Summary of the 52-week interim data analysis

of the phase I/II, open label, multicenter, multinational (Japan, Brazil, US) extension study of JR-171-101 for the treatment of MPS I.

(ClinicalTrials.gov identifier NCT04453085)

October 4, 2023

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This presentation contains forward-looking statements that are subject to a number of risks and uncertainties, many of which are outside our control. All forward-looking statements regarding our plans, outlook, strategy and future performance 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.

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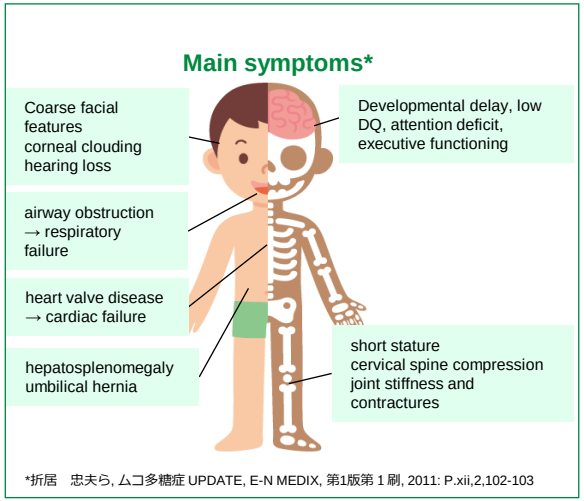
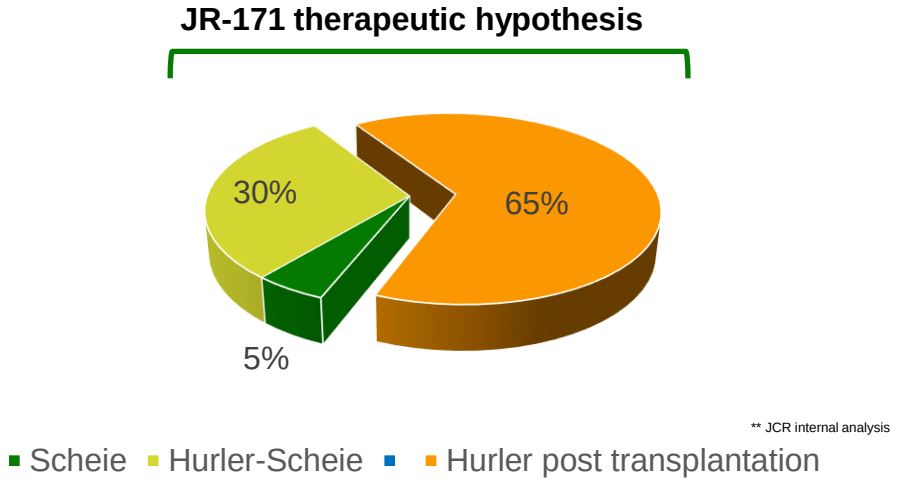
Mucopolysaccharidosis type I (MPS I) – Disease Introduction

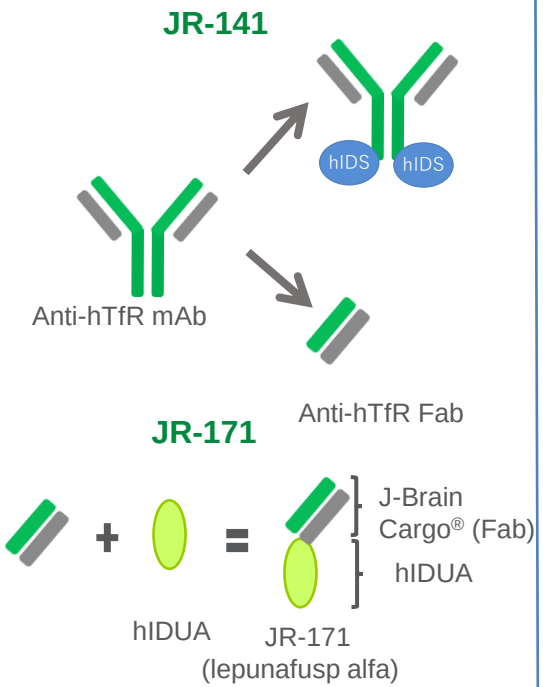




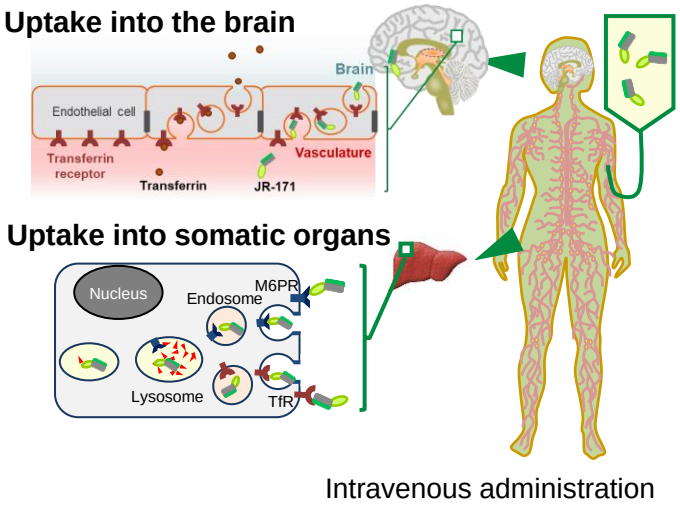
	Attenuated (MPS IS, MPS IHS)	Severe MPS I
Disease presentation	Stable DQ, organomegaly, cardiac, pulmonary, orthopedic	Severe cognitive dysfunction, severe orthopedic and multi-organ disease burden
HSCT	-	+
Unaddressed signs and symptoms	Deficiencies in attention, short term memory, executive functioning, etc.	Low but stable DQ, poor QoL, deficiency in short term memory, attention, executive functioning, do not live an independent life, orthopedic burden, etc.

Lepunafusp alfa (JR-171) – Molecular Design and postulated MoA

Molecular Design



Mechanism of Action



Postulated therapeutic benefit

1. **Superior** efficacy of on CNS disease compared to standard ERT.
2. Somatic disease control **comparable** to standard ERT.

TfR: Transferrin receptor
M6PR: mannose-6-phosphate receptor
CNS: Central nervous system

Objectives of the JR-171-101/102 Clinical Trial

Primary Objectives

- To determine the safety and tolerability of JR-171 in patients with MPS I.

Secondary Objectives

- To evaluate the plasma PK of JR-171 after intravenous administration.
- To explore the efficacy of JR-171 on central nervous and somatic symptoms of MPS I.

Executive Summary of Interim Results

52 Weeks Interim Results of Ph1/2 Study

Safety

- No serious adverse drug reactions.
- All drug related IARs were manageable and reversible:
  - All IARs were controlled by common medications.
  - No drop-outs from study due to IARs.
- No significant difference in safety profile of JR-171 at 2 mg/kg versus 4 mg/kg.
- Expected/preferable pharmacokinetic profile.
- No significant impact of ADAs on PK/PD profile.
- Well-tolerated in subjects down to 6 months of age.

Efficacy

- Stabilized organ volumes and walking ability in ERT-exposed individuals
- Reduction in organ volume in treatment naïve subject.
- Significant reduction in CSF biomarker.
- Significant reduction in peripheral biomarkers in ERT-naïve subject, stabilized biomarkers in ERT-switched subjects.
- Positive trend in developmental assessment:
  - Stabilized/improved scores in neurological test (BSID for severe pts, Wechsler for attenuated pts)
  - Positive changes reported by parents/caregivers (narrative reports)

Main Conclusions:

Data support that JR-171 is safe and well-tolerated for the long-term treatment of MPS I. Biomarker and efficacy data support somatic disease control and indicate trend towards neurocognitive benefit.

CSF : cerebrospinal fluid

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Clinical Trial Outline of Study JR-171-101 and JR-171-102

Open label, multicenter, multinational trial to evaluate the safety, PKs and explore the efficacy for the treatment of MPS I

Part 1

Status: Completed w/o safety concerns

4 subjects with MPS I

Target Population:
- 18 years of age or older
- No or mild intellectual disability

2.0 mg/kg/wk → 4.0 mg/kg/wk

4 weeks

Primary Endpoints

- Frequency and severity of adverse events
- Anti-drug antibody production
- Safety assessment: changes in vital signs, etc.

Secondary Endpoints

- Drug concentrations; plasma and CSF
- HS and DS concentrations; urine, serum and CSF
- Somatic assessment: liver volume etc.

Part 2

Status: 52 weeks Completed w/o safety concerns

Extension study

14 subjects

Target Population:
- Aged 0 years and older (2 years and older for US) can participate regardless of disease severity
- After Safety Evaluation in Part 1

2.0 mg/kg/wk → 4.0 mg/kg/wk

2.0 mg/kg/wk → 4.0 mg/kg/wk

Optimal Dose

12 weeks (101 study)

Long-term follow up (102 study)

HS : heparan sulfate
DS : dermatan sulfate

Patient Demographics in the JR-171-102 Study

	Overall	Brazil	Japan	US
Participants	14	10	2	2
Age range	6M-32Y	6M-32Y	4-14Y	16-17Y
Male/Female	9/5	7/3	1/1	1/1
Treatment-naïve	1	1	0	0
MPS IS	1	1	0	0
MPS IHS	4	1	2	1
MPS IH	8	8	0	0
MPS I post HSCT	1	0	0	1

S : Scheie syndrome
HS : Hurler-Scheie syndrome
H : Hurler syndrome

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Assessment of Safety

Summary of Adverse Events

	JR-171-101/102 study (Part 2)					
	2.0 mg/kg (n=6)		4.0 mg/kg (n=8)		Overall (n=14)	
	n (%)	events	n (%)	events	n (%)	events
Adverse events	6 (100)	74	8 (100)	109	14 (100)	183
Serious adverse events	1 (16.7)	1	1 (12.5)	2	2 (14.3)	3
Adverse drug reactions	2 (33.3)	6	4 (50)	13	6 (42.9)	19
Infusion-associated reactions	2 (33.3)	6	4 (50)	12	6 (42.9)	18
Serious adverse drug reactions	0 (0)	0	0 (0)	0	0 (0)	0

- Overall safety profile is comparable to somatic ERT.
- No overt differences in safety at 2 mg/kg compared with 4 mg/kg.
- No drug-related SAEs, drug-related AEs were reversible and manageable.
- The full assessment of potential anti-drug antibody formation at week 52 was not available at time of presentation.

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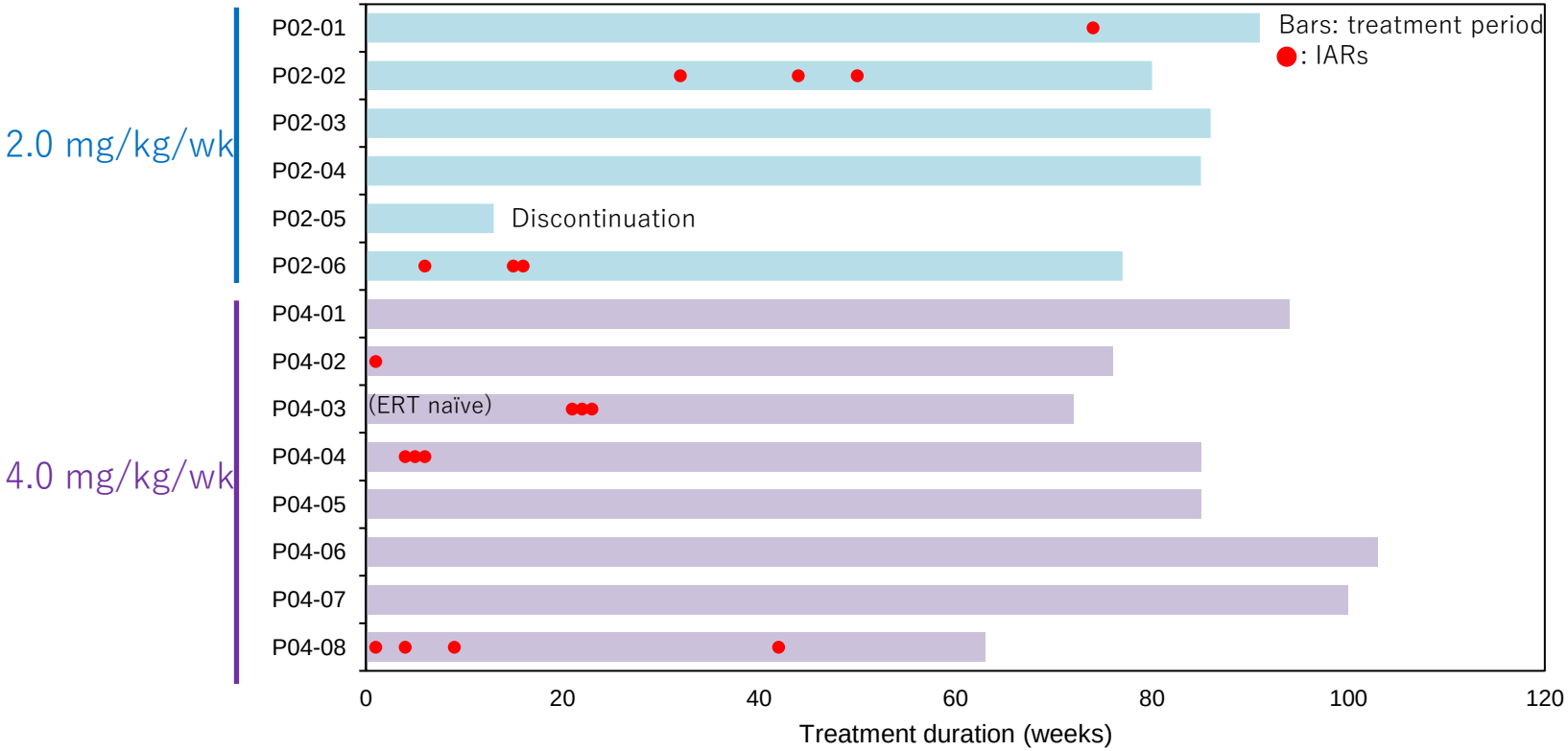
Occurrence of IARs

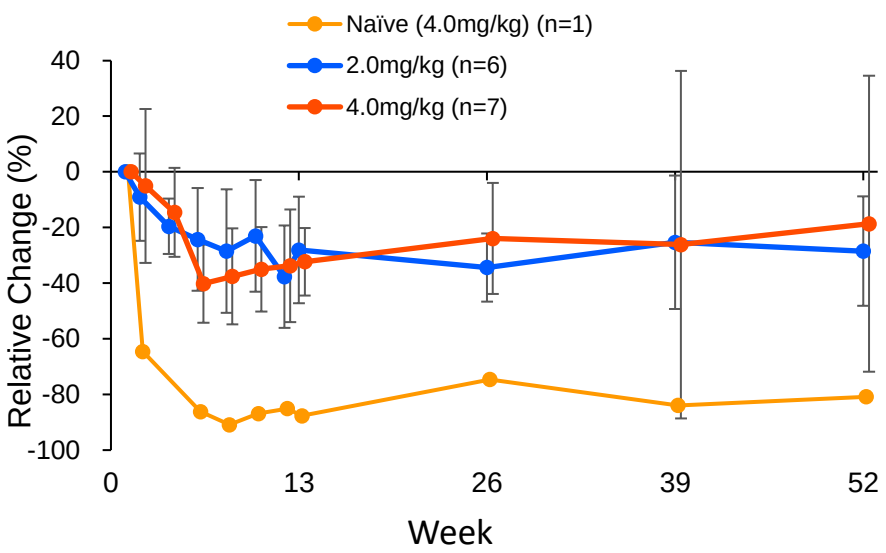


Consistent with other ERTs, IARs appear to be less frequent upon extended treatment periods

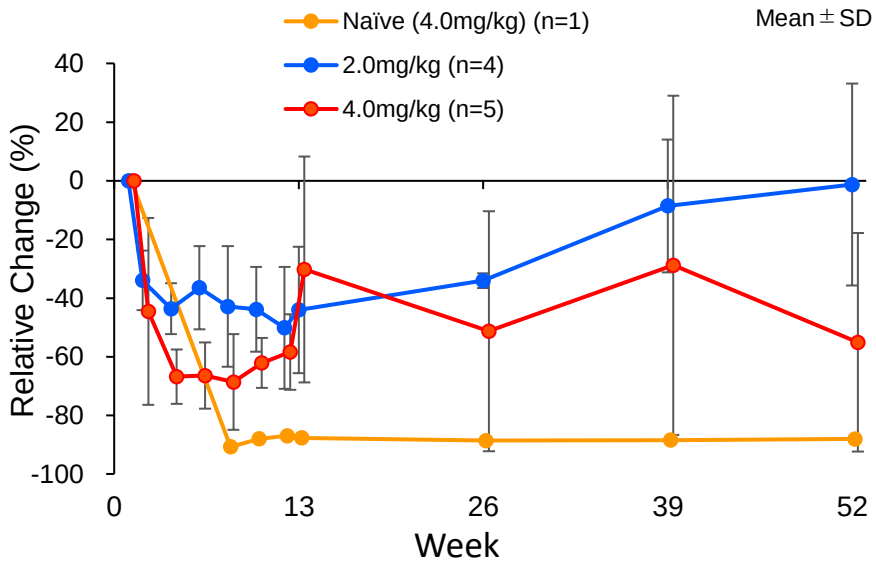
Assessment of somatic Efficacy

Relative Changes in Serum/Urine Heparan Sulfate Levels

A Serum Heparan Sulfate



B Urine Heparan Sulfate



- Relative peripheral substrate levels in ERT-pre-exposed subjects tend to decrease and decreased sharply in naïve subject

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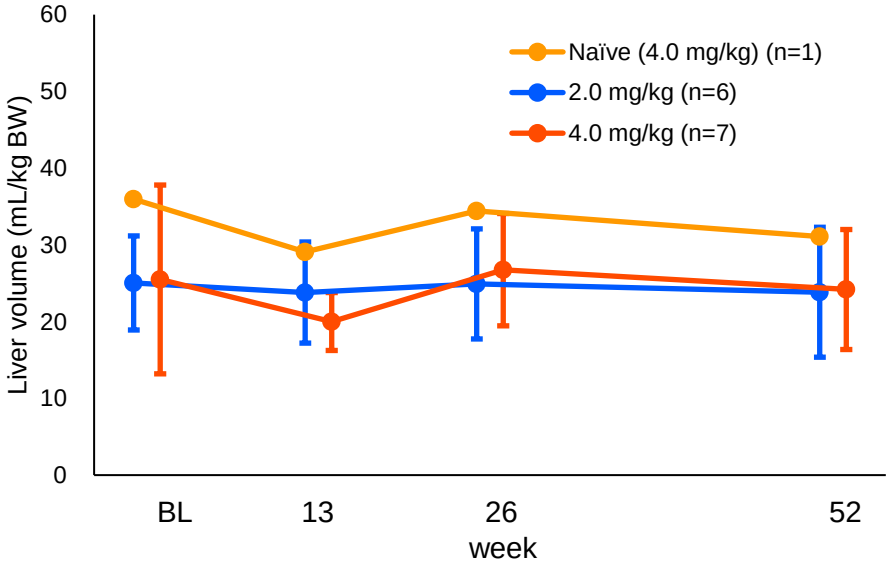
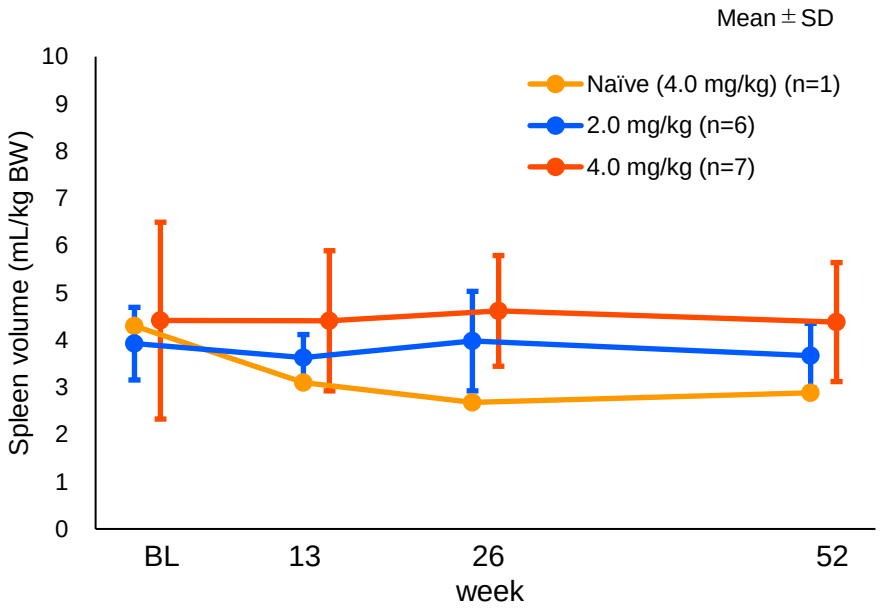
Changes in Organ Volumes

A Mean Changes in Liver Volume

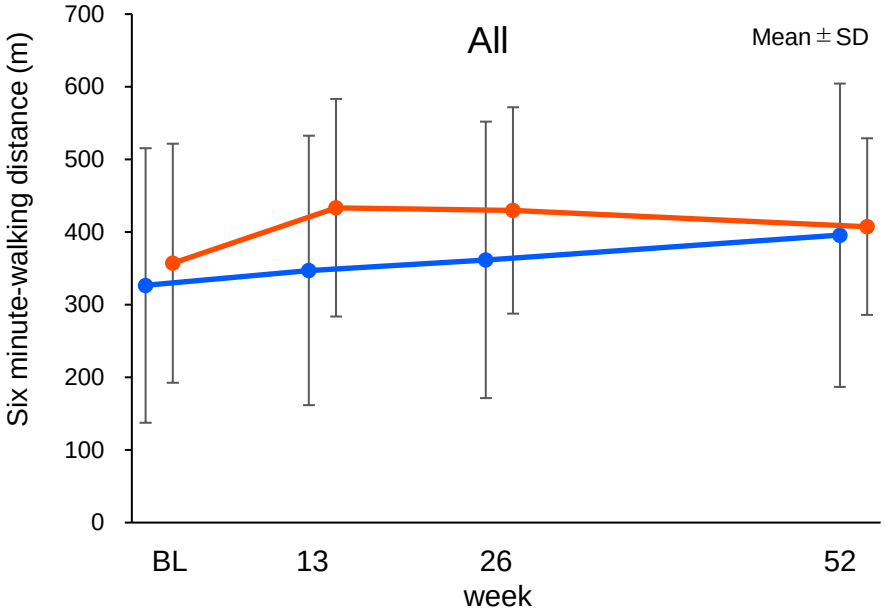


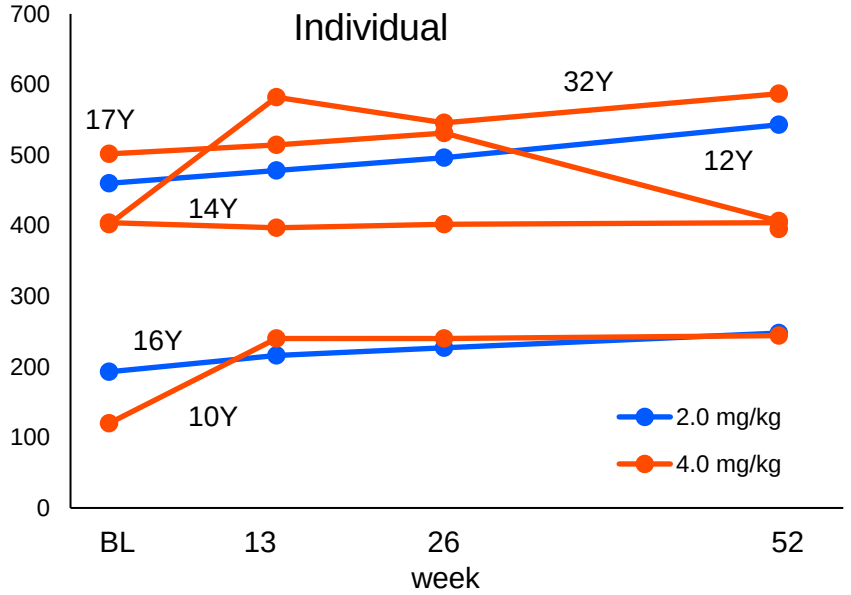
B Mean Changes in Spleen Volume



- Organ volumes stabilized in pre-exposed individuals and decreased in treatment naïve patient, being indicative of somatic disease control
- Organ volumes at baseline were not pathologic in subjects enrolled in the study

Changes in Six-Minute Walk Test





- An increase in 6MWD was observed in 5 out of 6 evaluable subjects.
- Notably, one subject (32 years of age) improved by 50% from 400 to ~ 600 meters

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Summary of Assessment of somatic Efficacy

- Stabilization or decrease in somatic biomarkers (urinary and serum heparan sulfate and dermatan sulfate (not shown)) and organ volumes indicate that JR-171 at either dose provides appropriate somatic disease control.

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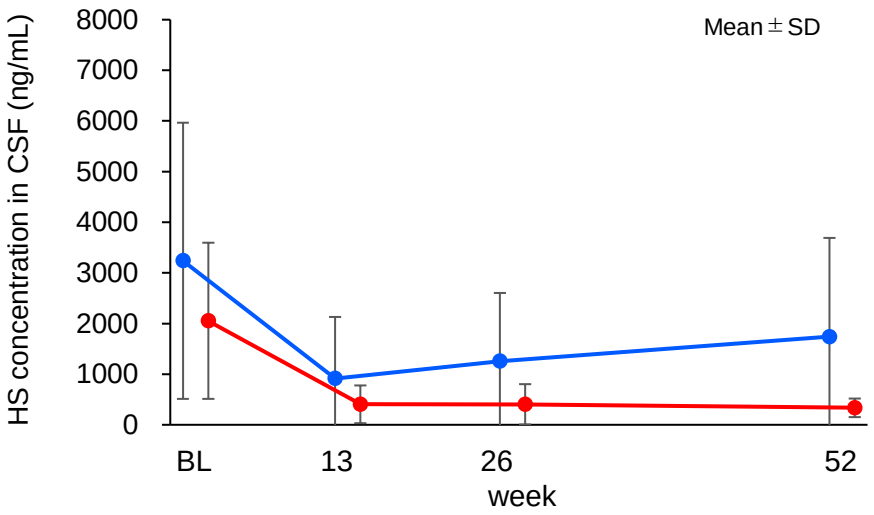
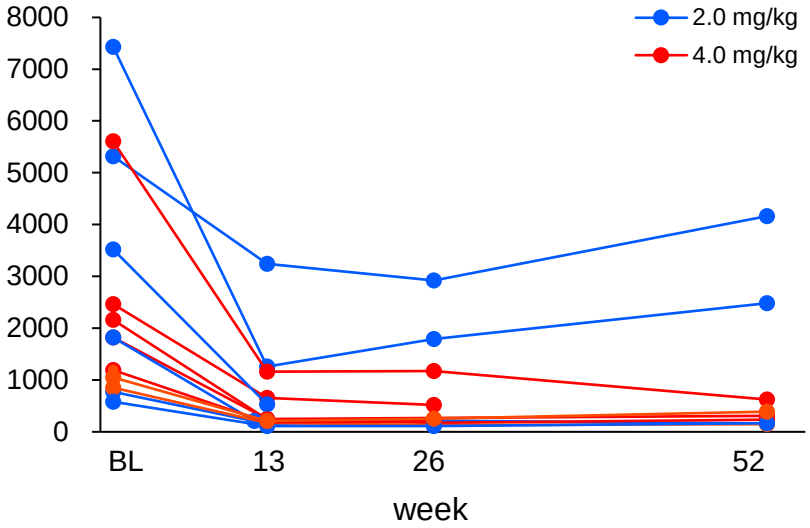
Assessment of Exploratory Efficacy on Central Nervous Signs and Symptoms

Changes in Heparan Sulfate Levels in the Cerebrospinal Fluid

A All subjects



B Individual subjects



- A significant reduction in CSF biomarker compared to baseline was observed in all patients.

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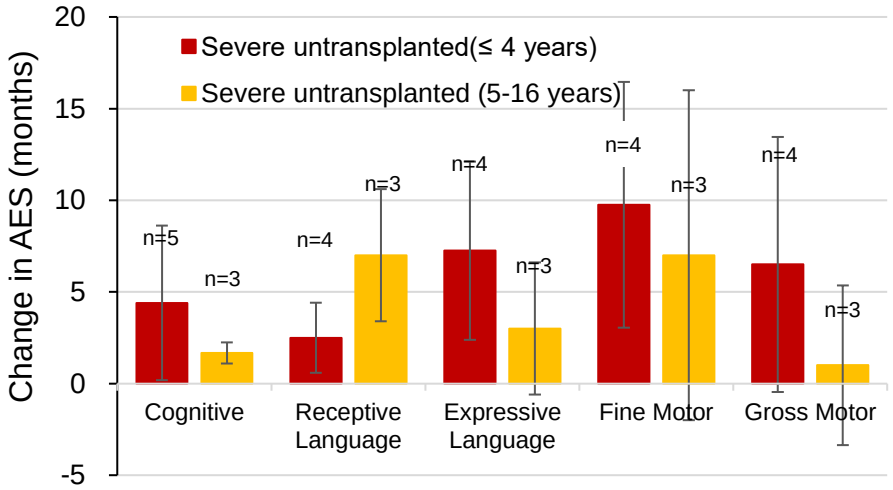
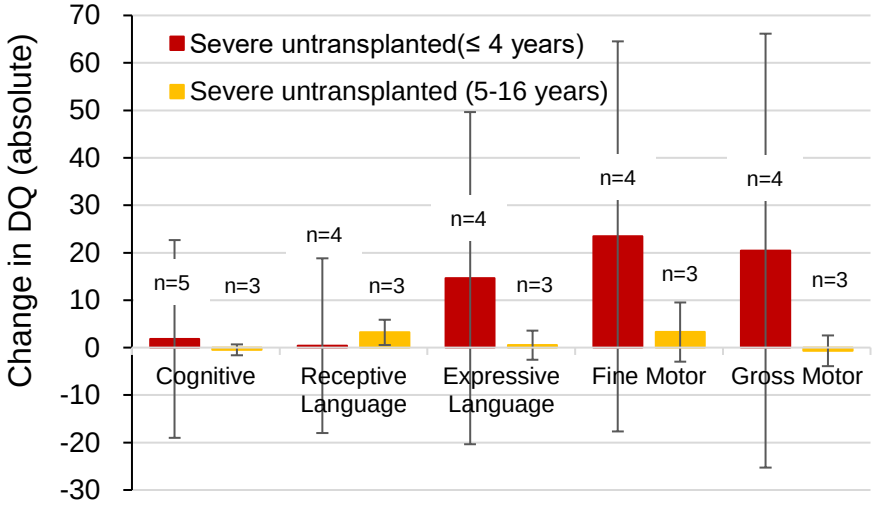
Changes in Neurocognitive Function in Severe MPS I Subjects

Measured using the Bayley Scales of Infant Development (BSID)

A Changes in Age-Equivalent Score (in months) at 52 Weeks compared to Baseline



B Changes in Development Quotient at 52 Weeks compared to Baseline



- Despite low number of subjects, a trend towards a neurological benefit was observed in severe untransplanted MPS I subjects of all age ranges enrolled.

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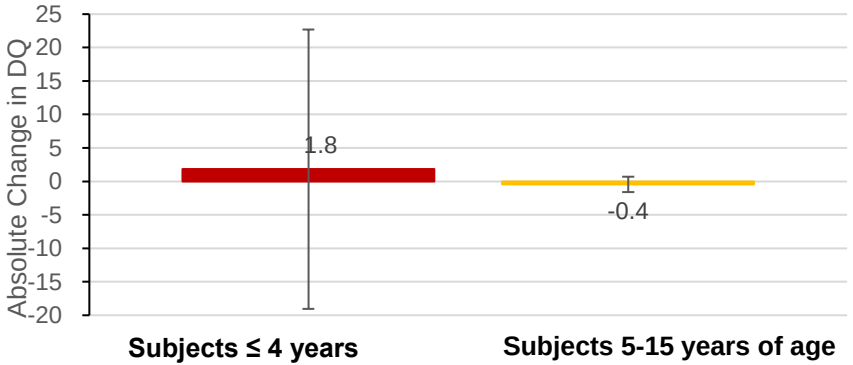
Changes in Neurocognitive Function in Severe MPS I Subjects
- Comparison with Natural History of Severe non-Transplanted MPS I -

Changes in Cognitive Domain of Development Quotient measured by BSID at 52 Weeks compared to Baseline



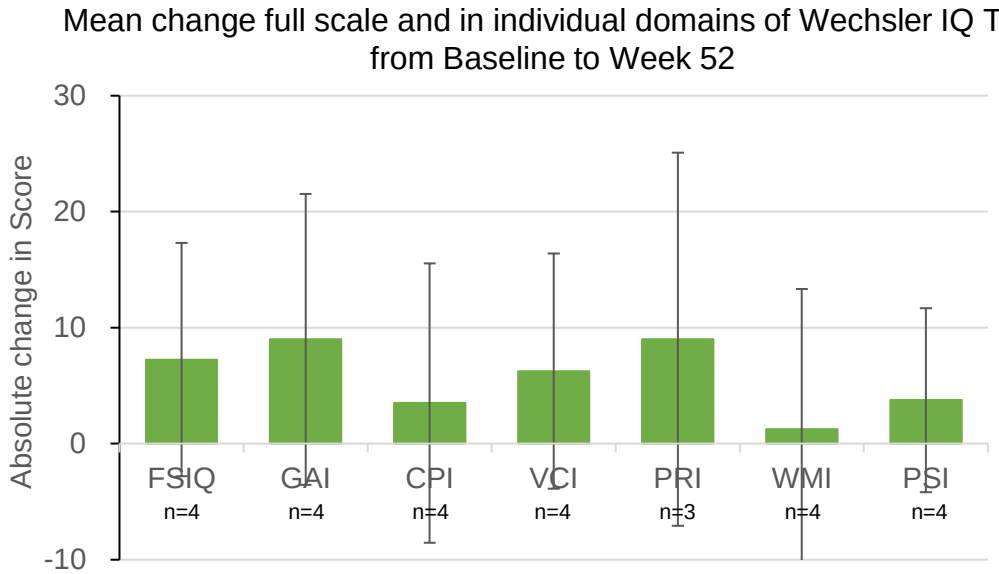
	Subjects ≤ 4 years	Subjects 5-15 years of age
Expected change per the natural history*	~ - 10 DQ points/year	~ - 8 DQ points/year

- Compared to the natural history of severe untransplanted MPS I, there is a trend towards DQ stabilization upon treatment with JR-171.
- A significant decrease in DQ would have been expected per the natural history in severe untransplanted MPS I

*Grosse et al. Genet. Med. (2017) doi:10.1038/gim.2016.223 and references therein
Shaipro et al. Orphanet J. Rare Dis. 13:76 (2018)

Changes in Neurocognitive Function in Attenuated MPS I Subjects

Measured using various forms of the Wechsler Test (depending on age)



FSIQ	Full scale IQ
GAI	General ability index
CPI	Cognitive Proficiency Index
VCI	Verbal Comprehension Index
PRI	Perceptual reasoning index
WMI	Working memory index
PSI	Processing Speed Index

- Despite a low number of subjects evaluable, a positive trend towards neurocognitive benefit was observed in attenuated subjects with MPS I

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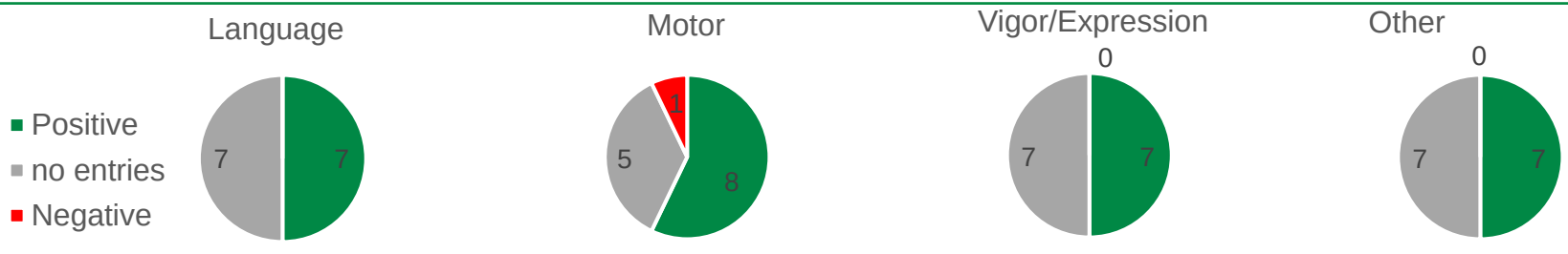
Narrative Reports – Entries in the Clinical Database



	Language	Motor	Vigor/Expression	Other
Number of Positive comments	10	24	9	23
Negative comments	0	1	0	0

Examples				
	• Livelier conversations • Communicating with examiner • More focused conversations • Asks questions	• Improved gait, balance, muscle strength, hand strength, stair climbing, • Swings in hammock • Improved joint ROM • Strength asymmetry not changed	• More active • Social relationships • Interpersonal contact • Less fatigue • Improved daily activities	• Better sleep • Less sleep apnea • Improved attention, concentration • Less agitation • Improved decision-making • Smiling • More engaged while playing

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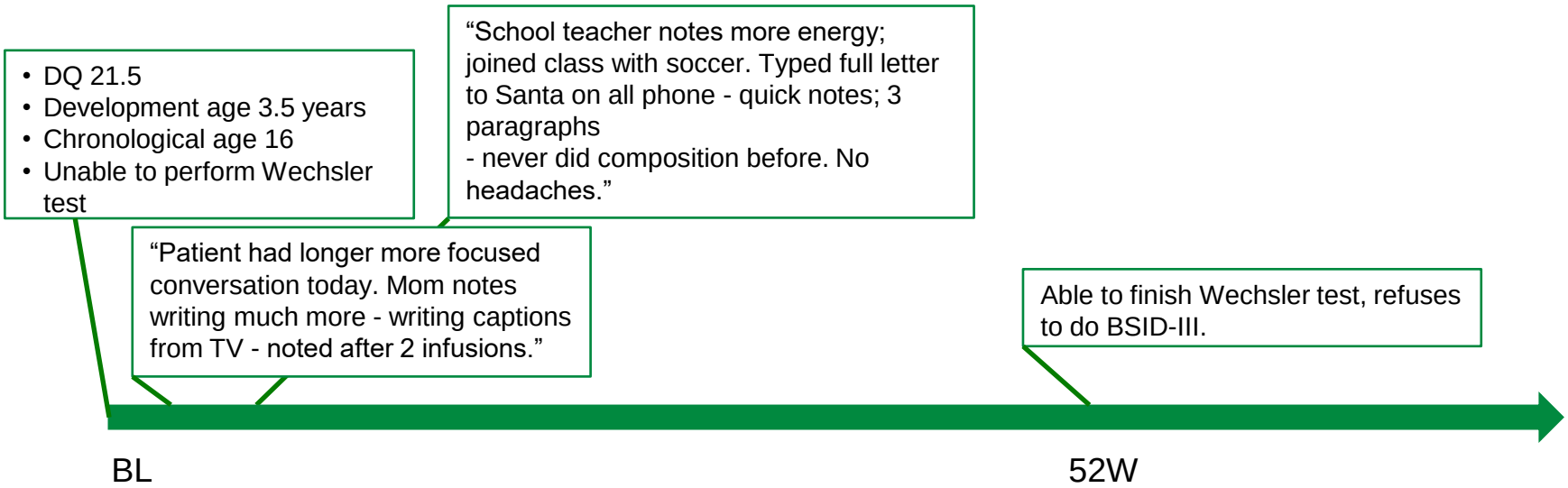
Narrative Report US-01-01

Background:

- 16-years old female post HSCT with baseline DQ of 21.5 (severe); cognitive development age ~ 42 months
- Conducted BSID-III at baseline but was unable to perform Wechsler test



Summary of Exploratory Efficacy on CNS Signs and Symptoms

- A significant reduction of heparan sulfate substrate in the cerebrospinal fluid was observed in all subjects.
- Despite a low number of subjects enrolled, signals of neurological benefit were observed in subjects with severe and with attenuated phenotype.
- Summary of documented narrative reports indicate that subjects benefitted by improved social interactions, increased liveliness, more vigor, improved mobility, less fatigue, better sleep, improved executive functioning.

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Overall Conclusions from 52-Week Data of the JR-171-101 Study

- The overall safety/tolerability profile of JR-171 (lepunafusp alfa) indicates that it is suited for the long-term treatment of individuals with MPS I.
- Given the small sample size and limited follow-up, interim analysis indicate that JR-171 may provide somatic disease control and a neurological benefit for MPS I individuals with neurological signs and symptoms.
- Long-term follow up of all participants continuing in the study will provide further insights into the overall safety and efficacy of JR-171.

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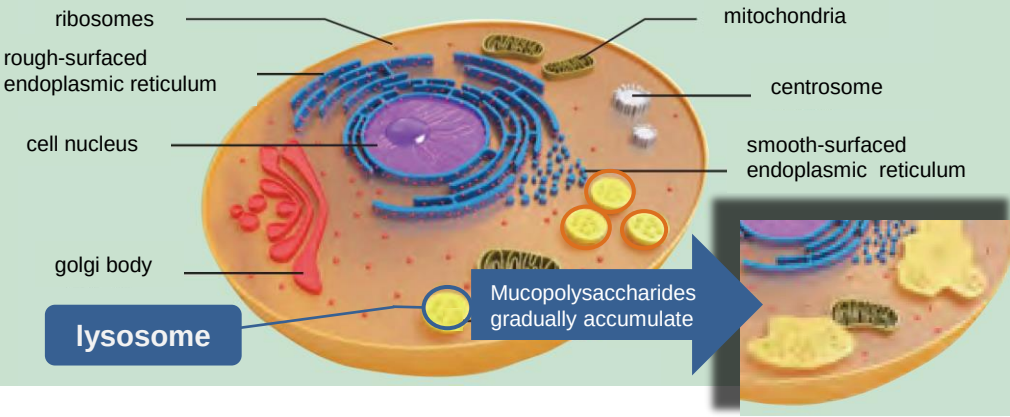
Appendix

MPS (Mucopolysaccharidosis)

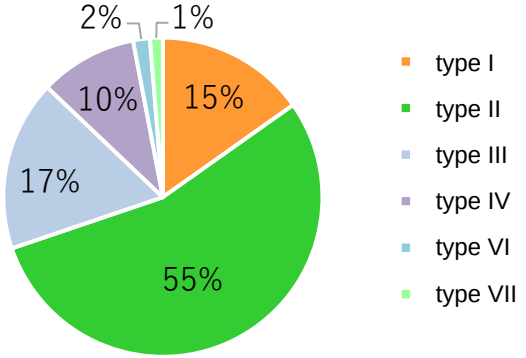
MPS is a group of LSD in which mucopolysaccharides such as dermatan sulfate (DS) and heparan sulfate (HS) accumulate.
Accumulation of mucopolysaccharides causes severe central nervous system (CNS) disorders, organ enlargement, soft tissue disorders, osteoarthritis, and cartilage disorders.



Classification of MPS (some excerpts)

MPS type	Enzyme deficiency	Accumulated substances
I	α-L-iduronidase	HS, DS
II	Iduronate-2-sulfatase	HS, DS
IIIA	Heparan N-sulfatase	HS
IIIB	α-N-acetylglucosaminidase	HS
VII	β-glucoronidase	DS, HS

Frequency of Incidence by MPS Type (Japan)*

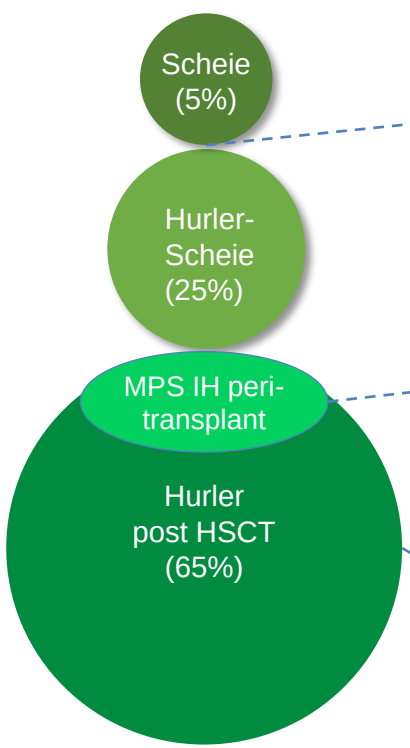


*折居　忠夫ら, ムコ多糖症 UPDATE, E-N MEDIX, 第1版第１刷, 2011: 1-2, P.8

Unmet Need and Value Proposition of JR-171

JR-171 market Potential*1

~$1,000M/Y



Attenuated MPS I	
Disease presentation	Stable DQ, organomegaly, cardiac, pulmonary, orthopedic burden
Unmet medical need (neurol.)	Deficiencies in attention, short term memory, attention, executive functioning

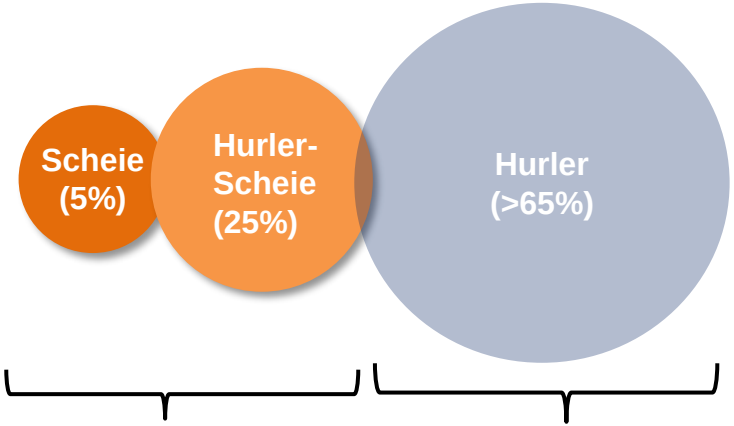
MPS I untransplanted and peri-transplant	
Disease presentation	Significant decline in DQ pre-, peri- and post transplant. *2
Unmet medical need (neurol.)	Stabilization of DQ

Severe MPS I post HSCT	
Disease presentation	Severe cognitive dysfunction, low QoL and independent living skills*3
Unmet medical need (neurol.)	Improvement in DQ, QoL,attention, executive functioning, ability to live an independent life*2

1.JCR Internal Data
2.M Aldenhoven et al., blood 125:2164-2172(2015)

MPS I – Disease Introduction

MPS I is the only LSD in which hematopoietic stem cell transplantation is an established SoC for the severe form of the disease.



	Attenuated MPS I	Severe MPS I
Disease presentation	Stable DQ, organomegaly, cardiac, pulmonary, orthopedic	Severe cognitive dysfunction, severe orthopedic and multi-organ disease burden
HSCT	-	+
Unaddressed signs and symptoms	Deficiencies in attention, short term memory, attention, executive functioning, etc.	Low but stable DQ, poor QoL, deficiency in short term memory, attention, executive functioning, do not live an independent life, orthopedic burden, etc.