Clinical Trials
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The National Foundation for Ectodermal Dysplasias (NFED) started this journey in 1989 by giving a $5,000 seed grant to Dr. Jonathan Zonana to identify the gene for XLHED. Over the next 24 years, our families willingly came forward to complete surveys, give blood, undergo sweat gland testing, provide skin biopsies and a battery of other tests. Because of their efforts, research has advanced to the point that we are testing a treatment in human trials.

The choice to participate in a clinical trial or consider a particular treatment is a personal one. Our purpose in this newsletter is to update you on our research progress, to inform you of the clinical trial and to provide information that could potentially aid your decision making. If you have extended family members who are affected by XLHED but may not be in contact with the NFED, we encourage you to share this newsletter with them.

Characteristics of Hypohidrotic Ectodermal Dysplasia

Hypohidrotic Ectodermal Dysplasia (HED) is a rare genetic condition characterized by a reduced ability to sweat, missing teeth, and fine sparse hair. Individuals affected by HED share a similar facial appearance with thin, dark skin around the eyes with extra folds or wrinkles, a depressed “saddle” nose, small narrow jaw, and small pointed teeth. Eruption of the teeth may be delayed, or only a few teeth may erupt. Additional features include dry eyes, eczema, asthma, ear wax impaction, dry nasal concretions, respiratory illness, sinusitis, or sparseness of saliva. Nails, facial hair in males, and the appearance of pubic hair in adolescence are normal. With the exception of heat intolerance, general health and overall development, including intelligence, is within normal limits.

Diagnosis/Testing
HED can be diagnosed after infancy on the basis of physical features in most affected individuals. Newborns may have dark circles around their eyes because that skin is thin and the underlying blood vessels create a bluish shadow. The skin also may appear to be “peeling” at birth. Infants may not be able to tolerate heat and may be irritable in warm environments or may have unexplained fevers. More often, the diagnosis is not made until the teeth do not erupt at the expected age or the teeth appear to be pointed when they do erupt.

Diagnosis can be made through molecular genetic testing, which is available for all three types of HED. Changes or mutations in the EDA, EDAR, EDARADD, and WNT10A genes are most commonly associated with HED. These genes tell the body to make proteins that are needed early in life (before birth and shortly after) for the normal development of sweat glands, teeth, hair, skin, and other mucous glands.

Mode of Inheritance
HED may be inherited in one of three patterns: X-linked recessive, autosomal recessive and autosomal dominant. Ninety-five percent of randomly selected individuals with HED have the X-linked recessive form. The remaining 5% have either the autosomal recessive or autosomal dominant form of HED. The mode of inheritance may be determined in some instances by family history and in others by molecular genetic testing. It is important to note that this research report focuses on the X-linked recessive form or XLHED.

Genetic Counselling
Carrier testing is possible for XLHED, if the syndrome-causing mutation in the family is known. Prenatal testing is also possible for pregnancies at increased risk for XLHED.

How Is XLHED Passed from Parent to Child?
For XLHED, the mutated gene, called EDA, is found on the X chromosome.
MalesAffected by XLHED
A man affected by XLHED passes his X chromosome to his daughters and his Y chromosome to his sons. Because the changed gene is only on the X chromosome, his daughters will be carriers and the sons will not be affected. Daughters may then pass on the gene to her children. Fathers cannot pass on the mutated gene to their sons because they only pass on their Y chromosome.

Female Carriers of XLHED
A woman with XLHED, or a “carrier”, has the EDA gene on one of her X chromosomes. Women who are carriers for XLHED may have some symptoms, such as thin hair, reduced sweating, one or more missing teeth, and sometimes have difficulty breastfeeding. The way each woman experiences symptoms of XLHED is unique.

Since women have two X chromosomes, when one X is changed, the healthy X can help compensate.

This working copy can partially (or fully in some cases) control the development of some, or all, of the skin, hair, nails, teeth, and sweat glands. This helps women have less severe XLHED symptoms than men.

There is a 50% chance that a woman with XLHED will pass the gene to her son. Sons who inherit this gene will be affected by XLHED. This is because their only copy of the X chromosome does not work correctly. If the woman who is a carrier has a daughter, there is a 50% chance the daughter will inherit the changed gene. Then she can also pass XLHED to a future child, like her mother did.

Prevalence
Although not specifically known, it is estimated that at least one in 5,000-10,000 newborns has HED. This is probably an underestimate of the prevalence, as many cases may be missed during infancy before the cardinal features become obvious.

How is X-Linked Hypohidrotic Ectodermal Dysplasia Inherited?

What is EDI200?
Ectodysplasin-A1 (EDA-A1) is a protein that occurs naturally in the body. When a person is first growing and developing as a baby, EDA-A1 has a very important job, which is to signal the normal growth of hair, teeth, skin and certain glands like sweat and mucous glands.

In people who are affected by XLHED, EDA-A1 is missing due to an alteration in the EDA gene.
EDI200 is a synthetic version of EDA-A1 being developed by Edimer Pharmaceuticals, Inc. EDI200 given to newborn dogs who have XLHED can restore the growth of their teeth, skin structures and mucous glands. By replacing the missing EDA-A1 with EDI200 while a baby with XLHED is still growing and developing, Edimer hopes to provide a life-long improvement in their health.

The official title of Edimer's clinical trial is called, “Phase 2 Study to Evaluate Safety, Pharmacokinetics and Pharmacodynamics/ Efficacy of EDI200 in Male Infants With X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED) (ECP-002).”

We posed the following questions to the team at Edimer Pharmaceuticals to learn more about the clinical trial. If you seek more details, visit [http://www.clinicaltrials.gov](http://www.clinicaltrials.gov).

**What is the purpose of the clinical trial?**

**Edimer:** Clinical trials are an important part of developing new medical treatments. They help doctors and scientists determine if new drugs are safe, effective, and prescribed at the correct dosage. The newborn XLHED clinical trial is a Phase II study evaluating EDI200. Trials conducted in Phase II determine how well the new drug meets the goals of the study for safety, effectiveness, and optimal dosing to achieve the best results.

**Who’s eligible?**

**Edimer:** Baby boys between two and 14 days old who have had genetic testing confirming a diagnosis of XLHED are eligible to participate.

The process of skin, gland, tooth and hair development is highly controlled by the body - both time and location are very important. In humans, most of the groundwork for developing full functional sweat glands, hair and teeth (both primary and adult) is started and nearly completed at the time we are born. That is why it was such a remarkable finding in mice and dogs with XLHED that EDI200 treatment of newborn pups could have such a dramatic impact in these structures. We seek to understand how the windows for EDA-A1 (or EDI200) activity might be extended in humans, and whether there is a treatment that could reopen these windows of biological activity in adult patients.

However, at the moment, we believe the best benefit will be when EDI200 is given during the newborn period, very early within the first two weeks after birth. We have so much to learn and are very excited to pursue all the ways that may provide real benefits to XLHED-affected patients at all ages.

We recognize that a lot of carrier girls also have symptoms of XLHED. The boys tend to have more consistent and similar symptoms that are typically more severe. Therefore, the first clinical study will only enrol newborn boys as they have the best opportunity to see a benefit in receiving EDI200. Once the safety of EDI200 is confirmed, future studies may involve all XLHED-affected patients.

**Will it help adults?**

**Edimer:** Studies of fish, mouse and dog models of XLHED tell us that the protein that EDI200 replaces, EDA-A1, has a very important early role in the development of sweat glands, teeth, hair follicles, skin, etc. EDI200 functions very well in filling the role for missing EDA-A1 for these parts of the body as long as they still are “receptive” to being stimulated to grow. All the data we have to date suggests that the window for “receptivity” may end early in life, shortly after birth humans. This means that we believe the best benefit will be if EDI200 is given during the newborn period, very early within the first two weeks after birth.

Also, we have been looking very hard to see what role, if any, EDA-A1 may play after the newborn period. This could be in stabilizing glands (like those that produce mucous and tears), or even enhancing the growth of the hairs that are already present in XLHED-affected children. There may be a subset of people affected by XLHED who have specific gene mutations (a change in a gene) that may respond to ongoing EDI200 treatment, even if started later in life. Proving there is meaningful benefit that has been hard to come by but we are continuing in this effort.
How do you enrol?

**Edimer:** Families who are interested in participating should contact Professor Angus Clarke, Geneticist, Institute of Medical Genetics, Cardiff University, Wales 012920 744058 or Diana Perry, ED Society 01242 261332.

**Edimer:** It is helpful if you contact one of the above people as early as possible in your pregnancy, so we can answer any questions you may have and provide you with as much information as you need to consider participating in the clinical trial. Additionally, it is helpful for the study team to get information about your family’s history with XLHED and help to arrange any travel or operational details that might be required. Contacting a member of the team is not a commitment to participate in the clinical trial - participation is always voluntary. You can choose not to participate at any time and for any reason. Not participating will have no effect on the current medical care you or your family are receiving or may receive in the future.

What does the treatment entail?

**Edimer:** Five doses of EDI200 are given over the course of two weeks. EDI200 is delivered by an intravenous infusion. EDI200 is only available at one of the clinical study sites listed below.

Where are the sites?

**Edimer:** Currently, we have the following sites in the United States and Europe:

- United States, California - University of California, San Francisco
- United States, District of Columbia - Children’s National Medical Centre
- United States, Missouri - Washington University School of Medicine
- Germany - University Hospital Erlangen, Bavaria
- United Kingdom - University Hospital of Wales, Cardiff

How many patients do you need?

**Edimer:** The current protocol includes enrolling 6 - 10 newborn boys in this Phase II clinical study of EDI200.

How many babies have been given EDI200

**Edimer:** We were pleased to share with the NFED and XLHED communities that the first baby was enrolled in the clinical trial in September 2013 and he successfully completed dosing with EDI200.

An independent committee that monitors the safety of the babies in the study has given the green light to enrol the next baby boy. We are unable to provide an update with each baby that is enrolled, however, we can share that the study is actively enrolling and moving forward.

When will you know if the treatment is successful? When will you share publicly the results?

**Edimer:** In the first Phase 2 study to involve XLHED-affected newborns, we will follow all aspects of growth and development as well as health issues specifically related to XLHED. Some testing will be done soon after EDI200 is given and some results are best collected later. It is important to remember that seeing a change in one baby will not be enough to be sure of an EDI200 effect. It is very important for us and for the XLHED community that when we share study results they are accurate and well documented.

What are potential challenges?

**Edimer:** The window of treatment is very small, between two days and 14 days old. Additionally, while we have clinical sites across the United States and Europe, it is likely that travel will be require for families to participate. Therefore, whenever possible, it is very important for families to be in touch with a member of the team before the arrival of their baby boy so arrangements can be made. If you decide to participate in the clinical trial all costs associated with travelling to and from staying at the clinical study site will be covered.

One of the most helpful pieces of information to have is genetic confirmation that the baby boy’s mother is a carrier of XLHED. This can be done by a genetic test where the mother has a small tube of blood drawn and sent to a laboratory for CLHED genetic testing. If you need assistance with arranging or the cost of this genetic test please contact Prof. Clarke or Diana Perry.
What are the side effects?

Edimer: We have data regarding safety and adverse side effects from a number of studies that are outlined below. This is the standard for all new drugs that are being developed for human patients.

- **Animal models of XLHED (XLHED - affected newborn dogs and mice)**
  Over the last decade, dozens of puppies and hundreds of mouse pups have received EDI200. No adverse reactions related to the new drug were demonstrated in these animals. The puppies received EDI200 in a manner consistent with how it will be administered to babies (same number of doses and by intravenous infusion). These animals developed well into adulthood and are still being followed.

- **FDA required toxicology (drug safety) studies in unaffected animals**
  The FDA requires these types of studies in two different animal species before any drug can be given to humans. The two animal species tested with EDI200 in newborns were mice and dogs. The animals in the FDA-required testing were not affected by XLHED. These newborn animals were given doses of EDI200 far in excess of what would be given in the human studies. This is called the margin of safety. The results of these studies did not demonstrate any consistent drug-related side effects. All of this data was sent to the FDA for review prior to being allowed to start the human studies with EDI200.

- **XLHED adult safety study in humans**
  Six XLHED affected adults (four men and two women) were dosed with EDI200 in the first human safety trial late in 2012 through early 2013. Each of the six subjects received all five doses of EDI200 they were supposed to, the same number as neonates will receive. The study is now completed and all are doing well. The data from this study has been reported to an independent Data Safety Monitoring Board and it shows that when EDI200 is administered by slow IV infusion, the only drug related adverse effect was some irritation at the injection site. This was a rare finding that cleared within 24 hours.

  Given these results, we do not anticipate any significant EDI200-related adverse effects in newborn baby boys. Of course, we will be extremely vigilant in following these patients through the use of laboratory blood tests and frequent vital sign and clinical monitoring. Unanticipated effects (like allergic reactions) are always a possibility, and the experts at the clinical site are available to assess and treat appropriately.

For more information or just want to chat? Visit xlhednetwork.com or contact:

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