News Release

March 23, 2021
JCR Pharmaceuticals Co., Ltd.

JCR Pharmaceuticals Announces Approval of IZCARGO® (Pabinafusp Alfa) for Treatment of MPS II (Hunter Syndrome) in Japan

- First Approved Enzyme Replacement Therapy for MPS II to Penetrate Blood-Brain Barrier via Intravenous Administration, Validating JCR's J-Brain Cargo® Technology -

Hyogo, Japan, March 23, 2021 – JCR Pharmaceuticals Co., Ltd. (TSE 4552; "JCR") today announced that the Ministry of Health, Labour and Welfare (MHLW) in Japan has approved IZCARGO® (pabinafusp alfa 10 mL, intravenous drip infusion) for the treatment of mucopolysaccharidosis type II (MPS II, or Hunter syndrome). IZCARGO® (formerly known as JR-141) is a recombinant iduronate-2-sulfatase enzyme replacement therapy (ERT) that relies on J-Brain Cargo®, a proprietary technology developed by JCR, to deliver therapeutics across the blood-brain barrier (BBB). It is the first-ever approved ERT that penetrates the BBB via intravenous administration, a potentially life-changing benefit for individuals with lysosomal storage disorders (LSDs) such as MPS II.

Many patients with MPS II show complications not only in somatic symptoms but also in the central nervous system (CNS), which are often severe, with significant effects on patients' neurocognitive development, independence, and quality of life. By delivering the enzyme to both the body and the brain, IZCARGO® treats the neurological complications of Hunter syndrome that other available therapies have been unable or inadequate to address so far.

"Approval of IZCARGO® in Japan under SAKIGAKE designation is a key milestone in JCR Pharmaceuticals' global expansion. It comes on the heels of Fast Track designation from the US FDA, orphan designation from the European Medicines Agency, and the FDA's acceptance of the JR-141 Investigational New Drug application, enabling JCR to begin our Phase 3 trial in the US," said Shin Ashida, chairman and president of JCR Pharmaceuticals. "These critical regulatory milestones in Japan, where we have such a strong record of success, and those in the US and Europe, provide important validation of the value of our J-Brain Cargo® technology to deliver therapies across the blood-brain barrier, which we believe is essential to addressing the central nervous system complications of lysosomal storage disorders. We will continue our uncompromising effort to take on the challenge of providing new treatment options for patients with lysosomal storage disorders around the world as soon as possible."

The MHLW's approval of IZCARGO® is based on totality of evidence from non-clinical and clinical studies[1-4]. In a phase 2/3 clinical trial conducted in Japan, all 28 patients experienced significant

reductions in heparan sulfate (HS) concentrations in the cerebrospinal fluid (CSF) – a biomarker for effectiveness against CNS symptoms of MPS II – after 52 weeks of treatment, thus meeting the trial's primary endpoint. IZCARGO® maintained somatic disease control in patients who switched from standard ERT to IZCARGO®. The study also confirmed an improvement in somatic symptoms in participants who had not previously received standard ERT prior to the start of the trial. Additionally, a neurocognitive development assessment demonstrated maintenance or improvement of age-equivalent function in 21 of the 28 patients. There were no reports of serious treatment-related adverse events in the trial, suggestive of a favorable safety and tolerability profile for IZCARGO®.[4]

"Subsequent to this approval in Japan, I look forward to further accumulation of clinical evidence for pabinafusp alfa in Brazil, the US and EU," said Dr. Paul Harmatz of University of California – San Francisco (UCSF) Benioff Children's Hospital Oakland, Oakland, CA, United States. "The availability of an enzyme replacement therapy that crosses the blood-brain barrier is expected to treat both CNS and somatic symptoms associated with this devastating and life-threatening disorder, including developmental and cognitive delays, bone deformities, and abnormal behavior, which have, historically, been unaddressed."

JCR recently filed an application with the Brazilian Health Surveillance Agency (Agência Nacional de Vigilância Sanitária [ANVISA]) for marketing approval of IZCARGO® for the treatment of patients with MPS II. JCR is also preparing to launch a Phase 3 trial of IZCARGO® in the US, Brazil, the UK, Germany, and France.

About pabinafusp alfa

Pabinafusp alfa (10 mL, intravenous drip infusion) is a recombinant fusion protein of an antibody against the human transferrin receptor and idursulfase, the enzyme that is missing or malfunctioning in subjects with Hunter syndrome. It incorporates J-Brain Cargo®, JCR's proprietary BBB-penetrating technology, to cross the BBB through transferrin receptor-mediated transcytosis, and its uptake into cells is mediated through the mannose-6-phosphate receptor. This novel mechanism of action is expected to make pabinafusp alfa effective against the CNS symptoms of Hunter syndrome.

In pre-clinical trials, JCR has confirmed both high-affinity binding of pabinafusp alfa to transferrin receptors, and passage across the BBB into neuronal cells, as evidenced by electron microscopy. In addition, JCR has confirmed enzyme uptake in various brain tissues. The company has also confirmed a reduction of substrate accumulation in the CNS and peripheral organs in an animal model of Hunter syndrome.[1]

In several clinical trials of pabinafusp alfa, JCR obtained evidence of reduced HS concentrations in the CSF, a biomarker for assessing effectiveness against CNS symptoms. The results were consistent with those obtained in pre-clinical studies. Clinical studies have also demonstrated positive effects of pabinafusp alfa on CNS symptoms.[2]

About J-Brain Cargo® Technology

JCR's first-in-class proprietary technology, J-Brain Cargo®, enables the development of therapies that cross the BBB and penetrate the CNS. The CNS complications of diseases are often severe, resulting in developmental delays, an impact on cognition and, above all, poor prognosis, which affect patients' independence as well as the quality of life of patients and their caregivers. With J-Brain Cargo®, JCR seeks to address the unresolved clinical challenges of LSDs by delivering the enzyme to both the body and the brain.

About Mucopolysaccharidosis II (Hunter Syndrome)
Mucopolysaccharidosis II (Hunter syndrome) is an X-linked recessive LSD caused by a deficiency of iduronate-2-sulfatase, an enzyme that breaks down complex carbohydrates called glycosaminoglycans (GAGs, also known as mucopolysaccharides) in the body. Hunter syndrome, which affects an estimated 7,800 individuals worldwide (according to JCR research), gives rise to a wide range of somatic and neurological symptoms. The current standard of care for Hunter syndrome is ERT. CNS symptoms related MPS II have been unmet medical needs so far.

About JCR Pharmaceuticals Co., Ltd.
JCR Pharmaceuticals Co., Ltd. (TSE 4552) is a global specialty pharmaceuticals company that is redefining expectations and expanding possibilities for people with rare and genetic diseases worldwide. We continue to build upon our 45-year legacy in Japan while expanding our global footprint into the US, Europe, and Latin America. We improve patients' lives by applying our scientific expertise and unique technologies to research, develop, and deliver next-generation therapies. Our approved products in Japan include therapies for the treatment of growth disorder, Fabry disease, acute graft-versus host disease, and renal anemia. Our investigational products in development worldwide are aimed at treating rare diseases including MPS I (Hurler syndrome, Hurler-Scheie, and Scheie syndrome), MPS II (Hunter syndrome), Pompe disease, and more. JCR strives to expand the possibilities for patients while accelerating medical advancement at a global level. Our core values – reliability, confidence, and persistence – benefit all our stakeholders, including employees, partners, and patients. Together we soar. For more information, please visit https://www.jcrpharm.co.jp/en/site/en/.

Cautionary Statement Regarding Forward-Looking Statements
This document contains forward-looking statements that are subject to known and unknown risks and uncertainties, many of which are outside our control. Forward-looking statements often contain words such as "believe," "estimate," "anticipate," "intend," "plan," "will," "would," "target" and similar references to future periods. All forward-looking statements regarding our plans, outlook, strategy and future business, financial performance and financial condition are based on judgments derived from the information available to us at this time. Factors or events that could cause our actual results to be materially different from those expressed in our forward-looking statements include, but are not limited to, a deterioration of economic conditions, a change in the legal or governmental system, a delay in launching a new product, impact on competitors' pricing and product strategies, a decline in marketing capabilities relating to our products, manufacturing difficulties or delays, an infringement of our intellectual property rights, an adverse court decision in a significant lawsuit and regulatory actions.

This document involves information on pharmaceutical products (including those under development). However, it is not intended for advertising or providing medical advice. Furthermore, it is intended to provide information on our company and businesses and not to solicit investment in securities we issue.

Except as required by law, we assume no obligation to update these forward-looking statements publicly or to update the factors that could cause actual results to differ materially, even if new information becomes available in the future.

References
[1] Sonoda H, Morimoto H, Yoden E, et al. A blood-brain-barrier-penetrating anti-human transferrin receptor antibody fusion protein for neuronopathic mucopolysaccharidosis II. Molecular Therapy. 2018;26(5):1366-1374.

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[3] Okuyama T, Eto Y, Sakai N, et al. Iduronate-2-sulfatase with anti-human transferrin receptor antibody for neuropathic mucopolysaccharidosis II: a phase 1/2 trial. Molecular Therapy. 2019;27(2):456-464.
[4] Okuyama T, Eto Y, Sakai N, et al. A phase 2/3 trial of pabinafusp alfa, IDS fused with anti-human transferrin receptor antibody, targeting neurodegeneration in MPS-II. Molecular Therapy. 2021;29(2):671-679.

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