

An open-label Phase 2 trial
to investigate efficacy and
safety of intra-amniotic
administrations of ER004
in male subjects
with X-linked hypohidrotic
ectodermal dysplasia (XLHED)

We invite you to take part in a research study

Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve.

This leaflet is meant to explain to you what the EDELIFE study is about and what commitment it will require from you.

Important things that you need to know about the EDELIFE study

We want to try and find a treatment for boys affected by XLHED.

We are conducting a study on a treatment called ER004, an experimental medicine. ER004 has been created to replace a protein that is missing in those affected by XLHED. ER004 will be given before birth. The study is being conducted in several centres in Europe and the US. In the UK, there will be one centre open, in Cardiff.

You are being asked to participate in this study

You are pregnant with a boy and your son is affected with XLHED

- The treatment will be given to your unborn son at pregnancy weeks 26, 28-29 and 31-32.
- No treatment will take place after he is born.
- Your son will remain in the study for follow up checks for 5 years after his birth, to understand the full effects of the treatment.
- This study will come on top of your normal pregnancy care and will require study-specific visits to Cardiff.

You are an XLHED male relative of a pregnant woman whose unborn son is affected with XLHED and who is participating in the study

- Your participation in the study is required for 1 visit only, to gather data on your XLHED symptoms.

1. Why are we doing this study?
2. Who can take part in the study?
3. What do I need to know about the experimental medicine, ER004, and the procedure to give it?
4. I am a pregnant woman: what will I need to do if I decide to take part?
5. What are the possible side effects of the treatment?
6. Things to consider before deciding to participate in the study for pregnant women
7. I am a XLHED-affected male blood relative of a pregnant woman: what will I need to do if I decide to take part?
8. More information about taking part

How to contact us

If anything is unclear or if you have any questions about this study, please talk to the study doctor who is in charge of the study,

Professor Angus Clarke:
clarkeaj@cardiff.ac.uk

or to Diana Perry, from the UK ED association:
diana@edsociety.co.uk

1. Why are we doing this study?

As you know, there is currently no treatment for XLHED.

Pierre Fabre and the EspeRare Foundation, known as the Sponsors* of the study, are conducting a research study or clinical study*, called EDELIFE, on the safety* and possible health benefits of an experimental medicine for XLHED called ER004*.

Previously, six XLHED-affected boys received the ER004 treatment before birth (prenatal treatment*). After birth, all six babies showed improvement in some symptoms, particularly regarding their ability to sweat. Some of these results have been reported in a scientific journal (N Engl J Med 2018; 378:1604-1610).

These prenatal treatments using ER004 indicated the potential of this experimental medicine to prevent or at least significantly reduce the severity of some XLHED symptoms.

We now want to confirm these preliminary results in a robust clinical study, with 2 aims:

We want to find out if prenatal treatment with ER004 is well tolerated

We want to find out if prenatal treatment with ER004 can lead to a long-lasting improvement of some symptoms in XLHED-affected boys

If successful, this study could lead to ER004 being approved as the first commercially available treatment for XLHED.

2. Who can take part in the study?

These two groups will help us to better evaluate and quantify the effects of the treatment by comparing data collected from the boys who have received ER004 with the data collected from XLHED-affected males who have not received ER004. If a male blood relative cannot be included in the study, we will use existing and previously collected data for the comparison.

There are two different profiles of participants we are looking for in our EDELIFE study:

The treated subjects group:*

We need approximately 20 participants* to take part in our study and who will be treated with ER004. This "treated subjects group" will be made up of pregnant women with a confirmed genetic diagnosis* of XLHED, and who will be expecting a baby boy.

The comparator (comparison, or control) group: *

We also need 20 participants who are XLHED-affected male blood relatives of the pregnant women to form a "comparator group". This group will not be treated with ER004.

You are being asked to take part in this study because

- You are a pregnant woman (aged 18 or over), with a confirmed genetic diagnosis of XLHED, you are expecting a boy and your unborn son might be affected by XLHED. As the treatment is to be given to your XLHED-affected son before he is born, you, as the pregnant woman, are being asked to participate in this study and agree to the treatment of your son whilst in your womb.

We will ask you for the contact details of an XLHED-affected male blood relative of yours who would be willing to participate in the comparator group. If you do not have this information or if your relative is unable to participate, this should not affect your participation in this study as comparator data may be obtained from other sources.

- You are an XLHED-affected male blood relative of a pregnant woman whose son will be treated in the study.

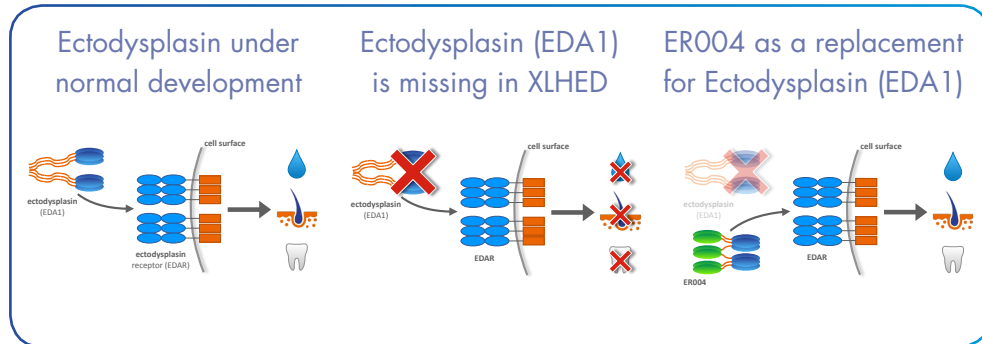
You will not receive any treatment if you decide to take part in this study. However, your participation in the comparator group* is crucial for the success of this study as we need to gather data from non-treated XLHED males to demonstrate whether or not the treatment has worked.

3. What do I need to know about the experimental medicine, ER004, and the procedure to give it?

What is ER004?

ER004 is an experimental medicine*. It is not approved for use except in clinical studies and is not available for sale.

It is hoped ER004 will replace an important protein called EDA (Ectodysplasin-A) which is missing in those affected by XLHED. Absence of this protein during the baby's development in the womb leads to some important structures not forming properly (sweat glands, hair, teeth etc). When given to XLHED-affected baby boys at the right time in the womb, ER004 should act as a replacement for the missing EDA and trigger the process that leads to the normal development of a baby's skin, teeth, hair, and sweat glands, leading to better formation of these structures.



Giving ER004 to your baby while still in the womb might sound scary. However, we think this is the only time at which the treatment might work. You may remember that Edimer Pharmaceuticals, who previously developed the treatment, conducted a research study giving ER004 to affected newborn babies in the first fourteen days of life. While ER004 did not lead to any major or significant side effects, it did not work on improving XLHED symptoms. We now understand that replacing the missing EDA protein with ER004 after birth came too late as the development of the structures had already occurred. Therefore, for the replacement ER004 to have a chance to work, it must be given during the development of the important structures (sweat glands, hair, teeth etc.), before birth.

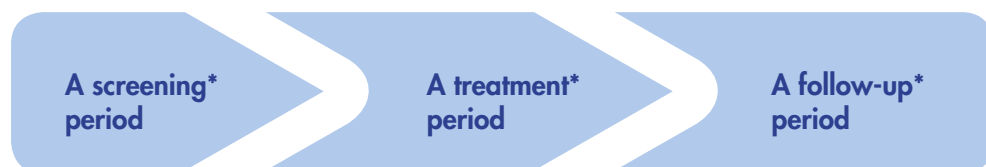
How is ER004 given to your child in your womb?

ER004 is given in a procedure that closely resembles an amniocentesis*. Using a needle and a syringe filled with ER004, and under ultrasound* guidance, an experienced doctor will inject ER004 into the water (amniotic fluid*) around your baby. During this stage of pregnancy, babies regularly swallow amniotic fluid and will therefore swallow the added ER004 at the same time. Once swallowed, ER004 will be absorbed into your baby. This procedure will be repeated twice more during your pregnancy (i.e. three treatments in all).

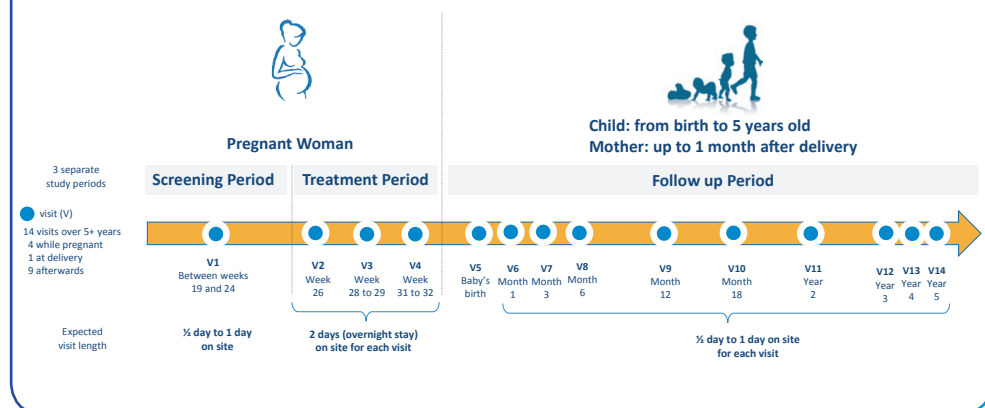
We believe ER004 does not cross to the pregnant woman and you should therefore expect no benefits for your own health. During the treatment period, and up until 1 month after your baby's birth, your health will be closely monitored alongside that of your baby.

4. I am a pregnant woman: what will I need to do if I decide to take part?

If you are a male relative of the pregnant woman, you can skip this part and go directly to part 7



Below is a graphical representation of the study, its different phases, the different visits and how long they take:



If you choose to participate in this study, you will be asked to come to visits to the clinical site in Cardiff for each study period. It is also recommended that you give birth in Cardiff. Altogether, there will be 14 visits over 5 years.

The screening period

- The screening consists of 1 visit to the clinical site in Cardiff. This visit is anticipated to take half a day to a full day and must take place between pregnancy week 19 and the end of week 24.
- This visit will confirm that you are carrying a boy. The study team will check if your unborn son is affected or not by XLHED using a non-invasive ultrasound* scan.
- The doctors will take a blood sample and conduct a series of other, non-invasive medical tests on you, to ascertain whether you and your unborn son can participate in the study (i.e. decide whether you are eligible*).
- You will get a chance to discuss the study in person with Prof Angus Clarke, the doctor responsible for the study in Cardiff, or his deputy.

Below is a graphical illustration of the panel of tests that you will undergo at the Screening visit



If you are eligible* and choose to participate in the study, you will come back later for treatment of your unborn son.

If you do not choose to participate or if you are not eligible, you will not be asked to come back to the centre in Cardiff for the study. Please be reassured that your medical care will not be affected by this decision.

The treatment period

- Treatment for your unborn child will take place at the Cardiff site over 3 visits, approximately 3 weeks apart, at pregnancy weeks 26, 28-29 and 31-32.
- At each visit, you will receive one ER004 injection. Each visit will require you to attend the site for 2 days. Before each injection, a health check for both you and your baby will be conducted, to ensure all is well and you can receive the treatment. After the injection, you will rest and be required to spend the night on site for observation.
- At the first treatment visit, we will ask you to have an MRI scan*. This is to assess the tooth development of your baby before ER004 treatment. The procedure is not generally considered to be painful, but the machine makes a loud noise. The procedure should not last more than 90 minutes.
- As part of the first treatment visit, we will ask to interview you. This interview will be conducted remotely and you will not need to go to the Cardiff site for this. This interview will be conducted by a trained interviewer, the aim of which is to hear your viewpoints, experiences, feelings and opinions on XLHED and the ER004 treatment. This interview is recorded (audio only) and should not last longer than 25 minutes.
- No treatment will take place after your baby is born.

Below is a graphical illustration of the procedures that you will undergo at a Treatment visit



Follow-up

The follow-up period starts with the birth of your child and will last until your son is 5 years old.

After delivery, you will be asked to come to the clinical site for 9 more visits, with your son.

He will be

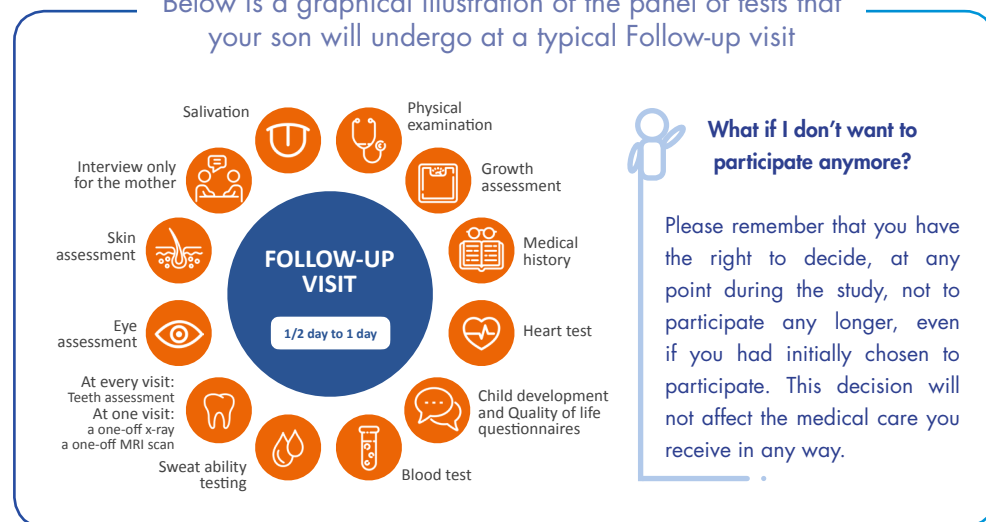


Medical examinations of your son will allow us to evaluate if the treatment has worked and how safe it is.

- Each visit will last between a half and a full day. Slightly different tests will be conducted at different visits.
- At these follow-up visits, your son will undergo many tests to check his XLHED symptoms and make sure he is doing well. These tests are all non-invasive.
- The doctors will take a blood sample from your son on 3 separate follow up visits. Analysing your son's blood will show very important information on how well your son has coped with the treatment. Altogether, the blood volume taken over these 3 visits will represent less than a teaspoon (5 mL). Blood will be drawn by a trained professional who is used to dealing with small infants.

- It is important to assess the outcome of the treatment on your son's tooth growth and his teeth will be examined at each visit.
 - One MRI assessment is planned between the ages of 3 and 6 months. For this, your son will not require sedation. Throughout this procedure, you will remain next to your son. The procedure is not generally considered to be painful, but the machine makes a loud noise. The whole procedure should take no more than 90 minutes.
 - One X-ray will be taken between 36 and 60 months of age.
- At some visits, you will be asked to fill in questionnaires about your and your son's quality of life. This should take no longer than 40 minutes.
- As mentioned in the treatment period, we will ask to interview you again. These interviews will be conducted in the same way as during the treatment period. Your child does not need to be present. This interview is recorded (audio only) and should take no longer than 40 minutes.
- You will also undergo some tests, but only at delivery and at the follow-up visit immediately after delivery, to ensure your health has not been affected by your son's treatment.

Below is a graphical illustration of the panel of tests that your son will undergo at a typical Follow-up visit



5. What are the possible side effects of the treatment?

Side effects can come from the experimental medicine, ER004, and from the injection procedure itself. If you would like more information on the potential risks associated with ER004 injection, please ask the study doctor.

- So far, ER004 has not been found to have any major significant undesirable side effects, but it is a product in development and may therefore have unknown side effects. You will be informed about this later on if you decide to participate in the study.
- The injection procedure is like an amniocentesis, and we think the risks associated with it are the same. Complications range from mild discomfort at the point of injection to early delivery of your baby, and the potentially serious ensuing health issues for him because of preterm birth. These risks and how likely they are to occur will be made clear to you later on.



Safety of the participant is always our first concern in a research study, and your and your unborn son's safety will be closely monitored for any untoward occurrences throughout your participation in the EDELIFE study.

6. Things to consider before deciding to participate in the study for pregnant women

- You will need to have a genetic confirmation of your XLHED carrier status to be able to participate in the study. If you are unsure about this, please contact your GP or clinical geneticist, who should be able to help you with this requirement.
- Please be advised that the procedures and tests you will undergo as part of the study do not in any way replace your standard pregnancy care, which will need to carry on as usual. Study visits come on top of all other routine medical care.
- Please note that ER004 treatment is not a gene therapy treatment and will not make any changes to the DNA inside your baby's cells. Instead, ER004 is designed to correct your baby's development during the third trimester only. You son will be able to pass on the faulty XLHED gene to his daughters.

- We ask you to consider giving birth at the site in Cardiff. While this is not obligatory, it is preferred, as this makes collection of important data more likely to be successful.
- If you choose to participate in the study, a home-birth will not be permitted.
- Covid vaccination is not a requirement to take part in the study. However, you will be required to take a Covid test before each of visits for the ERO04 injections. If you test positive for Covid at this time, the decision to carry on or not with the treatment will be taken by the Study Doctor and the Sponsors on a case-by-case basis. A Covid test will also be conducted at delivery.
- We ask you to consider that this study is a very long-term commitment. Your son will be followed up in Cardiff until he is 5 years old and there will be 10 visits to the Cardiff site from birth onwards. We know this is a really big ask but we do need to make sure the potential benefits of the treatment are long-lasting for the medicine to be considered properly tested. To confirm this, we need to see your son regularly until he is 5.
- While you and your son are participating in the study, you will not be allowed to take part in another research study.
- Being interviewed and recorded as part of the study might be upsetting or might make you feel uncomfortable. You will be able to pause or stop the interview at any point. Signposting for support will also be given to you.

7. I am a XLHED-affected male blood relative of a pregnant woman: what will I need to do if I decide to take part?

If you are a pregnant woman, you can skip this part

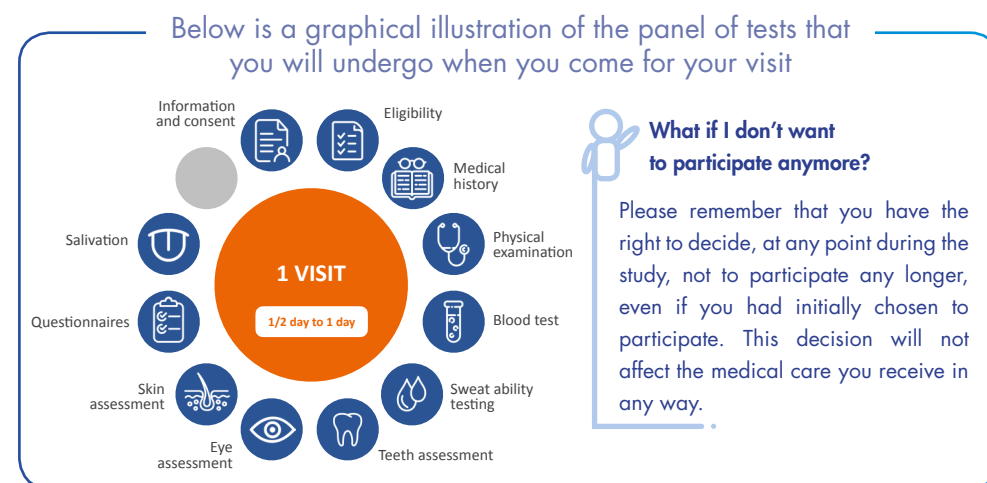
To participate, you must be aged between 6-months and 60 years old and must be a XLHED-affected blood relative of the pregnant woman. You must not have been treated with ERO04 previously.

You will be asked to come to the clinical site in Cardiff for one visit only. This visit must take place before the treated baby reaches 6 months of age. Before the visit, the medical team at Cardiff will have shared with you more detailed information about the study to help you decide whether or not to participate.



If you do choose not to participate, your involvement in the study will end and we will not contact you again. Please be reassured that your medical care will not be affected by this decision. If you choose to participate in the study, you will come for one visit to the medical site in Cardiff.

- This visit will take between a half and a full day
- Medical tests will be conducted on you. Most of these tests are non-invasive and should not lead to any major discomfort for you, but a blood sample may be required to confirm the XLHED mutation.



8. More information about taking part

If you are interested in the study, please contact Prof Clarke, the doctor responsible for the study in the UK, who will then share more information with you on the study, including, should you wish to, the full Information Sheet that details the whole study.

Please take all the time you need to reflect before the Screening visit. If it helps, discuss the study with your family, friends or medical team (midwife, GP etc) before giving your consent or deciding not to participate.

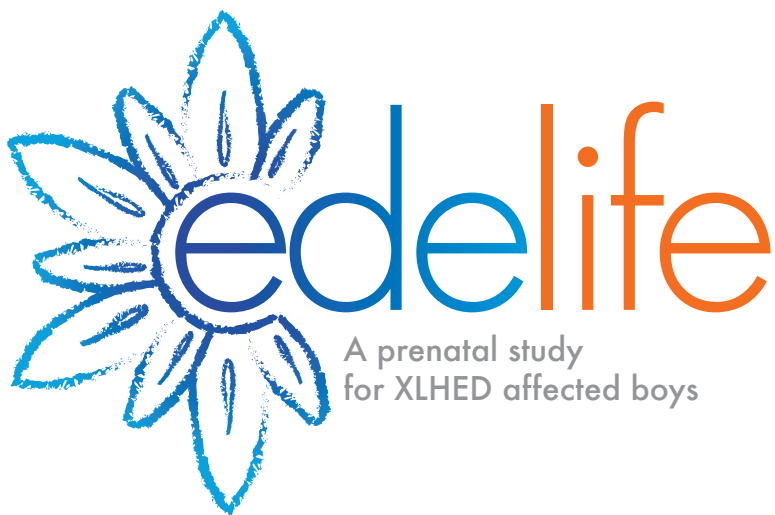
At the Screening visit, you will get a chance to discuss in person the study with Prof Clarke. It might be a good idea that you prepare and have ready some written questions.

EDELIFE clinical trial website: <https://edelifeclinicaltrial.com>

clinical trials information: <https://clinicaltrials.gov/ct2/show/NCT04980638?term=EDELIFE&draw=2&rank=1>

Amniocentesis	A procedure used during pregnancy to take out a small sample of the amniotic fluid for testing
Amniotic fluid	Liquid that surrounds your baby during pregnancy
Clinical study/trial	An experiment or research study involving people, intended to gain medical knowledge.
Comparator group	XLHED-affected male relatives of the pregnant woman, who have not received the treatment and will serve as a reference point for what the untreated symptoms are like
Confirmed genetic diagnosis	DNA testing Medical test to identify the changes (mutation) on the EDA gene
Data	Information gathered in studies to help address research questions, such as assessing treatment effects
Eligible	Confirmation that a participant has met all the requirements to be included in the study
ER004	A replacement for the EDA protein that is made in a laboratory.
Experimental medicine	A medicine that has not yet been approved for use and is therefore not commercially available
Follow-up	The part of the study where children are checked for the impact of the treatment, from birth to 5-years of age
Genotype	Genetic constitution of an organism
Informed consent	The process of learning the key facts about a clinical study before deciding whether or not to participate

MRI	Type of scan that uses strong magnetic fields and radio waves to produce detailed images of the inside of the body
Participants, subjects	Names given to the people taking part in a clinical study
Prenatal treatment	Treatment given to the unborn baby before he is born, in his mother's womb
Safety	Detection, assessment, understanding and prevention of side effects
Screening	The part of the treatment where pregnant woman decides whether to join the study or not and is checked for eligibility.
Side effect	Any undesired actions or effects of a drug or treatment
Sponsor	The parties responsible for initiating and/or financing the EDELIFE study
Standard of care	A treatment plan that the majority of the medical community would accept as appropriate
Study doctor	The doctor who directs the study or some of its activities
Treated subject group	Babies and children who will have taken part in the study and who will have received the treatment, ER004
Treatment	The part of the study where the treatment takes place, during the pregnancy
Ultrasound	Type of scan that uses high-frequency sound waves to create an image of part of the inside of the body



If you would like more information about the EDELIFE study, please contact the study doctor for this study in the UK, Professor Angus Clarke (clarkeaj@cardiff.ac.uk), or contact Diana Perry (diana@edsociety.co.uk), the UK ED Patients Association representative <https://edsociety.co.uk/>