BELSOMRA SAFETY AND EFFICACY

Presented by NCHR at Patient Training Workshop

June 3, 2017

(Slides adapted by NCHR from Nadine Margaretten's Merck Presentation)

Introduction to Belsomra (Suvorexant)

- New chemical entity with novel mechanism of action
- 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

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Phase 3 Dose Selection

- **Doses selected:**
  - High dose = 40 mg: showed maximum and most consistent efficacy, chosen as primary dose
  - Low 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
  - 80 mg: no additional benefit over 40 mg

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Clinical Development: Phase 3 Trials

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 • 12-month treatment; 2-month rand. discon. (RD) phase • Suvorexant HD	• N=2030; 1263 with suvorexant • 3-month treatment; 3-month extension in P028 • Suvorexant HD and LD

HD = high dose; LD = low dose

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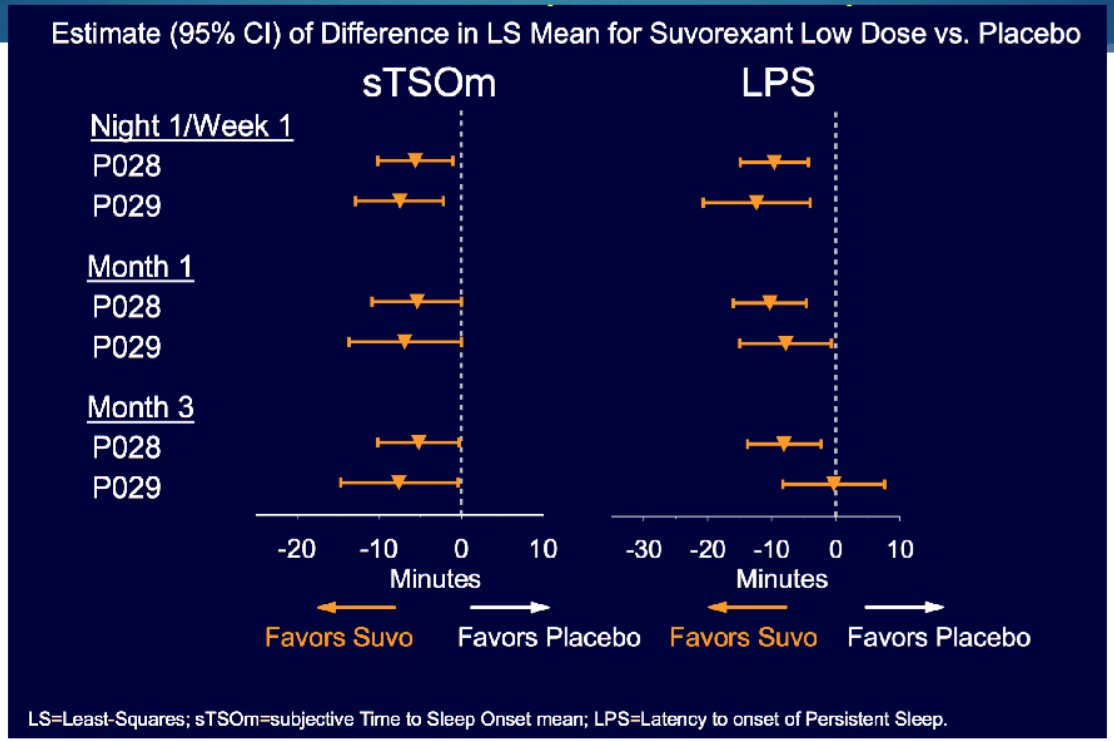
Belsomra LD Improves Sleep Onset



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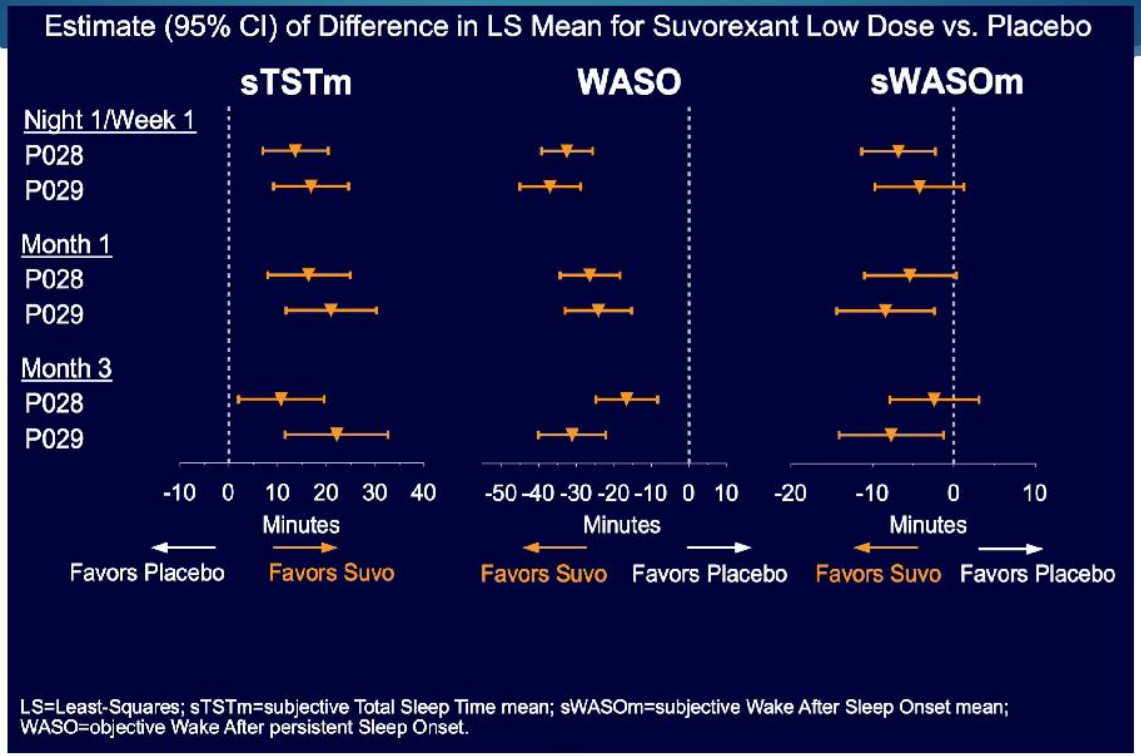
Belsomra LD Improves Sleep Maintenance



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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) Belsomra doses were efficacious, with consistent results in elderly and nonelderly
- HD consistently delivered more efficacy across endpoints than LD

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Belsomra Safety

- 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 Belsomra HD asked to discontinue due to somnolence
- Objective measures of next-day performance, including driving, indicated Belsomra 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

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re-specified Adverse Events of linical 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

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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 Belsomra**
- **Belsomra 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 Belsomra was not associated with withdrawal or clinically meaningful insomnia rebound**
- **Belsomra appears to have a low risk for abuse**

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Conclusions

- Belsomra is a first in class orexin receptor antagonist that specifically targets the regulation of wakefulness
- Belsomra 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
- Belsomra was generally safe and well-tolerated acutely and chronically
- Belsomra's clinical profile meaningfully expands the options available to patients suffering with insomnia

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