PATIENT INFORMATION AND CONSENT FORM

Protocol Title: "A PHASE II STUDY OF JR-141 IN PATIENTS WITH MUCOPOLYSACCHARIDOSIS II"

Protocol number: JR-141-BR21

Name of Sponsor: JCR Pharmaceuticals Co., Ltd.

Name of the Principal Investigator: XXXXX

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XXXXXX

Introduction

You (your child) are being invited to take part in this trial because you (your child) have been diagnosed with mucopolysaccharidosis type II (MPS II, Hunter syndrome), which is a disorder caused by absence (or reduced activity) of the enzyme iduronate-2-sulfatase (IDS), which is a substance found in our cells. Its absence (or reduced activity can confound the functions of the bones, joints, heart, liver, and spleen, and can also affect intellectual development. If not treated appropriately, MPS II may result in organ failure (organs stop working) that can lead to even death. This clinical trial of "JR-141" a drug for the treatment of this disorder, is currently underway in this site. This document, called Informed Consent Form, has information regarding this clinical trial of this drug to you (your child). in which you (your child) are being asked to participate and it describes the study to help you decide if you want to participate or not. This form will tell you what you (your child) will have to do during the study, the risks and benefits and the alternatives available for treatment. You (your child) are asked to understand the explanation, think well, and decide whether to take part in this clinical trial or not. Your participation in this clinical trial is completely voluntary. Your opinion will be respected, and even if you refuse to participate in the trial, you will not lose any benefits to which you are otherwise entitled. You may also leave the trial at any time during the course of the trial even after you start participation in the trial. Please be assured that you will never suffer from any penalty in such a case.

If you find it difficult to understand something in the explanation given by your doctor or the sentences given below, or you need further explanation, please feel free to ask your doctor or the study staff. You may take an original copy of this document home to think about or discuss with your family or friends before making a decision or signing the form.

After fully understanding the contents of this informed consent document, if you (your child) agree to take part in this study, you or your child's legal representative need to sign and initial all pages of the document in two original copies. You will receive one original of this document and the other will be kept on file by your study doctor. Your signature means that you have been told about the study, what the risks are and that you (your child) want to take part in this study.

This clinical trial that you (your child) is being invited to participate intends to evaluate the safety of JR-141 in three different age groups of participants with MPS II (Hunter

syndrome) treated with JR-141 and also evaluate the efficacy in a general way in participants with MPS II among the above sets of participants.

This clinical trial that you (your child) is being invited to participate is sponsored by JCR Pharmaceuticals, Co., Ltd.. which is paying the hospital and all study procedures. The study physician will not receive financial payment for any specific study results.

JR-141 is an investigational medication. An investigational medication is one that is not approved by the Brazilian National Surveillance Agency (ANVISA) for use by the general public. After study completion, the research participants will continue to receive the study drug at no cost, if it proves beneficial according to study doctor and/or his assistant doctor and/or your personal doctor (and not only the study doctor) discretion. The provision of JR-141 will continue for as long as necessary and until 5 years after the drug is commercialized in Brazil, according to the National Health Council's (CNS) current regulation.

This clinical trial that you (your child) are being invited is conducted in accordance with rules specified by the government (such as Good Clinical Practice [GCP], that ensures the quality of the study and the protection of the welfare of the study participants), ethical committees, regulatory and health agencies to protect the rights of participants. One of these rules is a system in which whether to properly conduct a clinical trial or not is reviewed, and the organization responsible for this review is called the "Institutional Review Board (IRB)." The IRB consists of medical/dental/pharmaceutical experts and specialists in other medical areas or clinical studies, as well as non-specialists and individuals who have no personal interest with the medical institutions participating in the clinical trial, and assumes the responsibility to examine if any of the study procedures interfere with the rights and safety of study participants from scientific, ethical and other perspectives. This trial follows the current National Health Council (CNS), ANVISA and any other applicable regulations/legislations.

The conduct of this clinical trial has been submitted, reviewed and approved by the IRB, CONEP (National Commission of Ethics in Research) and ANVISA, and whether to continue this clinical trial or not will be reviewed by those same institutions on an ongoing basis.

1. New Drug Used in the Clinical Trial (Study Drug)

The new drug used in this clinical trial (study drug) is called "JR-141." JR-141 is an intravenous fluid (administered into a vein), that is a type of antibody (antibodies are normally present in your blood and serve to help to fight infections and other diseases) attached to an the substance (enzyme) that is absent or reduced in patients with MPS II (Hunter syndrome). This portion is nearly the same as Elaprase, which has already been approved as a drug for the treatment of MPS II (Hunter syndrome). The antibody that the enzyme is attached to (anti-transferrin receptor antibody, which tricks the brain to take up the drug through its usual mechanism of absorption of iron, that is needed to the brain function) helps the enzyme to cross a barrier that we have in our bodies (the blood-brain barrier) that prevents the drug to enter the brain, therefore with this the drug can be sent into the brain.

2. What are the Objectives and Procedures of This Clinical Trial?

The objectives of this clinical trial that you (your child) are being invited to participate are to evaluate the safety of JR-141 in three different age groups of participants with MPS II (Hunter syndrome) treated with JR-141 and also evaluate the efficacy in a general way in patients with a severe form of MPS II among the above sets of participants.

2.1. How the grouping will occur?

If you (your child) agree to take part in this clinical trial and after you provide informed consent, if you (your child) are considered by your doctor to be eligible for participation, you will be randomized (you [your child] be assigned through a system like a toss of a coin, which chance will decide, no human intervention) to any of the treatment groups:

- The group in which JR-141 will be administered at a dose of 1.0 mg per kg of body weight once weekly for 26 weeks,
- The group in which JR-141 will be administered at a dose of 2.0 mg per kg of body weight once weekly for 26 weeks, and
- The group in which JR-141 will be administered at a dose of 4.0 mg per kg of body weight once weekly for 26 weeks.

After switching from the previous treatment (if you have received enzyme replacement therapy before), treatment with the study drug JR-141 will be started.

To assure your safety, JR-141 will be administered over a period of 3 hours in all the treatment groups but may be extended to a period longer than 3 hours, taking into account the reactions to the infusion of JR-141, or other reaction, always prioritizing your (your child) safety.

2.2. What Should Be Done Before Treatment with JR-141?

If you (your child) agree to take part in this clinical trial and providing informed consent, you (your child) will be asked to undergo screening assessments to check whether you (your child) satisfy the criteria for participation in the clinical trial or not. Please note that if you (your child) are found not to satisfy the criteria for participation in the clinical trial (presented below) prior to treatment with JR-141, your participation in the trial cannot be continued and will therefore be discontinued. However, as presented before, you will not lose any of rights.

2.3. What is the Criteria for Participation in the Clinical Trial?

The criteria that are listed below have been specified to properly evaluate JR-141 as well as to assure your (your child) safety. Male participants who have a diagnosis of MPS II (Hunter syndrome) and who satisfy all of the criteria in the inclusion criteria (presented below) and do not meet any of the criteria in exclusion criteria (presented below) are eligible for this clinical trial.

2.3.1. Inclusion Criteria (You Must Satisfy All of the Following Criteria to Be Eligible for Participation in the Clinical Trial)

- If you (your child) are a male with confirmed diagnosis of MPS II, based on deficient activity of IDS in the cells and/or pathogenic mutations was identified in the IDS gene (if enzyme diagnosis was done in dried blood spots or plasma, molecular genetics confirmation is mandatory)
- If you (your child) are in one of the following age groups:
  - 0 to 3 years and 11 months old (6 participants, 2 in each dose)
  - 4 years to 7 years and 11 months old (6 participants, 2 in each dose)
  - 8 years or older (6 participants, 2 in each dose)
- If you are capable of providing written consent by himself, unless the participant is under the age of 18 years at the time of informed consent process, or it is not possible to obtain consent from the participant himself due to his intellectual

disabilities associated with MPS II

- If your child is under the age of 18 years or from whom it is not possible to obtain consent due to his intellectual disabilities associated with MSP II, he may be included if written consent can be provided by you; written assent should be obtained from your participant child too, wherever possible (if is your child who is participating on this trial)
- If you (your child) is a naïve (never have been treated for this disease before) patient or if you (your child) are receiving enzyme replacement therapy with idursulfase (approved drug for this disease) could be included provided treatment has been stable in the last 6 months and you (your child) agree to interrupt the treatment at least one week (which is the usual time between this kind of treatment infusions, therefore you (your child) will not be untreated) before the first study drug infusion, and agree in suspending this treatment for the duration of the trial

2.3.2. Exclusion Criteria (You Must Not Meet Any of the Following Criteria to Be Eligible for Participation in the Clinical Trial)

- If you (your child) refuse to sign the informed consent form
- If you (your child) are unable to perform the study procedures, except for neurocognitive tests (listed below)
- If you (your child) had been previous engrafted with Bone Marrow Transplant (BMT)/Hematopoietic Stem Cell Transplantation (HSCT, transplant of the mother cells of our body, these cells have the ability to transform into any of the cells in our body)
- If you (your child) have a surgical or other major medical intervention planned to occur before week 26
- If you (your child) have participated in a clinical trial with an investigational drug in the last 12 months
- If you (your child) are judged by the investigator or subinvestigator as being unable to undergo lumbar puncture, including those if you (your child) have difficulty taking a position for lumber puncture due to joint contracture or are likely to have difficulty breathing during the lumbar puncture process
- If you (your child) are judged by the investigator or subinvestigator to be ineligible to participate in this clinical trial due to a history of serious drug allergy or sensitivity
- If you (child) are judged by the investigator or subinvestigator to be ineligible to participate in this clinical trial in consideration of your (your child's) safety

2.4. What are the Study's Procedures?

If you (your child) decide to participate in this trial, there are some procedures that will have to be performed during your (your child's) participation. The tests and when they will happen are listed below:

- Medical History: The study doctor will ask you specific questions about your (your child's) health and the history of your (your child's) MPS II disease and about any medications that you (your child) are taking or have taken within the past month. This will only happen during the screening visit (previous to the trial drug's administration);

- Complete physical and neurological exam: You (your child) will have a physical examination, including height. This will happen during the visits of screening, baseline, week 13, and week 26 (final visit).

- Vital Signs and weight: Your (your child's) vital signs (body temperature, blood pressure, and pulse) will be measured during all the study's visits (from screening to week 26);
- Infusion of Study drug: The trial's drug will be administered to you (your child) through intravenous infusion during the visits of week 1 to the week 26 (once per week);
- Confirmation of Adverse Events, Concomitant drugs and Therapies: The study doctor will ask you if you (your child) had an adverse event (any untoward symptom that occurs during the study), what drugs and/or therapies you have been taking since the last visit. Adverse events (and their probable relation to the drugs and/or therapies you (your child) is under) will be confirmed to ensure your safety. This will occur during the visits of screening to week 26;
- Routine laboratory tests: About 8mL (equivalent to two teaspoon) of blood will be drawn from a vein and your (your child's) urine (a collection small bottle) will be collected for routine laboratory tests during the visits of screening, baseline and weeks 1, 5, 9,13,17, 22 and 26. A total of 72ml (equivalent to fifteen teaspoon) of your (your child's) blood you be necessary for these tests during the course of the trial. Those tests shall be performed at the clinical site's own laboratory, and after the tests are performed the materials collected will be destroyed;
- GAG Testing: GAGs are substances that mark how active your disease is, where decreasing levels mean your (your child's) disease is being affected by the treatment, and in this case the GAGs tested are Heparan Sulfate and Dermatan Sulfate. To perform this test, urine will be collected, blood will be drawn from a vein and a sample of fluid removed (called cerebrospinal fluid or CSF) from your (your child's) spine will be collected during the visits of baseline, week 13 and week 26. The total amount of blood and CSF required will be less than a teaspoon;
- Antibodies anti-drug (anti-JR-141 and anti-elaprase) test: Antibodies (substances responsible for the defense our organism) can sometimes attacks the study drug, rendering ineffective. In addition, antibody formation may cause infusion associated reaction (IAR), such as fever and nausea (please refer 5.1.2). Therefore during the visits of screening, baseline, week 4, week 13 and week 26, about 2 teaspoons of blood will be drawn from a vein to perform this test;
- MRI: You (your child) will have an MRI scan (a test using magnetic fields and radiowaves to create an image) of your (your child's) head and abdomen to assess their brain, and to see how big your (your child's) liver and spleen are. This will happen during the visits of baseline, week 13 and week 26;
- Echocardiography and Electrocardiography: You (your child) will have an echocardiogram (a test using sounds waves to create an image of your heart) to determine the size of your (your child's) heart, and an electrocardiogram (a painless recording of the electrical activity of your heart). These tests will be performed during the visits of baseline and week 26;
- Development and Quality of life tests: a series of questions will be asked by the study doctors or study staff to verify how well you (your child) can answer them and how is your quality of life. These questionnaires will be applied during the visits of baseline, week 13 and week 26.
- Actigraphy measurement: In order to assess the quality of your (your child's) sleep, you (your child) will be asked to use an equipment (similar to a watch) to measure how much do you move during your sleep. The measurements will occur during the visits of screening, week 1, week 13 and week 26.
- Drug concentration in the blood (pharmacokinetic test): This will only be applied if you (your child) have more than 8 years old. The blood will be drawn from a vein to measure the

amount of drug that is in your (your child's) blood. This will occur during the visits of week 1 and 26. A less than a teaspoon will be collected in total for this test.

- Leukocyte or fibroblasts iduronate-2-sulfatase enzyme activity level: This test will assess the activity (how well it is performing its job) of the enzyme iduronate-2-sulfatase (the substance in your body that your disease affects). This test will only be asked to you if you (your child) do not already have medical records showing enzyme activity, a small skin sample (biopsy) will be taken to measure enzyme level in your (your child's) cells, you (your child). For this procedure, it will be given a local numbing medicine by injection to the area to be biopsied so that it does not hurt as much and then a small incision with a small surgical knife and a sample will be taken (3 to 5 mm) of tissue for laboratory analysis. Normally it's not necessary to give stitches in the end of this procedure. This test will be analyzed at clinical site. After the skin biopsy analysis (to measure the enzyme activity) this sample will be destroyed or discarded following the regular procedures and respecting your confidentiality. This will occur during the visit of screening.

- Oxygen (O2) Saturation: This test will assess how much oxygen there is in your blood. This is a painless test that will place an equipment (like a clip) on your (your child's) finger and will measure the quantity of oxygen in the blood. This test will be performed before and after the infusions for all of the infusions (from week 1 to 26).

Note: The GAG testing, Drug concentration and Antibodies anti-drug test will not be performed at the site, therefore your materials collected for those tests will be sent to Japan for a Central Laboratory designated by the sponsor. The materials collected will be used only for the mentioned tests, no more test will be performed with them. The materials will be destroyed after the described tests are finalized.

2.5. How long will I (my child) participate in the Clinical Trial?

If you (your child) decide to participate in this clinical trial it is expected to you (your child) to participate from the time when you provide informed consent to the Week-26 assessment (about 6 months).

2.6. How many people will participate in this clinical trial?

This study will be conducted only in Brazil and a total of 18 participants consisting of 6 participants per group will take part in this clinical trial.

3. What are alternative treatments that I (my child) could get if I do not participate in this study?

If you decide not to participate in this trial, you (your child) can continue to receive the medication(s) you (your child) currently take. MPS II is generally treated with enzyme replacement by IV infusion (giving the drug into a vein). Elaprase, a recombinant idursulfase, is one of the drugs that have been approved for the treatment of MPS II (Hunter syndrome) to date. However, Elaprase cannot pass through brain capillary walls and has therefore not been demonstrated to be effective in improving cerebral symptoms.

Some of the patients undergo hematopoietic stem cell transplantation.

4. Will there be any benefits for me (my child) if I (he) participate in this clinical trial?s

If you (your child) decides to participate in this study, it is expected that the medication JR-141 to be effective for brain-related symptoms of MPS II (Hunter syndrome), such as

intellectual disability. JR-141 is also expected to be as effective as Elaprase for systemic symptoms, such lever liver and spleen enlargement. However, since this is early phase study in human, the effect and safety of JR-141 in humans have not yet been fully clarified at the present moment.

5. Are there risks to me (my child) if I am (he is) in this study?

Everyone taking part in the study will be watched carefully for any side effects. It is possible that side effects may occur and require medications or other treatment. Side effects may be mild or very serious, may last a long time or cause permanent bad effects, or could even result in death. You should be sure to talk to your study doctor about any side effects that you (your child) have while taking part in the study. Potential risks to study treatment and the study procedures are listed below.

5.1. Potential risk associated to the Use of JR-141 (study drug)

Side effects (untoward symptoms that occur during the treatment and can be related to the use of the drug taken) may occur with use of JR-141. Since JR-141 contains anti-transferrin receptor antibody, the transportation of iron in the system might be effected, leading to side effects related to the lack of iron (such as anemia). JR-141 is also considered to cross the blood-brain barrier, therefore side effects, such as vomiting, headache, etc., may occur. Furthermore, since the enzyme port of JR-141 is nearly the same as Elaprase (drug marketed for MPS II), similar side effects reported with use of Elaprase may occur, as presented below:

Common (probability of equal to or more than 5 out of 100 chances to occur) side effects: headache, dizziness, tremor, increased tear production, hypertension (increase of blood pressure), flushing (to blush), hypotension (low blood pressure), cough, tachypnoea (increase of breathing rate), wheezing (whistling sound when you breathe), abdominal pain, nausea (motion sickness), diarrhea, swollen tongue, rash (change of the skin's texture or color), pruritus (an itch), urticaria (allergic reaction that leaves red stains on the skin), rash pruritic (rash that itches), erythema (redness of the skin, inside of the mouth, nose, etc.), fever and oedema peripheral (swelling of body parts, most common to the legs and feet).

Less common (probability less than 5 out of 100 chances to occur) side effects: anemia (decrease of red blood cells), lymphadenitis (is the inflammation or enlargement of a lymph node, that are located throughout the body and function as a filter for bacteria and other things that can harm you), thrombocytopenia (decrease of the cells responsible for the blood clothing [platelets]), anxiety, depressed level of consciousness (difficult to stay awake or aware), hyperaesthesia (increased sensations such as sounds, lights, tastes, feeling and pain), allergic conjuctivitis , vision blurred, vertigo (dizziness), arrhythmia (heart beating out of compass), cyanosis (bluish or purplish discoloration of the skin due to lack of oxygen), heart palpitations, shortness of breath (dyspnea), nasal congestion, bronchospasm (narrowing of lung muscles that leads to shortness of breath, chest pain, fatigue and wheezing), pharyngitis (inflammation of the back of the throat), pulmonary embolism (a clot in a lung vein that leads to chest pain and shortness of breath), rhinorrhea (runny nose), upper abdominal pain, gastroenteritis (inflammation of the stomach and intestines), faeces soft, rash macular (flat or raised red bump on the skin), eczema (inflammation of skin), face oedema (swollen face), arthralgia (joint pain), muscle pain, muscle cramp, neck pain, back pain, bone pain, enuresis (involuntary urination), nocturia (increased number of urination during the night), chills, malaise, feeling cold, topical inflammation (skin inflammation), injection site joint swelling, pain, sensation of foreign body, Blood alkaline phosphatase increased, Blood lactate dehydrogenase increased, increase of blood substances (bilirubin, uric acid), haemoglobin (substance responsible for the oxygen transportation in the blood) decreased, heart rate

decreased, heart rate increased.

Side effects that may occur due to the characteristics of JR-141, as well as responses to such side effects are explained below.

5.1.1. Potential Risk of Anaphylactic Shock and the Response

Since JR-141 is a protein product, there is the potential risk of an anaphylactic. An anaphylactic shock is the term that refers to a range of symptoms including skin symptoms such as urticaria, digestive symptoms such as abdominal pain and vomiting, respiratory symptoms such as a shortness of breath, and shock symptoms such as sudden pallor and clouding of consciousness. Above all, a condition in which blood pressure sharply drops, leading to disturbance of consciousness, is specifically called anaphylactic shock.

If you (your child) decide to participate in this trial, you (your child) will be monitored adequately; if any abnormal finding is observed, the treatment will be discontinued and appropriate measures will be taken. Drug rechallenge will not be performed. Tests/examinations will be performed to identify the cause of the event. In this clinical site, we are well prepared to provide urgent treatment in case of anaphylactic shock symptoms.

5.1.2. Potential risk of Infusion-associated Reactions (IARs) and the Response

The treatment with JR-141 may cause infusion-associated reactions (IARs). IARs are adverse reactions occurring in the living body in response to infusion (e.g., chill, fever, a feeling of body temperature fluctuation, nausea, and hypertension). If you (your child) develop an IAR, the rate of your infusion will be reduced or the infusion of JR-141 will be discontinued, and administration of appropriate drugs (adrenal corticosteroids, antihistamines, antipyretic analgesics, or anti-inflammatory agents), oxygen administration, or other treatment will be provided to you (your child). If you (your child) have once experienced IARs, subsequent doses will be given with due caution, while taking appropriate measures such as pretreatment (adrenal corticosteroids, antihistamines, antipyretic analgesics, or anti-inflammatory agents) prior to the start of infusion and adjustment of the infusion rate.

In a Japanese phase I/II study in MPS II participants that is currently underway, mild redness, etc. have been reported as IARs.

5.1.3. Potential risk of Antibody Reaction to the Drug and the Response

The human body has a defense mechanism called the immune system, by which a substance called “antibody” can be produced to eliminate foreign substances that enter the body. Antibodies play an important role in immunity, whereas they also recognize drugs as foreign substances and may diminish the effect of the drugs.

When JR-141 is administered to participants with MPS II (Hunter syndrome), antibodies against JR-141 may be produced. These antibodies may diminish the effect of JR-141. Also, the antibodies against JR-141 may act on both JR-141 and Elaprase.

5.1.4. Results of Safety Studies in Animals

In a study in which JR-141 was given to monkeys for 26 weeks (once weekly, a total of 26 doses), no abnormal findings considered attributable to JR-141 were observed.

5.1.5. Serious Adverse Events Reported in the Japanese Phase I/II Study of JR-141

A phase I/II study of JR-141 in 14 participants is currently underway in Japan. In this study, “delirium” has been reported as a serious adverse event in one participant. This patient has already recovered from the event. The effect of the antiepileptic drug that was concomitantly used with JR-141 has been suggested as a cause of the event; however, the relationship to JR-141 was not completely ruled out.

5.2. Potential Risk of Pain and Side Effects Arising from Tests/Examinations

Performed in the Clinical Trial

If you (your child) decide to participate in this trial, you (your child) may have experience the following discomforts and risks related to the tests/examinations:

Blood Tests: blood sampling may cause bruising, swelling or pain at the site where the blood was drawn. It also is associated with a small chance of infection. You (your child) may become lightheaded or feel sick.

Electrocardiograms: when you (your child) are having an ECG done, electrodes (small adhesive patches) will be placed on your (your child's) body. You (your child) may have irritation, redness, and itching at the sites on the skin where the electrodes are placed. The doctor or study staff might need to shave areas on your (your child's) chest, arms, or legs to place the electrodes.

Lumbar Puncture (for CSF collection): a small amount of the fluid in your (your child's) spine will be taken by a procedure called a lumbar puncture (LP) or spinal tap. After having an LP some people get a bad headache. This can occur because the spot where the needle goes in does not always close up right away and if the hole stays open some fluid can leak out which causes a headache. This generally goes away in 1-2 days and can be treated with pain medicines or lying down.

Rare problems from an LP include infection, bleeding and pain or numbness in the back or legs.

Very rarely a problem called cerebral herniation can occur, generally in patients who already have a severe problem with their brain. This herniation can cause death.

Skin Biopsy for Enzyme Level (IDUA): you (your child) may have a small biopsy of your skin to see how much enzyme you (your child) have in tissues. In this procedure, you will be given a local numbing medicine by injection to the area to be biopsied and then a small incision will be performed with a scalpel and a sample will be taken (3 to 5 mm) of tissue for laboratory analysis.

The risks associated with this procedure include: bleeding, infection, and allergic reaction to numbing drug used or to the bandage tape (if tape is used).

MRI Scan: as long as you (your child) have no metal plates in your (your child's) body and follow the procedures told to you, MRI scans have little specific risks or side effects.

6. Will I be Informed if Any New Information Arise that Might Affect my Decision (my child's) to Participate in the Trial?

If any information that may affect your (your child's) intention to continue participation in this clinical trial while you (your child's) are participating in the trial, your study doctor will explain the information to you in a prompt manner. Your study doctor will then reconfirm your intention to continue participating in the trial. If you decide to leave the trial at this time, you won't suffer from any penalty.

7. What will Happen If the Clinical Trial Drug Is Discontinued?

If any of the following items apply, the clinical trial drug will be discontinued to ensure your (your child's) safety:

- When you request for withdrawal from the trial.
- When it becomes impossible to continue the trial for your (your child's) personal reasons such as transfer to another hospital or change of residence during the course of the trial.
- When you (your child) are found not to satisfy the criteria for participation in the trial after the start of the trial.

- When anaphylactic shock develops.
- When your (your child's) study doctor decides it necessary to discontinue the trial due to abnormal laboratory findings (blood tests, urinalysis, etc.), other side effects, or medically untoward events.
- Other cases where your study doctor decides it undesirable to continue the trial drug treatment any longer in light of your (your child's) health condition.

In case of a serious problem that makes it hard to continue the development of JR-141, the entire clinical trial will be discontinued.

Even after the treatment with the clinical trial drug is discontinued, your (your child) study doctor takes the responsibility to treat you (your child) appropriately, free of charge, as long as it is necessary.

8. What if I (my child) get hurt or sick while I am in the study?

If you (your child) have any damage resulting from participation in this clinical trial, the sponsor and the study doctor will provide to you (your child) immediate and full assistance, free of charge, as long as you (your child) requires it. If you (your child) feel something strange in your physical condition, please immediately contact your doctor or a study staff at any time without hesitation. If you (your child) experience any side effect, the sponsor and the study doctor will make the best effort to immediately give you (your child) treatment. The sponsor and/or the study doctor will also provide a specialist physician to give you (your child) a diagnosis and treatment, as necessary. By signing this form, you have not given up any of the legal rights that you (your child) otherwise would have as a participant in study. In case of injury or damage resulting from your (your child's) participation on this trial, you have the right to seek compensation.

9. What Should You (Your Child) Follow During the Clinical Trial?

- **You are asked to follow instructions explained by your doctor and visit the clinical site as scheduled** to allow to properly evaluate the state of your (your child's) disease.
- **You are instructed to immediately contact your (your child's) study doctor or study staff and follow their instructions if you (your child) feel something strange in your physical condition,** to ensure your (your child's) safety.
- **There are some drugs you (your child) cannot use during the trial; if you additionally use a drug** that is prescribed in another hospital or at another department of this clinical site, **please contact your (your child's) study doctor or study staff before using the drug. Please also inform your (your child') study doctor of all drugs you (your child) are using, if any.**
- If you (your child) are receiving medical attention or additionally seek medical attention at other departments, you are asked **to show the "Clinical Trial Participation Card" supplied by this clinical site and tell that you (your child) are taking part in the clinical trial.**
- You are asked to don't put or write any information related to this clinical trial, including materials used in the trial, adverse events that have been reported, tests/examinations you have undergone, and your personal opinions about the study drugs, on websites, through social networking services (SNSs; Facebook, Twitter, etc.), or in any other information media (newspapers, journals, advertisements, etc.).
- Since the investigational drug might damage sperm which could cause harm to a child you (your child) may father while on this study, and if you (your child) are sexually active, have means to get a woman pregnant and perform reproductive sex, you (your

child) must agree to use a medically acceptable form of birth control (such as a condom with spermicidal gel) in order to be in this study. The form of birth control should be decided by you and the study doctor and the chosen form would be provided by you free of charge through the study doctor. If your (your child's) partner becomes pregnant during the study, you should inform your study doctor immediately. As the risk for your (your child's) partner and the baby is unknown, it will be guaranteed full monitoring and support throughout pregnancy and during the postpartum period by the necessary time to ensure the safety of mother and baby. Expenses related to the monitoring and care during pregnancy will be fully covered by the sponsoring company the study, not encumber the participant, your particular health plan or the Unified Health System - SUS. You may also be asked to give you (your child) and your (your child's) partner's consent to collect information about your (your child's) health and the baby.

10. Will it cost anything to be in this study or will I (my child) get payment for being in the study?

Costs of all the tests/examinations performed while you are being treated with JR-141 will be paid by sponsor of this clinical trial. JR-141 will also be supplied for free. Also, among follow-up assessments performed to monitor your subsequent clinical course, extra tests/examinations performed for the clinical trial will also be paid by the sponsor. You will never face any increasing financial burden by participating in the clinical trial.

On the other hand, due to more frequent visits in the clinical trial than in routine practice, expenses incurred such as for transportation from your home, and for food and lodging (if applicable related to your participation in this study) for you and your caregiver will be reimbursed by the study sponsor through the doctor responsible for the study.

You may request the results of your exams/tests related to the study, to your doctor. If you want more information about the tests and procedures, you should discuss it with your study doctor who can also help you analyze the results of your exams/tests and possible treatments.

11. Handling of Data Obtained in the Clinical Trial

All data obtained during the study relating to you (your child) will be treated as confidential. No information containing your (your child's) name will be available to anyone outside the study doctor. Clinical records that might identify it will be kept confidential, according to the Resolutions of the National Health Council to provide protection for your privacy, security and authorized access. You (your child) will not be identified by ID number or SSN, address, phone number or any other information that directly identifies you (your child in study records. The data are recorded in this research center and if developed out of the research center for any reason (whether other researchers or the study sponsor, for example) receive a unique numeric code that does not identify you (your child) in any way to protect your (your child's) identity.

To see if this clinical trial is being conducted properly, while ensuring that your human rights are protected, people assigned by the sponsor of this clinical trial (monitors and auditors), the ethics committee, representatives of the government that is responsible for reviewing and approving new drugs, may view (access) your medical records (hospital charts, etc.). In such cases, the confidentiality of your personal information is protected (the identity is always protected, your name and address never are in these documents); by signing the informed consent form, you are authorizing just the access to medical records, and other documents, to the people listed above.

Your data collected in this clinical trial may be submitted as application dossier to the

government or utilized for research purposes by regulatory authorities. These data may also be published outside as academic papers or presentations in scientific meetings, and will therefore be retained at the hospital giving you treatment and the sponsor. However, please rest assured that even in such cases, your personal information will never be disclosed and will be kept confidential.

12. Who can I (my child) talk to about the study?

Your (your child's) participation in this clinical trial is voluntary and you (your child) cannot be forced to participate in the trial. If you have any words you do not understand or questions in the explanation, or you have something you want to be once more explained, please feel free to use the following contact information for your questions and inquiries.

In case any problem arises from this clinical trial, you are asked to immediately contact your doctor.

The Principal Investigator of this study, ie, the doctor responsible for the study is Dr. Roberro Giugliani, who can be found at the following address: Centro de Pesquisa Clínica do Hospital de Clínicas de Porto Alegre, rua Ramiro Barcelos, 2350, Prédio do Centro de Pesquisa Clínica, room 21 506 (Porto Alegre, RS, CEP: 90035-903) or by the following numbers:(51) 999850919 or (51) 33596338.

This clinical trial has been sufficiently reviewed from the perspectives of ethical, scientific, and medical validity and approved by the IRB of this hospital and CONEP. The IRB and CONEP are a group of people who review research studies to protect the rights and welfare of research participants. If you have questions about what it means to be in a research study or about your (your child's) rights as a research participant, you can also contact the Comitê de Ética em Pesquisa do Hospital de Clínicas de Porto Alegre (CEP/HCPA), Rua Ramiro Barcelos, 2350,on the 2nd floor of HCPA, room 2227, Porto Alegre, RS, CEP: 90035-903, from Monday to Friday, from 8:00 am to 5:00pm or by the following number (51) 33597640 for further clarification.

Or

Comissão Nacional de Ética em Pesquisa (CONEP)

Endereço: SEPN 510 NORTE, BLOCO A, 3º Andar - Edifício Ex-INAN - Unidade II - Ministério da Saúde

CEP: 70750-521 - Brasília-DF

Telephone number: (61) 3315-5878 (business hour: 08h to 18h, Monday to Friday)

Informed Consent Form

I understand that my (my child's) participation in this study is voluntary. I understand that I (my child) may refuse to participate without any resultant loss of care or benefits to which I (my child) am otherwise entitled. I understand that I (my child) may withdraw at any time from the study without any resultant loss of care of benefits to which I (my child) am otherwise entitled. I agree to inform the research team if I (my child) intend to withdraw from the study.

I understand that the Sponsor (JCR Pharmaceuticals Co., Ltd.) and any member of this research team may discontinue my (my child's) participation upon presentation of justification to the Ethics Committee (EC), which will review and approve the withdrawal, except in cases of justified urgency, as in the case of safety of participants.

I understand that I (my child) will not receive any monetary benefits from participation in this study. I understand that if I (my child) suffer any loss damage as a direct, indirect, immediate or delayed result, result, the assistance will be paid for by the study Sponsor.

I have read or have had read to me, in my primary language, the above informed consent. I understand the contents of the informed consent and I have received an original version of the consent form, fully signed by me and the researcher, with all the initialed by both. I freely and voluntarily consent to (my child's) participate in this study.

Person providing consent (participant)

(Date of consent) _____ Name _____

(The participant is required to write by himself.)

Legally acceptable representative (relationship:),
Name of study participant:_____

(Date of consent) _____ Name _____

(The participant's legal representative is required to write by himself.)

Researcher

(Date of consent confirmation)_____

Name _____

(Please affix the signature or name and seal.)