STUDY TITLE: A phase 3, randomized, controlled, multicentric, open-label clinical trial to prove the non-inferiority of fosfomycin vs meropenem in the targeted treatment of bacteraemic urinary tract infection UTI due to Escherichia coli producing extended-spectrum beta-lactamases (ESBLs).

SPONSOR CODE: FOREST

SPONSOR: Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla

INTRODUCCION

We are writing to you to inform you about a research study in which you are invited to participate. The study was approved by the Clinical Research Ethics Committee concerned and the Spanish Agency for Medicines and Health Products, according to the legislation, the Royal Decree 223/2004, for which clinical trials with medication are regulated.

Our intention is just that you receive the correct and sufficient information so you can evaluate and judge whether or not to participate in this study.

VOLUNTARY PARTICIPATION

The participation in this study will be completely voluntary and you will be able to retract your consent at any time without consequences for your future treatment and with any effect in your relation with your doctor or your level of care. Also, your doctor will have to option of retiring your participation if he believes this is advisable taken into account your clinical evolution, the conditions on which that can happen are described in the study.

GENERAL STUDY DESCRIPTION

The initial localization of the infection you are suffering is the urinary tract but the bacterium causing the infection has even reached the blood stream causing what is called a “bacteraemia”. The name of the bacteria which causes the infection is Escherichia coli which has the peculiarity of being resistant to many antibiotics commonly used to treat this type of infection, so doctors do not have many alternatives to use for treating them. Among the possible alternatives to treat this specific condition we have the two antibiotics used in this study meropenem and fosfomycin.

Although meropenem is the more commonly prescribed drug in recent years to treat these infections, fosfomycin is also approved by the Spanish Agency for Medicines and Health Products for this infection.

SCOPE OF THE STUDY

The main objective of the study is to demonstrate that intravenous fosfomycin is at least as effective as meropenem in the treatment of bacteremia of urinary origin caused by Extended-Spectrum beta-Lactamase-Producing *Escherichia coli* (ESBLs). Because resistance to meropenem is increasing, we would have an alternative treatment for future patients, helping to prevent the further increasing resistance to meropenem.

Both drugs have been commercialized from ages and the physicians are so used to its prescription and management, but no direct comparison have been performed to date to test that they are at least, equal in efficacy.

STUDY DESIGN

The participation of approximately 200 Spanish older men and women with the same infection that you are suffering are foreseen for this study.

This study is a clinical trial, which means the treatment you will receive will be chosen at random by a computer (something like flipping a coin).

You may receive one of the following treatments:

- Treatment in research: disodium fosfomycin, a dose of 4 g every 6 hours in a serum administered intravenously over 1 hour.

- Treatment Control: meropenem at doses of 1 g every 8 hours, serum administered intravenously for 15-30 minutes.

You will receive the assigned antibiotic intravenously for at least 5 days and after that and according to evolution, you will be advised to continue with oral treatment even at home. This practice differs from what is usual.

During the study, the study team will perform a series of visits. You will be closely followed during the first five days of treatment and at the end of antibiotic administration. After completing the treatment two visits of follow up are performed, one after 5-7 days and another two months after the finalization of antibiotics; if you have already been discharged, you will be asked to go to the hospital for these follow-up visits.

You will be asked to be taken samples of blood and / or urine repeatedly at baseline and some of subsequent visits: that blood will be taken to understand and control the evolution of the infection at study starting day, at 2 days, 5 days and at the end of treatment. You will also be taken urine samples at baseline, at 2 days, after 5 days of treatment and follow-up visits after treatment 5-7 days and 60 days. Similarly, at baseline or within 72 hours after inclusion, a renal ultrasound will be performed.

Also, if you receive fosfomycin, (your doctor will tell you if this part of the study is done at your hospital) several blood samples are taken (3 ml after one hour and after 2 and 4 hours after the initiation of the fosfomycin administration, and just before the next dose) at Visit 2 (Day 3) and with the intention to assess the levels of this antibiotic in blood.

We want to ask you if you agree with the withdrawal of blood samples for the level of antibiotics in the bloodstream study:

□ **YES I AGREE**
□ **I DO NOT AGREE**

Finally, in order to assess the impact that antibiotics may have in the normal bacterial flora, you will take a rectal swab (a cotton swab is inserted into the anus, rotated gently, and removed) with a swab (ball wrapped cotton gauze) at the time of inclusion in the study, the fifth day of treatment, and at the end thereof, or in an unscheduled follow-up visit if it is needed. Similarly, your doctor will tell you if this part of the study is done at your hospital.

We want to ask you if you agree with the performance of rectal swaps:

□ **YES I AGREE**
□ **I DO NOT AGREE**

BENEFITS OF YOUR PARTICIPATION IN THE STUDY

The infection that you have necessarily requires an antibiotic treatment. Since both antibiotics tested in this study are active against the bacterium that causes the infection, participation in the study ensures that you will receive an appropriate antibiotic to the infection; as well as close monitoring by study personnel.

Participating in a clinical trial is a voluntary and altruistic act because the data obtained with this study will be useful to other patients in the same situation in the future. In any case, you should know that whether you participate or no, it is possible that your participation in this study does not produce you a direct benefit.

Treatments and most of the tests performed in this study are part of routine care provided to patients with the same condition but not participating in the study.

POSSIBLE RISKS ARISING FROM YOUR PARTICIPATION IN THE STUDY

Drawing blood is sometimes associated with pain and bruising at the puncture site. Rarely dizziness or fainting may occur. Samples of urine (and rectal swabs) do not usually have any adverse effects on the patient. In any case, the research team will put all the diligence in his hand for matching the samples necessary for the study with those that would be made if you were not in the study.

There are sparse and minimal risks to the intravenous administration of drugs. It may cause mild pain at the puncture site, bruising, bleeding, dizziness and rarely infection.

In the case of participation of **women of childbearing potential**, a negative pregnancy test will be required for study inclusion.

Are there side effects associated with the antibiotics used in this study?

No medication is free of side effects. Those used in this study, despite being marketed for many years and be considered safer drugs in general, neither.

Adverse effects which rarely occur with fosfomycin are: allergic reactions affecting the skin and exceptionally the whole body (anaphylaxis), nausea, vomiting, diarrhea, liver disorders (transient increases in transaminases), increased blood sodium levels and fluid retention and swelling of the vein through which the drug is administered.

The most common side effects with meropenem are diarrhea, rash, nausea / vomiting, swelling at the injection site, increased platelet count and increased transaminases. A secondary objective of this study is to assess the safety of drugs, so you will be asked in each of the visits of the study if you have experienced any adverse event and will be evaluated for your continuation and care if it is the case.

What if my medication administered as part of the study does not work well?

Your health comes first for everyone involved in the study. If your infection worsens after 48-72 hours from the initiation of the study, your attending physicians and study personnel may change your treatment if this is necessary.

INSURANCE

The sponsor of this study has an insurance policy with the company HDI, with 130/002/001941 policy number, which conforms to the law and which will provide compensation and compensation for impairment of your health or injury which may occur in connection with your participation in the study.

CONFIDENTIALITY

The treatment, communication and transfer of personal data from all participating subjects shall comply with the provisions of Law 15/1999, of December 13 of Protection of Personal Data, and Royal Decree 1720 / 2007 of December 21, approving the Regulations implementing of this law. According to the provisions of that legislation, you may exercise the rights of access, rectification, opposition and cancellation of data, for which should be addressed to your study doctor.

The data collected for the study will be only identified by a single code and only your study doctor / partners have the codification in order to correlate these data with you and your clinical records. Therefore, your identity will not be disclosed to any person except exceptions, such as in case of medical emergencies or by legal requirement.

Access to your personal information is restricted to the study doctor / partners, health authorities (Spanish Agency for Medicines and Health Products), the Ethics Committee

for Clinical Research and persons authorized by the sponsor, when they need to check the data and study procedures, but always maintaining the confidentiality of such data in accordance with current legislation.

ECONOMIC COMPENSATION

The study sponsor is responsible for managing the financing thereof. For this study the sponsor has signed a contract with the facility on which this study is performed and the study doctor, which in this case will not receive any financial compensation.

Your participation in the study will not incur any extraordinary expenses and you will not have to pay for the study drugs.

OTHER RELEVANT INFORMATION

Any new information concerning the drugs used in the study which could affect your willingness to participate or continue in the study found during your participation, will be notified by your doctor as soon as possible.

If you decide to withdraw your consent to participate in this study, no new data will be added to the database and you can require the destruction of all previously retained identifiable samples to avoid the implementation of new analysis.

You should also know that you can be excluded from the study if the study investigators consider it is appropriate, either for safety reasons for any adverse event that can be related to the study medication or because they consider that you are not accomplishing with the procedures asked for the study. In either case, you will receive an adequate explanation of the reason that caused your withdrawal from the study.

By signing the attached consent, you agree to comply with study procedures which have been exposed to you. When your participation is finished you will receive the best treatment available your doctor considers the most appropriate for your condition.

The head of the studio in your hospital is Dr / Dr _____ (phone _____). He/she will be available for any question, or clarification you may need regarding your participation in the study. If you agree, please sign the attached consent. A copy of the signed informed consent is for you.

PATIENT INFORMED CONSENT

A phase 3, randomized, controlled, multicentric, open-label clinical trial to prove the non-inferiority of fosfomycin vs meropenem in the targeted treatment of bacteraemic urinary tract infection UTI due to Escherichia coli producing extended-spectrum beta-lactamases (ESBLs).

I, ...
(Name and Surname)

- I have read the Information leaf facilitated by the medical team

- I have had the opportunity to express my questions and doubts

- I have received sufficient information on the study

- I have spoken with……..

(Name of the researcher)

I understand that my participation is voluntary

I understand that I can retire of the study:

- When I want
- Without having to give explanations
- Without this affects in the medical cares

I freely give my conformity to participate in the study.

Signature of the person that gives his consent Date (dd/mm/yy)

Name of the person that gives his consent Date (dd/mm/yy)

Signature of the Investigator Date (dd/mm/yy)

Name of of the Investigator