Daridorexant – Successful first pivotal study

Investor Webcast – April 2020
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“While we designed daridorexant to have the optimal profile for a sleep medicine, I am none-the-less stunned by the results.”

Jean-Paul Clozel
Chief Executive Officer
“The results have made working for over 20 years on the project completely worthwhile and prove that we were right to persevere.”

Martine Clozel
Chief Scientific Officer
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 hangover)
- Human Pharmacokinetic and Pharmacodynamics prediction

> 25,000 compounds synthesized in the orexin program

1,361

236

83

12

High affinity in receptor binding and functional assays

\textit{In vitro} cytochrome P450 profile

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

Physicochemical properties and confirmation \textit{in vivo}
“The results from this pivotal study are truly remarkable... this is the first study to demonstrate an insomnia product can improve how the patient feels during the day.”

Guy Braunstein
Head of Global Clinical Development
Insomnia: A disease of the night and the day

- ≥ 3 nights/week
- ≥ 3 months

Insomnia patients’ desire from a pharmaceutical intervention:

1. Increase in total sleep time
2. Improvement in daily performance

- Difficulty falling asleep
- Difficulty staying asleep
- Waking too early
- Impaired daytime performance
Key assessments in daridorexant Phase 3 studies

Objective sleep assessment

Objective measures of night parameters by polysomnography (PSG) in the sleep lab

Patient’s oriented outcome daily recorded

Subjective measures of night parameters by the sleep diary questionnaire (SDQ)

Assessment of impact of insomnia during the day by the insomnia daytime symptoms and impact questionnaire (IDSIQ)
Objective sleep assessments
Repeated polysomnography recordings in a sleep lab in all patients

- Assess insomnia objectively
- Ensure well-characterized insomnia patients are randomized
- Establish solid baseline during placebo run-in
- Measure primary endpoint at Month 1 and Month 3
  - Latency to persistent sleep
  - Wakening after sleep onset
- Assess the potential for rebound
- Collect comprehensive information on total sleep time and sleep architecture

Sensors measure brain activity, eye movements, muscle tone, respiratory, and heart parameters.
Sleep diary questionnaire (SDQ) daily recording

**Morning questionnaire**
- 10 questions related to medication, quantification of sleep, awakenings
- 3 visual analog scales related to quality and deepness of sleep and feeling in the morning

**Evening questionnaire**
- 2 questions related to napping
- 2 visual analog scales related to alertness and ability to perform

**Total sleep time**
Secondary endpoint
Subjective assessment of daytime performance

Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) validated according to FDA guidelines

Measures

<table>
<thead>
<tr>
<th>1 Clear-Headed</th>
<th>&quot;Alert/cognition&quot; domain score</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Concentrate</td>
<td></td>
</tr>
<tr>
<td>3 Forgetful</td>
<td></td>
</tr>
<tr>
<td>4 Worried</td>
<td></td>
</tr>
<tr>
<td>5 Frustrated</td>
<td></td>
</tr>
<tr>
<td>6 Irritable</td>
<td></td>
</tr>
<tr>
<td>7 Stressed</td>
<td></td>
</tr>
<tr>
<td>8 Energetic</td>
<td>&quot;Mood&quot; domain score</td>
</tr>
<tr>
<td>9 Effort</td>
<td></td>
</tr>
<tr>
<td>10 Refreshed</td>
<td></td>
</tr>
<tr>
<td>11 Mentally Tired</td>
<td></td>
</tr>
<tr>
<td>12 Physically Tired</td>
<td></td>
</tr>
<tr>
<td>13 Sleepy</td>
<td>&quot;Sleepiness&quot; domain score</td>
</tr>
<tr>
<td>14 Awake</td>
<td></td>
</tr>
</tbody>
</table>

Daytime performance measured by sleepiness domain score

Secondary endpoint

"Sleepiness" domain score: 14 Awake, 13 Sleepy, 12 Physically Tired, 11 Mentally Tired, 10 Refreshed, 9 Effort, 8 Energetic, 7 Stressed, 6 Irritable, 5 Frustrated, 4 Worried, 3 Forgetful, 2 Concentrate, 1 Clear-Headed

"Mood" domain score: 11. How mentally tired did you feel today?

0: Not at all mentally tired
1: Very mentally tired

"Alert/cognition" domain score: Clear-Headed, Concentrate, Forgetful
Daridorexant registration program

Robust program in adult and elderly insomnia patients

Following completion of Phase 2 studies, two similar pivotal studies of 3-month duration in moderate and severe insomnia

**Efficacy**
- Objective and subject sleep parameters (onset and maintenance) by PSG and SDQ
- Daytime performance assessed by IDSIQ
- Replicated in two confirmatory studies

**Safety**
- Adverse events, vital signs, biochemistry and hematology
- Next morning residual “hang-over” effect
- Withdrawal/physical dependence, and rebound insomnia

**Comprehensive clinical pharmacology program including:**
- Driving performance, interaction (medicines, alcohol), Safety in specific population (COPD, obstructive sleep apnea, liver and renal impairment), drug abuse potential
Study design

- Screening: 20-31 days
- Treatment Period: 84 days
- Safety Follow-up: 30 days

**Screening**
- Single-blind placebo run-in

**Treatment Period**
- Placebo or 25 mg or 50 mg daridorexant
- Double-blind

**Randomization**

**1st month**
- V1
- V2
- V3
- V4
- V5
- 25 mg
- 50 mg
- Placebo

**2nd month**
- V6
- V7
- EODBT
- V8
- V9

**3rd month**
- V10
- EOS

**Safety Follow-up**
- Single-blind placebo run-out

**Extension study**

- daily assessment of sleep and daytime performance

- \( V \) = site visit
- \( \bigcirc \) = 1 polysomnography night
- \( \bigotimes \) = 2 consecutive polysomnography nights
- EODBT = End of double-blind treatment
- EOT = End-of-Treatment
- EOS = End-of-Study

Daridorexant is investigational, in development and not approved or marketed in any country.
Study objectives

**Primary objective**

- To evaluate the efficacy of 25 mg and 50 mg daridorexant on objective sleep parameters in patients with insomnia.

**Secondary objective**

- To evaluate the efficacy of 25 mg and 50 mg daridorexant on subjective sleep parameters and daytime performance in patients with insomnia.

**Safety objective**

- To assess the safety and tolerability of daridorexant in patients with insomnia during treatment and upon treatment discontinuation.
Primary and secondary endpoints and analysis

Study-wise type 1 error controlled at 0.05 (across 16 comparisons to placebo)

- **Primary endpoints (night)**
  - Waking after sleep onset by PSG
  - Latency to persistent sleep by PSG

- **Secondary endpoints (night and day patients’ feeling)**
  - Subjective total sleep time by SDQ
  - Sleepiness score during the day by IDSIQ

- **Two dose levels**
  - 50 mg vs. placebo
  - 25 mg vs. placebo

- **Two assessment time points**
  - Month 1
  - Month 3
Study patient disposition

Entry

3326 screened

28%

placebo run-in

930 randomized

92%

853 completed treatment

847 completed placebo run-out

392 enrolled in long-term double blind extension

Sleep diary & polysomnography
Subjective & objective confirmation of chronic insomnia
Demographics and baseline characteristics

N = 930

### Demographic characteristic

<table>
<thead>
<tr>
<th>Demographic characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>624 (67.1)</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>55.4 (15.3)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>39.5%</td>
</tr>
<tr>
<td>25 – ≤ 30</td>
<td>41.7%</td>
</tr>
<tr>
<td>&gt;30</td>
<td>18.8%</td>
</tr>
<tr>
<td>Median time from diagnosis, years</td>
<td>7.1</td>
</tr>
</tbody>
</table>

The study was conducted at 75 hospitals and sleep centers in 10 countries (Germany, Australia, Canada, Denmark, Italy, Poland, Serbia, Spain, Switzerland and the United States).

**BMI**, body mass index; **LPS**, latency to persistent sleep; **SD**, standard deviation; **TST**, Total Sleep Time; **WASO**, wake after sleep onset.

### Well-characterized moderate and severe insomnia patients

<table>
<thead>
<tr>
<th></th>
<th>Self-reported insomnia at entry</th>
<th>Confirmed by polysomnography at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep induction</strong></td>
<td>≥ 30 minutes to fall asleep</td>
<td>Mean LPS ≥ 20 min</td>
</tr>
<tr>
<td><strong>Sleep maintenance</strong></td>
<td>Wake time during sleep ≥ 30 minutes</td>
<td>Mean WASO ≥ 30 min</td>
</tr>
<tr>
<td><strong>Total sleep time</strong></td>
<td>Total sleep time ≤ 6.5 h</td>
<td>Mean TST &lt; 420 minutes</td>
</tr>
</tbody>
</table>
Objective sleep parameters
At both doses of 50 and 25 mg vs. placebo: highly consistent effect

The study demonstrated the efficacy of daridorexant in *inducing* and *maintaining* sleep

- Statistically **significant improvement** in LPS at **1 month**
- Statistically **significant improvement** in WASO at **1 month**

The effect observed at 1 month was **sustained** at 3 months

- Statistically **significant improvement** in LPS at **3 month**
- Statistically **significant improvement** in WASO at **3 month**

LPS, latency to persistent sleep; WASO, wake after sleep onset
Subjective sleep parameter

SDQ

The study demonstrated the efficacy of daridorexant in increasing patient’s assessed total sleep time at both doses of 50 and 25 mg vs. placebo

- Statistically significant improvement in sTST at 1 month
- Statistically significant improvement in sTST at 3 month

sTST, subjective Total Sleep Time
Daytime performance
IDSIQ

The study demonstrated the efficacy of daridorexant in improving patient’s daytime performance

50 mg
• Statistically significant improvement in IDSIQ sleepiness domain at 1 month
• Statistically significant improvement in IDSIQ sleepiness domain at 3 month

25 mg
• Numerical improvement in IDSIQ sleepiness domain at 1 and 3 months

IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire
Overview of treatment emergent adverse events

<table>
<thead>
<tr>
<th>Subjects with at least one:</th>
<th>Daridorexant 25 mg n = 310</th>
<th>Daridorexant 50 mg n = 308</th>
<th>Placebo n = 309</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE during the double-blind study period</td>
<td>117 (37.7)</td>
<td>116 (37.7)</td>
<td>105 (34.0)</td>
</tr>
<tr>
<td>AEs leading to premature discontinuation of double-blind study treatment</td>
<td>7 (2.3)</td>
<td>3 (1.0)</td>
<td>10 (3.2)</td>
</tr>
<tr>
<td>Serious AE*</td>
<td>2 (0.6)</td>
<td>3 (1.0)</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>AE of special interest (after blinded, independent adjudication)</td>
<td>4 (1.3)</td>
<td>2 (0.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>AE with fatal outcome**</td>
<td>1 (0.3)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Placebo: syncope (2), depression (2), anal abscess (1), ankle fracture (1), herpes zoster (1), panic attack (1); 25 mg daridorexant: cardiac arrest (1), influenza-like illness (1) 50 mg daridorexant: syncope (1), adenocarcinoma (1), hemoglobin decrease (1), post-procedural hemorrhage (1) renal colic (1)

** A 78-year male patient died due to cardiac arrest in the ER after presenting with chest pain. The patient had a history of stroke, hypertension and systolic murmur and the investigator assessed the case as not related to the study drug.
Adverse events during the DB study period

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Daridorexant 25 mg N = 310 n (%)</th>
<th>Daridorexant 50 mg N = 308 n (%)</th>
<th>Placebo N = 309 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with at least one event</td>
<td>117 (37.7)</td>
<td>116 (37.7)</td>
<td>105 (34.0)</td>
</tr>
<tr>
<td>Most frequent adverse events (based on 50 mg daridorexant)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>21 (6.8)</td>
<td>20 (6.5)</td>
<td>20 (6.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>16 (5.2)</td>
<td>19 (6.2)</td>
<td>12 (3.9)</td>
</tr>
<tr>
<td>Accidental overdose</td>
<td>4 (1.3)</td>
<td>8 (2.6)</td>
<td>5 (1.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (2.3)</td>
<td>7 (2.3)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (1.9)</td>
<td>7 (2.3)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (0.3)</td>
<td>7 (2.3)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Most clinically relevant adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>11 (3.5)</td>
<td>5 (1.6)</td>
<td>6 (1.9)</td>
</tr>
<tr>
<td>Rapid eye movements sleep abnormal</td>
<td>0</td>
<td>3 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>Vertigo</td>
<td>1 (0.3)</td>
<td>2 (0.6)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Fall</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>8 (2.6)</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Overdose</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Sleep paralysis</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Syncope</td>
<td>0</td>
<td>1 (0.3)</td>
<td>2 (0.6)</td>
</tr>
</tbody>
</table>
Study conclusion
Daridorexant 25mg and 50 mg

Consistency of efficacy across
• Objective and subjective endpoints
• Doses
• Timepoints

<table>
<thead>
<tr>
<th>Primary endpoints</th>
<th>Daridorexant 25 mg</th>
<th>Daridorexant 50 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 month</td>
<td>3 months</td>
</tr>
<tr>
<td>WASO</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>LPS</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary endpoints</th>
<th>sTST</th>
<th>IDSIQ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

| IDSIQ | NS* | NS* |

* Numerical trend

Safety and tolerability profile at the tested doses
• Rate of AE similar between placebo and daridorexant at both treatment doses
• No next morning hang-over effect
• No sign of rebound insomnia
• No withdrawal symptoms

LPS, latency to persistent sleep; WASO, wake after sleep onset; sTST, subjective Total Sleep Time; IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire
Idorsia is entering a new era
Study conclusion: Daridorexant 25mg and 50 mg

Treatment demonstrated statistically significant and clinically meaningful improvements at month 1 and at month 3

Efficacy during the night and the day

- Sleep onset
- Sleep maintenance
- Total sleep time
- Daytime performance

Safety and tolerability profile at the tested doses

- Rate of AE similar between placebo and daridorexant at both treatment doses
- No next morning hang-over effect
- No sign of rebound insomnia
- No withdrawal symptoms