News Release

October 15, 2021
JCR Pharmaceuticals Co., Ltd.

Translation

JR-141 (Pabinafusp Alfa) for Hunter Syndrome
Notice on the Publication of a nonclinical and clinical evidence
in International Journal of Molecular Sciences

Oct. 15 -- JCR Pharmaceuticals Co., Ltd. (TSE 4552; Chairman and President: Shin Ashida; "JCR") announced today that an article summarizing the preclinical and clinical data of JR-141 (INN: pabinafusp alfa) for the treatment of mucopolysaccharidosis II (MPS II; Hunter syndrome) has been published in International Journal of Molecular Sciences,an open access journal published by MDPI, as a part of its special issue: Genetic and Metabolic Molecular Research of Lysosomal Storage Disease. JR-141 is a blood-brain-barrier (BBB)-penetrating recombinant iduronate-2-sulfatase product for the treatment of patients with MPS II, which applies JCR's proprietary J-Brain Cargo®, BBB technology.
In May 2021 JCR has started to market JR-141 as "IZCARGO® I.V. infusion 10mg" in Japan . In December 2020, an application for marketing authorization was filed with the Brazilian Health Surveillance Agency (Agência Nacional de Vigilância Sanitária [ANVISA]) for the treatment of patients with MPS II. JCR is also preparing to initiate a global phase 3 clinical trial for JR-141 which will enroll patients at sites in the US, Brazil and Europe (ClinicalTrials.gov Identifier: NCT04573023).

A summary of the article is as follows.

◆ Title:
Enzyme replacement therapy with pabinafusp alfa for neuronopathic mucopolysaccharidosis II: an integrated analysis of preclinical and clinical data.
Int. J. Mol. Sci. 2021, Volume 22, Issue 20, 10938

◆ Digital Object Identifier:
10.3390/ijms222010938

◆ Summary
Although enzyme replacement therapy (ERT) improves somatic manifestations in mucopolysaccharidoses (MPS), because intravenously administered enzymes cannot cross the blood–brain barrier (BBB), ERT is ineffective against the progressive neurodegeneration and resultant severe central nervous system (CNS) symptoms in neuronopathic MPS. Attempts to surmount this problem have been made with intrathecal and intracerebroventricular ERT, but the burdens on patients are inimical to long-term administrations. Pabinafusp alfa, a human iduronate-2-sulfatase fused with a BBB-crossing anti-transferrin receptor antibody, showed both central and peripheral efficacy in a mouse model, subsequent clinical trials in a total of 62 patients with MPS-II (Hunter syndrome) in Japan and Brazil substantiated this dual efficacy. This article summarizes the hitherto obtained and updated preclinical and clinical data of this drug, and discusses the preclinical, translational, and clinical challenges of evaluating, ameliorating, and preventing neurodegeneration in MPS-II.

About JR-141

JR-141 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 JR-141 effective against the CNS symptoms of Hunter syndrome.

In pre-clinical trials, JCR has confirmed both high-affinity binding of JR-141 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 decrease in substrate accumulation in an animal model of Hunter syndrome.[1,2]

In several clinical trials of JR-141, JCR obtained evidence of reduced HS concentrations in the CSF, a biomarker for assessing effectiveness against CNS symptoms; these results were consistent with those obtained in pre-clinical studies. Clinical studies have also demonstrated positive effects of JR-141 on CNS symptoms.[3,4,5,6]

JR-141 was approved by the Ministry of Health, Labour and Welfare and marketed since May 2021 under the brand name "IZCARGO® I.V. Infusion 10mg."

In September 2021, JCR and Takeda announced a geographically-focused exclusive collaboration and license agreement to commercialize JR-141. Under the agreement, Takeda will exclusively commercialize JR-141 outside of the United States, including Canada, Europe, and other regions (excluding Japan and certain other Asia-Pacific countries). Takeda also received an option for an exclusive license to commercialize JR-141 in the U.S. upon completion of the Phase 3 program. The two companies will collaborate to bring this therapy to patients as quickly as possible upon completion of the global Phase 3 program, which will be conducted by JCR.

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 46-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, MPS II (Hunter syndrome), acute graft-versus host disease, and renal anemia. Our investigational products in development worldwide are aimed at treating rare diseases including MPS I (Hurler, Hurler-Scheie and Scheie syndrome), 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, 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.
2: Morimoto, et al. Clearance of heparin sulfate in the brain prevents neurodegeneration and neurocognitive impairment in MPS II mice. Mol. Ther. 2021.
3: Okuyama, et al. Iduronate-2-sulfatase with Anti-human Transferrin Receptor Antibody for Neuropathic Mucopolysaccharidosis II: A Phase 1/2 Trial. Mol Ther. 2020; 27(2): 456-464.
4: Okuyama, et al. A Phase 2/3 Trial of Pabinafusp Alfa, IDS Fused with Anti-Human Transferrin Receptor Antibody, Targeting Neurodegeneration in MPS-II. Mol Ther. 2021; 29(2): 671-679.
5: Giugliani, et al. Iduronate-2-sulfatase fused with anti-human transferrin receptor antibody, pabinafusp alfa, for treatment of neuronopathic and non-neuronopathic mucopolysaccharidosis II: Report of a phase 2 trial in Brazil. Mol Ther. 2021.
6: Giugliani, et al. Enzyme Replacement Therapy with Pabinafusp Alfa for Neuronopathic Mucopolysaccharidosis II; an Integrated Analysis of Preclinical and Clinical Data. Int. J. Mol. Sci. 2021, Volume 22, Issue 20, 10938.

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