Media Release
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Long-term safety and tolerability results with daridorexant in patients with insomnia disorder published in CNS Drugs

- Daridorexant, taken every night for up to 12 months, was well-tolerated with no signs of tolerance (loss of effect) or physical dependence, and no evidence of withdrawal or rebound insomnia upon treatment discontinuation
- Exploratory efficacy endpoints show sustained improvements in nighttime sleep variables and daytime functioning

Allschwil, Switzerland – December 12, 2022
Idorsia Ltd (SIX: IDIA) today announced the publication of "Long-term safety and tolerability of daridorexant in patients with insomnia disorder" in *CNS Drugs*[1]. The publication reports the results from the 40-week safety extension study with daridorexant in patients with insomnia disorder, which found that treatment with daridorexant, taken every night for up to 12 months, was well tolerated, consistent with the 12-week study findings as published by Mignot, E., et al. Lancet Neurol. 2022;21:125–39.

Dieter Kunz, MD, Clinic for Sleep- & Chronomedicine, St. Hedwig-Krankenhaus Berlin and lead author, commented:
"It is interesting to see how different the mechanism of dual orexin receptor antagonism works for patients with insomnia disorder. Rather than inducing sleep through broad inhibition of the brain, the over-active wakefulness causing their insomnia is gradually brought under control with nightly administration of daridorexant. The improvement in sleep onset, sleep maintenance and daytime functioning seen with 50 mg daridorexant were sustained for up to 12 months. Importantly, as we publish in this manuscript, long-term treatment with daridorexant was not associated with any tolerance or physical dependence, neither did we see withdrawal symptoms nor rebound insomnia upon cessation of administration."

The Phase 3, international, randomized, double-blind, parallel-group, placebo-controlled extension study was designed to evaluate the long-term use of daridorexant in patients with insomnia disorder who had completed one of the two pivotal 12-week Phase 3 studies. The primary objective was to assess the long-term safety and tolerability of daridorexant. Exploratory objectives were to evaluate the efficacy of daridorexant on sleep (self-reported total sleep time, sTST) and daytime functioning (Insomnia Daytimes Symptoms and Impacts Questionnaire, IDSIQ). In total, 804 adults with insomnia disorder who completed the 12-week studies were included in this extension study. Patients originally randomized to daridorexant 10 mg, 25 mg, or 50 mg remained on their respective treatments; patients randomized to placebo were re-randomized to either daridorexant 25 mg or placebo. The 40-week treatment period was followed by a 7-day placebo run-out.

The overall incidence of treatment-emergent adverse events was similar across groups (35-40%). The most commonly reported TEAE during double-blind treatment in all groups was nasopharyngitis. All other TEAEs, including falls, headache and somnolence were reported in <3% of patients, with dizziness and fatigue in <2% of patients in any group. Daridorexant did not induce next-morning sleepiness and no withdrawal-related symptoms or rebound insomnia were observed after treatment discontinuation. Improvements in sleep and daytime functioning were maintained through to end of the treatment and were most pronounced with daridorexant 50 mg. The authors conclude that

treatment with daridorexant for up to 12 months, was well tolerated and that exploratory efficacy analyses suggest that the sustained improvements in sleep and daytime functioning with daridorexant 50 mg support its use for long-term treatment of insomnia disorder.

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.[5] 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.[5]

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.[10,11] It is a common problem with an estimated prevalence in Europe of 6-12% of the adult population.[4]

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.[5,6] It is a persistent condition with a negative impact on daytime functioning.[5] 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.[9,12] 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.[8,9] Orexin promotes wakefulness through its receptors OX1R and OX2R.[8,9] 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.[13] Under normal circumstances, orexin levels rise throughout the day as wakefulness is promoted and then fall at night.[14] Overactivity of the wake system is an important driver of insomnia.[7,12]

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

Daridorexant is a dual orexin receptor antagonist, which blocks the binding of the wake-promoting neuropeptides orexins. Rather than inducing sleep through broad inhibition of brain activity, daridorexant blocks only the activation of orexin receptors. Consequently, daridorexant is thought to decreases the wake drive, allowing sleep to occur, without altering the proportion of sleep stages.

Global regulatory status of daridorexant

In January 2022, QUVIVIQ (daridorexant) was approved by the US Food and Drug Administration (FDA) and subsequently made commercially available in May 2022. For more information about QUVIVIQ (daridorexant) CIV in the US, see the Full Prescribing Information[2]. In April 2022, marketing authorization of QUVIVIQ 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. For more information about QUVIVIQ in the EU, see the Summary of Product Characteristics[3]. Launch preparations are underway in the major European markets and QUVIVIQ was made available in both Italy and Germany in November 2022. Marketing authorization of QUVIVIQ was granted by Swissmedic in December 2022, the company aims to make QUVIVIQ available to patients in Switzerland around mid-2023. For more information about QUVIVIQ in Switzerland, see the Patient Information and Information for Healthcare Professionals. Daridorexant is under review with Health Canada.

The daridorexant Phase 3 registration program[7]

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,[15] around 40% of the recruited population was at least 65 years of age.

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.

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.[16] 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.

Important Safety Information

Contraindications

- Hypersensitivity to daridorexant or any of the excipients
- Narcolepsy
- Concomitant use with strong CYP3A4 inhibitors

Warnings and precautions for use

Use with caution in elderly patients because of the general risk of falls. Efficacy and safety data in patients >75 are limited.

Patients should be cautioned about drinking alcohol during treatment.

Sleep paralysis and hypnagogic/hypnopompic hallucinations can occur, mainly during the first weeks of treatment. Symptoms similar to mild cataplexy have been reported with dual orexin receptor antagonists. Prescribers should explain this to patients and should consider discontinuing in case events occur.

Use with caution in patients exhibiting symptoms of depression.

Use with caution in patients with psychiatric co-morbidities due to limited efficacy and safety data.

Daridorexant did not have significant respiratory effects in patients with mild or moderate OSA or moderate COPD. In the absence of data, use with caution in patients with severe OSA and severe COPD.

There was no evidence of abuse or withdrawal symptoms indicative of physical dependence upon treatment discontinuation in clinical studies with daridorexant in subjects with insomnia. Because individuals with a history of abuse or addiction to alcohol or other substances may be at increased risk for abuse of QUVIVIQ, these patients should be followed carefully.

Use is not recommended in patients with severe hepatic impairment.

Effects on availability to drive and use machines

Patients should be cautioned about engaging in potentially hazardous activities, driving, or operating heavy machinery unless they feel fully alert, especially in the first few days of treatment. In order to minimize this risk, a period of approximately 9 hours is recommended between taking QUVIVIQ and driving or using machines.

About Dieter Kunz

Dieter Kunz graduated in 1989, performed residencies in neurology / psychiatry, and was appointed supervising physician in 1996 at the Freie Universität Berlin. After three years at Lübeck University, he was appointed head of the Psychiatric University Clinic Charité in St. Hedwig Hospital in 2002. He transformed this former community-based clinic into an efficient 120-inpatient

university clinic, established teaching, research, and clinical practice in academic level. Dr. Kunz's main interest, however, is neurological/psychiatric sleep research. In January 2008, he was appointed head of the newly founded *Clinic of Sleep- & Chronomedicine* in St. Hedwig Hospital. He also is director of the group *Sleep Research & Clinical Chronobiology* at Charité – Universitätsmedizin Berlin. Main areas of research are circadian aspects of human sleep including the nonvisual effects of light and the pharmacological effects of melatonin (hormone of darkness) on human physiology and behavior.

Dr. Kunz is frequent grant reviewer such as for National Science Foundation (NSF), the European Commission (EU), European Space Agency (ESA), and Wellcome Trust. As principal investigator he successfully applied for public European and German grants and industry grants including pharmacological phase-2 and -3 studies. He has published over 80 original papers in peer reviewed journals. Dr Kunz serves as a consultant to Idorsia.

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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 broad portfolio of innovative drugs in the pipeline, an experienced team of professionals covering all disciplines from bench to bedside, state-of-the-art facilities, and a strong balance sheet – the ideal constellation to translate R&D efforts into business success.

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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