INTRODUCTION

We are writing to inform you about a research study in which you are invited to participate. The study has been approved by the Committee for Clinical Trials with medicinal products and the Spanish Agency for Medicines and Health Products, in accordance with the current legislation, Royal Decree 1090/2015, of 4 December, which regulates clinical trials with medicinal products.

You can read about the medical examination in this patient information sheet. You can take as much time as you want to read the information and then decide whether you want to participate. To this end, please read this information sheet carefully and we will clarify any doubts you may have. In addition, you can consult with the people you consider appropriate.

VOLUNTARY PARTICIPATION

You are invited to participate in the study because you have been diagnosed with bacteraemia due to bacteria called Enterococcus faecalis/Enterococcus faecium. This means that a certain type of bacteria is causing an infection in an organ of your body and has managed to pass transiently into your blood. This situation is relatively common when infections such as pyelonephritis (kidney infections), bile duct infections or vascular catheter infections among others occur, and are associated with varying severity. When such infections occur, antibiotic treatment of the patient is necessary.

In these cases, experts recommend treatment between 7 and 14 days, but as you can see, this implies a great variability in the possible duration of treatment and there is no accurate data to indicate if a short treatment of 7 days with appropriate antibiotics will be better than a long treatment of 14 days. This study is designed to obtain data on the efficacy and safety of these two treatment options, and for this reason, we would like to ask you to participate in the study to participate in the study.

You should be aware that your participation in this study is voluntary, and that you may decide not to participate or to change your decision and withdraw your consent at any time, without altering the relationship with your doctor or altering your treatment in any way.
OBJECTIVE OF THE STUDY

This study aims to find out whether we can improve antibiotic treatment of enterococcal bacteraemia by optimising the duration of antibiotic treatment. Excessively prolonging the duration of treatment when the infection is already cured runs the risk of receiving antibiotics unnecessarily, exposing you to the adverse effects that these drugs have and the risk of developing infections by resistant bacteria. In this study, we will compare the efficacy and safety of antibiotic treatments given for 7 or 14 days.

To maintain the safety of this study, we will make sure that you are receiving an appropriate antibiotic treatment for the bacteria causing the infection, and we will perform any necessary diagnostic tests. You will also be closely monitored for up to 90 days after completion of treatment to confirm a favourable outcome.

GENERAL DESCRIPTION OF THE STUDY

This study will be conducted in 22 hospitals across Spain and requires the participation of 284 patients with your same diagnosis.

The study consists of two possible treatments with a fixed duration:

- In the first group (experimental group), antibiotic treatment shall be withdrawn after 7 days, demonstrate that signs of infection have disappeared, and the focus of infection is well controlled.

- In the other group (control group), antibiotic treatment will be withdrawn after 14 days, demonstrate that the signs of infection have disappeared, and the source of infection is well controlled.

The allocation by groups will be done by "random allocation", the probability of belonging to one group and the other is the same. It is like flipping a coin, the probability of heads is the same as the probability of tails, and the same is true for these groups. However, the doctor and you will always know which group you belong to.

If you decide to participate in this study, we will follow-up you for up to 90 days after the end of the assigned treatment. You will perform all the tests that are normally carried out while you are in hospital.

The study includes 4 visits, two of which may be by phone call:

- The first visit (visit 0) will be the day when you sign the informed consent form and you are enrolled in the trial. This visit will be 5-6 days after starting antibiotic treatment, and you will undergo a clinical interview, a physical examination, a pregnancy test (if you are a woman), and a blood sample will be drawn.

- The second visit is at the end of treatment (day 7 or 14 from the start of treatment, depending on the group you have been included in). At this visit, your doctor will review your clinical condition and the usual follow-up of this infection. This visit may be by phone call if you have already been discharged.

- The third visit will be face-to-face (30 days after the end of treatment), during which a blood sample will be taken, and a clinical interview and physical examination will be carried out.
- The last follow-up visit will be in person (90 days after the end of treatment), during which a blood sample will be taken, and a clinical interview and physical examination will take place. This visit may be by phone call if you have been discharged from the hospital.

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Visit 0 (Día 5-6)</th>
<th>End of treatment (Day 7 or 14)</th>
<th>Healing test (Day 30 after completion of treatment)</th>
<th>Follow-up visit (Day 90 after the end of treatment)</th>
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<tbody>
<tr>
<td>Informed consent</td>
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<tr>
<td>Pregnancy test</td>
<td>X</td>
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<td>Clinical interview</td>
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<td>Physical examination</td>
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<td>Analytics</td>
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**COLLECTION AND USE OF BIOLOGICAL SAMPLES**

Your participation in this clinical trial involves the collection and use of biological samples (blood, urine, samples from the source of infection) for research purposes, for which the Biomedical Research Act 14/2007 and Royal Decree 1716/2011 will be observed, regulations that guarantee respect for the rights you have. By signing this document, which has been reviewed and favourably evaluated by the Ethics Committee for Research involving medicinal products that has approved this clinical trial, you agree to the use of your samples for the purposes of this study.

The samples necessary for the study are part of those normally obtained during the course of this type of infection, and are obtained during the usual follow-up of your illness or process. We will also need you to send us a "culture" of each of these samples for specific complementary analysis of the study in a central laboratory located in the Microbiology Service of the Virgen Macarena University Hospital, Seville, for which we ask for your consent.

**BENEFITS AND RISKS OF PARTICIPATING IN THE STUDY**

If the hypothesis is met, this trial will serve to improve antibiotic treatment for patients like you who have these types of infections, preventing them from receiving prolonged and unnecessary antibiotic treatment, and thus suffering from adverse effects and infections by resistant bacteria. You may not gain any health benefit from participating in this study, but the data obtained may be useful for future patients in your situation.

All drugs to be used in this study are approved by the Spanish Agency of Medicines and Health Products, duly marketed, and are part of the antibiotics that are used in routine clinical practice. Due to the different diseases included in this study, depending on the type of patient, one or another antibiotic or a combination of several of the following drugs will be used: ampicillin, vancomycin, linezolid daptomycin, amoxicillin/clavulanic acid, piperacillin/tazobactam and amoxicillin.
Most of these antibiotics have side effects, some of which can be life-threatening. Side effects that you may experience as a result of taking these drugs include, but are not limited to: digestive upset, rash, allergic reactions, muscle discomfort, blood and liver problems, kidney problems (including kidney failure), and neurological problems. In any case, the risk of suffering any of these adverse effects due to participation in this study is no greater than if you were to receive the usual treatment established for your disease.

In addition, all side effects or undesirable episodes that occur during the study will be monitored and followed up, so we ask you to let the study doctors know if you encounter any discomfort or other new findings.

**ALTERNATIVE TREATMENTS**

Since this is a study in which the medication used is the usual medication, if you were not participating in the trial, the medications you would receive are the same as those offered to you in the study.

**PROCESSING OF PERSONAL DATA**

As of 25 May 2018, the new EU legislation on personal data, namely Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on Data Protection (GDPR), is fully applicable. It is therefore important that you are aware of the following information:

In addition to the rights you already know (access, modification, opposition and cancellation of data) you can now also limit the processing of data that is incorrect, request a copy or that the data you have provided for the study be transferred to a third party (portability). To exercise your rights, please contact the principal investigator of the study. We remind you that the data cannot be deleted, even if you stop participating in the trial in order to ensure the validity of the research and to comply with legal obligations and drug authorisation requirements. You also have the right to contact the Data Protection Agency if you are not satisfied.

Both the Centre and the Sponsor are respectively responsible for the processing of your data and undertake to comply with the data protection regulations in force. The data collected for the study will be identified by a code, so that no information that can identify you is included, and only your study doctor/collaborators will be able to relate this data to you and your medical history. Therefore, your identity will not be disclosed to any other person except to health authorities, when required or in cases of medical emergency. Research Ethics Committees, representatives of the Health Inspection Authority and personnel authorised by the Sponsor will only have access to verify personal data, clinical trial procedures and compliance with the standards of good clinical practice (while maintaining the confidentiality of the information).

The Investigator and the Sponsor are obliged to retain the data collected for the study for at least 25 years after completion of the study. Thereafter, your personal information will only be retained by the Facility for your health care and by the Sponsor for other scientific research purposes if you have given your consent to do so, and if permitted by applicable law and ethical requirements.
If we transfer your coded data outside the EU to our group entities, service providers or collaborating scientific researchers, the participant's data will be protected by safeguards such as contracts or other mechanisms by data protection authorities. If the participant would like to know more about this, please contact the principal investigator of the study or the Delegado de Protección de Datos de la Consejería de Salud de la Junta de Andalucía at Avenida de la Innovación, 5, 41020-Sevilla (dpd.csalud@juntadeandalucia.es).

INSURANCE POLICY

An application will be made to the ethics committee for consideration as a low-intervention clinical trial in accordance with the definition established in RD 1090/2015. In case of not being accepted The Andalusian Public Foundation for the Management of Health Research in Seville, FISEVI, will contract, in accordance with Spanish legislation, a civil liability insurance policy, in accordance with current legislation (RD 1090/2015, article 9). This policy will cover all possible damages that the subject may suffer as a result of the application of the product under study. This policy will be paid for and will be effective before the start of the clinical trial, if the trial is approved by the corresponding health authorities.

OTHER RELEVANT INFORMATION

Information about this study is publicly available at https://reec.aemps.es/reec/public/web.html according to Spanish law, and there will also be an international registry www.clinicaltrials.com.

Any new information regarding the drugs used in the study that may affect your willingness to participate in the study, which is discovered during your participation, will be communicated to you by your doctor as soon as possible.

You may leave the study at any time without explanation. If you decide to withdraw your consent to participate in this study, no new data will be added to the database, and you may require the destruction of all identifiable samples previously retained to prevent further analysis.

You should also be aware that you may be excluded from the study if the sponsor, principal investigator, health authorities or ethics committee deems it appropriate, either for safety reasons, because of any adverse event arising from the study medication or because they consider that you are not complying with the established procedures. In either case, you will receive an adequate explanation of the reason for your withdrawal from the study and you will continue to receive the necessary medical care.

By signing the attached consent form, you agree to comply with the study procedures outlined to you.

At the end of your participation you will receive the best available treatment that your doctor considers most appropriate for your condition.

QUESTIONS

If you have any doubts or questions regarding the study or the disease, please do not hesitate to tell the doctor or his team.
You may contact Dr. _______________________________ on the phone __________________________. They will be happy to answer all your questions before, during and after the study.

Reminder: A completed copy of this form, as well as an original of the informed consent form, must be given to the subject.
EudraCT 2021-003891-15

WRITTEN INFORMED CONSENT FORM

<table>
<thead>
<tr>
<th>TITLE OF THE STUDY</th>
<th>Randomised non-inferiority clinical trial to assess the efficacy and safety of short course treatment of uncomplicated enterococcal bacteraemia</th>
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I (participant's name and surname),

☐ I have read the information sheet I have been given about the study.
☐ I have been able to ask questions about the study.
☐ I have received sufficient information about the study.
☐ I have spoken to ...................................................................... (name of researcher)
☐ I understand that my participation is voluntary.
☐ I understand that I can withdraw from the study:
  - Whenever you want.
  - Without having to explain.
  - Without impacting on my medical care.

I will receive a signed and dated copy of this information and informed consent form. I agree to participate in this clinical trial and consent to the access and use of the data under the conditions detailed in this document.

Patient's signature
Date: ___ / ___ / ___
(Name, signature and date to be filled in by the participant)

Researcher's signature
Date: ___ / ___ / ___
**WRITTEN INFORMED CONSENT FORM OF THE LEGAL REPRESENTATIVE**

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I (name and surname of the representative),

................................................................................................................

As............................................................................................................. (specify patient relationship) from (participant's name and surname), ...........................................................................................................................

declare that:

☐ I have read the information sheet I have been given about the study.
☐ I have been able to ask questions about the study.
☐ I have received sufficient information about the study.
☐ I have spoken to ....................................................................................(name of researcher)
☐ I understand that my participation is voluntary.
☐ I understand that I can withdraw from the study:
  - whenever you want.
  - without having to explain.
  - without impacting on my medical care.

The patient will receive a signed and dated copy of this information and informed consent form.

In my presence, the patient has been given all information relevant to his/her level of understanding and agrees to participate, and I hereby consent to his/her participation in this clinical trial and consent to the access and use of the data under the conditions detailed in this document.

Signature of representative/legal guardian

Family member or de facto related person

Date: ___/___/___

(Name, signature and date to be filled in by the legal representative, family member or de facto related person)

Signature of researcher

Date: ___/___/___
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I (name and surname of witness),

as a witness, I affirm that in my presence Mr/Mrs (name and surname of participant) has been informed that and you have read the information sheet you have been given about the study, so that:

- He/She has been able to ask questions about the study.
- He/She has received enough information about the study.
- He/She has spoken to (researcher's name).
- He/She understands that his/her participation is voluntary.
- He/She understands that he/she can withdraw from the study:
  - When he/she wants.
  - Without having to explain.
  - Without impacting on his/her medical care.

The patient will receive a signed and dated copy of this information and informed consent form.

The patient freely agrees to participate in the clinical trial and consents to access and use of the data under the conditions detailed in this document.

Signature of the witness: ____________
Date: ___/___/___

Researcher's signature: ____________
Date: ___/___/___

(Name, signature and date to be filled in by the witness)

The study participant has indicated that he/she is unable to read/write.

The Patient Information Sheet document has been read to the patient by a study staff member, reviewed and discussed with the participant, and the participant has been given the opportunity to ask questions or consult with others.

The witness must be an impartial person, external to the study.