Clinical Study Protocol

Phase I/II study of JR-171 in patients with mucopolysaccharidosis type I

Protocol Number: JR-171-101

Version Number: ver. 6.00

Compound: JR-171

Study Phase: Phase I/II

Sponsor: JCR Pharmaceuticals Co., Ltd.

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National Clinical Trial (NCT) Identified Number/IND Number:

NCT04227600

Approval Date: 12 November 2021

Sponsor Responsible:

[redacted]

Clinical Study Manager, Development Division

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Signature page:

I have read Protocol JR-171-101. I agree to conduct the study as detailed in this protocol and in compliance with Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practices (ICH-GCP) and all applicable regulatory requirements and guidelines.

Principal Investigator		**Date**

As the sponsor representative, I confirm that JCR Pharmaceuticals Co., Ltd. will comply with all sponsor obligations as detailed in all applicable regulations and guidelines. I will ensure that the Principal Investigator is informed of all relevant information that becomes available during the conduct of this study.

Clinical Study Manager **JCR Pharmaceuticals Co., Ltd.**		**Date**

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Ver. 1.00.000 (Original Protocol)	8 January 2020
Ver. 2.00.000	20 April 2020
Ver. 2.01.000	18 June 2020
Ver. 2.02.000	20 July 2020
Ver. 2.03.000	31 August 2020
Ver. 3.00	27 November 2020
Ver. 4.00	5 February 2021
Ver. 5.00	20 August 2021
Ver. 6.00	12 November 2021

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Statement of Compliance

The study will be carried out in accordance with the following: the Declaration of Helsinki- Ethical Principles for Medical Research Involving Human Subjects- which was adopted by the 18th World Medical Association General Assembly and its amendments; ICH-GCP and related regulations/regional requirements; this protocol.

In the United States (US), the US Code of Federal Regulations (CFR) is applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56 and 21 CFR Part 312).

The protocol, informed consent form(s) (ICF(s)), and all subject materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the ICF(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the ICF will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from patient or the patient's legally acceptable representative.

1. Protocol Summary

1.1 Synopsis

Protocol Title:
Phase I/II study of JR-171 in patients with mucopolysaccharidosis type I

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To determine the safety and tolerability of JR-171 in patients with mucopolysaccharidosis type I (MPS I)	• Frequency and severity of adverse events (AEs) and their relationship to JR-171 • Changes in laboratory parameters (hematology, biochemistry, serum iron tests and urinalysis) • Changes in vital signs (pulse rate, body temperature, blood pressure, respiratory rate and percutaneous oxygen saturation) • Clinically meaningful changes in 12-lead electrocardiogram • Anti-drug antibody production (anti-human α-L-iduronidase (anti-human IDUA) and anti-JR-171 antibodies) • Frequency of infusion associated reactions (IARs)
Secondary	
To evaluate the plasma pharmacokinetics (PKs) of JR-171 after intravenous administration	• Assessment of plasma drug concentrations and pharmacokinetic parameters
To explore the efficacy of JR-171 for central nervous system (CNS) and somatic symptoms of MPS I	• [redacted] • Changes in heparan sulfate (HS) and dermatan sulfate (DS) concentrations in the CSF from baseline to Week 4 in Part 1 or Week 12 in Part 2 • Changes in CSF opening pressure from baseline to Week 4 in Part 1 or Week 12 in Part 2 • Changes in urinary HS and DS concentrations from baseline to each time point • Changes in serum HS and DS concentrations from baseline to each time point • Changes in liver and spleen volumes from baseline to Week 5 in Part 1 or Week 13 in Part 2 • Changes in cardiac function from baseline to Week 5 in Part 1 or Week 13 in Part 2 • Changes in 6-minute walk test from baseline to Week 13 (Part 2 only)

	• Assessment of the other clinical findings related to neurocognitive and behavioral changes • Changes in outcome of the Brief Visuospatial Memory Test-Revised (BVMT-R) and Hopkins Verbal Learning Test-Revised (HVLT-R) from baseline* to Week 13 (Part 2 only) • Changes in outcome of the Test of Variables of Attention (T.O.V.A.) from baseline* to Week 13 (Part 2 only) • Changes in outcome of the Pediatric Quality of Life Inventory Family Impact Module (PedsQL-FIM) from baseline* to Week 13 (Part 2 only)

* Use the data determined in the screening period as the baseline data.

Study Population:
Male or female MPS I patients (18 years old or older in Part 1, and 2 years or older (any age in Japan and Brazil) in Part 2).

Inclusion Criteria
1. A patient aged 18 years or older in Part 1 or 2 years or older (any age in Japan and Brazil) in Part 2, at the time of informed consent.
2. A patient from whom written informed consent can be obtained. If the patient is aged under 18 years (20 years in case of Japan) at the time of assent or willingness to participate in the study cannot be confirmed due to MPS I-related intellectual disability, informed permission from the patient's legally acceptable representative (*e.g.*, his/her parents or guardians) needs to be obtained instead of his/her consent. Even in this case, written informed consent should be obtained from the patient, wherever possible.
3. A patient diagnosed with MPS I based on any one of the following criteria:
   - Activity of the IDUA enzyme below 10% of the lower reference level in leucocytes or cultured skin fibroblasts, AND increased age-related urinary levels of glycosaminoglycans (GAGs) (before enzyme replacement therapy (ERT)).
   - Activity of the IDUA enzyme below 10% of the lower reference level in leucocytes or cultured skin fibroblasts, AND presence of one pathogenic mutation in each of the alleles of the IDUA gene.
   - Increased age-related urinary levels of GAGs (before ERT), AND presence of one pathogenic mutation in each of the alleles of the IDUA gene.
4. A patient diagnosed as having mild or no MPS I-related intellectual disability (able to report their own subjective symptoms) by the principal investigator or subinvestigator (Part 1 only).
5. A patient who has received laronidase continuously for at least 12 weeks and has received laronidase at a stable dosage for the 2 weeks immediately before the initial administration of JR-171 (except for a laronidase naïve patient or a patient who has previously been treated by hematopoietic stem cell transplantation (HSCT)).
6. Female patient or male patient whose co-partner is of child-bearing potential agrees to use a medically accepted, highly effective method of contraception, such as spermatocidal gel plus condom, an intrauterine device or oral contraceptives until one month after the final administration.

Exclusion Criteria
1. A patient who has received gene therapy treatment.
2. A patient who, in the opinion of the principal investigator or subinvestigator, cannot undergo lumbar puncture, including those who have a difficulty in taking position for lumbar

puncture due to joint contracture and those who are likely to develop dyspnea during lumbar puncture.
3. A patient who is pregnant or lactating.
4. A patient who has developed serious drug allergy or hypersensitivity to any drugs, in the opinion of the principal investigator or subinvestigator, is inappropriate for participation in the study.
5. A patient who has received another investigational product within the 12 months prior to enrollment in the study.
6. A patient who, in the opinion of the principal investigator or subinvestigator, is ineligible to participate in the study in consideration of patient's safety.

Investigational Product:
JR-171

Overall Design:
This is a phase I/II, open-label, multicenter (six sites in total are planned), multinational (Japan, Brazil and the US) study for the treatment of MPS I.

Disclosure Statement:
This is an open-label, first-in-human study of JR-171 designed to evaluate the safety, PKs and explore the efficacy.

Dosing and Administration:
Part 1
Subjects aged 18 years or older shall receive an initial administration of JR-171 as an intravenous infusion at a dose of 0.1 mg per kg of body weight. The dose level shall be then increased to 1.0 mg/kg for the second administration, to 2.0 mg/kg for the third administration, and to 4.0 mg/kg at the fourth administration. When the principal investigator or subinvestigator concludes that JR-171 dose increase will pose no problem based on the safety information collected from the administered dose to the first and second subject, JR-171 will be increased to the next dose upon approval of the sponsor. The start date of JR-171 administration of the second subject should be at least 1 week after the start date of JR-171 administration of the first subject. Once the two subjects complete all the four times of administrations and the safety of JR-171 is confirmed, then the administration for the third and subsequent subjects may be started. If the first or second subject is discontinued from the study during the dose-escalation phase (until the safety evaluation of the fourth administration), the next third subject will stay in the hospital and will be supervised until 21 hours after the end of each administration to assess safety. JR-171 is to be administered at intervals of 1 week. The total volume of infusion should be administered over approximately 3 hours, but may be extended to a longer period at the discretion of the principal investigator or subinvestigator, considering safety concerns, including any IARs, etc.

Part 2
The first subject aged 6-17 years and the first subject aged 2-5 years (0-5 years in Japan and Brazil) shall each receive an initial dose of JR-171 as an intravenous infusion at a dose of 1.0 mg per kg of body weight. The dose level shall be then increased to 2.0 mg/kg for the second administration, and to 4.0 mg/kg for the third administration. From the fourth to twelfth administrations, JR-171 shall be administered at 4.0 mg/kg. If the first subject aged 6-17 years or the first subject aged 2-5 years (0-5 years in Japan and Brazil) is discontinued from the study during the dose-escalation phase (until the safety evaluation of the third administration), the next subject for the same age group shall receive JR-171 in a dose-escalation manner as described above (the schedule of assessments will also be the same as those for the first subject in each age group).

The first subject aged 2-5 years (0-5 years in Japan and Brazil) can receive the initial administration at least 1 week after the first subject aged 6-17 years receives the initial administration. The second subject in each age group in Part 2 could be administered with JR-171 after the safety evaluation of the third administration of the first subject in each age group.
Subjects other than the above of aged 2 years or older (any age in Japan and Brazil) shall be randomly assigned to either one of 2 groups in a 1:1 ratio, and receive 2.0 or 4.0 mg of JR-171 per kg of body weight 12 times as an intravenous infusion. JR-171 will be administered over approximately 3 hours every week over a 12 week period. The treatment time may be extended to a longer period at the discretion of the principal investigator or subinvestigator, considering safety concerns, including any IARs, etc.

In Part 1 and Part 2, the dose of JR-171 will be calculated based on the latest body weight value collected at a scheduled visit.

Concomitant Therapies/Medications:
Concomitant therapies/medications can be used during this clinical study when required.
Transfusions or maintenance transfusions for purpose of establishment an intravenous line, diluents for injections, bases for in-hospital preparations, disinfectants and drugs used in preparative treatments *e.g.,* anesthetic (other than drugs with anticipated effects) are not considered as concomitant therapies/medications.

Prohibited Therapies/Medications:
Investigational products other than JR-171, laronidase, HSCT

Number of Subjects
Part 1: 4 subjects
Part 2: Approximately 15 subjects in total.

Duration of Study:

Study start (enrollment start)	Enrollment end	Study end	Completion of data analyses
September 2020	March 2022	August 2022	January 2023

Part 1: 5-8 weeks (including 1-4 weeks as a screening period)
Part 2: 13-16 weeks (including 1-4 weeks as a screening period)

Independent Data Safety Monitoring Committee (IDSMC): Yes

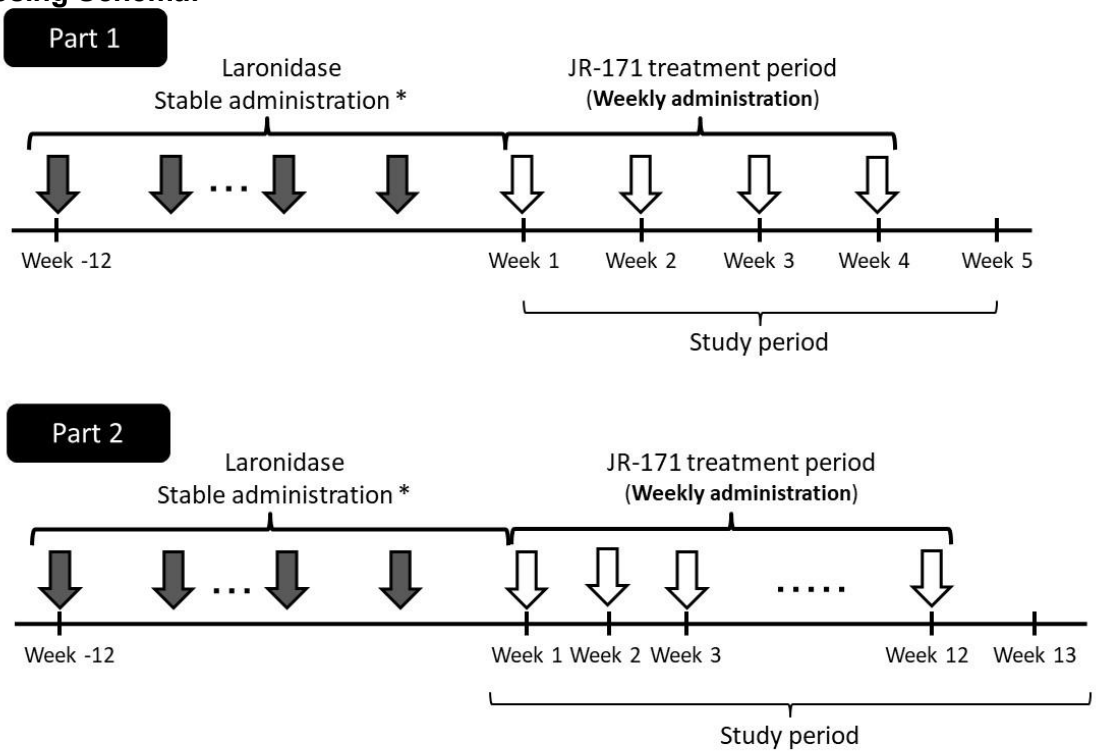
1.2 Schema
Since this is a first-in-human study of JR-171, the JR-171-101 study will proceed in stages while confirming that safety is ensured. For the detailed procedures to confirm safety, refer to Section 6.6.1.

Part	Number of subjects	Dose
Part 1	4 subjects	Initial administration : 0.1 mg/kg single dose Second administration : 1.0 mg/kg single dose Third administration : 2.0 mg/kg single dose Fourth administration : 4.0 mg/kg single dose
Part 2[a), b)]	At least 2 subjects[c)]	Initial administration : 1.0 mg/kg single dose Second administration : 2.0 mg/kg single dose Third administration : 4.0 mg/kg single dose After third administration : 4.0 mg/kg/week, 9 times Twelve administrations in total
	2.0 mg/kg/week group: At least 6 subjects 4.0 mg/kg/week group: At least 6 subjects	2.0 mg/kg/week, 12 times 4.0 mg/kg/week, 12 times

a) Part 2 is started only after the safety is confirmed in Part 1 by the IDSMC. Subjects participating in Part 1 are excluded from Part 2.
b) Approximately 15 subjects will be enrolled in total.
c) Starting dose of 1 mg/kg in the first subject aged 6-17 years and the first subject aged 2-5 years (0-5 years in Japan and Brazil).

Subjects who complete Part 2 of the JR-171-101 study will be eligible to participate in the extension study (protocol number: JR-171-102 study) and to continue receiving JR-171.

Dosing Schema:



***Only for subjects who have been given enzyme replacement therapy before this study:**
Subjects receiving laronidase at the stable dose for at least 12 weeks as standard treatment are to be switched to JR-171.

1.3 Schedule of Activities

Part 1

Observation/test timing	Pre-screening	Screening test	Registration	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Discontinuation
Visit window	-	28 days before Day 1 (Day -28) to Day -7	-	Day -2 to Day 1	Day 1	Day 8 to Day 11	Day 15 to Day 18	Day 22 to Day 25	Day 29 to Day 32	Within 28 days from discontinuation
JR-171 administration					X	X	X	X		
Informed consent	X									
Subject baseline characteristics[a]		X								
Assessment based on inclusion/exclusion criteria			X							
Pregnancy testing (female subjects of childbearing potential only)		X								
Vital signs[b]		X[c]		X[d]	X[e]	X[e]	X[e]	X[e]	X[c], [f]	X[c]
Laboratory tests[f]		X		X		X	X	X	X	X
Antibodies[f]				X[g]		X[h]			X[g]	X[g]
Plasma drug concentration[i]					X	X	X	X		
Drug concentration in CSF				X[f]				X[j]		X[k]
HS and DS concentrations in CSF				X[f]				X[j]		X[k]
CSF opening pressure				X[f]				X[j]		X[k]
Urinary HS and DS concentrations (including measurement of creatinine for concentration adjustment)[f]				X		X	X	X	X	X
Serum HS and DS concentrations[f]				X		X	X	X	X	X
Liver and spleen volumes[f]				X					X	X
Cardiac function[f]				X					X	X
Other clinical findings related to neurocognitive and behavioral changes					→	→	→	→	→	→
12-lead electrocardiogram[f]		X							X	X
Cross-reactive immunologic material[l]				→	→	→	→	→	→	→
AEs	→	→	→	→	→	→	→	→	→	→
Concomitant therapies/medications					X	X	X	X	X	X

a) Neurocognitive testing and adaptive behavior assessment will be performed before the first infusion of JR-171.
b) Vital signs: pulse rate, body temperature, blood pressure, respiratory rate, percutaneous oxygen saturation and body weight. During the infusion of JR-171, it is necessary to monitor other than body weight (see Section 6.1 and 8.2.3).
c) Excluding body weight
d) Only body weight is measured.
e) Perform before and after administration of JR-171 except for body weight. Body weight will be measured at either measuring point.
f) Perform before administration of JR-171 (or before laronidase at Week 5, for subjects who will receive laronidase after completing the JR-171-101 study)
g) Anti-IDUA and anti-JR-171 antibodies
h) Anti-JR-171 antibodies
i) Blood specimens should be collected by following the "PK sampling schedule (plasma drug concentration)".
j) Performed within 5 hours after the end of administration of JR-171
k) Performed if deemed feasible by the principal investigator or subinvestigator
l) Samples will be collected once in Part 1 and obtained before JR-171 administration during the visit.

Part 2

Observation/test timing	Pre-screening	Screening test	Registration	Baseline	Week 1	Week 2	Week 3	Week 4
Visit window	-	Day -28 to Day -7	-	Day -2 to Day 1	Day 1	Day 8 to Day 11[a)] Day 8±3[b)]	Day 15 to Day 18[a)] Day 15±3[b)]	Day 22±3
JR-171 administration					X	X	X	X
Informed consent	X							
Subject baseline characteristics[c)]		X						
Assessment based on inclusion/exclusion criteria			X					
Allocation for treatment group			X					
Pregnancy testing (female subjects of childbearing potential only)		X						
Vital signs[d)]		X[e)]		X[f)]	X[g)]	X[g)]	X[g)]	X[g)]
Laboratory tests[h)]		X		X		X		X
Antibodies[h)]				X[i)]		X[j)]		X[j)]
Plasma drug concentration [b), k)]					X			X
Drug concentration in CSF				X[h)]				
HS and DS concentrations in CSF				X[h)]				
CSF opening pressure				X[h)]				
Urinary HS and DS concentrations (including measurement of creatinine for concentration adjustment)[h)]				X		X		X
Serum HS and DS concentrations[h)]				X		X		X
Liver and spleen volumes[h)]				X				
Cardiac function[h)]				X				
6-minute walk test[m)]				X[h)]				
Other clinical findings related to neurocognitive and behavioral changes					→	→	→	→
12-lead electrocardiogram[h)]		X						
BVMT-R and HVLT-R[m)]		X[p)]						
T.O.V.A. [m)]		X[p)]						
PedsQL-FIM[n)]		X[p)]						
Cross-reactive immunologic material[o)]				→	→	→	→	→
AEs	→	→	→	→	→	→	→	→
Concomitant therapies/medications					X	X	X	X

Part 2 cont.

Observation/test timing	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13	Discontinuation
Visit window	**Day 29±3**	**Day 36±3**	**Day 43±3**	**Day 50±3**	**Day 57±3**	**Day 64±3**	**Day 71±3**	**Day 78±3**	**Day 85±3**	**Within 28 days from discontinuation**
JR-171 administration	X	X	X	X	X	X	X	X		
Vital signs[d]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[e], [h]	X[e]
Laboratory tests[h]		X		X		X		X	X	X
Antibodies[h]				X[j]					X[i]	X[i]
Plasma drug concentration[b], [k]								X		
Drug concentration in CSF								X[l]		X[m]
HS and DS concentrations in CSF								X[l]		X[m]
CSF opening pressure								X[l]		X[m]
Urinary HS and DS concentrations (including measurement of creatinine for concentration adjustment)[h]		X		X		X		X	X	X
Serum HS and DS concentrations[h]		X		X		X		X	X	X
Liver and spleen volumes[h]									X	X
Cardiac function[h]									X	X
6-minute walk test[m]									X	X
Other clinical findings related to neurocognitive and behavioral changes	→	→	→	→	→	→	→	→	→	→
12-lead electrocardiogram[h]									X	X
BVMT-R and HVLT-R[m]									X[q]	
T.O.V.A.[m]									X[q]	
PedsQL-FIM[n]									X[q]	
Cross-reactive immunologic material[o]	→	→	→	→	→	→	→	→	→	→
AEs	→	→	→	→	→	→	→	→	→	→
Concomitant therapies/medications	X	X	X	X	X	X	X	X	X	X

a) The first subject aged 6-17 years and the first subject aged 2-5 years (0-5 years in Japan and Brazil)
b) Excluding the first subject aged 6-17 years and the first subject aged 2-5 years (0-5 years in Japan and Brazil)
c) Neurocognitive testing and adaptive behavior assessment will be performed before the first infusion of JR-171.
d) Vital signs: pulse rate, body temperature, blood pressure, respiratory rate, percutaneous oxygen saturation and body weight. During the infusion of JR-171, it is necessary to monitor other than body weight (see Section 6.1 and 8.2.3).
e) Excluding body weight
f) Only body weight is measured.
g) Perform before and after administration of JR-171 except for body weight. Body weight will be measured at either measuring point.
h) Perform before administration of JR-171 (or before laronidase at Week 13, for subjects who will receive laronidase after completing the JR-171-101 study)
i) Anti-IDUA and anti-JR-171 antibodies
j) Anti-JR-171 antibodies
k) Blood specimens should be collected by following the “PK sampling schedule (plasma drug concentration)”.
l) Performed within 5 hours after the end of administration of JR-171
m) Performed if deemed feasible by the principal investigator or subinvestigator
n) Only for subjects accompanied by their family, caregiver or equivalent thereof.
o) Samples will be collected once in Part 2 and obtained before JR-171 administration during the visit.
p) Should be performed before the first infusion of JR-171.
q) Visit window: ±10 days

PK sampling schedule (plasma drug concentration)

Test timing	Part 1: Week 1, Week 2, Week 3 and Week 4 Part 2: Week 1, Week 4 and Week 12					
Elapsed time	Before administration	1 hour after the start of administration	At the end of administration	3 hours after the end of administration	6 hours after the end of administration	21 hours after the end of administration
Time window (min)	-60 to 0	±15	+10	±15	±15	±60

2. Introduction

2.1 Study Rationale[1)]

MPS I is an autosomal recessive disorder caused by a deficiency of IDUA, a lysosomal enzyme involved in the breakdown of GAGs, which results in systemic accumulation of GAGs, particularly DS and HS. The accumulation of GAGs causes various symptoms, including deafness, otitis media, bone or joint deformity, joint contracture, obstructive respiratory disorder, apnea syndrome, cardiac valvulopathy, and CNS symptoms. MPS I is classified into three forms based on age of onset, clinical manifestation, severity, and degree of disease progression: Hurler syndrome, which is the most severe form, and Hurler-Scheie syndrome and Scheie syndrome, which are milder than Hurler syndrome. The most severe form, Hurler syndrome, clinically manifests in early childhood and progresses rapidly. It has been reported that approximately 75% of naïve patients with Hurler syndrome die before 10 years of age due to obstructive respiratory disorder, respiratory infection, cardiac complications, etc. On the other hand, the mildest form Scheie syndrome initially manifests as heart valve disease, corneal opacity, joint contracture, hernia, carpal tunnel syndrome, etc., but these symptoms are mild or associated with other diseases, often leaving Scheie syndrome undiagnosed until adulthood. Patients with Hurler syndrome have CNS symptoms, whereas Scheie syndrome involves no CNS symptoms. Hurler-Scheie syndrome is of intermediate severity and involves only mild CNS symptoms or none at all.

MPS I is a very rare disease, with an estimated prevalence of 0.11-3.62 per 100000 live births. In particular, the prevalence in Japan, the US, and Brazil is estimated to be 0.23, 0.34, and 0.24 per 100000 live births, respectively.[2)] A study of 987 patients with MPS I registered in the Global MPS I Registry reported that Hurler syndrome, Hurler-Scheie syndrome, and Scheie syndrome accounted for 60.9%, 23.0%, and 12.9% of patients, respectively (unknown in 3.2% cases).[3)]

MPS I is usually treated with HSCT or ERT. HSCT is a treatment option for the severe form involving CNS symptoms. After HSCT, uptake of the enzyme secreted from the transplanted cells by the patient's cells results in a reduction in accumulated GAGs and improvement of clinical symptoms (*e.g.*, hepatosplenomegaly, joint contracture, respiratory symptoms), and these effects are permanently maintained after successful engraftment. It has been reported that early HSCT preserves intellectual development. The management and treatment guidelines for MPS I recommend to select the therapy based on the risk/benefit ratio for HSCT versus ERT individually for each patient with MPS I.[4)] HSCT is recommended for patients <2 years of age who are cognitively intact, and for the other patients, ERT is the more reasonable option for palliative therapy. A European consensus panel recommends HSCT for Hurler syndrome diagnosed before 2.5 years of age.[5)] However, HSCT may cause fatal complications such as graft-versus-host disease and infection. In 258 patients with Hurler syndrome who underwent HSCT in 1995 to 2007, the post-transplant 5-year survival rate was reportedly 74%.[6)] Due to the aforementioned risks and the necessity of human leukocyte antigen-compatible donors, HSCT is not indicated for every patient.

On the other hand, ERT is exogenous enzyme supplementation using cellular uptake of the enzyme via the cation-independent mannose-6-phosphate receptor (M6PR). Laronidase (laronidase solution for intravenous infusion; brand name: Aldurazyme), the first enzyme preparation approved in the US and the European Union (EU) in 2003, is indicated for patients with Hurler and Hurler-Scheie forms of MPS I and for patients with the Scheie form who have moderate to severe symptoms. Based on clinical study results and post-marketing experience over more than 10 years, laronidase is known to improve cardiopulmonary function, ability to walk, hepatosplenic volume, cardiac function, joint function, visual acuity, quality of life, etc. However, laronidase, which does not penetrate the blood-brain barrier, is not effective for CNS symptoms.[7)]

In conclusion, early HSCT is effective for CNS symptoms of MPS I, but there are risks and an upper age limit for treatment. ERT is shown to be effective for systemic symptoms, but not for CNS symptoms. Therefore, it is desirable to establish a safe and effective treatment for MPS I

that also addresses the CNS symptoms.

2.2 Background

JR-171 is a fusion protein genetically modified to penetrate the blood-brain barrier and consists of IDUA and the Fab fragment of a humanized antibody that specifically recognizes human transferrin receptor 1 (hTfR).
JR-171, which binds to hTfR and M6PR, may be transported to the cerebral parenchyma via hTfR on the cerebrovascular endothelium and to peripheral organ cells via M6PR and hTfR. In a repeated dose study where human transferrin receptor 1 knock-in/α-L-iduronidase knock-out mice (hTfR KI/Idua KO mice), an animal model of MPS I, received JR-171 once a week for 4 or 12 weeks, GAG concentrations in the brain and peripheral organs decreased to almost the normal range. Therefore, JR-171 is expected to decrease intracellularly accumulated GAGs and inhibit the progression of CNS and systemic symptoms. In addition, no safety concerns have been raised in nonclinical studies.

Therefore, based on the conclusion that it is scientifically and ethically appropriate to conduct a clinical study of JR-171, which is an innovative treatment for MPS I of high clinical significance, the sponsor is planning a phase I/II study in patients with MPS I.

2.3 Benefit/Risk Assessment

2.3.1 Known Potential Risks

As JR-171 contains anti-hTfR antibody, the ordinary iron transport system (binding of transferrin to the transferrin receptor) might be inhibited, which may lead to the development of adverse drug reactions (anemia, etc.). JR-171 is also considered to cross the blood-brain barrier, and adverse drug reactions (vomiting, headache, etc.) may therefore occur. Furthermore, the enzyme portion of JR-171 is similar to laronidase, and similar adverse drug reactions reported with use of laronidase may occur, including those potential risks, anaphylactic shock, and IARs as well as anti-JR-171 antibody and anti-IDUA antibody production.

2.3.2 Known Potential Benefits

JR-171 is expected to be effective for CNS symptoms of MPS I. JR-171 is also expected to be as effective as laronidase for systemic symptoms.

2.3.3 Assessment of Potential Risks and Benefits

Given its current battery of nonclinical studies results, JR-171 is expected to suppress central nervous and systemic symptoms of MPS I by being transported to the cerebral parenchyma via hTfR and to peripheral organ cells via M6PR and hTfR to decrease intracellularly accumulated GAGs. In addition, no safety concerns have been raised in the nonclinical studies that have been conducted to date.

3. Objectives and Endpoints

Objectives	Endpoints	Justification for endpoints
Primary		
To determine the safety and tolerability of JR-171 in patients with MPS I	• Frequency and severity of AEs and their relationship to JR-171 • Changes in laboratory parameters (hematology, biochemistry, serum iron tests, and urinalysis) • Changes in vital signs (pulse rate, body temperature, blood pressure, respiratory rate and percutaneous oxygen saturation) • Clinically meaningful changes in 12-lead electrocardiogram • Anti-drug antibody production (anti-human IDUA and anti-JR-171 antibodies) • Frequency of IARs	For safety endpoints, those which are commonly used (AEs, routine laboratory tests, vital signs, and 12-lead electrocardiogram) have been chosen. The determination of serum iron levels was included based on the involvement of hTfR, responsible for iron transport, in the mechanism of cellular uptake of JR-171. Given the possibilities of the administration of JR-171 leading to antibody production and occurrence of IAR, the antibody tests and IAR have been included. The antibody tests will measure anti-IDUA and anti-JR-171 antibodies.
Secondary		
To evaluate the plasma PKs of JR-171 after intravenous administration	Assessment of plasma drug concentrations and pharmacokinetic parameters	[redacted]

Objectives	Endpoints	Justification for endpoints
Secondary (cont.)		
To explore the efficacy of JR-171 for CNS and somatic symptoms of MPS I	[redacted]	[redacted]
	Changes in HS and DS concentrations in the CSF from baseline to Week 4 in Part 1 or Week 12 in Part 2	Given accumulation of HS and DS in patients with MPS I, this endpoint was selected to explore the efficacy of JR-171 on CNS symptoms.
	Changes in CSF opening pressure from baseline to Week 4 in Part 1 or Week 12 in Part 2	This endpoint was selected to explore the efficacy of JR-171 on CNS abnormalities.
	Changes in urinary HS and DS concentrations from baseline to each time point	Given increased urinary excretion of HS and DS in patients with MPS I, this endpoint was selected to explore the efficacy of JR-171 on systemic symptoms.
	Changes in serum HS and DS concentrations from baseline to each time point	Given systemic accumulation of HS and DS in patients with MPS I, this endpoint was selected to explore the efficacy of JR-171 on systemic symptoms.
	Changes in liver and spleen volumes from baseline to Week 5 in Part 1 or Week 13 in Part 2	This endpoint was selected to explore the efficacy of JR-171 for hepatosplenomegaly, which results from accumulation of HS and DS in the liver and spleen in patients with MPS I.
	Changes in cardiac function from baseline to Week 5 in Part 1 or Week 13 in Part 2	This endpoint was selected to explore the efficacy of JR-171 for reduced cardiac function, which results from accumulation of HS and DS in the heart of patients with MPS I.
	Changes in 6-minute walk test from baseline to Week 13 (Part 2 only)	This endpoint was selected to explore the efficacy of JR-171 for systemic symptoms, especially respiratory, musculoskeletal and cardiovascular system.
	Assessment of the other clinical findings related to neurocognitive and behavioral changes	This endpoint was selected to explore clinical findings (especially the effect of JR-171 on CNS related symptoms) which cannot be evaluated by other endpoints.
	Changes in outcome of BVMT-R and HVLT-R from baseline* to Week 13 (Part 2 only)	BVMT-R was selected to evaluate the efficacy of JR-171 on visuospatial memory. HVLT-R was selected to evaluate the verbal learning and memory.
	Changes in outcome of T.O.V.A. from baseline* to Week 13 (Part 2 only)	To evaluate the efficacy of JR-171 on the early attention complaints in patients with MPS I.
	Changes in outcome of PedsQL-FIM from baseline* to Week 13 (Part 2 only)	PedsQL-FIM was selected to evaluate how the QoL changed in patient's family, caregiver or equivalent thereof.

* Use the data determined in the screening period as the baseline data.

4. Study Design

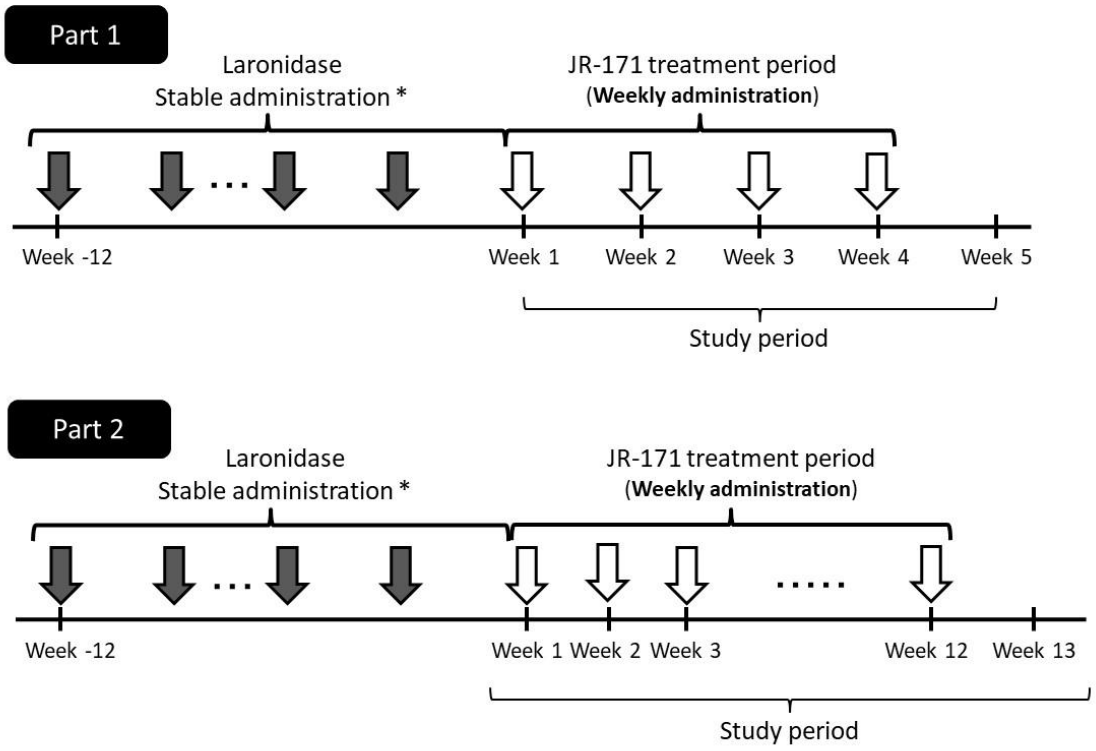
4.1 Overall Design

A Phase I/II, open-label, multicenter (six sites in total are planned), multinational (Japan, Brazil and the US), designed to evaluate the safety, PKs and explore the efficacy for the treatment of MPS I.

The JR-171-101 study will consist of Part 1 and Part 2.
In Part 1, subjects aged 18 years or older shall receive administration of JR-171 as an intravenous infusion in a dose-escalation manner. When the principal investigator or subinvestigator concludes that JR-171 dose increase will pose no problem based on the safety information collected from the administered dose to the first and second subject, JR-171 will be increased to the next dose upon approval of the sponsor. The start date of JR-171 administration of the second subject should be at least 1 week after the start date of JR-171 administration of the first subject. Once the two subjects complete all the four times of administrations and the safety of JR-171 is confirmed, then the administration for the third and subsequent subjects may be started. If the first or second subject is discontinued from the study during the dose-escalation phase (until the safety evaluation of the fourth administration), the next third subject will stay in the hospital and will be supervised until 21 hours after the end of each administration to assess safety.
In part 2, the first subject aged 6-17 years and the first subject aged 2-5 years (0-5 years in Japan and Brazil) shall each receive an initial dose of JR-171 as an intravenous infusion at a dose of 1.0 mg per kg of body weight. The dose level shall be then increased to 2.0 mg/kg for the second administration, and to 4.0 mg/kg for the third administration. From the fourth to twelfth administrations, JR-171 shall be administered at 4.0 mg/kg. If the first subject aged 6-17 years or the first subject aged 2-5 years (0-5 years in Japan and Brazil) is discontinued from the study during the dose-escalation phase (until the safety evaluation of the third administration), the next subject for the same age group shall receive JR-171 in a dose-escalation manner as described above (the schedule of assessments will also be the same as those for the first subject in each age group).
The first subject aged 2-5 years (0-5 years in Japan and Brazil) can receive the initial administration at least 1 week after the first subject aged 6-17 years receives the initial administration. The second subject in each age group in Part 2 could be administered with JR-171 after the safety evaluation of the third administration of the first subject in each age group.
Subjects other than above of 2 years or older (any age in Japan and Brazil) shall be randomly assigned to one of either 2 groups in a 1:1 ratio and receive 2.0 or 4.0 mg/kg of JR-171.
Since this is a first-in-human study of JR-171, the JR-171-101 study will proceed in stages while confirming that safety is ensured. For the detailed procedures to confirm safety, refer to Section 6.6.1.
Subjects who complete Part 2 of the JR-171-101 study will be able to participate in the extension study (protocol number: JR-171-102 study) and continue receiving JR-171.

Part	Number of subjects	Dose
Part 1	4 subjects	Initial administration : 0.1 mg/kg single dose Second administration : 1.0 mg/kg single dose Third administration : 2.0 mg/kg single dose Fourth administration : 4.0 mg/kg single dose
Part 2[a), b)]	At least 2 subjects[c)]	Initial administration : 1.0 mg/kg single dose Second administration : 2.0 mg/kg single dose Third administration : 4.0 mg/kg single dose After third administration : 4.0 mg/kg/week, 9 times Twelve administrations in total
	2.0 mg/kg/week group: At least 6 subjects 4.0 mg/kg/week group: At least 6 subjects	2.0 mg/kg/week, 12 times 4.0 mg/kg/week, 12 times

a) Part 2 is started only after the safety is confirmed in Part 1 by the IDSMC. Subjects participating in Part 1 are excluded from Part 2.
b) Approximately 15 subjects will be enrolled in total.
c) Starting dose of 1 mg/kg in the first subject aged 6-17 years and the first subject aged 2-5 years (0-5 years in Japan and Brazil).



***Only for subjects who have been given enzyme replacement therapy before this study:**
Subjects receiving laronidase at the stable dose for at least 12 weeks as standard treatment are to be switched to JR-171.

4.2 Scientific Rationale for Study Design

JR-171 is expected to provide clinical benefit to MPS I patients especially those who show CNS manifestations. Since many patients with MPS I are receiving ERT[8)] or/and have received an HSCT,[5)] and it is very difficult to enroll naïve patients, the JR-171-101 study is designed to target MPS I patients with or without previous HSCT treatment and to mainly focus on the switch in treatment from laronidase to JR-171. Laronidase will be totally eliminated from the subject's body within 1 week because its mean $t_{1/2}$ ranges from 1.5 to 3.6 hours. Moreover,

given that there is no evidence of accumulation of laronidase,[7] no extended washout period prior to switching from laronidase is included to evaluate the safety and exploratory efficacy of JR-171. Since interruption of ERT for MPS I over a certain period of time may result in irreversible progression of the disease, no placebo control group is included from an ethical perspective. The JR-171-101 study will be conducted, in part, to evaluate the safety of JR-171 and to explore its efficacy.
Since this is a first-in-human study of JR-171, in Part 1, four MPS I patients aged 18 years or older will receive 4 times JR-171 administration in a weekly dose-escalation manner. When it is concluded that there are no safety issues in Part 1 and JR-171 can be shown to potentially penetrate the blood-brain barrier in humans, treatment in Part 2 will be started in approximately 15 subjects with MPS I.
Since no accumulation of HS and DS is observed in non-MPS patients,[9), 10)] and there are risks that the administration of protein drug to healthy volunteers, in terms of neutralizing antibody production, this phase I/II study is conducted in subjects with MPS I to assess the relationship between PKs and pharmacodynamics.
The nonclinical safety of JR-171 was demonstrated in a repeated intravenous dose toxicity study where male and female cynomolgus monkeys received JR-171 at a dosage of 40 mg/kg once a week for 4 weeks. Furthermore, a 13-week toxicity study will be completed before this phase I/II recruits subjects. Given a decrease in accumulated GAGs in the brain and other peripheral organs in a repeated intravenous dose study where hTfR KI/Idua KO mice received JR-171 once every week or once every 2 weeks for 12 weeks, the duration of the present study is considered to be appropriate to evaluate the efficacy in an exploratory manner.

4.3 Justification for Dose

Given a no-observed-adverse-effect-level (NOAEL) of 40 mg/kg in a nonclinical toxicity study in male and female cynomolgus monkeys, dose equivalence in human is calculated to be approximately 1.0 mg/kg with safety margin of 10. In this first-in-human study of JR-171 one-tenth of the aforementioned dose is selected as the initial dose level in Part 1 for safety considerations, and the dose level is increased each week.
In a repeated dose study where hTfR KI/Idua KO mice received JR-171 once every week or once every 2 weeks for 12 weeks, the drug at dosages of 2.0 and 4.0 mg/kg/every 2 weeks was shown to be as effective for systemic symptoms as laronidase at dosage of 0.58 mg/kg/week. In addition, unlike laronidase, JR-171 also decreased HS and DS concentrations in the brain and CSF at all doses. However, slightly greater reductions in the HS and DS levels in some tissues were observed in treatment groups receiving every week regimen than the treatment groups receiving every 2 weeks dosing regimen. Furthermore, based on the results of nonclinical pharmacology, ADME, and toxicology studies, it is considered that there are no serious safety concerns in intravenous administration of JR-171 to MPS I patients at the dose levels up to 4.0 mg/kg, which is the planned maximum dose in Phase I/II study.
Based on these findings, 2.0 and 4.0 mg/kg were selected as doses to be administered every week in Part 2 of the JR-171-101 study.
Part 2 is started only after the safety is confirmed in Part 1 by the IDSMC, and all subjects aged 18 years or older will have received 2.0 or 4.0 mg/kg for weekly administration. Considering the safety for subjects under 18 years, the first subject aged 6-17 years and the first subject aged 2-5 years (0-5 years in Japan and Brazil) in Part 2 will each receive the administration of JR-171 by dose-escalation manner, and its initial dose of JR-171 shall start from 1.0 mg/kg. A previous report indicated that concentration of soluble transferrin receptor gradually decreases from the neonatal period to adolescence, and then reduces further to the adult level after which the concentration remains stable.[11)] However, no marked reduction of the soluble transferrin receptor was found in adults, indicating that effect of JR-171 is not expected to vary with the subject's age. Therefore, the initial dose of JR-171 shall start from 1.0 mg/kg as part of dose-escalation, and 2 years (0 years in Japan and Brazil) or older patients, including naïve ones, can also be enrolled in consideration of ethical perspective because it is desirable to start treatment earlier in order to suppress progressive neurodegeneration. Second and subsequent subjects under 18 years in each age group will

receive 2.0 or 4.0 mg/kg for weekly administration, after the safety evaluation of the third administration of the first subject.

4.4 End of Study Definition

A subject is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities, Section 1.3.

The end of the study is defined that the point of when all subjects complete all procedures relating to the JR-171-101 study.

5. Study Population

In order to be eligible to participate in the JR-171-101 study, a patient must meet all of the inclusion criteria, and none of the exclusion criteria.

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

1. A patient aged 18 years or older in Part 1, or 2 years or older (any age in Japan and Brazil) in Part 2, at the time of informed consent.
2. A patient from whom written informed consent can be obtained. If the patient is aged under 18 years (20 years in case of Japan) at the time of assent or willingness to participate in the study cannot be confirmed due to MPS I-related intellectual disability, informed permission from the patient's legally acceptable representative (*e.g.*, his/her parents or guardians) needs to be obtained instead of his/her consent. Even in this case, written informed consent should be obtained from the patient, wherever possible.
3. A patient diagnosed with MPS I based on any one of the following criteria:
   - Activity of the IDUA enzyme below 10% of the lower reference level in leucocytes or cultured skin fibroblasts, AND increased age-related urinary levels of GAGs (before ERT).
   - Activity of the IDUA enzyme below 10% of the lower reference level in leucocytes or cultured skin fibroblasts, AND presence of one pathogenic mutation in each of the alleles of the IDUA gene.
   - Increased age-related urinary levels of GAGs (before ERT), AND presence of one pathogenic mutation in each of the alleles of the IDUA gene.
4. A patient diagnosed as having mild or no MPS I-related intellectual disability (able to report their own subjective symptoms) by the principal investigator or subinvestigator (Part 1 only).
5. A patient who has received laronidase continuously for at least 12 weeks and has received laronidase at a stable dosage for the 2 weeks immediately before the initial administration of JR-171 (except for a laronidase naïve patient or a patient who has previously been treated by HSCT).
6. Female patient or male patient whose co-partner is of child-bearing potential agrees to use a medically accepted, highly effective method of contraception, such as spermatocidal gel plus condom, an intrauterine device or oral contraceptives until one month after the final administration.

Rationale for the Inclusion Criteria:

1. In this first in human study of JR-171, the minimum age of 18 years was defined in Part 1 for safety considerations. In Part 2, pediatric patients will be also eligible to participate since treatment of MPS I often starts in childhood.
2. Signed informed consent (*i.e.*, written consent) is necessary for the study registration.
3. This criterion was defined to enroll only patients with MPS I in the study.

4. Since JR-171 is administered to patients for the first time in Part 1, only patients who will be able to report their own subjective symptoms are eligible to participate to collect and evaluate safety information carefully.
5. The result of the phase I/II study for laronidase showed that urinary GAG concentrations was 60 to 80% below the baseline after 8 to 12 weeks of intravenous administration of Aldurazyme.[12)] Based on these results, we set the duration of laronidase administration before the initial administration of JR-171 as at least 12 weeks for a patient who does not have a history of HSCT.
6. This criterion was defined because the safety of reproductive and developmental toxicity and genotoxic have not been proven when JR-171 is administered to patients with MPS I.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in the JR-171-101 study:

1. A patient who has received gene therapy treatment.
2. A patient who, in the opinion of the principal investigator or subinvestigator, cannot undergo lumbar puncture, including those who have a difficulty in taking position for lumbar puncture due to joint contracture and those who are likely to develop dyspnea during lumbar puncture.
3. A patient who is pregnant or lactating.
4. A patient who has developed serious drug allergy or hypersensitivity to any drugs, in the opinion of the principal investigator or subinvestigator, is inappropriate for participation in the study.
5. A patient who has received another investigational product within the 12 months prior to enrollment in the study.
6. A patient who, in the opinion of the principal investigator or subinvestigator, is ineligible to participate in the study in consideration of patient's safety.

Rationale for the Exclusion Criteria:

1. CNS and systemic symptoms could have been alleviated in patients responsive to gene therapy treatment. This criterion was defined to explore the efficacy of JR-171 for CNS and systemic symptoms.
2. This criterion was defined due to the necessity of collecting CSF by lumbar puncture to evaluate the efficacy of JR-171 for CNS symptoms.
3. This criterion was defined because the safety of reproductive and developmental toxicity as well as genotoxicity have not been proven at the point that JR-171 is administered to patients with MPS I.
4. This criterion was defined in consideration of the patient's safety.
5. This criterion was defined in consideration of the patient's safety.
6. This criterion was defined in consideration of the patient's safety.

5.3 Lifestyle Considerations

It is not applicable for the JR-171-101 study.

5.4 Screen Failures

Screening failures are defined as subjects for whom consent to participate in the clinical study is given but who are not registered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details and eligibility criteria.

5.5 Strategies for Recruitment and Retention

- Target: Male or female MPS I patients
- Target sample size:
  Part 1: 4 subjects (18 years or older)
  Part 2: Approximately 15 in total
- Description of sites/facilities enrolling subjects: 6 sites (Japan, Brazil and the US) are planned.

For compensation or any incentives that subjects may receive, please refer to the informed consent documents.

6. Study Intervention

Study intervention is defined as any investigational interventions intended to be administered to a study subject according to the study protocol.

6.1 Study Interventions Administered

Intervention Name	• Investigational product name (Code): JR-171 • Generic name: Applications under preparation for International Nonproprietary Names (INN) and application under preparation for Japanese Accepted Names for Pharmaceuticals (JAN)
Dosing and administration	**Part 1** Subjects aged 18 years or older shall receive an initial administration of JR-171 as an intravenous infusion at a dose of 0.1 mg per kg of body weight. The dose level shall be then increased to 1.0 mg/kg for the second administration, to 2.0 mg/kg for the third administration, and to 4.0 mg/kg at the fourth administration. When the principal investigator or subinvestigator concludes that JR-171 dose increase will pose no problem based on the safety information collected from the administered dose to the first and second subject, JR-171 will be increased to the next dose upon approval of the sponsor. The start date of JR-171 administration of the second subject should be at least 1 week after the start date of JR-171 administration of the first subject. Once the two subjects complete all the four times of administrations and the safety of JR-171 is confirmed, then the administration for the third and subsequent subjects may be started. If the first or second subject is discontinued from the study during the dose-escalation phase (until the safety evaluation of the fourth administration), the next third subject will stay in the hospital and will be supervised until 21 hours after the end of each administration to assess safety. JR-171 is to be administered at intervals of 1 week. The total volume of infusion should be administered over approximately 3 hours, but may be extended to a longer period at the discretion of the principal investigator or subinvestigator, considering safety concerns, including any IARs, etc. **Part 2** The first subject aged 6-17 years and the first subject aged 2-5 years (0-5 years in Japan and Brazil) shall each receive an initial dose of JR-171 as an intravenous infusion at a dose of 1.0 mg per kg of body weight. The dose level shall be then increased to 2.0 mg/kg for the second administration, and to 4.0 mg/kg for the third administration. From the fourth to twelfth administrations, JR-171 shall be administered at 4.0 mg/kg. If the first subject aged 6-17 years or the first subject aged 2-5 years (0-5 years in Japan and Brazil) is discontinued from the study during the dose-escalation phase (until the safety evaluation of the third administration), the next subject for the same age group shall receive JR-171 in a dose-escalation manner as described above (the schedule of assessments will also be the same as those for the first subject in each age group). The first subject aged 2-5 years (0-5 years in Japan and Brazil) can receive the initial administration at least 1 week after the first subject aged 6-17 years receives the initial administration. The second subject in each age group in Part 2 could be administered with JR-171 after the safety evaluation of the third administration of the first subject in each age group is completed.

	Subjects other than the above of aged 2 years or older (any age in Japan and Brazil) shall be randomly assigned to either one of 2 groups in a 1:1 ratio, and receive 2.0 or 4.0 mg of JR-171 per kg of body weight 12 times as an intravenous infusion. JR-171 will be administered over approximately 3 hours every week over a 12 week period. The treatment time may be extended to a longer period at the discretion of the principal investigator or subinvestigator, considering safety concerns, including any IARs, etc. In Part 1 and Part 2, the dose of JR-171 will be calculated based on the latest body weight value collected at a scheduled visit.
Route of Administration	Intravenous infusion
Packaging and Labeling	[redacted]

In both Part 1 and Part 2, the principal investigator or subinvestigator is to ensure that each subject receives JR-171 in such a way that his/her general condition can be checked on, including timely vital sign monitoring, under supervision, in order to monitor and respond to IARs or anaphylactic shock. Especially, vital signs are recommended to be obtained when infusion rate is increased, and to be obtained at least every 30 minutes while the infusion rate does not change.
Use of pretreatment with antihistamines, adrenal corticosteroids, etc. is accepted to prevent IARs as necessary considering the potential for development of IARs during treatment with laronidase or JR-171. Subjects who have already been receiving pretreatment with antihistamines, adrenal corticosteroids, etc. when receiving laronidase are allowed to continue to receive pretreatment when receiving JR-171 from the initial administration onward.

Response to IAR
If an IAR occurs, it is recommended to reduce the infusion rate or interrupt the infusion of JR-171, and perform appropriate procedures (medicated with adrenal corticosteroids, antihistamines, analgesic antipyretics, anti-inflammatory drugs, etc.), and emergency procedures such as oxygen administration, airway management, and adrenaline administration. Pretreatment with antihistamines, adrenal corticosteroids, etc. may be considered to prevent IARs for subsequent infusions. It is recommended ensuring that each subject receives JR-171 in such a location where these procedures are immediately available.

Response to anaphylaxis
If an anaphylaxis (see section 8.3.6) occurs, in addition to the above, the following blood tests described below are to be performed. If performed, the sample collection date and results of measurement should be recorded in the eCRF.

Detail of Anaphylaxis Test

Test items	Timing of sample collection*
Total IgE	• Between 15 minutes and 3 hours after occurring the anaphylaxis • From at least 24 hours after recovering from the anaphylaxis until next infusion of JR-171 or laronidase
Total IgG	
Acute phase reactants (C-reactive protein (CRP), Haptoglobin and Fibrinogen)	
Serum tryptase	
Complement activation (C3 and C4)	

*Prioritize the treatment of the subject, and collect sample within the above range as much as possible.

Response to anaphylactic shock
If an anaphylactic shock occurs, it is required to discontinue the infusion of JR-171, perform appropriate procedures (emergency procedures such as oxygen administration, airway management, adrenaline administration, and medication with adrenal corticosteroids,

antihistamines, analgesic antipyretics, anti-inflammatory drugs, etc.), and discontinue the subject from the study. It is recommended ensuring that each subject receives JR-171 in such a location where these procedures are immediately available.

6.1.1 Composition

Each vial of JR-171 contains the following ingredients:

Table 6-1 Composition of JR-171 formulation

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

Detailed procedures for the management of the investigational product are provided in the sponsor's instruction for administration of investigational product in a separate document.

The sponsor will confirm that the study sites are ready to conduct the study, and that the study contract has been concluded with each of them, before delivering the investigational product to the study sites.

Before the investigational product is delivered, the person in charge of managing the investigational product and the study monitor is to check the quantity to be delivered, the manufacturer's serial number, the method of storage, the expiration date, etc. and exchange the required set of documents for the drug release process.

Investigation study sites should manage the investigational product in accordance with the instruction of investigational product (*e.g.*, receipt, handling, and storage instructions) and the Institution's standard operating procedures (SOP). Investigation study sites should register investigational product specific details (regarding receipt, amount used, disposal, etc.) in an Interactive Response Technology (IRT) system.

After the completion of the study, the investigation study site will return any undispensed investigational product with due consideration to the protection of personal information of the subjects.

6.2.2 Product Storage and Stability

[redacted]

6.2.3 Preparation

[redacted]

6.3 Measures to Minimize Bias: Randomization and Blinding

This is an open-label trial.

In Part 2, subjects without previous HSCT treatment will be stratified by their phenotype (Scheie or other than Scheie) and randomized into one of the 2 treatment groups (2.0 or 4.0 mg/kg/week JR-171 group) using an IRT system except for subjects who receive JR-171 administration in a dose-escalation manner. Those subjects with previous HSCT treatment will be allocated into a treatment group without stratification by their phenotype. The handling of randomization lists is described in a separate document.

6.4 Study Intervention Compliance

In the JR-171-101 study, the investigational product will be administrated under supervision of the principal investigator or subinvestigator in order to assure compliance with investigational product administration. Site monitors will check subject's compliance with the investigational product administration.

6.5 Concomitant Medication/Therapy

All the concomitant medications/therapies used should be recorded from the initial administration of the investigational product to the end of the study period. For all concomitant medications, the status of use (drug name, route of administration, duration of treatment, and reason for administration) should be recorded in the electronic case report form (eCRF). Transfusions or maintenance transfusions for purpose of establishment an intravenous line, diluents for injections, bases for in-hospital preparations, disinfectants and drugs used in preparative treatments *e.g.,* anesthetic (other than drugs with anticipated effects) are not considered as concomitant medications. For all concomitant therapies, the status of use (therapy name, duration of treatment, and reason for therapy) should be recorded in the eCRF.

6.5.1 Prohibited Concomitant Medications/Therapies

Concomitant use of the following drugs and therapies is prohibited during the period from the screening test to the end of the study period:

- Investigational products other than JR-171
- HSCT

Concomitant use of the following drug is also prohibited during the period from the initial administration of JR-171 to the end of the study period:

- Laronidase

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the eCRF are concomitant prescription medications and over-the-counter medications.

6.5.2 Rescue Medicine

Appropriate medication will be immediately provided to the subject when a principal investigator or subinvestigator deems this to be necessary.

6.6 Dosing and Administration

6.6.1 Confirmation of Safety

Part 1: Doses in Part 1 are 0.1, 1.0, 2.0, 4.0 mg/kg and will be administered to a subject at intervals of 1 week. Considering that this is a first-in-human study of JR-171, the safety of JR-171 will be initially evaluated in four adult MPS I patients aged 18 years or older in Part 1. In Part 1, each subject will stay in the hospital and will be supervised until 21 hours after the end of each administration to assess safety. When the principal investigator or subinvestigator concludes that JR-171 dose increase will pose no problem based on the safety information collected from the administered dose to the first and second subject, JR-171 will be increased to the next dose upon approval of the sponsor.

The sponsor will establish an IDSMC. If any IARs with Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ III occur up to 24 hours after the end of each administration in the first and second subjects, the sponsor will consult with the IDSMC to ask their opinion about the appropriateness of the JR-171 dose increase. The dose increase determination will be made according to the same procedures for each dosage. The start date of JR-171 administration of the second subject should be at least 1 week after the start date of JR-171 administration of the first subject. Once the two subjects complete all the four times of administrations and the safety of JR-171 is confirmed, then the administration for the third and subsequent subjects may be started. If the first or second subject is discontinued from the study during the dose-escalation phase (until the safety evaluation of the fourth administration), the next third subject will stay in the hospital and will be supervised until 21 hours after the end of each administration to assess safety.

After completing the clinical study for all subjects who participated in Part 1, the sponsor will convene the IDSMC and ask their opinion about the appropriateness of the initiation of Part 2 based on all safety data collected from the start of administration to Week 5. After taking into consideration the opinion of the IDSMC, when the sponsor concludes, that initiation of Part 2 will pose no problem, from ethical, scientific, and medical perspective, then Part 2 may be initiated.

Part 2: The first subject aged 6-17 years and the first subject aged 2-5 years (0-5 years in Japan and Brazil) shall each receive an initial dose of JR-171 as an intravenous infusion at a dose of 1.0 mg per kg of body weight. The dose level shall be then increased to 2.0 mg/kg for the second administration, and to 4.0 mg/kg for the third administration. From the fourth to twelfth administrations, JR-171 shall be administered at 4.0 mg/kg. If the first subject aged 6-17 years or the first subject aged 2-5 years (0-5 years in Japan and Brazil) is discontinued from the study during the dose-escalation phase (until the safety evaluation of the third administration), the next subject for the same age group shall receive JR-171 in a dose-escalation manner as described above (the schedule of assessments will also be the same as those for the first subject in each age group).

The first subject aged 2-5 years (0-5 years in Japan and Brazil) can receive the initial administration at least 1 week after the first subject aged 6-17 years receives the initial administration.

Subjects other than the above of aged 2 years or older (any age in Japan and Brazil) shall be allocated to receive either 2.0 or 4.0 mg/kg/week JR-171 group. The safety evaluation in Part 2 will be conducted in subjects aged 2-17 years (0-17 years in Japan and Brazil). The first subject aged 6-17 years will stay in the hospital and will be supervised until 21 hours after the end of each administration at Week 1, Week 2 and Week 3 to assess safety. When the principal investigator or subinvestigator, and the

sponsor confirm the safety in the first subject aged 6-17 years after the end of third administration, the second and subsequent subjects aged 6-17 years can be assigned to either 2.0 or 4.0 mg/kg/week JR-171 group. If any IARs with CTCAE grade ≥ III occur up to 24 hours after completion of the administration among the dose-escalating infusions in the first subject aged 6-17 years, the sponsor should convene the IDSMC and ask their opinion about the appropriateness of the JR-171 dose increase.
The first subject aged 2-5 years (0-5 years in Japan and Brazil) can receive the initial administration at least 1 week after the first subject aged 6-17 years receives the initial administration. The first subject aged 2-5 years (0-5 years in Japan and Brazil) will stay in the hospital and will be supervised until 21 hours after the end of administration at Week 1, Week 2 and Week 3 to assess safety. When the principal investigator or subinvestigator, and the sponsor confirm the safety in the first subject aged 2-5 years (0-5 years in Japan and Brazil) after the end of third administration, the second and subsequent subjects aged 2-5 years (0-5 years in Japan and Brazil) can be assigned to either of 2.0 or 4.0 mg/kg/week JR-171 group. If any IARs with CTCAE grade ≥ III occur up to 24 hours after completion of the administration among the dose-escalating infusions in the first subject aged 2-5 years (0-5 years in Japan and Brazil), the sponsor should convene the IDSMC and ask their opinion about the appropriateness of the JR-171 dose increase.

The sponsor's Safety Evaluation Manual in a separate document will be followed for the confirmation of safety procedure.

6.7 Instructions for Subjects

The principal investigator or subinvestigator must fully inform the subjects about the purpose and significance regarding the clinical study, and must instruct subjects according to the following items.

1. Female subject or male subject whose co-partner is of childbearing potential is required to refrain from conception during the study period and/or to use an adequate method of contraception. The subject or co-partner should contact the principal investigator or subinvestigator immediately if they suspect that they might be pregnant.
2. The subject and co-partner must be willing to use a medically accepted, highly effective method of contraception, such as spermatocidal gel plus condom, an intrauterine device or oral contraceptives.
3. The subject or co-partner must use an adequate method of contraception until one month after the final administration.

6.8 Intervention after the End of the Study

The sponsor is planning an extension study of the Study JR-171-101 of over 5 years' duration to confirm the long-term safety and efficacy of JR-171.

7. Discontinuation of Study Intervention and Subject Discontinuation /Withdrawal

7.1 Discontinuation of Study Intervention

7.1.1 Criteria for Termination or Suspension

The sponsor will consider the discontinuation/cessation of the whole or part of the clinical study in any situation described in the information below. In this case, all principal investigators will be immediately informed by the sponsor.

1. Occurrence of a serious adverse event (SAE) with CTCAE grade ≥ IV
2. Occurrence of serious adverse drug reactions coded to same preferred term (PT) in 2 or more subjects
3. A research report that suggests the tendency of occurrence of adverse drug reactions,

such as the number of reactions that occur, the frequency of occurrence, and occurrence conditions, have significantly changed
4. A research report that shows the clinical study may cause serious diseases including cancer, disabilities, or death
5. When the clinical study suggests that there is no efficacy of JR-171 in this population
6. A research report that demonstrates that there is no efficacy or effectiveness for the disease that the clinical study aims to treat
7. When either the sponsor, the study institution, or the principal investigator has committed a grave breach of ICH-GCP, the protocol, or the contract, leading to a situation where the proper continuation of the clinical study is considered problematic
8. When the continuation of the clinical study is considered difficult due to changes of the structure or environment for conducting the clinical study (*e.g.*, a transfer of the principal investigator)
9. Other cases in which the continuation of the clinical study is considered inappropriate due to new information or a change in the situation identified during the clinical study

When the clinical study is discontinued the following examinations/observations described below are to be performed as much as possible, if the subject agrees, after final administration of the investigational product. The details should be recorded in the eCRF listed below except for items 3, 4, 5, 7 and 9, it is not necessary to record measurements in the eCRF. The date of discontinuation and the reason for discontinuation will also be recorded in the eCRF.
1. Vital signs (pulse rate, body temperature, blood pressure, respiratory rate and percutaneous oxygen saturation)
2. Laboratory tests (hematologic test, blood biochemical test, determination of serum iron levels, and urinalysis)
3. Antibody tests (anti-IDUA and anti-JR-171 antibodies)
4. Drug concentration in CSF
5. HS and DS concentrations in CSF
6. CSF opening pressure
7. Urinary HS and DS concentrations
8. Urinary creatinine
9. Serum HS and DS concentrations
10. Liver and spleen volumes
11. Cardiac function
12. 6-minute walk test (Part 2 only)
13. Other clinical findings related to neurocognitive and behavioral changes
14. 12-lead electrocardiogram
15. AEs
16. Concomitant medications/therapies

Note that the items below are very invasive tests and will be conducted only when the principal investigator or subinvestigator deems them possible by considering matters including the condition of a subject and the frequency of lumbar puncture. For items 1 and 2, it is not necessary to record measurements in the eCRF. For the reporting of the results, data should be reported by the laboratory.
1. Drug concentration in CSF
2. HS and DS concentrations in CSF
3. CSF opening pressure

After completion of examinations/observations at discontinuation, the principal investigator or subinvestigator should consider the necessity of (re)starting of laronidase in consideration of the subject's status (*e.g.*, progression to underlying disease or a significant worsening of their clinical parameters including serum and urinary HS and DS concentrations).

7.2 Subject Discontinuation/Withdrawal from the Study

Subjects are free to withdraw from participation in the study at any point of time upon request

to the principal investigator. Subjects who are prematurely withdrawn from the study will not be replaced.
A principal investigator or subinvestigator may discontinue or withdraw a subject from the study for the following reasons:

1. When a subject or his/her legal representative wishes to discontinue the clinical study
2. When the continuation of the study became impossible for reasons including a transfer to another hospital/change of address during the clinical study
3. When a subject was found to be ineligible after the start of the clinical study such that continued participation would compromise safety of the subject or integrity of the study
4. When the continuation of the clinical study becomes impossible for reasons including the occurrence of an AE*
5. When a subject experiences anaphylactic shock
6. Other cases in which the principal investigator or subinvestigator deems it necessary to discontinue the clinical study because compliance with the protocol has become difficult

*When the occurrence of an SAE with CTCAE grade ≥ IV, the principal investigator or subinvestigator should consider the discontinuation/temporary cessation of the study. If the principal investigator or subinvestigator can rule out a causal relationship with JR-171 based on the additional information and CTCAE grade improved to III or less, administration could be resumed, but otherwise subjects must be discontinued.

For examinations/observations at the time of the subject discontinuation from the study, see Section 7.1.1.

7.3 Lost to Follow-up

For subjects who do not visit the hospital, the principal investigator or subinvestigator will inquire into reasons and their subsequent progress and record the information in the eCRF.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (see Section 10.1.18).

8. Study Assessments and Procedures

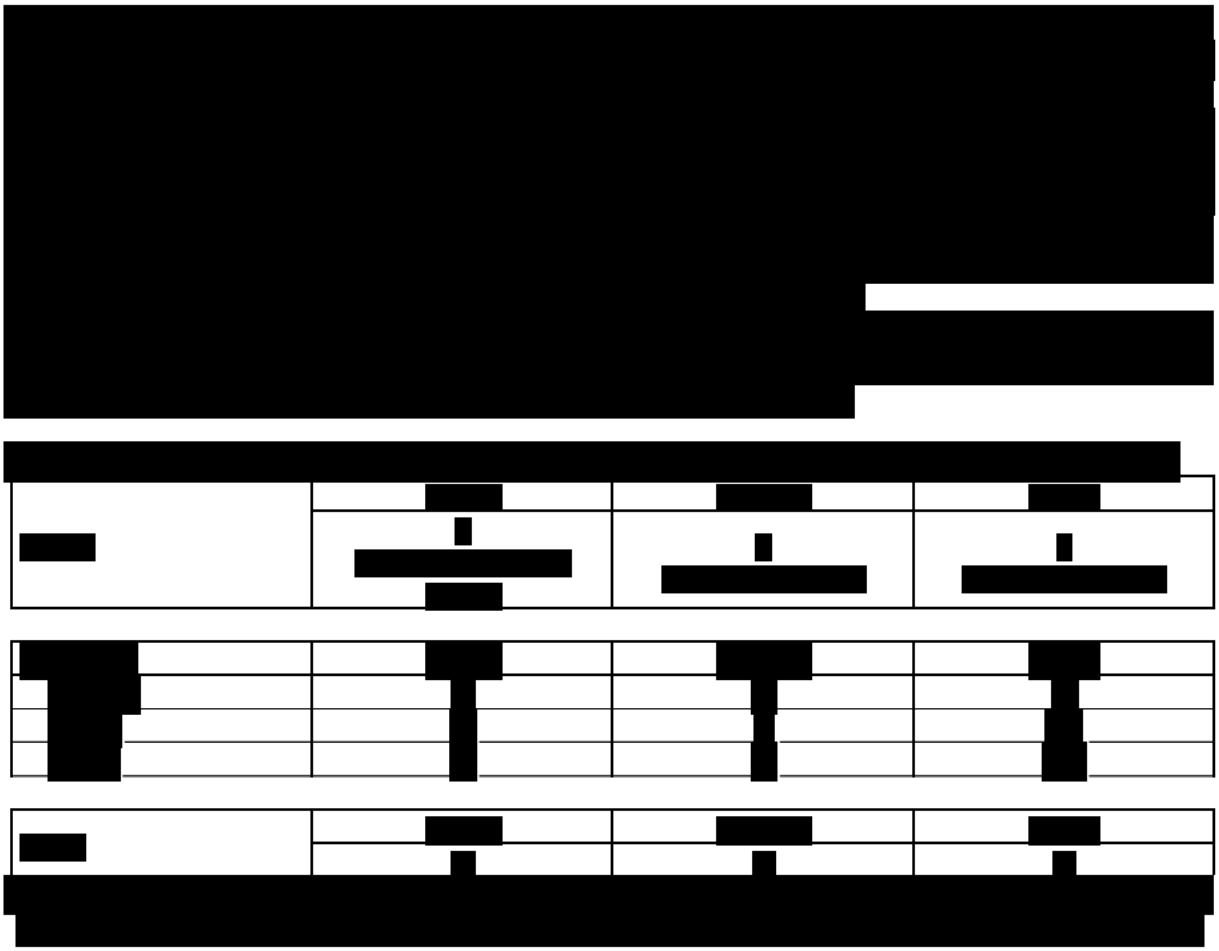
- Study procedures and their timing are summarized in the Schedule of Activities. Protocol waivers are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The principal investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (*e.g.*, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

8.1 Demographic and Other Baseline Characteristics

The following will be investigated and recorded in the eCRF:

- Date of written consent obtained from the subject and, if applicable, written permission from his/her legally acceptable representative
- Age at the time of informed consent
- Date of diagnosis of MPS I
- Presence or absence of use of laronidase, and start date (if applicable)

- Presence or absence of HSCT treatment, and treatment date (if applicable)
- Phenotype of MPS I (Hurler, Hurler-Scheie or Scheie)
- Presence or absence of intellectual disabilities
- Presence or absence of MPS I-related/-unrelated concurrent disease (events occurring at the time of informed consent) and, if applicable, the name of these diseases
- Presence or absence of medical history (MPS I-related medical occurrence), and if applicable, the name of any disease
- Enzyme activity in leucocytes or cultured skin fibroblasts and the date of measurement (if applicable)
- Urinary GAG concentration, or uronic acid concentration, and date of the measurement (if applicable)
- Genetic analysis results (for subjects who do not have the result, genetic analysis will be performed during this clinical study)
- Presence or absence of laronidase-related IAR
- Race
- Country
- Sex (as well as ability to get pregnant, if female)
- Inclusion and exclusion criteria



8.2 Safety Assessments

8.2.1 Pregnancy Testing (Female Subjects of Childbearing Potential Only)

Pregnancy testing will be conducted during screening for female subjects of childbearing potential (female subjects of non-childbearing potential are confirmed by being either post-

menopausal for more than 1 year prior to the time of informed consent or surgically sterile). In the eCRF, whether or not a measurement has been performed as well as the sample collection date and results of measurement, if performed, should be recorded.

8.2.2 Administration Information

For each dose of JR-171, the status of administration should be recorded in the eCRF: whether or not JR-171 has been administered, date of administration, start time of administration, ending time of administration, start time of interruption if applicable, time of administration resumed if applicable, applied dose, whether or not administration has been discontinued/interrupted, whether or not the infusion rate has been reduced.

8.2.3 Vital Signs

Pulse rate, body temperature, blood pressure (systolic and diastolic blood pressure) respiratory rate, and percutaneous oxygen saturation will be measured before and after administration of JR-171 or laronidase. Body weight will be measured only once at each measurement point. In principle, blood pressure will be measured in the same posture throughout the JR-171-101 study. In the eCRF, whether or not a measurement has been performed as well as the date and time and results of measurement, if performed, should be recorded. When JR-171 is administered, vital signs will be also measured at the end of administration, and the time of measurement as well as the results of pulse rate, body temperature and blood pressure should be recorded in the eCRF.
During infusion of JR-171, the principal investigator or subinvestigator ensure vital signs are taken in a timely manner. Especially, vital signs are recommended to be obtained when infusion rate is increased, and to be obtained at least every 30 minutes while the infusion rate does not change. The measurements during infusion of JR-171 do not have to be recorded in the eCRF, but if AEs occur, the detail of the AEs should be recorded in the eCRF.

8.2.4 Laboratory Tests

Blood and urine will be collected before administration of JR-171 or laronidase to measure the parameters listed below. In the eCRF, whether or not a measurement has been performed as well as the sample collection date and results of measurement, if performed, should be recorded.

8.2.4.1 Hematology

White blood cell count, differential leukocyte count, red blood cell count, hemoglobin, hematocrit, platelet count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), reticulocyte ratio, prothrombin time, and activated partial thromboplastin time (APTT).

8.2.4.2 Biochemistry

Total protein, albumin, albumin/globulin ratio, haptoglobin, CK, total bilirubin, aspartate aminotransferase (AST [GOT]), alanine transaminase (ALT [GPT]), γ-GT (γ-GTP), alkaline phosphatase (ALP), total cholesterol, triglycerides, creatinine (enzymatic method), Na, K, Cl, Ca, and P.

8.2.4.3 Serum Iron Tests

Serum iron, unsaturated iron binding capacity (UIBC), total iron binding capacity (TIBC), ferritin, and transferrin saturation (TSAT).

8.2.4.4 Urinalysis

Determination of glucose, protein, and occult blood.

8.2.5 Antibodies

Antibodies will be measured centrally by the laboratory under contract with the sponsor. If the test results of anti-JR-171 antibodies are positive, then neutralizing activity against M6PR binding and hTfR binding of JR-171 will be measured.

Venous blood will be collected from each subject before administration of JR-171 or laronidase to measure anti-IDUA and anti-JR-171 antibodies. In the eCRF, whether or not a measurement has been performed and, if applicable, the sample collection date should be recorded. Data should be reported by the laboratory.

8.2.6 12-lead Electrocardiogram

Electrocardiography will be performed before administration of JR-171 or laronidase. In the eCRF, whether or not a measurement has been performed as well as the date of measurement and the presence or absence of abnormal finding, including its details and whether or not it will be considered an AE, should be recorded.

8.2.7 Concomitant Medication/Therapy

All concomitant medications/therapies taken by the subjects will be collected from the Week 1 dose to the last visit (Week 5 in Part 1/Week 13 in Part 2, or discontinuation). In the eCRF, presence or absence of usage of concomitant medication/therapy, and if applicable, its details (see Section 6.5) should be recorded.

Rationale for the Safety Assessments

For the safety evaluation, systemic endpoints, that is, AEs (see Section 8.3), laboratory tests, vital signs, and 12-lead electrocardiogram were selected. Serum iron tests were included based on the involvement of TfR, which is responsible for iron transport, in the mechanism of cellular uptake of JR-171.

8.3 Adverse Events and Serious Adverse Events

In the event of AEs, the safety of subjects is ensured by providing appropriate medical care to subjects.
AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).
The principal investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE (Appendix 2 (see Section 10.2.1 and 10.2.3)) and remain responsible for following up on AEs that are serious, considered related to the study intervention or study procedures, or that caused the subject to discontinue the study (see Section 7).
If an AE occurs, the name, severity, seriousness, day of onset, presence or absence of treatment for study treatment, outcome of the AE (including date of assessment), relationship between the AE and investigational product, comments as appropriate, and whether or not with IAR should be recorded in the eCRF.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the time of informed consent until the last visit (Week 5 in Part 1/Week 13 in Part 2, or discontinuation) at the time points specified in the Schedule of Activities (see Section 1.3). Events occurring within 28 days after the time of observation at Week 5 in Part 1/Week 13 in Part 2 or discontinuation that are considered related to the investigational product will be collected as adverse drug reactions in the JR-171-101 study, except for events that are occurred during the extension study of the JR-171-101 study (JR-171-102). In the eCRF, presence or absence of AEs and, if applicable, its details (Appendix 2 (see Section 10.2.4)) should be recorded.
Data of MPS I-related medical occurrences that begin before obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the case report form not in the AE section.
All SAEs will be recorded and reported to the sponsor immediately and under no circumstance should exceed 24 hours, as indicated in Appendix 2 (see Section 10.2). The principal investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
Principal investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the principal investigator learns of any SAE, including a death,

at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the principal investigator must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2 (see Section 10.2.4).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the principal investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs, and AEs of special interest (see Section 8.3.6), will be followed until resolution, stabilization, or the event is otherwise explained. Further information on follow-up procedures is provided in Appendix 2 (see Section 10.2.4).

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the principal investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/Independent Ethics Committees (IEC), and principal investigators.
- For all studies except those utilizing medical devices principal investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to principal investigators as necessary.
- A principal investigator who receives a principal investigator safety report describing an SAE or other specific safety information (*e.g.*, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy (Female Subjects and Subject's Female Co-partners of Childbearing Potential Only)

- For female subjects, details of all pregnancies in childbearing potential (female subjects of non-childbearing potential are confirmed by being either post-menopausal for more than 1 year prior to the time of informed consent or surgically sterile) will be collected after the start of study intervention and until a miscarriage, an abortion or 1 month after the delivery. The follow-up for infants will be about one month after the birth.
- If a pregnancy is confirmed in a female subject or subject's female co-partner of childbearing potential, the principal investigator should inform the sponsor within 24 hours of learning of the pregnancy using the designated form.
- Abnormal pregnancy outcomes (*e.g.*, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- For female subjects, whether or not a measurement of pregnancy testing has been performed as well as the sample collection date and results of measurement, if performed, should be recorded in the eCRF.

8.3.6 AEs of Special Interest

In this clinical study, in light of the characteristics of the investigational product, when the AEs

described below occur, they will be defined as significant AEs and evaluated.

- Anaphylaxis, anaphylactic shock
  Cutaneous symptoms including urticaria, digestive symptoms including abdominal pain and vomiting, respiratory symptoms including a feeling of dyspnea, and shock symptoms including sudden pallor and clouding of consciousness are called anaphylaxis. When the principal investigator or subinvestigator diagnoses the anaphylaxis, refer to criteria described below.[16] A condition in which a sharp drop in blood pressure occurs and symptoms like disturbance of consciousness are seen is specifically called anaphylactic shock.

  When any 1 of the 3 criteria are fulfilled, regard the event as an anaphylaxis.
  1. Acute onset of an illness (minutes to hours) with involvement of Skin/mucosal tissue (*e.g.*, hives, generalized itch/flush, swollen lips/tongue/uvula)
     AND
     Compromised airway (*e.g.*, dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow)
     OR
     Reduced blood pressure or associated symptoms (*e.g.*, hypotonia, syncope)
  2. Two or more of the following after exposure to known allergen for that patient (minutes to hours)
     History of severe allergic reaction
     Skin/mucosal tissue symptoms (*e.g.*, hives, generalized itch/flush, swollen lips/tongue/uvula)
     Compromise airways (*e.g.*, dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow)
     Reduced blood pressure or associated symptoms (*e.g.*, hypotonia, syncope)
     In suspected food allergy: gastrointestinal symptoms (*e.g.*, crampy abdominal pain, vomiting)
  3. Hypotension after exposure to known allergen for that patient (minutes to hours)
     Infants and children: low systolic blood pressure (age-specific) or >30% drop in systolic blood pressure*
     Adults: systolic blood pressure, <100 mm Hg or >30% drop from the last measurement

  Caution: These criteria describe so-called classic cases of anaphylaxis. Other presentations may also indicate anaphylaxis (*e.g.*, early presentation, generalized flushing; isolated presentation, sudden hypotension only in a patient without evidence of allergen exposure; classic presentation but with a non-allergenic cause, such as exercise). Conversely, clinicians need to remember the potential for false-positive symptoms or signs (*e.g.*, difficulty breathing from panic, faintness from vasovagal episode).

  *Low systolic blood pressure for children is defined as <70 mm Hg from 1 month to 1 year; less than (70 mm Hg + (2 × age)) from 1 to 10 years; and <90 mm Hg from age 11 to 17 years.

- IAR[17]
  Reactions harmful to the living body that are caused by administration of the infusion, occurring during or within 24 hours after completion of the infusion (*e.g.*, chill, fever, a feeling of body temperature fluctuation, nausea, high blood pressure).

Also, in addition to reported SAEs, all the events that have significantly abnormal laboratory values or require such action as the discontinuation, temporary cessation, or addition of important combination therapy with respect to the investigational product should be evaluated as significant AEs.

8.4 Pharmacokinetics

8.4.1 Plasma Drug Concentration

Plasma drug concentration is designated as a centrally measured parameter and will be measured by the laboratory under contract with the sponsor.
Venous blood will be collected from each subject to measure plasma drug concentration. In Part 1, each subject will stay in the hospital and will be supervised until 21 hours after the end of each administration to collect the venous blood sample. In Part 2, each subject randomized to one of the 2 treatment groups (2.0 or 4.0 mg/kg/week JR-171 group) will stay at hospital and will be supervised until 21 hours after the end of each administration at Week 1, Week 4 and Week 12 to collect the venous blood sample.
In the eCRF, whether or not a measurement has been performed and, if applicable, the sample collection date and time should be recorded. For the reporting of results, data should be reported by the laboratory.

Rationale for the Pharmacokinetics Assessments

The PK endpoints were selected to determine the PKs of and exposure to JR-171 after continuous intravenous infusion in patients with MPS I by calculating parameters from plasma drug concentration. In a nonclinical PK study in cynomolgus monkeys, measured plasma JR-171 concentrations showed that the plasma exposure to JR-171 up to 24 hours after the start of administration ($AUC_{0\text{-}24}$) accounted for almost 100% of the plasma exposure from the start of administration to infinity ($AUC_{0\text{-}\infty}$). It was therefore decided to measure drug concentration up to 21 hours after the end of administration (the last blood sampling time point) in order to calculate PK parameters.

8.5 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the Schedule of Activities.

8.5.1 Drug concentration in CSF

Drug concentration in CSF is designated as a centrally measured parameter and measured by the laboratory under contract with the sponsor.
CSF will be collected from each subject once before administration of JR-171 at the initial administration and within 5 hours of the end of administration of JR-171 at Week 4 in Part 1 or Week 12 in Part 2 to measure drug concentration in the CSF. In the case of discontinuation, the measurement will be performed if deemed feasible by the principal investigator or subinvestigator. In the eCRF, whether or not a measurement has been performed and, if applicable, the sample collection date and time should be recorded. For the reporting of results, data should be reported by the laboratory.

Rationale for this Exploratory Assessment

This assessment was selected to confirm the penetration of JR-171 into the CNS.

8.5.2 HS and DS concentrations in CSF

HS and DS concentrations in CSF is designated as a centrally measured parameter and measured by the laboratory under contract with the sponsor.
Care is to be taken not to contaminate the sample with blood, heparin or heparin-like compounds when collecting samples. In the eCRF, whether or not a measurement has been performed as well as the sample collection date, if performed, should be recorded. For the reporting of results, the measurement results should be reported by the laboratory.
Subjects will undergo lumbar puncture under sedation or general anesthesia to obtain CSF. Fluoroscopy with anesthesia may be needed in subjects with difficult access to CSF.
To minimize the risks associated with lumbar puncture procedures in the subjects with MPS I, the principal investigator or subinvestigator should consider the following:
- Intravenous or oral administration of sedatives prior to the procedure should be considered when subject's discomfort, anxiety or agitations are such that they affect the safe and smooth

conduct of the procedure.
- Subjects during the sedation should be closely monitored with respect to potential complications, in particular respiratory inhibition, so that appropriate measures can be taken whenever these complications occur.

Rationale for this Exploratory Assessment
Given accumulation of HS and DS in patients with MPS I, this assessment was selected to explore the efficacy of JR-171 on CNS symptoms.

8.5.3 CSF Opening Pressure
Before the CSF sample collection, the CSF opening pressure will be measured once a needle is in position. End-tidal carbon dioxide pressure will be monitored and maintained during the measurement from 35 to 40 mm Hg to ensure the opening pressure accuracy. In the eCRF, whether or not a measurement has been performed, the date of measurement and the result should be recorded.

Rationale for this Exploratory Assessment
This assessment was selected to explore the efficacy of JR-171 on CNS abnormalities.

8.5.4 Urinary HS and DS Concentrations
Urinary HS and DS concentrations are designated as a centrally measured parameter and measured by the laboratory under contract with the sponsor. Urinary creatinine concentration will be measured to enable urinary HS and DS concentrations to be calculated and will be measured by an in-house laboratory.
Urine will be collected from each subject before administration of JR-171 or laronidase to measure urinary HS and DS concentrations. Care is to be taken not to contaminate the sample with heparin or heparin-like compounds when collecting samples. In the eCRF, whether or not a measurement has been performed and the sample collection date and urinary creatinine concentration should be recorded. For urinary HS and DS concentrations, the measurement results should be reported by the laboratory.

Rationale for this Exploratory Assessment
Given increased urinary excretion of HS and DS in patients with MPS I, this assessment was selected to explore the efficacy of JR-171 on systemic symptoms.

8.5.5 Serum HS and DS Concentrations
Serum HS and DS concentrations are designated as centrally measured parameters and will be measured by the laboratory under contract with the sponsor.
Venous blood will be collected from each subject before administration of JR-171 or laronidase to measure serum HS and DS concentrations. Care is to be taken not to contaminate the sample with heparin or heparin-like compounds when collecting samples. In the eCRF, whether or not a measurement has been performed and, if applicable, the sample collection date should be recorded. The measurement results should be reported by the laboratory.

Rationale for this Exploratory Assessment
Given systemic accumulation of HS and DS in patients with MPS I, this assessment was selected to explore the efficacy of JR-171 on systemic symptoms.

8.5.6 Liver and Spleen Volumes
Computed tomography (CT) or magnetic resonance imaging (MRI) will be performed before administration of JR-171 or laronidase to measure liver and spleen volumes. The same modality (CT or MRI) should be used throughout the study for the same subject. When selecting CT or MRI, the principal investigator or subinvestigator should pay attention to the subject's condition, treatment status or radiation exposure doses, including conduct of other imaging tests in order to protect the subject's safety. In the eCRF, whether or not a measurement has been performed as well as the date and results of measurement should be

recorded.
Anticipated radiation exposures by abdominal CT scan are as follows:

	Male	Female
All age[13),14)]	[redacted]	[redacted]
Child (27-36 kg)[15)]	[redacted]	[redacted]
Infant (4-5.9 kg)[15)]	[redacted]	[redacted]

Rationale for this Exploratory Assessment
This assessment was selected to explore the efficacy of JR-171 on hepatosplenomegaly, which results from accumulation of HS and DS in the liver and spleen in patients with MPS I.

8.5.7 Cardiac Function
Echocardiography will be performed before administration of JR-171 or laronidase to measure the left ventricular posterior wall thickness, interventricular septal thickness, left ventricular mass index, left ventricular fractional shortening, left ventricular ejection fraction, and E/A ratio. In the eCRF, whether or not a measurement has been performed as well as the date and results of measurement should be recorded.

Rationale for this Exploratory Assessment
This assessment was selected to explore the efficacy of JR-171 on reduced cardiac function, which results from accumulation of HS and DS in the heart of patients with MPS I.

8.5.8 6-minute Walk Test
Walking distance for 2 and 6 minutes from the test start will be measured in Part 2. The Walking distance for 2 and 6 minutes will be performed only in subjects who are able to comply with the testing procedures. Detailed procedures for the 6-minute walk test are provided in the separate sponsor manual. In the eCRF, whether or not a measurement has been performed as well as the date and results of measurement should be recorded.

Rationale for this Exploratory Assessment
This assessment was selected to explore the efficacy of JR-171 on systemic symptoms, especially respiratory, musculoskeletal and cardiovascular system.

8.5.9 Other Clinical Findings Related to Neurocognitive and Behavioral Changes
If the other clinical findings related to neurocognitive and behavioral changes are found, the principal investigator or subinvestigator should record in the eCRF. The contents of the changes (language, motor, vigor/expression, other) should be recorded in the eCRF as well as the date of the change. If no change is found, the principal investigator or subinvestigator should record as such in the eCRF at the last visit (Week 5 in Part 1/Week 13 in Part 2, or discontinuation).

Rationale for this Exploratory Assessment
This assessment was selected to explore the meaningful clinical findings (especially the effect of JR-171 for CNS related symptoms) which cannot be evaluated by other endpoints.

8.5.10 BVMT-R and HVLT-R
The BVMT-R and HVLT-R will be measured in Part 2. The BVMT-R and HVLT-R will be performed only in subjects who are able to comply with the testing procedures. The testing will be performed by qualified personnel. Testing should be performed after adequate sleep to avoid interference resulting from patient fatigue, and conditions should be the same at each testing.
In the eCRF, whether or not a measurement has been performed as well as the date and results of measurement should be recorded. For the detailed procedures of BVMT-R and

HVLT-R, refer to the separate sponsor manual.

Rationale for this Exploratory Assessment
The BVMT-R will be used to measure the visuospatial memory, and the HVLT-R will be used to assess the verbal learning and memory.

8.5.11 T.O.V.A.
The T.O.V.A., version 9 (T.O.V.A.) (visual test) will be measured in Part 2, and will be performed only in subjects at least 4 years of age and able to comply with the testing procedures. Testing should be performed after adequate sleep to avoid interference resulting from patient fatigue, and conditions should be the same at each testing.
In the eCRF, whether or not an assessment has been performed as well as the date and results should be recorded.
For the detailed procedures of T.O.V.A., refer to the separate sponsor manual.

Rationale for this Exploratory Assessment
This assessment was selected to evaluate the attention deficits.

8.5.12 PedsQL-FIM
The PedsQL-FIM, standard version will be tested in Part 2, and will be performed only for subjects accompanied by their family, caregiver or equivalent thereof. The PedsQL-FIM will be performed to assess specifically caregiver's and family's burden. In the eCRF, whether or not a test has been performed as well as the date and results of the test should be recorded.

Rationale for this Exploratory Assessment
This assessment was selected to explore how the QoL has changed, because it is known that burden of caregiver and family of patients with MPS I is high and gathering data of QoL is important.

8.5.13 Status of Cross-Reactive Immunologic Material (CRIM)
A blood specimen and fibroblasts will be collected once in the JR-171-101 study from subjects who agreed to the sample collection to determine the CRIM status, and the samples will be obtained before the JR-171 administration during the visit. The sample collection date should be recorded in the eCRF. The assay for the CRIM status will be performed by the laboratory under contract with the sponsor.

Rationale for this Exploratory Assessment
This assessment was selected to evaluate the impact of the CRIM status on the PKs, pharmacodynamics, safety and efficacy endpoints.

9. Statistical Considerations

9.1 Statistical Hypotheses
For the exploratory endpoint analyses, a paired sample t-test will be conducted on HS and DS concentrations in CSF. The quantity of interest is the mean change from baseline. The null hypothesis for comparison (H_0) with threshold value of delta (Δ) and the alternative hypothesis of effect of JR-171 (H_1) are defined as follow, where μ denotes mean change from baseline in HS or DS concentrations in CSF and $\Delta = 0$.

H_0: $\mu = \Delta$
H_1: $\mu > \Delta$ *or* $\mu < \Delta$.

No hypothesis testing is planned for the other exploratory endpoints, safety and PK assessments.

9.2 Sample Size Determination

Part 1: 4 subjects (18 years or older)
Part 2: Approximately 15 subjects in total

Rationale for the Target Sample Size

In this first-in-human study of JR-171, adult patients (18 years old or older) with mild MPS I who can report their own subjective symptoms are deemed appropriate to confirm the safety of JR-171 in Part 1. MPS I is an extremely rare disease, which is estimated to have the birth prevalence of approximately 0.11 to 3.62 per 100000 live births.[2)] In addition, 60.9% of the patients are reported to have severe disease manifestations with intellectual disability,[3)] indicating that there may be very few adult patients with mild MPS I who have little or no intellectual disability. Based on these considerations and the target sample size of 4 subjects was selected for Part 1 in view of feasibility.

In Part 2, pediatric patients will be able to participate since treatment of MPS I often starts in childhood. It is assumed that only a small number of patients could undergo lumbar puncture. Furthermore, it is reported that 54.9% of severe MPS I patients have a history of HSCT.[8)] Therefore, it is assumed only a very limited number of patients would be eligible to participate in the study. Based on these considerations and in view of feasibility, the target sample size of approximately 15 subjects was selected to evaluate the safety and efficacy of JR-171.

9.3 Populations for Analyses

The following populations are defined:

Population	Description
Safety set (SS)	All subjects who sign the ICF.
Pharmacokinetic set (PKS)	Subjects assigned to study intervention and have data for plasma drug concentration after administration of JR-171.
Full analysis set (FAS)	Subjects assigned to study intervention and have data for at least one exploratory endpoint after administration of JR-171

9.4 Statistical Analyses

The statistical analysis plan will be finalized prior to First Patient First Visit, and it will include a more technical and detailed description of the statistical analyses as well as the handling of subjects and individual data determined in consultation with the medical and statistical experts as appropriate. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

9.4.1.1 Significance Level and Confidence Interval

Unless otherwise specified, all statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance and all confidence intervals will be 2-sided 95% confidence intervals. All statistical tests and confidence intervals will be parametric assuming normally distributed sample means.

9.4.1.2 Definitions of Baseline

Unless otherwise specified, the baseline value will be defined as the measurement prior to and closest to the date of the first dose of JR-171.

9.4.1.3 Definitions of Study Period

Data for regular scheduled visits will be summarized as below.

Visit	Actual Point	Visit Window
Screening	Day -28 to Day -7	-
Baseline	Day -2 to Day 1	-
Week 1	Day 1	-
Week 2[a)]	Day 8 to Day 11	-
Week 3[a)]	Day 15 to Day 18	-
Week X	Week X	Part 1; +3 days Part 2; ±3 days

a) The first subject aged 6-17 years and the first subject aged 2-5 years (0-5 years in Japan and Brazil) in Part 2

9.4.1.4 Unscheduled Assessments

In case there are measurements from an unscheduled visit after the first dose of JR-171, measurements at scheduled and unscheduled visits are chronologically presented in the subject list whereas the summary of descriptive statistics by time point will only include measurements at scheduled visits.

9.4.1.5 Handling of Missing Data

If any value is missing at any time point, they will be handled as missing and will not be imputed. If any value is reported as 'Below the limit of quantification' or the value cannot be used for calculations, handling of these data will be determined in a separate document which describes standard of adoption for data and subjects.

9.4.1.6 Imputation of Incomplete Dates

For following subject's baseline characteristics data, in case day or month is omitted thus collected as 'Unknown', these missing date units will be imputed with '1' for calculation of some durations.

- date of diagnosis of MPS I
- start date of treatment with laronidase
- date of HSCT treatment
- date of measurement of Enzyme activity in leucocytes or cultured skin fibroblasts
- date of measurement of urinary GAG concentration or uronic acid concentration

For concomitant medication and concomitant treatment used after the first administration of JR-171, in case the day is omitted from the start or end date thus collected as 'Unknown', only collected date units will be used without any imputation of the date.

9.4.2 Demographic and Other Baseline Characteristics

Major demographic variables, such as age, sex, country, race, phenotype, and some variables about MPS I related characteristics will be summarized by study period and dose group, by the number and percentage of subjects using descriptive statistics for continuous variables and counts and percentages for categorical variables.

9.4.3 Safety Analyses

This section outlines the planned safety analyses in the JR-171-101 study. Safety analyses will be performed on the SS.

All AEs will be coded to PT and system organ class (SOC) using the latest version of the Medical dictionary for regulatory activities terminology (MedDRA).
All AEs occurred after the first dose of JR-171 will be considered as treatment-emergent AEs and will be summarized by study period and dose group. For each study period and dose group, the incidence proportion of AEs will be summarized with frequency and percentage by MedDRA SOC and PT.
AEs occurring before the first dose of JR-171, include AEs that occurred in screen failure, will be pooled regardless study period or dose group and summarized in the same way.

For laboratory tests, summary statistics of measured values at each time point as well as changes from baseline will be calculated for Part 1 and each group in Part 2, and time courses

or shift tables will be created for each subject.
For vital signs, summary statistics of measured values at each time point as well as changes from baseline will be calculated for Part 1 and each group in Part 2, and time courses will be created.
For 12-lead electrocardiogram, the presence or absence of abnormality will be tabulated.
For antibody tests, shift tables will be created with respect to the presence or absence of antibody development at each time point.

9.4.4 Analysis of the Pharmacokinetic endpoints

This section outlines the planned analyses of the PK endpoints of the JR-171-101 study.
PK analyses will be performed on the PKS.

Part 1
For the plasma drug concentration at each time point, summary statistics, geometric mean, and geometric coefficient of variation (CV) will be calculated for each dose. In addition, time courses of mean and standard deviation (SD) will be created for each dose, and a listing and time courses will be created for each subject.
The following PK parameters will be calculated for each subject using a non-compartment model analysis, and summary statistics, geometric mean, and geometric CV will be calculated for each dose. In estimating the parameters, the plasma drug concentration calculated by the plasma drug concentration at baseline, and the actual blood collection time will be used.

Part 2
For the plasma drug concentration at each time point, summary statistics, geometric mean, and geometric CV will be calculated for each group. In addition, time courses of mean and SD will be created for each group, and a listing and time courses will be created for each subject.
The following PK parameters will be calculated for each subject using a non-compartment model analysis, and summary statistics, geometric mean, and geometric CV will be calculated for each group. In estimating the parameters, the plasma drug concentration will be calculated using the plasma drug concentration at baseline, and the actual blood collection time will be used.

[PK Parameters]
- $AUC_{0\text{-}t}$
- C_{max}
- $AUC_{0\text{-}\infty}$
- t_{max}
- k_{el}
- $t_{1/2}$
- $MRT_{0\text{-}t}$

9.4.5 Analyses of the Exploratory Endpoints

The following section outlines the planned analyses of the exploratory endpoints of the JR-171-101 study. Analyses will be performed on the FAS, unless otherwise specified.

9.4.5.1 Drug Concentration in CSF

For drug concentration in CSF, summary statistics of measured values will be calculated by each period and dose group (2.0 or 4.0 mg/kg).

9.4.5.2 HS and DS Concentrations in CSF

For HS and DS concentrations in CSF, summary statistics of measured values at each time point will be calculated, and time courses will be created for Part 1 and each group in Part 2. In addition, difference from baseline, ratio to baseline and relative change from baseline at Week 4 in Part 1 or Week 12 in Part 2 and corresponding 2-sided 95% confidence interval will be calculated. [redacted]

[redacted].

9.4.5.3 Urinary HS and DS Concentrations and Serum HS and DS Concentrations

The following analyses will be performed for subjects in FAS excluding naïve subjects in Part 2.
For urinary HS and DS concentrations, and serum HS and DS concentrations, summary statistics of measured values at each time point will be calculated, and time courses will be created for Part 1 and each group in Part 2. In addition, difference from baseline, ratio to baseline and relative change from baseline at Week 4 in Part 1 or Week 12 in Part 2 and corresponding 2-sided 95% confidence interval will be calculated.
For naïve subjects, a list of their individual data will be created. If 3 or more naïve subjects are allocated into one dose group and their data are available for these analyses described above, the same assessments will be also performed for these naïve subjects.

9.4.5.4 Other Clinical Findings Related to Neurocognitive and Behavioral Changes

For symptoms and signs related to MPS I, change from the previous scheduled visit and details of the assessment will be summarized in a list by study period and dose group.

9.4.5.5 BVMT-R and HVLT-R

For the BVMT-R and HVLT-R, summary statistics of total score over Trial 1-3 (Recall trials), score on Trial 4 (Delayed recall trial) and the recognition discrimination index at each time point will be calculated for each group in Part 2. In addition, relative change from baseline to Week 13 will be calculated.

9.4.5.6 T.O.V.A.

For the T.O.V.A., summary statistics of following parameters at each time point will be calculated for each group in Part 2. In addition, relative change from baseline to Week 13 will be calculated.

- Response time variability
- Response time
- Commission errors
- Omission errors

9.4.5.7 PedsQL-FIM

For the PedsQL-FIM, summary statistics of scaled scores, total score, parent health-related quality of life summary score and family summary score at baseline and Week 13 will be calculated for each group in Part 2. In addition, the absolute change from baseline to Week 13 will be calculated.

9.4.5.8 Other Exploratory Endpoints

The following analyses will be performed for subjects in FAS excluding naïve subjects in Part 2.
For other exploratory endpoints; CSF opening pressure, liver and spleen volumes, 6-minute walk test and cardiac function, summary statistics of measured values at each time point as well as change from baseline will be calculated for Part 1 and each group in Part 2.
For naïve subjects, a list of their individual data will be created. If 3 or more naïve subjects are allocated into one dose group and their data are available for these analyses, the same assessments will be also performed for the naïve subjects allocated into that dose group.

9.4.6 Subgroup Analyses

Analyses described in Section 9.4.5.2, 9.4.5.3 and 9.4.5.7 will be performed on following subgroups in Part 2.

[redacted]

[redacted].

9.5 Interim Analyses

No interim analyses will be performed in the JR-171-101 study.

9.6 Independent Data Safety Monitoring Committee (IDSMC)

For the purpose of consistent and objective safety assessment, the sponsor will establish an IDSMC completely independent from the sponsor.
The sponsor will immediately set up the IDSMC. The IDSMC will evaluate safety and report the results to the sponsor.
Detailed procedures for the IDSMC are provided in the Safety Evaluation Manual which is created by the sponsor as a separate document.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

The study will be conducted in accordance with the guidelines in ICH-GCP, the 18th World Medical Association's Declaration of Helsinki, applicable regulatory/regional requirements and this protocol.

The appropriate IRB/IEC must approve the protocol, patient information sheet and informed consent document, and where appropriate, agree to monitor the conduct of the study and agree to review periodically. The principal investigator will provide the sponsor with documentation that the IRB/IEC has approved the study before the study may begin.

In addition, the principal investigator must provide the sponsor with the IRB/IEC approval of any revisions to the patient information sheet and informed consent document or amendments to the protocol.

Details of the IRB/IEC's composition including names of their members, their qualifications and what function they perform in the committee (*e.g.*, chairman, specialist, lay-member) will be made available to conform to regulations governing the conduct of clinical studies within each country. The constitution of the IRB/IEC must be supplied to the sponsor.

10.1.2 Protocol Compliance, Deviations or Changes, and Amendments

Compliance with Protocol

The principal investigator shall fully discuss the ethical and scientific validity of the conduct of the clinical trial with the sponsor based on the data and information provided, such as the protocol and the latest Investigator's Brochure, and agree on the content and compliance with the protocol. The principal investigator and the sponsor will sign to the Agreement Form and date it in order to confirm the above agreement.

Protocol Deviations or Changes

The principal investigator or subinvestigator must not make a deviation from or change to the protocol without obtaining prior written agreement from the sponsor and a review-based written approval from the IRB/IEC in advance (except in medically unavoidable circumstances such as to avoid the immediate danger to a subject, or cases in which changes are related only to the administrative matters of the clinical study).

In medically unavoidable circumstances, such as avoiding an immediate danger to a subject, the principal investigator must submit, as promptly as possible, the details of and reasons for deviations or changes to the sponsor, as well as to the head of medical institution (in countries where applicable) and to the IRB/IEC of the study institution to obtain approval for such deviations or changes. In addition, the principal investigator will submit, without delay, a report of any change of the clinical study that can have a significant impact on the conduct of the clinical study or increase a danger to a subject, to the sponsor as well as to the head of medical institution (in countries where applicable) and to the IRB/IEC of the study institution.

Note that the principal investigator or subinvestigator will record in source documents all deviations from the protocol.

Of all the deviations from the protocol, the sponsor will define the five items below as critical deviations and will collect and evaluate information regarding them.

1. A deviation in which a subject had been enrolled in the clinical study without meeting the entry criteria
2. A deviation in which a subject fell under the discontinuation criteria during the clinical study period but had not been withdrawn
3. A deviation in which a subject violated the assigned dosage (administration requirements)
4. A deviation in which a subject received a concomitant medication/therapy that is prohibited
5. Other critical deviations

Protocol Amendment
If the sponsor finds it necessary to amend the protocol, the sponsor shall provide the principal investigator with the necessary documents and information, including the protocol and the latest Investigator's Brochure.
Based on the revised protocol and the latest Investigator's Brochure, the principal investigator should fully discuss with the sponsor the information and agree on the content and compliance with the protocol. The principal investigator and the sponsor will sign to the Agreement Form and date it in order to confirm the above agreement.
Submit the revised protocol to the head of the medical institution (in countries where applicable).
In addition, when changes are made in administrative matters, etc. that are not related to the nature of the clinical trial plan, the revised edition should be reported to the principal investigator and the head of the medical institution (in countries where applicable) at any time.

10.1.3 Financial Payment and Insurance
With respect to any liability directly or indirectly caused by the investigational products in connection with this clinical trial, the sponsor assumes liability by law on behalf of the principal investigator(s) and his/her assistants, only in cases that meet all of the following; the principal investigator(s) and his/her assistants have followed the instructions of the sponsor in accordance with this protocol and any amendments; the investigational products administered to the subject in this clinical trial have been supplied by the sponsor; the principal investigator and his/her assistants have performed this clinical study in accordance with current medical and scientific practice.
A letter of indemnity will be signed between the sponsor and the principal investigator(s) (between the sponsor and the head of the medical institution in countries where applicable), and the sponsor will insure according to local requirements.

Compensation for health damages
When the causal relationship between the JR-171 administration and the health damage cannot be reasonably ruled out, the sponsor compensates for the health damage unless it is caused for any reason attributable to the medical institution or subject.

Medical cost
In the event of study-related health damage, the patient's out-of-pocket expenses excluding benefits from health insurance, etc. shall be reimbursed by the sponsor.

Compensation claim
In the event that a request for compensation from a subject has been filed or a matter subject to compensation is suspected, the participating medical organization should immediately contact the sponsor. The sponsor will respond promptly in accordance with the SOP for health damage compensation for test subjects in-house.

Insurance
The sponsor will purchase insurance to ensure the performance of these procedures.

10.1.4 Financial Disclosure
Principal investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Principal investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

10.1.5 Audit
Authorized representatives of the sponsor and/or a national regulatory authority may visit the center to perform audits or inspections, including source data verification. The purpose of a the sponsor audit or inspection is to systematically and independently examine all study related

activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, ICH-GCP guidelines and any applicable regulatory requirements. The principal investigators should contact the sponsor immediately if contacted by a regulatory agency about an inspection at their center.
The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.6 Training of Staff

The principal investigator at each participating study site will maintain a record, “authorized representative signature sheet”, of all individuals involved in the study (medical, nursing and other staff). In collaboration with the sponsor, the principal investigator will ensure that appropriate training relevant to the study and/or study procedures is given to all of these staff, and that any new information of relevance to the performance of the JR-171-101 study is forwarded to the staff involved.

10.1.7 Informed Consent Process

The principal investigator is to review and submit to the IRB/IEC for approval of the ICF for the patients and written permission form for patient’s legally acceptable representative as well as written information for them modified from the master sponsor ICF to comply with each country’s applicable regulations.

The ICF and written information should include explanations of the elements as described in points 1 to 21 below:

1. That the study involves research;
2. The purpose of the study;
3. Principal investigator’s name, job title and contact information;
4. Methods of study (including the experimental aspects of the study, subject inclusion criteria, and the probability for random assignment (if applicable) to each treatment);
5. The reasonably expected clinical benefits and risks or inconveniences (When there is no intended clinical benefit to the subject, the subject should be made aware of this);
6. If a patient is to be a subject, whether or not there is any alternative procedure(s) or course(s) of treatment that may be available to the patient, and their important potential benefits and risks;
7. The expected duration of the subject’s participation in the study;
8. That the subject’s participation in the study is voluntary and that the patient or the subject’s legally acceptable representative may refuse to participate or withdraw from the study, at any point of time, without penalty or loss of benefits to which the subject is otherwise entitled if not participating in the study;
9. That the monitor(s), the auditor(s), the IRBs, and the regulatory authority(ies) will be able to access the subject’s original medical records, without violating the confidentiality of the subject, and that, by signing a written ICF, the patient or the subject’s legally acceptable representative is authorizing such access;
10. That the subject’s identity will remain confidential even if the results of the study are published;
11. The point of contact at the study institution to make an inquiry to, or make a contact with, for further information regarding the study and the rights of study subjects, and in the event of study-related injury;
12. The compensation and treatment available to the subject in the event of study-related injury;
13. The number of subjects to be involved in the study;
14. That the subject or the subject’s legally acceptable representative will be informed as soon as possible if information becomes available that may be relevant to the subject’s willingness to continue participation in the study;
15. The circumstances or reasons under which the subject’s participation in the study may be terminated;

16. The anticipated expenses, if any, to the subject for participating in the study;
17. Details of reimbursement to be made to the subject for participating in the study (agreements on how the amount is determined, etc.);
18. The rules the subject should comply with;
19. The type of the IRB that examines or discusses whether or not the study is appropriate, matters that are to be examined or discussed by individual IRBs, and other matters associated with IRBs that directly concern the study (including the name of the organizer of an individual institutional review committee and its location, and information concerning such an organizer that is available to view);
20. That the written SOP for the IRB is made available to view by the public on the website or at the office of the study institution, etc. and that the subject should come forward if he/she wishes to view these documents;
21. That the data used in applying for an approval may be used by the regulatory agency in each country for research purposes.

The principal investigator or subinvestigator will provide each patient with an explanation on any and all activities associated with the study before it is performed and written consent from each patient will be obtained. In the case of a patient who is under the age of 18 (20 years in Japan) at the time of informed consent process, or if it is not possible to obtain consent from the patient him/herself due to his/her intellectual disabilities associated with MPS I, the principal investigator or subinvestigator will perform the following procedures for the patient's legally acceptable representative and written consent should be obtained from the patient him/herself too, wherever possible.
The principal investigator or subinvestigator at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Patients must also be notified that they are free to discontinue from the study at any point in time. The patient should be given the opportunity to ask questions and be allowed time to consider the information provided.
The patient's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The signed and dated ICFs will be kept by the principal investigator and will be available for inspection by the sponsor and the authorities. A copy of the signed written ICF must be given to the patient.
The global ICF will be approved by the sponsor if modifications are made according to local requirements; the new version has to be approved by both the sponsor and the IRB/IECs.
The written ICF will explain that the study data will remain confidential in accordance with national data legislation. The subject ID code will only identify subjects in the database. The written ICF will also explain that for data verification purposes, authorized representatives of the sponsor, regulatory authority, and IRB/IEC require direct access to parts of the hospital records relevant to the study, including the subject's medical history.
The ICF may need to be revised during the study, should important new information become available that may be relevant to the safety of the subject. In this instance, the IRB/IEC should always give approval; if applicable, existing subjects should be informed of the changes, and signed consent obtained for the new changes.
The principal investigator should, with the consent of the subject, inform the subject's primary physician about their participation in the clinical study.
As used in this protocol, the term "informed consent" includes all consent given by patients or their legal representatives.

10.1.8 Blood and CSF Volume

Blood and CSF volumes that will be collected in this study are described below. Additonal testing that accompanies blood sampling will be performed as deemed necessary by the principal investigator or subinvestigator.

Study period	Purpose	Sample volume	Number of sample collection	Volume of sampling for each purpose
Part 1	Hematologic test	[redacted]	[redacted]	[redacted]
	Biochemical test			
	Serum iron test			
	Serum HS and DS concentrations			
	Antibody test			
	Plasma drug concentration			
	Assay for CRIM status			
	Anaphylaxis test**			
	Drug concentration in CSF			
	HS and DS concentrations in CSF			
Part 2	Hematologic test			
	Biochemical test			
	Serum iron test			
	Serum HS and DS concentrations			
	Antibody test			
	Plasma drug concentration			
	Assay for CRIM status			
	Anaphylaxis test**			
	Drug concentration in CSF			
	HS and DS concentrations in CSF			

*Blood will be collected in each study site for laboratory tests (hematology, biochemistry and serum iron tests). The volume of blood sampling depends on the study sites.
**If an anaphylaxis occurs (see section 6.1 for detail), blood will be collected in each study site for laboratory tests. The volume of blood sampling depends on the study sites.

10.1.9 Data Protection

In handling the eCRF, as well as raw data and ICFs related to the conduct of the clinical study, sufficient attention will be given to protect subject privacy. In preparing the eCRF, subjects will be identified only by the subject ID code.
Information about subject identity, known by authorized persons through direct access to source documents, will be protected by all proper preventive measures according to related laws and regulations.
Subject privacy will be protected in the same way when the result of the clinical study is published.

10.1.10 Future Use of Stored Specimens and Data

It is not applicable as all samples will be discarded after completion of the JR-171-101 study.

10.1.11 Key Roles and Study Governance

Medical monitor(s) will be appointed as a central consultant in to enable principal investigators to discuss any clinical aspects of the study, to provide medical governance as well as to oversee safety in each Part.

10.1.12 Safety Oversight

Each study institution will undergo, at least once a year, a review by the IRB/IEC as to whether continuing the clinical study is appropriate.
Furthermore, in the cases described below, each study institution will properly undergo a

review by the IRB/IEC as to whether continuing the clinical study is appropriate, according to each institution's SOP.

1. When the sponsor notifies the principal investigator of new information, including safety information (when the sponsor notifies the study Institution Head of new information in countries where applicable).
2. When the principal investigator notifies the study Institution Head of a SAE (when the principal investigator becomes aware of a SAE in countries where applicable).
3. When the principal investigator revises the ICF and reports to that effect to the study Institution Head (when the principal investigator revises the ICF in countries where applicable).

10.1.13 Clinical Monitoring

Clinical site monitoring will be conducted by the sponsor representative to ensure that the rights and well-being of study subjects are protected, that the reported study data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol/amendment(s), with ICH-GCP, and with applicable regulatory requirement(s).

Before the study begins, a monitor representing the sponsor will visit the investigational site to determine the adequacy of the facilities and to discuss with the principal investigator(s) and other personnel involved in the study their responsibilities with regard to protocol adherence, and the responsibilities of the sponsor or its representatives.
During the study, a monitor representing the sponsor will have regular contact with the investigational site, including visits to:

- provide information and support to the principal investigator(s)
- confirm that facilities remain acceptable
- confirm that the investigational team is adhering to the protocol
- confirm that data are being accurately recorded in the eCRF
- confirm that the study is conducted according to the ICH-GCP
- confirm that an update of the screening log is performed, and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's records at the hospital or practice, and other records relevant to the study.)

This will require direct access to all original records for each subject (*e.g.*, clinic charts).
The monitor, medical monitor or the sponsor representatives will be available between visits if the principal investigator(s) or other staff at the investigational site need information and advice.

10.1.14 Data Quality Assurance

In order to verify the proper conduct of the clinical study, which is compliant with this protocol as well as ICH-GCP and related notifications, and data reliability, the sponsor will perform quality control according to the SOP that are defined separately.
In order to ensure the conduct of the clinical study, as well as the creation, recording, and reporting of data are compliant with this protocol as well as ICH-GCP and related notifications, the sponsor will conduct audits that are performed by a controller of audit/auditor, who is independent of the department involved in the clinical study, in the company and the study institution or an outsourcing contractor as needed, according to the SOP that are defined separately.

At the request of a monitor, controller of audit/auditor, the IRB/IEC, or the regulatory authority, the principal investigator/the study institution head will provide direct access to all the records related to the clinical study, including source documents.

10.1.15 Data Collection and Management Responsibilities

The management of data and each specific data point will be determined before data are locked, through discussion(s) with medical specialists and statisticians, as needed.

Data collection is the responsibility of the clinical study staff at the site under the supervision of the principal investigator. The principal investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.
All source documents should be completed in a neat, legible manner to ensure accurate recording of data in the eCRF.
Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.
Clinical data (including AEs and concomitant medications) will be entered into an eCRF, a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks to identify data that appear to be inconsistent, incomplete, or inaccurate. Clinical data will be entered directly into the eCRF from the source documents.
For completion/correction of the eCRF, refer to the separate sponsor manual.

10.1.16 Source Documents

JCR Pharmaceuticals Co., Ltd. is the sponsor for the JR-171-101 study. Subject data will be registered at the study site. The sponsor will supply the study site with all necessary material and eCRF at the initiation of the study. Each eCRF and the subject's medical records will be verified carefully by monitors representing the sponsor to ensure full protocol compliance with the planned procedures with to regard to data completion and follow-up. The sponsor provides project oversight at all times. A project representative from the sponsor will be available to the study sites by telephone and/or by visit.
The principal investigator is responsible for completing the eCRF forms and including all relevant data. The eCRF forms will be monitored by representatives of the sponsor who will contact the principal investigator should the need arise for further clarification. Data lists will be generated from the database enabling a direct comparison between the original case report forms and the database. This will facilitate the clarification of any errors. These corrected documents, and other study documents, will be retained as the final study documentation.
The principal investigator must arrange for the retention of the ID codes of subjects (*i.e.*, hospital/unit code, study ID code and study number) for as long as the sponsor requests after completion or discontinuation of the clinical study. Other source documents, such as subject files and clinic case notes, must be retained for the maximum period of time permitted by the hospital, institution or private practice and if this is less than the sponsor requires after the completion or discontinuation of the clinical study, then the sponsor must be notified to arrange record retention.
If the principal investigator relocates or retires, or otherwise withdraws his/her responsibility for maintaining the study documentation, the sponsor must be notified in writing so that adequate provision can be made with regard to the ID codes of subjects, copies of the study documentation (*e.g.*, copies of eCRFs) and other source data (if available). This responsibility may be transferred to the sponsor, who will make arrangements to store the data. An inventory of stored data will be held by the principal investigator and a copy by the sponsor.
Data without a written or electronic record will be identified before study start and should be recorded directly on the eCRF, which will be documented clearly as being the source data.

10.1.17 Storage of Records and Other Documents

The principal investigator/institute shall store the essential documents and records related to the clinical trial for either of the following periods, 1 or 2, whichever comes later.

1. The sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor.
2. If the sponsor discontinues the clinical development of an investigational product (*i.e.*, for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

Principal investigators/institutes take measures to ensure that these records are stored

appropriately during this storage period and that they can be retrieved on request. No records will be destroyed without the written consent of the sponsor.

10.1.18 Study and Site Start and Closure

The first act of recruitment will be after the first site open.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed by the sponsor.
The principal investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
Reasons for the early closure of a study site by the sponsor or principal investigator may include but are not limited to:

- Failure of the principal investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or ICH-GCP guidelines
- Inadequate recruitment of subjects by the principal investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Principal Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The principal investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.1.19 Publication Policy

When publishing an academic paper or making a presentation at a conference in relation to this clinical study, the principal investigator will obtain prior written approval from the sponsor. Note that a patent, manufacturing method, and pharmaceutical formulation related to this investigational product will not be disclosed without approval of the sponsor.
The sponsor has the right to use the result of this clinical study to promote sales after obtaining approval.

10.1.20 Conflict of Interest Policy

Any actual conflict of interest of the principal investigator, subinvestigator or persons who have a role in the design, conduct, analysis, publication, or any aspects of this clinical study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the study.

10.1.21 Additional considerations

It is not applicable for the JR-171-101 study.

10.2 Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1 Definition of AE

AE Definition

An AE is any untoward or unintended illness or its sign (including an abnormality observed in laboratory tests or physiological tests) in a subject, which does not necessarily have to have a causal relationship with the investigational product. AEs that occur after the administration of an investigational product, those that have an undeniable causal relationship with the investigational product are considered adverse drug reactions.

- Any patient having received any amount of investigational product should be evaluated for safety. The schedule of assessments is shown in the Schedule of Activities, Section 1.3.
- Any AE must be documented and the following guidelines will be used for this purpose. An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (***e.g.***, nausea, chest pain), signs (***e.g.***, tachycardia, enlarged liver) or the abnormal results of an investigation (***e.g.***, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any point of time after the patient consented to participate. This definition includes intercurrent illnesses or injuries, and exacerbation of pre-existing conditions.
- Where a diagnosis is possible, it is preferable to record it in the eCRF rather than as a series of terms relating to the diagnosis.
- An event that is solely due to progression of disease should not be reported as AEs.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (*e.g.*, ECG, radiological scans, vital signs measurements), including those that worsen from the time of informed consent, considered clinically significant in the medical and scientific judgment of the principal investigator or subinvestigator (*i.e.*, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either the study intervention or a concomitant medication. An overdose, per se, will not be reported as an AE/SAE unless it is an intentional overdose undertaken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy should be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the principal investigator to be more severe than expected for the subject’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject’s condition.
- Medical or surgical procedures (***e.g.***, endoscopy, appendectomy): the other condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience based admission to a hospital).

Events NOT Meeting the AE Definition
• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2 Definition of Clinically Relevant Changes in Laboratory Assessments

Criteria for clinically relevant changes in laboratory test values
• When the value varies from within the reference range to outside the reference range • When the value outside the reference range changes in the discretion of deterioration • When the value varies from outside the reference range to outside the reference range

10.2.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (serious condition; *e.g.*, hospitalization for signs/symptoms of the disease under study).

An SAE is defined as any untoward medical occurrence that, at any dose:	
a.	**Results in death**
b.	**Is life-threatening** In the opinion of the principal investigator or subinvestigator, the AE places the patient at immediate risk of death from the event as it occurred; it does not include a reaction that, had it occurred in a more severe form, might have caused death.
c.	**Requires inpatient hospitalization or prolongation of an existing hospitalization, unless the hospitalization is for;** • Admission for treatment that was scheduled before the clinical study or that for examinations • Monitoring of the studied indication, not associated with any deterioration in condition • Social reasons and respite care in the absence of any deterioration in the patient's general condition
d.	**Results in persistent or significant disability or incapacity**
e.	**A congenital anomaly or birth defect**
f.	**Other situations:** • An important and significant medical event that, based upon appropriate medical judgment, may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed above

10.2.4 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording
• In the event of an AE/SAE, the name of the AE, severity, seriousness, the date of occurrence, whether or not there was a procedure for the administration of the investigational product as well as its details, the outcome of the AE (including the date of its determination), a causal relationship between the AE and the investigational product, and comments as needed should be recorded in the eCRF. • It is the responsibility of the principal investigator or subinvestigator to document any AE occurring from the time of informed consent obtained in the subject's hospital notes and in the eCRF. MedDRA will be used to code AEs by the data management and pharmacovigilance groups.

Assessment of Severity
The principal investigator or subinvestigator will determine the severity of AEs reported on the eCRF as follows: If the AE is listed in the CTCAE Version 5 table, then the highest level that the AE reached should be noted. If the AE is not listed in the CTCAE Version 5, then the highest level reached should be noted, according to the following description:

Assessment of Severity

- Grade I = Slight: An AE, which is easily tolerated by the patient. It only incurs a minimum of discomfort and does not influence ordinary daily tasks.
- Grade II = Moderate: An AE, which is of sufficient severity to have a negative influence on ordinary daily tasks.
- Grade III = Severe: An AE, which effectively hinders ordinary daily tasks.
- Grade IV = Life threatening: An AE, which puts the patient's life at risk.
- Grade V = Death: Death related to AE.

Assessment of Causality

- The principal investigator or subinvestigator are obligated to assess the relationship between study intervention and occurrence of each AE/SAE.
  Related: The causal relationship between the investigational product and the AE may be at least reasonable and may not be denied because of disappearance after discontinuation of administration, recurrence after resumption of administration, establishment of a causal relationship with the investigational product or similar drug, absence of confounding risk factors, consistency with exposure and duration of exposure, almost definite explanation for the contribution of the investigational product by supporting an accurate medical history, and lack of reasonable possibility of causal relationship between the concomitant medications/therapies and the AE.
  Unrelated: in cases other than the above.
- The principal investigator or subinvestigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The principal investigator or subinvestigator will also consult the Investigator's Brochure and/or Product Information for marketed products, in his/her assessment.
- For each AE/SAE, the principal investigator or subinvestigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the principal investigator or subinvestigator have minimal information to include in the initial report to sponsor. However, it is very important that the principal investigator or subinvestigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor.
- The principal investigator or subinvestigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Assessment of Outcome

The outcome of an AE will be determined according to the criteria described below.

Outcome

Recovery	Disappearance of symptoms/findings, normalization of laboratory values or recovery to values measured at baseline
Remission	Reduction in severity, disappearance of the most part of symptoms/findings, recovery of laboratory values to a level close to values measured at baseline
Unrecovered	No changes in symptoms/findings or laboratory values
Recovered with sequelae	Dysfunction that can interfere with daily activities
Death	Death

Follow-up of AEs and SAEs

- The principal investigator or subinvestigator will continually monitor any subject with an AE and SAE until either the event has returned to the baseline grade or ≤Grade I; or if the AE is determined to be chronic, a cause is identified.
- If a subject has an ongoing AE at Week 5 in Part 1/Week 13 in Part 2 or discontinuation, then the subject will be followed until a time when the principal investigator or subinvestigator judges that the clinical condition of the subject is stable and safety can be ensured, or when a causal relationship with the investigational product is not found. The follow-up as part of the clinical study may be terminated at 4 weeks (28 days) after the completion (discontinuation) of the clinical study.
- Follow-up of all AEs must be documented in the subject's medical record and on the eCRF.
- When a subject withdraws from participation in the study before the first administration, a follow-up with the subject is unnecessary.

Reporting events to subjects

If any event could disturb the subject's daily activities, such an event should also be presented to the subject promptly to confirm their willingness to continue study participation.

Management of pregnancy

In case of the subject's or the subject's partner's pregnancy after the administration of an investigational product, it should be reported to the sponsor as soon as possible and followed for the full duration of the pregnancy and/or until outcome is known. If a miscarriage or stillbirth occurs as a result of pregnancy, it should be reported to the sponsor within 24 hours of becoming aware. These kinds of events should be reported per the SAE reporting process indicated in Section 10.2.5.
In case of a subject's partner's pregnancy, the principal investigator or subinvestigator must obtain the signed and dated informed consent from the subject's partner before collecting necessary information about her pregnancy.

10.2.5 Reporting of SAEs

SAE Reporting via e-mail or facsimile equipment

Any SAE, occurring at any point of time during the clinical study must be reported by the principal investigator to the Pharmacovigilance group by fax/e-mail within 24 hours after obtaining knowledge of the SAE ([redacted]). The principal investigator is furthermore legally obliged to report any SAE in accordance with local country requirements. SAE information will be added to the Investigator's Brochure at a minimum on an annual basis.
At the time the AE is initially reported the principal investigator will be asked to supply detailed information regarding the nature and severity of the event including, but not limited to:

- Protocol number and subject ID code
- Dose, date and time of JR-171 administration
- Start and stop date (if known)
- Maximum intensity of the event (CTCAE version 5 grading if applicable)
- Likelihood of its relationship to the study medication
- Treatment administered as a result of the event
- Any concomitant medications taken before or as a result of the event

All SAEs will be followed until satisfactory resolution or until the site principal investigator deems the event to be chronic or the subject is stable. Other supporting documentation of the event may be requested by the sponsor and should be provided as soon as possible.

Suspected unexpected serious adverse drug reactions must be reported to regulatory

SAE Reporting via e-mail or facsimile equipment

agency in each country as soon as possible but no later than within **15 calendar days** following the sponsor's initial receipt of the information.

Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported to the regulatory agency in each country as soon as possible but no later than **7 calendar days** following the sponsor's initial receipt of the information.

Expectedness should be considered as described in the JR-171 Investigator's Brochure.

Follow-up reporting: Any relevant additional information obtained by the sponsor that pertains to a previously submitted investigational new drug application (IND) safety report must be submitted as a Follow-up IND Safety Report. Such report should be submitted without delay, as soon as the information is available but no later than 15 calendar days after the sponsor receives the information.
The sponsor or sponsor's designee will submit expedited safety reports to the applicable regulatory agency as appropriate and also will inform all of the principal investigators involved in the study. Principal investigators must submit safety reports as required by their IRB/IECs within the specified timelines given by the agency. Documented information must also be provided as appropriate.

10.3 Appendix 3: Abbreviations

Abbreviations	Definition of Terms
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to 24 hours
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last blood sampling time point
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
BSID	Bayley scales of infant and toddler development
BVMT-R	Brief Visuospatial Memory Test-Revised
CFR	Code of Federal Regulations
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRIM	Cross-reactive immunologic material
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DS	Dermatan sulfate
eCRF	Electronic case report form
EP	European Pharmacopoeia
ERT	Enzyme replacement therapy
EU	European Union
FAS	Full analysis set
GAG	Glycosaminoglycan
HS	Heparan sulfate
HSCT	Hematopoietic stem cell transplantation
hTfR	Human transferrin receptor 1
hTfR KI/Idua KO mice	Human transferrin receptor 1 knock-in/α-L-iduronidase knock-out mice
HVLT-R	Hopkins Verbal Learning Test-Revised
IAR	Infusion associated reaction
ICF	Informed consent form
ICH-GCP	International Conference on Harmonisation Good Clinical Practices
IDSMC	Independent data safety monitoring committee
IDUA	α-L-iduronidase
IEC	Independent Ethics Committees
IND	Investigational new drug application
INN	International Nonproprietary Names
IRB	Institutional Review Board
IRT	Interactive Response Technology
JAN	Japanese Accepted Names for Pharmaceuticals
JP	Japanese Pharmacopoeia
JPE	Japanese Pharmaceutical Excipients
k_{el}	Elimination rate constant
M6PR	Cation-independent mannose-6-phosphate receptor
MCH	Mean corpuscular hemoglobin

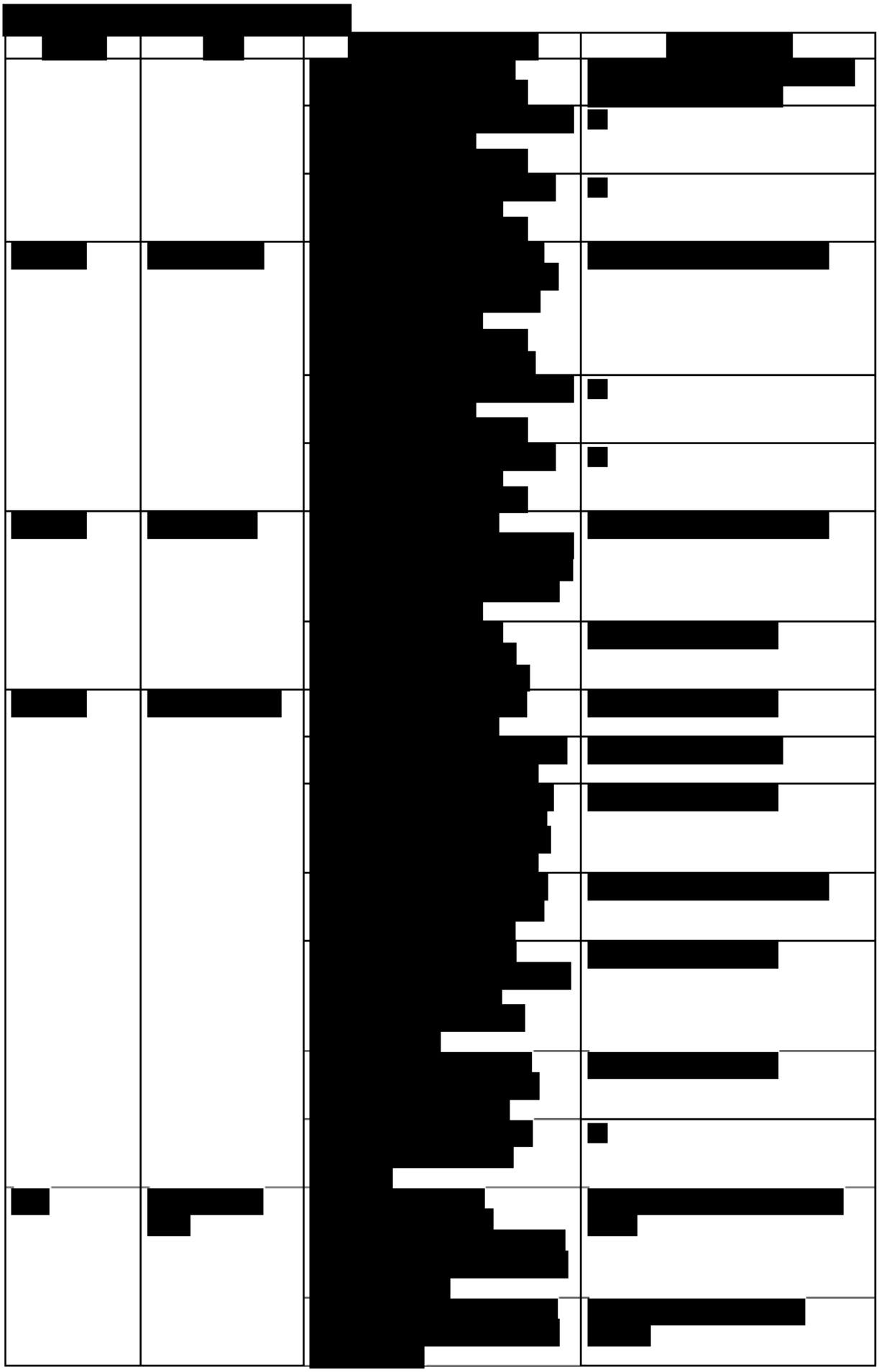
Abbreviations	Definition of Terms
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities terminology
MRI	Magnetic resonance imaging
MPS I	Mucopolysaccharidosis type I
MRT_{0-t}	Mean residence time from time zero to the last blood sampling time point
NF	National Formulary
PedsQL-FIM	Pediatric Quality of Life Inventory Family Impact Module
PK	Pharmacokinetic
PKS	Pharmacokinetic set
PT	Preferred term
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedures
SS	Safety set
$t_{1/2}$	Elimination half-life at terminal phase
TIBC	Total iron binding capacity
t_{max}	Time to reach maximum plasma concentration
T.O.V.A.	Test of Variables of Attention
TSAT	Transferrin saturation
UIBC	Unsaturated iron binding capacity
US	United States
USP	United States Pharmacopeia
VABS	Vineland adaptive behavior scales
WAIS	Wechsler adult intelligence scale
WISC	Wechsler intelligence scale for children
WPPSI	Wechsler preschool and primary scale of intelligence

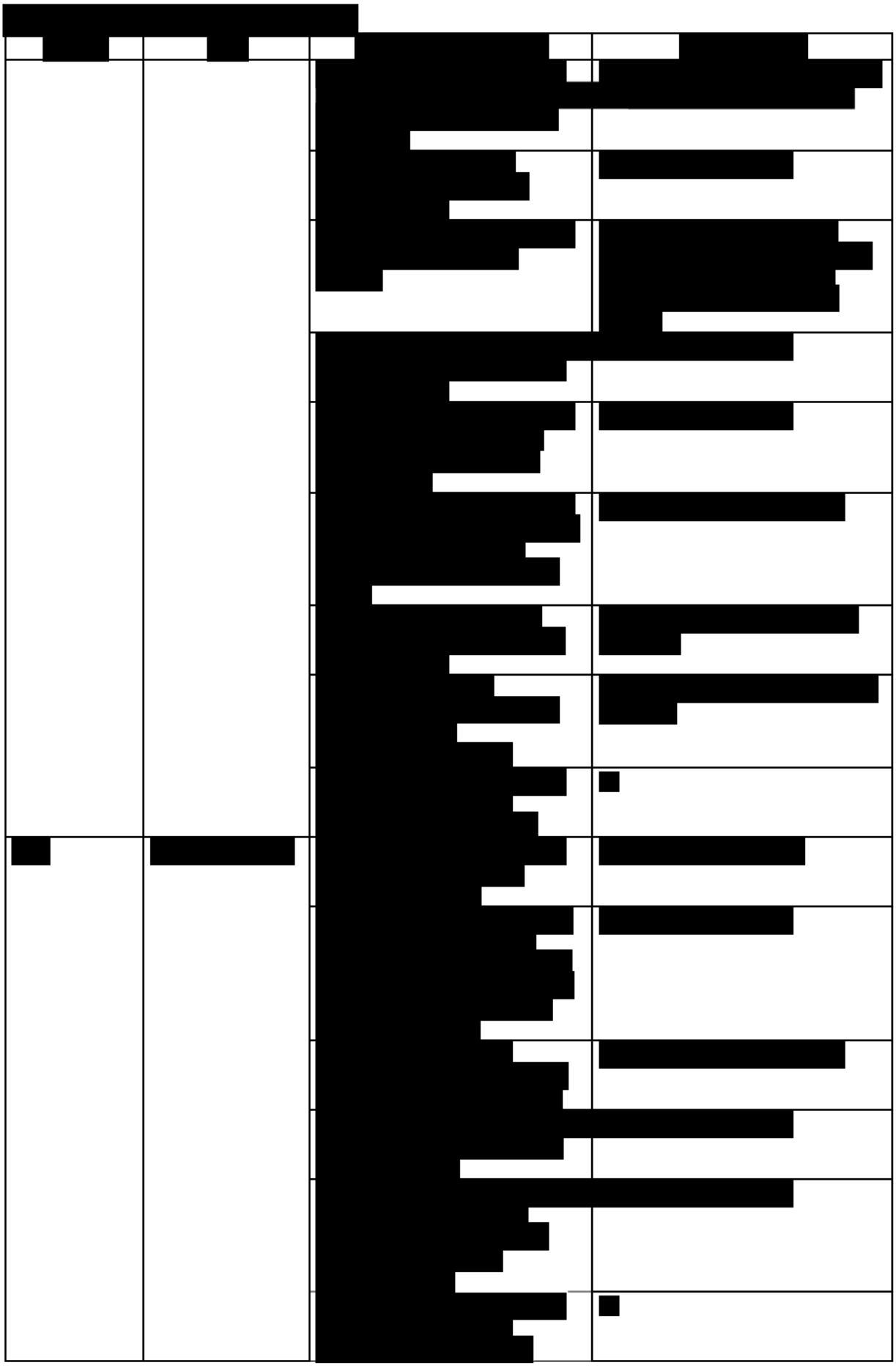
10.4 Appendix 4: Protocol Amendment History

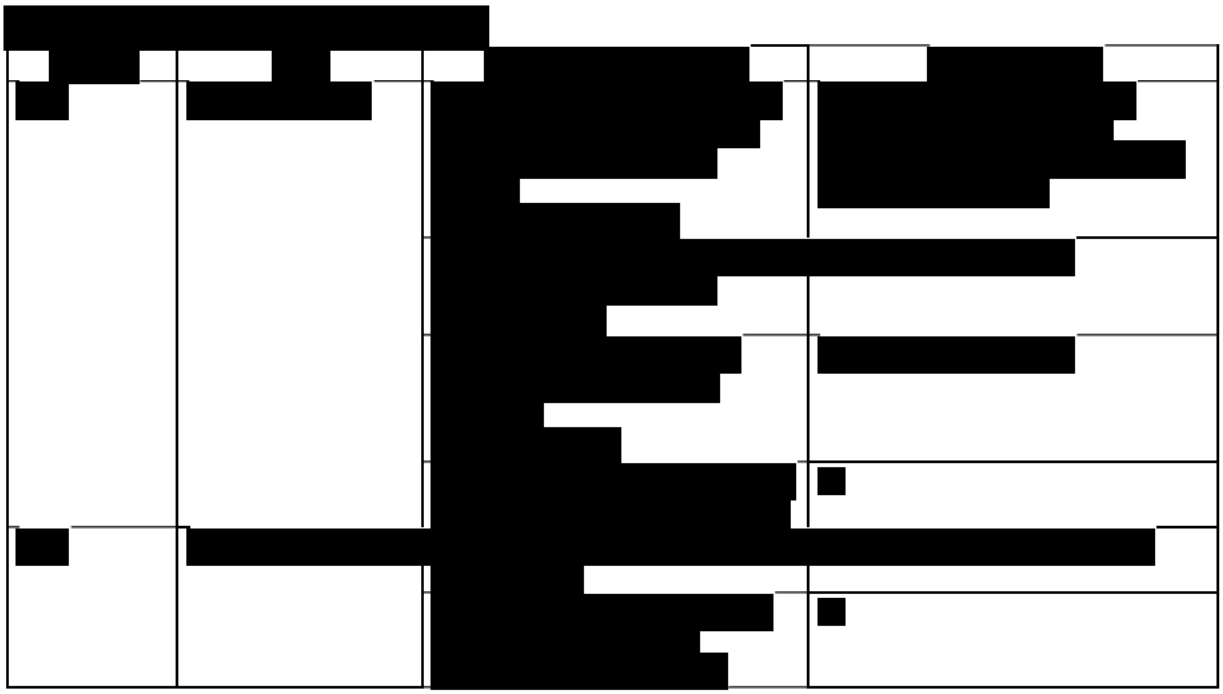
The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Protocol Amendment History

Version	Date	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]	[redacted]







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