News Release

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JCR Pharmaceuticals Co., Ltd.

Translation

JCR Pharmaceuticals Presents Research at WORLD*Symposium*™ 2021 Showing Potential Benefits of JR-141 (Pabinafusp Alfa) in Patients with MPS II (Hunter Syndrome)

- Company Prepares to Initiate Global Phase 3 Trial of JR-141 and Advances Drug Development Programs for Additional Lysosomal Storage Disorders -

Feb. 16, 2021 – JCR Pharmaceuticals Co., Ltd. (TSE 4552; Chairman and President: Shin Ashida; "JCR") announced today the presentation of multiple clinical datasets demonstrating the potential benefits of JR-141 (INN: pabinafusp alfa), the company's investigational therapy for mucopolysaccharidosis type II (MPS II, or Hunter syndrome). JR-141 is a recombinant iduronate-2-sulfatase product candidate that relies on J-Brain Cargo®, a proprietary technology developed by JCR, to deliver medicine across the blood-brain barrier (BBB).

In a series of presentations last week at the 17th Annual WORLD*Symposium*™2021, an international research conference dedicated to lysosomal storage disorders (LSDs), JCR reported clinical data suggesting potential neurocognitive benefits and effects on other MPS II disease markers resulting from JR-141 therapy, underscoring the importance of early diagnosis and treatment in patients with MPS II. Other JCR presentations focused on:

- the design of a global Phase 3 clinical trial of JR-141 in MPS II;
- the effects of JR-141 on neurocognition in a mouse model of MPS II;
- the design of a Phase 1/2 trial of JR-171 for the treatment of MPS I (Hurler syndrome or Hurler-Scheie syndrome); and
- preclinical data for additional investigational therapies for the treatment of Pompe disease (JR-162), MPS IIIA (Sanfilippo A)(JR-441), and MPS IIIB (Sanfilippo B)(JR-446).

"The WORLD*Symposium* presentations strengthen the rationale for using 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 – a capability that available treatments lack," said Shin Ashida, chairman and president of JCR Pharmaceuticals. "We look forward to further characterizing the potential effects of our investigational therapies on these severe and debilitating symptoms as we seek regulatory approval of JR-141 in Japan and Brazil and prepare for our Phase 3 trial of JR-141 in the United States and other Western countries."

In a pivotal clinical trials conducted in Japan and Brazil, JR-141 markedly decreased concentrations of heparan sulfate (HS, a biomarker for effectiveness against central nervous system [CNS] symptoms) in the cerebrospinal fluid (CSF). The trial also confirmed a decrease of dermatan sulfate (DS) concentration in blood in enzyme-replacement therapy (ERT)-naïve subjects, and stabilization in patients switched from standard ERT to JR-141. Additionally, assessment of neurocognitive development demonstrated maintenance or improvement of age-equivalent function in 39 out of 45 patients during the 52 weeks of treatment. 104-week follow-up data confirmed a neurocognitive benefit in patients with both severe and attenuated disease.

Based on those clinical results, JCR filed an application with the Ministry of Health, Labour and Welfare of Japan (MHLW) and the Brazilian Health Surveillance Agency (Agência Nacional de Vigilância Sanitária [ANVISA]) for marketing approval of JR-141 for the treatment of patients with MPS II. The following WORLD*Symposium* presentations provide additional evidence and context for the use of JR-141 in the treatment of MPS II:

***A Comparison of Developmental Trajectories in Sibling Cases with Neuropathic MPS-II Receiving Conventional and Novel Enzyme Replacement Therapies* (Abstract LB-50)**
In a Late-Breaking ePoster presentation, Kazuyoshi Tomita, M.D., from Department of Pediatrics, Osaka City University Graduate School of Medicine, Japan, reported on the case of two siblings with MPS II, one of whom (Sibling 1) was diagnosed at 2 years of age and the other (Sibling 2) diagnosed prenatally. Sibling 1 was started on conventional ERT shortly after diagnosis. Sibling 2 received conventional ERT from 1 month to nearly 2 years of age, and then switched to JR-141. Compared to Sibling 1, Sibling 2 exhibited notable preservation of neurocognitive development, as well as a significant decline in HS levels in the CSF. Sibling 2, who is now 4 years old, has exhibited normal development over the 42 months since his first administration of JR-141 at 1 year and 11 months. The marked difference in the developmental trajectories in these siblings highlights the importance of early diagnosis and treatment in MPS II, along with the potential benefits of BBB-penetrating ERT.
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***Therapy for Mucopolysaccharidosis Type II with an Intravenous Blood-Brain Barrier-Crossing Enzyme (JR-141): Phase III Global Clinical Trial Design* (Abstract 242)**
Sairei So, Ph. D., from JCR presented the design for a randomized, active-controlled, assessor-blinded, global Phase 3 trial to assess the efficacy and safety of JR-141, compared to standard-of-care idursulfase, in patients with MPS II. The trial will enroll patients with neuronopathic (early progressive, more severe) and attenuated (slowly progressive, milder) disease as two separate cohorts to evaluate efficacy on CNS and somatic (i.e., pertaining to body parts and systems other than the brain) symptoms. Participants will be randomized to receive either JR-141 or idursulfase until the interim analysis at Week 53, after which all patients will receive JR-141 until Week 104 if the efficacy of JR-141 is deemed substantial. JCR plans to initiate the trial in the US, UK, Brazil, Germany, and France in the second quarter of 2021.
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***Exploration of the Efficacy of Pabinafusp-alfa (JR-141) on Neurocognitive Development in Hunter Syndrome (MPS-II): 52-week Data from Clinical Trials in Japan and Brazil* (Abstract 84)**
In an ePoster, Roberto Giugliani, M.D., Ph.D., from the Federal University of Rio Grande do Sul in Porto Alegre, Brazil, reported that weekly treatment with JR-141 led to stabilization or improvement of neurocognition in 47 patients across two trials (2.0 mg/kg for 52 weeks in Japan; 1.0, 2.0, and 4.0 mg/kg for 25 weeks in Brazil, followed by extension studies). Both studies documented stabilization or improvement in developmental scores and positive changes in behavior, suggesting that JR-141 may ameliorate the neurological disease burden of MPS II, in addition to the somatic signs and

symptoms of the disease.
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Drug Delivery across the Blood-Brain Barrier and Resultant Reduction of Heparan Sulfate in the Cerebrospinal Fluid in the Patients with Hunter Syndrome (MPS-II): An Integrated Analysis of 25-Week Japanese and Brazilian Data on Pabinafusp Alfa (JR-141) **(Abstract 176)**
In a separate ePoster, Torayuki Okuyama, M.D., Ph. D., from the National Center for Child Health and Development in Tokyo, Japan, presented 25-week clinical data from Japan and Brazil showing that HS concentrations in the CSF were reduced significantly after treatment with JR-141. As the potential neurocognitive effects of JR-141 are thought to result from substrate reduction in the CNS, HS levels in the CNS may serve as both a valid surrogate endpoint and as a clinically informative indicator of treatment response and prognosis in MPS II.
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Reduction of Heparan Sulfate in the Brain by Pabinafusp Alfa Results in Prevention of Neurodegeneration and Neurocognitive Impairment in a Mouse Model of Mucopolysaccharidosis II **(Abstract 163)**
Hideto Morimoto from JCR reported that JR-141 reduced HS deposition in the brain in a mouse model of MPS II, resulting in prevention of neurodegeneration and neurocognitive impairment. In addition, HS concentrations in the CSF highly correlated with those in the brain, demonstrating CSF HS levels to be a valuable surrogate biomarker for CNS symptoms in MPS II.
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Other JCR Datasets
In addition to the above presentations on JR-141, JCR researchers presented several other ePosters showcasing the company's pipeline of innovative, BBB-penetrating ERT products for the treatment of other LSDs, including:

- ***Phase I/II Clinical Trial Design for a Novel Therapy for Mucopolysaccharidosis Type I with an Intravenously Administered Blood-Brain Barrier-Crossing Enzyme (JR-171)*** **(Abstract 99)**: Ryo Higurashi from JCR USA, presented the design for a global, first-in-human, open-label, multicenter Phase 1/2 trial assessing the safety, plasma pharmacokinetics, and efficacy of JR-171 in patients with MPS I (Hurler syndrome).
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- ***Usefulness of Hexose Tetrasaccharide as a Biomarker for Monitoring Glycogen Accumulation in Peripheral Tissues and Brain in Pompe Disease*** **(Abstract 94)**: Hidehiko Hashimoto from JCR reported that JR-162 markedly reduced glycogen accumulation in peripheral tissues and the brain in a mouse model of Pompe disease. In addition, JR-162 reduced hexose tetrasaccharide (Hex4) concentrations in the urine and CSF, which correlated with those in peripheral tissues and the brain, respectively. These results suggest that JR-162 has efficacy against Pompe disease and that the potential utility of Hex4 as a biomarker for monitoring glycogen accumulation in patients with Pompe disease.
  Poster: https://ssl4.eir-parts.net/doc/4552/ir_material_for_fiscal_ym6/95187/00.pdf

- ***Non-Clinical Evaluation of a Blood-Brain Barrier-Penetrable N-Sulfoglucosamine Sulfohydrolase in a Mouse Model of Mucopolysaccharidosis IIIA*** **(Abstract 252)**: Satowa Tanaka from JCR reported that intravenously administered JR-441 penetrated the brain by crossing the BBB in mice and monkeys. Repeated intravenous administration of JR-

441 reduced substrates accumulated in peripheral and CNS tissues of a mouse model of MPS IIIA (Sanfilippo syndrome type A), suggesting that JR-441 has therapeutic potential for MPS IIIA.
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- ***Non-Clinical Evaluation of a Blood-Brain Barrier-Penetrable α-N-Sulfoglucosamine Sulfohydrolase in a Mouse Model of Mucopolysaccharidosis IIIB* (Abstract 103)**: Atsushi Imakiire from JCR reported that intravenously administered JR-446 penetrated the brain by crossing the BBB in mice and monkeys. Repeated intravenous administration of JR-446 reduced substrates accumulated in peripheral and CNS tissues of a mouse model of MPS IIIB (Sanfilippo syndrome type B), suggesting that JR-441 has therapeutic potential for MPS IIIB.
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For more information about JCR at the 17th Annual WORLD*Symposium*™2021, visit https://congress.jcrpharm.co.jp.

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]

JR-141 has already been filed and under review for regulatory approval in Japan and Brazil.

About J-Brain Cargo® Technology

JCR's first-in-class proprietary technology, J-Brain Cargo®, enables the development of therapies that cross the blood-brain barrier 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 (MPS II, Hunter syndrome)

MPS 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, though its clinical utility is limited by its inability to cross the BBB, a shortcoming that prevents it from addressing the CNS symptoms of the disease, which are often the most severe, as they result in developmental delays, cognitive defects, and above all, poor prognosis.

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, HurlerScheie and Scheie syndrome 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. (DOI: https://doi.org/10.1016/j.ymthe.2018.02.032)

[2] Morimoto H, Kida S, Yoden E, et al. Clearance of heparan sulfate in the brain prevents neurodegeneration and neurocognitive impairment in MPS II mice. Molecular Therapy. 2021 Jan 25;S1525-0016(21)0027-7. (DOI: https://doi.org/10.1016/j.ymthe.2021.01.027)

[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. (DOI: https://doi.org/10.1016/j.ymthe.2018.12.005)

Contact:
Investors & Media:
JCR Pharmaceuticals Co., Ltd.
Corporate Communications
ir-info@jcrpharm.co.jp

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