A Phase III Study of JR-141 in Patients with Mucopolysaccharidosis Type II (Hunter Syndrome) [JR-141-GS31 Study]

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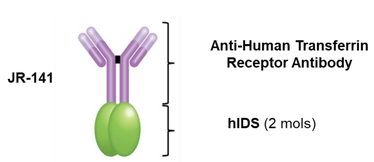
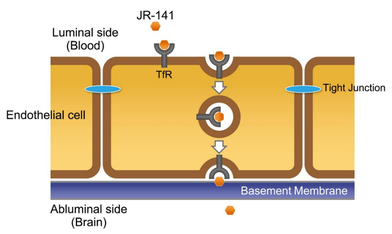
Introduction

- JR-141 (Pabinafusp alfa) is genetically fused protein of a humanized lgG1 antibody targeting hTfR to cross the blood-brain barrier (BBB) and iduronate 2-sulfatase (IDS), an enzyme missing or malfunctioning in Mucopolysaccharidosis Type II. The fusion protein is designed to address both, the neurological and somatic disease burden in MPS II. Here, we present the clinical data obtained with Pabinafusp alfa from past clinical trials and the design of a planned global clinical phase 3 study to start in 2021.





Molecular design and mechanism of BBB transfer of JR-141

Past Clinical Studies

JR-141-101 study (Phase 1/2, first in human dose escalation study) [1)]

Endpoints
- Safety
- Pharmacokinetics
- Exploratory Efficacy (CSF HS)

Part 1 (n=2)
- 0.01 mg/kg
- 0.1 mg/kg
- 1.0 mg/kg
- 2.0 mg/kg total 4 weeks

Part 2 (n=6/group)
- 1.0 mg/kg/w 4weeks
- 2.0 mg/kg/w 4weeks

Main Conclusions
- JR-141 had comparable efficacy to idursulfase on somatic symptoms.
- JR-141 strongly reduced CSF HS, indicative of substrate reduction in the brain.
- JR-141 was well tolerated at doses up to 2.0 mg/kg.

JR-141-BR21 study (Phase 2 study)

Endpoints
- Safety
- Efficacy (CSF HS, Serum HS & DS, neurocognitive evaluation)
- Pharmacokinetics

Idursulfase / Naïve → Treatment/Assessment period (26 weeks)
- 4.0 mg/kg/week
- 2.0 mg/kg/week
- 1.0 mg/kg/week

Age group	Patient number
0 to 3 years	6 patients, 2 in each dose
4 to 7 years	6 patients, 2 in each dose
8 or older	6 patients, 2 in each dose

Main Conclusions
- CSF HS levels decreased in almost all subjects at 2.0 mg/kg and 4.0 mg/kg.
- Development scores at week 26 stabilized or improved in the most subjects.
- Based on the safety and efficacy data, 2.0 mg/kg/week was chosen as recommended phase 3 dose.

JR-141-301 study (Phase 2/3, first in human study) [2)]

Endpoints
- Efficacy (CSF HS, serum HS & DS, neurocognitive evaluation)
- Long Term Safety

Idursulfase / Naïve → Treatment/Assessment period (52 weeks)
- 2.0 mg/kg/week

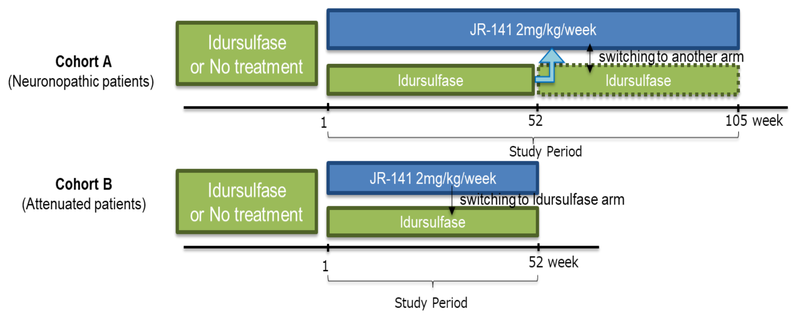
- Age range 1 to 26 years
- 28 subjects (20 severe, 8 attenuated)

Main Conclusions
- CSF HS concentrations decreased in 27 out of 28 subjects.
- Development scores at Week 53 stabilized or improved in almost all subjects.
- The somatic efficacy of JR-141 was comparable to idursulfase.
- No significant safety concerns were observed during the study period.

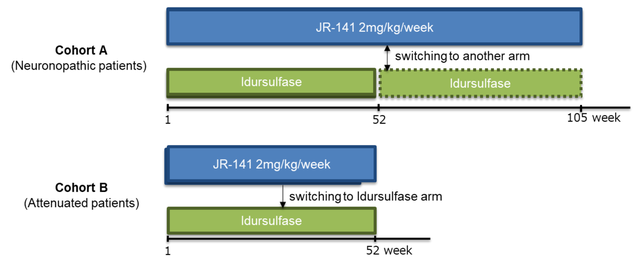
Upcoming JR-141-GS31 Global Phase 3 Study ※This study is still in the planning stage. The design can be changed.

Objectives
- To demonstrate the efficacy of JR-141 on Central Nervous System (CNS) symptoms and somatic symptoms in MPS II patients
- To evaluate the safety of JR-141 in patients with MPS II

Study Design



Qualification for Rescue Option



Idursulfase to JR-141
- Decrease in Age Equivalent score or Nonverbal Index standard score from screening period for 2 consecutive tests.

JR-141 to idursulfase
- Increase in Liver volume from baseline (BL)
- Increase in urinary HS and DS concentrations from BL for 2 consecutive tests

Study Details
- An interim efficacy analysis in cohort A will be conducted after 12 months
- Subjects in cohort A with a confirmed neurocognitive decline on idursulfase will be offer to switch to JR-141 after 12 months
- 1:1 randomization between JR-141 and idursulfase
- Study period: Q2 2021 to Q2 2024

Study Cohorts

	Cohort A	Cohort B
Number of Subjects	30 subjects	20 subjects
Cohorts	Subjects with neuronopathic MPS II, age 30 to 71 months	Subjects with attenuated MPS II ≥ 6 years of age with 70 or higher score of intelligence quotient (IQ) on a Wechsler test at screening

Key Efficacy Endpoints

	Cohort A	Cohort B
Primary Endpoint	• Change in level of CSF HS from BL to Week 53 and Week 105 • Change in neurocognitive testing from screening to Week 53 and Week 105 by the BSID-III or the KABC-II • Relative change in the liver volume and spleen volume relative to body weight from BL to Week 53	• Change in the liver volume and spleen volume relative to body weight from BL to Week 53 • Change in the distance walked in 6 minutes walk test from BL to Week 53
Secondary Endpoint	• Relative change in the liver volume and spleen volume relative to body weight from BL to Week 105 • Change in neurocognitive testing at Week 53 and 105 by VABS II	• Change in the Test of Variables of Attention T.O.V.A or the Test of Working memory Wechsler tests from screening period to Week 53 • Change in CSF HS from BL to Week 53 • Change in the absolute forced vital capacity (FVC) from BL to Week 53

Key Safety Assessment
- Adverse events
- Physical examinations
- Vital signs and weight
- Electrocardiograms
- Clinical safety laboratory assessments

Major Inclusion Criteria
- Males diagnosed with MPS
- Naïve patients or patients who are treated with idursulfase and on a stable regimen for the past 12 weeks
- **Cohort A**
  -Males aged 36-71 months old whose DQ on the BSID-III or KABC-II is between 55-75 at the time of ICF signed OR
  -Males aged 30-35 months old at the time of ICF signed, with presence of one of the prescribed mutations in the IDS gene, and who are judged as having the severe phenotype
- **Cohort B**
  -Males aged ≥6 years at the time of ICF signed and whose IQ on a Wechsler test is ≥70 or higher at screening
  -Patients with 1SD deficiency in the omission errors or variability domains of the T.O.V.A test or Processing Speed or Working memory on the Wechsler tests at screening

Major Exclusion Criteria
- Subjects with a history of hematopoietic stem cell transplantation (HSCT), excluding those who need enzyme replacement therapy (ERT) even after HSCT
- Subjects who have received gene therapy
- Subjects who are judged as being unable to undergo lumber puncture, including those who have difficulties in taking position for lumbar puncture due to joint contracture or those who are likely experience breathing difficulties during the lumbar puncture process

Conclusions
- JR-141 (Pabinafusp alfa) has demonstrated in several clinical studies to maintain somatic disease control comparable to idursulfase.
- The neurological effect of JR-141 has been demonstrated by its ability to stabilize or improve the development score in subjects with severe and attenuated MPS II. Moreover, JR-141 induced a significant reduction of the HS substrate in subjects treated with 2 mg/kg/week or higher.
- Clinical studies have demonstrated that JR-141 is well tolerated upon long-term administration at the tested dose of 2 mg/kg/week .
- MAAs have been filed in Japan and Brazil.
- A global clinical study of JR-141 in subjects with attenuated and severe MPS II aims to demonstrate the long term neurocognitive and somatic benefit of JR-141.

Acknowledgements

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References

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