News Release

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JCR Pharmaceuticals Co., Ltd.

Translation

JCR Pharmaceuticals' Research Presentations at WORLD*Symposium*™ 2023 Showcase JR-141 (INN: pabinfusp alfa), JR-171 (INN: lepunafusp alfa) and Other Investigational Treatments for Lysosomal Storage Disorders

- JCR continues to approach unmet medical needs for lysosomal storage disorders -

Hyogo, Japan, Feb. 27, 2023 – JCR Pharmaceuticals Co., Ltd. (TSE 4552; Chairman and President: Shin Ashida; "JCR") today announced the presentation of several datasets demonstrating the potential benefits of our investigational therapies which apply J-Brain Cargo®, our proprietary blood-brain barrier (BBB)-penetrating technology, for lysosomal storage disorders (LSDs) at the 19th Annual WORLD*Symposium*™ in Oraland, FL, USA. In a series of oral and poster presentations, we highlight that our investigational therapies will add value to the unmet medical needs tor the treatment of lysosomal storage disorders (LSDs).

Four of the presentations focused on the long-term safety and efficacy and behavioral effects of JR-141 (INN: pabinafusp alfa) for mucopolysaccharidosis type II (MPS II, or Hunter syndrome). These data sets suggest the importance of early diagnosis and treatment in patients with MPS II.

In addition to the four JR-141 presentations, we presented update safety and efficacy data from global phase 1/2 clinical trial of JR-171 (INN: lepunafusp alfa) for MPS I (Hurler, Hurler-Scheie and Scheie syndrome).

Other JCR presentations focused on:

- efficacy of JR-441 on CNS and somatic symptoms in a mouse model of MPS IIIA (Sanfilippo syndrome type A)
- efficacy of JR-471 on CNS and somatic symptoms in a mouse model of fucosidosis
- results of a survey of patients and families living with fucosidosis
- efficacy data on the drug candidate which apply J-Brain Cargo® for the treatment of Krabbe's disease; and
- a case report of AGT-194 for the treatment of CLN1.

JCR is currently conducting a global phase 3 clinical trial of JR-141 in the U.S., Brazil and Europe. In addition, JCR plan to start global Phase 1 clinical trails of JR-441 and JR-446 and global phase 3 clinical trial of JR-171 in FY 2023.

A summary of all presentations is shown below:

JR-141 Datasets

Real-world data of enzyme replacement therapy with pabinafusp alfa for neuronopathic MPS-II: Updated clinical data from Japan

Presenter: Yoshikatsut Eto, M.D. (Advanced Clinical Research Centre & Asian Lysosomal Storage Disorder Centre, Institute of Neurological Diseases, Kanagawa, Japan)

Safety and efficacy data are reported on a total of 69 patients with MPS II enrolled in the two post-marketing clinical studies (JR-141-302 and JR-141-401) and post-marketing surveillance of pabinafusp alfa, approved in Japan in May 2021. Pabinafusp alfa is generally well tolerated, and most infusion associated reactions (IARs) were mild and manageable with premedication and/or adjustment of infusion time. IARs appeared to decrease after the first 26 weeks of treatment. In terms of efficacy for neuronopathy, treatment prognosis may be related to developmental quotient at the onset of treatment. Organ volume, a proxy for somatic efficacy, was controlled both in patients who were previously naïve to treatment and those who had previously received idursulfase. Early introduction of pabinafusp alfa may be of importance for the preservation of neurocognitive development in severe MPS II. The chronic treatment with pabinafusp alfa of individuals with MPS II is justified by the long-term safety profile and observed clinical benefits.

Changes in quality of life reflecting neurobehavioral improvements observed by caregivers/physicians of patients with neuronopathic mucopolysaccharidosis: An interview-based survey from Brazil following clinical trials with pabinafusp alfa

Presenter: Ana Maria Martins, M.D., Ph.D. (Reference Center in Inborn Errors of Metabolism, Universidade Federal de São Paulo, Brazil)

To identify the actual difficulties in daily life by patients with neuronopathic MPS II and their families, the caregivers of 9 patients on pabinafusp alfa for up to 104 weeks were interviewed to assess their perceptions of treatment outcomes using a standardized questionnaire to register their observations and perceptions of mental/emotional status and behavioral, physical, and psychological symptoms. Significant enhancement was noted in the patients' comprehension and ability to perform day-to-day activities, attention span, focus, and concentration. These improvements had led to the resumption of 'normal' family life after years of disruption, e.g. their protégés could now be taken out for dinner and on excursions, or that the caregivers slept better without awakening their parents. These nuanced but critical changes may represent early responses to treatment with pabinafusp alfa and require further evaluation.

Long-term neurodevelopmental changes in subjects with MPS II following long-term treatment with pabinafusp alfa: An integrated analysis from pre- and post-approval clinical trials in Brazil and Japan

Presenter: Roberto Giugliani, M.D., Ph.D. (Federal University of Rio Grande do Sul, Brazil)

The long-term neurological changes in 48 patients in Japan and Brazil enrolled in clinical trials upon treatment with weekly infusions of JR-141 have been followed up for up to 3 years. We stratified the patients by developmental quotient (DQ) and severity at the onset of JR-141 and analyzed the results of neurocognitive and adaptive behavior tests. Treatment with JR-141 is suggested to be beneficial to maintain neurocognitive development in the patients with MPS II and a DQ score of ≥70, while it may stabilize neurocognitive development in those with a DQ score of <70. The adaptive behavior tests showed stabilization and improvements in communication, daily living skills, and sociality, regardless of the patient's severity. These data suggest that JR-141 may be of therapeutic benefits to MPS II regardless of the hitherto utilized dichotomous disease classification (attenuated or severe).

Intravenous treatment with pabinafusp alfa dose-dependently prevents neurological impairment and bone deformities in a mouse model of mucopolysaccharidosis type II
Presenter: Hideto Morimoto (JCR)

The long-term treatment of MPS II mice with pabinafusp alfa reduced HS concentrations in peripheral and central Nervous system (CNS) tissues, improved histopathological abnormalities in CNS tissues, and suppressed the loss of spatial learning ability, in a similar dose-depending manner. In addition, pabinafusp alfa dose dependently ameliorated skeletal abnormalities. Our results suggest that a BBB-penetrating iduronate-2-sulfatase pabinafusp alfa is effective for the treatment of peripheral (including bone) and CNS manifestations in MPS II. This study also provides nonclinical evidence for a quantitative relationship between a biomarker heparan sulfate(HS) in the CNS and neurological function in MPS II.

JR-171 Presentation

Interim results of a phase 1/2 study of JR-171 (lepunafusp alfa), a novel brain-penetrant enzyme replacement therapy for MPS I
Presenter: Paul Harmatz, M.D. (UCSF Benioff Children's Hospital Oakland, United States)

Interim results are reported on a total of 18 subjects with MPS I enrolled in the ongoing Phase I/II clinical trial of JR-171. Significant reductions in the HS concentrations in the cerebrospinal fluid, a predictive biomarker for the central nervous system symptoms, were observed in all subjects treated with JR-171. In some subjects, neurobehavioral improvements were also reported. Urine and serum HS and dermatan sulfate concentrations, a biomarker for somatic signs and symptoms, are well-controlled after switching from the current enzyme replacement therapy as well as volumes of the liver and spleen. No significant safety concern was observed. These results suggest a potential therapeutic benefit for the treatment of the neurological and somatic symptoms of MPS I.

JR-441 Presentation

Nonclinical pharmacodynamics, pharmacokinetics and safety profiles of anti-human transferrin receptor antibody-fused N-sulfoglucosamine sulfohydrolase for mucopolysaccharidosis type IIIA
Presenter: Asuka Inoue, Ph.D. (JCR)

JR-441 was distributed not only to the peripheral tissues but also to the CNS tissues in mice and monkeys. Intravenous administration of JR-441 decreased HS concentrations in CNS and peripheral tissues in a mouse model of MPS IIIA. Additionally, treatment with JR-441 suppressed progressive glial activation and maintained retinal function in MPS IIIA mice. No test drug-related changes were observed in toxicity studies in monkeys. These results suggest that JR-441 has a potential to exert therapeutic benefit on the CNS and somatic symptoms in patients with MPS IIIA.

JR-471 Datasets

A fusion protein of anti-human transferrin receptor antibody and alfa-L-fucosidase 1 is a prospective candidate for the treatment of the symptoms in CNS and visceral tissues of fucosidosis
Presenter: Eiji Yoden (JCR)

Intravenous administration of JR-471 reduced the substrate accumulated in CNS and peripheral tissues in a mouse model of fucosidosis. Additionally, JR-471 also ameliorated pathological changes such as loss of neuron and neuroinflammation in fucosisdosis mice. These results suggest that JR-471 has a potential to exert therapeutic benefit on the CNS and somatic symptoms in patients with fucosidosis.

International online survey of fucosidosis: Key symptoms and the family experience
Presenter: Kohtaro Hamauchi (JCR)

Fucosidosis is an ultra-rare lysosomal storage disorder, with approximately 120 cased worldwide, while its effective treatment is yet to be established. To understand the impact of fucosidosis on the patients' and the families' expectations for treatment, members of the International Society for Mannosidosis & Related Diseases (ISMRD) and the MPS Society UK were invited to complete an online survey. In total, 28 respondents, almost a quarter of known patients with fucosidosis worldwide, completed the survey from 13 countries. The mean age of living patients was 17.8 years, and among deceased patients, mean age of death was 9.8 years. Fourteen percent of the patients had undergone haematopoietc stem cell transplantation (HSCT). Both untreated and HSCT-treated patients experienced significant functional effects including the inability to speak, loss of cognitive skills, wheelchair use. Irrespective of the patient's age and disease severity, most families regard issues with speech and communication, learning and understanding and mobility as symptoms in critical need of better treatments. These results indicate that patients with fucosidosis experience significant burden due to the disease. Further efforts are urgently needed to reduce disease burden and to improve these patients' quality of life.

Other Programs

Life-span extension in Krabbe disease mice by treatment with a transferrin receptor-targeted galactocerebrosidase
Presenter: Atsushi Imakiire (JCR)

The hTfR-targeted galactocerebrosidase (JBC-GALC) was delivered into the brain by crossing the BBB in mice. Intravenous administration of JBC-GALC gained body weight and prolonged life span in Galc KO mice. Additionally, JBC-GALC suppressed the progression of motor deterioration and histopathological changes in the brain along with the reduction of substrate accumulation in Galc KO mice. These results suggested that JBC-GALC has a potential to exert therapeutic benefit on the severe CNS/peripheral nervous system (PNS) symptoms in patients with Krabbe disease.

Treatment of CLN1 disease with a blood-brain barrier penetrating lysosomal enzyme AGT-194
Presenter: Andreas Hahn M.D., Ph.D. (Department of Child Neurology, Justus-Liebig University Gießen, Gießen, Germany)

Neuronal ceroid lipofuscinosis type 1(CLN1 disease) is a rare autosomal recessive lysosomal storage disease caused by genetic defects of palmitoyl protein thioesterase-1(PPT1), leading to progressive neurodegeneration and early death. Currently, no therapy is available. We report a 68-month-old boy with CLN1 treated on a compassionate use basis weekly for 26 months with the human PPT1 enzyme fused to an anti-human insulin receptor antibody (AGT-194). The CNS symptoms started at 6 months of age with slowing of psychomotor development. At 18 months, a genetic diagnosis of CLN1 disease was made, while treatment-resistant epilepsy started and rapidly exacerbated. At 42 months, weekly intravenous administration of AGT-194 was started and continued without notable safety issues including abnormalities in glucose levels. His general condition slowly improved, while epilepsy became distinctly better controlled, with no generalized seizures observed for more than 12 months. The patient has become emotionally stabilized with improved quality of life. This case documents for the first time that treatment of CLN1 by an intravenous BBB penetrating enzyme replacement therapy. Observed positive findings in efficacy and safety need to be further evaluated in robust clinical trials.

About JR-141 (Pabinafusp Alfa)
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 MPS II. It incorporates J-Brain Cargo®, JCR's proprietary blood-brain barrier (BBB)-penetrating technology, to cross the BBB through transferrin receptor-mediated transcytosis. Its uptake into cells is mediated through the mannose-6-phosphate receptor and the transferrin receptor. This novel mechanism of action is expected to make JR-141 effective against the CNS and somatic symptoms of MPS II. 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. 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 MPS II.[1,2]

In several clinical trials of JR-141, JCR obtained evidence of reducing heparan sulfate (HS) concentration in the CSF, a biomarker used for the assessment of substrate reduction in the CNS; 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] Several studies are currently ongoing to investigate the long-term effect of JR-141 in individuals with MPS II.

JR-141 was approved by the Ministry of Health, Labour and Welfare for the treatment of MPS II 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 global Phase 3 program. The two companies is collaborating to bring this therapy to patients as quickly as possible upon completion of the global Phase 3 program, which is 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 48-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, Hurler-Scheie and Scheie syndrome), MPS II (Hunter syndrome), MPS III A and B (Sanfilippo type A and B), 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

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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.
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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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