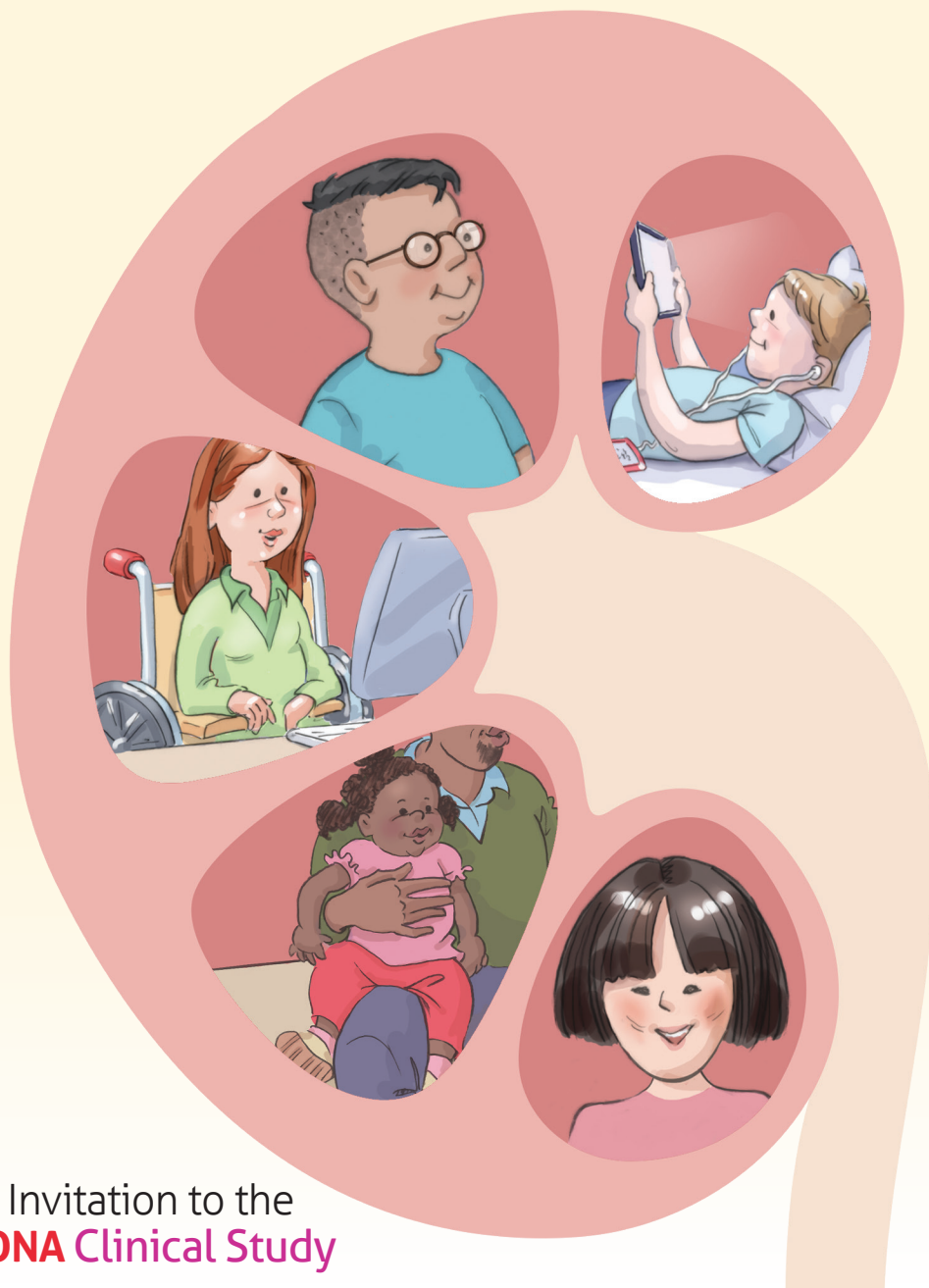


Chronic Kidney Disease

IN YOUNG PATIENTS

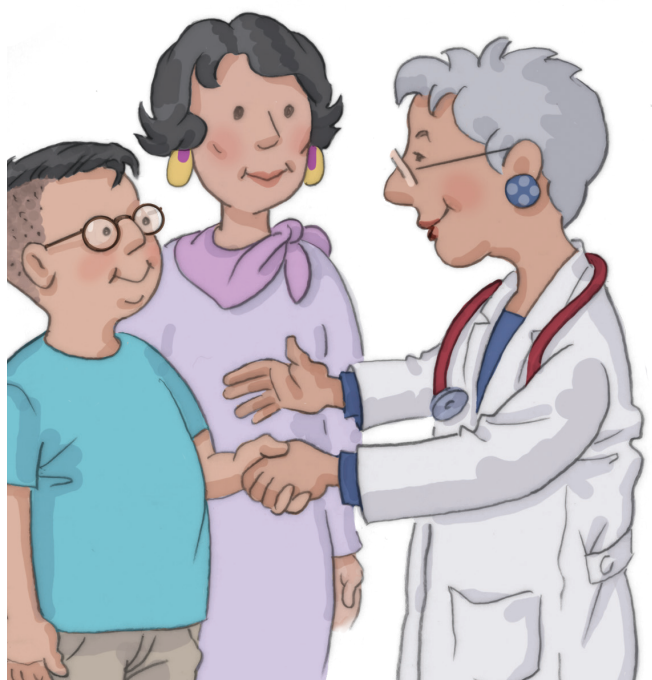


An Invitation to the
FIONA Clinical Study



FIONA

AN INVITATION TO The **FIONA** Study



Your child's doctor would like to ask you to consider having your child take part in the FIONA study. Participating in this program is voluntary. Take your time to decide and ask your child's study doctor as many questions as you like. You may also discuss with your doctor or healthcare provider.

On the following pages you will find information about chronic kidney disease, about the study drug and you will find out what happens during the study.

Why has my baby/child been invited to participate?

Your child is being treated for chronic kidney disease (also called CKD) and proteinuria (having abnormal amounts of protein in the urine) and he/she may be eligible to participate in the FIONA study.

What is the purpose of the study?

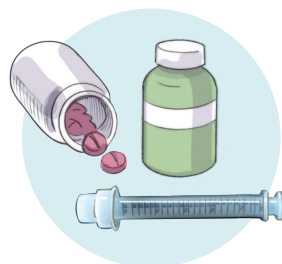
The main purpose of this study is to learn how well the study drug works (compared to placebo) in children (aged between 6 months and 18 years) with chronic kidney disease in addition to standard of care treatment. The study drug is being developed by a pharma company called Bayer.

Which drug is being evaluated?

The study drug works by blocking the effects of aldosterone. Aldosterone is a substance produced by the body which can be harmful for the heart and kidneys if there is an excessive amount of it.

The study drug is called finerenone. It is an investigational drug in pediatric populations. This means it can only be used in studies like this one in pediatric populations.

The study drug is taken by mouth, once a day, as a tablet or as a suspension (liquid).





The FIONA study will be evaluating 4 different age groups. It will begin with the oldest age range stepping down to the youngest age range. Age groups will be open for participation as information is collected and evaluated by medical committees throughout the study.

What is a clinical study?

A clinical study is a type of research that studies treatments for medical conditions. Doctors and Scientists conduct the study with a limited group of people to assess if it is working and

safe before the treatment is made available to all patients. These studies move through a series of steps (called **phases**) to test how well a medication or treatment works and how safe it is.

Phase 1:



The treatment is tested for the first time in humans, among a small group of healthy people, to evaluate a safe dose range.

Phase 2:



The treatment is tested in up to several hundred people with the disease or condition to record how effective and safe it is.

Phase 3:



The treatment is given to a larger population of patients who have the disease or condition for which the treatment is being tested. Side effects and effectiveness are assessed.

FIONA is a phase 3 clinical study. If the treatment or drug is safe and effective in phase 3, it is ready to be submitted for approval by health authorities in each country.

Phase 4: The approved drug is monitored for its use and effects over time on a large scale after the approval. Monitoring of side effects continues:

side effects might become clearer once more people have access to the treatment and after a longer period of time goes by.

How the kidneys work

One of the kidney's most important functions is blood filtration. Every day, the two kidneys filter about 115 to 140 liters of blood and produce about 1 to 2 liters of urine, composed of waste, salt and extra fluid. Children produce less urine than adults and the amount produced depends on their age.

Kidney anatomy

The kidneys are part of the urinary system (the group of organs involved in making and removing urine). They are two bean-shaped organs, located behind the abdomen, just below the rib cage.

Kidneys

Ureters

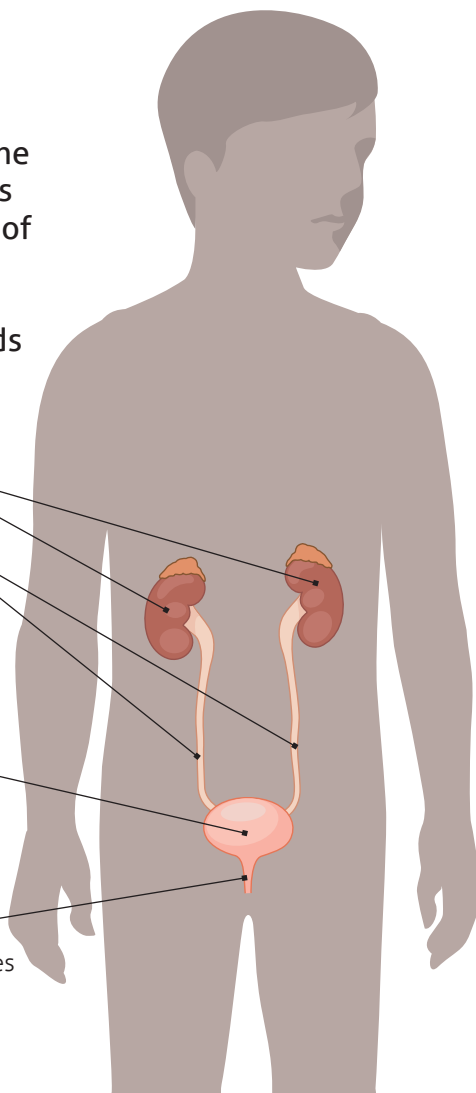
the thin tubes that carry urine from the kidneys to the bladder.

Bladder

the bag that stores urine until we are ready to expel it.

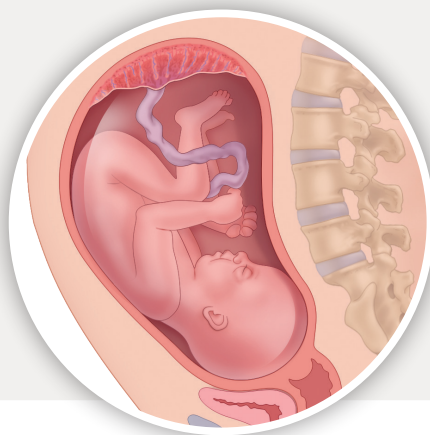
Urethra

the tube that carries urine from the bladder to outside the body.



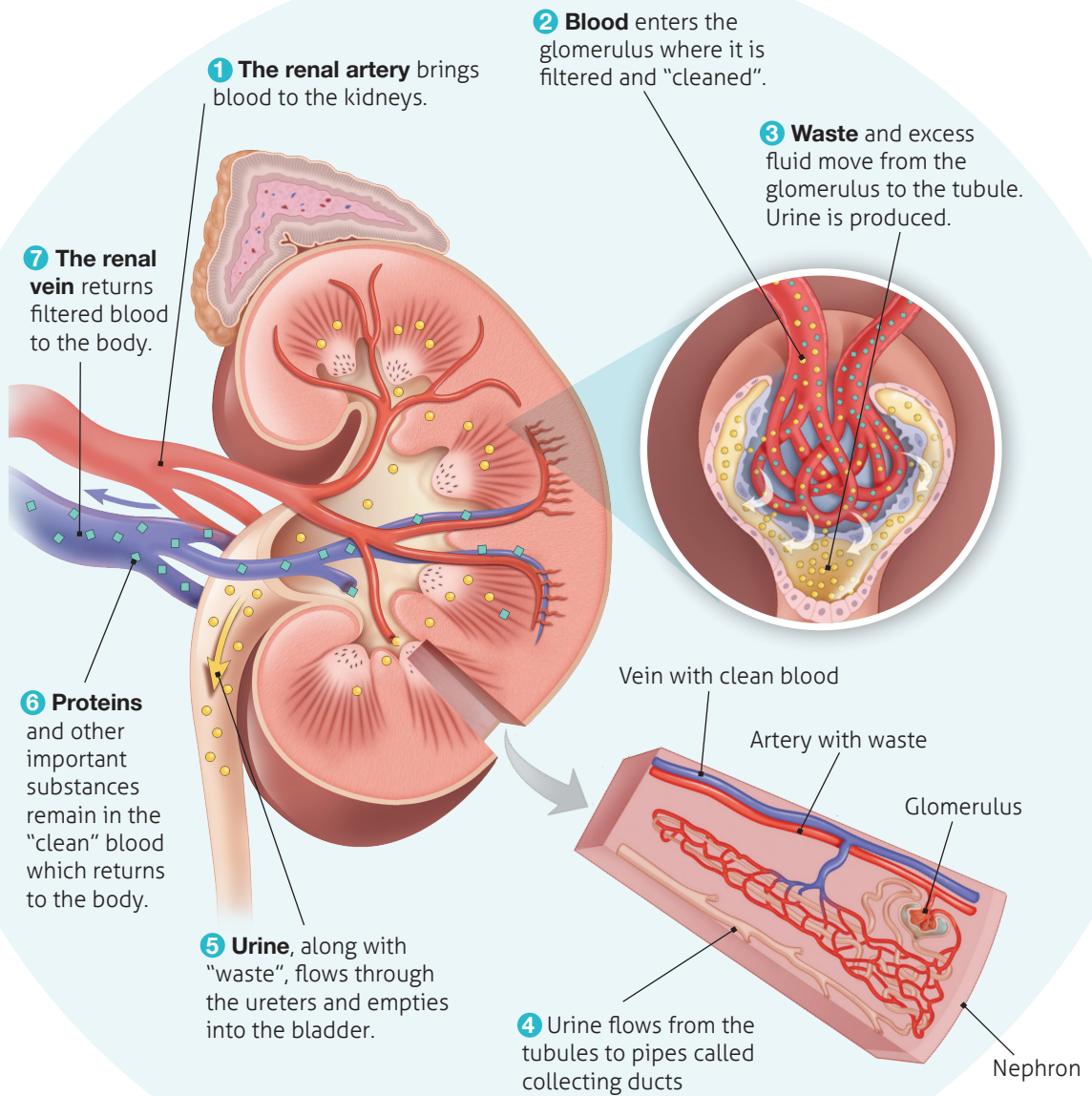
Kidneys develop before birth

Kidneys complete their development while the baby is still in the womb, at around 36 weeks of gestation. By that time, each kidney has about one million small filtering units called nephrons. **Nephrons** are made up of a **glomerulus** (a bundle of blood vessels that filters blood) and a **tubule** (a pipe that collects urine). No new nephrons are formed after birth.



Kidneys filter blood

The kidneys filter blood by **removing waste and excess liquids** and regulate the amount of minerals (such as sodium, potassium, calcium and phosphorus) in blood. Substances which are useful for the body (such as proteins) are kept in the blood.

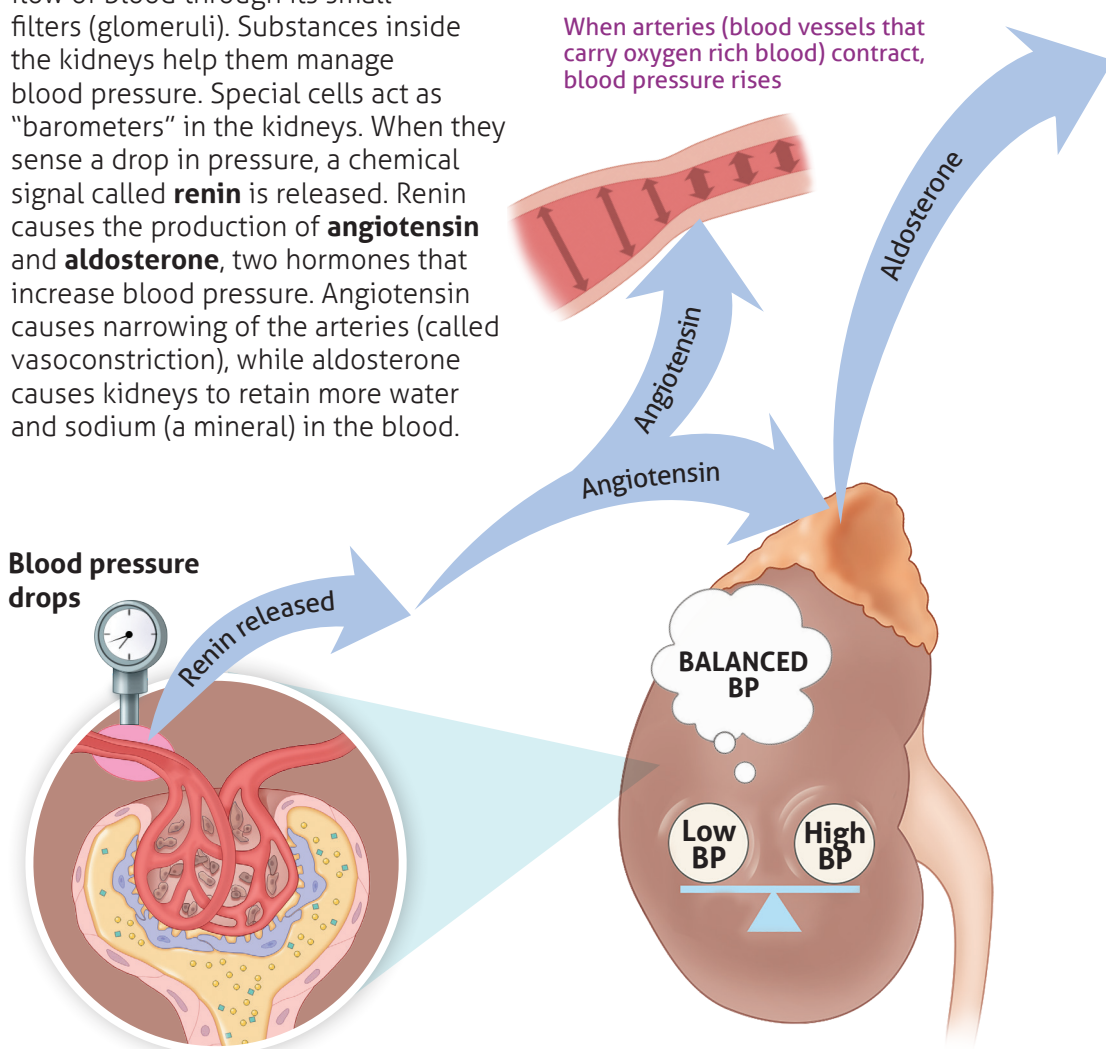


Balancing blood pressure

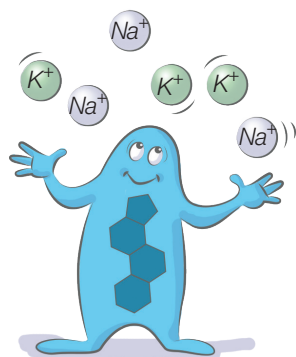
Kidneys, together with the heart and blood vessels, play a very important role in keeping your blood pressure at the right level. Too much pressure can damage blood vessels, while low pressure may not allow enough blood to flow through the body and through the kidneys.

How kidneys control blood pressure

Kidneys are constantly balancing blood pressure to maintain a proper flow of blood through its small filters (glomeruli). Substances inside the kidneys help them manage blood pressure. Special cells act as “barometers” in the kidneys. When they sense a drop in pressure, a chemical signal called **renin** is released. Renin causes the production of **angiotensin** and **aldosterone**, two hormones that increase blood pressure. Angiotensin causes narrowing of the arteries (called vasoconstriction), while aldosterone causes kidneys to retain more water and sodium (a mineral) in the blood.

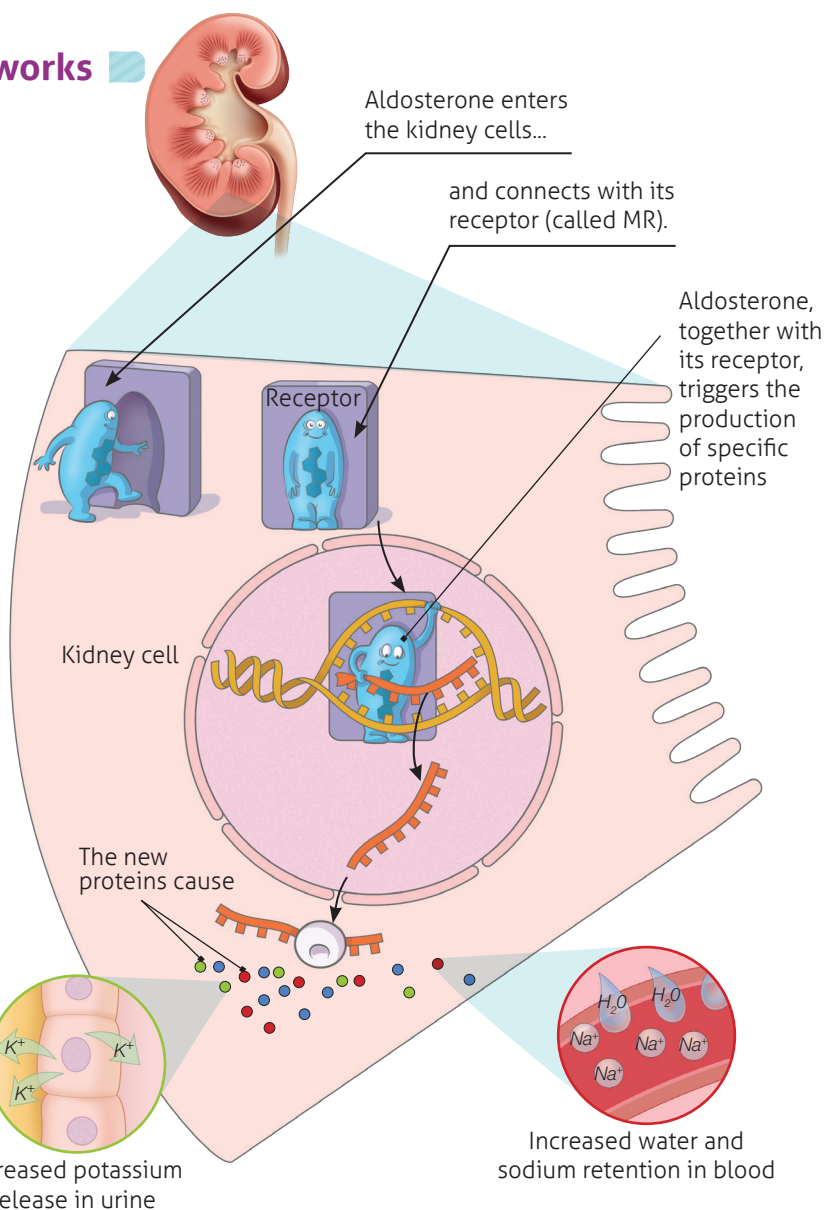


How aldosterone works

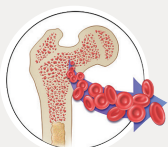


Aldosterone acts in many parts of the body. Aldosterone's main job in kidneys is to:

- ★ regulate the amount of sodium and potassium (two important minerals) in your blood. Aldosterone causes kidneys to retain sodium in blood and to release potassium in urine.
- ★ help control blood pressure by causing kidneys to retain more water in the blood.



Other functions of the kidneys



- ★ Kidneys release a hormone called erythropoietin that stimulates the production of red blood cells in the bone marrow. Red blood cells carry oxygen around the body.
- ★ Kidneys contribute to keeping bones healthy by regulating the amount of calcium and phosphorus in the blood and activating vitamin D. Vitamin D and a correct balance of calcium and phosphorus is important for bone health.



Chronic Kidney Disease (CKD)

The word chronic in CKD means that the kidney disease lasts for a long time and does not disappear completely. In CKD, the kidneys gradually are not working as well as they should: the kidney's filtering units are less able to clean the blood, so waste, extra water and salts can build up in the blood. Kidneys may gradually lose their ability to perform their other jobs as well - such as controlling blood pressure, keeping bones healthy and strong, and promoting the production of red blood cells.

Causes of CKD in children

Kidney disease in children can be caused by:

☆ congenital anomaly: a problem that happens while a baby is developing in the mother's womb (having only one kidney, having dilatation or narrowing of the ureters or urethra, or having kidneys in an unusual position)



☆ hereditary diseases: illnesses passed from parent to child through the genes, such as polycystic kidney disease or Alport syndrome



☆ infections: in rare cases some infections can damage the small blood vessels in the glomeruli. In some children the damage can be permanent and cause CKD.



☆ systemic diseases, such as systemic lupus erythematosus (SLE or lupus) or diabetes



☆ nephrotic syndrome: a collection of symptoms that indicate damage in the glomeruli. Children with this syndrome have high levels of proteins in urine, low levels in the blood, high blood cholesterol and, usually, swelling in the face or legs.



☆ acute kidney injury caused by very low blood pressure or toxins



☆ urine blockage or reflux: when urine flow is blocked, it can back up (reflux) in the kidneys and damage them.



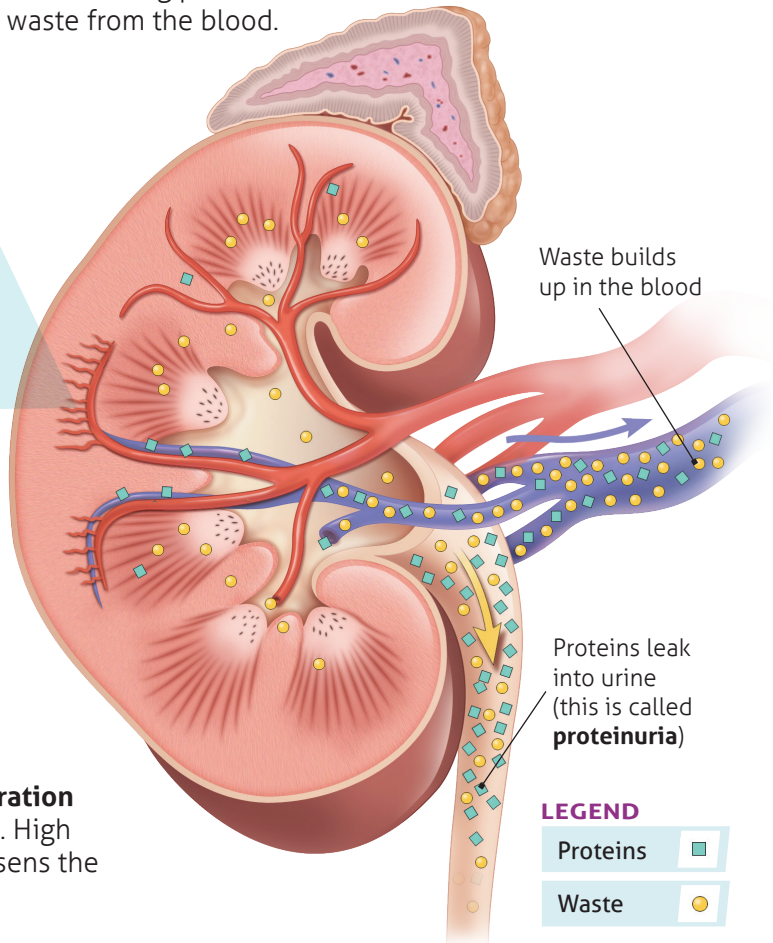
What happens in the kidneys

Injured glomeruli are incapable of retaining proteins in the blood and of removing all the waste from the blood.



Proteins in urine worsen kidney disease further by damaging the kidney cells and structure. In addition, when some glomeruli are not working properly, others have to work harder. This overwork can, over time, damage the other glomeruli.

Kidneys may react to low filtration by increasing blood pressure. High blood pressure, however, worsens the damage.



LEGEND

Proteins

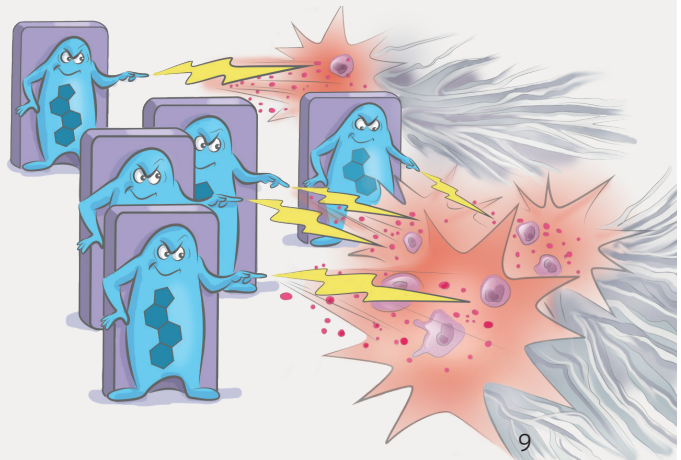


Waste



Aldosterone contributes to kidney damage

In CKD aldosterone levels may increase. Too much aldosterone can cause or worsen high blood pressure. Additionally, if it acts for a long period of time, it can have negative effects by causing inflammation. In the long run, inflammation can impair kidney function and cause scarring (fibrosis). Fibrosis is when the normal tissue (normal body cells) is replaced by scars. The areas of the kidneys with fibrosis cannot work properly and kidney disease worsens.



Stages and Treatment

There are 5 stages of CKD. In the first stages the treatment is aimed at slowing down the progression of CKD by controlling the risk factors that damage kidneys (high blood pressure, protein in urine and any other risk factors your child may have). In the later stages, children may develop symptoms and treatment is aimed at managing the symptoms. In stage 5, a kidney transplant or dialysis is needed.

CKD stages

CKD, as time goes by, progresses through different stages:

- ✧ In the early stages children often do not have symptoms.
- ✧ In the later stages children may start having symptoms. At stage 5 a kidney transplant or dialysis is required.

Many children with CKD do not progress through all stages. Many do not reach stage 5 CKD until adulthood.

The FIONA study involves children with CKD stages 1 to 3.

Stage	Kidney function	GFR (ml/min per 1.73m ²)
1	Normal or high	≥90
2	Mildly decreased	60-89
3	Moderately decreased	30-59
4	Severely decreased	15-29
5	Kidney failure	<15

The stages of CKD are defined on the basis of the glomerular filtration rate (GFR) in older children and on creatinine levels in children aged less than 1 year. GFR is a number that tells how well the glomeruli are eliminating waste from the blood. It is assessed based on creatinine (a waste) levels found in blood.

Treatment in stages 1 - 3

It is important that your child's blood pressure is controlled and kept in the healthy range. Even in early CKD stages, children are at risk of hypertension (high blood pressure), which can also cause further damage to their kidneys and may speed up CKD progression.

Your child may need to eat a specific diet and/or take medication. In addition, the doctor may recommend lifestyle changes, such as a healthy diet or physical exercise, that can help keep blood pressure under control. Avoiding drugs or other substances that can damage the kidneys is important.



Measuring blood pressure

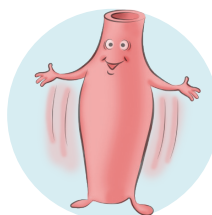
Blood pressure is recorded with two values. The first, systolic pressure, is measured right after the heart contracts. It is the higher number. The second, diastolic pressure, is measured before the heart contracts. It is the lower number.

Checking blood pressure regularly and keeping it at the optimal level is one of the most important treatments for slowing down the progression of kidney damage.

Blood pressure lowering drugs

In order to keep high blood pressure under control, your child may have to take one of the following types of drugs. These drugs act on the systems that kidneys use to increase blood pressure and that, in CKD, may further damage the kidneys.

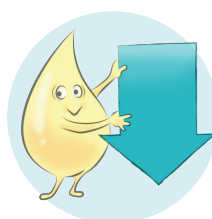
★ **Angiotensin-converting enzyme inhibitors (ACE-I)** block the production of angiotensin, the hormone involved in the contraction of arteries. Arteries can therefore relax and expand: blood pressure decreases.



ACE-I and ARBs lower blood pressure by expanding blood vessels.

★ **Angiotensin II receptor blockers (ARBs)** block the action of angiotensin. Their final effect is similar to that of ACE-I.

Both ACE-I and ARBs can also help reduce loss of proteins in the urine.



They also decrease the loss of protein in urine.

Signs and Symptoms

In the early stages of CKD, there are generally no symptoms. As the disease progresses, your child may experience some symptoms. With specific treatments, doctors can help keep most symptoms under control and improve your child's quality of life. It is important to follow your doctor's recommendations and attend all follow up visits to detect any sign or symptom.



Changes in urinating

As kidneys lose their ability to retain water, children pass a greater amount of urine and need to drink lots of water



Slower growth

Children with CKD may grow at a slower rate than their peers. This may be due, among other factors, to poor nutrition (because of poor appetite or vomiting) or to a decreased activity of the growth hormone.



Swelling

Swelling in different parts of the child's body (in particular in the face, feet and legs). This can be caused by excess water retention in the body because of low levels of proteins (in particular albumin) in blood.



Anemia

If kidneys produce less erythropoietin, your child may have low levels of red blood cells. This can cause your child to feel weak and tired and look paler than usual.



Nausea and vomiting

High amounts of waste in blood can cause your child to feel sick (nausea) and have a poor appetite.



Feeling tired

Urinary incontinence

Urinary incontinence is the loss of bladder control, which results in the accidental loss of urine. It occurs in some children with CKD. It can have different causes, one of which is the increased volume of urine. There are several strategies and treatment options available that may help. Please encourage your child to talk with you and the doctor if your child is experiencing any bladder control problem.

Other effects of CKD on children

In addition, children with CKD may face other challenges, such as:

- ✧ a negative self-image, relationship problems or behavior problems due to the stress of living with a chronic condition
- ✧ learning problems, trouble concentrating, delayed language or motor skills development (because of the build-up of waste in the body that can slow down brain function)

How you and other adults can help your child in daily life

Adults can do a lot to help children with CKD fit in at school, deal with low self-esteem, make friends, be physically active, and follow their treatment regimen. For example, by:

- ✧ helping children feel empowered by giving them as much control and responsibility over their own care as possible (sharing information on medication and involving them in treatment decision making)
- ✧ providing teachers, school administrators and classmates with information on the effects of CKD
- ✧ encouraging children to participate in regular classrooms and extracurricular activities may help children improve their social skills
- ✧ encouraging them to participate in physical activities, including sports, unless instructed otherwise by a health care provider.



Your Child's Experience

During the study, your child will be asked to attend about 10 visits for up to 10 months. This may involve missing some school time. The study doctor will ensure your child is getting the standard of care treatment for CKD, in addition to the study examinations and treatment.



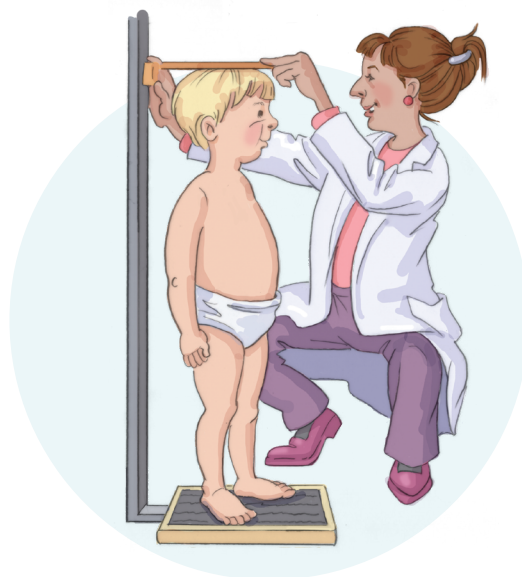
What happens during the study?

Run-in visit

You and your child will be asked if you agree to participate in the study. If you agree, the study doctor will evaluate whether your child is a candidate for the study during the run-in visit. The study doctor will review your child's medical history, check your child's weight, height, heart rate, temperature and blood pressure and perform blood and urine tests. The study doctor will also check if your child is taking the optimal dose of blood pressure lowering drugs and, if needed, will adjust it.

Screening visit

The screening will begin after your child is on the best dose of blood pressure lowering medication. The study team will ensure that your child can safely start treatment during this phase, which can take up to 14 days. During this phase, the study doctor will perform a routine physical examination, will check your child as in the run-in visit and will perform blood and urine tests.



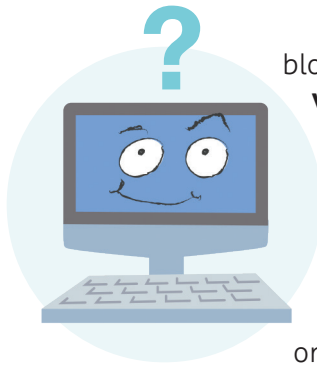
Study visits

You and your child should attend all study visits as scheduled. If there is a need to reschedule the visit, contact the study staff.

Treatment phase

Once screening is completed, a computer program will randomly choose if your child will take the study drug or placebo (a placebo looks like the study drug but does not have any medicine in it). Your child will have a 2 in 3 chance of getting the study drug and a 1 in 3 chance of receiving placebo. Neither you nor the study doctor will know which drug your child will be taking, but the study doctor can find out in case of an emergency. **Your child will have to take the assigned drug every day, with a glass of water, milk or juice, for 6 months.** There will be at least 7 visits during these 6 months.

During these visits, the study doctor will ask about your child's health and about all medications your child has taken since the last visit. You will have to bring to the visit all used and unused study drug packages. Heart rate, blood pressure and temperature will be checked and your child will have



blood samples taken. **On specific visit days, you will also be asked to bring your child's morning urine samples.**

At the beginning and end of this phase, you and your child will be asked to answer a questionnaire on your child's

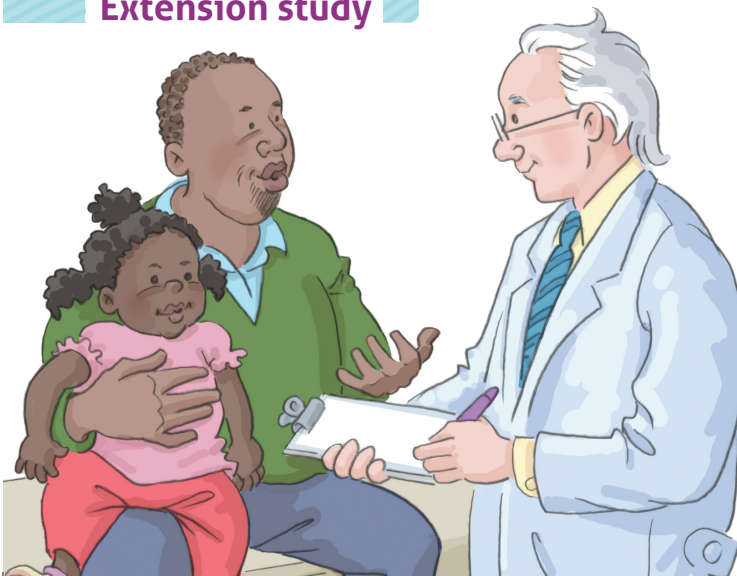
quality of life. Details of what is going to happen will be explained to you and your child. The study doctor will answer any questions you or your child may have.



Follow up

The study will end with a follow up visit 1 month after the end of the treatment phase. During this visit, blood and urine tests will be performed.

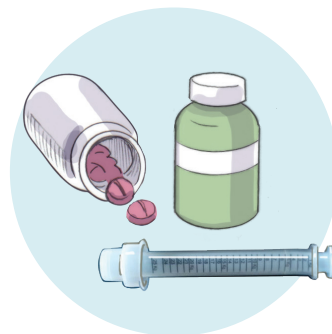
Extension study



Once your child has finished the FIONA study, you and your child may be offered the possibility to take part in an extension study called **FIONA OLE**. This study will last 18 months. All patients who participate will receive the study drug.

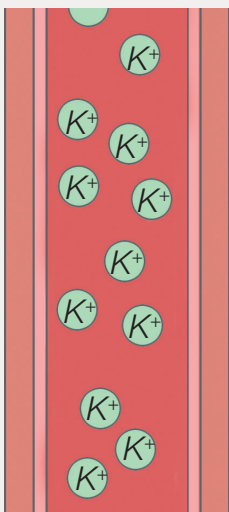
Understanding the study drug

The study drug that will be tested in the FIONA study acts by blocking the action of aldosterone.



Will my child benefit from taking part in the study?

It is not known whether your child will get any benefit from participating in this study. However, your child may benefit from the additional close monitoring during the study. The information the doctors will receive from your child's participation may help develop better treatments for children with CKD in the future.



Hyperkalemia means having too much potassium (K⁺) in the blood.

What are the side effects?

A common side effect seen is the build up of potassium in blood (**hyperkalemia**). If hyperkalemia is mild, it may not cause any symptom. If hyperkalemia is severe, it may affect the heart and cause heart rhythm problems (arrhythmia) which might be life-threatening. **Doctors will take actions to lower this risk by checking your child's blood potassium levels regularly and by starting with a lower dosage of the study drug.**

In previous studies, hyperkalemia occurred in up to 18% of adults with CKD taking the study drug compared to 9% taking placebo.

What is blood potassium?

Potassium is a mineral that the body needs to work properly. It helps nerves to function and muscles to contract. It is also involved in maintaining a regular heartbeat.

The body gets the potassium it needs from food and drinks. Kidneys then filter it and get rid of any excess, in order to keep a balanced amount in the blood.

Your child's participation

Why do you need to test my child's blood so often?

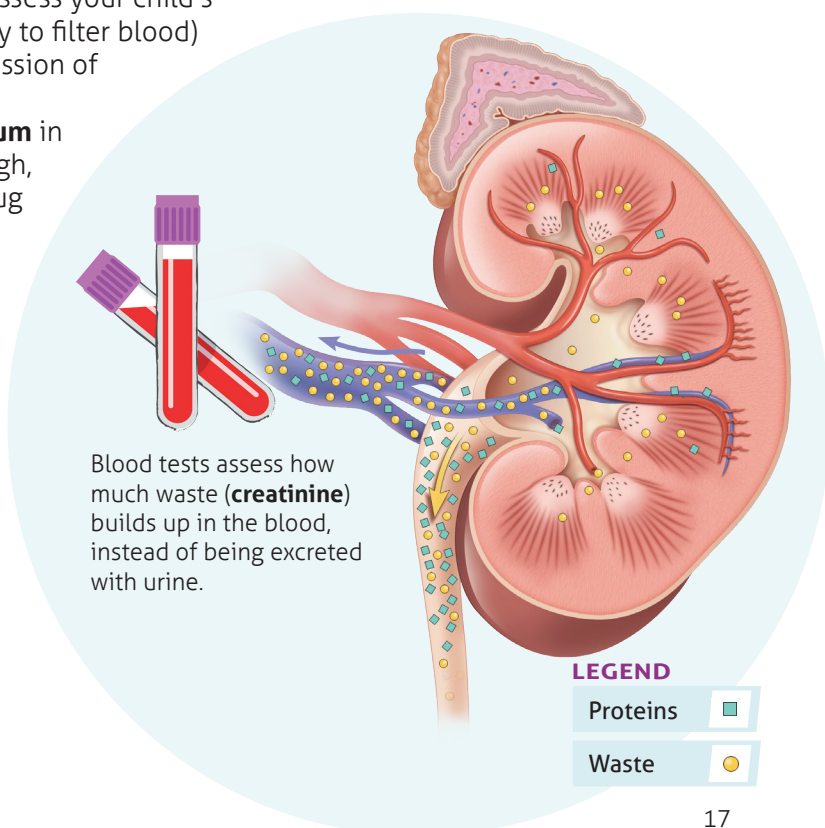
Several blood tests are planned in the FIONA study to help ensure your child's safety and to keep a close check on the dose that your child is receiving. Frequent sampling called **PK (Pharmacokinetics) blood samples** enables scientists to understand how the drug is absorbed and the way it moves within your child's body. PK sampling records the levels of drug in the blood of the study participants. Usually, these tests must be done before your child takes the dose and afterwards, for comparison. This is common practice in drug research to ensure that the dose has the best potential for working.

To help be sure that your child is safe, there will also be safety blood tests that will check:

- ★ How much waste has built up in blood. This will help doctors assess your child's **GFR** (the kidneys' ability to filter blood) and monitor the progression of CKD.
- ★ The amount of **potassium** in blood (K^+). If it is too high, the dosage of study drug your child is taking may be reduced, or treatment might be interrupted until the potassium level is normal again.



The study team has taken extra efforts to combine all the blood sampling to keep the number of blood draws to the minimum and, at the same time, keep your child as safe as possible.



Blood tests assess how much waste (**creatinine**) builds up in the blood, instead of being excreted with urine.

LEGEND

Proteins



Waste



Your child's participation

Why do you need my child's urine samples?

The amount of protein in your child's urine will be assessed. Scientists will measure the amount of proteins lost in urine.

You will receive instructions on how to collect urine samples.

Urine tests assess how much protein is lost with urine, instead of remaining in the blood.



LEGEND

Proteins



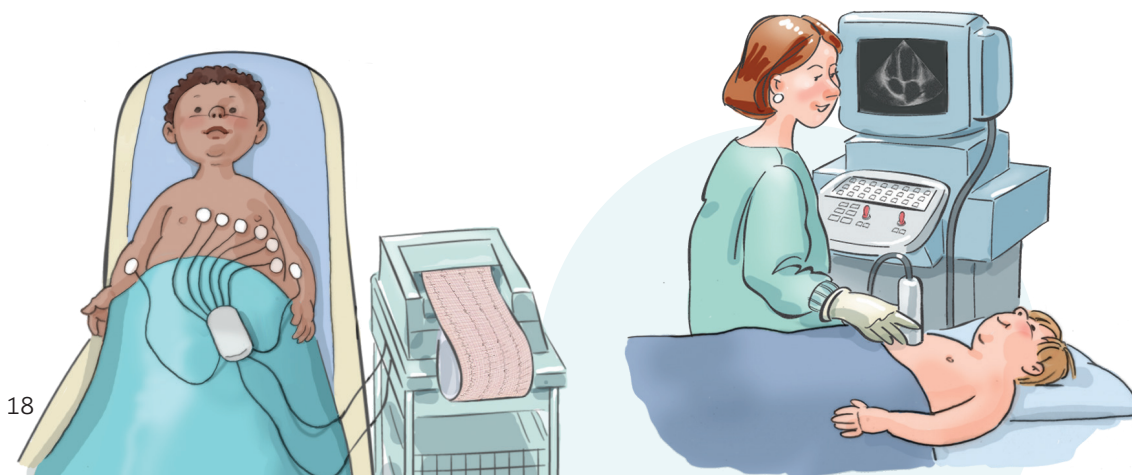
Waste



Are there any other tests that my child might have during the study?

At some visits, an ECG (electrocardiogram) and a heart ultrasound will be performed to check your child's heart. To perform the ECG, patches will be applied to your child's arms, legs and chest. They record the electrical activity of the heart.

Heart ultrasound (echocardiography) is an imaging test that uses ultrasound to make moving pictures of the heart. During this test, a gel and an ultrasound probe is put on your child's body.



Support during the FIONA study

If you decide to have your child take part in the study, you will receive study materials containing:

- ★ full information on all study visits
- ★ instructions on how to take the study drug
- ★ instructions on how to collect urine samples
- ★ study doctor's contact information

The information in this booklet can help you learn more about participation in the FIONA study. Remember that the study doctor is available to answer questions, give you further details about the study and support you in making your decision.

If your child agrees to participate, he/she may also receive age appropriate information about his/her health and wellness, about the study and access to items that will support your child during study visits.



Caring for your child

Can my child take other drugs?

Please talk with the study doctor before making any changes to your child's medication, including giving new medications or stopping current medications. In an EMERGENCY, inform the doctor of your child's participation in the FIONA study and inform your study doctor of the emergency as soon as possible.

Some medications, including pain and fever lowering medicines, may have an effect on kidneys. Consult the study doctor before giving your child any new medication.



If your child sees another doctor

Please tell all doctors that your child sees (including a dentist) that your child is taking part in this study and that he/she may contact your child's study doctor for information.

Dehydration

Dehydration occurs when the body does not have as much water as it needs. It can cause worsening of kidney function, low blood pressure, acute kidney injury and hyperkalemia. Please contact your doctor in case of diarrhea, nausea and vomiting and/or if your child



cannot keep up with the fluid intake, e.g. in hot weather or when he/she has a fever.

Pregnancy

The study drug has not been evaluated in pregnancy or breastfeeding. If your child is pregnant or breastfeeding, she cannot take part in this program. A negative blood or urinary pregnancy test will be required for all menstruating girls at different moments of the study (at screening and during visits 7 and 10). If your adolescent girl is of childbearing age and sexually active, she will need to use appropriate and efficient methods of contraception. The methods of contraception will be recommended by the study doctor.

Call the study doctor, if your child has any of these symptoms

These symptoms may be related to high potassium levels or to worsening of CKD:



Unusual sleepiness



Dizziness



Confusion



Tingling, numbness



Diarrhea or constipation



Nausea, vomiting



Muscle weakness



If you notice that your child's symptoms get worse or if new expected or unexpected symptoms appear, call the study doctor.

How is the children's safety watched?

To help monitor the safety of children participating in the FIONA study, a committee of independent physicians with expertise in pediatric nephrology and the performance of pediatric clinical studies is reviewing, on an ongoing basis, all information regarding safety throughout the study. They will ask for changes or even stop a study, or the program, if they have safety concerns.

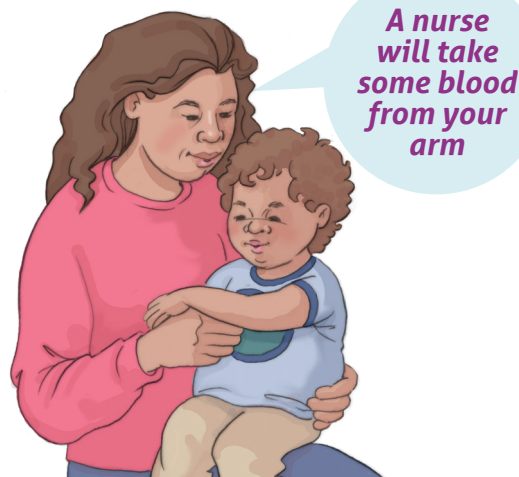


Supporting your child

Tips for empowering your child

Providing information to children on their disease and on the treatment and exams may help them to feel more confident, can allow them to take control over their disease and lower stress. This is important for all ages: toddlers may need very simple information, while teenagers will be interested in more detailed explanations. Take in consideration the following tips when discussing the study and CKD in general with your child:

✧ Before going to the study doctor's appointment or study visit, take time to explain what will happen. For example, you can tell a four-year old: "as soon as you wake up, I will help you pee in this cup", "we will go to the hospital", "once we arrive, we will meet the doctor", "the doctor will check your heart", "a nurse will then take some blood from your arm".... Regardless of their age, children are more positive about any health treatment if they are aware of what will happen. Once you enroll in the study, you will receive a booklet for children that will help your child better understand the study.



It is important to explain to your child what he/she will do with the study staff at each visit.



Will my child miss many school days?

Your child may miss about 10 days over 10 months for study-related purposes. The dates of your appointments will be available in advance so that you will be able to plan ahead.

☆ Encourage your child to be involved: your child may help you remember the date of study visits (for example by writing them down on the calendar or by coloring in the date), he/she may help in getting ready for the visit or by engaging with the study doctor or nurse during the visit.

☆ Encourage your child to ask questions directly to the study doctors or nurses. Reassure him/her that there are no stupid questions.

☆ Let your child know that he/she is not alone. There are other children in other cities and other parts of the world who are going through the same experience and taking part in this same study.

Are there other kids taking part in the study?

Yes, all around the country and in other parts of the world, too



Can my child exercise?

Your child may perform the physical activity he/she is used to.



Are there food restrictions?

Your child may maintain his/her normal diet throughout the study. No specific restrictions are given when participating in this study.

DISCUSS ANY DOUBTS OR QUESTIONS YOU MAY HAVE



The study doctor will take time to explain every detail of the study, the disease and the effects of the study drug. However, even if doctors and nurses think they have given all of the information, you may still have more questions, or may need further information or explanations. This is a common situation, so please don't be shy: use the space below to note down your questions and ask them to the study doctor or study nurse. Remember that you can withdraw your child from the study at any time for any reason.

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