News Release

September 8, 2025
JCR Pharmaceuticals Co., Ltd.

JCR Pharmaceuticals Presents Long-Term Clinical Data on Pabinafusp Alfa for the Treatment of Mucopolysaccharidosis Type II (MPS II) at ICIEM 2025

– Oral Presentation Highlights Long-Term Neurocognitive Benefits of Pabinafusp Alfa for Patients with MPS II –

– Additional Posters Underscore Broad Potential of J-Brain Cargo® Platform, Including Preclinical Data for Pabinafusp Alfa in MPS II and Nonclinical Data for JR-446 in MPS IIIB –

Hyogo, Japan – **September 8, 2025** – JCR Pharmaceuticals Co., Ltd. (TSE 4552; "JCR"), a global biopharmaceutical company dedicated to developing therapies for rare and genetic diseases, presented new data from its pipeline of brain-penetrant enzyme replacement therapies at the 15th International Congress of Inborn Errors of Metabolism (ICIEM) in Kyoto, Japan, held September 2-6, 2025. Key findings included five-year clinical data demonstrating sustained neurocognitive and somatic benefits of pabinafusp alfa (JR-141) in patients with mucopolysaccharidosis type II (MPS II, or Hunter syndrome), suggesting improvements in patients treated prior to significant neuronopathy and stabilization in those with advanced disease. Additional posters highlighted five years of safety data of pabinafusp alfa in MPS II, preclinical cardiovascular effects of pabinafusp alfa in MPS II, and nonclinical efficacy of JR-446, an investigational therapy for mucopolysaccharidosis type IIIB (MPS IIIB, also known as Sanfilippo syndrome type B).

"The data presented at ICIEM add to the growing body of clinical evidence and real-world experience supporting pabinafusp alfa as the first approved treatment in Japan to cross the blood-brain barrier and address the central nervous system complications of MPS II," said Shin Ashida, Chairman, President, and CEO of JCR Pharmaceuticals. "We look forward to bringing this treatment to more patients worldwide through planned regulatory submissions. Our work continues across a broad range of lysosomal storage disorders, leveraging our proprietary J-Brain Cargo® technology to deliver therapies that target neurological symptoms by penetrating the blood-brain barrier."

Pabinafusp alfa, approved and marketed only in Japan as IZCARGO®, is a recombinant fusion protein of an antibody against the human transferrin receptor (hTfR) and iduronate-2-sulfatase, the enzyme that is missing or malfunctioning in people with MPS II. Developed using JCR's proprietary J-Brain Cargo® technology, pabinafusp alfa is designed to cross the blood-brain barrier (BBB) and deliver enzyme replacement therapy (ERT) directly to the central nervous system (CNS) to address the neurological symptoms of the disease.

JCR showcased the following presentations at ICIEM 2025:

Long-term (up to 5 years) efficacy of pabinafusp alfa on neurocognition in patients with mucopolysaccharidosis type II – a pooled,* post hoc *analysis of clinical trials (Oral Presentation 24)
Presenter: Roberto Giugliani, M.D., Ph.D. (Federal University of Rio Grande do Sul, Brazil)

In this oral presentation, researchers reported that patients treated with pabinafusp alfa experienced a long-term (up to five years) reduction in cerebrospinal fluid (CSF) heparan sulfate (HS) levels, a relevant biomarker reasonably likely predict clinical benefit in neuronopathic MPS disorders.Treatment with pabinafusp alfa was associated with improvements in neurocognition and adaptive behavior when administration began before evidence of significant neuronopathy and mean change from baseline (CFB) in cognitive scores continued to improve as studies progressed in these patients.

In a longitudinal, integrated, *post hoc* analysis of 63 patients with attenuated or severe MPS II receiving weekly doses of pabinafusp alfa (2.0 mg/kg) in five open-label trials, the researchers observed rapid and sustained decreases in CSF HS levels by week 13; the decrease was maintained until the end of follow-up and was evident regardless of previous exposure to ERT. The researchers also reported a rapid and sustained decrease in levels of serum dermatan sulfate (DS, another MPS II biomarker) in previously untreated patients, while DS levels remained stable compared to baseline levels in patients previously treated with standard ERT (or idursulfase).

Over the 261 weeks follow up, marked improvement was observed in mean change from baseline (CFB) in the raw scores of two validated measures of neurocognition and adaptive behavior -- the Bayley Scales of Infant and Toddler Development, third edition (BSID-III) and the Vineland Adaptive Behavior Scales, second edition (VABS-II) – in the severe patient population with a developmental quotient (DQ) of 55 or greater, and those younger than 30 months of age at baseline. These patients also experienced greater CFB in VABS-II scores compared to those with a DQ below 55 or those aged 30 months or older.

No new significant safety concerns emerged during the follow-up period. Most treatment-emergent adverse events (TEAEs) and infusion-associated reactions (IARs) were mild in severity.

“MPS II is a devastating, life-threatening lysosomal storage disorder that can significantly impact patients’ neurocognitive development, independence, and quality of life,” said Roberto Giugliani, M.D., Ph.D., *Federal University of Rio Grande do Sul, Brazil*. “These long-term results further reinforce the safety and efficacy of pabinafusp alfa and suggest that early treatment may offer meaningful neurocognitive benefits for patients living with this complex disease.”

Long-term safety of pabinafusp alfa in patients with mucopolysaccharidosis type II: interim 5-year data from a clinical trial in Japan (P-306)
Presenter: Norio Sakai (Center for Promoting Treatment of Intractable Diseases, ISEIKAI International General Hospital, Osaka, Japan)

Investigators reported five-year follow-up data on pabinafusp alfa in patients with MPS II, and they did not find any new significant safety concerns in severe or attenuated patients with MPS II who received at least one dose of pabinafusp alfa in a phase 2/3 study and continued in an open-label extension trial. The most frequently reported adverse events (AEs) were pyrexia (77.8%), upper respiratory tract infection (63.0%), nasopharyngitis (63.0%), otitis media (55.6%), and gastroenteritis (51.9%). The number of treatment-related adverse events and infusion-associated

reactions (IARs) per patient per year declined over the study period. There were no clear relationships between anti-pabinafusp alfa antibodies and IARs or reductions in CSF HS levels.

Therapeutic effect of JR-141 (pabinafusp alfa) on cardiovascular system in a mouse model of mucopolysaccharidosis type II (P-311)
Presenter: Kenta Arisumi (JCR Pharmaceuticals)

Researchers reported that early intervention with pabinafusp alfa may prevent cardiovascular disease progression in a mouse model of MPS II. Chronic, once-weekly treatment with pabinafusp alfa for 40 weeks (from 10 to 50 weeks of age) resulted in dose-dependent corrections in HS and DS levels in cardiovascular tissues, with marked improvement observed in mice receiving a 2.0 mg/kg dose. Cardiovascular function in the 2.0 mg/kg dosing cohort was assessed by ejection fraction, aortic dilation, and aortic regurgitation; cardiac function was not statistically different from what was observed in a control group of healthy mice.

Nonclinical pharmacology of JR-446, a novel blood-brain barrier penetrant α-N-acetylglucosaminidase (BP-15)
Presenter: Jun Ito (JCR Pharmaceuticals)

In a mouse model of MPS IIIB, administration of JR-446 – blood brain barrier penetrant human α-N-acetylglucosaminidase (NAGLU) – resulted in statistically significant decreases in HS, GM2 and GM3 gangliosides concentrations in the CNS tissues compared to vehicle-treated the disease model mice. JR-446 also suppressed the development of histological changes in the brains of MPS IIIB mice. Importantly, the performance of JR-446-treated MPS IIIB mice on the neurobehavioral test – a tool for assessing the cognitive functions associated with diseases – was comparable with that of vehicle-treated MPS IIIB mice, suggesting preservation of learning and memory function in the disease model mice. According to the investigators, the results provide non-clinical evidence supporting the clinical application of JR-446 for the treatment of MPS IIIB patients.

Post-marketing surveillance of pabinafusp alfa for the treatment of mucopolysaccharidosis type II: an interim report up to 4 years (Abstract 11285)
Presenter: Shungo Okamoto (Osaka Metropolitan University)

In an interim analysis of a general drug-use results survey administered as part of JCR's post-marketing surveillance commitment following approval of IZCARGO® in Japan, treatment with pabinafusp alfa for MPS II was well tolerated and no new safety signals were reported. JCR will continue to study the safety and effectiveness of IZCARGO® in patients with MPS II receiving commercial drug until 2030.

About the International Congress of Inborn Errors of Metabolism (ICIEM) 2025
The International Congress of Inborn Errors of Metabolism (ICIEM) is a major international conference held every four years, focusing on the study and treatment of inherited metabolic disorders. ICIEM conferences bring together researchers, clinicians, and other professionals to discuss the latest advancements in the field of inborn errors of metabolism.

About the J-Brain Cargo® Platform Technology
JCR Pharmaceuticals has developed a proprietary blood-brain barrier (BBB)-penetrating technology, J-Brain Cargo®, to bring biotherapeutics into the central nervous system (CNS). The first drug developed based on this technology is IZCARGO® (INN: pabinafusp alfa), which is

approved in Japan for the treatment of MPS II (mucopolysaccharidosis type II). 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 Pabinafusp Alfa (JR-141)
Pabinafusp alfa is a recombinant fusion protein of an antibody against the human transferrin receptor and iduronate-2-sulfatase, the enzyme that is missing or malfunctioning in subjects with Hunter syndrome. It incorporates J-Brain Cargo®, JCR's proprietary blood-brain barrier (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 central nervous system (CNS) symptoms of Hunter syndrome.

In pre-clinical trials, 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 of pabinafusp alfa, JCR obtained evidence of reducing heparan sulfate concentrations in the cerebrospinal fluid, a biomarker for assessing effectiveness against CNS symptoms; these results were consistent with those obtained in pre-clinical studies.[3] Clinical studies have also demonstrated the positive effects of pabinafusp alfa on CNS symptoms.[4,5,6]

Pabinafusp alfa was approved in Japan by the Ministry of Health, Labour and Welfare and marketed since May 2021 under the brand name "IZCARGO® I.V. Infusion 10mg."

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 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. A 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 JR-446
JR-446 is a fusion protein consisting of a fragment of human transferrin receptor (hTfR) antibody and modified human α-N-acetylglucosaminidase (NAGLU) and is a novel drug in development for the treatment of mucopolysaccharidosis type IIIB (MPS IIIB), also known as Sanfilippo syndrome type B. It was developed using JCR Pharmaceuticals' proprietary J-Brain Cargo® technology and is currently in phase 1/2 clinical trials in Japan. JR-446 has been granted Orphan Drug Designation (ODD) by both the US Food and Drug Administration and the European Commission. In September 2023, MEDIPAL and JCR entered into a licensing agreement in which MEDIPAL will commercialize JR-446 for MPS IIIB outside of Japan. In addition, MEDIPAL will support JCR in the clinical development of JR-446 in Japan, including the distribution of investigational drugs, disease awareness, and clinical trial advancement.

About Mucopolysaccharidosis Type II (Hunter Syndrome)
Mucopolysaccharidosis type II (MPS II, or Hunter syndrome) is an X-linked recessive lysosomal storage disorder 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 2,000-3,000 individuals worldwide (according to JCR research), is almost exclusively found in boys, although it occasionally affects girls. The disease gives rise to a wide range of somatic (affecting various body systems and tissues) and neurological symptoms.

MPS II disease onset usually occurs between the ages of 2 and 4 years. Affected children generally show signs of developmental decline between the ages of 18 and 36 months, followed by progressive loss of skills. Other notable symptoms can include hydrocephalus (increased pressure in the skull), joint stiffness, visual impairment, and progressive hearing loss.[7]

The current standard of care for Hunter syndrome is enzyme replacement therapy (ERT). However, ERT does not address the central nervous system (CNS)-related symptoms of the disease, underscoring the need for a therapy that targets both the somatic and neurological symptoms of MPS II.

About Mucopolysaccharidosis Type IIIB (Sanfilippo Syndrome Type IIIB)

Mucopolysaccharidosis type IIIB (MPS IIIB, or Sanfilippo syndrome type IIIB) is a rare lysosomal storage disorder caused by mutations in the gene that encodes for α-N-acetylglucosaminidase (NAGLU), an enzyme that breaks down heparan sulfate (HS), a type of glycosaminoglycan (mucopolysaccharide). The resulting aggregation of HS within cell lysosomes leads to progressive and severely debilitating neurological dysfunction.[7]

MPS IIIB is characterized by behavioral changes, sleep disorders, cognitive changes (including memory loss and intellectual disability), hearing loss, and impaired vision. Children with MPS IIIB may also experience seizures and difficulty walking as well as delayed cognitive and motor skill development.[8] MPS IIIB affects an estimated 500 to 1,000 individuals worldwide, based on data from Japan's Ministry of Health, Labour and Welfare, as well as JCR research.

About JCR Pharmaceuticals Co., Ltd.

JCR Pharmaceuticals Co., Ltd. (TSE 4552) is a global specialty pharmaceutical company that develops treatments that go beyond rare diseases to solve the world's most complex healthcare challenges. We continue to build upon our 50-year legacy in Japan while expanding our global footprint into the U.S., 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, MPS II (Hunter syndrome), 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, MPS IIIA and B (Sanfilippo syndrome type A and B), and more. Our core values – Putting people first, Forging our own path, Always advancing, and Committed to excellence – mean that the work we do benefits all our stakeholders, including partners, patients and employees. We strive to expand the possibilities for patients while accelerating medical advancement at a global level. For more information, please visit JCR's global website: https://jcrpharm.com/.

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.

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