Adaptive Design in Phase 2: Potential Treatment for Insomnia Disorder

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Challenges When Developing Sleep-Promoting Drugs

- Insomnia not one symptom type
  - Difficulty initiating sleep, maintaining sleep, waking too early
  - Combination of types

- Drug should work well on the first night and in the longer term, without potential for tolerance and dependence following repeated use

- Sleep-promoting effect needs to last across the night, but not into the morning
  - FDA focusses on potential for residual morning sleepiness, especially for morning driving

- Balance between efficacy and safety critical
Phase 2 Study Planned after POC Achieved in SAD Study

• Program needed to accelerate development
  – Second in class
  – Preserve patent life

• Sleep studies amenable to adaptive design approach
  – Fast recruitment
  – Objective, rapidly reporting endpoints permitting IAs to occur frequently

• Advantages over traditional crossover for Phase 2 sleep compounds
  – More subjects enrolled onto doses likely to be used in future studies
  – More doses studied concurrently
  – Can stop early for success or futility, hence saving time, subjects exposed and resources
2 Primary Objectives Used to Identify Doses for Phase 3

- Identify a dose or doses of E2006 that maximize efficacy and minimize next-day residual sleepiness in subjects with chronic insomnia at the beginning of treatment
  - Comparing the effect of 6 doses of E2006 with placebo using a composite utility function incorporating change from baseline on sleep efficiency (SE) and change from baseline on the Karolinska Sleepiness Scale (KSS) at 1 hour after morning waketime after dosing on D2/D3
- Compare the effect of 6 doses of E2006 with placebo on the KSS at 1 hour after morning waketime D15/D16 in subjects with chronic insomnia
  - Confirms that doses identified in first primary objective are not associated with an emerging signal of sleepiness
A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Bayesian Adaptive Randomization Design, Dose Response Study of the Efficacy of E2006 in Adults and Elderly Subjects with Chronic Insomnia

<table>
<thead>
<tr>
<th>SCR</th>
<th>BL</th>
<th>Treatment</th>
<th>Rebound</th>
<th>Follow-up</th>
<th>EOS</th>
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<td>1 2 3</td>
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-4 -3

to

Placebo
E2006 1 mg
E2006 2.5 mg
E2006 5 mg
E2006 10 mg
E2006 15 mg
E2006 25 mg

All
Placebo
D16/17
for
Rebound
Insomnia
Assessment

= 8h PSG recording

= KSS/DSST/RTI (morning residual sleepiness)

= POMS/WFB (mood and daytime functioning)

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Development of the Primary Objectives

• First Primary Objective
  – SE used as it combines LPS and WASO endpoints
  – D1/D2 used to show an immediate effect on efficacy
  – KSS evaluates subjective sleepiness, so clinically very important to assess residual morning sleepiness
  – Utility function developed to combine the above
    • Defined minimally clinically significant CfB for SE (D1/D2) and KSS (D2/D3)
      – CfB compared to placebo was considered to be 6% for SE and 4 units for KSS
      – Simulations produced to review possible different dose response scenarios

• Second Primary Objective
  – KSS on D15/D16 determined if residual sleepiness present after dosing for 2 weeks
  – KSS for D15/D16 acceptable if the lower boundary of a 90% confidence interval was less than 4 units (mean difference of CfB in KSS 1 hour after waketime of dose relative to placebo)
  – Study could not stop for early success if the above definition of acceptable KSS was not met
Operationalizing the Adaptive Design Process

- At each Interim Analysis (IA):
  - Analyze current study data
  - Assess for early success of a dose or futility of all doses
  - Update randomization allocations
  - RAR = Response Adaptive Randomization

<table>
<thead>
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<th></th>
<th>PBO</th>
<th>1 mg</th>
<th>2.5 mg</th>
<th>5 mg</th>
<th>10 mg</th>
<th>15 mg</th>
<th>25 mg</th>
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15 day Treatment
300 subjects max

Fixed Randomization

Adaptive

Burn-in Interim analyses – every 2 weeks

# of Subjects

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<tr>
<th></th>
<th>105</th>
<th>~20</th>
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IA  IA  IA  IA  IA  IA  IA  IA
PSG1-PSG2

D1-D2 PSG  
D2-D3 KSS

Score PSG

Enter KSS

Extract KSS

Provide rando info to  
External Stats

Eisai Mgmt

Site (with CRO)

Central Scoring

Eisai DM

Eisai Stats

External Stats

Independent  
Monitoring Comm

IVR

Eisai Management

Calculate  
CFB of  
mean SE and  
mean KSS

Enter updated rando  
probabilities in IRT

OR

STOP

Provide SE and KSS to Biostats

Provide data to  
External Stats

Provide report to IMC

Confirm decision  
with Eisai then  
communicate  
decision to IVR

Run algorithm

Review report  
and decide to  
continue or stop

Transfer SE to Eisai in a.m. following recording

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Bayesian Adaptive Design
Response Adaptive Randomization

• Adaptive design study used accrued data reviewed on an interim basis by an independent monitoring committee
• Decisions made in a blinded manner
  – Sponsor, investigators, sites and patients will be completely blinded to the interim analyses
• Utility definition: Utility function balancing efficacy and safety determined that a dose had utility if
  \[ \text{SE} \geq 5\% \text{ higher versus placebo} \]
  \[ \text{and} \]
  \[ \text{KSS} \leq 4 \text{ points higher than placebo} \]
  – Interim analysis on available data for these endpoints every 2 weeks
  – When a given dose reached 85\% probability of being a dose with utility >1, study would stop for success
  – If not stopped, randomization adapted according to utility of dose, with more subjects allocated to ‘better’ doses
  – By the 5\textsuperscript{th} interim analysis (n=262), the study stopped for success
    • At that time all doses above 5 mg met the 85\%
  – Final Bayesian analysis (n=291), all doses except 1 mg met the threshold for success
• Early futility threshold
  – If there was <20\% probability that the “best” dose has sufficient utility
Probability of Success at Interim Analyses

![Graph showing the probability of success at different doses and interim analyses.](image)

- **Success threshold:** 0.8
- **Doses:** 1, 2.5, 5, 10, 15, 25 mg
- **Sample sizes:**
  - N = 262
  - N = 240
  - N = 216
  - N = 167
  - N = 122

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Response Adaptive Randomization

- Resulted in different number of subjects allocated to each dose

After Interim Analysis #5
N= 291

<table>
<thead>
<tr>
<th>Dose</th>
<th>Number Randomized</th>
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<tr>
<td>PBO</td>
<td>56</td>
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<tr>
<td>1</td>
<td>32</td>
</tr>
<tr>
<td>2.5</td>
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<tr>
<td>5</td>
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<td>10</td>
<td>32</td>
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<td>15</td>
<td>56</td>
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<td>25</td>
<td>50</td>
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Important Time Savings

• Phase 2B: First subject dosed to meeting success criteria was 16.5 weeks (27 weeks: FPI to TLGs)
Lessons Learned

• Need to ensure recruitment and enrollment is appropriately paced to avoid issues with next IA
  – Recruitment that is too rapid could be problematic
  – Study based IAs on time - every 2 weeks - rather than # of subjects to account for uncertainty in recruitment rate
• Processes for each IA must be conducted on time to avoid compromising next IA
  – Testing each step of the adaptive process in a dry run is critical
• Understand that not all data will be cleaned by the time of the IA
  – Focus on key variables
Conclusions

• Novel design allowed for wide dose range to be tested concurrently without issues inherent in typical Phase 2 crossover designs
• Doses successfully identified for Phase 3 program
• Rapid progression to full development milestone