FY2021 First-Half Results Briefing Session
−Research and Development Highlights−

November 2, 2021

JCR Pharmaceuticals Co., Ltd

【Securities code】4552, 1st Sec. TSE

Contents

- Research and Development Topics(Period : June to October 2021)
- Lysosome treatment pipeline
  - JR-171
  - JR-141
  - Others, Expected timeline
- Growth hormone, Regenerative medicine area
  - JR-401X
  - Others, Expected timeline

Contents

Research and Development Topics (Period : June to October 2021)

2021

◆Jul. Presentation at 16th International Symposium on MPS and Related Diseases (MPS2021)

Development pipeline for lysosomal storage diseases which apply the J-Brain Cargo® (JR-141, 171, 441, 446) were conducted oral and poster presentations in MPS2021.

◆Sep. Conclusion of **an exclusive co-development and commercialization agreement for JR-141 with Takeda Pharmaceutical** Co., Ltd in certain regions.

The two companies will collaborate to bring this therapy to patients as quickly as possible upon completion of the global Phase 3 program, which will be conducted by JCR.

◆Sep. **JR-171** was granted **Fast Track Designation** from US FDA.

Fast track is a process that expedite the review of drugs to treat serious conditions and fill an unmet medical need, so accelerated clinical development and early approval can be expected.

◆Oct. **JR-141** was granted **PRIME Designation** from the EMA.

PRIME is a scheme launched by EMA to enhance support for the development of medicines that target an unmet medical need. With PRIME designation, JCR can expect to be eligible for accelerated assessment of JR-141 at the time of application for a marketing authorization in Europe.

Development Pipeline

■ Lysosomal Storage Diseases (LSDs) ■ Other Recombinant Protein Therapeutics
■ Regenerative Medical Product

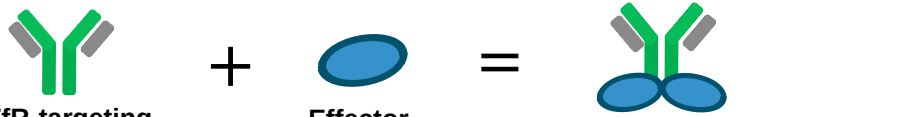
Code	Indication	Preclinical	Cinical Trials	Filed	Approved	Remarks
JR-141	MPS type II (Hunter Syndrome)		**Filed**			• ERT • J-Brain Cargo®
			Phase 3			
JR-171	MPS type I (Hurler Syndrome etc.)		**Phase 1/2**			• ERT • J-Brain Cargo® • J-MIG System®
JR-162	Pompe disease	**Preclinical**				• ERT • J-Brain Cargo®
JR-441	MPS type IIIA (Sanfilippo A Syndrome)	**Preclinical**				• ERT • J-Brain Cargo®
JR-443	MPS type VII (Sly Syndrome)	**Preclinical**				• ERT • J-Brain Cargo®
JR-446	MPS type IIIB (Sanfilippo B Syndrome)	**Preclinical**				• ERT • J-Brain Cargo®
JR-401X	SHOX deficiency		**Phase 3**			• Expanded indication of GROWJECT®
JR-142	Pediatric growth hormone deficiency		**Phase 2**			• J-MIG System® • Recombinant long-acting GH
JR-031HIE	Hypoxic ischemic encephalopathy in neonates		**Phase 1/2**			• Expanded indication of TEMCELL®HS Inj.
JTR-161/ JR-161	Acute cerebral infarction		**Phase 1/2**			• Co-developed with Teijin Limited

Contents

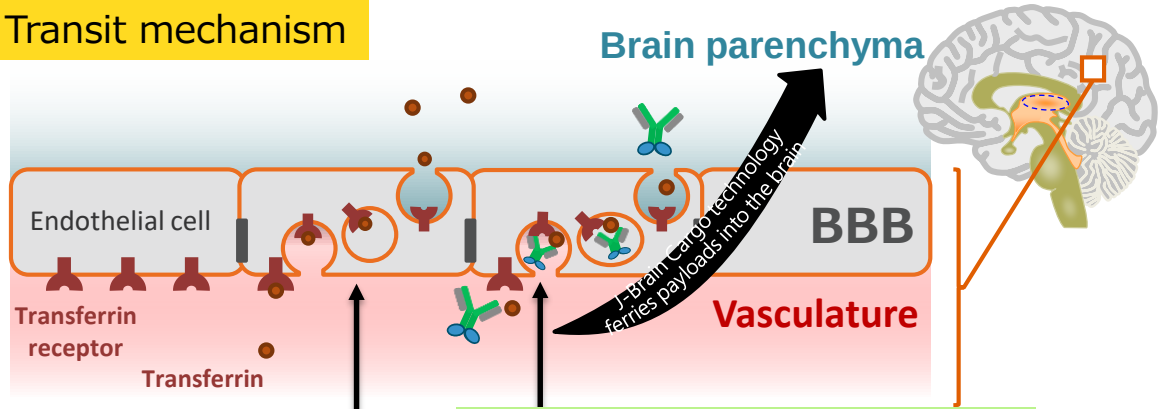
JCR's proprietary blood-brain-barrier (BBB)-penetrating technology, J-Brain Cargo®

Penetrating BBB through transferrin receptor to deliver the active ingredient into the brain

Molecular concept



Transit mechanism



Pathways which transferrin is taken up into the brain

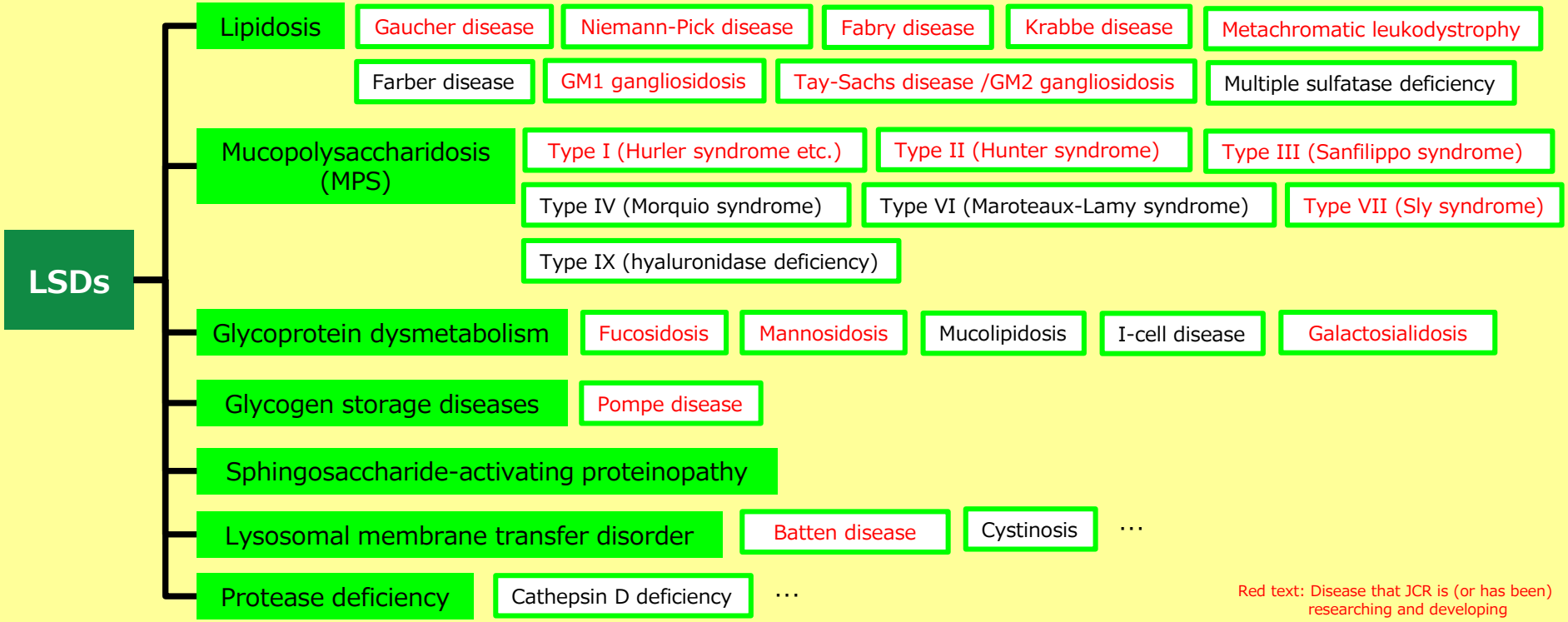
J-Brain Cargo® technology allows drugs (enzymes) that do not pass through the BBB to be taken into the brain.

Possibility of development

- Lysosomal storage diseases
- Alzheimer's disease
- Parkinson's disease
- Neuro-Oncology
- Neuro-Inflammation

Lysosomal Storage diseases（LSDs）

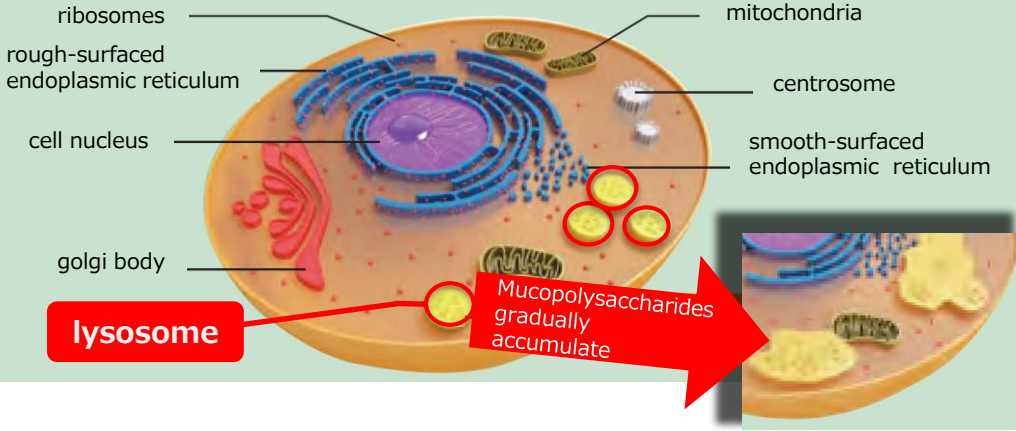
LSD is a group of rare inherited diseases in which one of enzymes in the lysosomes is congenitally missing or functionally deficient, resulting in the accumulation of metabolic waste-which fails to dissolve. Symptoms vary depending on the affected enzymes and the accumulated substrates.



Red text: Disease that JCR is (or has been) researching and developing

MPS (Mucopolysaccharidosis)

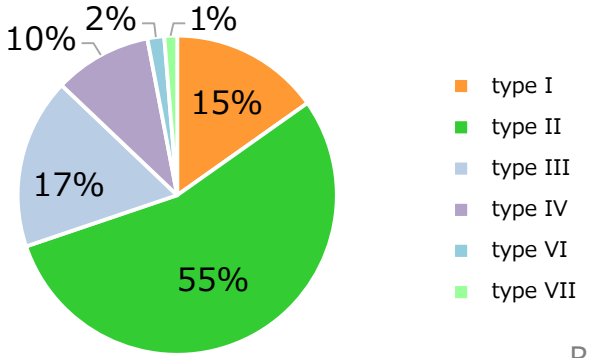
MPS is a group of LSD in which mucopolysaccharides such as dermatan sulfate (DS) and heparan sulfate (HS) accumulate.
Accumulation of mucopolysaccharides causes severe central nervous system (CNS) disorders, organ enlargement, soft tissue disorders, osteoarthritis, and cartilage disorders.



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

MPS type Ⅰ（Hurler, Hurler-Scheie, Scheie syndrome）

MPS Ⅰ（ratio）*1	Symptoms*2	Central nervous system symptoms (CNS)*2	Conventional treatments*3
Hurler (≒60%)	the most severe form, symptoms emerge shortly after birth and progress rapidly	significant developmental delay and cognitive decline	HSCT* ERT**
Hurler-Scheie (≒20%)	an intermediate phenotype	mild cognitive impairment	
Scheie (≒10%)	typically milder symptoms and a slower disease progression	mostly nomal intelligence	

※Approximately 10% of patients were classified as having an unknown or undetermined phenotype.

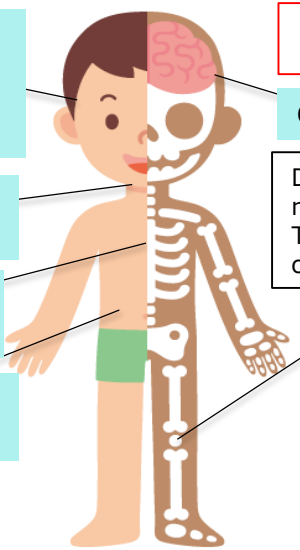
*HSCT: Hematopoietic Stem Cell Transplantation
**ERT: Enzyme Replacement Therapy

characteristic coarse facial features
corneal clouding
hearing loss

airway obstruction
→ respiratory failure

heart valve disease
→ cardiac failure

hepatosplenomegaly
umbilical hernia



Main symptoms*2

CNS symptoms

Develop symptoms such as psychomotor retardation.
The developmental age peaks at 2-3 years of age.

short stature
cervical spine compression
joint stiffness and contractures

◆It greatly reduces quality of life (QOL) in patients with CNS or systemic symptoms.

JR-171

Drugs are delivered to both the body and the brains, by adapting **J-Brain Cargo®** and passing the BBB, can be **expected to improve** the systemic symptoms and **CNS symptoms.**

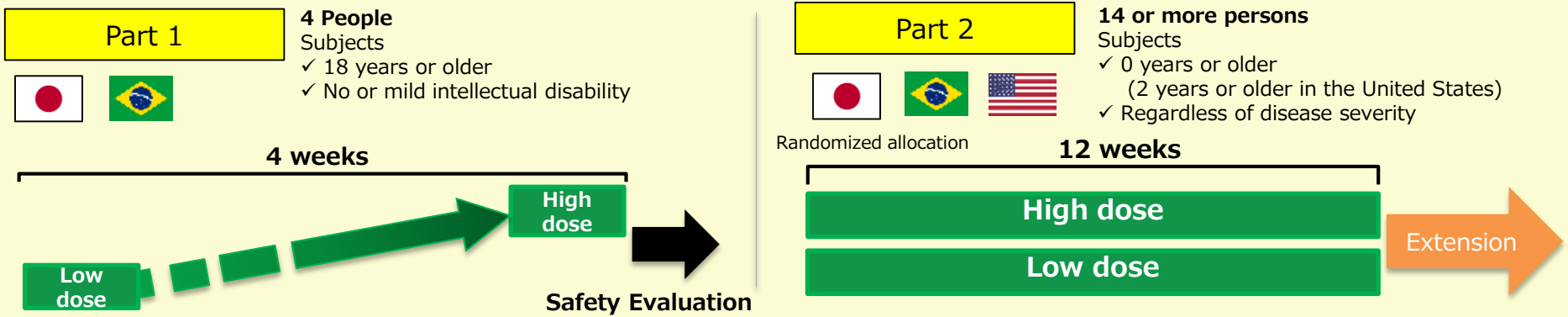
*1:Tomatsu S, Lavery C, Giugliani R, Harmatz P, Scarpa M, Wegrzyn G, et al. Mucopolysaccharidoses Update (2 Volume set); 2018. Chapter 9, Mucopolysaccharidosis type I: clinical feautures biochemistry, diagnosis, genetics, and treatment. Mucopolysaccharidoses update; p. 143-64.
*2:折居 忠夫ら, ムコ多糖症 UPDATE, E-N MEDIX, 第1版第1刷, 2011: P.xii,2,102-103
*3:Michael Beck, MD, The natural history of MPS I: global perspectives from the MPS I Registry, Genetics in Medicine, October 2014: P.759-765.

Progress of JR-171

JR-171 BBB-penetrating α-L-iduronidase (rDNA origin)

Phase 1/2 Global Clinical Trial（JR-171-101）: Brief Summary

◆ **JR-171 was granted Fast Track Designation from US FDA in Sep. 2021.**



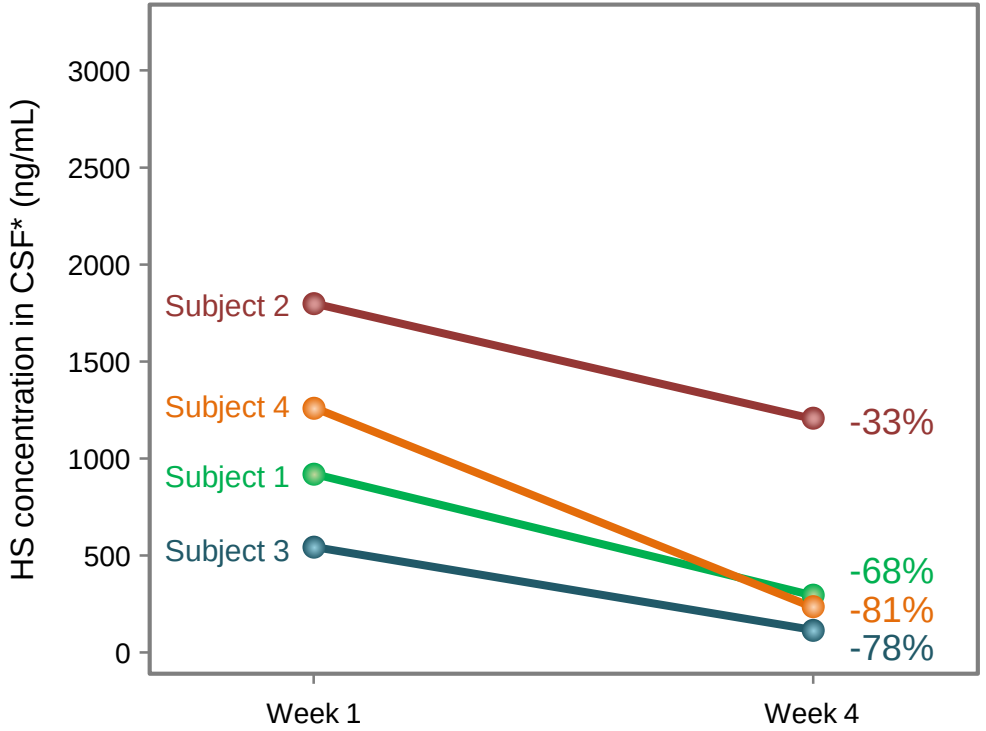
	Part 1	Part 2
Primary endpoint	Safety	
Secondary and exploratory endpoints	・Plasma drug concentrations and pharmacokinetic parameters ・Exploratory Efficacy for Central Nervous System Symptoms and Systemic Symptoms	
Allocation	Japan・Brazil	Japan・Brazil・USA
Summary	clinicaltrials.gov Identifier : NCT04227600	

Progress of JR-171

JR-171 BBB-penetrating α-L-iduronidase (rDNA origin)

Phase 1/2 Global Clinical Trial（JR-171-101）： CSF*-heparan sulfate (HS) levels in Part 1 subjects

*CSF: Cerebrospinal fluid



Subjects background（N＝4）

- Scheie syndorome
- No intellectual disability
- Prior treatment with existing ERT
- No history of HSCT

Results

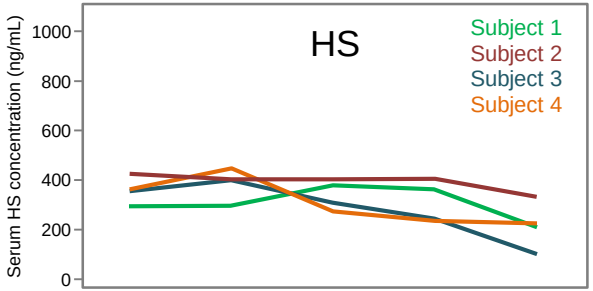
CSF HS concentrations decreased in all subjects (mean decrease of 65%)

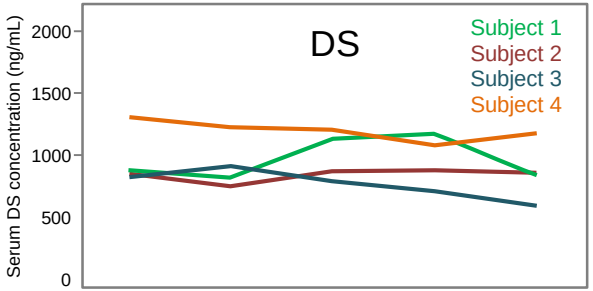
Progress of JR-171

JR-171 BBB-penetrating α-L-iduronidase (rDNA origin)

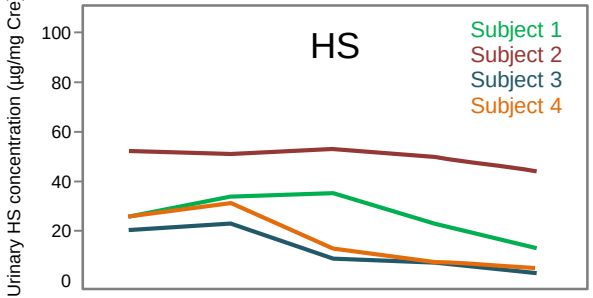
Phase 1/2 Global Clinical Trial（JR-171-101）: heparan sulfate/dermatan sulfate (HS/DS) levels in Part1 subjects

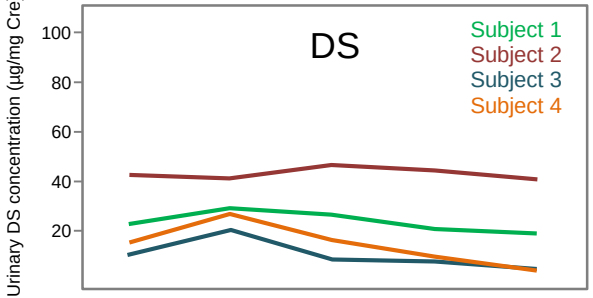
serum





urine





Results

HS/DS concentrations remained stable in all subjects throughout the treatment period.

Progress of JR-171

JR-171 BBB-penetrating α-L-iduronidase (rDNA origin)

Phase 1/2 Global Clinical Trial（JR-171-101）: Brief Summary

Part1 : Summary

- CSF HS levels decreased from baseline in all subjects
- There were no serious safety concerns.

Current Status and Future Planning

- JR-171-101 Part 2 with a 12-week treatment is in progress.
- Phase 3 pivotal study to confirm long-term safety and efficacy of JR-171 is planned

Progress of JR-141

JR-141

IZCARGO® (Brand name in Japan)
pabinafusp alfa (BBB-penetrating iduronate-2-sulfatase, rDNA origin)

JR-141 Cinical Development Package

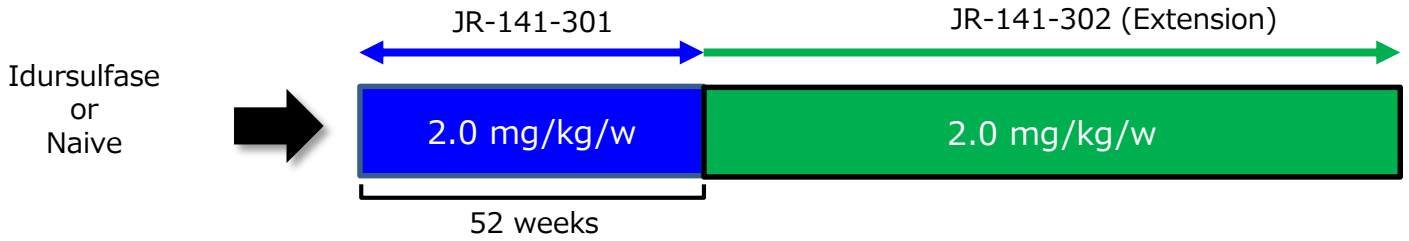
	Japan	Brazil	Global (US, Brazil, UK, France, Germany, Spain)
Clinical trials for application for manufacturing and marketing approval	• Phase 1/2 clinical trial • Phase 3 clinical trial ↓ Manufacturing and marketing approval (Mar. 23, 2021) Listed in the National Health Insurance (NHI) reimbursement price list and launched (May 19, 2021)	• Phase 2 clinical trial ↓ **Application for marketing approval (Dec. 22, 2020)**	• Phase 3 clinical trial ↓ **Initiated recruitment for Global Phase 3 clinical trial (2022)**
Clinical trials to obtain long-term clinical data	↓ **Post-marketing clinical trials (approx. 10 years) in progress**	↓ **Long-term administration study ongoing**	

Progress of JR-141

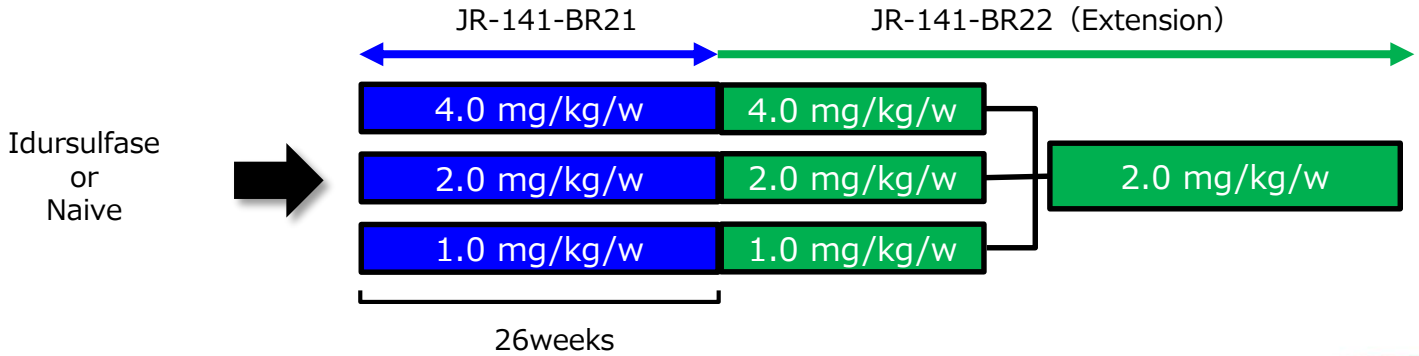
JR-141

IZCARGO® (Brand name in Japan)
pabinafusp alfa (BBB-penetrating iduronate-2-sulfatase, rDNA origin)

JR-141-301(phase 2/3) and JR-141-302(Extension) clinical trials in Japan



JR-141-BR21(phase 2) and JR-141-BR22(Extension) clinical trials in Brazil



Progress of JR-141

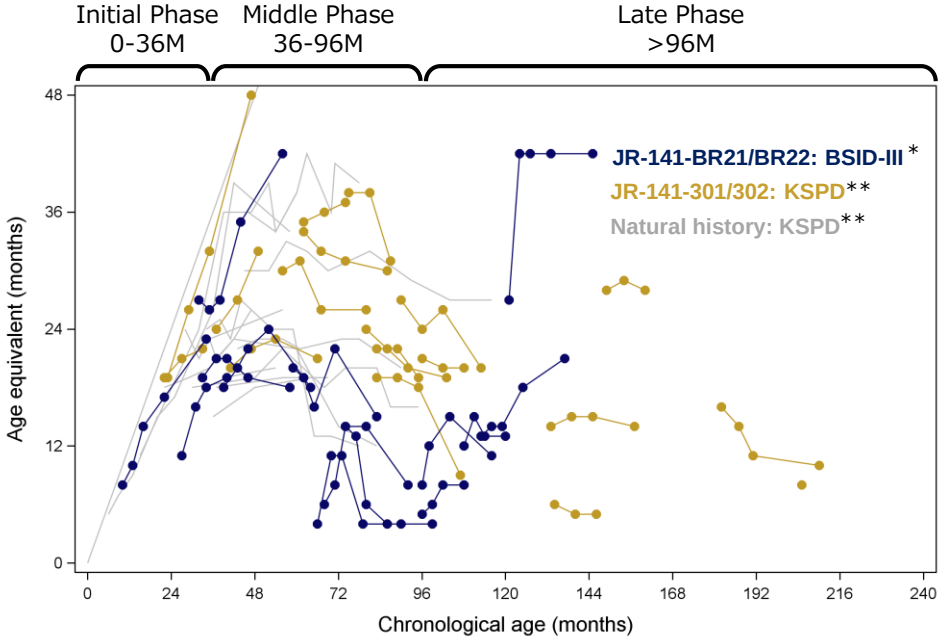
JR-141

IZCARGO® (Brand name in Japan)
pabinafusp alfa (BBB-penetrating iduronate-2-sulfatase, rDNA origin)

Phase 3 clinical trials in Japan (JR-141-301/302)

Phase 2 clinical trials in Brazil (JR-141-BR21/BR22)

Merged age equivalent score in severe patients overlaid with the natural history



- Subjects who began treatment with JR-141 in infancy showed long-term improvement over the trials period.
- It showed that stable developmental trends for up to 2 years, in contrast to the natural history of severe MPS type II.

*BSID-III (The Bayley Scales of Infant and Toddler Development, Third Edition) : Assessment of cognitive, language, motor, social-emotional, and adaptive behaviors in infants aged 1-42 months

**KSPD (Kyoto. Scale of Psychological. Development) :
Observations and evaluations of responses to test items arranged by age group for three domains: postural motor, cognitive/adaptive, and language/social.

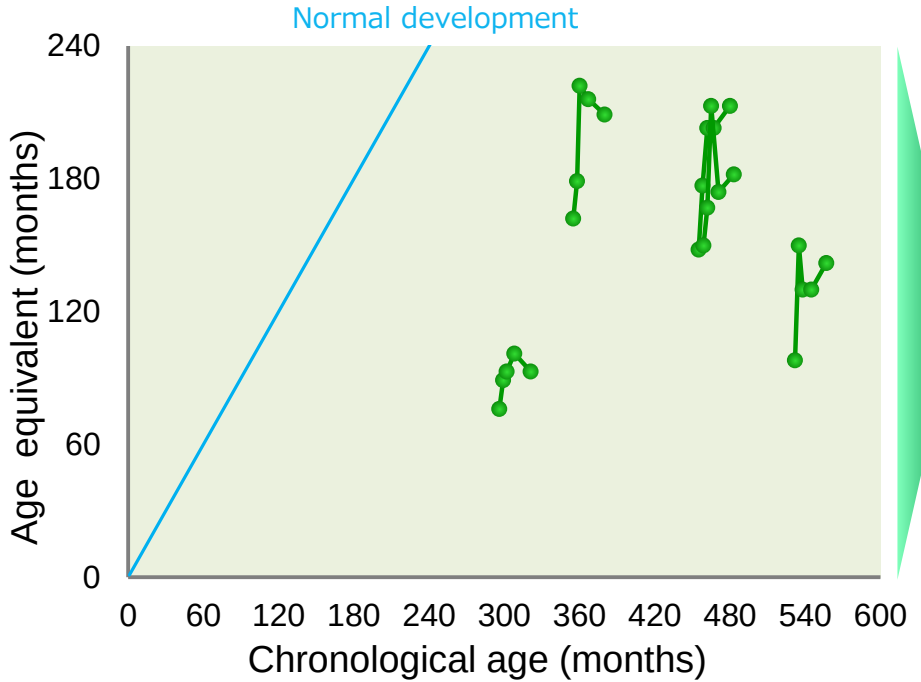
Progress of JR-141

JR-141

IZCARGO® (Brand name in Japan)
pabinafusp alfa (BBB-penetrating iduronate-2-sulfatase, rDNA origin)

Phase 2 clinical trials in Brazil (JR-141-BR21/BR22)

Kaufman (KABCII)* Assessment in subjects with attenuated symptoms.



Observations and conclusions:

- Mean AE in attenuated subjects changed by ~41 months during a 24- months treatment period, indicating a neurological improvement in this adult population

Absolute change from baseline

VISIT	Mean (SD)	Median [min - max]
Week 52	37.7 (15.3)	32.2 [23.4 – 54.8]
Week 104	40.9 (17.9)	44.0 [16.8 – 64.8]

*KABCII is a test that measures intelligence from two measures: "cognitive processing ability" and "mastery" in children from 2 years and 6 months to 18 years of age. Cognitive processing is focused on "successive, concurrent, planning, and learning" and learning is focused on "word record, reading, writing, and arithmetic".

JR-141 Clinical Trials

JR-141

IZCARGO® (Brand name in Japan)
pabinafusp alfa (BBB-penetrating iduronate-2-sulfatase, rDNA origin)

Narrative Reports (JR-141-301 and JR-141-BR22)

Japan (JR-141-301)

Language

- 12/18 of narrative reports from severe patients showed an improvement in language.
- Changes observed include increase word count, increased number of conversations, and resumed singing.

Liveliness/Expression

- 11/18 of narrative reports demonstrated an improvement in liveliness/expression
- Changes observed include increase in activity, richer facial expression

Brazil (JR-141-BR21/BR22)

General changes observed

- Generally positive changes were found in language, motor skills and liveliness/ expression
- Even the patients without marked improvement in language or motor function showed positive changes in liveliness/ expression

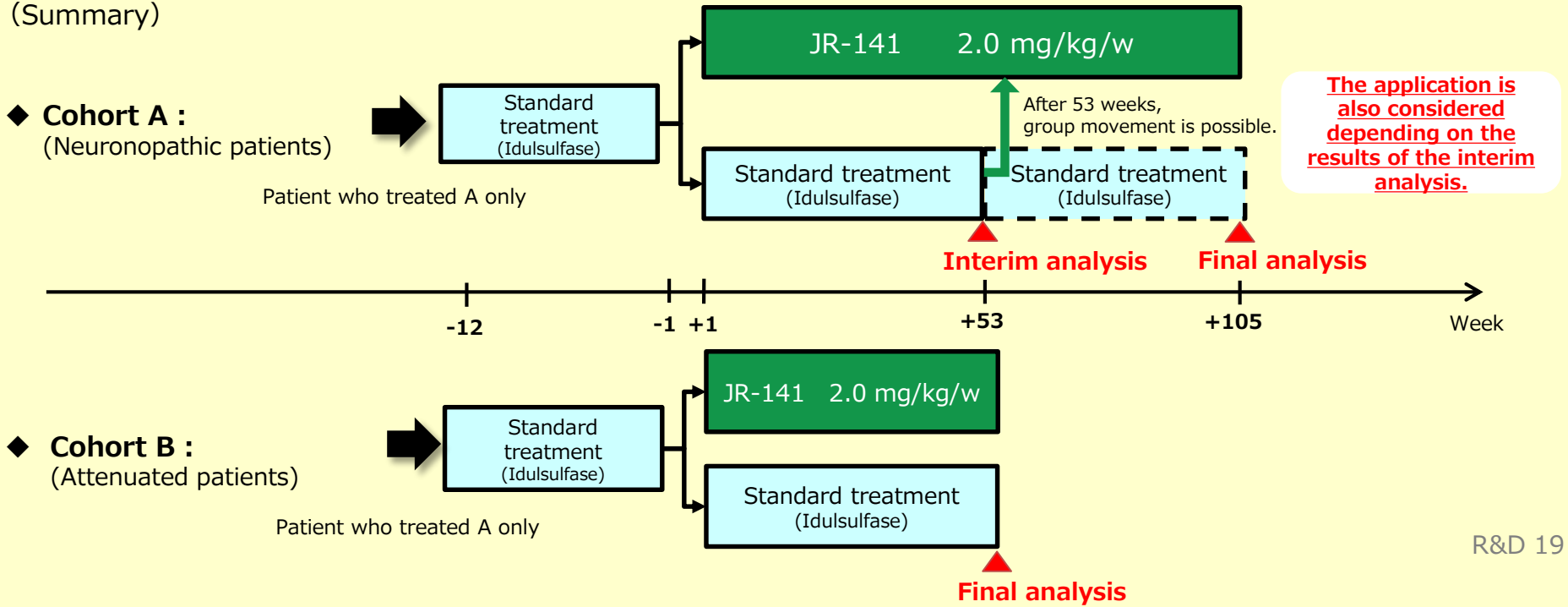
JR-141 Global Trial Phase 3 (JR-141-GS31)

JR-141

IZCARGO® (Brand name in Japan)
pabinafusp alfa (BBB-penetrating iduronate-2-sulfatase, rDNA origin)

◆ **Designation of PRIME from the EMA in Oct. 2021**

(Summary)



Lysosomal diseases : Expected timeline

Note: Information after 2022 is a plan at this stage and is subject to change

	2021	2022	2023	2024
JR-141 pabinafusp alfa (MPS II)	Brazil : Filed **Global : Initiation of Phase 3 trial**			• SAKIGAKE（PMDA） • Orphan Drug（PMDA） • Orphan Drug（FDA） • Fast Track（FDA） • Orphan Drug（EC） • PRIME（EMA）
JR-171 (MPS I)	**Global : Phase 1/2 trial (Ongoing)**		Initiation of Phase 3 trial	• Orphan Drug (FDA) • Fast Track（FDA） • Orphan Drug（EC）
JR-441 (MPS IIIA)	**Non-clinical (Ongoing)**	Initiation of Phase 1/2 trial		
JR-162 (Pompe disease)	**Non-clinical (Ongoing)**		Initiation of Phase 1/2 trial	
JR-443 (MPS VII)	**Non-clinical (Ongoing)**		Initiation of Phase 1/2 trial	
JR-446 (MPS IIIB)	**Non-clinical (Ongoing)**		Initiation of Phase 1/2 trial	

JCR's 17 ERT pipeline for Lysosome diseases

★ : Presentation at 18th Annual **WORLD*Symposium*™2022**　□ : Project with progress in development stage since May 2021

	Indications with existing somatic ERT (Worldwide)	Indications with no established standard of care (Worldwide)
Filed	JR-141 Brazil: MPS II (Hunter) ★	
Clinical	JR-171 Global: MPS I (Hurler etc.) ★; JR-141 Global: MPS II (Hunter)	
Non-clinical	JR-162: Pompe	JR-441: MPS IIIA (Sanfilippo A) ★; JR-446: MPS IIIB (Sanfilippo B)
Process development	JR-443: MPS VII (Sly)	Fucosidosis; Krabbe disease; Batten, Infantile (CLN1); Tay-Sachs disease
PoC in model mouse	Niemann-Pick; Batten, Late-infantile; Gaucher	GM1 Gangliosidosis; MLD; α-Mannnosidosis
Basie Res.		Galactosialidosis

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- Lysosome treatment pipeline
  - JR-171
  - JR-141
  - Others, Expected timeline
- Growth hormone, Regenerative medicine area
  - JR-401X
  - Others, Expected timeline

JR-401X: About SHOX deficiency

JR-401X Expanded indication of GROWJECT® : SHOX deficiency

- SHOX deficiency is a congenital disorder caused by micro deletions, duplications, or mutations that result in loss of function of a growth-gene SHOX (Short stature homeobox containing gene) present on the sex chromosomes.
- The potential number of patients in Japan is expected to range from 450 to 500 patients/year, but the number of patients diagnosed in clinical practice is extremely small, because of necessary for genetic diagnosis.

Recombinant Human Growth Hormone

GROWJECT®

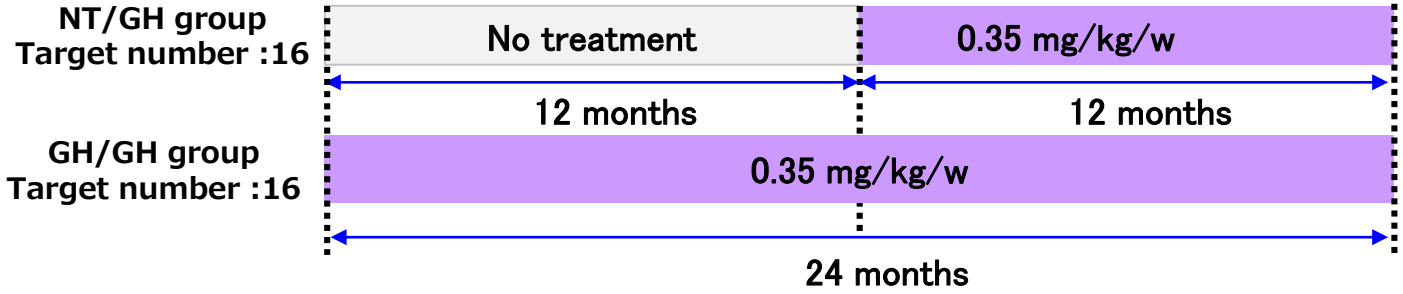
Indications (As of Nov. 2021)

- Growth Hormone Deficiency
- Turner Syndrome
- Adult Growth Hormone Deficiency
- Small for Gestational Age

JR-401X Clinical Trials Phase 3

JR-401X GROWJECT® additional indication: SHOX deficiency

JR-401X-301 : Design（JAPIC trial ID : JapicCTI-183946）



Efficacy endpoints

- Primary endpoint
  - ✓ Δ chronological age - equivalent height SDS（for 12 months after the start of the study）
- Secondary endpoints
  - ✓ chronological age - equivalent height SDS
  - ✓ chronological age - growth velocity SDS
  - ✓ Δchronological age - growth velocity SDS
  - ✓ growth velocity
  - ✓ bone age
  - ✓ Δ bone age
  - ✓ Δ bone age ／Δchronological age
  - ✓ bone age - equivalent height SDS
  - ✓ Δ bone age - equivalent height SDS
  - ✓ IGF-I SDS in serum

JR-401X: Results of efficacy data analysis (At the end of 12 months)

JR-401X

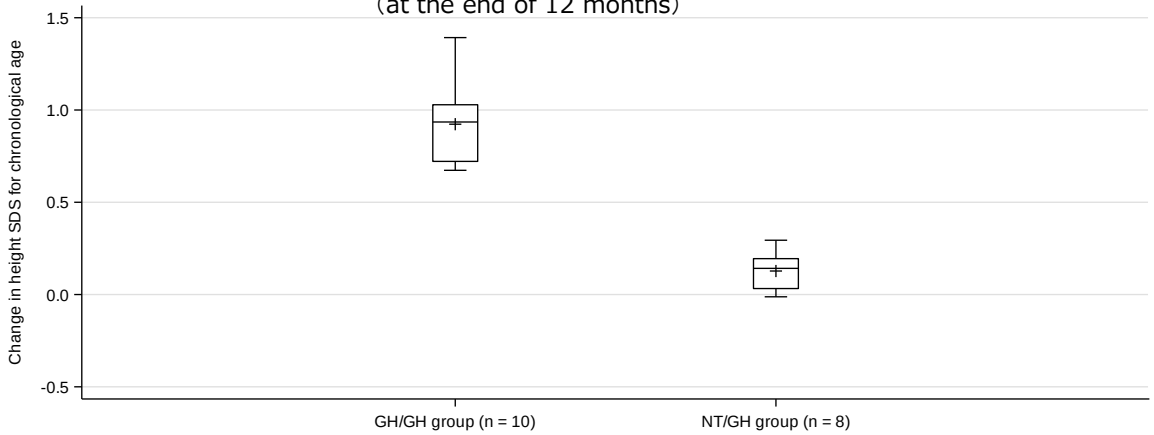
Long-acting recombinant growth hormone
Growject ® additional indication: SHOX deficiency

		GH/GH group N=10	NT/GH group N=9	Difference
Change in height SDS for chronological age	N	10	8	
	mean(SD)	0.932(0.213)	0.127(0.105)	0.796(0.174)
	median	0.935	0.142	p<0.001
	[min-max]	[0.67 - 1.39]	[-0.01 - 0.29]	
	95%CI	0.771 – 1.075	0.040 - 0.215	0.621 - 0.971

CI : confidence interval, SD : standard deviation

ΔSummary statistics of chronological age-equivalent height
(at the end of 12 months)

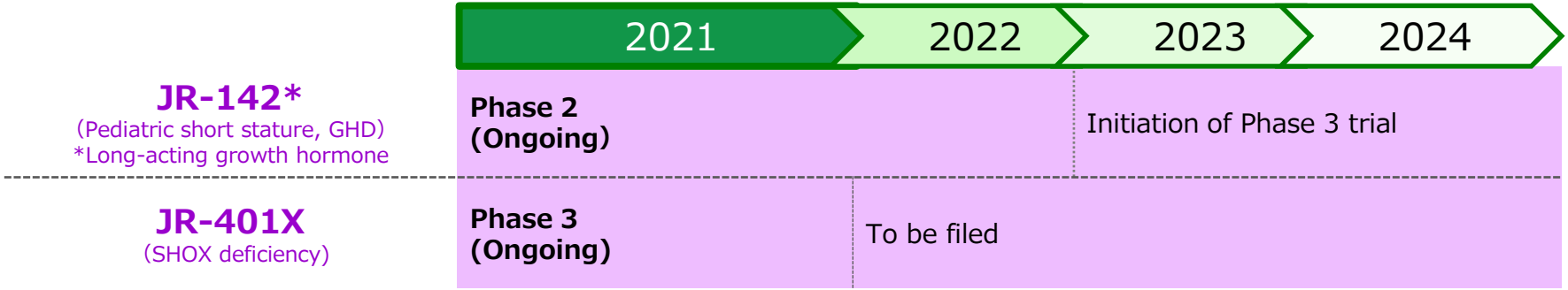
Analysis set : FAS



Statistically significant differences were observed in the primary and secondary endpoints between the GROWJECT® group and the no-treatment group.

Other pipeline (Growth Hormone and regenerative medicine area)

Expected timeline (Growth Hormone area)



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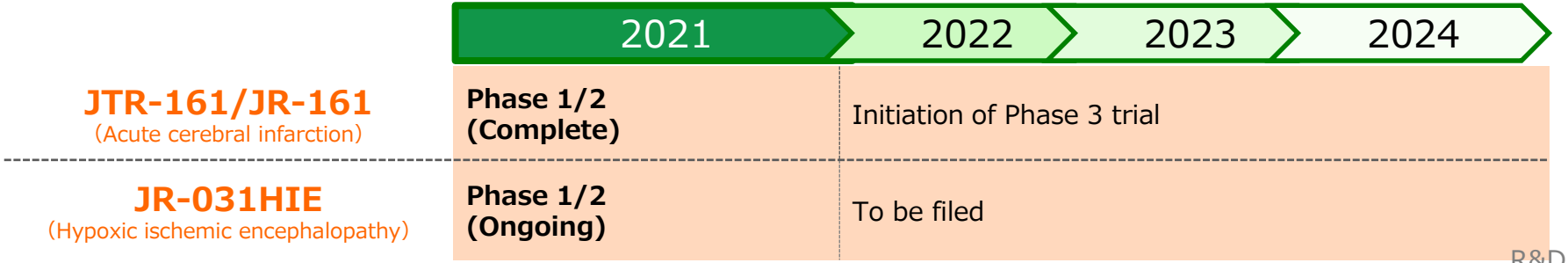
Expected timeline (regenerative medicine area)



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– REVOLUTION into the Future –