



July 29, 2021  
JCR Pharmaceuticals Co., Ltd.

Translation

**JCR Pharmaceuticals Announces Presentation  
at 16<sup>th</sup> International Symposium on MPS and Related Diseases.**

Jul. 29 -- JCR Pharmaceuticals Co., Ltd. (TSE 4552; Chairman and President: Shin Ashida; “JCR”) announced today that it has given two oral and three poster presentations at the 16<sup>th</sup> International Symposium on MPS and Related Diseases (July 23-25, 2021). These presentations highlight JCR’s development pipeline for lysosomal storage disorders which apply the J-Brain Cargo<sup>®</sup>, JCR’s proprietary BBB technology.

A summary of the article is as follows.

Oral presentations

Title
Enzyme replacement therapy with pabinafusp alfa (JR-141) for neuropathic and non-neuropathic MPS-II: a report on integrated efficacy and safety data from three clinical trials in Japan and Brazil.
Phase I/II clinical trial for mucopolysaccharidosis type I with an intravenously administered blood-brain barrier-crossing enzyme (JR-171): preliminary results.

Poster presentations

Title
Efficacy and safety of a blood-brain barrier-penetrable antibody-fused alfa-L-iduronidase in non-clinical studies
Neurologic and systemic effectiveness of a blood-brain barrier-penetrable N-sulfoglucosamine sulfohydrolase in a mouse model of Mucopolysaccharidosis IIIA
Therapeutic effects of a blood-brain barrier-penetrable $\alpha$ -N-acetylglucosaminidase in a mouse model of Mucopolysaccharidosis IIIB

Code	Title
JR-141	Enzyme replacement therapy with pabinafusp alfa (JR-141) for neuropathic and non-neuropathic MPS-II: a report on integrated efficacy and safety data from three clinical trials in Japan and Brazil

### Outline

Clinical trials of JR-141 were conducted in Japan and Brazil to treat MPS II (Hunter Syndrome). In Japan, weekly doses of 2.0 mg/kg were administered for 52 weeks and in Brazil, weekly doses of either 1.0, 2.0, or 4.0 mg/kg were administered for 25 weeks. Continued weekly doses of 2.0 mg/kg were administered for the extension study in both countries. The following is a report of results including long-term data, focusing on the efficacy of JR-141 treating central nervous symptoms.

### Summary of results

- Cerebrospinal fluid (CSF) heparan sulfate (HS) concentrations decreased in all MPS II subjects treated with weekly doses of 2 mg/kg of JR-141, regardless of disease phenotype.
- For most MPS II patients, developmental age either increased or sustained over a long period of time. Particularly for MPS II patients starting JR-141 treatment from an early age, normal development continued. Behavioral improvements such as expanded vocabulary as well as improvement of agitation and socialization were reported.
- Liver and spleen volumes in patients switching from standard enzyme replacement therapy (ERT) to JR-141 remained stable.. For naïve patients who have not been treated with current ERT, liver and spleen volumes decreased after JR-141 treatment.
- JR-141 was generally well tolerated up to 104 weeks. Serious adverse events related to JR-141 were not reported.
- Based on the results above, long-term safety and efficacy of JR-141 were confirmed for the treatment of MPS II patients with central nervous and somatic symptoms. A global phase III study will be initiated to confirm efficacy of JR-141 in comparison to standard somatic ERT.

Code	Title
JR-171	Phase I/II clinical trial for mucopolysaccharidosis type I with an intravenously administered blood-brain barrier-crossing enzyme (JR-171): preliminary results.

### **Outline**

The Phase I/II study for MPS I (Hurler, Hurler-Scheie and Scheie syndrome) is ongoing as a global, open-label, multicenter clinical trial. In part 1, 4 adult MPS I subjects have been administered JR-171. The preliminary results of part 1 were presented.

### **Summary of results**

- In part 1, 4 adult MPS I subjects were intravenously administered with JR-171 in a dose-escalation manner for 4 weeks.
- All 4 subjects were attenuated type (Scheie syndrome), and have been previously treated with enzyme replacement therapy.
- Pharmacokinetic evaluation demonstrated dose-dependent increase in plasma concentration, and JR-171 was undetectable the day after administration.
- Heparan sulfate concentration in cerebrospinal fluid, a biomarker for the central nervous system symptoms, decreased by JR-171 in all 4 subjects. (the average reduction was 65%).
- Heparan sulfate and dermatan sulfate concentrations in serum, biomarkers for the somatic disease control, remained stable throughout the study period.
- No safety concerns were revealed so far and part 2 of the study is ongoing.

Code	Title
JR-171	Efficacy and safety of a blood-brain barrier-penetrable antibody-fused alfa-L-iduronidase in non-clinical studies

#### Outline

Mucopolysaccharidosis I (MPS I) is caused by defects in  $\alpha$ -L-iduronidase (IDUA), leading to accumulation of glycosaminoglycans (GAGs) including heparan sulfate (HS) and dermatan sulfate (DS) in cells throughout the body. Enzyme replacement therapy for MPS I is currently available but does not address the neurological symptoms as the enzyme does not cross the blood-brain barrier. JCR developed JR-171, a fusion protein consisting of anti-human transferrin receptor (hTfR) antibody moiety and human IDUA, which can cross the BBB by transferrin receptor-mediated transcytosis. The aim of this study was to elucidate the efficacy and safety of JR-171 in Hurler mice and monkeys.

#### Summary of results

JR-171 distribution to the brain as well as to peripheral tissues of the mice and monkeys was demonstrated. Repeated administration of JR-171 reduced substrate accumulated in CNS and peripheral tissues of a mouse model of MPS I. JR-171 also suppressed histopathological changes observed in CNS tissues of the MPS I mice. In a repeated-dose toxicity study of JR-171 in monkeys, no toxic findings were observed. These results indicate that JR-171 has therapeutic potential to treat neurologic and somatic symptoms of MPS I and can be safely administered to individuals with MPS I.

Code	Title
JR-441	Neurologic and systemic effectiveness of a blood-brain barrier-penetrable N-sulfoglucosamine sulfohydrolase in a mouse model of Mucopolysaccharidosis IIIA

#### Outline

Mucopolysaccharidosis type IIIA (MPS IIIA, also known as Sanfilippo syndrome type A) is caused by genetic defect of N-sulfoglucosamine sulfohydrolase (SGSH) gene, leading to accumulation of glycosaminoglycan heparan sulfate (HS) throughout the body, followed by severe neurological symptoms along with several somatic symptoms. There is no specific treatment for MPS IIIA approved at present. JCR developed JR-441, a fusion protein consisting of a Fab fragment of an anti-human transferrin receptor (hTfR) antibody and SGSH, which has potential to cross the blood-brain barrier, by transferrin receptor-mediated transcytosis. The aim of this study was to evaluate the biodistribution and pharmacodynamics of JR-441 in mice and monkeys.

#### Summary of results

JR-441 was detected in the brain as well as in peripheral tissues of the hTfR-KI mice and cynomolgus monkeys after a single intravenous dose. Immunohistochemical analysis showed that JR-441, but not rhSGSH, was delivered to neuronal cells. Progressive microglial activation in the CNS observed in hTfR-KI/Sgsh-KO mice was fairly suppressed when treated with JR-441. Moreover, JR-441 markedly reduced HS concentrations in both CNS and peripheral tissues. These data suggested that enzyme-replacement therapy with JR-441 is a promising approach for the treatment of central nervous and somatic symptoms in patients with MPS IIIA.

Code	Title
JR-446	Therapeutic effects of a blood-brain barrier-penetrable $\alpha$ -N-acetylglucosaminidase in a mouse model of Mucopolysaccharidosis IIIB

### Outline

Mucopolysaccharidosis type IIIB (MPS IIIB, also known as Sanfilippo syndrome type B) is caused by mutations in  $\alpha$ -N-acetylglucosaminidase (NAGLU) gene, leading to accumulation of glycosaminoglycan heparan sulfate (HS) throughout the body, followed by mild somatic features and severe neurological diseases. There is no definite treatment available for MPS IIIB patients so far. We have developed JR-446, a fusion protein consisting of Fab fragment of anti-human transferrin receptor (hTfR) antibody and NAGLU, which has potential to cross the BBB, by transferrin receptor-mediated transcytosis.

### Summary of results

After a single intravenous administration, JR-446 was detected in the brain as well as in peripheral tissues of hTfR-KI mice. Distribution of the drug to the brain was also confirmed in cynomolgus monkeys after a single intravenous dose. When administered repeatedly to hTfR-KI/Naglu-KO mice, an animal model of MPS IIIB, JR-446 markedly reduced HS concentrations in both CNS and peripheral tissues. JR-446 treatment also suppressed histopathological changes in the brain of MPS IIIB mice. These results suggest that JR-446 has a potential to exert therapeutic effects on the CNS signs and symptoms in patients with MPS IIIB.

### 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, Hurler-Scheie and Scheie 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.*

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