STUDY TITLE: TREATMENT WITH RECOMBINANT HUMAN INSULIN-LIKE GROWTH FACTOR 1 (RHIGF-1) IN PATIENTS WITH PAPPALYSIN-2 (PAPP-A2) GENE MUTATION.

STUDY NUMBER: #2015-6218

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INTRODUCTION

Your child has been invited to be part of a research study that might benefit him and other children with short stature in the future. Your child's participation is voluntary. Your decision whether or not to allow our child to participate will not affect your or your child's relationship with Cincinnati Children's Hospital and the Center for Growth Disorders. If you decide to allow your child to participate, you may change your mind at any time during the study. Please take all the time you need to make your choice. Ask us any questions you have. It is also okay to ask more questions after you decide to be in the study. You can ask questions at any time.

WHY ARE WE DOING THIS RESEARCH?

As you know, your child has PAPP-A2 deficiency which results in short stature. The PAPP-A2 mutation causes your child to have high levels of total IGF-1 but very low levels of free IGF-1 which is very important for normal growth. For the past several years, your child has been receiving twice daily injections of IGF-1 with the goal to increase the levels of free IGF-1 and improve his growth. So far, he has responded well to the medicine and he appears to be growing faster. Therefore, with this research study we want to continue treating him with the same medication until Dr. Backeljauw decides that he has stopped growing.

We can't guarantee that your child will continue to respond well to the IGF-1, and he might not benefit from being in this study and from receiving long-term treatment with IGF-1. If your child stops growing and treatment is discontinued, we will ask your child to come back for one more follow up visit one year after the treatment was stopped.

IGF-1 is a hormone produced by the liver which plays a key role in childhood growth. Treatment with IGF-1 for PAPP-A2 deficiency is investigational and it has not been approved by the FDA.

With this research study we also want to learn more about the physical features of patients with PAPP-A2 deficiency; including the shape of your child's bones, how his body handles sugar and the appearance of his liver and spleen and how these change over time.

WHO IS IN CHARGE OF THE RESEARCH?

Dr. Philippe Backeljauw is the researcher at Cincinnati Children's Hospital Medical Center (CCHMC) that is in charge of this study. Dr. Backeljauw has received additional payments from IPSEN, the company that makes the drug, for consulting, speaking, and serving on an advisory board. If you have any questions, please speak with Dr. Backeljauw.

WHAT WILL HAPPEN IN THE STUDY?

We will see your child at Cincinnati Children's Hospital every 4 months for the second year of treatment, and every 6 months for the following years. During these visits we will carefully examine and measure your child and we will obtain fasting blood draws. The total amount of blood drawn at each visit will be approximately or less than 8-9 teaspoons. At the last visit, we will put in an IV (which is a small plastic tube) and draw multiple blood samples. A glucose tolerance test will be done once per year. He will need to drink a sugary drink for this test. Also at the yearly visits, we will do an electrocardiogram, an ultrasound of his kidneys and spleen, an X-Ray of the left hand, and a DXA bone density scan, which is a specialized type of X-ray. All of these X-rays are non-invasive and just require lying down on a table. He has previously had all of these tests done.

At home, your child will continue to receive IGF-1 injections twice daily for a total of one year. We will continue the same dose per weight that he has been receiving for the past year.

WHAT ARE THE GOOD THINGS THAT CAN HAPPEN FROM THIS RESEARCH?

This study will hopefully continue to improve your child's growth. It will also tell us more about his bone density and it may improve his bone density. In addition, this may help other people with short stature in the future. Please note that your child might not receive any benefit from being in this study.

WHAT ARE THE BAD THINGS THAT CAN HAPPEN FROM THIS RESEARCH?

The major risks from this study are the risks related to the IGF-1treatment. The most common side effect from this medication is low blood sugar (hypoglycemia). When the blood sugar is low, people can feel "shaky, sweaty and confused". If the blood sugar is very low (usually less than 40-50) this can cause a seizure. To prevent this from happening, you should continue to give the medicine with food. Also, you will have a blood glucose monitor (glucometer) at home and we will give you all the supplies necessary to measure his blood sugar at home. Your child could also have an allergic reaction to the medication. Allergic reactions are rare but they can range from a simple rash to a severe anaphylactic reaction that can produce difficulty breathing and low blood pressure. If that happens, we will treat your child for the allergic reaction. This is unlikely since your child has been receiving the medication and he has not had any reactions.

Other rare side effects from the medication include growth of the tonsils, headache secondary to increased pressure around the brain, slipped capital femoral epiphysis (SCFE), which is a shift of the upper part of the hip bone, which results in a weakened hip joint, and possibly increased risk for the formation or progression of malignant tumors. The latter has been observed in patients who received Increlex for unapproved use or at higher than recommended doses.

Your child can have some discomfort from the injections. You might notice some redness, bruising, or thinning of the skin at the site of the injection. To prevent this, we recommend changing the injection site at each injection (injection site rotation).

Your child will also be exposed to a very small amount of radiation from the radiology studies (X-ray of the hand, DXA scan). We are all exposed to radiation every day of our lives originating from soil, rocks, outer space and within the body itself. Radiation dose in humans can be measured using a unit called the mSv. The average person in Cincinnati receives a radiation dose of about

3 mSv per year. The radiology studies proposed in this study will expose your child to the following amounts of radiation:

- DXA scan of total body, lumbar spine, hip and forearm: 0.013 mSv; two DXA scans:0.027 mSv
- Bone age (X –ray of the hand): 0.005 mSv; two bone age studies: 0.01 mSv

Including all the studies, your child will be exposed to approximately 0.05 mSv. This is approximately the amount of radiation that he would receive in 6 days from background radiation. This radiation exposure involves minimal risk, no more than encountered in everyday life.

This is not an approved use of IGF-1 as approved by the Federal Drug Administration (FDA). This study will be monitored by the FDA.

WHAT ARE THE REASONS TO STOP THE STUDY?

We will stop the study if your child develops any of the following side effects from the medication:

- Severe hypoglycemia (low blood sugar, less than 50) on more than one occasion.
- Your child is diagnosed with intracranial hypertension (increased pressure about the brain).
- Your child is diagnosed with SCFE (slipped capital femoral epiphysis).
- Your child develops malignant tumors.

WHAT OTHER CHOICES ARE THERE?

Instead of being in this study, you can choose not to be in it.

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE?

Making sure that information about you remains private is important to us. To protect your privacy in this research study we will keep all information about you locked in an office or on a computer drive that only approved people have access to.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the study results. You can search this website at any time.
The Food and Drug Administration (FDA) may choose to inspect your child's records since he is a subject in the investigation of a drug.

Please note that your child's protected health information will be shared with IPSEN (the company that makes the drug) but they won't have access to his personal information.

WHAT IF WE LEARN NEW INFORMATION DURING THE RESEARCH?

The study doctor will tell you if they find out about new information from this or other studies that may affect your health, safety or willingness to stay in this study.

WILL IT COST YOU ANYTHING EXTRA TO BE IN THE RESEARCH STUDY?

It will not cost you anything to be in this study. Study drug is being donated by Ipsen (the drug manufacturer) and will be provided to the research subjects by the study team at no cost.

WILL YOU BE PAID TO BE IN THIS RESEARCH STUDY?

You will not be paid to be in this research study. However, we understand that it will cost you and your family money to travel to Cincinnati for this study. The study will pay for the costs of travel to and from Cincinnati for you and your family.

You and your family will also be reimbursed up to $50 per day per person to cover food costs. You will submit your food expenses and these will be reimbursed.

Tissues or body fluids collected for this research may result in the development of a product that could be patented/licensed and sold. You will not be paid if this happens.

WHAT HAPPENS IF YOU ARE INJURED FROM BEING IN THIS STUDY?

If you believe that you have been injured as a result of this research you should contact Dr. Backeljauw as soon as possible to discuss the concerns. Treatment for injuries is available at CCHMC. If you go to the Emergency Room or to another hospital or doctor it is important that you tell them that you are in a research study. If possible, you should give them a copy of this consent form.

CCHMC follows a policy of making all decisions about compensation for the medical treatment of physical injuries that happened during or were caused by research on an individual basis.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

For questions, concerns, or complaints about this research study you can contact the study person listed on page 1 of this document.

If you would like to talk to someone that is not part of the research staff or if you have general questions about your research study rights or questions, concerns, or complaints about the research, you can call the CCHMC Institutional Review Board at 513-636-8039.

AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION FOR RESEARCH

To be in this research study you must also give your permission (or authorization) to use and disclose (or share) your "protected health information" (called PHI for short).

What protected health information will be used and shared during this study?
CCHMC will need to use and share your PHI as part of this study. This PHI will come from:

- Your CCHMC medical records
- Your research records

The types of information that will be used and shared from these records include:

- Laboratory test results, diagnosis, and medications
- Reports and notes from clinical and research observations
- Imaging (like CT scans, MRI scans, x-rays, etc.) studies and reports

- If applicable, information concerning HIV testing or the treatment of AIDS or AIDS-related conditions, drug or alcohol abuse, drug-related conditions, alcoholism, and/or psychiatric/psychological conditions (but not psychotherapy notes).

Who will share, receive and/or use your protected health information in this study?

- Staff at all the research study sites (including CCHMC)
- Personnel who provide services to you as part of this study
- Other individuals and organizations that need to use your PHI in connection with the research, including people at the sponsor and organizations that the sponsor may use to oversee or conduct the study.
- The members of the CCHMC Institutional Review Board and staff of the Office of Research Compliance and Regulatory Affairs.

How will you know that your PHI is not misused?

People that receive your PHI as part of the research are generally limited in how they can use your PHI. In addition, most people who receive your PHI are also required by federal privacy laws to protect your PHI. However, some people that may receive your PHI may not be required to protect it and may share the information with others without your permission, if permitted by the laws that apply to them.

Can you change your mind?

You may choose to withdraw your permission at any time. A withdrawal of your permission to use and share your PHI would also include a withdrawal from participation in the research study. If you wish to withdraw your permission to use and share PHI you need to notify the study doctor, listed on the first page of this document, in writing. Your request will be effective immediately and no new PHI about you will be used or shared. The only exceptions are (1) any use or sharing of PHI that has already occurred or was in process prior to you withdrawing your permission and (2) any use or sharing that is needed to maintain the integrity of the research.

Will this permission expire?

Your permission will expire at the end of the study. If the study involves the creation or maintenance of a research database repository, this authorization will not expire.

Will your other medical care be impacted?

By signing this document you are agree to participate in this research study and give permission to CCHMC to use and share your PHI for the purpose of this research study. If you refuse to sign this document you will not be able to participate in the study. However, your rights concerning treatment not related to this study, payment for services, enrollment in a health plan or eligibility of benefits will not be affected.

SIGNATURES

The research team has discussed this study with you and answered all of your questions. Like any research, the researchers cannot predict exactly what will happen. Once you have had enough time to consider whether you should participate in this research you will document your consent by signature below.

You will receive a copy of this signed document for your records.

_____
Printed Name of Participant

_____
Printed Name of Guardian

_____ _____
Signature of legal guardian Indicating Consent Date

_____ _____
Signature of Legally Authorized Representative* Date

_____
* If signed by a legally authorized representative, a description of such representative's authority must be provided

_____ _____
Signature of Individual Obtaining Consent Date