NAME OF THE STUDY: Phase III randomized, multi-center, open-label, controlled clinical trial to demonstrate the non-inferiority of the narrow-spectrum directed antibiotic therapy versus a broad-spectrum antipseudomonal beta-lactam therapy in the treatment of patients with Enterobacter bacteremia.

SPONSOR´S CODE: SIMPLIFY

SPONSOR: Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla (FISEVI), "*Andalusian Public Foundation for the Management of Clinical Research of Seville*".

INTRODUCTION

Through this document we invite you to participate in a research study. The study has been approved by the Ethics Committee of Clinical Research of your hospital and the Spanish Agency of Pharmaceuticals and Health Products, according to the current legislation, Royal Decree 1090/2015, of December 4th, which regulates clinical trials with pharmaceuticals, the Ethics Committees of Research with Pharmaceuticals and the Spanish Registry of Clinical Trials.

WHY DO WE ASK FOR YOUR PARTICIPATION?

You must know that your participation in this study is voluntary and that you can decide not to participate or change your decision and terminate your participation whenever you want to, with no questions asked, and without that altering the relationship between you and your GP or jeopardizing your treatment in any way.

GENERAL DESCRIPTION OF THE STUDY

You have been diagnosed with bacteremia (an infection caused by a bacterium that reaches the bloodstream), which requires antibiotic treatment. The number of bacteria resistant to several antibiotics is increasing significantly. Thereby, there is a series of programs that aim to improve the way in which antibiotics are used, since that is directly related to the emergence of antibiotic resistances.

This study is absolutely not intended for testing the efficacy of new antibiotics.

PURPOSE OF THE STUDY

The main goal of the study is to demonstrate that the use of an antibiotic treatment, selected according to microbiological data (of the bacterium), in patients with Enterobacter bacteremia, is safe and efficient enough to meet the first standard of broad-spectrum antibiotics (i.e., an antibiotic capable of curing infections by many types of bacteria). This would improve the use of antibiotics, since we would use specific antibiotics for the isolated bacterium.

It is important to highlight that any of the treatment options you will receive if you participate in the study will be used in the standard-of-care, with a comparable efficacy in terms of experience gathered, although no other studies have done this before, which is why this trial was designed.

WHAT DO WE OFFER YOU?

This study is a clinical trial, which means that the treatment you will receive will be randomly selected by a computer; you will have the same probability to receive one of the two treatments (experimental or control) and we will compare the effects in both groups.

WHAT DOES THE TREATMENT CONSIST OF?

All the antibiotics included in the study are regularly used in patients with the same infection you suffer from. None of them is a new antibiotic and they will be used for the indications approved. You may receive one of the following treatment groups:

- Experimental group: following the criteria of your physician and according to the evolution of the disease, you may receive one of these antibiotics intravenously at the usual doses: ampicillin, trimethoprim/sulfamethoxazol, cefuroxime, cefotaxime, amoxicillin/clavulanic, ciprofloxacin, ertapenem.

It does not mean you will receive all of them, but you will be administered one of them in that order until your infection has been controlled.

- Control group: in this case you will continue to be administered the same antibiotic you are currently receiving (only one of them) at the usual dose: piperacillin/tazobactam, meropenem, imipenem, aztreonam, ceftazidime, cefepime.

In both cases, if your GP estimates that you suffer from a polymicrobial infection (caused by several bacteria), the previous antibiotic could be combined with one of the following: vancomycin, teicoplanin, daptomycin, linezolid, clindamycin or metronidazole.

The duration of the treatment will be the usual for the infection you suffer from (between 7 and 14 days).

After completing at least 5 days of intravenous treatment, your physician will decide whether it is possible to switch from intravenous (vein) to oral (mouth) medication.

During the study, the research staff will carry out a series of visits. The day the antibiotic treatment ends (if you are still in the hospital) and approximately one week after, a revision visit will be conducted. We will phone you to check how you feel, approximately 30 days after the antibiotic treatment started.

Then, after 60 days from the beginning of the treatment, you will have a new and final follow-up to see how you are feeling.

The number and type of analytical samples that we are going to collect are very similar to those of any patient with the same infection you are suffering from. At the beginning of the study and in some of the subsequent visits, we will take blood samples from you to evaluate how your infection is evolving.

In some centers, in order to assess the impact that the antibiotics could have on your intestinal flora, a rectal smear will be collected from you (a cotton swab is introduced in the anus, gently rotated and removed) at the moment you are included in the study, at the end-of-the-treatment visit, at the recovery-check visit, and at the 30th day visit. Agreeing to have a rectal smear performed is not required to be able to participate in the rest of the study. Your GP will tell you if this part of the study is carried out in your hospital.

We only ask you to indicate here if you agree to have a rectal smear collected from you:

I ACCEPT □

I DO NOT ACCEPT □

HOW CAN YOU BENEFIT FROM THIS?

If the hypothesis is proven correct, this trial will help improve the antibiotic treatment of patients who have the same type of infections that you have, which will prevent them from receiving antibiotic treatments with spectra broader than the essential range. You may not get any benefit for your health from participating in this study; however, the data obtained from it could be very helpful for future patients that may find themselves in your current condition.

WHAT ARE THE RISKS INVOLVED IN YOUR PARTICIPATION?

The treatments and the tests conducted in this study are part of the standard-of-care.

In the case of **participating women of childbearing age**, these must have a negative pregnancy test as a previous requirement to be included in the trial.

All the pharmaceuticals that will be used in this study have been approved by the Spanish Agency of Pharmaceuticals and Health Products, duly commercialized, and they are among the antibiotics that are used in the regular clinical practice.

Most of these antibiotics may present side effects of different severity. The adverse effects that you could suffer as a consequence of the administration of these

pharmaceuticals include the following: digestive discomfort, skin eruption, allergic reactions, muscular discomfort, blood and hepatobiliary alterations, kidney problems (including kidney failure), and neurological alterations. In any case, the risk of suffering from any of these adverse effects as a consequence of your participation in this study is not higher than the risk you would have if you received the regular treatment established for your disease. Moreover, all the side effects or undesired episodes that take place during the study will be monitored and followed up; therefore, we ask you to let the physicians of the study know if you find any discomfort or other new find.

In addition to these effects, blood draw and the intravenous administration of pharmaceuticals could cause pain or hematomas at the puncture site, among other things.

INSURANCE

The sponsor of this study has an insurance policy with Zurich Insurance PLC (insurance number: 00000084548718), which complies with the current legislation and will provide you with a compensation in case your health is impaired or if you suffer from lesions that could result from your participation in the study.

CONFIDENTIALITY

The treatment, communication and transfer of the personal data of all the participating subjects will comply with the Organic Law 15/1999, of December 13th, on personal data protection, and the Royal Decree 1720/2007, of December 21st, by which the development Regulation of such law is approved. According to what is established by the mentioned legislation, you have the right to access, modify, oppose and cancel data, for which you will have to refer to your study physician.

The data collected for the study will be identified through a code and only your study GP/collaborators will be able to relate such data with you and your medical history. Therefore, your identity will not be revealed to anybody, except in some cases, such as a medical emergency or legal requirement.

Access to your personal information will be limited to the study physician/collaborators, health authorities (Spanish Agency of Pharmaceuticals and Health Products), the Ethics Committee of Clinical Research and the staff authorized by the sponsor, when they need it to check the data and the procedures of the study, but always confidentially, complying with the current legislation.

The results of the study will be presented in scientific meetings, medical conferences and scientific publications; however, the identity of the participating patients will be kept strictly confidential.

FINANCIAL COMPENSATION

The sponsor is in charge of managing the funding of the study. For the realization of the study, the sponsor has signed a contract with the center in which it will be carried out and with the study physician, who in this case will not receive any financial compensation.

Your participation in the study will not incur any extraordinary cost for you for the pharmaceuticals used in the study.

OTHER RELEVANT INFORMATION

Any new information about the pharmaceuticals used in the study and other information that could affect your availability to participate in the study, which may be discovered during your participation, will be given to you by your GP as soon as possible.

If you decide to cancel your consent to participate in this study, no new data will be added to the database, and you can also request the destruction of all the identifiable samples, previously retained, to avoid the realization of new analyses.

You must also know that you may be excluded from the study if the sponsor and the researchers consider it appropriate to do so, either for safety reasons, any adverse event caused by the study medication or because they consider that you are not complying with the established procedures. In any of these cases, you will receive an appropriate explanation for the reason that caused your dismissal from the study.

By signing the attached consent form, you agree to comply with the study procedures that have been explained to you. When your participation in this study is over, you will receive the best treatment available, which will also be the one that your GP considers most appropriate for your disease.

QUESTIONS

If you have any questions related to the study or the disease, do not hesitate to tell your physician or his/her team. You can contact Dr._____ _____ through the following phone number: _____.

They will be willing to answer all your questions before, during and after the study.

INFORMED CONSENT OF THE PATIENT

Name of the study: Phase III randomized, multi-center, open-label, controlled clinical trial to demonstrate the non-inferiority of the narrow-spectrum directed antibiotic therapy versus a broad-spectrum antipseudomonal beta-lactam therapy in the treatment of patients with Enterobacter bacteremia.

I, _____

(Full name of the patient, hand written by him/herself, in capital letters)

- I have read and understood the information sheet about the study
- I was able to ask questions about the study and these were answered
- I spoke with (Name of the researcher) .....
- I understand that my participation is voluntary
- I understand that I can leave the study:
  - at any time
  - with no questions asked
  - without my decision affecting my medical care

I authorize the use of my personal data for the realization of this study, according to the information sheet.
I freely agree to participate in the study.

_____

Patient´s signature Date (dd/mm/yy)

_____

Patient´s name

_____

Researcher´s signature Date (dd/mm/yy)

_____

Researcher´s name

INFORMED CONSENT OF THE LEGAL REPRESENTATIVE OF THE CONSENTIMIENTO INFORMADO DEL REPRESENTANTE LEGAL

Name of the study: Phase III randomized, multi-center, open-label, controlled clinical trial to demonstrate the non-inferiority of the narrow-spectrum directed antibiotic therapy versus a broad-spectrum antipseudomonal beta-lactam therapy in the treatment of patients with Enterobacter bacteremia.

I (name and surname of the representative) _____,

as _____ (specify the relation with the patient) of _____

_____ (name of the patient).

DECLARE THAT:

☐ I have read the informative document attached to this consent form (the information sheet is for the patient) (please, keep a copy for yourself)

☐ I was able to ask questions about the study

☐ I received enough information about the study. I spoke with the informing health professional: (name of the researcher) _____

☐ I understand that participation is voluntary and that the patient can leave the study

- at any time
- with no questions asked
- without that affecting his/her future medical care

IN MY PRESENCE, (name of the patient) _____

was given all the pertinent information adapted to his/her level of understanding and he/she agrees to participate; thereby, I GIVE MY CONSENT for him/her to participate in the study.

_____

Legal/family representative´s signature Date (dd/mm/yy)

_____

Legal/family representative´s name

_____

Researcher´s signature Date (dd/mm/yy)

_____

Researcher´s name