Drug Delivery Across the Blood-Brain Barrier and Resultant Reduction of Heparan Sulfate in the Cerebrospinal Fluid in the Patients with Hunter Syndrome (MPS-II): an Integrated Analysis of 25-week Japanese and Brazilian Data on Pabinafusp alfa (JR-141)

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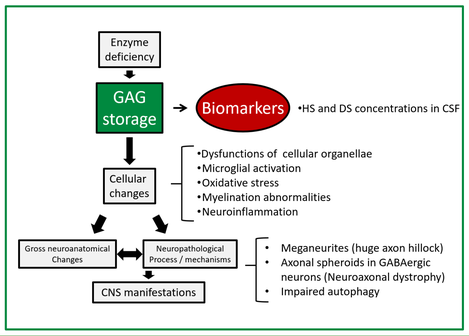
Introduction

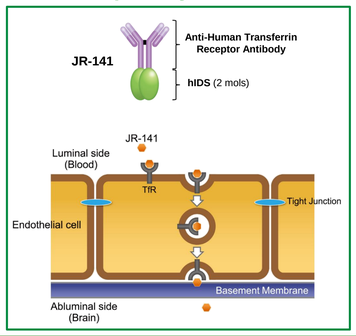
Aim of the Study

- MPS II is an X-linked lysosomal storage disease, caused by mutations in the iduronate-2-sulfatase (IDS) gene, resulting in pathological accumulation of glycosaminoglycans (GAGs) including heparan sulfate (HS) in lysosomes of tissues and organs including the brain.
- Current enzyme replacement therapy (ERT) does not address the neurologic disease burden as it cannot cross the blood-brain barrier (BBB).
- JR-141 is an anti-human transferrin receptor antibody fused IDS expected to cross the BBB and thereby addressing a serious unmet medical needs in the treatment of the disease.
- We measured HS concentrations in the cerebrospinal fluid of patients treated with JR-141 for extended times in two phase II/III studies to understand the importance of this biomarker in predicting disease severity, response to JR-141 and improvement of cognitive signs and symptoms.

The pathway towards neurodegeneration

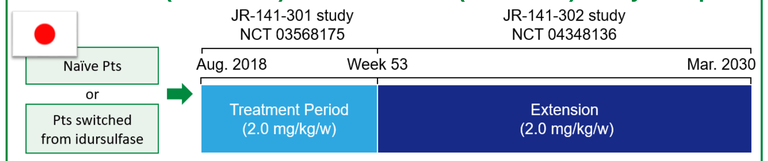


Molecular design and postulated BBB passage of JR-141

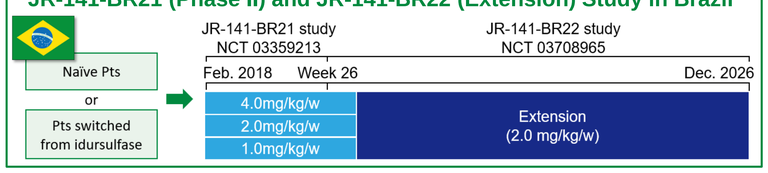


Trial Design and Objectives

JR-141-301 (Phase II/III) and JR-141-302 (Extension) Study in Japan



JR-141-BR21 (Phase II) and JR-141-BR22 (Extension) Study in Brazil

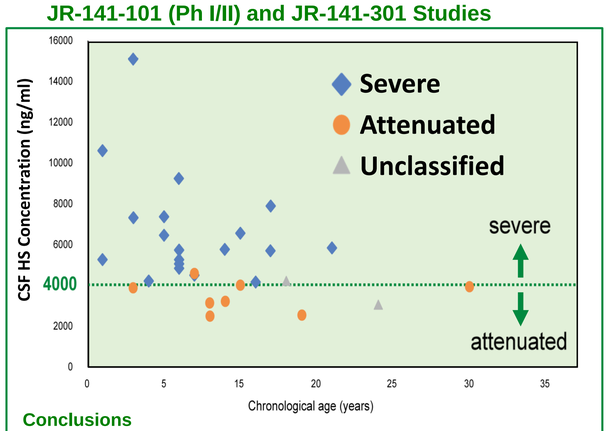


Study Design	A phase II/III open-label, single-group, multicenter
Study objectives	To evaluate the efficacy and the long-term safety of JR-141 in MPS II patients
Primary Endpoint	Change in HS Concentration in CSF
Secondary Endpoint	• Serum, and Urinary HS • DS concentrations in CSF, Serum, and Urinary • Neurocognitive Testing • Adaptive Behavior Testing ...and others
Number of Patients	20 (severe), 8 (attenuated)
Study Design	A phase II open-label, randomized, parallel group, 2 sites
Study objective	To evaluate safety and efficacy of 3 doses of the study drug for the treatment of the MPS II
Primary Endpoint	Safety
Secondary and Exploratory Endpoint	• HS and DS concentrations in CSF, Serum, and Urinary • Neurocognitive Testing • Adaptive Behavior Testing ...and others
Number of Patients	14 (severe), 5 (attenuated)

Results

1. Disease Severity

Disease Severity and CSF HS Levels at Baseline in JR-141-101 (Ph I/II) and JR-141-301 Studies

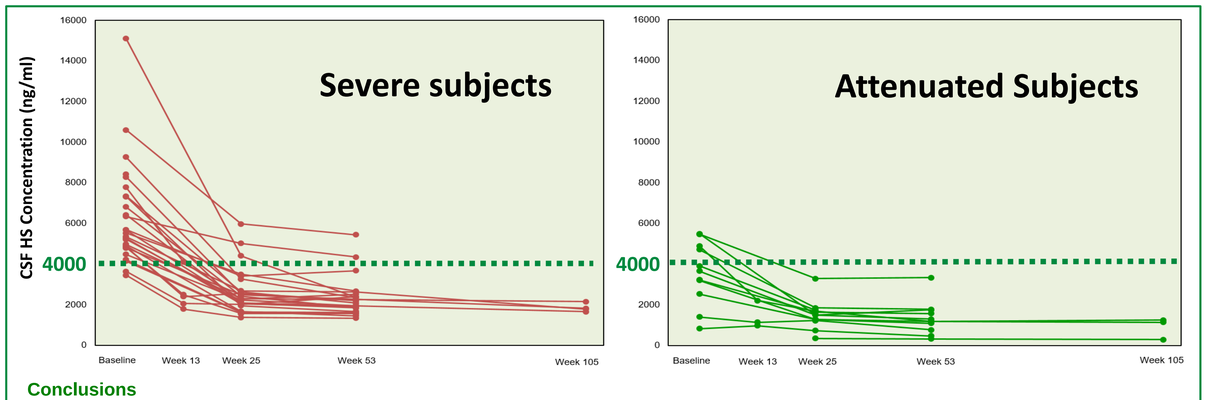


Conclusions

- CSF HS levels strongly correlate with disease severity
- Patients with severe CNS display CSF HS levels >4,000 ng/ml

2. Effect of JR-141 Treatment on CSF HS Levels

CSF HS Concentrations in JR-141-301/302 and JR-141-BR21/22 Studies *

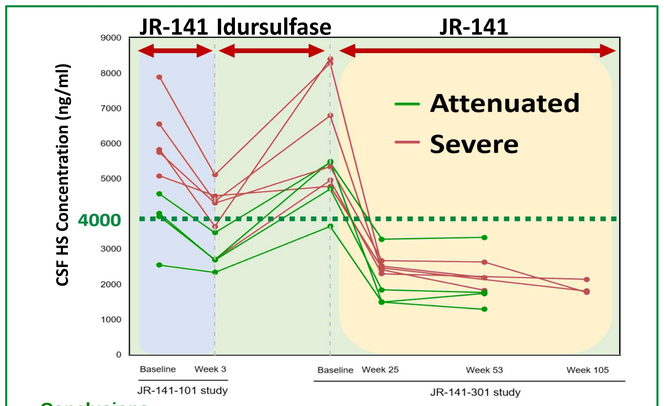


Conclusions

- CSF HS concentrations decreased in all subjects in the 2.0 and 4.0 mg/kg groups
- CSF HS concentrations decreased in most subjects to < 4,000 ng / mL, a level typical for attenuated subjects

* Patients received JR-141 at a dose of 2 or 4 mg/kg/week for one year or longer

Changes in CSF HS Levels through JR-141-101 and JR-141-301 Studies



Conclusions

- CSF HS decreased during the JR-141 treatment periods and increased when patients returned to idursulfase

3. Efficacy of JR-141 on CNS Symptoms

Changes in Age-equivalent Scores of Severe Subjects in JR-141-301 and JR-141-BR21 Studies

Method of assessment

- Kyoto Scale of Psychological Development (JR-141-301)
- Bayley scales of infant and toddler development, third edition (JR-141-BR21)
- AE (Age Equivalence) : Change from baseline to 52 weeks
- AE Scoring: Improved : AE >3M; Stabilized : AE change ±3M; Worsened : AE <-3M

Group	CSF-HS concentration	AE scores	Number of subjects
Group A	<4,000 ng/mL	improved or stabilized	18/23 (78%)
Group B	>4,000 ng/mL, but reduction	improved or stabilized	2/23 (9%)
Group C	<4,000 ng/mL	worsened	3/23 (13%)

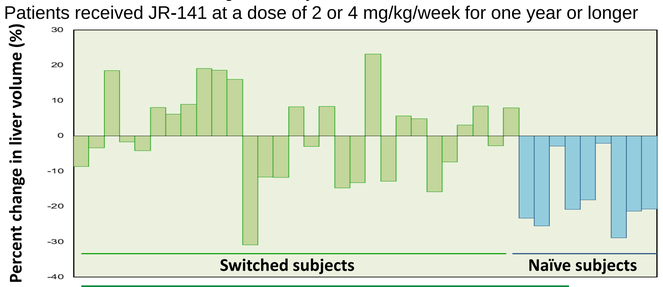
Results

- AE improved in most subjects (Group A)
- Improvement or stabilization of AE tended to correlate with a decrease of CSF HS concentration below 4,000 ng/mL

4. Efficacy on Somatic Symptoms

Reduction of Liver Volume from Baseline to 52 weeks in Subjects in JR-141-301 and JR-141-BR21 Studies

No correction based on weight or body surface area
Patients received JR-141 at a dose of 2 or 4 mg/kg/week for one year or longer



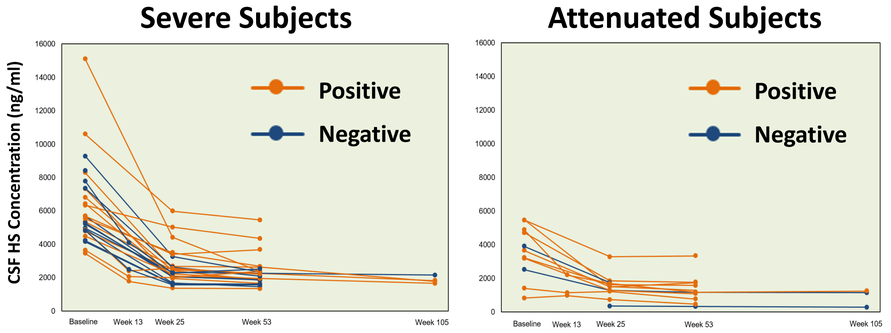
Mean value of change in liver volume (%)	
Switch	+0.8
Naïve	-18.2

Results

- A significant reduction of liver volume was observed in ERT-naïve patients while liver volume remain stable in patients switched from idulsulfase to JR-141

5. Effect of Anti-Drug Antibodies

Effect of Anti-JR-141 Antibody Development on CSF HS Concentration Upon Treatment with JR-141



Results

- Anti-JR-141 antibody formation was observed in some subjects. Titers were generally low
- ADA formation did not have a significant impact on the reduction of CSF HS levels

Summary

Safety and Efficacy

- Various clinical studies demonstrate that JR-141 is safe and well tolerated for the long-term treatment of MPS II.
- CSF HS levels decreased in all patients treated with 2.0 or 4.0 mg/kg. Formation of ADAs did not significantly impact reduction of CSF HS.
- Reduction in CSF HS correlated well with improvement or stabilization of AE, which was achieved in 87% of all subjects.

HS concentration as Biomarker

- CSF HS levels appear to be a good predictor disease severity. Reduction of CSF HS to a level below 4,000 ng/ml by therapeutic interference with JR-141 appears to be a good predictor of efficacy on the CNS disease burden.

Outlook

- A global phase III study with JR-141 is under preparation in the U.S., Brazil and Europe.
- JR-141 has been submitted for marketing authorization approval in Japan and Brazil, respectively.

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