Media Release
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Ad hoc announcement pursuant to Art. 53 LR

QUVIVIQ (daridorexant) recommended for approval in Europe as a new treatment for adults with insomnia disorder

- Idorsia receives a positive opinion from the Committee for Medicinal Products for Human Use for QUVIVIQ™ (daridorexant) for the treatment of adult patients with insomnia characterized by symptoms present for at least three months and considerable impact on daytime functioning
- A CHMP positive opinion is one of the final steps before marketing authorization can be granted by the European Commission – a final decision is expected in approximately two months

Allschwil, Switzerland – February 25, 2022
Idorsia Ltd (SIX: IDIA) today announced the Committee for Medicinal Products for Human Use (CHMP), the scientific committee of the European Medicines Agency (EMA), adopted a positive opinion for the use of QUVIVIQ™ (daridorexant) as the first dual orexin receptor antagonist in the European Union (EU) for the treatment of adult patients with insomnia characterized by symptoms present for at least three months and considerable impact on daytime functioning.

The positive CHMP opinion is supported by robust pivotal Phase 3 data, recently published in The Lancet Neurology, which demonstrated that daridorexant improved nighttime symptoms and daytime functioning in adults with insomnia disorder at months one and three compared to placebo, with a favorable safety profile.[1] The efficacy and safety of QUVIVIQ are further supported by a long-term follow-up extension study, which together with the pivotal trials, provides clinical data for up to 12 months of continuous treatment.[2]

Jean-Paul Clozel, MD and Chief Executive Officer of Idorsia, commented:
"The recommendation from the CHMP is an important milestone for Idorsia and a significant step towards delivering a new treatment option for European patients with insomnia disorder. If approved, QUVIVIQ would not only be the first dual orexin receptor antagonist made available in Europe, but also the first insomnia medicine to improve daytime functioning. In addition, with periodic reassessment of the need for therapy, QUVIVIQ can be used for long-term treatment, addressing a key limitation of existing therapies. This is represented in the unique indication adopted by the CHMP, for patients who have considerable impact on daytime functioning, and for those who have been experiencing difficulty sleeping for an extended period. I am very proud that Idorsia will be the company to effect real change across Europe by bringing this innovation to patients."

Insomnia disorder is defined as difficulty initiating or maintaining sleep, causing clinically significant distress or impairment in important areas of functioning.[3] 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.[3] A wide range of daytime complaints, from fatigue and reduced energy to mood alteration and cognitive difficulties, are reported by people with insomnia. Impaired daytime functioning is a critical concern of people living with insomnia disorder.[4]

Professor Ingo Fietze, University Hospital Berlin, commented:
"The Phase 3 program with daridorexant was the first to comprehensively measure the impact of pharmacological treatment on all aspects of the condition, including daytime functioning as perceived by patients. Results demonstrated that daridorexant not only significantly improved sleep onset, sleep maintenance and total sleep time in adults with insomnia disorder, but also patients' daytime functioning, all while maintaining a favorable safety profile. Having the evidence that treatment can provide benefits on both nighttime symptoms and daytime functioning without the limitations associated with existing insomnia treatments, such as rebound insomnia upon discontinuation of treatment, withdrawal symptoms, risk of dependence, or next-morning residual effects, is going to completely change the treatment landscape for our patients."

Professor Luigi Ferini-Strambi, Vita-Salute San Raffaele University, Milan, commented:
"Insomnia affects between 6 and 12% of the adult population in Europe. For patients with insomnia disorder, the medical condition can have a negative impact on many aspects of daily life from studying and employment to social activities and relationships. It can also have a significant economic impact due to an increased risk for injuries and motor vehicle accidents, as well as reduced workplace productivity. This CHMP recommendation marks an important step in changing the lives of patients with insomnia disorder across Europe."

QUVIVIQ (daridorexant) in insomnia disorder

Insomnia is associated with overactive wake signaling in the brain.[5,6] QUVIVIQ is a dual orexin receptor antagonist, which blocks the binding of the wake-promoting neuropeptides orexins and is thought to turn down overactive wakefulness, as opposed to treatments that generally sedate the brain.[7]

The Phase 3 registration program comprised two three-month studies, together with a long-term double-blind extension study.[1] The program enrolled around 1,850 patients with insomnia disorder.[1] As insomnia often presents later in life, and older adults are more susceptible to experience fragmented sleep, early awakening and daytime sleepiness,[8] around 40% of the recruited population was at least 65 years of age.[1]

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.[1] 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.[1,9]

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.[2]

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.[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 disorder, as assessed by the IDSIQ.[1] IDSIQ is a patient-reported outcomes instrument specifically developed and validated according to FDA guidelines, to measure daytime functioning in patients with insomnia.[9] 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.[1] Daridorexant 50 mg demonstrated highly statistically significant improvement in daytime sleepiness at month one and month three.[1] The sleepiness domain score was not significantly improved on 25 mg in either study at either timepoint.[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]

The CHMP has adopted a positive opinion for the use of QUVIVIQ 50 mg for the treatment of adult patients with insomnia characterized by symptoms present for at least three months and considerable impact on daytime functioning. In addition, QUVIVIQ 25 mg will be available for specific patient populations, e.g. taking certain concomitant drugs.

Regulatory status of daridorexant

The positive opinion recommending QUVIVIQ, is a scientific recommendation issued by the EMA's CHMP, which is sent to the European Commission (EC) for the adoption of a decision on an EU-wide marketing authorization. An EC marketing authorization through the centralized procedure is valid in all European Union Member States, as well as the European Economic Area countries Iceland, Liechtenstein and Norway, and Northern Ireland under the Northern Ireland Protocol.

For Great Britain, a separate application for the use of daridorexant for the same indication will immediately be made to the Medicines and Healthcare products Regulatory Agency (MHRA) via the European Commission Decision Reliance Procedure, a post-Brexit, temporary administrative process, under which the MHRA will rely on the decision taken by the EC on the approval of the product.

Daridorexant is currently under review with Swissmedic and Health Canada. In January, QUVIVIQ (daridorexant) was approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with insomnia.

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.[3] 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.[3]

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.[6,10] It is a common problem with an estimated prevalence in Europe of 6-12% of the adult population.[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.[3] 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.[1] 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.[14] 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.[17] Overactivity of the wake system is an important driver of insomnia.[10,13]

About Professor Ingo Fietze

Professor Ingo Fietze completed his studies in Biophysics in Moscow and earned his degree in Medicine in Berlin, Germany. In 1990, he founded the first sleep laboratory at the Charité-Universitätsmedizin Berlin and became the Director and Head of the Interdisciplinary Center for Sleep Medicine at the institute in 2005. In 2015, he was appointed to Adjunct Professor. He specializes in pathophysiology, internal medicine, pulmonology, sleep medicine and somnology.

Professor Fietze is an active member of numerous societies: the German Sleep Society (DGSM), German Society for Clinical Neurophysiology (DGKN), German Respiratory Society (DGP), German Cardiac Society (DKG), European Respiratory Society (ERS), European Sleep Research Society (ESRS), World Sleep Federation (WSF), American Association of Sleep Medicine (AASM), "Schlafmedizin Berlin Brandenburg e.V.", and member of the (occupational) unions: "Association for Pulmonologists", "Berliner Wirtschaftsgespräche e.V.", and the Koch Metchnikoff Forum (KMF), Director of the German Sleep Foundation.

He has authored more than 250 original scientific publications, four text books on healthy and disturbed sleep and contributes to books and congresses. He serves on the editorial board of the journals Somnology, Sleep and Breathing, and Frontiers in Neurology, and has an active role as a reviewer of several scientific journals.

His main focus of research is in the methods of diagnosis and therapy of sleep disorders, cardiovascular risks through sleep disorders, medicine and chronobiology. He is a part of several International Research Networks (ESADA, SAGIC, EIN, EURLSSG). Aside from his clinical-scientific commitments, Professor Fietze also advises on sleep medicine and consults within operational health promotion and sport medicine.

Professor Fietze serves as a consultant to Idorsia.

About Professor Luigi Ferini-Strambi

Professor Luigi Ferini-Strambi earned his degree in Medicine at the State University in Milan, Italy. In 1983, he completed a fellowship in the Sleep Disorders Center at the Baylor College of Medicine in Houston, Texas, USA, and earned his Postgraduate Degree in Neurology at the State University in Milan, Italy, in 1984.

He is currently a Professor of Neurology at the Vita-Salute San Raffaele University in Milan, the Chair of the Department of Neurology, and Director of Sleep Disorders Center at Scientific Institute H San Raffaele-Turro, Milan. He serves as the Field Editor of "Sleep Medicine" journal, and is a member of the Editorial Board of the European Journal of Neurology and Behavioral Neurology. He has published more than 390 scientific papers in international journals and is currently a reviewer of several journals: Neurology, Sleep, Journal of Sleep Research, Journal of Neurology, Brain, and The Lancet Neurology.

Professor Ferini-Strambi is also the Past-President of the Italian Association of Sleep Medicine and a founder member of the International RBD Study Group. Between the years 2015 to 2017, he was also the President of the World Association of Sleep Medicine Society.

Professor Ferini-Strambi serves as a consultant to Idorsia.

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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 1,200 highly qualified specialists dedicated to realizing our ambitious targets.

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