Media Release
July 6, 2020

Idorsia announces positive results in the second Phase 3 study of daridorexant

- Results confirm and reinforce the efficacy and safety profile from the first pivotal study
- Company targets filing the New Drug Application (NDA) around the end of 2020
- Idorsia to host an investor webcast to discuss the second Phase 3 results today at 14:00hrs CEST

Allschwil, Switzerland – July 6, 2020
Idorsia Ltd (SIX: IDIA) today announced positive top-line results of the second pivotal Phase 3 study investigating 10 and 25 mg doses of its dual orexin receptor antagonist, daridorexant, in 924 adult and elderly patients (39.3% ≥ 65 years) with insomnia. The study confirms the findings of the first pivotal study, demonstrating efficacy of treatment with daridorexant on objective and subjective sleep parameters and showed positive effects on daytime functioning, with patients reporting no morning sleepiness and no evidence of rebound or withdrawal symptoms upon treatment discontinuation.

On April 20, 2020, the company reported (media release) the results of the **first pivotal study** with daridorexant where both **25 and 50 mg** daridorexant significantly improved both sleep onset and sleep maintenance. Daridorexant 50 mg also significantly improved daytime functioning. All results were sustained over the 3 months of the trial.

In the second study, daridorexant 25 mg significantly improved **sleep maintenance** as measured objectively in a sleep lab by polysomnography. Daridorexant 25 mg also significantly improved **subjective total sleep time** as measured daily with a patient diary at home. The results were statistically significant at month 1 and at month 3 for these sleep measures, showing sustained benefit.

Furthermore, the effect of daridorexant 25mg on **sleep onset** and **daytime functioning** were numerically consistent with the effects seen in the first study. However, due to the control of the Type 1 error rate for 16 comparisons, these endpoints – despite the low p values – did not reach statistical significance.

The 10 mg dose of daridorexant showed numerical improvements, across all efficacy measures, of a smaller magnitude than observed on 25 mg, none of which reached statistical significance.

The results of the two large pivotal studies, testing daridorexant at three doses from 10 to 50 mg, now provide a deep understanding of its efficacy and tolerability profile. Furthermore, the similar design of the two Phase 3 studies allows for the two groups of 25 mg and placebo to be pooled and a pre-planned analysis to be made. This pooled analysis will further characterize the effect of daridorexant.

Guy Braunstein, MD and Head of Global Clinical Development of Idorsia, commented:
"I want to start with a thank you to the study participants, investigators and their support staff, and the Idorsia team for delivering another comprehensive set of robust data. I am delighted to see the replicated effect of 25 mg of daridorexant in this large confirmatory study. The consistency of the treatment effect across both studies is remarkable. I believe the fact that daridorexant improves daytime functioning is a real breakthrough for patients. I am looking forward to the integration of all aspects of the program, including the pooled data, the long-term extension data, the clinical pharmacology program, and all that we can learn from the patient reported outcome instruments. There is a lot of work for us to do as we interact with the health authorities and share the data with the scientific community."

About safety in the study

The safety profile was consistent with the results of the first study. Treatment-emergent adverse events (TEAEs) during the double-blind study period were reported in 38.2% and 39.3% of the patients treated with 10 and 25 mg daridorexant, respectively (32.7% for placebo). The most frequent TEAEs reported over 3% incidence and higher on 25 mg of daridorexant than placebo were nasopharyngitis, headache, somnolence and fatigue. The number of patients experiencing serious adverse events was low and balanced across treatment groups (10 mg, 3 patients; 25 mg, 3 patients; placebo, 4 patients). Based on independent blinded adjudication committee assessment, the number of patients reporting excessive daytime sleepiness as AE was low (10 mg, 1 patient; 25 mg, 4 patients; and placebo, 1 patient); 3 patients had AEs of special interest related to sleep paralysis and hallucination. No events denoting cataplexy-like events were reported or adjudicated. There was no next-morning residual effect as assessed every morning by the patients using a visual analog scale; 2 patients reported suicidal ideation (10 mg, 1 patient; 25 mg, 1 patient) with clear alternative causes; no suicide or self-injury were observed. There was no evidence of rebound insomnia, and no withdrawal symptoms upon discontinuation.

Emmanuel Mignot, MD and Professor of Psychiatry and Behavioral Sciences at Stanford University, commented:
"The daridorexant program demonstrates the full potential of orexin receptor antagonism – excellent effect and a good safety profile. It is exciting to see this, 20 years after the discovery of the role of orexin in sleep regulation. For me, the improved daytime functioning seen with daridorexant is most impressive. What is important to patients is not only to improve their night sleep but also how they feel during the day. By measuring the benefits of the drug through the day as well as through the night, the program has put patients back at the center of the equation and raised the standard for what we need to see with sleep medications. This ensures the patient need is at the center of prescription decisions when treating insomnia."

Jean-Paul Clozel, MD and Chief Executive Officer of Idorsia, commented:
"I was stunned by the excellent results of the first study with daridorexant, this time I'm struck by the consistency of the efficacy results, including daytime functioning and the safety profile. I am very proud of the great science behind daridorexant and that Idorsia has designed and executed such a comprehensive program, focused on patients, in such a short time. I am convinced that with daridorexant, Idorsia has a unique drug which is going to have a disruptive impact on the insomnia market. The whole company is united in the effort to file the NDA with the US FDA around the end of this year and to prepare for a successful launch. There is certainly a lot of work to be done, but we are already making great progress on all fronts."

Detailed results of the Phase 3 studies will be made available through scientific disclosure at upcoming congresses and in peer-reviewed publications.

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.

Investor webcast

On April 20, 2020, the company held an investor webcast to discuss the results of the first Phase 3 study with daridorexant. On that occasion, Martine Clozel, MD, Chief Scientific Officer presented a brief overview of the tailored drug discovery efforts that led to the synthesis of daridorexant. This was followed by Guy Braunstein providing an overview of insomnia, the objectives of the Phase 3 program, the methodologies used to measure the effect of daridorexant on patients with insomnia, and the results of the first study. This webcast is available for replay on the corporate website.

The company will hold an investor conference call and webcast to discuss the results of the second Phase 3 study with daridorexant. On the call, Guy Braunstein will present the study results, followed by a Q&A session with Jean-Paul Clozel, Guy Braunstein, and Martine Clozel.

Date: Monday July 6, 2020
Time: 14:00 CEST | 13:00 BST | 08:00 EDT

Webcast participants should visit Idorsia's website www.idorsia.com 10-15 minutes before the webcast is due to start.

Conference call participants should start calling the number below 10-15 minutes before the conference is due to start.

Dial-in CH: +41 (0)44 580 65 22 **/ UK:** +44 20 3009 2470 **/ US:** +1 (877) 423-0830
PIN: 24890393#

Notes to the editor

About insomnia

Insomnia is a condition of overactive wake signaling that can have a profound effect on the lives of patients. Insomnia can be defined as difficulty falling asleep and / or staying asleep, occuring at least three times a week for a minimum of three months.

It is estimated that as many as one in ten people suffer from insomnia and its impact is often underestimated. In reality, 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 circle. Chronic insomnia is associated with cardiovascular and cerebrovascular diseases, and increased mortality.

The goal of treatments for insomnia is to improve sleep quality and quantity, as well as reducing insomnia-related impaired daytime functioning, while avoiding adverse events and next morning residual effect. 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-morning residual effects, anterograde amnesia, and risk of tolerance and dependence.

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 and consolidate wakefulness. There are two forms of orexin neuropeptides – Orexin A and Orexin B. Orexin promotes wakefulness through its receptors OX_1R and OX_2R. In combination, these neuropeptides and receptors comprise the orexin system. The orexin system stimulates target 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 consolidated and fall at night. Overactivity of the orexin system is thought to be an important driver of insomnia.

Idorsia's research team has been working on the science of orexin and orexin receptors since they were first described in 1998. The teams 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 started to design a dual antagonist with a rapid effect, and a duration of action sufficient for the night but short enough to avoid any negative residual activity the following morning at optimally effective doses.

About dual orexin receptor antagonism

Dual orexin receptor antagonists – or DORAs – are an entirely different approach to treating insomnia than previous drug classes, turning down overactive wakefulness by blocking the activity of orexin. DORAs specifically target the orexin system by competitively binding with both receptors and thereby reversibly blocking the activity of orexin. It is hypothesized that blocking orexin receptors reduces the downstream activity of the other wake promoting neurotransmitters that are overactive in insomnia, leading to the clinical efficacy demonstrated by orexin receptor antagonists.

Data supporting daridorexant in insomnia

Results of the first Phase 3 study, investigating daridorexant doses 25 and 50mg, were reported in April 2020. The study demonstrated efficacy of treatment with daridorexant on objective and subjective sleep parameters and daytime functoning with no residual effect in the morning, and no evidence of rebound or withdrawal symptoms upon treatment discontinuation.

Daridorexant at both 25 and 50 mg significantly improved sleep onset and sleep maintenance as measured objectively in a sleep lab by polysomnography. Daridorexant also significantly improved subjective total sleep time as measured daily with a patient diary at home. The results were consistently statistically significant at month 1 and at month 3, indicating sustained benefit. Furthermore, treatment with daridorexant improved patients' daytime functioning from baseline at month 1 and month 3.

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 37.7% and 37.7% of the patients treated with 25 and 50 mg daridorexant, respectively (34.0% for placebo). The most frequent TEAE reported over 3% incidence and higher than placebo was nasopharyngitis, headache.

Prior to the Phase 3 program, the safety and efficacy of daridorexant in adult and elderly patients with insomnia was evaluated in a comprehensive Phase 2 program, comprising two studies, one of which included zolpidem 10 mg as an active reference. Both studies showed the desired effect on sleep maintenance and onset, with a significant dose-response relationship; treatment was generally well tolerated.

A comprehensive clinical pharmacology program is being conducted totaling approximately 20 studies and including, amongst others, studies assessing abuse liability, drug-drug interactions, next-morning driving, the effect of daridorexant on respiratory function in patients with chronic obstructive pulmonary disease (COPD) or obstructive sleep apnea (OSA), and the pharmacokinetics of daridorexant in patients with liver and renal impairment.

Emmanuel Mignot, MD and Professor of Psychiatry and Behavioral Sciences at Stanford University
He is a former student of the Ecole Normale Superieure (Ulm, Paris, France) and received his M.D. and Ph.D. from Paris V and VI University in France. He practiced medicine in France for several years before joining Stanford as a faculty member in 1991 and was named Director of the Stanford Center for Narcolepsy in 1993. Dr. Mignot was named the Craig Reynolds Professor of Psychiatry and Behavioral Sciences in 2001. He served as the Director of the Stanford Center of Sleep Sciences and Medicine from 2009 to 2019.

Dr. Mignot is internationally recognized for discovering the cause of narcolepsy. His findings led to the development of new hypnotics that block the hypocretin (orexin) receptor and is likely to have other therapeutic applications as well. His research also demonstrated that narcolepsy is a selective autoimmune disease of the hypocretin system showing the involvement of molecular mimicry in humans with influenza A.

He has received numerous research grants and honors including National Sleep Foundation and National Institute of Health Research Awards, Howard Hughes Medical Institute Investigator and McKnight Neuroscience awards, the Narcolepsy Network professional service award, the Drs. C. and F. Demuth 11th Award for Young Investigators in the Neurosciences, the WC Dement Academic Achievement Award in sleep disorders medicine, the CINP and ACNP awards in neuropharmacology and the Jacobaeus prize.

Dr. Mignot is an elected member of the Association of American Physicians, the Institute of Medicine, and of the National Academy of Sciences (USA). He is the co-author of more than 200 original scientific publications, and he serves on the editorial board of scientific journals in the field of sleep and biology research. Dr. Mignot is an active member of several professional and governmental organizations. He has served as President of the Sleep Research Society, Chair of the National Center on Sleep Disorders Research Advisory board of the National institutes of Health, and Chair of the Board of Scientific Counselors of the National Institute of Mental Health.

Most of Dr. Mignot's current research focuses on the neurobiology, genetics and immunology of narcolepsy, a disorder caused by hypocretin (orexin) cell loss, with indirect interest in the neuroimmunology of other brain disorders. His laboratory uses state of the art human genetics techniques, such as genome wide association, exome or whole genome sequencing in the study of human sleep and sleep disorders, with parallel studies in animal models. His laboratory is also interested in web-based assessments of sleep disorders, computer-based processing of polysomnography (PSG), and outcomes research. Dr. Mignot serves as a consultant to Idorsia.

References

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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 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.

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
www.idorsia.com

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