JCR Pharmaceuticals

ABSTRACT SUMMARY

WORLD*Symposium*™ 2022

JCR Pharmaceuticals Co., Ltd. is a global specialty pharmaceuticals company that is redefining expectations and expanding possibilities for people with rare and genetic diseases worldwide.

Please note that the therapies mentioned within these abstracts are investigational therapies and are not approved for commercial use. Any information on the investigational therapies contained herein is not intended to provide medical advice, nor should it be used as a substitute for the advice provided by your physician or other healthcare providers. Please visit the JCR Pharmaceuticals website for more information.

At WORLD*Symposium*™ 2022, JCR Pharmaceuticals is pleased to present a total of six abstracts focusing on investigational therapies intended to treat lysosomal storage disorders (LSDs).

Abstract for JR-141 (pabinafusp alfa, for the treatment of patients with MPS II)

Abstract 99:

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 (Giugliani et al.)

The clinical trials of JR-141 in Japan and Brazil have provided positive results suggesting efficacy against both somatic and central nervous system (CNS) symptoms, leading to its approval in Japan, along with a new drug application in Brazil. It has been clinically evaluated in a total of 46 patients in Japan and Brazil, generating 104-week efficacy and safety data for analysis so far. In the phase 2/3 study and the subsequent extension study of JR-141 in Japan, 2.0 mg/kg of JR-141 was weekly intravenously administered to 28 patients, while the phase 2 study and the subsequent extension study in Brazil tested 3 weekly dose levels (1.0, 2.0 and 4.0 mg/kg in the former, then 2.0mg/kg in the latter) of JR-141 intravenously administered to 20 patients. The study results suggest that JR-141 can address both CNS and somatic symptoms in MPS-II and is thus a novel treatment for neuronopathic MPS in particular, as the conventional enzyme replacement therapy (ERT) is not able to cross the blood-brain barrier (BBB) and reach the CNS.

Abstract 289:

Behavioral improvement in a 9-year-old patient with MPS II undergoing enzyme replacement therapy with pabinafusp alfa: A case report (Souza et al.)

This case report focuses on a nine-year-old male patient diagnosed with mucopolysaccharidosis II (MPSII). Enzyme replacement therapy with idursulfase was subsequently initiated, but psychomotor agitation, hyperactivity, and attention deficits progressed, while urinary glycosaminoglycans (uGAGs) remained above normal (166 ug/mg creatinine; age-related range: 53-115). The patient was subsequently enrolled in a clinical trial to receive pabinafusp alfa, an enzyme known to cross the blood-brain barrier to address neurodegeneration. After 24 months of treatment, the patient was seizure-free, less agitated with improved social interactions. The median uGAGs decreased to the reference range (104 ug/mg creatinine). The patient became more collaborative and started to better understand orders. These preliminary findings indicate that pabinafusp alfa may improve behavior of the patients with severe MPSII and positively impact the quality of life not only of those patients but also of their caregivers.

For more information:

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Abstracts for JR-171 (lepunafusp alfa, in development for the treatment of patients with MPS I)

Abstract 205:

Enzyme replacement with a blood-brain barrier-penetrating antibody-fused α-L-iduronidase prevents neurobehavioral performance of Mucopolysaccharidosis I mice (Morimoto et al.)

JR-171 has been shown to be distributed to the brain as well as to peripheral tissues and decreased heparan sulfate (HS) and dermatan sulfate (DS) concentrations in anti-human transferrin receptor (hTfR) knock-in/Idua-knockout (hTfR-KI/Idua-KO) mice, an animal model of MPS I. Here we report histopathological and neurobehavioral analyses in hTfR-KI/Idua-KO mice after chronic treatment of JR-171. Histopathological changes in the brain observed in untreated MPS I mice were suppressed by JR-171. Untreated MPS I mice were found to have deficient spatial learning ability in the Morris water maze test. Although rhIDUA failed to affect the ability, the mice treated with JR-171 showed comparable neurobehavioral performance to wild-type mice. Based on these results, JR-171 is expected to be effective in MPS I patients with CNS symptoms.

Abstract 113:

A phase I/II clinical study of intravenous administration of JR-171, a blood-brain barrier-crossing enzyme, in mucopolysaccharidosis type I: an update (Hamazakia et al.)

In this abstract, we report the first-in-human, open-label, multicenter phase I/II trial to evaluate its safety, pharmacokinetics, and efficacy in individuals with MPS I. In Part 1 of the phase I/II trial, 4 subjects previously receiving ERT with laronidase age 18 years or older without cognitive impairments were switched to JR-171 for 4 weeks in a dose-escalation manner. There were no serious adverse events observed in any of the subjects. All four patients showed reductions in heparan sulfate (HS) concentrations in the cerebrospinal fluid, indicating successful delivery of JR-171 across the BBB. Serum and urine heparan sulfate and dermatan sulfate concentrations remained stable with no significant change from laronidase treatment. Part 2 of the phase I/II trial has been initiated with a 12-week administration of JR-171 to patients with MPS I, including pediatric patients. Upon completion of Part 2, all subjects will be offered the option to enroll in an extension study, which will provide further insights into the long-term efficacy and safety of JR-171.

Abstracts for JR-441 (in development for the treatment of patients with Sanfilippo syndrome type A, or MPS IIIA)

Abstract 135:

Efficacy of an anti-human transferrin receptor antibody-fused N-sulfoglucosamine sulfohydrolase in Mucopolysaccharidosis IIIA mice (Inoue et al.)

Here we report the efficacy of JR-441 in hTfR-knock-in/Sgsh-knockout (hTfR-KI/Sgsh-KO) mice, an animal model of MPS IIIA, in terms of HS concentration, histopathology, and retinal function. JR-441 was repeatedly administered intravenously to hTfR-KI/Sgsh-KO mice and was found to decrease HS concentrations in central nervous system (CNS) as well as peripheral tissues, suggesting that the fusion protein has potential to exert beneficial effects on CNS disease in MPS IIIA. In accordance with this finding, a progressive microglial activation in the brain observed in MPS IIIA mice was fairly suppressed when treated with JR-441. Moreover, we found that retinal function assessed by ERG was impaired in MPS IIIA mice compared with wild-type mice. The function was recovered at least partly by the treatment with JR-441. These results suggest that intravenous enzyme-replacement therapy with JR-441 would be a promising approach for the treatment of patients with MPS IIIA.

Abstract for Early-Stage Research and Development Program (in development for the treatment of patients with Fabry disease)

Abstract 89:

Suppression of anti-α-GalA antibody production by blockade of T-cell costimulation in mice (Fukatsu et al.)

One of the burdens of the use of biopharmaceutical products is the development of anti-drug antibodies (ADA), which may decrease the efficacy of the drugs, in a subset of patients. Recombinant human α-GalA for treating patients with Fabry disease has also been known to develop ADA by chronic administration. We found that 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. Our results indicate that the blockade of T-cell costimulation, especially by inhibition of CD80/86-CD28 interaction with mCTLA4-mFc, can reduce anti-α-GalA antibody production.

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We continue to make progress with our investigational therapy JR-141 for the treatment of patients with mucopolysaccharidosis II (MPS II, Hunter syndrome). In December 2020, we filed an application for marketing approval of JR-141 in Brazil, which, when accepted, will mark our first approved therapy outside of Japan. JCR is currently conducting a Phase 3 trial for JR-141 in the US, UK, Brazil, Germany, France, and Spain.

Additionally, we continue to move forward with our investigational therapy JR-171 for the treatment of patients with mucopolysaccharidosis I (MPS I, Hurler Syndrome). JCR is conducting a Phase 1/2 clinical trial of JR-171. We are also developing therapies for patients with LSDs, including Pompe disease, MPS IIIA (Sanfilippo A), and MPS IIIB (Sanfilippo B).

Our first-in-class proprietary technology, **J-Brain Cargo®**, enables us to develop therapies that cross the cross the BBB and penetrate the CNS. With J-Brain Cargo®, we seek to address the unresolved clinical challenges of LSDs by delivering the enzyme to both the body and the brain. We strive to expand the possibilities for patients while accelerating medical advancement at a global level.

Together we soar.

At JCR, we continue to build upon our 46-year legacy in Japan while expanding our global footprint with clinical trials in the **US, Europe,** and **Latin America**. We are applying our scientific expertise and unique technologies to research, develop, and deliver next-generation therapies to patients with LSDs.

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