



Media Release August 28, 2020

Daridorexant Phase 3 results in insomnia presented at SLEEP 2020

Allschwil, Switzerland – August 28, 2020

Idorsia Ltd (SIX: IDIA) today announced that the positive results from the first pivotal Phase 3 study (evaluating 25 and 50 mg doses) of its investigational dual orexin receptor antagonist, daridorexant, in adult and elderly patients with insomnia, were presented by Dr Thomas Roth at [SLEEP 2020](#). The study demonstrated efficacy of treatment with daridorexant on objective and subjective sleep parameters, and daytime functioning, with no next-morning residual effect.

The Associated Professional Sleep Societies (APSS) event, SLEEP 2020, is the world's largest meeting devoted entirely to clinical sleep medicine, and sleep and circadian research and is currently taking place as a virtual meeting. The presentation, entitled "Efficacy and safety of daridorexant in adult and elderly patients with insomnia", is available for on-demand replay for registered participants through August 1, 2021.

Dr Thomas Roth, PhD, Director of the Sleep Disorder and Research Center at Henry Ford Hospital, commented:

"Daridorexant, a new dual orexin receptor antagonist, has a pharmacokinetic and pharmacodynamic profile optimized for sleep onset and duration of action to improve night-time efficacy, without residual effects. These pharmacological properties led us to hypothesize that daridorexant could also improve the impaired daytime functioning frequently observed in insomnia. A new patient-reported outcome instrument was developed – and validated according to FDA requirements – to specifically assess daytime functioning in patients with insomnia and we included it in the Phase 3 program. The results have been outstanding."

The Phase 3 trial was designed to measure the impact of daridorexant on objective and subjective sleep parameters as well as on daytime functioning, and to evaluate safety, in patients with moderate to severe insomnia. Sleep variables were assessed using polysomnography for wake after sleep onset (WASO) and latency to persistent sleep (LPS). A sleep diary questionnaire was used to measure subjective total sleep time (sTST). Daytime functioning was assessed using a newly developed and validated patient-reported outcome instrument, the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ). The IDSIQ comprises 14 items grouped into three domains that reflect daytime effects of insomnia that are commonly encountered in clinical practice: Alert/Cognition, Mood, and Sleepiness/Tiredness.

Daridorexant significantly **improved sleep maintenance** as measured by a larger decrease in WASO from baseline compared to placebo. The mean change from baseline in WASO (minutes) for placebo, 25 mg and 50 mg was -6.2, -18.4, and -29.0 at 1 Month and -11.1, -23.0 and -29.4 at 3 Months, respectively (all p values vs. placebo <0.0001).



Daridorexant significantly **improved sleep onset** as measured by a larger decrease in LPS from baseline compared to placebo. The mean change from baseline in LPS (minutes) for placebo, 25mg and 50mg was -19.9, -28.2 ($p=0.0005$) and -31.2 ($p<0.0001$) at 1 Month and, -23.1, -30.7 ($p=0.0015$) and -34.8 ($p<0.0001$) at 3 Months, respectively (p -values vs placebo).

Subjective total sleep time assessed daily by patients increased more with daridorexant from baseline compared to placebo. The mean change from baseline in sTST (minutes) for placebo, 25mg and 50mg was 21.6, 34.2 ($p=0.0013$), and 43.6 ($p<0.0001$) at 1 Month, and 37.9, 47.8 ($p=0.0334$), 57.7 ($p<0.0001$) at 3 Months, respectively (p -values vs placebo).

Daridorexant improved **daytime functioning**, as measured in a secondary efficacy endpoint by the Sleepiness/Tiredness domain of the IDSIQ. For this domain, the improved daytime functioning was demonstrated by a mean score reduction from baseline for placebo, 25mg and 50mg of -2.0, -2.8 ($p=0.0547$) and -3.8 ($p<0.0001$) at 1 Month, and of -3.8, -4.8 ($p=0.0534$) and -5.7 ($p=0.0002$) at 3 Months, respectively (p -values vs placebo). In addition, other efficacy endpoints from the IDSIQ patient-reported outcome instrument, namely the "Alert/Cognition" domain, "Mood" domain, and the "Total IDSIQ" scores, consistently showed a dose-dependent improvement, as presented.

The **most frequent AEs**, nasopharyngitis and headache, were balanced between arms. Somnolence was reported in 6 (1.9%) patients on placebo, 11 (3.5%) patients on daridorexant 25mg, and 5 (1.6%) of patients on daridorexant 50mg.

The late breaking abstract (LBA 4) is available in the [Virtual Sleep 2020 meeting guide](#).

Dr Roth concluded:

"As hypothesized, the optimized profile of daridorexant not only translated in this study into a dose-dependent improvement on objective and subjective sleep parameters, but also into improved daytime functioning, all of which was sustained over time. Very importantly, safety was comparable with daridorexant 25 mg and 50 mg, with no dose-limiting safety findings, no observed next-morning sleepiness compared to placebo, no signals suggestive of rebound insomnia compared to baseline sleep parameters, and no withdrawal effects. With these results daridorexant addresses important needs of patients with insomnia."

The Phase 3 program design was also presented as a poster entitled "Daridorexant (ACT-541468), a dual orexin receptor antagonist, for the treatment of insomnia disorder: Phase 3 program for assessing efficacy and safety in adult and elderly patients". The poster is available on demand to registered attendees of SLEEP 2020 and the abstract can be found in the [Abstract Supplement](#).

In April and July 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 the corporate website.

Notes to the editor

About daridorexant

Daridorexant is a potent, selective, dual orexin receptor antagonist (DORA) currently in development for the treatment of insomnia. Orexin neurons are localized in the lateral hypothalamus and function as a key regulator of wakefulness, signaling other wake promoting neurons to be active, thus maintaining a "wake state". Insomnia is a condition of overactive wake signaling. Studies have shown that areas of the brain associated with wakefulness remain more active during sleep in patients with insomnia. Blocking the activity of orexin reduces the downstream activity of other wake promoting neurotransmitters,

allowing sleep to occur. Daridorexant has a pharmacokinetic and pharmacodynamic profile that was tailored specifically for the treatment of insomnia, including fast absorption to support sleep onset, a half-life designed to promote sleep maintenance throughout the night and minimize the risk of relevant carry-over exposure in the morning, without accumulation over time. Daridorexant has shown clinical efficacy in Phase 2 and 3 clinical studies and is expected to be submitted for regulatory review around the end of 2020.

About the Phase 3 registration program

The Phase 3 registration program comprises two confirmatory studies of 3-month duration, together with a long-term 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, around 40% of the recruited population was aged 65 years or older. The confirmatory multi-center, double-blind, randomized, placebo-controlled, parallel-group, polysomnography studies investigated 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 the US Food and Drug Administration (FDA) Guidance for Industry. 806 patients decided to continue treatment in the ongoing 40-week extension study which will measure the effect of all three doses vs. placebo, generating data for long-term treatment of insomnia.

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, worldwide, the most commonly reported sleep disorder and its impact is often underestimated. It can be a distressing condition that can impair quality of life. Sleepless nights can leave people feeling irritable and out of sorts – this may affect many aspects of daily life, from studying and employment to social activities and relationships. People who suffer from insomnia may lack the energy or motivation to exercise or to take part in social activities. It can also have a significant economic impact as it increases the risk of accident and injury on the road or in the workplace and is a leading cause of absenteeism and reduced productivity at work. People with insomnia are more likely to experience feeling down or depressed, lack concentration, and suffer from poor energy levels during the day compared with people who sleep well. In addition, worrying about sleep can cause stress and may lead to negative thought patterns which may in turn make it more difficult to sleep, setting up a vicious cycle. Chronic insomnia is associated with cardiovascular and cerebrovascular diseases, and increased mortality.

The goal of treatment for insomnia is to improve sleep quality and quantity, as well as to reduce insomnia-related impaired daytime functioning, while avoiding adverse events and next morning residual effects. Current treatment of insomnia includes cognitive behavioral therapy, sleep hygiene recommendations, and pharmacotherapy. The most widely prescribed products on the market that are indicated for insomnia enhance the effects of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system. Such medications are only approved for short-term use and are associated with side effects such as next-day effects, anterograde amnesia, and risk of tolerance and dependence.

About Dr. Thomas Roth, PhD

Dr. Roth has been the Director of the Sleep Disorders and Research Center at Henry Ford Hospital in Detroit, since 1978. Dr. Roth is also a Professor in the Department of Psychiatry at Wayne State University, School of Medicine in Detroit, Michigan, and serves as a Clinical Professor in the Department of Psychiatry at the University of Michigan, College of Medicine in Ann Arbor.

After serving as president of the Sleep Research Society, and the founding president of the National Sleep Foundation (NSF), Dr. Roth became chairman of the National Center on Sleep Disorders Research advisory board. In addition, he was a member of the board of directors of the Associated Professional Sleep Societies (APSS), chaired the Association's Scientific Program Committee and the governing board of the World Federation of Sleep Research Societies.

Dr. Roth was instrumental in the formation of the Association of Sleep Disorders Center (ASDC) and served as the organization's second president. He is also the former Chairman of the World Health Organization's worldwide project on sleep and health. In addition to authoring and co-authoring numerous articles, Dr. Roth serves as past editor-in-chief of the journal *Sleep*. He currently sits on the editorial boards of *Sleep Reviews*, *Stress Medicine*, and *Advances in Therapy and Human Psychopharmacology*.

In 2002, Dr. Roth received the NSF's Lifetime Achievement Award for his accomplishments and contributions to sleep science, sleep medicine and public health. He received a Distinguished Research Award from the Sleep Research Society as well as the Nathaniel Kleitman Award from the Academy of Sleep Medicine. Dr. Roth's contributions to the sleep field are expansive, ranging from prolific research productivity and scholarship to multiple national leadership positions, as well as the mentoring of many students and colleagues. Dr. Roth serves as a consultant to Idorsia.



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 one of Europe's leading biopharmaceutical companies, with a strong scientific core.

Headquartered in Switzerland - a biotech-hub of Europe - Idorsia is specialized in the discovery and development of small molecules, to transform the horizon of therapeutic options. Idorsia has a broad portfolio of innovative drugs in the pipeline, an experienced team, a fully-functional research center, and a strong balance sheet – the ideal constellation to bringing R&D efforts to business success.

Idorsia was listed on the SIX Swiss Exchange (ticker symbol: IDIA) in June 2017 and has over 800 highly qualified specialists dedicated to realizing our ambitious targets.

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