



Children and
Teenager Guide to

The **FIONA**
Study





WELCOME TO THE **FIONA** Study

This is a special book reserved for children and teens like you around the world. It explains the FIONA clinical study you have been invited to take part in. Your participation is voluntary. You will make your decision together with your parents.

If you want more information or are not sure about any part of the study, talk with the study doctor and ask as many questions as you need to.

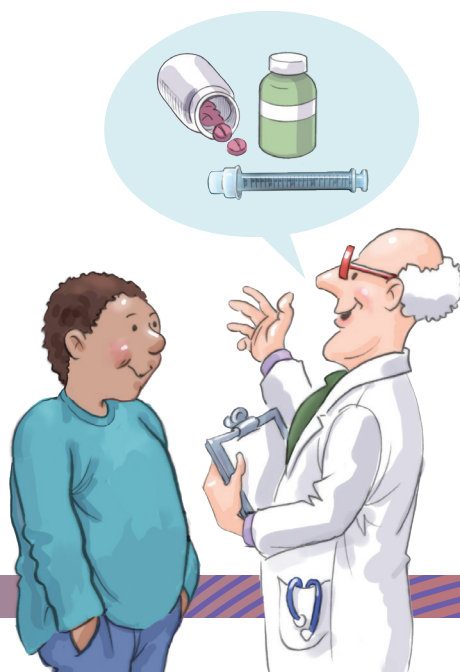
What is the FIONA Study?

The FIONA study is a clinical research study. The study sponsor (BAYER) and doctors want to learn how the study drug interacts with the body, and whether it is safe and effective in treating chronic kidney disease (CKD) of children and teens like you.



What is the study drug ?

The study drug is called finerenone. The goal of this study is to find out if it can be useful and safe for the treatment of CKD in children and teens.



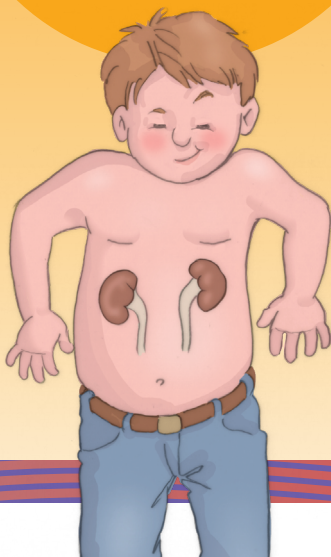
Hi, my name is **FIONA**

I am here to help guide you through this booklet explaining chronic kidney disease and the FIONA Study.



Why me?

You, and many other children and teenagers around the world, are invited to participate in this study because you have been diagnosed with CKD.



CKD is the short name for Chronic Kidney Disease

ABOUT THE STUDY

The purpose of this study is to look at how well the study drug works compared to a placebo (a placebo looks like the study drug but does not have any medicine in it), in children and teens with CKD, in addition to usual treatment. Other purposes of the FIONA study are to learn if the study drug is safe for children and teens and to look at how the study drug affects your body and how your body affects the drug.

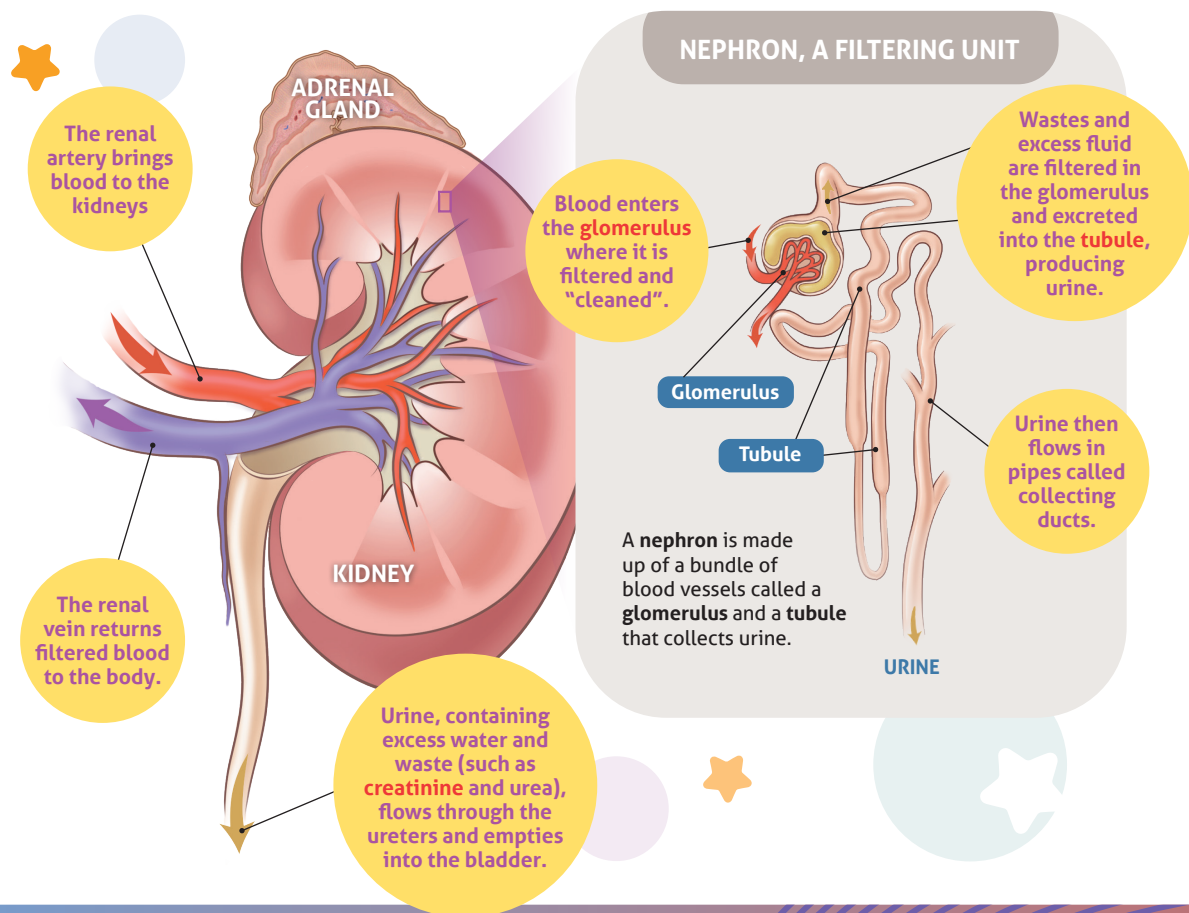
You will be asked to participate for up to 10 months. During that time, you will meet with the study doctor and staff about 10 times.

It is not known whether you will get any benefit from participating in this study. You will receive standard of care and additional doctor visits and assessments. What is certain is that the information collected in this study will help the study sponsor and doctors learn more about this study drug. This information may help future patients.

GET TO KNOW YOUR KIDNEYS

Each **kidney** has about a million small filtering units called **nephrons**. The kidneys clean the blood by filtering out waste (material that isn't needed) and extra fluid. Useful substances, such as proteins, remain in the blood. The **adrenal gland**, located on top of each kidney, produces a hormone, called **aldosterone**, that helps regulate blood pressure and other essential bodily functions.

Kidneys filter blood



Blood pressure is the force of circulating blood on the walls of the arteries.

The kidneys are two organs located behind the abdomen. One of the kidneys' most important jobs is to clean your blood.

Arteries are the vessels that carry oxygen-rich blood from the heart to the organs.

Did you know...

Nephrons in camels are longer than those found in whales' kidneys, even if the latter is a much larger animal! This is because a camel is a desert animal that needs to excrete little water with urine since water is rare in the desert habitat. Long nephrons help camels concentrate urine and save water.

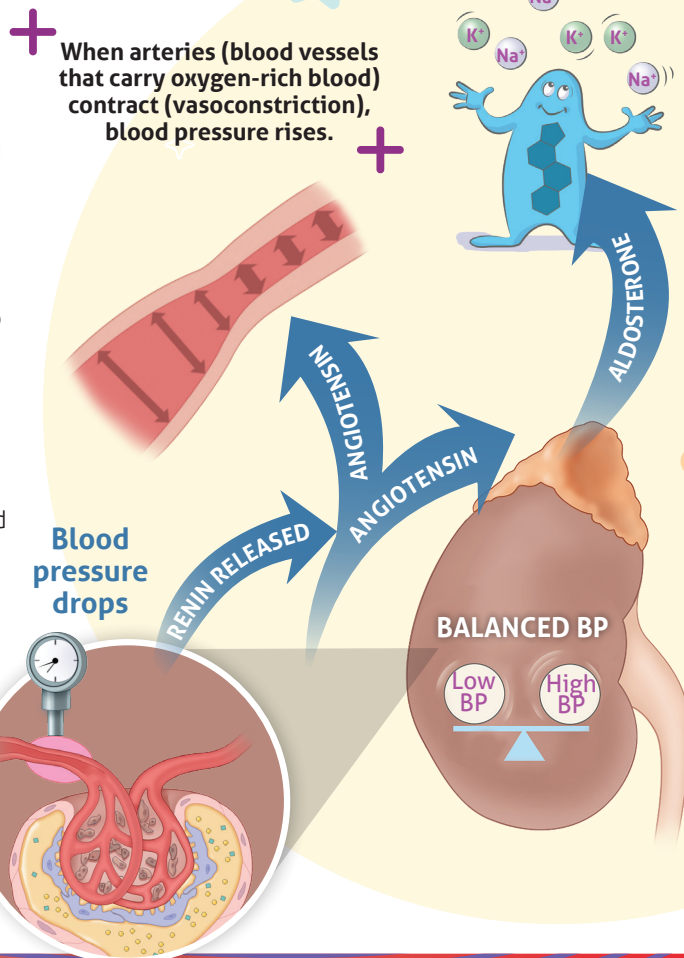
Kidneys regulate blood pressure

The kidneys help regulate:

- ✧ **blood pressure (BP)**
- ✧ **the amount of minerals (such as sodium and potassium) in the blood**
- ✧ **blood pH (acid-base balance)**

Kidneys are constantly balancing blood pressure to keep the correct flow of blood through its filters. A drop in pressure causes special "barometer" cells to release a chemical signal (renin). Renin triggers the production of angiotensin and of aldosterone, two chemicals that increase blood pressure:

- 1. Angiotensin** causes the arteries to contract so blood flows faster and blood pressure goes up.
- 2. Aldosterone** also raises blood pressure. It works by causing the kidneys to retain more water and sodium in the blood.



UNDERSTANDING CKD

Having CKD means your kidneys aren't working properly and waste may be building up in your body.

CKD starts when something harms the kidney and the damage cannot be repaired. Usually, it is the tiny blood vessels (glomeruli) in the kidneys that are damaged. The cause can be an infection, inflammation, high blood pressure, congenital anomaly or other conditions. CKD progresses over time as more and more glomeruli are affected.

Damaged glomeruli

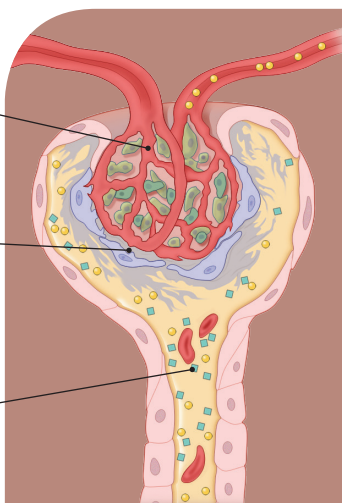
When kidneys are damaged, less blood may enter the glomeruli. The kidneys react to this by triggering the production of too much angiotensin and aldosterone. This causes an increase of blood pressure and, over time, inflammation and fibrosis (scarring). Inflammation and fibrosis damage the kidneys and create scar tissue that does not allow glomeruli to filter blood properly.

The formation of scar tissue inside the glomeruli, is called **glomerulosclerosis**.

Inflammation and stress occur in the glomeruli

Scar tissue develops (fibrosis)

Proteins are lost with urine, less waste is filtered



Protein loss

The injured glomeruli can't retain proteins in the blood. Proteins leak into the urine (**proteinuria**). Proteinuria can increase the damage. Over time, as more nephrons are damaged, kidneys begin failing to remove waste from the blood and start losing their ability in regulating the amount of water in the blood.

More proteins leak into urine



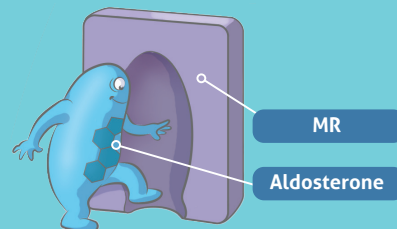
Legend

PROTEIN

WASTE

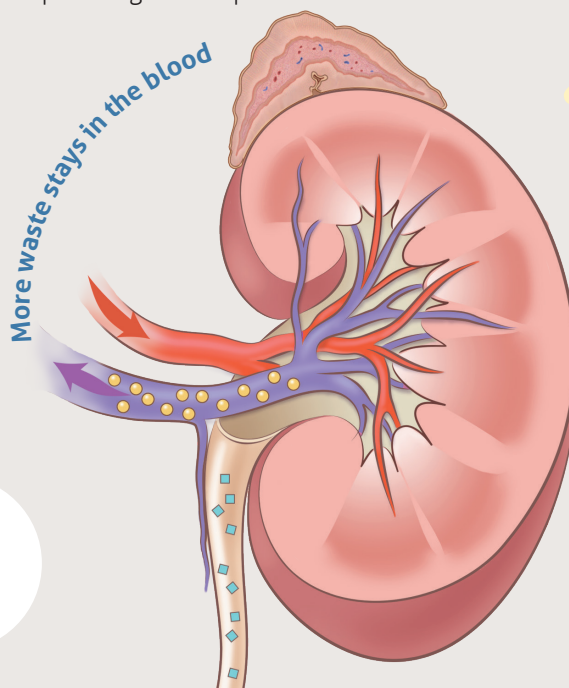
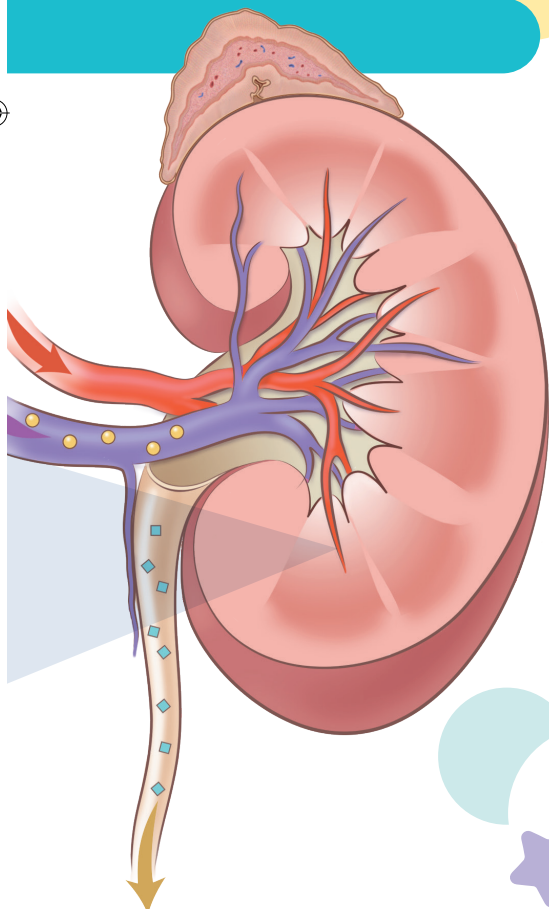
Did you know that the hormone aldosterone can worsen CKD?

In CKD, high levels of aldosterone can, over time, cause inflammation and scarring (fibrosis) in the kidney. Aldosterone can trigger this effect only if it connects with its receptor (called MR).



The kidneys begin to fail

The result, over time, is chronic kidney failure. CKD can worsen and even dialysis or a kidney transplant might be required.



EVALUATING HOW KIDNEYS ARE WORKING

To assess how your kidneys are working, the study doctor will use blood and urine tests. CKD is classified into 5 stages based on blood exam results. In the first stages, only a small part of the kidney is not working properly. As time goes by, kidneys' functions might worsen.

Stages of CKD

As kidney damage progresses, waste builds up in the blood instead of being removed through your urine. The amount of waste can be measured with a blood test. The doctor looks at the levels of a waste called creatinine, along with other factors such as age and gender to calculate the **glomerular filtration rate (GFR)**. The GFR number is a "score" for your kidney's performance. As kidney disease gets worse, the number goes down.

CKD is classified into five stages based on GFR.

STAGE	KIDNEY FUNCTION	GFR
1	Normal or high	≥ 90
2	Mildly decreased	60-89
3	Moderately decreased	30-59
4	Severely decreased	15-29
5	Kidney failure	<15

CKD stages and symptoms

Stage 1 is considered early CKD with normal or high GFR, while stage 2 is considered mild CKD. In these early stages, there may be no symptoms.

Starting from stage 3, some symptoms may occur more frequently such as:

- ☆ swelling
- ☆ feeling tired
- ☆ high blood pressure
- ☆ anemia (low red blood cell count)
- ☆ bone or joint pain (symptoms of a CKD complication called mineral bone disease)
- ☆ itchy skin

If you experience any one of these symptoms or if they get worse, tell your doctor.

You may also feel low or stressed because of CKD. Feel free to talk about it with your parents and/or with your study doctor.

The results of your blood and urine tests are precious to the FIONA scientists: these will help them understand if the study drug works in children and teens like you!

Your results will be pseudonymized (your name will be deleted and a code will be used to identify your data) and sent to the study sponsor's scientists. The scientists will gather and analyze your results together with those of every other child and teen enrolled in the FIONA study. This may help improve the future treatments of CKD in children and teens like you.

SEVERAL BLOOD TESTS

In the FIONA study several blood tests are planned to help ensure your safety and to check that the dose that the study participants, like you, receive is right. Frequent sampling called **PK (Pharmacokinetics)** blood samples enable scientists to see how the drug is absorbed and the way it moves within the body. PK sampling records the levels of drug in your blood plasma. Usually this must be done before you take the dose and afterwards, for comparison. This is common practice in drug research to ensure that the dose has the best working potential.

Message from the study team:

"We have taken extra efforts to keep the number of blood draws to the minimum and, at the same time, keep you as safe as possible."



URINE TESTS

Healthy kidneys keep proteins in the blood. One of the signs of kidney damage is the presence of proteins in urine (**proteinuria**). Urine tests also determine the concentration of protein in relation to the amount of creatinine, a waste eliminated by the kidneys (protein/creatinine ratio).

HOW IS CKD TREATED ?

Keeping blood pressure under control is central in delaying the progression of damage to your kidneys. High blood pressure is, in fact, both a cause of kidney damage and a consequence of it.

In addition to blood pressure lowering drugs, you may be advised to make some lifestyle changes, such as a healthy diet or physical exercise, that can help keep blood pressure under control.



Blood pressure drugs

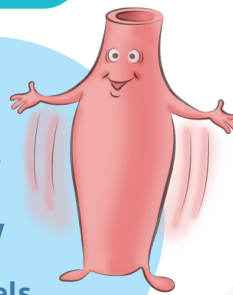
Even though high blood pressure is most common in adults, teens can have it too. To keep high blood pressure under control and prevent the negative effects of angiotensin, your doctor may already have or will prescribe one of the following types of drugs:

✧ **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.

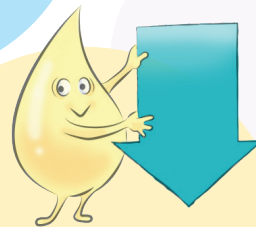
✧ **Angiotensin II receptor blockers (ARBs)** block the action of angiotensin allowing arteries to relax


You may also have to take a water pill (diuretic) and follow a low-salt diet to reduce water retention.

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



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





Did you know that alcohol and smoking damage kidneys?

Drinking alcohol and smoking may damage the kidney. Say no, if friends offer you alcohol or cigarettes!

Regular monitoring

Checking blood pressure regularly and keeping it at the correct level for your stage of CKD, is one of the most important treatments to slow down the progression of renal damage.

Depending on the stage of CKD, the optimal level of blood pressure may vary. Blood pressure goals in children and teens are different than those for adults and vary by age, height and gender.

Healthy Diet

Based on your condition, your doctor may recommend you follow a specific diet. In the first stages of CKD, a healthy diet may be beneficial in reducing the risk factors that may be damaging your kidneys. In more advanced stages, a specific diet, developed with the help of a dietitian, may be required. Follow your doctor's and dietitian's instructions on diet.

Drinking the correct amount of water is important to protect your kidneys. Check with the study doctor how much water you should drink each day.



WHAT WILL HAPPEN DURING THE STUDY

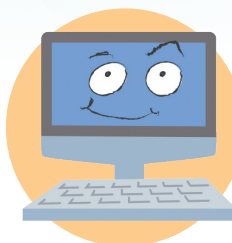
At each visit you will meet with the study staff to review your health, in addition to having exams and tests performed. This is done to help ensure your safety and to learn how the study drug is acting in your body, especially on your kidneys. There may be the option of having some of your visits done at home. Your study doctor can let you know if this is possible. Read more for details on the type of tests you may have completed during your study visits.

Run in and Screening

After your parents and you agree to take part in the FIONA study, the doctor will check if you are taking the best dose of blood pressure lowering drugs. If not, the best dosage will be prescribed and checked for up to 3 months. **This is called "run-in"** and is done to ensure you are taking the recommended treatment for high blood pressure, before starting the study. During the "run-in" your doctor will also examine your medical history, measure your vital signs, weight and height and perform some lab tests.

The study doctor will also verify if you are eligible for the study (**this is called screening**). During screening the study team will make sure that it is safe for you to begin treatment. You and your parents will be asked about your overall health, including medications you take and illnesses or diseases you have had in the past and at present. The study doctor will perform a routine physical examination, check your weight, height, heart rate, blood pressure and perform blood and urine tests. Screening can take up to 2 weeks.

Randomization



After screening, a computer will randomly decide if you will take the study drug or a placebo (a placebo looks like the study drug but does not have any medicine in it). The process the computer uses is similar to when you toss a coin.

You will not know if you are taking the study drug or the placebo. Your study doctor will give you a bottle with the study drug or placebo: you will have to take it once a day for 6 months. It will either be a tablet or an oral suspension (liquid) that you can take with water, milk or juice.

IF YOU ARE A FEMALE...

...and if you have had your first menstrual period your urine or blood will be tested once before your first dose of study drug and at visit 7 and 10, to make sure you are not pregnant. If you are of childbearing age and sexually active, you will be required to use a form of contraception during the entire study. Age-appropriate contraception will be discussed with your study doctor.



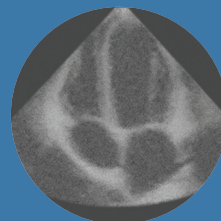
Did you know that ultrasound works in a way similar to a bat's orientation system?



Bats produce sound waves that travel through the air and bounce back off materials, such as trees and other animals.



Bats record the way the sound waves bounce back and mentally visualize their surroundings.



In a similar way, the heart ultrasound machine uses sound waves to create pictures of your heart.



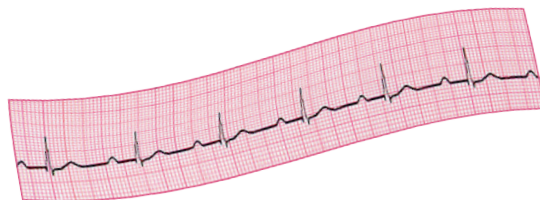
Study visits

At each visit, the study doctor will ask about your health and any medication that you've taken since the last visit. Your heart rate, blood pressure and temperature will be checked and you may have **blood samples** taken. **On some visits, you will also have to bring in morning urine samples.** Remember that you can ask your study doctor or nurse questions at any time. They will be happy to help you understand the clinical trial and procedures you are being asked to participate in.



Other tests

You should expect to have heart exams: an ECG (electrocardiogram) to check your heart's rhythm and a heart ultrasound to check your heart's shape and function. These exams are pain free. You will also be asked questions on the taste of the study drug and on your quality of life while attending the study.



Follow-up

Your study experience will end with a follow-up visit to check on your health. During this visit, blood and urine tests will be performed.



UNDERSTANDING THE STUDY DRUG

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



Are there side effects?

A common side effect, found in other studies, is the build up of potassium (K^+) 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 which may be life-threatening. The study doctor will take actions to lower this risk: he/she will check the amount of potassium in your blood regularly and will start with a lower dosage of the study drug.

If you participate in the study you will be asked to inform your parents and the study doctor about how you are feeling and about any expected or unexpected symptom or side effect you experience. Expected symptoms are: **unusual sleepiness, dizziness, confusion, tingling, numbness, diarrhea or constipation, nausea, vomiting, muscle weakness.**

There may also be other side effects that are not known yet.

Did you know that research on aldosterone started back in 1955?

In 1955, a scientist called Hans Selye described for the first time the role of aldosterone in fibrosis. Since then, research on how to block aldosterone has been ongoing. Scientists started studying the study drug in 2012. From 2015 to 2021 the study drug was tested in more than 10,000 adults with CKD and diabetes.



What is potassium?

Potassium is a mineral that the body needs to work properly. It helps your nerves to function and muscles to contract. Your heart uses potassium to function properly.

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. Aldosterone helps kidneys get rid of potassium. The study drug can, as some other drugs that act on kidneys, cause your kidneys to hold more potassium in the body.



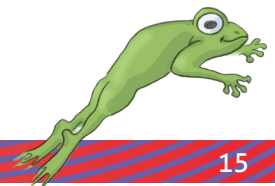
Is the study safe?

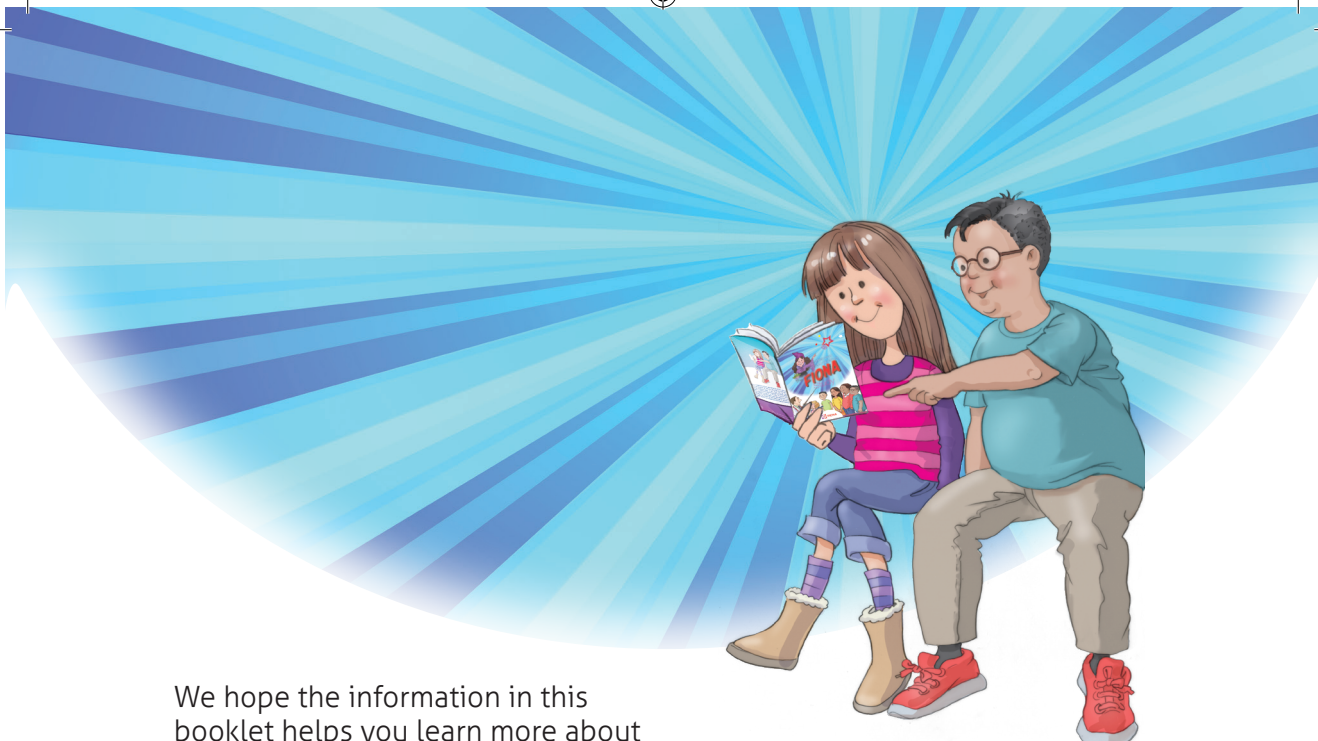
The FIONA study has been approved by Health Authorities/Independent Review Board.

A committee of independent doctors with expertise in children's and teen's kidney diseases and on the performance of clinical studies is reviewing, on an ongoing basis, all information regarding safety throughout the study. They will ask for changes or even stop the study if they have safety concerns.

Will I benefit from the study?

There is no certainty that you will benefit from this study. The information doctors will collect from your participation may help develop better treatments for children and teens like you, with CKD, in the future.





We hope the information in this booklet helps you learn more about the FIONA clinical study and about CKD. The study doctor and staff will also take time to review and explain things in more detail, including the chance of side effects with the study drug. You can ask questions at this time. It is important that you feel comfortable and understand what you are agreeing to participate in. Therefore, if you go home and think of more questions or need

clarifications about any of the information you have been told, you can always ask to talk with the study doctor/staff at any time. The study doctor and nurse are available and will be happy to answer all your questions.

Remember that, if you decide to participate, you can withdraw from the study at any time for any reason.

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



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