News Release

February 15, 2022
JCR Pharmaceuticals Co., Ltd.

Translation

JCR Announces First Patient Dosed in Phase 3 Global Clinical Trial of JR-141 for Treatment of MPS II (Hunter Syndrome)

Hyogo, Japan, February 15, 2022 -- JCR Pharmaceuticals Co., Ltd. (TSE 4552; Chairman and President: Shin Ashida; "JCR") announced today that the dosing of the first patient in the Phase 3 global clinical trial of JR-141 (INN: pabinafusp alfa) was initiated in the U.S. JR-141 is a blood-brain-barrier (BBB)-penetrating recombinant Iduronate-2-sulfatase for the treatment of patients with Mucopolysaccharidosis type II (MPS II also known as Hunter syndrome), linked to J-Brain Cargo®, JCR's proprietary BBB penetration technology.

MPS II is an X-linked recessive lysosomal storage disorder (LSD) characterized by multiple somatic and central nervous system (CNS) signs and symptoms which is caused by a deficiency or defective function of iduronate-2-sulfatase, an enzyme that breaks down glycosaminoglycans (mucopolysaccharides) in the body. JR-141 is the first-ever approved enzyme replacement therapy (ERT) in Japan that penetrates the BBB via intravenous administration for the treatment of MPS II. By delivering the enzyme to both the body and the brain, JR-141 is expected to treat not only the systemic symptoms but also the neuronopathic manifestations of MPS II.

The summary of this study is also available on clinicaltrials.gov (Identifier: NCT04573023).

In September 2021, JCR and Takeda announced a geographically-focused exclusive collaboration and license agreement to commercialize JR-141 (Related releases are here).

"Dosing of the first patient in our global phase 3 trial with JR-141 is a true milestone for JCR: After a successful launch of IZCARGO® in Japan we are very happy to take the next step towards bringing this innovation to patients across the globe", noted Mathias Schmidt, PD, Ph.D., Vice President and Head of Clinical Development, Global Business Strategy and Business Development at JCR Pharmaceuticals.

Following JR-141, JCR plans to harness its J-Brain Cargo® technology platform and progress its robust pipeline of innovative ERT products for other LSDs. JCR, as a specialty pharma in the rare disease arena, will continue to proactively engage in research and development of transformative treatment options for patients with rare diseases.

The impact of this progress on the consolidated business results for the fiscal year ending March 31, 2022 has been incorporated into the business forecast for current fiscal year.

About pabinafusp alfa (JR-141)
Pabinafusp alfa is a recombinant fusion protein of an antibody against the human transferrin

receptor and idursulfase, the enzyme missing or malfunctioning in subjects with Hunter syndrome. It utilizes J-Brain Cargo®, JCR's proprietary blood-brain barrier (BBB)-penetrating technology, to cross the BBB via transferrin receptor-mediated transcytosis. Uptake into cells is mediated through the mannose-6-phosphate receptor or the transferrin receptor. This novel mechanism of action is expected to make IZCARGO® effective against the CNS symptoms of Hunter syndrome.

In pre-clinical studies, JCR has confirmed both high-affinity binding of pabinafusp alfa to transferrin receptors and passage across the BBB into neuronal cells. 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.[1,2]

In several clinical trials with pabinafusp alfa, JCR obtained evidence of reducing heparan sulfate (HS) concentrations in the CSF, a biomarker that is believed to reflect substrate reduction in the brain and changes in CNS function. These results were consistent with those obtained in pre-clinical studies. Clinical studies have also demonstratedpositive effects of pabinafusp alfa on CNS symptoms.[3,4,5,6]

Pabinafusp alfa was approved by the Ministry of Health, Labour and Welfare in Japan 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.

Important Safety Information
INDICATION:

IZCARGO® is indicated for the treatment of mucopolysaccharidosis type II (MPS II), which is also known as Hunter syndrome. IZCARGO® is approved in Japan only.

CONTRAINDICATION:

IZCARGO® is contraindicated in patients with a history of anaphylactic shock to its any components.

WARNINGS AND PRECAUTIONS:

Warnings
Since serious anaphylaxis and shock may occur with use of IZCARGO®, adequate emergency measures should be made ready for execution before initiation of administration, and the patient should be closely monitored during and after the administration. If a serious infusion associated reaction (IAR) occurs, administration of IZCARGO® should be discontinued, and appropriate actions should be taken.

When IZCARGO® is administered to patients with severe respiratory failure or acute respiratory disease, an IAR may lead to acute exacerbation of symptoms. Patient's condition should be closely monitored and appropriate actions should be taken as needed.

Precautions for Use
IZCARGO® is a protein medicinal product and may cause anaphylactic shock, for which close monitoring is required. If any signs of anaphylaxis are noted, discontinue the infusion, and take appropriate actions. Considering the onset of such symptoms, emergency measures should be made ready for execution.

IZCARGO® may cause IARs such as headache, chills, syncope, fatigue, dizziness, pyrexia, rash, erythema, urticaria, or other symptoms. If an IAR occurs, reduce the rate or temporarily discontinue the infusion, and initiate appropriate drug treatment (e.g., corticosteroids, antihistamines, antipyretic analgesics, anti-inflammatory drugs) or emergency procedures (e.g., oxygen administration, securing of airway, adrenaline administration). Premedication with antihistamines, corticosteroids, etc. should be considered for the subsequent infusion of IZCARGO®.

ADVERSE REACTIONS:

The most commonly reported adverse reactions were pyrexia and urticaria.

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 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. Mol. Ther. 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; 29(5): 1853-1861.
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; 29(7): 2378-2386.
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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