Media Release
January 20, 2022

The Lancet Neurology reports impact of daridorexant on both nighttime symptoms and daytime functioning in adults with insomnia

- As reported in the Lancet Neurology, daridorexant is the first insomnia medication to demonstrate an effect of a drug therapy to improve both nighttime symptoms and daytime functioning[1]
- Daridorexant 50 mg, showed significant improvement versus placebo on sleep onset, sleep maintenance, and total sleep time
- Daridorexant 50 mg, which was evaluated in one of the two pivotal Phase 3 trials, in addition significantly reduced patient-reported daytime sleepiness, assessed through a new tool validated per FDA guidelines
- The overall incidence of adverse events was comparable between treatment groups
- Idorsia to host an investor webcast about the Lancet Neurology publication today at 14:00hrs CET

Radnor, PA US – January 20, 2022
Idorsia Pharmaceuticals, US Inc. today announced the publication of "Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials" in The Lancet Neurology. Daridorexant 25 mg and 50 mg improved sleep outcomes, and daridorexant 50 mg also improved daytime functioning, in people with insomnia disorder, with a favorable safety profile.[1] The overall incidence of adverse events was comparable between treatment groups in adults and older adults (aged 65 and over) with insomnia.[1] As reported, daridorexant 50 mg demonstrated statistically significant improvements in the primary endpoints of sleep onset and maintenance as well as the secondary endpoints of total sleep time and daytime sleepiness.[1]

Importantly, the trials were the first to investigate the effect of an insomnia treatment on daytime functioning, using a validated patient-reported outcomes tool, which includes three different domains (alert/cognition, mood, and sleepiness).[1] Daridorexant 50 mg, which was evaluated in one of the two trials, demonstrated improvements compared to baseline across all daytime functioning domains with a high level of consistency.[1]

Emmanuel Mignot, MD, Professor of Psychiatry and Behavioral Sciences at Stanford University and lead author, commented:
"People with insomnia often complain of impaired daytime functioning. This is a major issue often ignored in treating insomnia and in fact many sleep promoting drugs can impair daytime functioning when they have residual effects. In this program, not only did we see efficacy of daridorexant on sleep induction, maintenance and patient-reported sleep quantity and quality, but importantly, at the dose of 50 mg, on daytime functioning, notably in the sleepiness domain as measured with a new scale, the IDSIQ. Participants in the daridorexant 50 mg group reported improvements in multiple aspects of daytime functioning, as assessed by this newly developed and validated instrument that assessed mood, alert/cognition, and sleepiness. It is exciting to see that insomnia is finally not solely viewed as a nighttime problem but as a cause of daytime suffering."

Efficacy and Safety Outcomes
Daridorexant 50 mg significantly improved sleep onset, sleep maintenance and self-reported total sleep time at months one and three compared to placebo.[1] 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.[1] In all treatment groups the proportions of sleep stages were preserved, in contrast to findings reported with benzodiazepine receptor agonists.[1]

A major focus of the trials was to evaluate the impact of daridorexant on daytime functioning in patients with insomnia, as assessed by the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ). IDSIQ is a validated patient-reported outcomes instrument specifically developed according to FDA guidelines, including patient input, to measure daytime functioning in patients with insomnia.[1,2] The sleepiness domain score of the IDSIQ was evaluated as a key secondary endpoint in both pivotal studies and comparisons to placebo included control for multiplicity. Daridorexant 50 mg demonstrated highly statistically significant improvement in daytime sleepiness at month one and month 3.[1] The sleepiness domain score was not significantly improved on 25 mg in either study at either timepoint.[1] Daridorexant 50 mg also improved the additional IDSIQ domain scores (alert/cognition domain, mood domain) and total score (p-values < 0.0005 versus placebo not adjusted for multiplicity).[1] Improvements in daytime functioning by daridorexant 50 mg progressively increased over the three months of the study.[1]

The overall incidence of adverse events was comparable between treatment groups.[1] Adverse events occurring in more than 5% of participants were nasopharyngitis and headache.[1] There were no dose-dependent increases in adverse events across the dosing range, including somnolence and falls.[1] Further, no dependence, rebound insomnia or withdrawal effects were observed upon abrupt discontinuation of treatment.[1] Across treatment groups, adverse events leading to treatment discontinuation were numerically more frequent with placebo than daridorexant.[1]

Martine Clozel, MD, and Chief Scientific Officer of Idorsia, commented:
"These data published in The Lancet Neurology highlight the depth of evidence generated in the daridorexant development program and the properties of the drug that I believe explain the results. The drug was designed to have efficacy for sleep onset and maintenance at optimally efficacious doses while avoiding residual morning sleepiness. This profile, together with the equal blockade of both orexin receptors – which may lead to an inhibition of the chronic sympathetic hyperactivity characteristic of insomnia – may explain the improvement we see in daytime functioning with 50 mg of daridorexant."

Daridorexant in insomnia
Insomnia disorder is characterized by difficulties initiating or maintaining sleep and is associated with distress or impairment in daytime functioning.[1] A wide range of daytime complaints, from fatigue and reduced energy to mood alteration and cognitive difficulties, are reported by people with insomnia.[1] Insomnia is associated with an overactive wake system.[3]

Daridorexant, a novel dual orexin receptor antagonist, was designed and developed by Idorsia for the treatment of insomnia. Daridorexant targets the excessive wakefulness characteristic of insomnia by blocking the activity of orexin.[1,4] Daridorexant specifically targets the orexin system by competitively binding with both receptors, thereby reversibly blocking the activity of orexin.[5]

Daridorexant is FDA approved in the US under the tradename QUVIVIQ™ and will become available following scheduling by the US Drug Enforcement Administration in May 2022."

Important Safety Information

QUVIVIQ is a prescription medicine for adults who have trouble falling asleep or staying asleep (insomnia).

Do not take QUVIVIQ if you fall asleep often at unexpected times (narcolepsy).

QUVIVIQ may cause serious side effects, including:

- **Decreased awareness and alertness.** The morning after you take QUVIVIQ, your ability to drive safely and think clearly may be decreased. You may also have sleepiness during the day.
  - Do not take more QUVIVIQ than prescribed.
  - Do not take QUVIVIQ unless you are able to stay in bed for at least 7 hours before you must be active again.
  - Take QUVIVIQ at night within 30 minutes before going to bed.

QUVIVIQ is a federally controlled substance because it can be abused or lead to dependence.

Before taking QUVIVIQ, tell your healthcare provider about all of your medical conditions, including if you:

- have a history of depression, mental illness, or suicidal thoughts or actions; drug or alcohol abuse or addiction; a sudden onset of muscle weakness (cataplexy); daytime sleepiness
- have lung or breathing problems, including sleep apnea
- have liver problems
- are pregnant or plan to become pregnant
- are breastfeeding or plan to breastfeed

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements

- Taking QUVIVIQ with certain medicines can cause serious side effects. QUVIVIQ may affect the way other medicines work and other medicines may affect the way QUVIVIQ works.
- **Do not take QUVIVIQ with other medicines that can make you sleepy unless instructed by your healthcare provider.**

What should I avoid while taking QUVIVIQ?

- Do not drink alcohol while taking QUVIVIQ. It can increase the effects of alcohol, which can be dangerous.
- Do not drive, operate heavy machinery, do anything dangerous, or do other activities that require clear thinking if you do not feel fully awake, or you have taken QUVIVIQ and have less than a full night of sleep (at least 7 hours), or if you have taken more QUVIVIQ than prescribed.

QUVIVIQ may cause other serious side effects, including:

- **Worsening depression and suicidal thoughts.** Call your healthcare provider right away if you have any worsening depression or thoughts of suicide or dying**.**
- **Temporary inability to move or talk (sleep paralysis) for up to several minutes, or hallucinations while you are going to sleep or waking up.**
- **Complex sleep behaviors** such as sleep-walking, sleep-driving, preparing and eating food, making phone calls, having sex or doing other activities while not fully awake that you may not remember the next morning. Stop taking QUVIVIQ and call your healthcare provider right away if you experience a complex sleep behavior.

The most common side effects of QUVIVIQ are headache and sleepiness**.**

These are not the only side effects of QUVIVIQ. Call your doctor for advice about side effects.

For more information see the **Full Prescribing Information** (PI and Medication Guide).

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Notes to the editor

About insomnia

Insomnia is defined as a combination of dissatisfaction with sleep and a significant negative impact on daytime functioning.[6] 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.[6]

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.[7,8]

Insomnia is a common problem with a prevalence of approximately 10% of the adult population.[9] 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. In Europe, the estimated prevalence of insomnia is 6-12%[10] and in Canada, insomnia affects an estimated 10%.[11]

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.[12] It is a persistent condition with a negative impact on daytime functioning.[6] 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.[13]

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.[13,14,15] 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.[14] 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.[16] Under normal circumstances, orexin levels rise throughout the day as wakefulness is promoted and then fall at night.[13] Overactivity of the wake system is an important driver of insomnia.[7,8]

About Emmanuel Mignot, MD, 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.

Investor webcast

An investor conference call and webcast will be held to discuss the data published in The Lancet Neurology. The call will start with presentations by senior management, followed by a Q&A session (live access to the speakers).

Date: **Thursday January 20, 2022**
Time: **14:00 CET | 13:00 GMT | 08:00 EST**

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.

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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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