Media Release
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Idorsia is committed to further the science of sleep with a symposium and poster presentations at World Sleep 2023

Allschwil, Switzerland – October 23, 2023
Idorsia Ltd (SIX: IDIA) today announced that it is committed to further the science of sleep with a symposium and poster presentations at World Sleep 2023, a global scientific congress bringing the best of sleep medicine and research to Rio de Janeiro, Brazil, October 20-25.

An Industry Symposium entitled "Managing chronic insomnia disorder – what have we learned from clinical trials and real-world practice?" will be hosted by Idorsia on Tuesday, October 24, 12:30-14:00 BRT, Room 37, 3rd floor.

Antonio Olivieri, Senior Vice President, Head of Global Medical Affairs of Idorsia, commented:
"Chronic insomnia disorder is a distinct disease characterized by difficulty initiating or maintaining sleep, as well as impaired daytime functioning and is associated with significant acute and long-term medical consequences. Overactive wake signaling in the brain, promoted by the orexin system, is thought to be one of the key factors causing chronic insomnia disorder. The orexin system therefore provides a specific target for therapeutic intervention. In this symposium, key learnings will be presented both from clinical studies and real-world experience with daridorexant, Idorsia's dual orexin receptor antagonist."

In addition to the symposium, the following posters are being presented at World Sleep 2023:

- Di Marco T., *et al.* Effect of daridorexant on sleep micro-architecture in adult patients with insomnia disorder – An analysis of two pooled Phase 3 studies [Poster #070]
- Saskin P., et al. Real World Evidence of adverse events of prescribed medications for insomnia [Poster #090]
- Boof M.-L., Repeated dosing (5 nights) of 50 mg daridorexant in patients with severe obstructive sleep apnea: Effect on sleep-disordered breathing and sleep [Poster #187]
- Lettieri C.J., *et al.* The Effects of Daridorexant 50 mg on Patients with Comorbid Insomnia Disorder and Untreated Mild Obstructive Sleep Apnea: A Subgroup Post-hoc Analysis of a Phase 3 Clinical Trial [Poster #209]

Furthermore, the following posters on the real-world experience with daridorexant are being presented independently by three research groups:

- Fernandes M., *et al.* Daridorexant treatment effectiveness for chronic insomnia: A real-world retrospective study [Poster #075]
- Palagini L., *et al.* Early experience with the new DORA daridorexant in patients with insomnia disorder: results of a real world study with a 3 months follow up period [Poster #085]
- Winter Y., *et al.* Influence of daridorexant on the health-related quality of life in patients with chronic insomnia [Poster #096]

The abstracts can be found in the **Scientific Program for World Sleep 2023**.

Notes to the editor

About insomnia disorder

Insomnia disorder is defined as difficulty initiating or maintaining sleep, causing clinically significant distress or impairment in important areas of daytime functioning.[2] This impact on sleep quantity or quality should be present for at least three nights per week, lasts for at least three months, and occurs despite an adequate opportunity to sleep.[2]

Insomnia is a condition of overactive wake signaling and studies have shown that areas of the brain associated with wakefulness remain more active during sleep in patients with insomnia.[7,8] Chronic insomnia is a common problem with an estimated prevalence in Switzerland of 9.2% of the working-age population.[14]

Insomnia as a disorder is quite different from a brief period of poor sleep, and it can take its toll on both physical and mental health.[2,3] It is a persistent condition with a negative impact on daytime functioning.[2] Idorsia's research has shown that poor quality sleep can affect many aspects of daily life, including the ability to concentrate, mood, and energy levels.

The goal of treatments for insomnia is to improve sleep quality and quantity, as well as daytime functioning, while avoiding adverse events and next-morning residual effects. Current recommended treatment of insomnia includes sleep hygiene therapy, cognitive behavioral therapy, and pharmacotherapy.

About the orexin system

Wake and sleep signaling is regulated by intricate neural circuitry in the brain. One key component of this process is the orexin system, which helps promote wakefulness.[6,9] There are two forms of orexin neuropeptides – small protein-like molecules used by nerve cells (neurons) to communicate with each other in the brain – orexin A and orexin B.[5,6] Orexin promotes wakefulness through its receptors OX1R and OX2R.[5,6] Together, these neuropeptides and receptors make up the orexin system. The orexin system stimulates targeted neurons in the wake system – leading to the release of several chemicals (serotonin, histamine, acetylcholine, norepinephrine) – to promote wakefulness.[10] Under normal circumstances, orexin levels rise throughout the day as wakefulness is promoted and then fall at night.[11] Overactivity of the wake system is an important driver of insomnia.[4,9]

Idorsia's research team has been working on the science of orexin and orexin receptors since they were first described in 1998. The team's initial work led to the conclusion that antagonism of the orexin system was the key to preserving a natural sleep architecture for patients with insomnia. With this as the target, the team designed dual antagonists with the goal of rapid onset of effect and duration of action sufficient to cover the night but short enough to minimize any negative next-morning residual activity at optimally effective doses.

About daridorexant in insomnia disorder

Studies over the past decades have shown that hyperarousal processes in the brain play a key role in the pathology of insomnia.[5] Chronic insomnia disorder is the result of continued brain hyperarousal that requires sustained management with therapy suitable for daily use over months.[6] Orexin is a neuropeptide, a small protein-like molecule, produced by the brain that promotes wakefulness.[5] Daridorexant reduces nocturnal hyperarousal to improve sleep (onset and maintenance) without next-morning residual effects in insomnia patients, and thus improves daytime functioning.[4]

Global regulatory status of daridorexant

In January 2022, daridorexant was approved by the US Food and Drug Administration (FDA). In April 2022, marketing authorization of daridorexant was granted by the European Commission and subsequently by the Medicines and Healthcare products Regulatory Agency (MHRA) in Great Britain via the European Commission Decision Reliance Procedure. Marketing authorization of daridorexant was granted by Swissmedic in December 2022. In April 2023, Health Canada approved daridorexant in Canada.

The daridorexant Phase 3 registration program[4]

The Phase 3 registration program comprised two three-month studies, together with a long-term double-blind extension study. The program enrolled a total of 1,854 patients with insomnia disorder. As insomnia often presents later in life, and older adults are more susceptible to experience fragmented sleep, early awakening and daytime sleepiness,[12] around 40% of the recruited population was at least 65 years of age.[15]

The placebo-controlled studies investigated the effects of three doses of daridorexant (10 mg, 25 mg, and 50 mg) on sleep and daytime functioning parameters, objectively in a sleep lab by polysomnography and subjectively with a daily patient diary at home. The impact of insomnia on patients' daytime functioning was measured daily using the sleepiness domain score from the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ©) – a patient-reported outcome (PRO) instrument developed and validated according to the FDA Guidance for Industry.

More than 800 patients continued treatment in the 40-week extension study, which measured the effect of all three doses vs. placebo, generating data for long-term treatment of insomnia disorder.[16]

Phase 3 data has been reported in The Lancet Neurology: The pivotal studies demonstrated that daridorexant 50 mg significantly improved sleep onset, sleep maintenance and self-reported total sleep time at months one and three compared to placebo. The largest effect was observed with the highest dose (50 mg), followed by 25 mg, while the 10 mg dose did not have a significant effect. In all treatment groups the proportions of sleep stages were preserved, in contrast to findings reported with benzodiazepine receptor agonists.

A major focus of the trials was to evaluate the impact of daridorexant on daytime functioning in patients with insomnia disorder, as assessed by the IDSIQ. IDSIQ is a patient-reported outcomes instrument specifically developed and validated according to FDA guidelines, to measure daytime functioning in patients with insomnia.[13] The sleepiness domain score of the IDSIQ was evaluated as a key secondary endpoint in both pivotal studies and comparisons to placebo included type I error control for multiplicity. Daridorexant 50 mg demonstrated highly statistically significant improvement in daytime sleepiness at month one and month three. The sleepiness domain score was not significantly improved on 25 mg in either study at either timepoint.

The overall incidence of adverse events was comparable between treatment groups. The most frequently reported adverse reactions were headache and somnolence and, overall, the majority of adverse reactions were mild to moderate in intensity. No evidence of a dose-relationship for the frequency or severity of adverse reactions was observed.

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About Idorsia

Idorsia Ltd is reaching out for more – We have more ideas, we see more opportunities and we want to help more patients. In order to achieve this, we will develop Idorsia into a leading biopharmaceutical company, with a strong scientific core.

Headquartered near Basel, Switzerland – a European biotech-hub – Idorsia is specialized in the discovery, development and commercialization of small molecules to transform the horizon of therapeutic options. Idorsia has a 20-year heritage of drug discovery, a broad portfolio of innovative drugs in the pipeline, an experienced team of professionals covering all disciplines from bench to bedside, and commercial operations in Europe and North America – the ideal constellation for bringing innovative medicines to patients.

Idorsia was listed on the SIX Swiss Exchange (ticker symbol: IDIA) in June 2017 and has over 1,200 highly qualified specialists dedicated to realizing our ambitious targets.

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