SUVOREXANT SAFETY AND EFFICACY

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Introduction to Suvorexant/Belsomra

- 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
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
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

<table>
<thead>
<tr>
<th>Long-Term Safety (P009)</th>
<th>Confirmatory Efficacy (P028 &amp; P029)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=779; 521 with suvorexant HD</td>
<td>N=2030; 1263 with suvorexant</td>
</tr>
<tr>
<td>12-month treatment; 2-month rand. discon. (RD) phase</td>
<td>3-month treatment; 3-month extension in P028</td>
</tr>
<tr>
<td>Suvorexant HD</td>
<td>Suvorexant HD and LD</td>
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HD = high dose; LD = low dose
Belsomra LD Improves Sleep Onset

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

Night 1/Week 1
- P028
- P029

Month 1
- P028
- P029

Month 3
- P028
- P029

sTSO\textsubscript{m}:

-20 -10 0 10

Minutes

Favors Suvo Favors Placebo

LPS:

-30 -20 -10 0 10

Minutes

Favors Suvo Favors Placebo

LS=Least-Squares; sTSO\textsubscript{m}=subjective Time to Sleep Onset mean; LPS=Latency to onset of Persistent Sleep.
Belsomra LD Improves Sleep Maintenance

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

<table>
<thead>
<tr>
<th>Night 1/Week 1</th>
<th>sTSTm (Minutes)</th>
<th>WASO (Minutes)</th>
<th>sWASO (Minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P028</td>
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<tr>
<td>P029</td>
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<tr>
<th>Month 1</th>
<th>sTSTm (Minutes)</th>
<th>WASO (Minutes)</th>
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<tr>
<td>P028</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Month 3</th>
<th>sTSTm (Minutes)</th>
<th>WASO (Minutes)</th>
<th>sWASO (Minutes)</th>
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<tbody>
<tr>
<td>P028</td>
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</table>

Favors Placebo, Favors Suvo

LS = Least-Squares; sTSTm = subjective Total Sleep Time mean; sWASO = subjective Wake After Sleep Onset mean; WASO = objective Wake After persistent Sleep Onset.
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 nonelderly
- HD consistently delivered more efficacy across endpoints than LD
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
Pre-specified Adverse Events of Clinical Interest Were Uncommon

<table>
<thead>
<tr>
<th>ECIs = Pre-specified Events of Clinical Interest</th>
<th>Placebo(^{+}) (N=767)</th>
<th>Suvorexant LD (N=493)</th>
<th>Placebo (N=1025)</th>
<th>Suvorexant HD (N=1291)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex sleep behaviors</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Hypnagogic/hypnopompic hallucination</td>
<td>0 (0.0)</td>
<td>2 (0.4)</td>
<td>0 (0.0)</td>
<td>5 (0.4)</td>
</tr>
<tr>
<td>Sleep paralysis</td>
<td>0 (0.0)</td>
<td>1 (0.2)</td>
<td>0 (0.0)</td>
<td>5 (0.4)</td>
</tr>
<tr>
<td>Excessive daytime sleepiness</td>
<td>1 (0.1)</td>
<td>3 (0.6)</td>
<td>3 (0.3)</td>
<td>20 (1.5)</td>
</tr>
<tr>
<td>Cataplexy (confirmed by adjudication)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Falls (adjudicated to rule out cataplexy)</td>
<td>7 (0.9)</td>
<td>5 (1.0)</td>
<td>15 (1.5)</td>
<td>21 (1.6)</td>
</tr>
<tr>
<td>Adverse events of potential for abuse liability(^{+})</td>
<td>19 (2.5)</td>
<td>20 (4.1)</td>
<td>31 (3.0)</td>
<td>34 (2.6)</td>
</tr>
<tr>
<td>Drug administration errors</td>
<td>19 (2.5)</td>
<td>20 (4.1)</td>
<td>31 (3.0)</td>
<td>32 (2.5)</td>
</tr>
</tbody>
</table>

- 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
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
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