Media Release
October 3, 2022

Ad hoc announcement pursuant to Art. 53 LR

Idorsia Japan announces positive results with daridorexant in a Phase 3 study of Japanese patients with insomnia

- Daridorexant demonstrated significant improvement in the subjective measures of Total Sleep Time (sTST) and Latency for Sleep Onset (sLSO) in Japanese patients with insomnia
- Idorsia Japan expects to file a New Drug Application (NDA) with the Japanese Ministry of Health Labor and Welfare (MHLW) in the first half of 2023

Allschwil, Switzerland, and Tokyo, Japan – October 3, 2022
Idorsia Ltd (SIX: IDIA) and Idorsia Pharmaceuticals Japan today announced positive top-line results of the Japanese Phase 3 study investigating 25 and 50 mg doses of Idorsia's dual orexin receptor antagonist, daridorexant, in 490 randomized adult and elderly patients (30.1% ≥ 65 years) with insomnia disorder. In general, the results are in-line with the safety and efficacy profile of daridorexant as reported in The Lancet Neurology.

The study was a randomized, double-blind, placebo-controlled, Phase 3 study to investigate the efficacy and safety of daridorexant. Patients were randomized to receive 50 or 25 mg doses of daridorexant or placebo once daily for 28 days.

The study met both primary and secondary efficacy endpoint measures. Daridorexant significantly improved sTST from baseline compared to placebo at 28 days ($p<0.001$ for 50 mg, $p=0.042$ for 25 mg). Daridorexant also significantly improved sleep onset as measured by a decrease in sLSO from baseline compared to placebo at 28 days ($p<0.001$ for 50 mg, $p=0.006$ for 25 mg).

The rate of adverse events was comparable between placebo and daridorexant at both treatment doses. Treatment-emergent adverse events (TEAEs) during the double-blind study period were reported in 23.5% and 22.7%of the patients treated with 50 and 25 mg daridorexant, respectively (24.4% for placebo). The most frequent TEAEs reported over 3% incidence and higher than placebo were somnolence (6.8% and 3.7% for daridorexant 50 mg and 25 mg groups respectively, versus 2.4% in the placebo group), and pyrexia (0.6% and 3.7% for daridorexant 50 mg and 25 mg groups respectively, versus 1.2% in the placebo group).

Makoto Uchiyama, M.D., Ph.D., medical advisor of the Japanese Phase 3 study, Director of Tokyo Adachi Hospital, Visiting Professor of Nihon University, and Visiting Professor of Toho University commented:
"Insomnia is highly prevalent in Japan and is recognized as an important national health issue. Patients with insomnia have trouble falling or staying asleep, as well as waking up earlier than desired, all of which lead to detrimental effects on both physical and mental health. This Phase 3 trial showed that daridorexant increased total sleep time and shortened sleep latency in patients with insomnia without marked hangover symptoms the next morning which clearly indicates its potency to improve core symptoms of insomnia. Such a promising outcome was likely due to the unique characteristics of the drug, a dual orexin receptor antagonist with an optimal elimination half-life."

Satoshi Tanaka, Dr Med Sci. and President of Idorsia Pharmaceuticals Japan, commented:
"I want to say thank you to the patients who participated in the study, and the investigators and their staff for their dedication to running the study to a high quality. The Idorsia Japan team will now fully analyze the study data and I look forward to sharing the wealth of data generated with daridorexant with Japanese health authorities in the form of a new drug application for marketing authorization in Japan. Together with our partner Mochida, the whole team is eager to rapidly make daridorexant available to Japanese patients with insomnia."

About the Japanese Phase 3 study

The Japanese Phase 3 study was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of daridorexant in patients with insomnia disorder. The primary objective of the study was to demonstrate the efficacy of 50 mg of daridorexant once daily at bedtime versus placebo for 4 weeks in patients with insomnia disorder. The efficacy of daridorexant was measured by patient reported total sleep time and latency to sleep onset. The primary efficacy endpoint was change from baseline to Week 4 in sTST and change from baseline to Week 4 in sLSO with 50 mg daridorexant versus placebo. The secondary efficacy endpoint was change from baseline to Week 4 in sTST and change from baseline to Week 4 in sLSO with 25 mg daridorexant versus placebo. The study also evaluated the dose effect of 50 or 25 mg of daridorexant versus placebo using other patient reported sleep measures. The study enrolled 490 patients, randomized 1:1:1 to daridorexant 50, 25 mg or placebo. As insomnia often presents later in life, and older adults are more susceptible to experience fragmented sleep, early awakening, and daytime sleepiness, around 30% of the recruited population was at least 65 years of age. A long-term treatment safety study of 12-month duration is expected to deliver results before the end of the year.

About the license agreement in Japan

In December 2019, Idorsia and Mochida Pharmaceutical Co., Ltd. entered into an exclusive license agreement for the supply, co-development and co-marketing of daridorexant for insomnia and related disorders in Japan.

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. 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. Launch preparations are underway in the major European markets with the first launch expected before the end of the year. Daridorexant is currently under review with Swissmedic and Health Canada.

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. 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.

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. According to Japan Preventive Association of Life-style Related Disease, Insomnia is a common problem with an estimated prevalence in Japan of 20% of the adult population.

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

About the global daridorexant Phase 3 registration program (outside of Japan)

The global Phase 3 registration program comprised two double-blind 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, 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. 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. There was no evidence of dose-dependent increases in adverse events across the dosing range. Further, no dependence, rebound insomnia or evidence of abuse or withdrawal symptoms indicative of physical dependence upon treatment discontinuation was observed in clinical studies.

About Makoto Uchiyama, M.D., Ph.D.

Director, Tokyo Adachi Hospital, Tokyo
Visiting Professor, Departments of Psychiatry and Sleep Medicine, Nihon University School of Medicine, Tokyo
Visiting Professor, Department of Psychiatry, Toho University School of Medicine, Tokyo

Educational Achievements and certificates:
M.D., Tohoku University, School of Medicine, Sendai, 1980
Ph.D., Tokyo Medical and Dental University, Tokyo, 1994
Designated Physicians of Mental Health, Ministry of Health, Labor and Welfare, 1987
Certified Sleep Physician, Japanese Society of Sleep Research, 2002
Certified Psychiatrist, Japanese Society of Neurology and Psychiatry, 2006
Certified Electroencephalographer, Japanese Society of Clinical Neurophysiology, 2006

Dr Uchiyama serves as a consultant to Idorsia.

Key literature

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About Mochida

Mochida Pharmaceutical Co., Ltd. has been committed to research and development of innovative pharmaceutical products since its establishment thereby providing distinctive medicines to the medical field. Currently, the core pharmaceutical business focuses resources on the targeted areas of cardiovascular medicine, obstetrics and gynecology, psychiatry and gastroenterology, while also providing medicine for intractable disease as well as generics including biosimilars, to meet medical needs. For more information on Mochida Pharmaceutical Co., Ltd., please see https://www.mochida.co.jp/english

About Idorsia Pharmaceuticals Japan

Idorsia Pharmaceuticals Japan was established, under the leadership of Dr Satoshi Tanaka, in 2018 to conduct clinical development and prepare the commercialization of Idorsia's innovative and promising compounds for patients in Japan.

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.

For further information, please contact

Andrew C. Weiss
Senior Vice President, Head of Investor Relations & Corporate Communications
Idorsia Pharmaceuticals Ltd, Hegenheimermattweg 91, CH-4123 Allschwil
+41 58 844 10 10
investor.relations@idorsia.com – media.relations@idorsia.com
www.idorsia.com

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