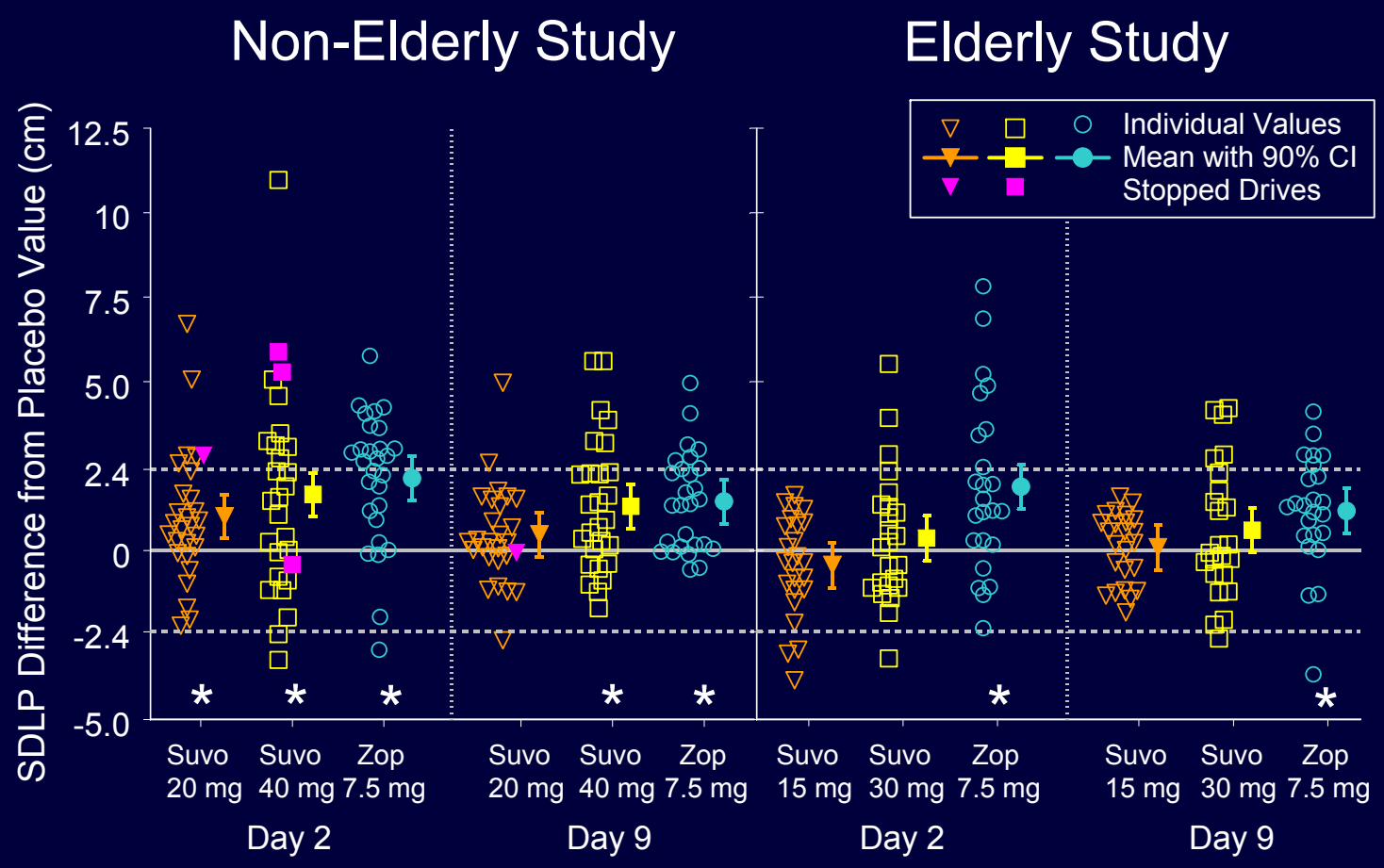
- Mean ΔSDLP:
  - Mean SDLP changes (90% CI) were below the standard cutoff of 2.4 cm
- Prematurely stopped drives:
  - 5/209 drives (2.4%) on suvorexant were stopped early in 4 subjects: 3 drives on 40 mg, 2 drives on 20 mg
  - 1/103 drives on placebo was stopped (1%)
  - All suvorexant stopped drives requested by subject
    - In contrast, 4:1 ratio of driving tests of other hypnotics stopped by driving instructor vs. subject[1]
  - All suvorexant stopped drives associated with self-reported somnolence



SDLP = Standard Deviation of Lane Position
Zopiclone 7.5 mg (single doses) = positive control

[1]Verster, JC and Roth, T. *Accident Analysis Prevention*. 45(2012) 498-506.

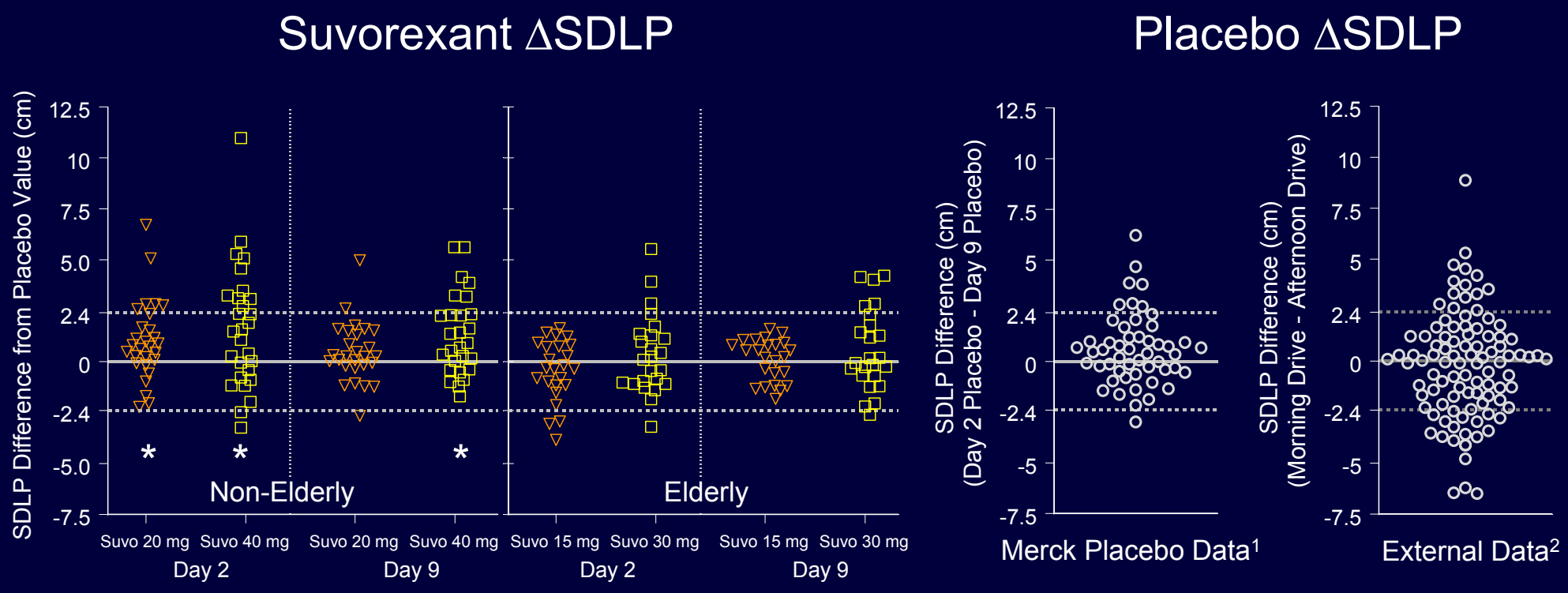
Symmetry Analysis of ΔSDLP



- Symmetry analysis tests for an imbalance in the number of subjects with ΔSDLP above +2.4 cm versus below -2.4 cm, the pre-specified threshold
- As assessed by symmetry analysis, a suvorexant treatment effect was observed on the driving task in the non-elderly study only (* = significant asymmetry)

Zop=zopiclone.

Individual ΔSDLP Values >2.4 cm Occur With Placebo vs. Placebo Drives



- When comparing results of two successive drives on placebo, ΔSDLP values for a number of subjects also exceed 2.4 cm

* significant asymmetry.

[1]Within-subject comparisons of SDLP for Day 2 placebo vs. Day 9 placebo from suvorexant non-elderly and elderly driving studies. [2] Placebo test-retest (morning drive and afternoon drive), data from Verster, JC and Roth, T. Also reported in *International Journal of General Medicine*. 2011;4:364.

No Increase in Reported Accidents in Prospective Phase 3 Driving Assessment

- Driving-related safety prospectively assessed based on patient reports of motor vehicle accidents and violations (MVAV; with patient as driver)

Accidents and Violations: Phase 3 – Months 0 to 12

	Placebo N=692 n (%)	Suvo HD N=891 n (%)	Difference in % vs. Placebo Estimate (95% CI)†
Patients with one or more MVAV events	22 (3.2)	36 (4.0)	0.9 (-1.1, 2.7)
Number with accidents	10 (1.4)	13 (1.5)	0.0 (-1.3, 1.2)
Number with citations (moving violations)	14 (2.0)	24 (2.7)	0.7 (-0.9, 2.2)

- The incidence of accidents and violations was comparable between suvorexant and placebo
  - No differences between age subgroups

† Post-hoc analysis of treatment difference based upon Miettinen & Nurminen method.
MVAV=motor vehicle accidents and moving violations.

Suvorexant Next-Day Profile Summary

- Potential for next-day effects was comprehensively assessed
- While the majority of patients did not report residual effects, somnolence was the most common adverse event
  - Somnolence was generally of mild-moderate severity, and usually resolved with continued treatment
  - A small minority of patients on suvorexant HD asked to discontinue due to somnolence
- Objective measures of next-day performance, including driving, indicated suvorexant was not associated with impairment for most patients
  - Driving model symmetry data and stopped drives indicate a treatment effect in some subjects
- Phase 3 assessment of driving in outpatient setting shows incidence of accidents and violations was low and comparable across treatments
- Results did not differ by age subgroup

Assessment of Other Factors Associated With the Use of Sleep Medications

Events of Clinical Interest

Potential for Mechanism-Related Effects

Rebound and Withdrawal

Abuse Potential

Pre-specified Adverse Events of Clinical Interest Were Uncommon

	Phase 3 Totals			
	0-6 Months		0-12 Months	
	Placebo† (N=767)	Suvorexant LD (N=493)	Placebo (N=1025)	Suvorexant HD (N=1291)
ECIs = Pre-specified Events of Clinical Interest	n (%)	n (%)	n (%)	n (%)
Complex sleep behaviors	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Hypnagogic/hypnopompic hallucination	0 (0.0)	2 (0.4)	0 (0.0)	5 (0.4)
Sleep paralysis	0 (0.0)	1 (0.2)	0 (0.0)	5 (0.4)
Excessive daytime sleepiness	1 (0.1)	3 (0.6)	3 (0.3)	20 (1.5)
Cataplexy (confirmed by adjudication)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Falls (adjudicated to rule out cataplexy)	7 (0.9)	5 (1.0)	15 (1.5)	21 (1.6)
Adverse events of potential for abuse liability‡	19 (2.5)	20 (4.1)	31 (3.0)	34 (2.6)
Drug administration errors	19 (2.5)	20 (4.1)	31 (3.0)	32 (2.5)

- Based on circumstances and timing, no instances of fall were suggestive of potential cataplexy, and none were adjudicated as cataplexy by a blinded external adjudication committee

† Subset of 0-12 month data.
‡ Terms include depersonalization, derealization, dissociation, euphoric mood, mania, hallucination, potential study medication misuse.

What Is Narcolepsy?

- Narcolepsy is a chronic neurological disorder
  - Associated with degenerative loss of orexin neurons
  - Inability to regulate sleep-wake cycles normally
- The ICSD-2 diagnosis of narcolepsy includes:
  - Excessive daytime sleepiness almost daily for at least 3 months
  - Laboratory confirmation of short sleep onsets and REM sleep in a sleep latency test[1]
  - Cataplexy in some patients (emotionally triggered episodes of muscle weakness)

[1] Billiard, M. *Sleep Medicine Reviews*. 2007;11:377-388.
ICSD-2=International Classification of Sleep Disorders Version 2.

No Pattern Suggestive of Pharmacologic Narcolepsy-Like Syndrome in Phase 3

- A small number of patients (1.8%) treated with suvorexant HD reported either severe somnolence or excessive daytime sleepiness
  - All cases fully reversible when treatment was stopped (except in 1 patient with no recorded stop date)
  - No case with other signs/symptoms (e.g. cataplexy)
  - One patient with severe somnolence had one unreplicated PSG with short-onset REM (≤15 minutes); no short-onset REM in EDS cases with PSGs (N=5)
  - Consistent with transient blockade of orexin receptors
- Suvorexant has not been studied in patients with narcolepsy and is not recommended for use in these patients

REM=Rapid Eye Movement sleep PSG=polysomnography; EDS=excessive daytime sleepiness.

Phase 3 Prospective Evaluation of Suicidal Ideation and Behavior Using C-SSRS

	Placebo (n)	Suvorexant LD (n)	Suvorexant HD (n)
Number of Patients in Phase 3:	1025	493	1291
With Suicidal Behavior	0	0	0
With Ideation and Intent but No Plan	0	0	1
With Ideation and No Intent	1	1	8

- Suicidal ideation was infrequent: 1 (0.1%) placebo, 1 (0.2%) suvorexant LD, and 9 (0.7%) suvorexant HD†
- All events occurred in the context of factors associated with increased risk, e.g. prior history, current depression, and/or precipitating life events
- As assessed by QIDS, suvorexant HD had no effect on depressive symptoms over the course of treatment for up to 1 year
- Clinicians should be made aware that, as with other hypnotics, suicidal ideation can occur and should be thoroughly evaluated

† Includes 3 patients with suicidal ideation not considered adverse event by investigator.
C-SSRS=Columbia Suicide Severity Rating Scale; QIDS=Quick Inventory of Depression Symptoms – SR16.

No Withdrawal or Clinically Meaningful Rebound Upon Stopping Suvorexant

- Withdrawal
  - No evidence for withdrawal by Tyrer Withdrawal Symptom Questionnaire, and no adverse events reported suggestive of potential withdrawal

- Rebound
  - No effects were seen on measures of sleep onset
  - Effects seen on some sleep maintenance measures had characteristics of the return of insomnia symptoms, and did not appear to be consistent with clinically meaningful rebound insomnia

Suvorexant Has Low Potential for Abuse

- In nonclinical studies, suvorexant did not have a profile consistent with risk for physical dependence or abuse
- In an abuse potential study in recreational polydrug users with a history of sedative-hypnotic drug use:
  - Suvorexant had similar “drug liking” as zolpidem, and both were different from placebo
- Across the clinical program, the incidence of adverse events potentially related to abuse potential was low
  - In Phase 3:
    - Most common event was drug administration error, representing a low incidence of pill count discrepancies, with no pattern consistent with abuse
    - Other events: <0.4% in any treatment group, with no euphoria reported

Safety Conclusions

- The Phase 3 program established a safety database in >2800 subjects and insomnia patients, with over 275,000 person nights of exposure to suvorexant
- Suvorexant has an acceptable safety profile, with a low incidence of next day residual effects
  - Few adverse events occurred at ≥2% and greater than placebo, with somnolence most common
  - Across multiple assessments, a dose-related increase in residual effects was observed
- Abrupt cessation of suvorexant was not associated with withdrawal or clinically meaningful insomnia rebound
- Suvorexant appears to have a low risk for abuse

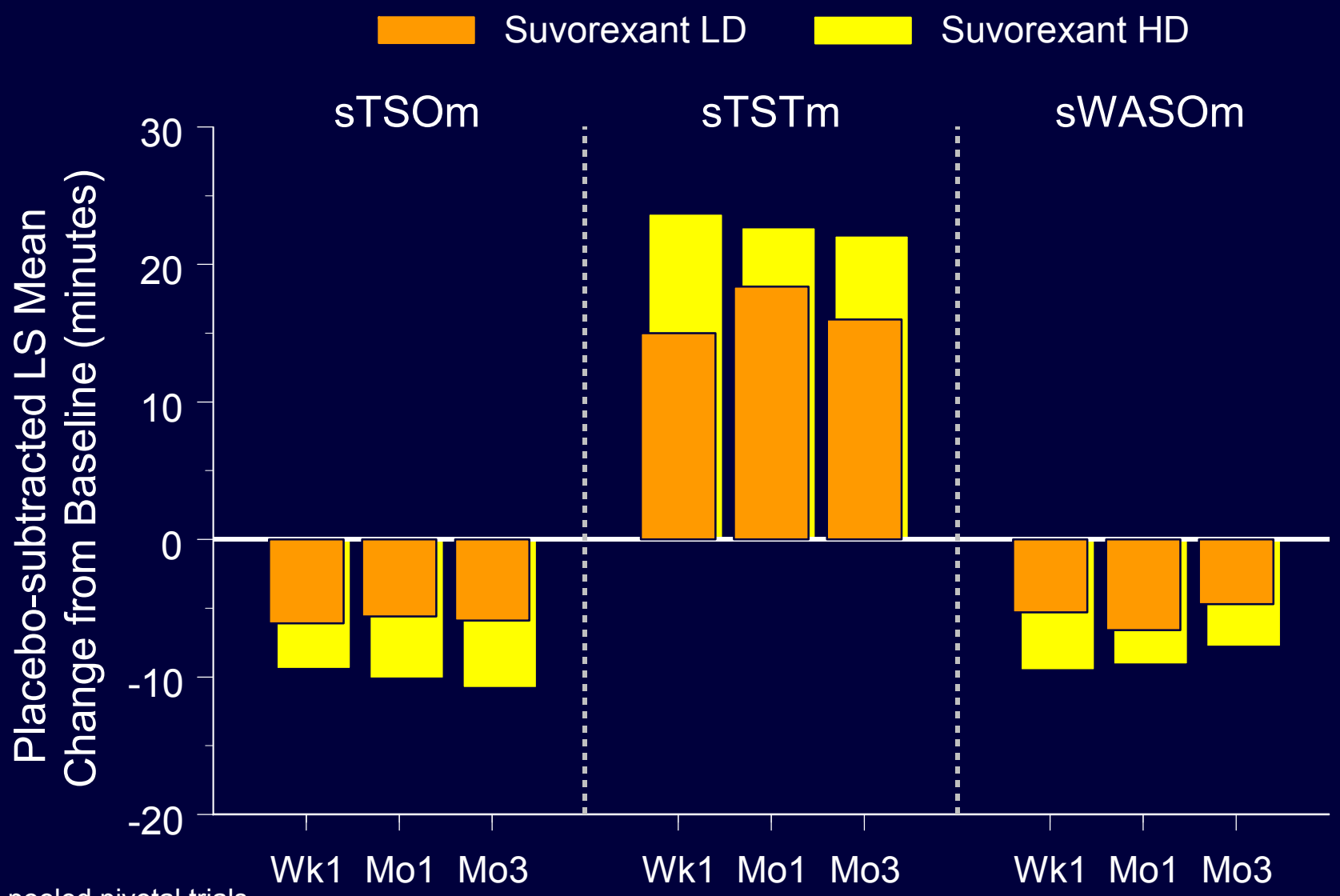
Benefit-Risk Assessment

David Michelson, M.D.
Merck Research Laboratories

Suvorexant Is Efficacious for the Treatment of Insomnia

- Suvorexant was studied in two pivotal 3-month studies, and chronically in a 1-year study
  - Suvorexant 40/30 mg and 20/15 mg both improved sleep onset and maintenance assessed objectively and subjectively
  - Efficacy was maintained over a full year
  - Efficacy was consistent for elderly and non-elderly
  - Suvorexant 40/30 mg was maximally efficacious and consistently showed greater symptom reduction than 20/15 mg

High Dose Provides Consistently Greater Subjective Improvement than Low Dose



Data from pooled pivotal trials.

sTSOm=subjective Time to Sleep Onset mean; sTSTm=subjective Total Sleep Time mean; sWASOm=subjective Wake After Sleep Onset mean; LS=Least-Squares.

Suvorexant's Safety and Tolerability Profile

- During the clinical development program
  - The most common adverse event was somnolence, which most often was mild or moderate
  - Next day effects were limited in number and severity
  - Potentially mechanism-specific events of clinical interest occurred infrequently
    - No events adjudicated as cataplexy

Insomnia Is an Important Medical Problem

- Insomnia is a common, chronic disorder of young and old associated with serious health concerns and social impact[1,2]
- Insomnia is a source of significant distress and anxiety for patients[3,4]
- Available treatments do not serve all patients well

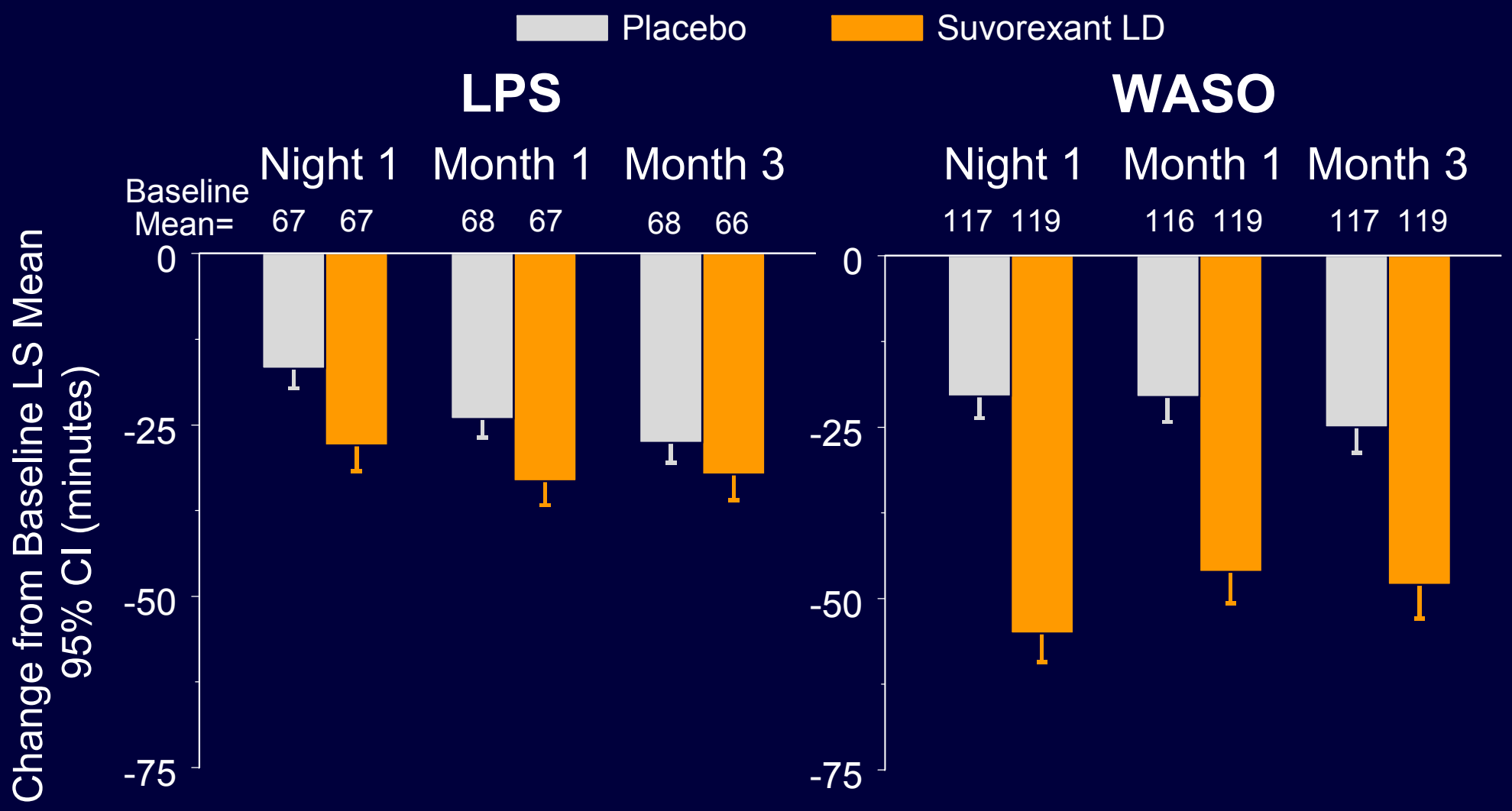
[1] Staner L. *Sleep Medicine Reviews*. 2010;14:35-46.
[2] Leger D, Massuel A, Metlaine A. *Sleep*. 2006;29:171-8.
[3] Taylor DJ, Lichstein KL, Durrence HH. *Behav Sleep Med*. 2003;1:227-247.
[4] Kyle, Morgan, and Espie. *Sleep Medicine Reviews*. 2010;14:69-82.

New Treatments Are Needed

- Shorter acting benzodiazepines and ‘z-drugs’ induce sleep well, but most maintain sleep less effectively, or not at all[1]
- Older benzodiazepines (e.g. quazepam) induce and maintain sleep well, but at the cost of increased risk (e.g. falls, next day effects)[2]
- Few treatment options available to patients today improve sleep induction and also improve sleep maintenance throughout the entire night while retaining a favorable residual effects profile
- The data from the clinical development program demonstrate that suvorexant’s clinical profile addresses this need

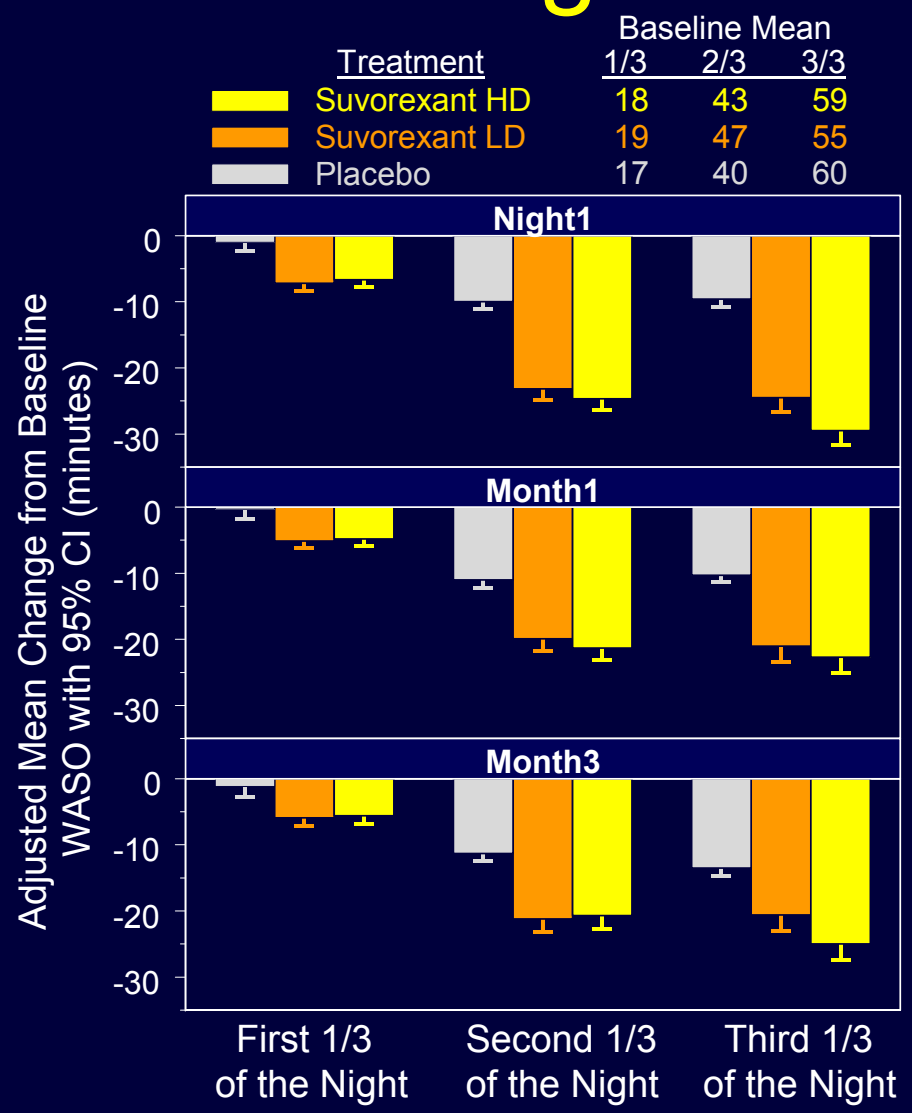
[1] Silber, MH. *N Engl J Med*. 2005;353:803-10.
[2] Riemann, D. *Sleep Med. Rev*. 2009;13:205-14.

Suvorexant Improves Both Sleep Onset and Sleep Maintenance



Data from pooled pivotal trials.

Suvorexant Maintains Sleep Throughout the Night



Note: Data from pooled pivotal trials. Nominal p-values <0.05 for suvorexant vs. placebo during each third of the night in each trial (P028 and P029) except in P028 at Month 3 for first 1/3 of the night (LD and HD) and third 1/3 of the night (LD).

LS=Least-Squares; WASO=objective Wake After persistent Sleep Onset.

Reported Next Day Somnolence on Suvorexant Is Comparable to Other Modern Hypnotics

- The frequency of somnolence reported by patients taking suvorexant is comparable to shorter-acting drugs that have less pronounced effects on sleep maintenance

	Somnolence (Increase above placebo non-elderly, self-report)	
	Low Dose	High Dose
Suvorexant† (3 weeks, 20 mg, 40 mg)	5%	8%
Zolpidem CR§ (3 weeks, 12.5 mg)	N/A	13%
Suvorexant† (6 weeks, 20 mg, 40 mg)	5%	9%
Eszopiclone‡ (6 weeks 2 mg, 3 mg)	7%	5%

† Kaplan-Meier estimates from pooled Phase 3 data; ‡ Data from Lunesta® (eszopiclone) package insert; § Data from Ambien CR® (zolpidem tartrate extended-release) package insert.

Suvorexant's Efficacy Is Perceived as Meaningful by Patients

- As measured by the Insomnia Severity Index, suvorexant low dose is associated with a greater likelihood that patients will experience a clinically meaningful response†

	Odds Ratio for Response (95% CI) (Higher favors suvorexant LD over placebo)	
	Month 1	Month 3
Pooled Pivotal Studies (P028+P029)	1.8 (1.4, 2.4)	1.8 (1.4, 2.3)

† *Response defined as ≥6 point improvement from baseline in ISI total score.*

Suvorexant's Safety Profile Is Maintained During Chronic Treatment

- During chronic treatment, clinical data do not suggest an association of suvorexant with unexpected risks or with late onset changes in safety or tolerability, nor with clinically meaningful rebound or withdrawal phenomena

Discontinuations Due to an Adverse Event		
	Placebo	Suvorexant HD
After 3 months	4.9%	6.2%
After 1 year	6.0%	7.8%

Conclusions

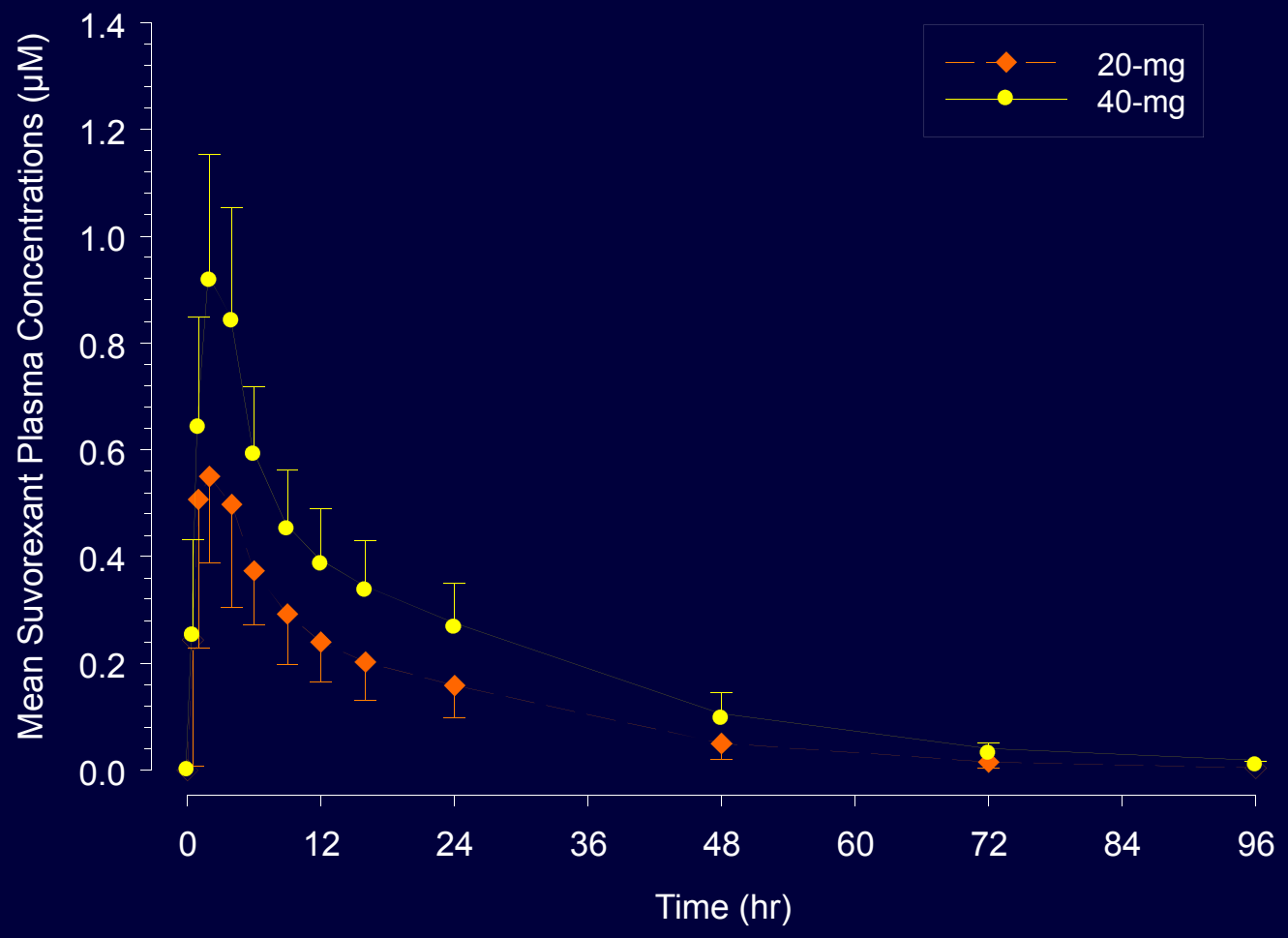
- Suvorexant is a first in class orexin receptor antagonist that specifically targets the regulation of wakefulness
- Suvorexant is efficacious
  - For sleep onset
  - For sleep maintenance throughout the night
  - For elderly and non-elderly
  - As early as night 1 and chronically over a year
- Suvorexant was generally safe and well-tolerated acutely and chronically
- Suvorexant's clinical profile meaningfully expands the options available to patients suffering with insomnia

Proposed Indication and Dose Considerations

Indication: treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance

- Revised Dose Considerations:
  - Use the lowest effective dose for the patient. The usual starting dose should be 20 mg (15 mg in elderly). For patients whose symptoms persist and who demonstrate acceptable tolerability, a dose increase may be considered.

Suvorexant Concentrations Increase in a Slightly Less than Dose-Proportional Manner



Depressive Symptoms Do Not Increase During Treatment

Analysis of Change From Baseline in QIDS Total Score by Month Treatment Phase P009 (Data-as-Observed)

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

† Results based on a mixed effects model with terms for baseline value, gender, region, treatment, time, and treatment-by-time interaction.
QIDS=Quick Inventory of Depressive Symptoms.

Analysis of Change From Baseline in QIDS Total Score by Month Treatment Phase: Baseline Total Score ≥10

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

† Results based on a mixed effects model with terms for baseline value, gender, region, treatment, time, and treatment-by-time interaction.
QIDS=Quick Inventory of Depressive Symptoms.

Analysis of Change From Baseline in QIDS Total Score by Month, Treatment Phase Baseline Total Score <10

Treatment	N	Baseline	Treatment	Change From Baseline	
		Mean (SD)	Mean (SD)	Mean (SD)	LS Mean† (95% CI)†
Month 1					
Placebo	228	4.0 (1.7)	4.0 (2.2)	0.0 (2.0)	-0.2 (-0.5, 0.1)
Suvorexant	464	4.1 (1.7)	3.8 (1.9)	-0.3 (2.1)	-0.4 (-0.6, -0.3)
Month 3					
Placebo	193	3.9 (1.7)	3.8 (2.1)	-0.1 (2.1)	-0.3 (-0.6, 0.0)
Suvorexant	409	4.1 (1.7)	3.7 (2.1)	-0.4 (2.1)	-0.5 (-0.7, -0.3)
Month 6					
Placebo	177	3.8 (1.7)	3.6 (2.0)	-0.2 (2.3)	-0.4 (-0.7, -0.1)
Suvorexant	364	4.0 (1.7)	3.7 (2.3)	-0.3 (2.3)	-0.4 (-0.6, -0.2)
Month 9					
Placebo	165	3.8 (1.7)	3.6 (2.1)	-0.1 (2.2)	-0.3 (-0.7, -0.0)
Suvorexant	335	4.0 (1.7)	3.6 (2.0)	-0.5 (2.2)	-0.5 (-0.7, -0.3)
Month 12					
Placebo	154	3.8 (1.7)	3.6 (2.5)	-0.2 (2.5)	-0.4 (-0.7, -0.0)
Suvorexant	312	4.0 (1.7)	3.4 (2.0)	-0.6 (2.3)	-0.5 (-0.8, -0.3)

† Results based on a mixed effects model with terms for baseline value, gender, region, treatment, time, and treatment-by-time interaction.
QIDS=Quick Inventory of Depressive Symptoms.

Distribution of Change From Baseline in QIDS Categories†

(Protocol 009/Full Analysis Set)

Category	Treatment			
	Placebo		Suvorexant HD	
	n/N	(%)	n/N	(%)
No Change/Improved	184/240	(76.7)	377/490	(76.9)
No Change	169/184	(91.8)	327/377	(86.7)
Improved 1 category	13/184	(7.1)	45/377	(11.9)
Improved 2 categories	2/184	(1.1)	5/377	(1.3)
Worsened	56/240	(23.3)	113/490	(23.1)
Worsened 1 category	52/56	(92.8)	106/113	(93.8)
Worsened 2 categories	3/56	(5.4)	6/113	(5.3)
Worsened 3 categories	1/56	(1.8)	1/113	(0.9)

† Based on most severe category observed during the treatment phase: 0=None (0 to 5), 1=Mild (6 to 10), 2=Moderate (11 to 15), 3=Severe (16 to 20), 4=Very severe (21 to 27).
QIDS=Quick Inventory of Depressive Symptoms.

Obesity And Next-Day Somnolence In Women Phase 3: 0-3 Months

(Protocols 028, 029 and 009, All Patients as Treated)

BMI	Proportion Reporting Somnolence	Placebo Subtracted Frequency of Somnolence	Obese vs. Non-Obese Difference (95% CI)
BMI >30.0	PBO (5/114)	----------	----------
	LD (1/41)	LD: -1.9%	LD: -9.4 (-16.4, -2.4)
	HD (21/144)	HD: 10.2%	HD: 1.9 (-5.4, 9.3)
BMI ≤30.0	PBO (10/526)	----------	----------
	LD (26/278)	LD: 7.5%	----------
	HD (65/639)	HD: 8.3%	----------

PBO=placebo; LD=suvorexant low dose; HD=suvorexant high dose.

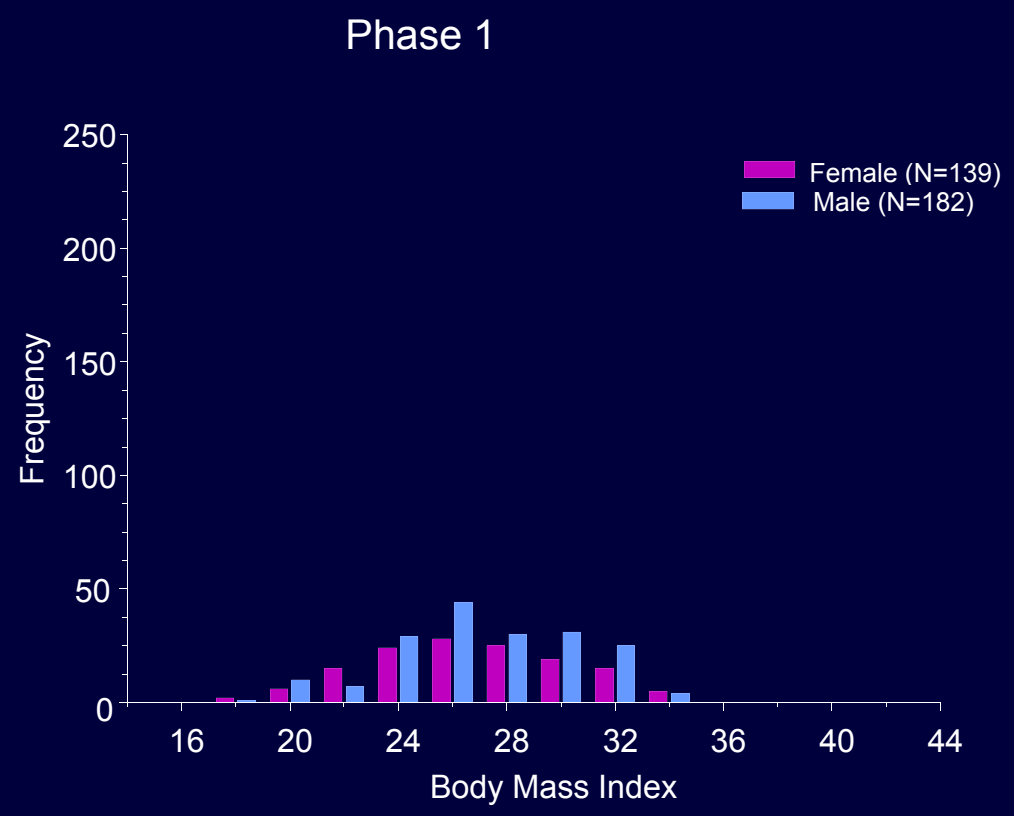
Modest Effects of Intrinsic Factors on Steady-State Suvorexant PK in Patients Receiving 40 mg Suvorexant

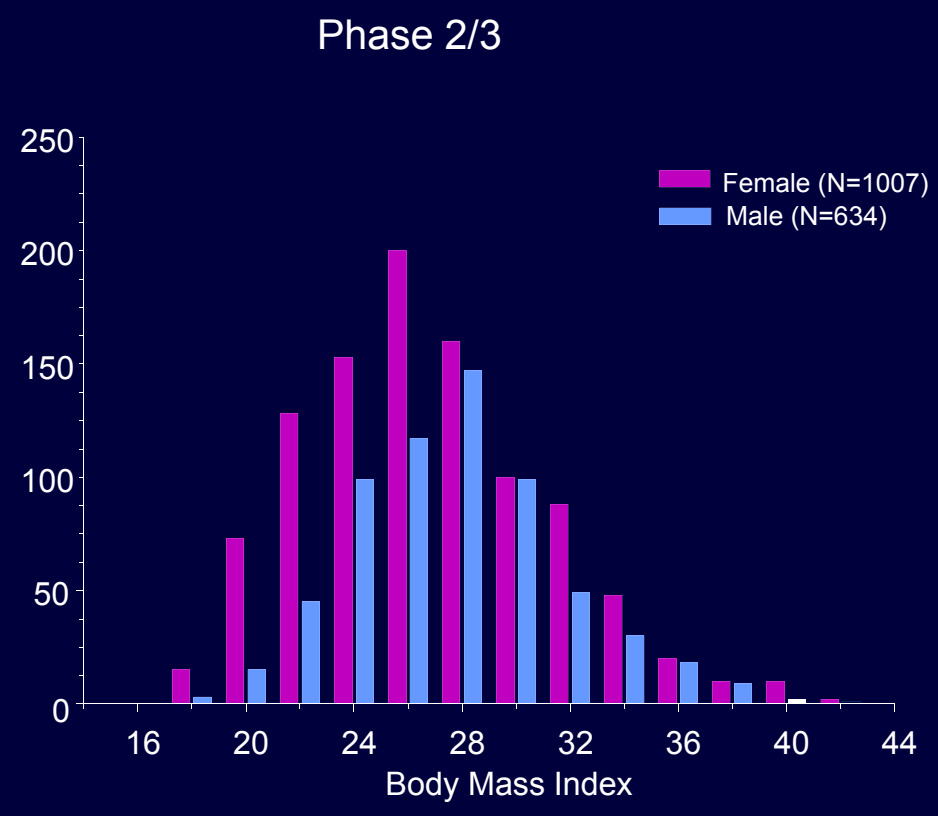
Geometric Mean Ratio (90% CI)

		Phase 1 Model-Predicted[a]	Phase 2/3[b]
		AUC_{0-24} (μM•h)	C_{9hr} (μM)
Gender	Female/Male	1.17 (1.14, 1.19)	1.05 (1.00, 1.06)
Body Mass Index	Underweight/Normal	0.78 (0.72, 0.84)	0.81 (0.77, 0.95)
	Overweight/Normal	1.23 (1.20, 1.26)	1.15 (1.07, 1.17)
	Obese/Normal	1.60 (1.56, 1.65)	1.19 (1.09, 1.21)
Age	Elderly/Nonelderly	1.04 (1.02, 1.07)	1.15 (1.13, 1.21)

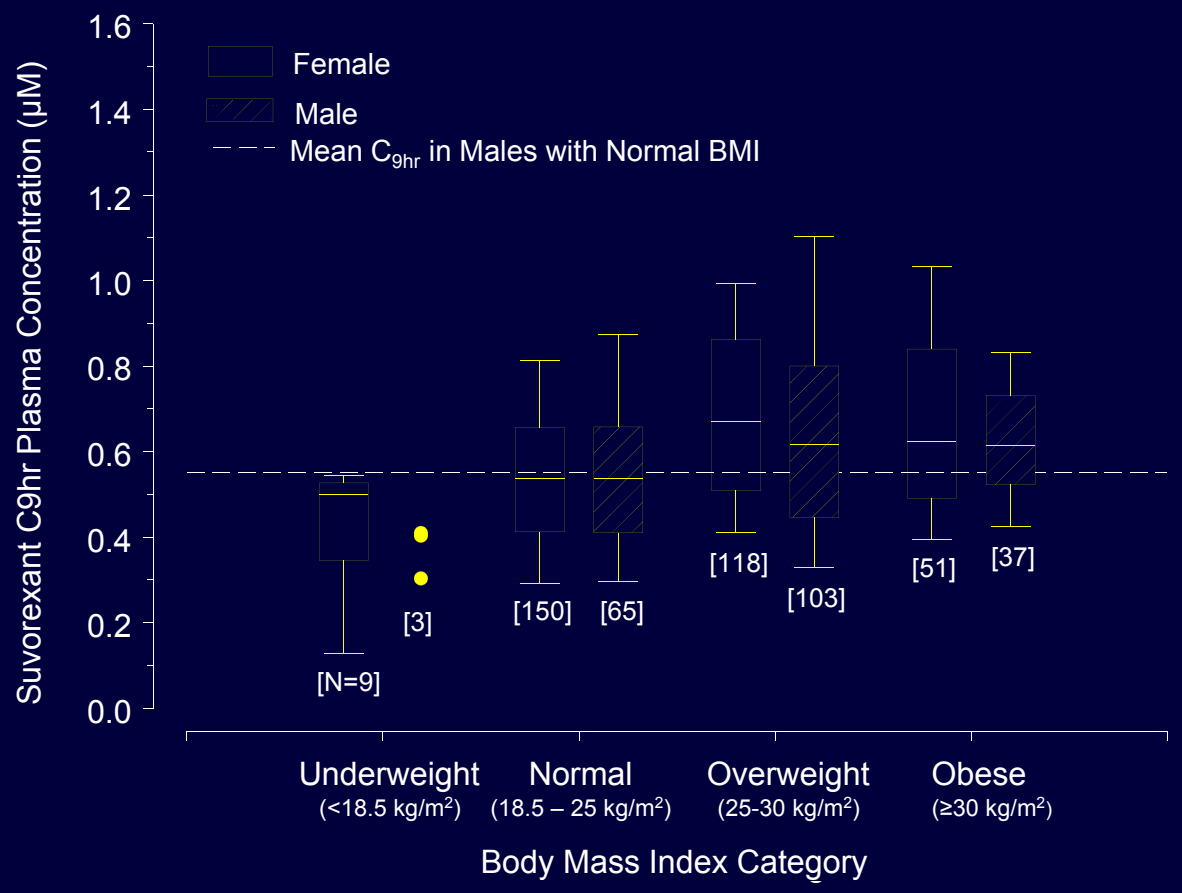
[a] Based upon ~320 healthy subjects.
[b] Based upon ~1640 patients.
Underweight:<18.5 kg/m^2; Normal: 18.5 – 25 kg/m^2; Overweight: 25-30 kg/m^2; Obese: ≥30 kg/m^2.

Frequency Distribution of Body Mass Index Stratified by Gender From Phase 1 and Phase 2/3 (All Doses)





Modest Differences in Suvorexant PK (C_{9hr}) Following 40 mg Administration Stratified by Body Mass Index From Phase 2/3



Box and line represent inter quartile and median; whiskers extend to the 10th and 90th percentile.

Exposure-Response Assessments for Onset, Maintenance, and Residual Effects

- Conducted using:
  - Phase 2b (P006 period 1), Phase 3 efficacy (P028, P029) and long-term (P009 – residual effects analysis only)
  - All timepoints 0-3 months pooled with time dependency tested
  - PK data limited to concentrations the morning after dosing (C_{9hr}) – no attempt made to extrapolate to AUC
  - Models contained terms to describe baseline, placebo, and drug effect components of response

- Model development methods focused on establishing:
  - Whether C_{9hr} or dose was a better predictor of response
  - Whether there is evidence of exposure response in data
  - Characterizing covariate effects, including age effects

Is Dose or C_{9hr} a Better Predictor of Response?

- Addressed by comparing models fit to pooled data in which dose or C_{9hr} was used to drive drug effect component
- For residual effects, C_{9hr} found to be the better predictor of response
  - Suvorexant concentrations the morning after bedtime dosing correspond to exposures at time of residual effect assessments
- For onset and maintenance efficacy, dose was a better predictor than C_{9hr} for all efficacy endpoints
  - C_{9hr} samples collected, not AUC or C_{max} which may better reflect time of efficacy assessment
  - Plasma PK may not reflect concentrations at site of action in brain

Is There Evidence of Exposure (Dose) Response in Data From 10-80 mg?

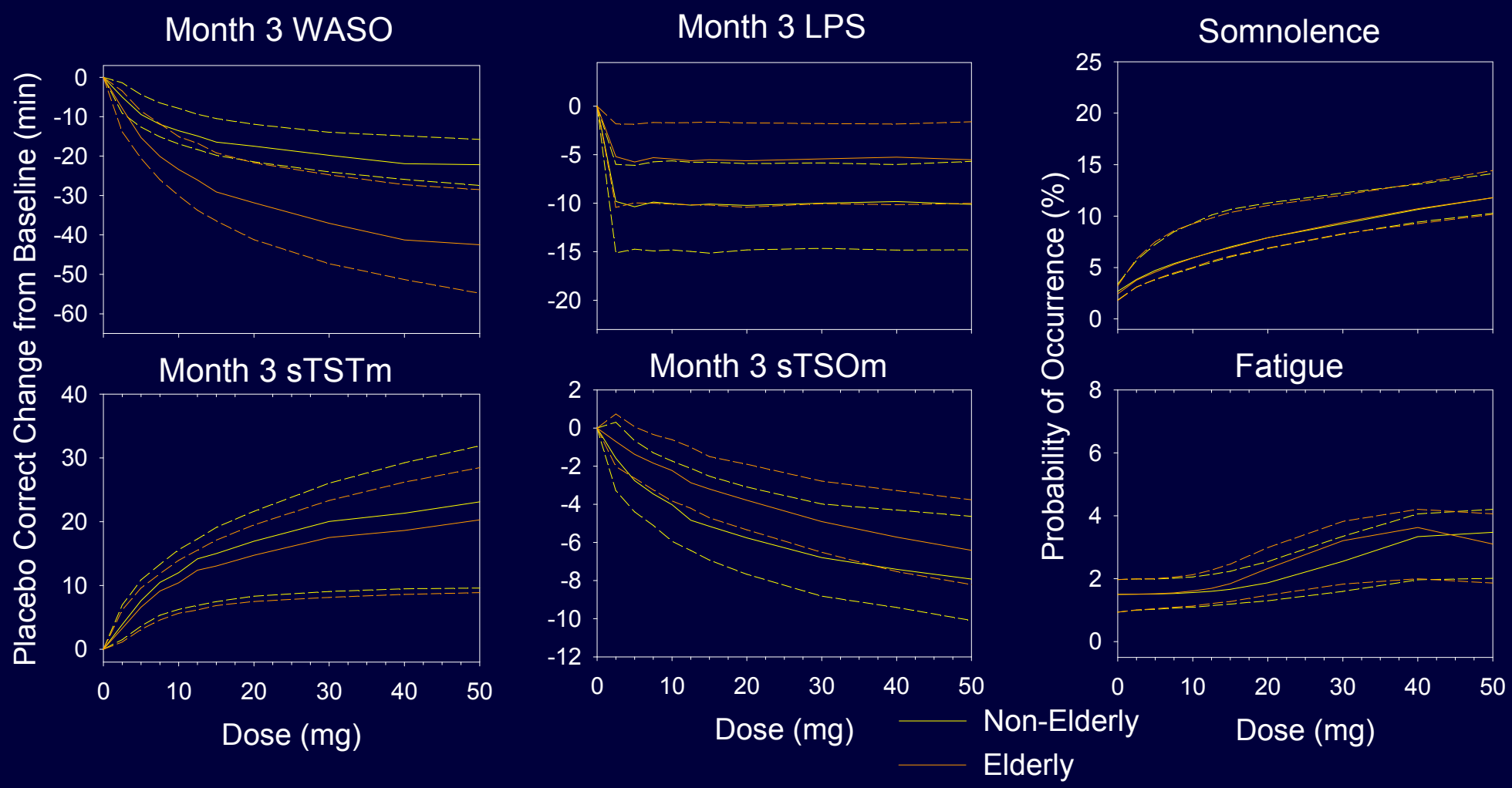
- Addressed by comparing models fit to pooled data in which drug effect component is assumed to be flat over clinical range vs. allowed to vary in a pharmacological manner (E_{max} relationship)

- All endpoints except LPS had significant evidence of exposure response in the clinical range

Model	Approximate p-Value	Non-elderly Drug Effect ED_{50}
LPS	NS	<<10 mg (flat)
sTSOm	<0.0001	18.1 mg
WASO	<0.0001	11.4 mg
sTSTm	0.0046	13.9 mg
sWASO	0.0084	Linear Relation

LPS=latency to onset of persistent sleep; sTSOm=mean subjective time to sleep onset; WASO=wake after persistent sleep onset; sTSTm=mean subjective total sleep time; sWASO=subjective wake after sleep onset.

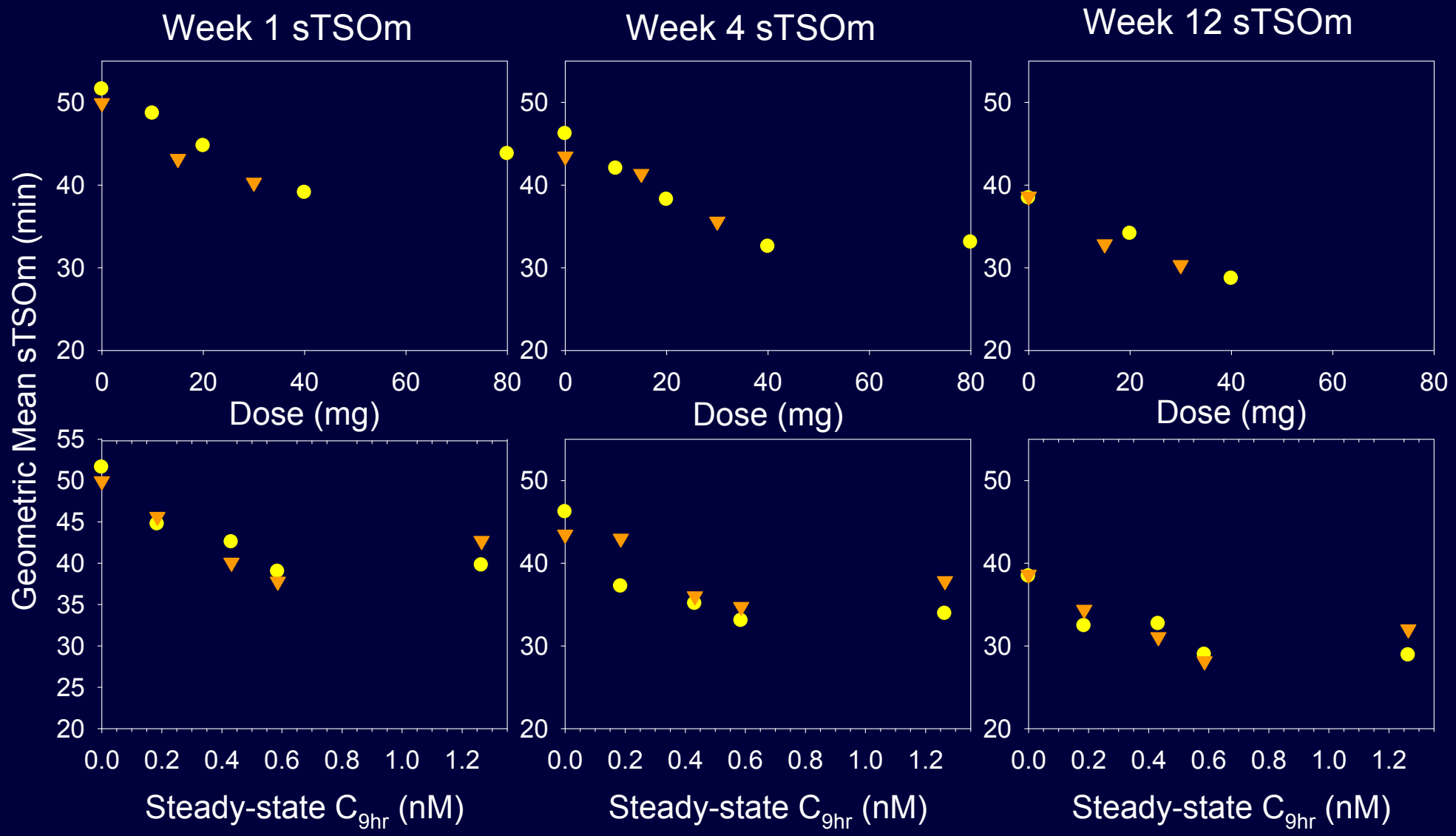
Model-Predicted Response of Efficacy and Residual Effects are Dose Related Over 15-40 mg



- Supports that there is a trade-off of efficacy versus residual effects in dose considerations in this range

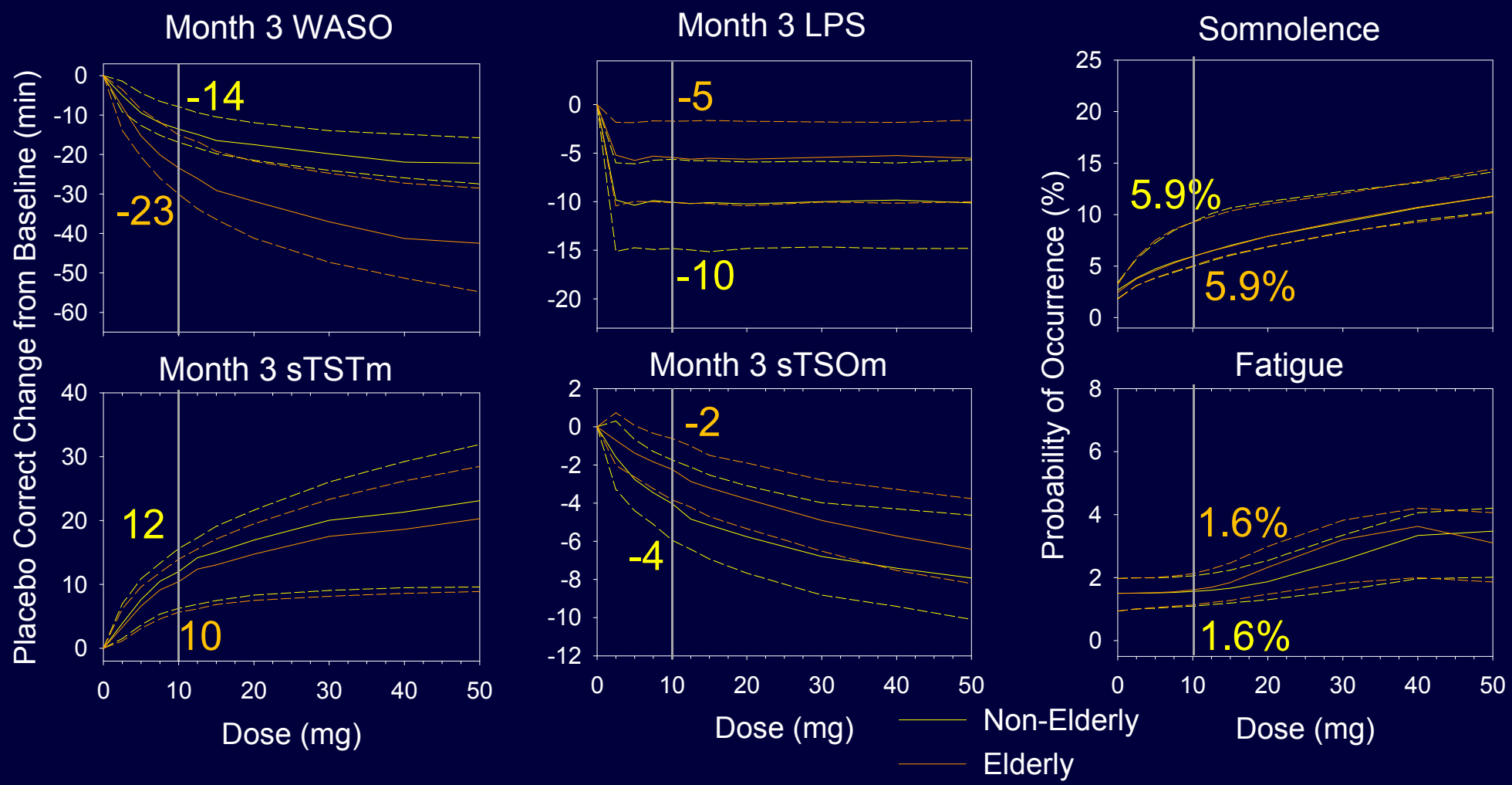
Mean PC-CFB shown in solid lines with 90% CI in dashed lines.
WASO=wake after persistent sleep onset; LPS=latency to onset of persistent sleep; sTSTm=mean subjective total sleep time; sTSOm=mean subjective time to sleep onset.

Comparison of sTSOm Dose Response vs. C_{9hr} Response (P006, P028, P029 pooled data)



sTSOm=mean subjective time to sleep onset.

Model-Predicted Response of Efficacy and Residual Effects at 10 mg



- Point Estimates of Response at 10 mg provided in numbers and line overlaid above

Mean PC-CFB shown in solid lines with 90% CI in dashed lines.
WASO=wake after persistent sleep onset; LPS=latency to onset of persistent sleep; sTSTm=mean subjective total sleep time; sTSOm=mean subjective time to sleep onset.

P006: Insomnia Severity Index (ISI)
Total Score at Day 28

Minimally Efficacious dose: 20 mg

Full Analysis Set

Data as observed

Pairwise Comparison vs. Placebo	N	Difference in LS Means (95% CI)	Nominal p-Value
Suvorexant 10 mg	60	-0.4 (-1.7, 1.0)	0.5786
Suvorexant 20 mg	57	-2.0 (-3.4, -0.6)	0.0049
Suvorexant 40 mg	57	-1.8 (-3.2, -0.4)	0.0099
Suvorexant 80 mg	54	-1.6 (-3.0, -0.2)	0.0283

Lower ISI scores indicate greater improvement of insomnia. LS Means=Least-Squares Means.