APPENDIX 2

INFORMATION SHEET

TITLE OF STUDY: A multicentre randomised study to assess the efficacy of daptomycin plus fosfomycin versus daptomycin monotherapy for treatment of methicillin-resistant *Staphylococcus aureus* bacteraemia in hospitalised patients

SPONSOR CODE: BACSARM

SPONSOR: Miquel Pujol i Rojo. Infectious Diseases Service. Tel: + 34 93 260 73 83.

STUDY COORDINATOR:

Miquel Pujol i Rojo. Infectious Diseases Service. Tel: + 34 93 260 73 83

CENTRE: Hospital Universitario de Bellvitge , Hospitalet de Llobregat (Barcelona)

INTRODUCTION

We are writing to you to give you some information about the research study in which you have been asked to take part. The study has been approved by the appropriate Clinical Research Ethics Committee and by the Spanish Medicines and Healthcare Products Regulatory Agency, in accordance with current legislation, Royal Decree 223/2004 of 6 February, which regulates clinical drug trials.

Our intention is that you receive correct and sufficient information to enable you to make an informed decision about whether you wish to participate in this study or not. Please read this information leaflet carefully and we will be happy to clarify any queries you may have after the explanation. You may also consult anyone you consider appropriate.

VOLUNTARY PARTICIPATION

You should know that your participation in this study is voluntary and that you can decide not to participate and you may also change your mind and withdraw your consent at any time, without it changing your relationship with your doctor or negatively affecting your medical treatment in any way.

GENERAL DESCRIPTION OF THE STUDY

The objective of the study is to show that a combination therapy of daptomycin + fosfomycin for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia, which is the medical condition that you have at present, provides better cure rates than treatment with daptomycin alone. If you have MRSA bacteraemia, it means that you have a microorganism circulating in your bloodstream that is able to attach itself to tissues throughout your body, so causing a serious infection that is difficult to treat.

Both daptomycin and fosfomycin are drugs that are already commercialized and routinely used in clinical practice.

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During this study, some patients will not only receive treatment with daptomycin (which is one of the authorized treatments for this type of infection) but will also receive another associated antibiotic, fosfomycin, since we think that these two antibiotics in combination will make it easier to treat the infection that you currently have.

The study has been designed so that both you and your usual doctor will know at all times which medication you are receiving. The duration of the treatment will be the same as that established in routine clinical practice (between 10 and up to 42 days, depending on the severity of the infection).

Whether you receive one treatment or the other (daptomycin alone or daptomycin + fosfomycin) will be determined randomly, a little like tossing a coin. You will have an equal chance of being placed in either of the two groups.

The medication will be administered intravenously in all cases and for the duration of the therapy.

MEDICAL VISITS:

If you agree to participate in this study, in addition to the visits made by your usual medical team, you will receive extra visits. There will be between four and nine of these extra visits, depending on whether you receive treatment for 2 weeks, or up to a maximum of 6 weeks (this will apply if you have a more severe form of the infection). In the course of these visits, the research team will ask you, among other things, whether you have diarrhoea or are experiencing muscle pains. There will also be a clinical evaluation, which will include checking for fever, taking your blood pressure and examining your skin, lungs, heart, and abdomen. The results of the blood tests (complete blood count, kidney and liver function and muscle enzymes), which your medical team will perform up to 3 days before or after the visit, will also be checked. If you do not have the results of these tests available, they will be requested for you. You will also be asked for blood samples at these visits to ensure that the microorganism that led to the infection has disappeared from your blood (these samples are called haemocultures).

In the event that you develop diarrhoea in the course of the study, your faeces will be tested for other possible infections.

During the study, no further analytical tests, other than those that are routinely carried out in the normal course of your medical condition will be made, unless some adverse effect is detected.

ADVERSE EFFECTS: The antibiotics used in this study are seldom associated with side effects. Those that have been described are generally mild to moderate in nature. **With respect to fosfomycin**, cases of hypokalaemia (a drop in potassium levels in the blood) have been described. This side effect will show up in the blood tests performed

throughout the study and can easily be remedied by administering the potassium via an intravenous (drip) solution or orally. Other side effects described for fosfomycin are: hypersensitive skin reactions such as rashes, a temporary increase in liver enzymes, nausea, vomiting, diarrhoea, and dyspepsia. In very rare cases, the signs and symptoms of bronchospasm, headache or visual disturbances have been reported. **With respect to daptomycin,** this drug has been associated in particular with inflammation of the muscles (an effect described by 2–8% of patients treated with this antibiotic). More often than not, the inflammation is asymptomatic, although you may possibly notice some muscle pain. If you do notice muscle pain while you are receiving treatment, you should tell the doctor in charge. Signs of inflammation will be detected in the routine blood tests carried out during the study. Other side effects described for daptomycin treatment are: anaemia, anxiety, insomnia, headaches, gastrointestinal pain, hot flushes, tachycardia, nausea, vomiting, diarrhoea, constipation, changes in liver enzymes, skin rash, and itching.

The least common but most serious reactions described for daptomycin include drug rash with eosinophilia, inflammation of the nerves in the legs (peripheral neuropathy), eosinophilic pneumonia, and rhabdomyolysis.

There is however little information about the adverse effects associated with the combination of daptomycin and fosfomycin, which may be the treatment you are allocated if you agree to participate in the study. In clinical experience involving the use of this combination, there have been no severe adverse effects. The adverse effects that have been described have generally been slight to moderate side effects associated with daptomycin.

The study investigators will monitor your progress during the study, so that if you develop any of these symptoms, speedy remedial action will be taken.

If you agree to participate in the study, you must tell the study investigator or collaborators of any discomfort that presents during the course of the study, or if there is any change in your medication.

If you agree to participate in the study, it is important for you to know that there are no available clinical data about toxic effects on pregnancies exposed to daptomycin, either alone or in combination with fosfomycin, so that both women and men of reproductive age should undertake to use a suitable contraceptive method and maintain it for the duration of the study and for six months after it has ended.

BENEFITS AND RISKS ARISING FROM YOUR PARTICIPATION IN THE STUDY

If you agree to participate in the study, you will be helping to answer the question of which of the treatments being compared is better and you will also be helping the

treatment of patients in the future. We are however unable to guarantee that you will obtain any benefit.

The combination of daptomycin + fosfomycin has been used in some cases of complicated MRSA bacteraemia affecting the heart valves and has shown greater cure rates. No significant adverse events deriving from this combination have been described.

ALTERNATIVE TREATMENTS

There are few alternative drugs to those used in this study (daptomycin alone or daptomycin in combination with fosfomycin) that are indicated for treatment of your medical condition. Vancomycin is the most commonly used treatment for MRSA bacteraemia, although its clinical response is not superior to the drugs used in the study; on the contrary, elderly patients who take it in particular often develop kidney failure in the course of their treatment. Other treatment alternatives are linezolid or teicoplanin, although there is less clinical experience of using these drugs to treat complicated MRSA bacteraemia compared to those previously mentioned.

In the event that you decide not to participate in this study, you will still be treated with therapies that are normally used for your medical condition, which includes daptomycin monotherapy.

Should you need further information about the study, please contact the principal investigator:

Dr _____Tel: _____

INSURANCE

The study sponsor has an insurance policy with Zurich Insurance PLC, Spanish Branch, policy number 70383054, which meets current legislation (RD 223/04 on clinical trials) and will provide you with compensation and indemnity should your health be affected or you suffer injuries related to your participation in the study.

CONFIDENTIALITY

The processing, communication and transfer of the data of all the participating subjects will be subject to the provisions of the Organic Law 15/1999 of 13 December on the Protection of Personal Data. In accordance with what is stipulated in the legislation mentioned, you can exercise your rights of access, rectification, opposition and cancellation of data, and to do this, you should consult your study doctor.

The data collected for the study will be identified by a code and only your study doctor and collaborators will be able to link those data with you and your clinical history.

Consequently, your identity will not be revealed to any other person, except in cases of medical emergency or if required to do so by law.

Access to your personal information will be restricted to the study doctor and collaborators, the health authorities (Spanish Medicines and Healthcare Products Regulatory Agency), the Clinical Research Ethics Committee, and personnel authorized by the sponsor when they need to check the data and procedures used in the study, but always maintaining the confidentiality of the said information in accordance with current legislation.

Only data collected for the study will be transmitted to third parties and other countries, and will not under any circumstances contain information that can identify anyone directly, such as first names, surnames, initials, address, social security number, and so on. Should there be transfer of data, it will be for the same purposes as described in the study and with the guarantee that the information is protected by at least the same degree of confidentiality as is offered by current legislation in our country.

OTHER IMPORTANT INFORMATION

Your study doctor will inform you immediately if any new information about the treatment drugs is discovered while the study is in progress, which might affect your willingness to continue taking part in it.

If you decide to withdraw your consent to participation in this study, no new data will be added to the database.

You should also know that you may be excluded from the study if the sponsor or study investigators consider it appropriate, whether for reasons of safety, or due to any adverse event occurring as a result of the study medication or because they consider that you are not complying with the established procedures. In any of these cases, you will receive a proper explanation for the reason that has led to your being withdrawn from the study.

You should also know that the sponsor may cancel the study at any time, whether for reasons of safety or for any other reason. In any case, you will receive a proper explanation for the reasons.

The study sponsor has entered into an agreement with the centre, although the research team will not receive any monetary compensation for participating in the study.

You should also know that neither the centre nor the principal investigator nor his team will receive remuneration as a result of the clinical trial.

By signing the attached consent form, you commit yourself to complying with the study procedures that have been explained to you.

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Once your participation is over, you will receive the best available treatment and the one that your doctor considers the most appropriate for your condition; however it is possible that he may not be able to continue administering the medication given during the study. In consequence, neither the investigator nor the sponsor makes any commitment to maintaining said treatment outside this study.

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INFORMED CONSENT

TITLE OF STUDY: A multicentre randomised study to assess the efficacy of daptomycin plus fosfomycin versus daptomycin monotherapy for treatment of methicillin-resistant *Staphylococcus aureus* bacteraemia in hospitalised patients.

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PRINCIPAL INVESTIGATOR OF THE CENTRE _____

I (name and surnames): _____

Have read the information sheet that was given to me.
Have had the opportunity to ask questions about the study.
Have received sufficient information about the study.

I have spoken to:
.....
(name of investigator)

I understand that my participation is voluntary.
I understand that I can withdraw from the study:

1. At any time
2. Without having to offer any explanation
3. Without it affecting the medical care given to me in any way

I freely consent to participate in this study and I give my permission for access to and use of my data in accordance with the conditions set out in the information sheet.

I give my consent for strains isolated in blood samples taken during this study to be used in other future analyses related to the medical condition or drugs used in this study that are not foreseen in the present protocol (the study does not include genetic analyses)

PARTICIPANT'S SIGNATURE *PRINCIPAL INVESTIGATOR'S SIGNATURE*

_____ _____
Print name of Participant *Print name of Principal Investigator*
DATE: *DATE:*

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INFORMED ORAL CONSENT BEFORE WITNESSES

TITLE OF STUDY: A multicentre randomised study to assess the efficacy of daptomycin plus fosfomycin versus daptomycin monotherapy for treatment of methicillin-resistant *Staphylococcus aureus* bacteraemia in hospitalised patients.

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PRINCIPAL INVESTIGATOR OF THE CENTRE:_____

I (name and surnames of the witness): _____
Hereby declare that (name and surnames of the patient):
_____

Has read the information sheet given to him/her, or that it has been read to him/her (if illiterate)
Has been given the opportunity to ask questions about the study
Has received sufficient information about the study

Has spoken to:
.....
(name of the investigator)

understands that his/her participation is voluntary
understands that he/she can withdraw from the study:

1 At any time
2 Without having to offer any explanation
3 Without it affecting in any way the medical care that he/she receives.

He/she freely agrees to participate in this study and gives his/her permission for his/her data to be accessed and used in accordance with the conditions set out in the information sheet.

He/she has given consent for strains isolated from his/her blood samples taken during this study to be used in other future analyses related to the medical condition or drugs used in this study not foreseen in the present protocol (the study does not include genetic analyses).

WITNES' SIGNATURE *PRINCIPAL INVESTIGATOR'S SIGNATURE*

_____ _____
Print name of witness *Print name of Principal Investigator*
DATE: *DATE:*

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INFORMED CONSENT OF THE LEGAL REPRESENTATIVE

TITLE OF STUDY: A multicentre randomised study to assess the efficacy of daptomycin plus fosfomycin versus daptomycin monotherapy for treatment of methicillin-resistant *Staphylococcus aureus* bacteraemia in hospitalised patients.

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PRINCIPAL INVESTIGATOR OF THE CENTRE:_____

I (name and surnames): _____

in my capacity as …….. (relationship to the patient) of ……

(name and surnames of the patient)

Have read the information sheet that was given to me
Have been given the opportunity to ask questions about the study
Have received sufficient information about the study
I have spoken to:
.....
(name of investigator)

I understand that the participation of the patient is voluntary
I understand that he/she can withdraw from the study

1. At any time
2. Without having to offer any explanation
3. Without it affecting in any way the medical care that he /she receives.

I agree to…….. (name of the patient) participating in the study and give my consent for his/her data to be accessed and used in accordance with the conditions set out in the information sheet.

I agree to strains isolated from blood samples obtained from …… (name of the patient) during this study being used in other future analyses related to the medical condition or drugs used in the study not foreseen in the present protocol (the study does not include genetic analyses).

PATIENT LEGAL REPRESENTATIVE *PRINCIPAL INVESTIGATOR*

_____ _____

Print name of patient's legal representative *Print name of Principal Investigator*
DATE: *DATE:*