STUDY TITLE: CLINICAL CHARACTERIZATION AND TRIAL OF GROWTH HORMONE TREATMENT IN PATIENTS WITH AGGRECAN DEFICIENCY

STUDY NUMBER: 2017-1956

FUNDING ORGANIZATION: Novo Nordisk

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INTRODUCTION

We are asking for your permission for your child to be in a research study so that we can learn new information that may help others with Aggrecan (ACAN) deficiency. Your child's participation is completely voluntary. If you decide not to give your permission for your child to be in this study, it will not affect their relationship with Cincinnati Children's Hospital and the Center for Growth Disorders. If you decide to allow your child to be in this study, you may change your mind at any time during the study and your child can stop being in the study. 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 allow your child to be in the study. You can ask questions at any time.

WHY ARE WE DOING THIS RESEARCH?

Through the research efforts of the Cincinnati Center for Growth Disorders and collaborating physicians, over twenty families affected by short stature have been identified with a genetic mutation in the ACAN gene. A mutation in the ACAN gene is characterized by having dominantly inherited short stature, a normal to advanced bone age and growth that stops too early. Prior to the discovery of the ACAN gene's effects on growth, these patients would have been diagnosed with idiopathic short stature (ISS).

Currently there is no approved treatment for patients with an ACAN mutation and care management can vary from doctor to doctor which is why we want to do a research study to look at the effects of growth hormone treatment over one year on pre-pubertal children with ACAN deficiency. We also want to learn more about the clinical and physical features of the phenotype, and how it influences joint health.

We are asking your child to be in this study because they have undergone genetic testing to confirm that they have an ACAN mutation, and they meet all of the study eligibility criteria.

WHO IS IN CHARGE OF THE RESEARCH?

Philippe Backeljauw, MD is the researcher at Cincinnati Children's Hospital Medical Center (CCHMC) that is in charge of this study. The growth hormone medication and funding for this study is provided by Novo Nordisk.

An investigator has received additional payments from Novo Nordisk for consulting, speaking, and serving on an advisory board.

WHAT WILL HAPPEN IN THE STUDY?

If your child qualifies and you decide you want them to be in the study, your child will be treated with a single dose regimen of daily growth hormone for a period of 12 months to examine the effects on growth response. The dose that will be used is 50 micrograms/kg/day. This is a dose that is already approved for children diagnosed with Turner and Noonan syndrome, which both result in short stature not caused by growth hormone deficiency. Your child's weight will be used to calculate the volume of their daily dose. Also, results of your child's blood test (IGF-I level) may be used to adjust your child's daily dose.

You and your child will come to CCHMC for three study visits over the course of 12 months. The study visits will last 6-10 hours. A parent/legal guardian will be asked to complete at least four check-in calls during the 12-month period.

These are the things that will happen at the study visits. We will:

- Complete a routine physical exam, including to see if your child has started puberty.
- Complete a detailed joint exam, including to check for curvature of the spine.
- Complete a detailed musculoskeletal evaluation which looks at knee and back health and includes an assessment of how your child walks.
- Collect vital signs, height and weight measurements.
- Collect blood samples.
- Take photographs.
- Ask you questions about your child's family and medical history that focus on growth and joint issues.
- Ask you questions about your child's quality of life and physical activity.
- Take an x-ray of your child's hand and knees.
- Take a bone density scan (DXA) of your child.
- Take MRI pictures of your child's knees (to look for early signs of joint disease). These may be repeated every other year from time of initial study if joint disease is present.
- A blood sample will need to be drawn at a local facility (i. e., lab, doctor's office) to monitor IGF-I levels at the time of the 3 month check in call. This will be subject to your insurance company and the study is not able to reimburse the cost.

Children that grow well enough (as outlined per study protocol) in the first year of treatment will be eligible to participate for another two years in the extension study If you and your child agree to participate, you will be asked to come to CCHMC every 6 months for four additional study visits. These study visits will last 2-6 hours. A parent/legal guardian will be asked to complete at least four check-in calls during the extension study as well.

These are the things that will happen at the extension study visits.

We will:

- Complete a routine physical exam, including to see if your child has started puberty.
- Complete a detailed joint exam, including to check for curvature of the spine.
- Collect vital signs, height, and weight measurements.
- Collect blood samples.
- Take photographs
- Take an x-ray of your child's hand (at yearly visits)
- Take a bone density scan (DXA) of your child (at yearly visits)
- May take MRI pictures of your child's knees every other year from time of their initial study if joint disease was present.
- If there are any study activities that your child did not complete in the first year of the study due to age, scheduling issues, or illness we may ask you/your child if they would be willing to complete the activity at a future visit.

These are the things that will happen during the check-in calls. We will:

- Discuss any issues with medication administration and compliance.
- Record any adverse events not previously reported.
- Confirm that new supplies/medication will be shipped to the participant (upon completion of the check-in call).
- A blood sample may need to be drawn at a local facility (i.e., lab, doctor's office) to monitor your child's IGF-I levels if the results meet the protocol criteria for dose adjustment. This will be subject to your insurance company and the study is not able to reimburse the cost.

The research staff will explain each visit to you in detail.

After completion of the study, your child will need to follow up with a local pediatric Endocrinologist to continue their growth hormone treatment and medical care for ACAN deficiency. At the 3-year study visit (final visit) we will give you up to 3 months of medication and supplies so that your child can continue treatment until they are able to start getting the medication clinically (not through the research study). Study staff is available to help you with this process if you need it, and we will follow up to ensure that appropriate medical care is received.

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

We hope that the treatment of daily growth hormone will help your child grow but being in this study may not help your child right now. We will provide you a copy of your child's growth chart with measurements from each study visit. Additionally, a letter with the lab results and exam findings will be sent to your child's primary care physician or pediatric Endocrinologist after the completion of each study visit.

When we finish the study, we hope that we will know more about joint disease and the effects of growth hormone in individuals with Aggrecan deficiency. This may help other children diagnosed with an Aggrecan mutation later on.

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

The major risks in this study are the same as the risks of being treated with daily growth hormone.

Injection Site Reactions: Occasionally subcutaneous injections can cause local reactions. Such as redness, bruising, lipoatrophy or lipohypertrophy at the site of administration.

Edema: Swelling of the feet. Edema occurs approximately < 2.5% of the time.

Scoliosis: Some children with scoliosis may experience a worsening of symptoms when they are on growth hormone therapy due to increased bone growth.

Intracranial Hypertension: Increased fluid pressure within the skull. Symptoms include persistent headache and/or blurred vision and vomiting. This occurs in approximately < 1 in 1000 patients on growth hormone therapy.

Slipped capital femoral epiphysis (SCFE): A hip condition that causes the top of the femur (thighbone) to slip off the neck of the bone in a backwards direction. Symptoms include hip or knee pain. This occurs in approximately < 1 in 1000 patients on growth hormone therapy.

The DXA scans, hand x-rays, and knee x-rays in this study involve exposure to ionizing radiation. We are all exposed to radiation every day of our lives from natural sources. Over the 3 years of this study, the radiation exposure from the DXA scans, hand x-rays, and knee x-rays in this study is similar to 6 days of natural background radiation. This amount of radiation is considered minimal risk, no greater than the activities of daily life.

Your child may feel some pain when their blood is drawn. Numbing medicine can be used. There is a small chance the needle will cause bleeding, a bruise, or an infection.

There may be other risks that we do not know about yet.

WHAT OTHER CHOICES ARE THERE?

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

HOW WILL INFORMATION ABOUT YOUR CHILD BE KEPT PRIVATE?

Making sure that information about your child remains private is important to us. To protect your child's privacy in this research study we will:
Assign code numbers to your child's samples, and any information about them and only study investigators will be authorized to link the code to your child.

Remove all identifying information from samples before they are released to other investigators.

De-identified data will be shared with Dr. Andrew Dauber, at Children's National Medical Center, who was the original principal investigator on this study before leaving Cincinnati Children's Hospital Medical Center.

We will not use your child's name or identity for publication or publicity purposes.

All other parties including employers, insurance companies, person physicians, and relatives will

be refused access to the information or samples, unless you provide written permission, or unless we are required by law to do so.

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 your child. 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 your child is a participant in an investigation that involves the study of an approved drug.

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 child's health, safety, or your willingness for your child to stay in this study.

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

It will not cost anything for your child to participate in this study, with the exception of the 3-month blood sample to check IGF-I levels and any study activities performed remotely with your child's local physician (i.e. safety labs, clinic appointments). The test procedures and evaluations occurring at Cincinnati Childrens Hospital are provided at no cost to you.

WILL YOU/YOUR CHILD BE PAID TO BE IN THIS RESEARCH STUDY?

You/your child will not be paid for this research study. However, the study will pay for the travel expenses incurred when coming to CCHMC for study visit appointments. The study will cover the cost of an economy class plane ticket for the primary research participant, one parent and for every affected family member participating in this study. Alternatively, the study will reimburse the family at the standard CCHMC mileage reimbursement rate if they choose to drive instead. For the initial 12-month trial period the study will cover the cost of the hotel room for up to 2 nights per study visit. Each individual will be reimbursed for the cost of their meals up to $35 per individual per day. In the extension trial period, the study will cover the cost of a hotel room for one night per study visit, and each individual will be reimbursed for the cost of their meals up to $40 per day.

WHAT HAPPENS IF YOUR CHILD IS INJURED FROM BEING IN THIS STUDY?

If you believe that your child has been injured as a result of this research you should contact Philippe Backeljauw, MD as soon as possible to discuss the concerns. Treatment for injuries is available at CCHMC. If your child goes to the Emergency Room or to another hospital or doctor it is important that you tell them that your child is in a research study. If possible, you should give them a copy of this parental permission 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 child's "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 child's PHI as part of this study. This PHI will come from:
- Your child's CCHMC medical records
- Your child's 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 child's protected health information in this study?
- Staff at all the research study sites (including CCHMC)
- Personnel who provide services to your child as part of this study
- Other individuals and organizations that need to use your child's 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 child's PHI is not misused?
People that receive your child's PHI as part of the research are generally limited in how they can use your child's PHI. In addition, most people who receive your child's PHI are also required by federal privacy laws to protect your child's PHI. However, some people that may receive your child's 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 child's PHI would also include a withdrawal from participation in the research study. If you wish to withdraw your permission to use and share your child's 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 your child 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 child's other medical care be impacted?
By signing this document you agree for child to participate in this research study and give permission to CCHMC to use and share your child's PHI for the purpose of this research study. If you refuse to sign this document your child will not be able to participate in the study. However, your child's 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 your child should participate in this research you will document your permission by signature below.

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

_____
Printed Name of Research Participant

_____ _____
Signature of Parent or 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