News Release

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JCR Pharmaceuticals Co., Ltd.

Translation

JCR Pharmaceuticals' Research Presentations at WORLD*Symposium*™ 2022 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, Feb. 14, 2022 – 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 this week at the 18th Annual WORLD*Symposium*™ in San Diego, Calif., JCR highlighted the potential benefits of therapies that rely on J-Brain Cargo®, a proprietary technology developed by JCR Pharmaceuticals, to deliver medicines across the blood-brain barrier (BBB).

Two of the presentations focused on the long-term safety and efficacy and behavioral effects of JR-141 (pabinafusp alfa 10 mL, intravenous infusion) for mucopolysaccharidosis type II (MPS II, or Hunter syndrome). JR-141 is a recombinant iduronate-2-sulfatase 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.

In addition to the two JR-141 presentations, the WORLD*Symposium*™ 2022 scientific program featured presentations focusing on:

- the neurological benefits of JR-171 observed in a mouse model MPS I (Hurler syndrome or Hurler-Scheie syndrome);
- updated safety, pharmacokinetics (PK), and efficacy data from a global Phase 1/2 trial of JR-171 in patients with MPS I;
- efficacy of JR-441 in a mouse model of MPS IIIA (Sanfilippo syndrome type A); and
- preclinical data from an early-stage research and development program in Fabry disease.

The MHLW approved IZCARGO® for the treatment of MPS II based on results from clinical trials conducted in Japan and Brazil, in which JR-141 markedly decreased concentrations of heparan sulfate (HS, a biomarker for assessing the drug's effectiveness in reducing disease-causing substrate in the central nervous system)) in the cerebrospinal fluid (CSF). The trial also confirmed a decrease of dermatan sulfate (DS) concentration in blood in ERT-naïve participants, and stabilization in patients switched from standard ERT to JR-141, while also demonstrating a neurocognitive benefit in patients with both severe and attenuated disease.

Based on these clinical results and the approval of IZCARGO® by the MHLW in Japan, organizers of the WORLD*Symposium*™ 2022 organizers honored JCR with the New Treatment Award for IZCARGO®.The award recognizes approval of new treatments that are viewed as providing value to patients with LSDs.

JR-141 Datasets

The following WORLD*Symposium*™ 2022 poster presentations provide additional evidence and context for the use of JR-141 in the treatment of MPS II:

***Long term efficacy and safety of pabinafusp-alfa (JR-141) in Hunter syndrome (MPS-II): 104-week data from the clinical trials in Japan and Brazil* (Abstract 99)**
Presenter: Roberto Giugliani, M.D., Ph.D. (Federal University of Rio Grande do Sul, Brazil)

Clinical trials of JR-141 were conducted in Japan and Brazil to treat MPS II (Hunter Syndrome).
In Japan, 2.0 mg/kg of JR-141 were weekly administered for 52 weeks, while, in Brazil, weekly doses of either 1.0, 2.0, or 4.0 mg/kg were administered for 25 weeks. Weekly administrations at 2.0 mg/kg were continued in the extension study in both countries. We report here the 104-week long-term data on the efficacy and safety of JR-141.
CSF HS concentrations decreased and remained low in all MPS II patients, most of whom showed developmental age either increased or sustained over a long period of time. The adult non-neuronopathic patients, in particular, markedly improved in neurocognitive functions. Liver and spleen volumes in the patients switching from the standard enzyme replacement therapy (ERT) to JR-141 remained stable, while they decreased after the JR-141 treatment in the naïve patients without prior ERT. No safety concerns were observed. These results demonstrate the long-term efficacy and safety of JR-141 for the MPS II patients with both central nervous system and somatic symptoms.

***Behavioral improvement in a 9-year-old patient with MPS II undergoing enzyme replacement therapy with pabinafusp alfa: A case report* (Abstract 289)**
Presenter: Carolina Souza, M.D., Ph.D. (Serviço de Genética Médica, Hospital das Clínicas de Porto Alegre, Brazil)

A 9-year-old boy was diagnosed with MPS II at 2 years of age and started conventional ERT with idursulfase. However, his neuropsychological symptoms progressed with age, along with the development of seizures and bilateral hearing loss at the age of 4 years and 6 years, respectively. At 6 years of age, he was subsequently enrolled in a clinical trial of JR-141. After 24 months of the treatment with JR-141, the patient was seizure-free, less agitated, improved social interactions and better understood orders. These preliminary findings indicate that JR-141 potentially improves behavioral and neuropsychological symptoms in patients with severe MPS II with positive impacts on the quality of life.

JR-171 Datasets

The following poster presentations focused on the use of JR-171 in the treatment MPS I:

***Enzyme replacement with a blood-brain barrier-penetrating antibody-fused alpha-L-iduronidase prevents neurobehavioral performance of mucopolysaccharidosis type I mice* (Abstract 205)**
Presenter: Hideto Morimoto (JCR)

Long-term treatment of JR-171 reduced GAG deposition in the CNS and peripheral tissues in the mouse model of MPS I, resulting in suppressing neurodegeneration and subsequent neurocognitive impairment. These results suggest therapeutic potentials of JR-171 for CNS symptoms of MPS I patient.

***A phase I/II clinical study of intravenous administration of JR-171, a blood-brain barrier-crossing enzyme, in mucopolysaccharidosis type I: An update* (Abstract 113)**
Presenter: Takashi Hamazaki, M.D., Ph.D. (Osaka City University Graduate School of Medicine, Japan)

The Phase I/II study for MPS I (Hurler, Hurler-Scheie and Scheie syndrome) is ongoing as a global, open-label, multicenter clinical trial. This report presents the preliminary 12-week results in the pediatric patients who completed part 2 of the study. Heparan sulfate concentrations in the cerebrospinal fluid, a biomarker for the central nervous system symptoms, markedly decreased by JR-171. No safety concerns were observed.

Other JCR Datasets

In addition to the above presentations on JR-141 and JR-171, JCR researchers presented the following posters showcasing the company's pipeline of innovative, BBB-penetrating ERT products for the treatment of other LSDs:

- ***Efficacy of an anti-human transferrin receptor antibody-fused N-sulfoglucosamine sulfohydrolase in mucopolysaccharidosis type IIIA mice* (Abstract 135)**:
  Presenter: Asuka Inoue, Ph.D. (JCR)

  Intravenous administration of JR-441 decreased HS concentrations in the CNS and peripheral tissues in the mouse model of MPS IIIA. Additionally, treatment with JR-441 was associated with the suppression of progressive microglial activation and partial recovery of retinal function. The results suggest potential therapeutic benefits of JR-441 on CNS symptoms in patients with MPS IIIA.

- ***Suppression of anti-alpha-GalA antibody production by blockade of T-cell costimulation in mice* (Abstract 89):**
  Presenter: Tomoki Fukatsu (JCR)

  Recombinant human α-GalA for the treatment of patients with Fabry disease has been known to develop anti-drug antibodies (ADA) by chronic administration, leading to a decrease in the efficacy of the drugs in a subset of patients. mCTLA4-mFc (inhibitor of CD80/86 and CD28), anti-CD40L (CD154) scFv-mFc (inhibitor of CD40 and CD40L), or their combination was injected intraperitoneally to examine their effects on anti-α-GalA antibody production in mice. ADA production was almost completely blocked by the treatment with a higher dose of mCTLA4-mFc or anti-CD40L (CD154) scFv-mFc alone or their combination. At a lower dose, however, mCTLA4-mFc alone, but not anti-CD40L (CD154) scFv-mFc alone, suppressed ADA production. The results suggest that the blockade of T-cell co-stimulation, especially by the inhibition of CD80/86-CD28 interaction with mCTLA4-mFc, can reduce anti-α-GalA antibody production.

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.

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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.

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

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