Media Release
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FDA accepts the new drug application for review of Idorsia's daridorexant for the treatment of adult patients with insomnia

- The application includes robust data from the Phase 3 registration program, which demonstrated efficacy of daridorexant on objective and subjective sleep parameters, and an improvement in daytime functioning, while maintaining a favorable safety profile

Allschwil, Switzerland – March 10, 2021
Idorsia Ltd (SIX: IDIA) today announced that the US Food and Drug Administration (FDA) has accepted the new drug application (NDA) for review of Idorsia's investigational dual orexin receptor antagonist, daridorexant, for the treatment of adult patients with insomnia.

Insomnia is a common problem with approximately 25 million adults in the US who meet the diagnostic criteria. Insomnia, a condition of overactive wake signaling, is defined as a combination of dissatisfaction with sleep and a significant negative impact on daytime functioning. Dissatisfaction with sleep refers to the difficulty to initiate and/or maintain sleep on at least three nights per week for at least three months, despite adequate opportunity to sleep.

Jean-Paul Clozel, MD and Chief Executive Officer of Idorsia commented:
"I'm very happy that this first regulatory hurdle is behind us. This was a huge NDA and the team has done an excellent job in preparing the dossier, on which the FDA can judge the properties and merits of daridorexant. We now stand-by to work with the FDA to answer any questions that might arise concerning the effect of daridorexant on sleep, daytime functioning and its safety profile."

The NDA includes data from a comprehensive clinical and non-clinical development program. In the Phase 3 registration program, daridorexant showed statistically significant and clinically meaningful improvements in sleep during the night and, for the first time for an insomnia treatment, in daytime functioning, which were sustained over time.

The Phase 3 program provided a deep understanding of the safety and tolerability profile of daridorexant. Adverse reactions reported with a frequency of ≥ 2% in daridorexant-treated patients and greater (≥ 1%) than in placebo-treated patients in 3-month efficacy trials were headache, somnolence, fatigue, dizziness, and nausea. The incidence of somnolence was low and did not increase with daridorexant 50 mg compared to placebo. Patients reported no next-morning sleepiness compared to placebo as assessed by the morning visual analogue scale (VAS).

These results make daridorexant the first sleep medication to demonstrate an improvement in sleep and daytime functioning, as measured by a newly developed and validated instrument, while keeping a favorable safety profile in adult and elderly patients.

In April and July of 2020, Idorsia reported positive results in each of the two pivotal Phase 3 studies of daridorexant in patients with insomnia. More details and commentary can be found in the dedicated press releases (first study release), (second study release) and the investor webcasts (first study webcast), (second study webcast) which are available for replay on Idorsia's corporate website: www.idorsia.com

The NDA was submitted to the US FDA on January 8, 2021 and the MAA to the European Union EMA on March 2, 2021. Should approval be received, the company anticipates launch in the US in the first half of 2022.

Notes to the editor

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 (dopamine, serotonin, histamine, acetylcholine, norepinephrine) which 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.

Dual orexin receptor antagonists (DORAs) offer an entirely different approach to treating insomnia than previous drug classes: by blocking the activity of orexin, they turn down overactive wakefulness, in contrast to insomnia treatments which act via general CNS sedation. DORAs specifically target the orexin system by competitively binding with both receptors, thereby reversibly blocking the activity of orexin. Blocking orexin receptors reduces the downstream activity of the wake-promoting neurotransmitters that are overactive in insomnia. As a result, orexin receptor antagonism targets the fundamental mechanism of insomnia.

About daridorexant

Daridorexant is a dual orexin receptor antagonist (DORA) designed and developed for the treatment of insomnia. Daridorexant reduces overactive wakefulness associated with insomnia by blocking the activity of orexin. Idorsia's research team has designed daridorexant to have a rapid onset of effect and a duration of action sufficient to cover the night but short enough to avoid any negative next-morning residual activity at optimally effective doses.

About the registration program

The Phase 3 registration program comprised two three-month studies, together with a long-term double-blind extension study. Both pivotal studies are complete, having enrolled around 1,850 patients with insomnia at over 160 sites across 18 countries. As insomnia often presents later in life, and elderly patients are more susceptible to fragmented sleep, early awakening and daytime sleepiness, around 40% of the recruited population was aged 65 years or older. 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 validated according to FDA industry guidance.

More than 800 patients continued treatment in the ongoing 40-week extension study, which will measure the effects of all three doses vs placebo, generating data for long-term treatment of insomnia.

The Phase 3 registration program demonstrated statistically significant and clinically meaningful improvements in sleep and daytime functioning which were sustained over time. The results showed efficacy during the night and the day, in respect of sleep maintenance, sleep onset, total sleep time and daytime functioning. The nighttime symptoms were improved while preserving the proportions of sleep stages.

The highest (50 mg) dose was the most effective, followed by 25 mg, while the 10 mg dose had only a marginal effect. A key consideration in the treatment of insomnia is the reversal of daytime functioning impairment associated with sleep difficulties – altered mood, cognition, and tiredness. To date, no insomnia studies have reported on the effects of pharmacological intervention on daytime functioning using an adequately developed and validated PRO instrument. At 50 mg, daridorexant

produced consistent and meaningful improvements in scores for daytime functioning across all IDSIQ domains. Patients on daridorexant felt more energetic and less sleepy, and reported better alertness, cognition and mood.

Daridorexant was well tolerated and had a favorable safety profile in adult and elderly patients. Adverse reactions reported with a frequency of ≥ 2% in daridorexant-treated patients and greater (≥ 1%) than in placebo-treated patients in 3-month efficacy trials were headache, somnolence, fatigue, dizziness, and nausea. There was no excess of morning sleepiness, as assessed by the morning visual analogue scale (VAS), even at 50 mg. The incidence of somnolence was low and did not increase with daridorexant 50 mg compared to placebo. The incidence of adverse events of special interest, considering the potential association of orexin deficiency with narcolepsy, was low, with isolated cases of sleep paralysis or hallucinations in the daridorexant treatment groups.

About insomnia

Insomnia is defined as a combination of dissatisfaction with sleep and a significant negative impact on daytime functioning. Dissatisfaction with sleep refers to the difficulty to initiate and/or maintain sleep on at least three nights per week for at least three months, despite 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.

Insomnia is a common problem with a prevalence of approximately 10%. On this basis, and assuming a US adult population of around 250 million, there are approximately 25 million adults in the US who suffer from insomnia.

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 recommendations, cognitive behavioral therapy and pharmacotherapy.

Key literature

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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 900 highly qualified specialists dedicated to realizing our ambitious targets.

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