News Release

February 14, 2024
JCR Pharmaceuticals Co., Ltd.

JCR Pharmaceuticals' Research Presentations at WORLD*Symposium*™ 2024 Showcase JR-141 (Pabinafusp Alfa) and Other Investigational Treatments for Lysosomal Storage Disorders

- Presentations Highlight Potential Benefits of Therapies Incorporating J-Brain Cargo®, JCR's Proprietary, Blood-Brain Barrier-Penetrating Technology -

Hyogo, Japan, February 14, 2024 – JCR Pharmaceuticals Co., Ltd. (TSE 4552; Chairman and President: Shin Ashida; "JCR") today announced the presentation of several datasets demonstrating the potential benefits of its investigational therapies for lysosomal storage disorders (LSDs). In a series of oral and poster presentations at the 20th Annual WORLD*Symposium*™ in San Diego, Calif., JCR highlighted several programs that rely on J-Brain Cargo®, a proprietary technology developed by JCR, to deliver medicines across the blood-brain barrier (BBB).

"Lysosomal storage disorders present a life-long burden for patients because of the somatic, and most importantly, the progressive neurological signs and symptoms associated with these devastating and life-threatening diseases for which there are no current treatment available. JCR is dedicated to approach the unmet medical needs for this community," said Shin Ashida, President and CEO of JCR Pharmaceuticals. "The clinical data that are presented at the WORLD*Symposium*™ demonstrate the safety and efficacy of JR-141 in individuals with MPS II and the potential of our proprietary J-Brain Cargo® technology across multiple lysosomal storage disorders. In addition, we're excited to present preclinical data focused on retinal function and bone abnormalities."

There are three JR-141 presentations, including one presentation focused on the long-term safety and efficacy and behavioral effects of JR-141 (pabinafusp alfa) for mucopolysaccharidosis type II (MPS II, or Hunter syndrome). JR-141 is a recombinant iduronate-2-sulfatase (I2S) enzyme replacement therapy (ERT) that was approved in March 2021 by the Ministry of Health, Labour and Welfare (MHLW) in Japan, where it is marketed as IZCARGO® for the treatment of patients with MPS II. The second JR-141 presentation details the global phase III clinical trial study. Finally, the third JR-141 presentation is pre-clinical and highlights the recovery of retinal function in mice with MPS II.

"We are pleased to be able to offer IZCARGO®, to patients with MPS II in Japan.," said Yoshikatsu Eto, M.D., Ph.D., Institute of Neurological Disorders, Advanced Clinical Research Center, Kanagawa, Japan. "As we continue gathering new data from the Japanese and Brazilian long-term efficacy study and from the ongoing phase III global JR-141 clinical study, currently in recruitment, we look forward to providing updates as appropriate. These data sets will make it more certain that JR-141 can treat not only the somatic symptoms of MPS II, but also the neurocognitive symptoms of this devastating and life-threatening disease."

In addition to the three JR-141 presentations, the WORLD*Symposium*™ 2024 scientific program featured presentations focusing on:

- 52-week interim data from the JR-171 phase I/II clinical trial (Hurler syndrome, Hurler-Scheie syndrome or Scheie syndrome);
- pre-clinical data on an ERT with JR-171 preventing bone deformities in a mouse model of MPS I;

- JR-441 global clinical trial study design (Sanfilippo syndrome type A).

JR-141 MPSII Datasets

The following poster presentation provides additional evidence and context for the use of JR-141 in the treatment of MPS II:

***Integrated long-term efficacy and safety data on enzyme replacement therapy with pabinafusp alfa for neuronopathic mucopolysaccharidosis II (MPS-II): updated clinical data from Japan and Brazil* (Abstract 81)**
Presenter: Yoshikatsu Eto, M.D., Ph.D. (Institute of Neurological Disorders, Advanced Clinical Research Center, Kanagawa, Japan)

This abstract analyzed the long-term efficacy and safety data on pabinafusp alfa for the treatment of individuals with MPS II. This study analyzed 104 patients over 260 weeks. In terms of safety, the data include four pabinafusp alfa-related serious adverse events (consciousness disturbance, hypotension, pyrexia and facial palour) in one individual, but all four were managed and resolved. Infusion-associated reactions were noted to gradually decrease in frequency as the length of exposure to pabinafusp alfa increased. The Kyoto Scale of Psychological Development, Bayley Scale for Infant Development, Kaufman Assessment Battery for Children, and Vineland Adaptive Behavioral Scale were used to evaluate the efficacy of pabinafusp alfa against neurocognitive impairment. A developmental quotient (DQ) of >70 was identified as the best predictor of treatment response in achieving age-equivalent neurodevelopment. Another predictor was age at initiation of treatment, with initiation before 36 months of age associated with the most favorable response in subjects with severe MPS II. Analysis of adaptive behavior showed a trend to overall improvement in most individuals with the attenuated subtype, and some improvement in those with the severe subtype and a DQ of >70, while changes, as expected, were limited in those with a DQ of <70. Notable sustained efficacy was seen in terms of liver and spleen volumes, joint range of motion, and left ventricular mass index. These outcomes of ERT with pabinafusp alfa for more than five years provide good evidence of its safety as well as peripheral efficacy, with preliminary data of central efficacy particularly in certain patients with attenuated form of the disease. Post-marketing studies will last for a total of 10 years and provide long-term evidence of pabinafusp alfa's safety and efficacy.

The following poster presentation provides an overview of the global phase III clinical trial study design for JR-141 in the treatment of MPS II:

***A global phase III study of pabinafusp alfa (JR-141) for neuronopathic mucopolysaccharidosis type II: updated study design* (Abstract 154)**
Presenter: Toshiaki Ikeda (JCR Pharmaceuticals)

This abstract provides an overview of the ongoing global phase III clinical trial of pabinafusp alfa (JR-141) for neuronopathic MPS II. The trial began in February 2022 and spans 10 countries as of now. The study consists of two cohorts with a total of 80 patients with MPS II. Cohort A includes individuals with the severe (neuronopathic) subtype aged 30 to 71 months, who are randomized into a treatment arm given a weekly administration of JR-141 at 2.0 mg/kg, and a control arm receiving ERT idursulfase; the total study duration is 24 months, and the purpose is to demonstrate that the efficacy of JR-141 in patients with neuronopathic MPS II is superior to that of conventional ERT. Cohort B consists of attenuated patients aged 6 years and older, randomized into two arms in the same manner as above; the study duration is 12 months, and the purpose is to evaluate the efficacy of JR-141 in patients with somatic symptoms in comparison with that of idursulfase. Primary efficacy endpoints are assessed on the basis of HS levels in the CSF and neurocognitive test (BSID-III) results. Key secondary outcome measures include liver and spleen volumes and further neurological outcomes. The study thus designed is expected to establish the efficacy of JR-141 against both the central nervous system (CNS) and peripheral/somatic symptoms. Details of other outcome measures and study design components will be presented at the symposium.

The following poster presentation provides preclinical data about retinal function for the use of JR-141 in the treatment of MPS II:

***Recovery of retinal function in MPS II mice by treatment with pabinafusp alfa* (Abstract 155)**
Presenter: Atsushi Imakiire (JCR Pharmaceuticals)

This abstract explains how pabinafusp alfa addresses one of the difficult-to-treat complications of MPS II: Retinal disorders in individuals with MPS II are known to be resistant to conventional intravenous ERT due to the presence of the blood-retinal barrier (BRB), which interferes with drug transport into the eye. The retinal function assessed by electroretinography (ERG) was found to worsen with age in a murine model of MPS II (hTfR knock-in/Ids knock-out mice). The presented study demonstrates that pabinafusp alfa crosses the BRB and reaches the retina in MPS II mice. Repeated intravenous dose of pabinafusp alfa started at an early age decreased HS deposition in the retina, optic nerve, and visual cortex and preserved or improved ERG response in MPS II mice. Retinal degeneration was also ameliorated by pabinafusp alfa. Recombinant non-fused I2S did not enter the retina and minimally affected the retinal disease. These results substantiate the postulate that pabinafusp alfa penetrates the BRB and exerts beneficial effects on retinal dysfunction in MPS II.

JR-171 MPSI Datasets

The following poster presentation focuses on the use of JR-171 in the treatment MPS I:

***Efficacy and safety data (52-week) from a phase 1/2 trial and extension study of JR-171 (lepunafusp alfa) used in enzyme replacement therapy for patients with MPS I* (Abstract 113)**
Presenter: Roberto Giugliani, M.D., Ph.D. (Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil)

This abstract reported the 52-week safety and efficacy data from the first-in-human, open-label, multicenter phase I/II trial and an extension study of JR-171 used to treat 14 individuals with MPS I. The 14 individuals had a broad spectrum of disease severity. 12 of them had received treatment with laronidase prior to enrollment, one was treated with laronidase after hematopoietic stem cell transplantation, and the other individual was treatment-naïve. The most common adverse drug reactions were infusion-associated reactions, all manageable without requiring discontinuation of the test drug. Ability to target the neuronopathy was evaluated by measuring HS levels in the CSF from baseline through weeks 13, 26, and 52, all of which were significantly reduced in all subjects. Also, in several individuals with the severe subtype whose treatment started early, neurocognitive data suggested some stabilization of neurodevelopmental decline in comparison with the natural history data. Liver and spleen volumes were stabilized in most of the patients. Other somatic signs and symptoms, including urine and serum HS/DS concentrations, were well-controlled in the subjects switched from laronidase, while they decreased significantly and then remained stable in the naïve patients. These data provide further evidence that JR-171 is delivered across the BBB to address the CNS manifestations of MPS I as well as the somatic/peripheral symptoms while maintaining an appropriate safety profile. A pivotal phase III clinical trial is planned to establish the efficacy and safety of the drug.

The following poster presentation preclinical data about bone deformities for the use of JR-171 in the treatment of MPS I:

***Enzyme replacement therapy with a blood-brain barrier-penetrating antibody-fused a-L-iduronidase prevents bone deformities in a mouse model of mucopolysaccharidosis I* (Abstract 229)**
Presenter: Hiroki Morioka (JCR Pharmaceuticals)

This abstract reported on the effect of JR-171 on the CNS and bone abnormalities in hTfR knock-in/Idua knock-out mice, an animal model of MPS I. JR-171 was intravenously administered to the mice once a week at 2.0 and 4.0 mg/kg for 24 weeks. The long-term intravenous treatment with JR-171 markedly reduced HS and DS concentrations and improved histopathological changes in the peripheral and CNS tissues. In addition, using micro-computed tomography, MPS I mice were found to have skeletal

abnormalities such as increased bone mass and density. The treatment with JR-171 prevented or improved the skeletal abnormalities observed in MPS I mice. These results suggest the potential efficacy of JR-171 against neurodegeneration and neurological impairments, and demonstrate the beneficial effects on bone deformities characteristic of MPS I.

The following late-breaking abstract discloses patient experiences upon treatment with JR-171:

The impact of lepunafusp alfa (JR 171) on the disease burden in MPS I: Patient reported outcomes (Abstract LB-39)
Presenter: Ana Maria Martins (Reference Center in Inborn Errors of Metabolism, Federal University of Sao Paulo, Brazil)

This late-breaking abstract presents data on patient reported outcomes of individuals treated in an ongoing phase I/II study with lepunafusp alfa, a fusion protein consisting of a transferrin-receptor binding domain and α-L-iduronidase, the enzyme missing or malfunctioning in MPS I.

JR-441 MPSIIIA Dataset

The following poster presentation, showcases the company's pipeline of innovative, BBB-penetrating ERT products for the treatment of MPS IIIA:

***A phase I/II clinical trial of JR-441 for treatment of Sanfilippo syndrome type A (MPS IIIA)* (Abstract 234)**:
Presenter: Nicole Muschol, M.D. (University Medical Center Hamburg-Eppendorf, International Center for Lysosomal Disorders (ICLD), Hamburg, Germany)

This abstract reported the Phase I/II clinical trial study design of JR-441 as a first-in-human, open-label, single-center trial to evaluate the optimal dose, safety/tolerability, pharmacokinetics and exploratory efficacy in individuals with MPS IIIA aged ≥1 year to ≤18 years. This study consists of a treatment period (52-week), a drug holiday period (6-week), and an extension period (202-week). After confirming the tolerability in the first 6 individuals with MPS IIIA in a dose escalating manner, a total of 12 individuals are then treated with JR-441 for approximately 5 years. During the drug holiday period, potential rebound effects due to withholding JR-441 are evaluated. Following dose escalation, all individuals are randomized to 2 treatment doses until an optimal dose is determined, which is applied thereafter to all of the enrolled subjects. A broad range of assessments are performed including substrate levels in the CSF, blood and urine, MRI of the brain, liver and spleen, neurodevelopmental function tests, adaptive behavior tests, quality-of-life questionnaires, and life-habit-related questionnaires regarding sleeping, eating and stool to identify and validate suitable endpoints to inform the design of a future global registrational trial.

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 demonstrated positive 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 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 III program.

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 any of its components.

WARNINGS AND PRECAUTIONS:

Warnings
Since serious anaphylaxis and shock may occur with the use of IZCARGO®, adequate emergency measures should be made ready for application 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. The 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 application.

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 the J-Brain Cargo® Platform Technology
JCR Pharmaceuticals has developed a proprietary BBB-penetrating technology J-Brain Cargo®, to bring biotherapeutics into the CNS. The first drug developed based on this technology and approved in Japan for the treatment of MPS II (mucopolysaccharidosis type II) is IZGARGO® (INN: pabinafusp alfa). Based on the same platform technology, JR-171 (INN:lepunafusp alfa) and JR-441 are advancing into global clinical stage. JCR intends to start clinical trials on four additional programs from its LSD pipeline by FY2028.

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 Mucopolysaccharidosis I (Hurler, Hurler-Scheie, Scheie syndrome)
MPS I is an autosomal recessive lysosomal storage disorders (“LSD”) caused by a deficiency of α-L-iduronidase, an enzyme that breaks down glycosaminoglycans (mucopolysaccharides) in the body. The current worldwide prevalence of MPS I is estimated to be approximately 3,000 (according to JCR internal research). MPS I gives rise to a wide range of somatic and neurological symptoms. A major limitation of current ERT is that it does not address CNS symptoms because of the enzyme’s inability cross the BBB. MPS I is the only LSD in which hematopoietic stem cell transplantation (“HSCT”) is part of the standard of case for the severe form of the disease. Significant unmet medical need persists in all forms of MPS I.

About Sanfilippo Syndrome (MPS III)
Sanfilippo syndrome is an autosomal recessive disease caused by a deficiency of the enzymes that metabolize mucopolysaccharides within the body. The disease is classified into four subtypes (A, B, C, and D) according to the respective deficient enzymes. Symptoms include accumulation of heparan sulfate in tissues throughout the body. Notably, the rapidly progressive form of the disease frequently affects neurologic development, which peaks around two or three years of age, before subsequently deteriorating, resulting in a complete loss of speech by the age of seven or eight. Progression further gives rise to symptoms such as sleep disorders, hepatosplenomegaly, seizures, and neurobehavioral abnormalities.

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 49-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.

Contact:

Investors & Media:

JCR Pharmaceuticals Co., Ltd.

Corporate Communications

ir-info@jcrpharm.co.jp

###