ACTELION’S NEW DUAL OREXIN RECEPTOR ANTAGONIST

Investor Webcast
July 2016
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Actelion’s New DORA is an investigational drug in development and not approved or marketed in any country.
THE BURDEN OF INSOMNIA

- Around 10% of adults report daytime impairment as result of insomnia
- Insomnia is associated with an increased risk of psychiatric disorders
  - Depression, Anxiety, Alcohol abuse, Drug abuse
- Insomnia increases the risk of accident and injury
- Insomnia is a leading cause of absenteeism and reduced productivity at work
  - Estimated global cost around USD 100 billion each year
MOST EXISTING SLEEP-PROMOTING AGENTS DO NOT INDUCE NATURAL SLEEP

...Leading to unmet patient needs

- Lack of continued benefit over time
- Lack of sustained effect through the night
- Impacted next day performance (hangover effect)
MOST EXISTING SLEEP-PROMOTING AGENTS HAVE SIGNIFICANT LIMITATIONS

…Leading to physician concerns

▶ Insufficient acute & long-term efficacy

▶ Abuse potential and withdrawal effect

▶ Problematic side effects
  – Next day residual effect (balance, ambulation, psychomotor response, etc.)
  – Rebound insomnia upon attempted discontinuation
  – Memory disorders (including anterograde amnesia)
  – Parasomnias
DUAL OREXIN RECEPTOR ANTAGONISTS (DORAs) HAVE DEMONSTRATED THE ABILITY TO RESTORE A NATURAL PHYSIOLOGICAL SLEEP…

…BUT WE NEED THE IDEAL DRUG!
SOME PATIENT POPULATIONS HAVE A GREATER MEDICAL NEED...

- Insomnia with dementia
- Insomnia with anxiety disorders
- Insomnia with sleep apnea

THE OPTIMAL DORA COULD BE HIGHLY BENEFICIAL FOR THESE PATIENTS
SIGNIFICANT EXPERTISE IN THE DISCOVERY AND DEVELOPMENT OF DORAs
RECENT ADVANCES IN ACTELION’S DORA PROGRAM

Martine Clozel
Chief Scientific Officer
DORAs HAVE A VERY DIFFERENT PROFILE TO GABA AGONISTS

- A natural sleep
- No deficit in motor function
- Better side effect profile
- Potential benefit in specific patient populations
DESIRED PROFILE FOR NEW DORA

- Optimized efficacy:
  - High *in vitro* and *in vivo* potency and efficacy
  - Fast onset of action
  - Appropriate duration of action

- Optimized safety:
  - No deterioration of next day performance
  - No unmanageable drug-drug interaction
  - No safety issue
The Optimization Process

Potent DUAL OX1 and OX2 receptor blockade \textit{in vitro}

No major drug-drug interaction

High brain penetration

Optimal \textit{in vivo} efficacy

Optimized duration of action (fast onset, no next day effects)

> 25'000 compounds screened in the orexin program

1361

High affinity in receptor binding and functional assays

\textit{In vitro} cytochrome P450 profile

Physicochemical properties and confirmation \textit{in vivo}

\textit{In vivo} efficacy tested in rats and dogs

Human Pharmacokinetic and Pharmacodynamics prediction

Actelion’s new DORA

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RAT EEG DATA: SLEEP EFFICACY / ARCHITECTURE

<table>
<thead>
<tr>
<th>Actelion New DORA (mg/kg)</th>
<th>Active wake</th>
<th>Quiet wake</th>
<th>non-REM sleep</th>
<th>REM sleep</th>
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<td>100</td>
<td>27.3</td>
<td>34.2</td>
<td>27.5</td>
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Time spent in sleep and wake stages (% of total time) over the first 6h of the active phase following administration

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MODELING DATA USED FOR FINAL SELECTION

- Human duration of action predicted by:
  - Estimating receptor occupancy needed for sleep
  - Predicting human pharmacokinetics

- Compound selection with estimated human PK giving sufficient receptor occupancy for 6 to 8 hours
OPTIMAL COMBINATION OF THE DESIRED EFFECT ON SLEEP AND A LOW POTENTIAL TO IMPACT NEXT-DAY PERFORMANCE

Guy Braunstein
Head of Global Clinical Development
PHASE I PROGRAM

- Single-ascending dose study in healthy young male adults
  - Doses evaluated from 5 mg to 200 mg
- 3-part study in male and female young adults and elderly
  - Multiple-ascending dose in adults
  - Single-ascending dose in elderly
  - Multiple night-time dosing in adult and elderly

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IDEAL PHARMACOKINETIC PROFILE FOR AN INSOMNIA MEDICATION

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Dose = 25 mg for 5 days
PHARMACODYNAMIC PROFILE: FAST ONSET OF ACTION IN ADULT & ELDERLY

Person performing eye movement test

Reduced speed of eye movements

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PHARMACODYNAMIC PROFILE: APPROPRIATE DURATION OF ACTION IN ADULT & ELDERLY

Adult Healthy Volunteer – Daytime dosing
Elderly Healthy Volunteer – Daytime dosing

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NEXT-DAY PHARMACODYNAMIC PROFILE
NO SLEEPINESS REPORTED ON NEXT MORNING

Karolinska Sleepiness Scale Score

Healthy adult with night-time administration

1= very alert,  3=alert, normal level,  5=neither alert nor sleepy,  7=sleepy, but no effort keeping awake,  9=very sleepy

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CURRENT SAFETY PROFILE

- No SAEs, no unexpected AEs after 110 healthy adults and elderly exposed
- Starting at 25 mg, transient AEs of mild to moderate intensity were observed such as: Disturbance of attention, somnolence, fatigue, headache and dizziness
- No significant effect on vital signs, ECG, and laboratory parameters

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ENTERING PHASE II WITH ACTELION’S NEW DORA IN INSOMNIA
PHASE II PROGRAM OVERVIEW

- Two studies in adult and elderly patients to evaluate the effect of Actelion’s DORA versus placebo

- Assessing sleep maintenance, sleep initiation, next day residual effect and next day performance

- Study 1: ~300 adult insomnia patients – treatment duration 4 weeks

- Study 2: ~50 elderly insomnia patients

- Adult study will also include an active-reference arm with zolpidem

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SUMMARY

- Actelion has significant expertise in the discovery and development of DORAs.
- DORAs have the potential to promote sleep and maintain a natural sleep architecture.
- PK/PD profile of Actelion’s New DORA suggests an optimal combination of effect on the CNS and low residual concentration next-day for a sleep medication.
- Phase II program will show whether the Phase I data will translate into both adult and elderly insomnia patients.
- Phase II program will provide all data required to design a differentiated Phase III program.

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NEUROLOGY PIPELINE UPDATE
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REVERSE: Phase II study to evaluate whether clazosentan has an early effect (within 3 hrs) in reversing angiographically-confirmed cerebral vasospasm in approximately 25 patients.

Clazosentan is an investigational drug in development and not approved or marketed in any country.
NEUROLOGY PIPELINE

Phase I | Phase II | Phase III
---|---|---
Ponesimod | Multiple Sclerosis |  
Clazosentan | Reversal of vasospasm post-aSAH |  
Dual Orexin Receptor Antagonist | Insomnia |  
Selective Orexin 1 Receptor Antagonist | Neurological disorders |  
T-type Calcium Channel Blocker | Neurological disorders |  

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SIGNIFICANT MEDICAL NEED

- No globally approved treatment for PAH in children
- Pediatric PAH physicians have to mostly rely on research data collected in adults when weighing up treatment options
Clinical studies in children are associated with specific requirements:

- Study endpoints must be meaningful for children
- Study assessments must be suitable and safe for children
- A child's growth and development can be affected by a drug
- A child, if considered developmentally capable, must be involved in the decision to participate
- Appropriate formulation to ensure accurate dosing and drug compliance
TOMORROW: long-term benefits of macitentan in children with PAH

- Wide age range as well as the use of safe, non-invasive measurements
- Dose determination phase with staggered patient recruitment by age category
- Dispersible tablet pediatric formulation in multiple strengths
- Global program received endorsement from the US FDA and in Europe’s EMA
NEWSFLOW

- Lucerastat future development
- Cardiovascular pipeline update with MERIT results
- Cadazolid Phase III program update
- Ponesimod Phase III program update
Q&A
Q&A

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