SUBJECT INFORMATION SHEET AND INFORMED CONSENT

Title: FGF23 and cardiovascular damage in anemia with an without chronic kidney disease.

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We are writing to inform you about a research study in which you are invited to take part. The study has been approved by the corresponding Clinical Research Ethics Committee. Before you decide whether or not you want to participate in this research study, you need to understand the possible risks and benefits of participating in this study. This process is known as "Informed Consent". The Research Ethics Committee of your Hospital has approved the information contained in this "Information Sheet for the Subject and Informed Consent" and has also approved that the study doctor can perform this study.

A Clinical Research Ethics Committee is an independent body made up of a group of independent people, both experts and non-specialists in the subject, in charge of ensuring the protection of the rights of the subjects who participate in research studies. This does not mean that the Clinical Research Ethics Committee has approved your participation in the study or that the study is risk-free. Our intention is only that you receive correct and sufficient information so that you can evaluate and judge whether or not you want to participate in this study. To do so, please read this fact sheet carefully. This document may contain words that you may not understand. Please ask your doctor or the study team to explain the meaning of any words or information that you do not understand clearly and they will clarify any doubts that may arise. An unsigned copy of this Informed Consent may be taken home with you for reflection or consultation with your family, friends, or others as you deem appropriate, before making a decision about your participation in the study.

If you decide to participate in this study, you will be asked to read, sign and date this Consent to confirm that you have been informed about the study and that you grant your permission to participate in all its conditions. You will be given a copy of the signed and dated form. Do not sign this document unless your study doctor or a member of the study team has answered your questions and you have decided that you want to participate in this study.

When reading this document, please note that the words “you” and “your” refer to the person participating in the study and not to representatives who can sign this document on behalf of the person participating in the study.

INTRODUCTION

You have been asked to participate in a research study in patients who suffer from iron deficiency anemia and who require treatment with it, in which we want to study its relationship with cardiovascular disease. Your participation in this study is not a substitute for your usual medical care.

Why is this study being done?

Patients with anemia have a higher risk of suffering from cardiovascular disease, our goal is to better understand this relationship to lay the foundations for the development of new drugs in the future.

What is the study about?

Approximately 401 patients with iron deficiency anemia (divided into two groups: patients with normal kidney function and patients with chronic kidney disease) will participate in this study.
Patients will receive the iron treatment prescribed by their doctor in consultation. We will analyze blood and urine samples before and after treatment. Please ask your study doctor or team any questions you have.

STUDY PROCEDURES

If you agree to participate in this study and sign this Consent, at each study visit, you will be asked about:

- any medicine you are taking or change in it,
- any problems you have,
- any side effects you may have, which may or may not be related to the study,
- if you have visited other doctors or hospitals.

After the explanation of the research project and the signing of the informed consent in the first screening visit, the patient's history will be evaluated, anthropometric measurements will be taken, and the existing biochemical data will be analyzed.
One to two weeks after the first visit, a new visit will be made in which blood will be drawn, the first morning urine collected, and hemodynamic parameters measured. From this moment on, the study and your treatment with the iron preparation prescribed by your doctor will begin.
Subsequently, another visit will be made at 3 months where blood samples (hematimetry and biochemistry), morning urine and hemodynamic parameters will be taken. Finishing the study.
Only in cases that have been treated with oral iron without obtaining a response and their doctor decides to treat them with IV iron, a third visit will be made 6 months after the first in which blood samples (hematimetry and biochemistry), morning urine and hemodynamic parameters will be recorded.
An attempt will be made as far as possible to match the blood draws of the study with those requested by your doctor, to avoid duplication.

The excess blood and urine samples from this study will be stored in the Biobank of the Reina Sofía University Hospital of Cordoba, and could be used later in other scientific studies. For this reason, you will receive an additional document in which you consent to the correct storage of the samples in the biobank.

What should I do for the duration of the study?

For reliable information to be obtained from this study, you are expected to do the following:

- Follow your study doctor's instructions.
- Attend all scheduled study visits and perform all procedures.
- Review all the medications you take with your study doctor. Certain medications that you are taking or have taken in the past may prevent you from participating in this study.

• Some procedures / illnesses that you have had in the past may prevent you from participating in this study.
• Do not share study medication with anyone. You are the only person authorized to take it.
• Keep the medication out of the reach and sight of children and people who are not able to read or understand all the information about it.
• Let the study staff know about any health problems you have, even if you don't think they are important.
• Let the study staff know if you want to stop taking part in this study.
• Do not participate in any other research study while you are in this study.

In an emergency, immediately call the Emergency Service in your area. If you require urgent medical assistance, be sure to tell the emergency room professional that you are participating in this study and contact your doctor or the study staff as soon as possible.
If you have any questions, concerns, or complaints regarding your participation in this study, your rights as a participant, or if at any time you believe that you have suffered a study-related injury or adverse effect, please contact the study physician whose phone number appears on the first page of this document.

What adverse (bad) effects can result from my inclusion in the study?

Risks of iron treatment
Participation in the study does not entail taking any additional treatment to the iron intake that your doctor has already prescribed. In any case, the possible adverse reactions and the contraindications, warnings and precautions are included in the Technical Data Sheet (FT) for iron preparations. The most common side effects are abdominal and epigastric pain, gastric hyperacidity, nausea, vomiting, diarrhea or constipation.
Regarding intravenous preparations, the most frequent are nausea, constipation, diarrhea, abdominal pain, increased transaminases, headache, dizziness, skin rashes, hypophosphatemia.
In any case, the study doctor will follow you closely to check for any adverse effects. It is important that you comment on any symptoms you have had right away. Your study doctor may give you other medicines to alleviate any possible side effects that are detected. If your doctor, or yourself, thinks that you cannot tolerate the side effects, you can stop taking the study treatment and terminate your participation in the study.
If you have questions about the symptoms of the adverse effects mentioned in this informed consent, ask the study doctor as well.

Risks related to blood draws
Blood sampling can cause pain, bleeding, infection, and bruising (blue or black marks) at the collection site. You may also feel faint. However, it is a technique used routinely with a very small number of adverse effects.

Unknown risks
You could suffer adverse effects or annoyances that are not mentioned in this consent. Some may not be known yet. Tell your doctor or study staff immediately if you experience any discomfort or unwanted effects.

IN CASE OF RESEARCH RELATED DAMAGES
The promoter of the study in compliance with Royal Decree 1090/2015, has contracted a liability insurance that covers the damages that may arise as a consequence of their participation in the study.

What BENEFITS will be obtained from this study?
The information obtained during this study may be scientifically relevant and therefore may be of use to other people who have the same disease in the future.

By participating in this study you will not directly obtain a greater benefit, the treatment for your disease if you do not participate in the study would be the same.

Do I have to reveal my identity?
The promoter guarantees the confidentiality of the data of the subjects and will ensure that the provisions of Organic Law 15/1999, of December 13, on the Protection of Personal Data and Royal Decree 1720/2007 are complied with at all times, of December 21, which approves the Regulations for the development of said law.

Data to be collected from you:
During this study, information regarding your health will be collected from your original Medical Record and all the data resulting from your participation in this research.
The information regarding your health may include the results of physical examinations, as well as any blood tests, X-rays, or other clinical tests that are performed.

How will my data appear?
The documents and information that may be collected from you during the study will not collect your name, your initials, or any other identifying information that allows the promoter to identify you.
The data collected for the study will be identified by a random code, so that only your study doctor and collaborators will be able to relate said data to you and to your medical history.

Why is this data collected ?
The information collected will only be used for clinical research. It can also be used in study reports or scientific presentations.
The documents and information that may be collected from you during the study will be handled in a strictly confidential manner, except for exceptions due to legal requirement, they will, in any case, be treated anonymously.
After this study is complete, it is possible that the data derived from the study, already coded, can be used for future research.

Who will have access to this data ?
Access to your personal information will be restricted to the study doctor and his collaborators, health authorities, the Research Ethics Committee who will be subject to the duty of secrecy inherent to their profession, when they need to check the data and procedures of the study, but always maintaining confidentiality according to the current legislation.

Rights over your data and the possibility of withdrawing your permission to use or disclose your data:
You will not be able to participate in this study unless you sign this Consent. In accordance with current regulations on data protection, all the data in your medical history as well as those resulting from your participation in the study are included in a personal data file under the responsibility of the Center.
You can exercise the rights of access, rectification, cancellation and opposition of data, for which you must go to the Center where the study is carried out: Reina Sofía University Hospital.
No data will be collected after you withdraw from the study. To ensure the validity of the results of this research and whenever your doctor considers it appropriate, we ask that if you wish to exercise your right to review the documents related to this research, you do so once your participation in this study has ended.

KNOWLEDGE OF YOUR PARTICIPATION BY THE FAMILY DOCTOR

If you decide to participate in this study, you must agree to the study doctor informing your family doctor of your participation in this study. This is necessary so that all doctors involved in your medical care are informed of all the treatments you are taking.

How is this study Funded?

This study has received funding from the Carlos III Health Institute for Health Research Projects (Health Research Projects modality), within the Strategic Action in Health, regulated by ISCIII Resolution of June 7, 2013-2016. Project code PI17 / 01010

VOLUNTARY PARTICIPATION AND WITHDRAWAL

You should know that your participation in this study is completely voluntary. You have the right not to participate in this study and if you decide to participate, you have the right to change your decision and withdraw your consent and suspend your participation at any time. In no case will your decision entail any damage or loss of benefits to which you are legitimately entitled in your health care, nor will the relationship with your doctor be altered.

Your study doctor may also terminate your participation in the study if they think it is in your best interest or if you will not be able to follow the study requirements.

Both the promoter and the study doctor may stop the study or their participation in it, always for a reasonable cause, in any of the cases contemplated in the protocol and current legislation, and without requiring their consent. In either case, you will receive an adequate explanation of the reason for your withdrawal from the study.

If for any reason you decide to discontinue your participation in the study, you will need to return all treatment provided for the study, including any unused and empty bottles, to the center. You will also be asked to return to the study center within 5 days of withdrawing your participation to perform the final visit procedures which may include a physical examination and / or laboratory tests.

INFORMED CONSENT

I have read and understood the Information Sheet that has been given to me and its content has been explained to me.

I have received enough information about the study to ask questions about it and have received satisfactory answers to my questions.

I understand that my participation is voluntary and that I can withdraw from the study at any time, without having to give explanations and without this affecting my medical care.

By signing this Consent, I consent to participate in this research project voluntarily and I authorize access to my personal data, as described in this Consent, without waiving any of the rights that correspond to me by law.

I agree that the blood or tissue samples obtained for the study may be used in the future for new analyzes related to the disease or study drugs not provided for in the current protocol (genetic analyzes being excluded, as long as they are not part of the study objectives):

☐ **Yes** ☐ **No**

_____

Subject name

_____ _____

Subject's signature Date

I certify that the aforementioned subject (and / or his representative if requested) has had sufficient time to consider the information about the study, may ask questions about it, and that he/she consents to participate in this research study voluntarily.

_____

Name of Physician Explaining Consent

_____ _____

Physician's signature explaining the Consent Date

LEGAL REPRESENTATIVE CONSENT

I have read and understood the Information Sheet that has been given to me and its content has been explained to me.
I have received enough information about the study, being able to ask questions about it myself and have received satisfactory answers to my questions.
By signing this Consent, I, as …… .. (relationship with the subject) and as representative of ……. …… … .. (subject's name), I agree that you participate in this study.
I understand that your participation is voluntary and that you can withdraw from the study at any time, without having to give explanations and without this having an impact on your medical care.

I assure that in my presence you have been given all the pertinent information adapted to your level of understanding and that you agree to participate.

I authorize access to your personal data, as described in this Consent, without waiving any of the rights that correspond to it by law.

I agree that their blood or tissue samples obtained for the study may be used in the future for new analyzes related to the disease or study drugs not provided for in the current protocol (genetic analyzes being excluded, as long as they are not part of the the objectives of the study):

☐ **Yes** ☐ **No**

I will receive a signed and dated copy of this Informed Consent.

I certify that I am the authorized legal representative of the aforementioned subject and that I am authorized to sign this Consent so that I can participate in the study.

_____

Name of the subject's representative

_____ _____

Subject's representative signature Date

I certify that the aforementioned subject (and/or his/her representative if requested) has had sufficient time to consider the information about the study, may ask questions about it, and that he/she consents to participate in this research study voluntarily.

_____

Physician's name explaining the Consent

_____ _____

Physician's signature explaining the Consent Date

INFORMED CONSENT BEFORE AN IMPARTIAL WITNESS

By signing this Consent, I declare under my responsibility that ……. ……. (subject's name), has freely expressed their consent to participate in this study.

You have read or have read and understood the Information Sheet that has been given to you and its content has been explained to you.

You have received enough information about the study to ask questions about it and have received satisfactory answers to your questions.

You understand that your participation is voluntary and that you can withdraw from the study at any time, without having to give explanations and without this having an impact on your medical care.

I assure that in my presence you have been given all the pertinent information and that you authorize access to your personal data, as described in this Consent, without waiving any of the rights that correspond to you by law.

You will receive a signed and dated copy of this Informed Consent.

He/she agrees that his blood or tissue samples obtained for the study may be used in the future for new analyzes related to the disease or study drugs not provided for in the current protocol (excluding genetic analyzes, as long as they are not part of the the objectives of the study):

☐ **Yes** ☐ **No**

The subject participating in the study has indicated that he/she is unable to read or that he/she has an impairment to write.

A member of the study team has read the Information and Consent Sheet to you or has read it directly and its content has been explained, and may ask questions about the study.

_____

Impartial witness name

_____ _____

Signature of the impartial witness* Date

* Impartial witness: Person independent of the research project who cannot be negatively influenced by the personnel involved in it, who is present during the informed consent process if the subject or the subject's representative cannot read or have a writing disability , being able to write and read the Informed Consent and any other information that is delivered in writing to the subject.