Phase I/II Clinical Trial Design for a Novel Therapy for Mucopolysaccharidosis Type I with an Intravenously Administered Blood-Brain Barrier-Crossing Enzyme (JR-171)

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Introduction

Mucopolysaccharidosis type I (MPS I)

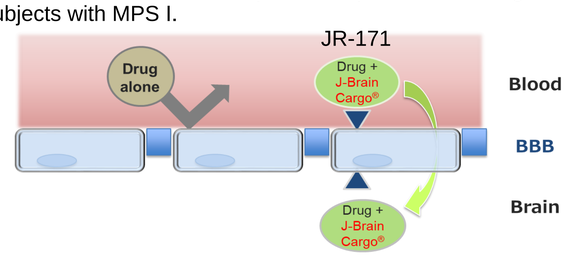
- MPS I is an autosomal recessive lysosomal storage disease characterized by missing or malfunctioning α-L-iduronidase (IDUA). GAGs, e.g. heparan sulfate (HS) and dermatan sulfate (DS), accumulate in various tissues and organs causing various symptoms. MPS I is classified into three forms.

Classification	Syndrome	Severity	CNS symptom
MPS I H	Hurler syndrome	Severe	Yes
MPS I H/S	Hurler-Scheie syndrome	Attenuated	Mild/No
MPS I S	Scheie syndrome	Attenuated	No

- Attenuated MPS I is usually treated with enzyme replacement therapy (ERT). Hematopoietic stem cell transplantation (HSCT) is only indicated for individuals with severe MPS I due to significant treatment-related morbidity and mortality. As IDUA does not cross the blood-brain-barrier(BBB), HSCT is currently the only treatment available for MPS I H.

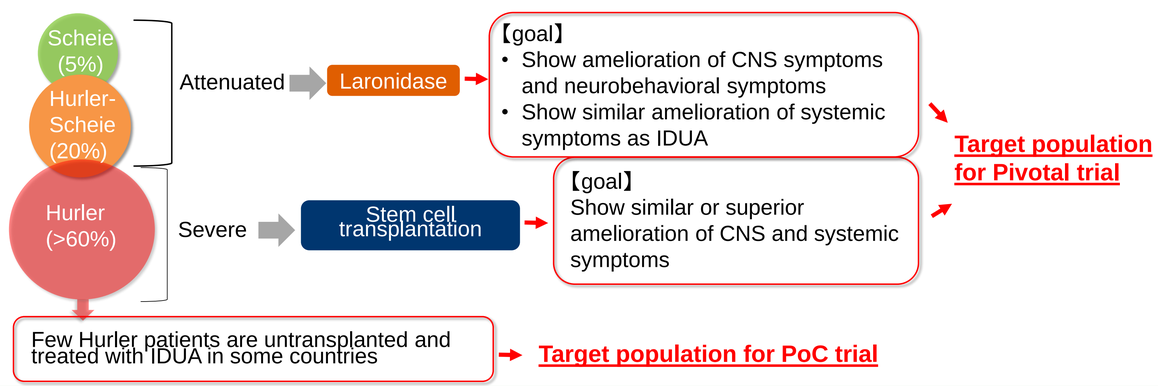
JR-171

- JR-171 is a fusion protein genetically modified to penetrate the BBB and consists of IDUA. The fusion protein is designed to address both, the neurological and somatic disease burden in MPS I. Thereby it may be of benefit for all three forms of MPS I. In this poster we present the design and objectives of our ongoing clinical phase I/II trial in subjects with MPS I.



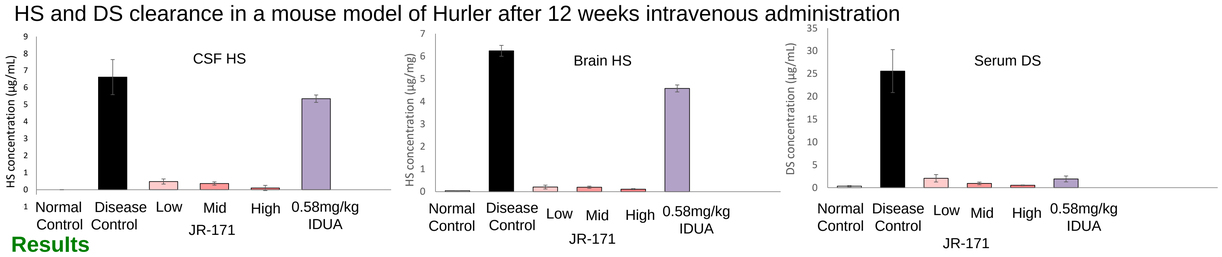
*J-Brain Cargo®: Novel technology to make it possible for the drug to cross the BBB

Target Population and Preclinical Efficacy



Non-Clinical Data

HS and DS clearance in a mouse model of Hurler after 12 weeks intravenous administration

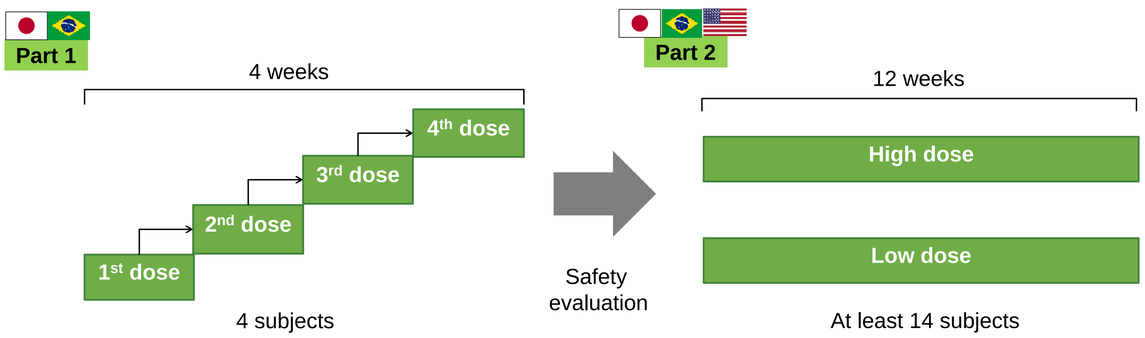


Results

Treatment with JR-171 resulted in clearance of substrate in the brain, cerebrospinal fluid (CSF) and serum, while IDUA cleared substrate in the serum only.

Clinical Study Design

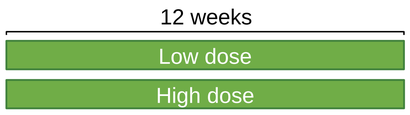
- This is a phase I/II, open label, multicenter, multinational trial, designed to evaluate the safety, PKs and explore the efficacy for the treatment of MPS I. This JR-171-101 study consists of two different parts.



Details of JR-171 Administration in Part2

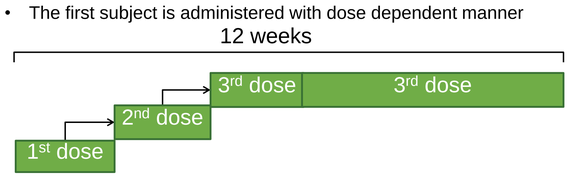
18 years old and over

- All subjects are randomized to either of the dose group.

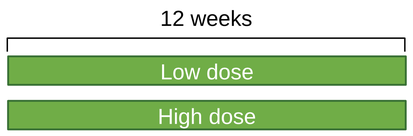


6 to 17 years old

- The first subject is administered with dose dependent manner

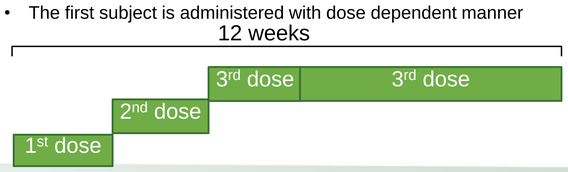


- The second and subsequent subjects are randomized to either of the dose group

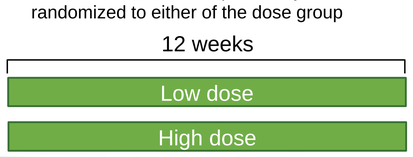


0 to 5 years old

- The first subject is administered with dose dependent manner



- The second and subsequent subjects are randomized to either of the dose group



Endpoints and Inclusion/Exclusion Criteria

	Part 1 (intra-patient dose escalation)	Part 2 (12 weeks treatment of including pediatric subjects)
Primary Endpoints	• Frequency and severity of adverse events (AEs) and their relationship to JR-171 • Anti-drug antibody production (anti-human IDUA and anti-JR-171 antibodies) • Changes in vital signs, laboratory parameter or 12-lead electrocardiogram • Frequency of infusion associated reactions	
Major Secondary Endpoints	• Assessment of plasma drug concentrations and pharmacokinetic parameters • Assessment of CSF drug concentration • Changes in HS and DS concentrations in urine, serum and CSF • Changes in CSF opening pressure • Changes in relative liver and spleen volume • Changes in 6-minutes walk test and cardiac function • Changes in T.O.V.A test (part 2 only) • Changes in BVMT-R and HVMT-R (part 2 only) • Changes in outcome of the Pediatric Quality of Life Inventory Family Impact Module (PedsQL-FIM) (part 2 only)	
Inclusion and Exclusion Criteria		
Major inclusion criteria	• Subjects ≥18 years with a confirmed diagnosis of MPS I and no or mild neurocognitive symptoms	• Subjects aged 2 years older in US and any age in Japan and Brazil with a confirmed diagnosis of MPS I
	• Subjects who have received IDUA for at least 12 weeks before the initial administration of JR-171 (except for a α-L-iduronidase naïve patient or a patient who has previously been treated by HSCT)	
Major Exclusion Criteria	• Subjects who have received prior gene therapy • Subjects who cannot undergo lumbar puncture • Subjects who are pregnant or lactating • Subjects who have developed serious drug allergy or hypersensitivity against IDUA or any ingredients of JR-171 • Subjects who have received another investigational product within the 12 months prior to the study	

Summary and Outlook

- The INDs for PI/II study in subjects with MPS I have been approved in Japan, Brazil and the US.
- As of January 2021, two subjects in Japan have already completed in the Part 1 of the study with no signs of safety concerns.
- CSF HS levels were decreased from baseline in these subjects.
- Extension study with JR-171 is planned to be offered to patients who completed part 2 of the JR-171-101 study.
- PII/III pivotal study to confirm long-term safety and efficacy is planned.
- Further details on the study can be found on ClinicalTrials.gov Identifier: NCT04227600.