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Daptomycin plus fosfomycin versus daptomycin monotherapy in treating MRSA: protocol of a multicentre, randomised, phase III trial

E Shaw,[1] J M Miró,[2] M Puig-Asensio,[3] C Pigrau,[3] F Barcenilla,[4] J Murillas,[5] G Garcia-Pardo,[6] E Espejo,[7] B Padilla,[8] A Garcia-Reyne,[9] J Pasquau,[10] J Rodriguez-Baño,[11] J López-Contreras,[12] M Montero,[13] C de la Calle,[2] V Pintado,[14] E Calbo,[15] O Gasch,[16] M Montejo,[17] M Salavert,[18] M J Garcia-Pais,[19] J Carratalà,[1] M Pujol,[1] on behalf of the Spanish Network for Research in Infectious Diseases (REIPI RD12/0015), Instituto de Salud Carlos III, Madrid, Spain, and GEIH (Hospital Infection Study Group)

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For numbered affiliations see end of article.

Correspondence to
Dr Evelyn Shaw;
eshawp@gmail.com

ABSTRACT

Introduction: Despite the availability of new antibiotics such as daptomycin, methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia continues to be associated with high clinical failure rates. Combination therapy has been proposed as an alternative to improve outcomes but there is a lack of clinical studies. The study aims to demonstrate that combination of daptomycin plus fosfomycin achieves higher clinical success rates in the treatment of MRSA bacteraemia than daptomycin alone.

Methods and analysis: A multicentre open-label, randomised phase III study. Adult patients hospitalised with MRSA bacteraemia will be randomly assigned (1:1) to group 1: daptomycin 10 mg/kg/24 h intravenous; or group 2: daptomycin 10 mg/kg/24 h intravenous plus fosfomycin 2 gr/6 g intravenous. The main outcome will be treatment response at week 6 after stopping therapy (test-of-cure (TOC) visit). This is a composite variable with two values: Treatment success: resolution of clinical signs and symptoms (clinical success) and negative blood cultures (microbiological success) at the TOC visit. Treatment failure: if any of the following conditions apply: (1) lack of clinical improvement at 72 h or more after starting therapy; (2) persistent bacteraemia (positive blood cultures on day 7); (3) therapy is discontinued early due to adverse effects or for some other reason based on clinical judgement; (4) relapse of MRSA bacteraemia before the TOC visit; (5) death for any reason before the TOC visit. Assuming a 60% cure rate with daptomycin and a 20% difference in cure rates between the two groups, 103 patients will be needed for each group (α:0.05, ß: 0.2). Statistical analysis will be based on intention to treat, as well as per protocol and safety analysis.

Ethics and dissemination: The protocol was approved by the Spanish Medicines and Healthcare Products Regulatory Agency (AEMPS). The sponsor commits itself to publishing the data in first quartile peer-review journals within 12 months of the completion of the study.

Trial registration number: NCT01898338.

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia is of concern to healthcare systems worldwide because of its high incidence rates and poor outcomes. Mortality rates range between 20% and 30%, which are higher than those associated with methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteraemia.[1] During the past decade, several epidemiological changes have been observed among patients with MRSA bacteraemia, such as an upward trend in patient age, more severe comorbidities, non-nosocomial healthcare acquisition and a non-intravascular catheter source.[2] These factors may be contributing to the high-mortality rate. In addition, one recent multicentre observational study in 21 Spanish hospitals, which focused on MRSA bacteraemia and included almost 600 episodes, found a mortality rate in excess of 30%, regardless of the type of antibiotic treatment administered.[3]

Vancomycin is still considered to be the standard treatment for MRSA bacteraemia, despite its association with poor patient outcomes such as persistent bacteraemia, treatment failure and nephrotoxicity.[4] The higher mortality rates associated with MRSA as compared with MSSA bacteraemia have been attributed to differences in host conditions, microbial pathogenicity and especially to the

inferior antistaphylococcal killing effect of glycopeptides when compared with β-lactam antibiotics.[5]

The approval of daptomycin for treating MRSA bacteraemia and right-sided endocarditis has expanded the therapeutic options for treating MRSA bacteraemia. Daptomycin is a cyclic lipopeptide antibiotic with clinical efficacy at least as effective as that of vancomycin for treating MRSA bacteraemia,[6] and at the same time it offers significant advantages over the latter, such as a more rapid bactericidal effect and less nephrotoxicity.[4] Daptomycin exhibits concentration-dependent bactericidal killing activity and is generally safe and well tolerated at higher doses,[7] although mortality rates, particularly in patients with persistent or complicated bacteraemia, have not declined significantly.[3] In one multicentre randomised clinical trial that compared daptomycin 6 mg/kg/d with vancomycin plus gentamicin for the treatment of MRSA bacteraemia or right-sided endocarditis, the success rate among patients treated with daptomycin was 44%, compared to 32% in the vancomycin–gentamicin group.[8]

There are increasingly favourable opinions concerning the use of high-dose daptomycin, although no randomised studies have been performed to support this change. Based on expert opinion, current Infectious Diseases Society of America (IDSA) clinical practice guidelines recommend higher doses of daptomycin (8–10 mg/kg/d) for the treatment of MRSA bacteraemia or infective endocarditis. The Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) also recommends high-dose daptomycin (10 mg/kg/d) for treating left-sided infective endocarditis.[9 10] At present, a daptomycin dosage of 8 mg/kg/day or more is safe for patients with complicated MRSA infections.[11]

Failures of therapy with daptomycin due to persistent or relapsing infection have been reported, especially in complicated bacteraemia, and in some of these cases an increase in daptomycin minimum inhibitory concentration (MIC) was also observed.[6] Recent in vitro data suggest that combination therapies might be an alternative to achieve better outcomes.[12 13] Among them, daptomycin in combination with rifampin or gentamicin has not been associated with a better response in the experimental model of endocarditis,[14 15] while daptomycin plus antistaphylococcal β-lactams, nafcillin or cloxacillin was effective for treating patients with refractory MRSA bacteraemia. The in vitro study showed that β-lactams enhanced daptomycin bactericidal activity by means of a reduction in membrane surface charges.[16]

Fosfomycin is a phosphonic acid derivative that exhibits bactericidal antimicrobial activity by binding to and subsequently inhibiting uridine diphosphate (UDP)-N-acetylglucosamine enolpyruvyl transferase, an enzyme involved in early-stage peptidoglycan synthesis. This unique mechanism of action of fosfomycin makes cross-resistance to other antibiotics highly unusual; furthermore, fosfomycin retains activity against the majority of MRSA strains.[17] However, it cannot be used alone because of the rapid development of resistance.

There is limited experience of in vitro synergistic activity of fosfomycin in combination with β-lactams, although it has been observed.[18] In vitro and in vivo synergy have also been observed between daptomycin and fosfomycin in an MRSA experimental endocarditis model,[19 20] and the combination of daptomycin plus fosfomycin was at least as active as daptomycin plus cloxacillin in the same MRSA experimental endocarditis model.[20] Indeed, some clinical cases of MRSA bacteraemia/endocarditis have been successfully treated with the combination of daptomycin plus fosfomycin.[19 21]

In spite of these encouraging data, there is no controlled clinical study comparing the efficacy and safety of daptomycin plus fosfomycin versus daptomycin alone.

Rationale

Despite the availability of new antibiotics such as daptomycin, MRSA bacteraemia continues to be associated with high clinical failure rates and poor outcomes. Recent data suggest that combination therapies might be an alternative to achieve better outcomes.[12 13] Fosfomycin and daptomycin have recently been associated with good clinical response.[19 21] We hypothesize that fosfomycin plus daptomycin will obtain higher clinical response than a therapy with daptomycin alone.

Investigators chose daptomycin as a comparator instead of vancomycin, which is still the standard therapy, because in the last decades MRSA bacteraemia affects elderly patients with more severe comorbidities[2] who have higher risk to renal impairment. In addition, vancomycin has been associated with poorer outcomes in bacteraemia with MRSA with elevated vancomycin MICs.[22 23] MRSA strains with vancomycin MIC ≥2 μg/mL have risen from 5.6% in 2004 to 11.1% in 2009, especially in some countries.[24]

Primary objective

To demonstrate that high-dose daptomycin combined with fosfomycin achieves a better response than therapy with high-dose daptomycin alone, measured in terms of clinical success plus microbiological success (treatment success) at week 6 after end of therapy (test-of-cure visit, TOC).

Secondary objectives

Clinical secondary objectives

1. To compare the clinical success of daptomycin plus fosfomycin versus daptomycin alone at end of therapy (EOT).
2. To evaluate the safety of the daptomycin plus fosfomycin combination compared with daptomycin alone.
3. To evaluate overall mortality between the two treatment arms, daptomycin plus fosfomycin versus daptomycin alone, at EOT and at week 6 after TOC.

Microbiological secondary objectives

1. To determine the frequency of persistent and relapsing bacteraemia between the two treatment arms.

2. To determine the emergence of daptomycin-resistant strains during therapy in the two treatment arms.
3. To determine the emergence of fosfomycin-resistant strains in the arm with fosfomycin treatment.

METHODS AND ANALYSIS

Study design

A multicentre, open-label, randomised, phase 3, interventional clinical trial stratified by centre with parallel allocation (1:1). The trial has a superiority design.

Study population

Patients with complicated or uncomplicated MRSA bacteraemia hospitalised in participating hospitals.

Inclusion criteria

1. Patients must be ≥18 years old
2. Must have at least one blood culture positive for MRSA in the 72 h up to randomisation
3. Written informed consent
4. Mandatory use of contraception methods for fertile participants during the study period and for 6 months after stopping antibiotic therapy.

Exclusion criteria

1. Polymicrobial bacteraemia(more than one microorganism in blood cultures)
2. Participants with pneumonia
3. Severe clinical status with expected survival of less than 24 h
4. Allergic to daptomycin or fosfomycin
5. A positive pregnancy test at the time of inclusion
6. Any clinical condition that requires additional antibiotic therapy with microbiological activity against MRSA (specific forbidden antibiotics are named in page 10, section: drugs accepted during the trial)
7. Patient is already included in another clinical trial
8. Severe liver disease (Child-Pugh score class C)
9. Prior history of eosinophilic pneumonia

Note: ≤72 h of active antibiotic therapy for MRSA bacteraemia will not be considered a criterion for exclusion

Setting

Patients will be recruited among different academic hospitals of Spain located in Barcelona; Madrid; Seville; Granada; Mallorca; Tarragona; Lleida; Barakaldo, Valencia and Lugo.

List of study sites: Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Barcelona; Hospital Universitari Clínic de Barcelona; Hospital Universitari Santa Creu i Sant Pau, Barcelona; Hospital Universitari Vall d'Hebron, Barcelona; Hospital Universitari Parc de Salut Mar, Barcelona; Hospital Universitari Joan XXIII, Tarragona; Hospital Universitari Arnau de Vilanova, Lleida; Hospital Universitari Mutúa de Terrassa, Barcelona; Hospital de Terrassa, Terrassa, Barcelona, Corporació Sanitaria Parc Taulí, Sabadell, Barcelona; Hospital Universitario Gregorio Marañón, Madrid, Hospital Universitario 12 de Octubre, Madrid; Hospital Universitario Ramón y Cajal, Madrid; Hospital Universitario Virgen Macarena, Sevilla; Hospital Universitario Virgen de las Nieves, Granada; Hospital Universitario de Cruces, Barakaldo; Hospital Universitari i Politècnic la Fe, Valencia; Hospital Universitari Son Espases, Mallorca; Hospital Universitario Lucus Augusti, Lugo.

Recruitment of patients

Patients will be identified at each participating hospital by checking daily for all blood cultures positive for MRSA. Microbiologists will alert trial researchers to assess for recruitment. Patients fulfilling all inclusion criteria and none of the exclusion criteria will be assigned in a randomised fashion to one of the treatment arms.

Randomisation and allocation concealment

A centralised electronic computer system will generate random lists based on randomly permuted blocks. Allocation sequences will be concealed by the system. The programme will randomly assign participants on a 1:1 basis to two parallel groups in two treatment arms, stratified by centre; 24 h web-based randomisation will be provided.

Intervention

Patients will be randomly assigned to one of the following arms:

1. Arm 1: Daptomycin 10 mg/kg intravenous, q/24 h
2. Arm 2: Daptomycin 10 mg/kg intravenous, q/24 h plus fosfomycin 2 gr/6 h intravenous

Note: No more than 24 h must elapse between randomisation and start of therapy.

Treatment of patients

Patients will receive the standard care of treatment for MRSA bacteraemia from the attending physician and study investigators will carry out extra scheduled visits.

Prescription of therapy

Daptomycin: 10 mg/kg, by intravenous infusion over a period of 30 min, once a day. The recommended dosage regimen for patients with creatinine clearance (CrCl) <30 mL/min, including patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD), will be 10 mg/kg once every 48 h.[25]

Note: Whenever possible on haemodialysis days, daptomycin will be administered following completion of haemodialysis.

Fosfomycin: 2 gr, by intravenous infusion over a period of 2 h, every 6 h a day. If there is renal impairment, the dose should remain constant (2 gr), with the interval between administrations varying according to creatinine clearance.[26] (table 1).

Duration of therapy

Duration of therapy will be 10–14 days for uncomplicated bacteraemia and 28 days and up to 42 days for

Table 1 Prescription of therapy

Creatinine clearance	Doses
40–20 mL/min	2 g every 12 h
20–10 mL/min	2 g every 24 h
≤10 mL/min	2 g every 48 h
Dialysis	2 gr following haemodialysis session

complicated bacteraemia. Cases of complicated bacteraemia considered by the PI to need 42-day therapy should be discussed previously with the sponsor.

Drugs accepted during the trial

Concomitant use of any kind of drug is accepted during the patient's participation in the clinical trial, except for antibiotics with activity against MRSA (rifampin, clindamycin, trimethoprim-sulfamethoxazole, doxycycline, gentamicin, linezolid, tigecycline and β-lactam antibiotics with proven in vitro activity against MRSA in combination with daptomycin as meropenem, piperacillin-tazobactam, cloxacillin, ampicillin or cefepime).

In addition, temporary suspension of agents associated with rhabdomyolysis, such as 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, should be considered for patients receiving daptomycin.

Definitions

Complicated bacteraemia: will be defined as patients with MRSA in at least one blood culture with evidence of spread of infection (metastatic infection), suspected endocarditis, infection involving a foreign material that cannot be removed in less than 4 days, or persistence of a positive blood culture at 72–96 h from start of antimicrobial therapy.

Uncomplicated bacteraemia: will be defined as patients with MRSA in at least one blood culture with exclusion of endocarditis and no evidence of haematogenous spread of infection at follow-up, plus negative results for blood culture at 72–96 h from start of antimicrobial therapy.

Participant timeline

All participants will be followed up by the study team for 6 weeks after stopping the study therapy. To assess outcome, all patients will be visited on day 3, day 7 (only if blood cultures at day 3 remain positive), weekly until the EOT (EOT: at days 10–14, day 28 or day 42), then a visit 6 weeks after stopping therapy (TOC). All data will be recorded on electronic eCRF (see figure 1; online supplementary appendix 1 shows the clinical trial assessment).

OUTCOMES

Primary end point

Treatment response at the TOC visit. This is a composite variable with two values.

Treatment success will be defined as the resolution of all clinical signs and symptoms (clinical success) plus negative blood culture (microbiological success) at the TOC visit.

Treatment failure will be defined as any of the following situations: (1) lack of clinical improvement at 72 h or more after the start of therapy; (2) persistent bacteraemia (positive blood culture on day 7 after the start of therapy); (3) premature discontinuation of therapy due to adverse effects or for any other reason based on clinical judgement; (4) relapsing MRSA bacteraemia before the TOC visit; (e) death for any reason before the TOC visit.

Secondary end point

- Treatment success at EOT visit (clinical success + microbiological success)
- Mortality at EOT and the TOC visit
- Severe adverse effects

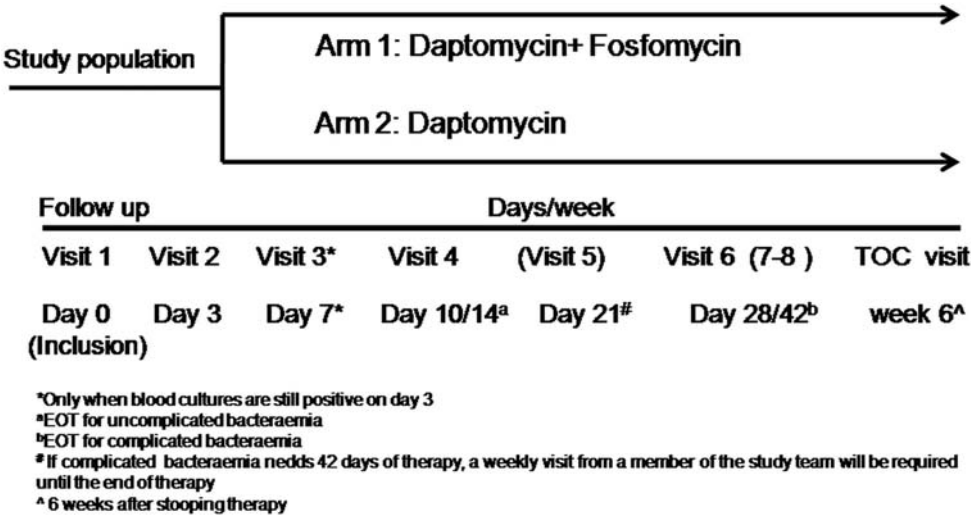

Figure 1 Participant timeline.

- Persistent MRSA bacteraemia
- Recurrence of MRSA bacteraemia (positive blood culture when previous ones were negative)
- Emergence of daptomycin resistance
- Emergence of fosfomycin resistance
- Days until negative results of blood culture
- Days to death
- Days to treatment failure

Note: Eucast Clinical break points have been considered to define daptomycin and fosfomycin susceptibility that were above 1 and 32 mg/L, respectively.

Criteria for withdrawing a patient from the study

Patients must be withdrawn from the study in any of the following situations:

- The criteria for clinical failure are fulfilled at 72 h after start of therapy (worsening of sepsis signs or symptoms).
- The criteria for treatment failure are fulfilled (positive MRSA blood culture on day 7 after start of therapy).
- The patient asks to be withdrawn from the study (at any time during the patient's participation in the study).
- A new clinical condition makes it necessary to add a new antimicrobial (different from those used in the study) with activity against MRSA.
- The principal investigator (PI) considers that there has been a serious protocol violation.
- The following occur during therapy: CPK values are >5, the upper limit of normal (ULN) plus muscle symptoms (cramps, muscle pain, weakness); signs or symptoms of peripheral neuropathy or suspicion of eosinophilic pneumonia.
- Any adverse event for which the clinicians consider that it is necessary to withdraw antibiotic therapy.
- Lost to follow-up.
- Pregnancy during the study.

Note: The following will not be considered a cause for withdrawal: any surgical intervention, such as debridement of an abscess, device removal and prosthesis valve replacement during therapy, since these are considered part of the standard care for complicated MRSA bacteraemia.

Managing withdrawals

When a patient has been withdrawn from the study, the investigator will record the reason/s for withdrawal on the clinical chart and the eCRF. If possible, all early withdrawal patients will be assessed up to the EOT visit. If the reason for withdrawal was a serious adverse event, the patient must be followed until the resolution or stabilisation of the event.

Note: Patients who withdraw early will not be replaced.

STATISTICAL ANALYSIS PLAN

Sample size and power calculations

We have assumed a 60% treatment success rate in the daptomycin group (based on success rates at the end of therapy shown in Fowler's clinical trial). Accepting an α risk of 0.05 and a β risk of 0.2 in a two-sided test, 103 patients per group would be necessary to find a statistically significant difference of 20% between treatment groups. A dropout rate of 20% has been anticipated.

Type of analysis

To assess differences between study groups in baseline variables and other efficacy end points, two independent sample procedures will be employed. Continuous variables will be compared using parametric t tests or non-parametric Mann-Whitney U tests, depending on whether the distribution can be assumed to be normal (after performing tests for normality). Categorical data will be compared by the χ^2 or Fisher's exact tests, as appropriate. Survival curves will be compared by means of the log-rank test. Logistic or Cox regression models will be used to explore associations between different efficacy end points, interventions and relevant baseline conditions, using two-sided tests and a 5% significance level.

A logistic regression model will be used to assess the effect of important prognostic factors on response to treatment. Covariates at a 0.10 level of significance in the univariate analysis will be included in the multivariate analysis. In addition, each component of the composite end point treatment response will be analysed separately.

Efficacy analyses will be performed for the intention-to-treat (ITT) population. Given that patients will be hospitalised during antibiotic treatment and close follow-up is expected, this population will consist of all randomised participants. To account for dropouts between end-of-therapy and TOC visits, we will explore the various dropout patterns and their impact on response. Appropriate multiple imputation procedures will be employed to account for missing data for treatment response. When analysing survival analysis end points (time to death, time to negative blood culture, time to treatment failure), relevant patients will be censored at the time of withdrawal. Safety analyses will be performed on all randomised patients.

MONITORING

Monitoring plans

The data monitoring board will ensure the correct progress of the research and the efficacy of the data towards achieving the goals of the study

A safety monitoring committee with independent investigators will review safety data and provide advice about the continuation, modification and/or termination of the study.

ADVERSE EVENTS REPORTING AND QUANTIFICATION

Definitions

Adverse event: any injury related to medical management (including all aspects of care) that occurs during the patient's participation in the clinical trial will be considered an adverse event. An adverse event may be related to the study medication or be non-related.

Adverse drug event: any medication-related adverse event occurring during the patient's participation in the clinical trial will be considered an adverse drug event.

Adverse drug reaction: any 'adverse drug event' that occurs when the medication is used as directed and in the usual dosage will be considered an adverse drug reaction.

Serious adverse event or reaction will be defined as an event or reaction that:

- Results in death
- Is life-threatening
- Causes persistent or significant disability
- Causes a congenital anomaly/birth defect
- Requires in-patient hospitalisation or prolongation of existing hospitalisation (not related to basal diseases)

Grading of adverse event or reaction: will be performed in accordance with the Division of Microbiology and Infection Diseases (DMID) adult toxicity table, May 2001.

Adverse drug event of particular interest for the study

- *Diarrhoea*: A stool test for detecting *Clostridium difficile*-associated diarrhoea should be considered if the patient develops diarrhoea during the study. The occurrence of this adverse event will not lead to discontinuation of the drug, unless the PI considers it necessary.
- *Elevated creatine phosphokinase (CPK)*: CPK levels >5 times the upper limit of normal (ULN)+symptoms (cramps, muscle pain, weakness) should lead to discontinuation of study medication and early patient withdrawal. For asymptomatic patients, a CPK >10 times the upper limit of normal (ULN) will be required for drug discontinuation. These adverse events should be notified to the sponsor.

Reporting

Any adverse event and its relationship to the study drug occurring during the patient's participation in the clinical trial should be recorded by the PI on the clinical chart at every scheduled visit.

On the electronic eCRF, there should only be recorded: serious adverse drug events; adverse events of any grade related to the study medication, in the opinion of the PI; adverse events of any grade leading to modification of study drug dosage, its interruption/early discontinuation.

All serious adverse events should be notified to the sponsor within 24–48 h of the investigator becoming aware of the event.

ETHICAL ISSUES

The trial will be conducted according to the principles of the Declaration of Helsinki (2008) and current Spanish legislation (Real decreto 223/2004). The principal investigator or collaborator at each site will obtain written informed consent from all patients, or their legal representatives (LRs) if they lack capacity, before enrolment. Patients (or their LRs) are free to withdraw from the trial at any time and this will be explicitly stated on the patient's information sheets (see online supplementary appendix 2).

The data collected for the study will be identified by a code and only the study doctor and collaborators will be able to link those data with patients and their clinical history. Consequently, the patient's 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 patient information will be restricted to the study doctor and collaborators, the health authorities (Spanish Medicines and Healthcare Products Regulatory Agency (AEMPS)), the Clinical Research Ethics Committee, and personnel authorised 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.

The trial protocol received research ethics committee approval in July 2013. Amendment was approved in June 2014 (V.4. 30th April 2014).

The informed consent form and information sheet received research ethics committee approval in July 2013 and AEMPS approval in September 2013.

Indemnities

In accordance with Spanish legislation governing clinical trials (RD 223/2004), this study has liability insurance covering possible damages to patients during their participation in the study, Zurich Insurance PLC, Spanish branch, policy number 70383054.

Publication plans

The sponsor commits itself to publishing the data within 12 months of the completion of the study. Results will be analysed and reported in accordance with CONSORT guidelines.

Protocol amendments

For communicating important protocol modifications, we will first notify the Clinical Research Ethics Committee and Spanish Medicines and Healthcare Products Regulatory Agency (AEMPS) in accordance with Spanish legislation. After their approval, all the Ethics Committee members and investigators of the participating sites will be informed.

DISCUSSION

Currently, there is a need to improve cure rates of patients with MRSA bacteraemia. Some in vitro studies showed a synergistic activity of fosfomycin in combination with β-lactams.[18] In addition, some patients with MRSA bacteraemia have recently been successfully treated with the combination of daptomycin and fosfomycin.[19–21]

We designed this open-label randomised study to demonstrate the hypothesis that fosfomycin (2 gr every 6 h a day) in combination with daptomycin (10 mg/kg once a day) will be better therapy for treating patients with MRSA bacteraemia than therapy with daptomycin alone. Therefore, the study design includes patients with uncomplicated and complicated MRSA bacteraemia, and the main end point includes clinical success plus microbiological success at week 6 after EOT (TOC visit)

Expected impact: this trial will help provide a response to the priority clinical question of whether treatment with daptomycin plus fosfomycin reduces mortality rates and also improves clinical outcomes associated with MRSA bacteraemia.

Author affiliations
[1]Hospital Universitari de Bellvitge-IDIBELL, Hospitalet de Llobregat, Barcelona, Spain
[2]Hospital Universitari Clínic-IDIBAPS, Barcelona, Spain
[3]Hospital Universitari Vall d'Hebron, Barcelona, Spain
[4]Hospital Universitari Arnau de Vilanova, Lleida, Spain
[5]Hospital Universitari Son Espases, Mallorca, Spain
[6]Hospital Universitari Joan XXIII, Tarragona, Spain
[7]Hospital Universitari de Terrassa, Terrassa, Barcelona, Spain
[8]Hospital Universitario Gregorio Marañon, Madrid, Spain
[9]Hospital Universitario 12 de Octubre, Madrid, Spain
[10]Hospital Universitario Virgen de las Nieves, Granada, Spain
[11]Hospital Universitario Virgen Macarena, Sevilla, Spain
[12]Hospital Universitari Santa Creu i Sant Pau, Barcelona, Spain
[13]Hospital Universitari Parc de Salut Mar, Barcelona, Spain
[14]Hospital Universitario Ramón y Cajal, Madrid, Spain
[15]Hospital Universitari Mutúa de Terrassa, Barcelona, Spain
[16]Corporació Sanitaria Parc Taulí, Sabadell, Barcelona, Spain
[17]Hospital Universitario de Cruces, Barakaldo, Spain
[18]Hospital Universitari i Politècnic la Fe, Valencia, Spain
[19]Hospital Universitario Lucus Augusti, Lugo, Spain

Collaborators *Other BACSARM investigators*: Hospital Universitari de Bellvitge-IDIBELL, Barcelona: Francisco Gudiol, M Angeles Dominguez, Anna Ferrer. Hospital Universitari Clínic de Barcelona-IDIBAPS, Barcelona: Alex Soriano, Manuel Almela, Gloria Molas. Hospital Universitari Vall d'Hebron, Barcelona: Maria Nieves Larrosa, Pilar Suñe. Hospital Universitari Santa Creu i Sant Pau, Barcelona: Beatriz Mirelis, Ainhoa Rodriguez-Arias. Hospital Universitari Parc de Salut Mar, Barcelona: Julià Gomez, Mercé Espona. Hospital Universitari Joan XXIII, Tarragona: Josepa Tapiol, Laura Canadell. Hospital Universitari Arnau de Vilanova, Lleida: Mercé Garcia, Laura Rumi. Hospital Universitari Mutúa de Terrassa, Terrassa: Cristina Badía, Mariona Xercavins, Susana Redondo. Hospital de Terrassa: Josefa Perez, Manuela Gonzalez. Corporació Sanitaria Parc Taulí, Sabadell: Dionisia Fontanals, Miquel Cruel. Hospital Universitario Gregorio Marañón, Madrid: Emilia Cercenado, Ana Mur. Hospital Universitario 12 de Octubre, Madrid: Tiago Sequeira, Fernando Chaves; Vicente Gallego. Hospital Universitario Ramón y Cajal, Madrid: Elena Loza, Cristina Pueyo, María Muñoz. Hospital Universitario Virgen Macarena, Sevilla: Isabel Morales, Marina de Cueto, Jose Manuel Carretero. Hospital Universitario Virgen de las Nieves, Granada: M Perez, Inma Zafra. Hospital Universitario de Cruces, Barakaldo: Mercedes Sota, Alazne Bustinza. Hospital Universitari i Politècnic la Fe, Valencia: Eva Gonzalez, Jose Luis López, Maria Tordera, Hospital Universitario Son Espases, Mallorca: Antoni Campins, Enrique Ruiz de Gopegui, Antonio Palomero. Hospital Universitario Lucus Augusti, Lugo: Juan Corredoira, Fernando Garcia, Araceli Iglesias. Note: Administrative information sheet and microbiological procedures are included in online supplementary appendix 3 and appendix 4.

Contributors MP and JC were the study sponsors; took part in study design and recruitment of patients. ES participated in study design; review of the protocol and recruitment of patients. JMM participated in study design and review of the protocol. CC, MPA, CP, JLC, MM, GGP, FB, EC, EE, OG, BP, AGR, VP, JRB, JP, MM, MS, JM and MJGP took part in review of the protocol and recruitment of patients.

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Competing interests None.

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APPENDIX 1 BACSARM trial assessment schedule

	V1 (d0) Inclusion	V2 (d3)	V3* (W1, d7)	V4 (W2) **EOT**	V5 (W3,4,5)	V6 (W4 or W6) **EOT**	V7 (6 weeks after end of therapy) **TOC**
Inclusion/exclusion criteria	**X**						
Patient information sheet and consent	**X**						
Randomisation	**X**						
Comorbidities (Charlson Index)	**X**						
Pitt score, on day of positive blood culture	**X**						
Concomitant medication	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Temperature and blood pressure	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Physical exam	**X**	**X**	**X**	**x**	**X**	**X**	**X**
Haemoglobin-WBCs	**X**	**X**[a]	**(X)**[c]	**X**[a]	**X**[a]	**X**[a]	**X**[a]
Liver function (ALT, AST)	**X**	**X**[a]	**(X)**[c]	**X**[a]	**X**[a]	**X**[a]	**X**[a]
CPK	**X**	**X**[a]	**(X)**[c]	**X**[a]	**X**[a]	**X**[a]	**X**[a]
Renal (creatinine)	**X**	**X**[a]	**(x)**[c]	**X**[a]	**X**[a]	**X**[a]	**X**[a]
Pregnancy test (urine)	**X**						
Adverse event assessment[b]		**X**[b]	**X**[b]	**X**[b]	**X**[b]	**X**[b]	**X**[b]
Clinical response assessment				**X**		**X**	**X**
Blood cultures		**X**[#]	**X**[#]	**X**[#]		**X**[#]	**X**[#]

*****This visit is required only if blood culture results are positive at 72h. W= week. V4: End of therapy (EOT) for uncomplicated bacteraemia. V6: EOT for complicated bacteraemia (all cases with prolonged therapy of up to 6 weeks require one clinical assessment per week until EOT). [a] A blood sample, which may be drawn up to 3 days before or after the visit, is required for haematology and chemistry tests, except for the V2 blood draw (at 72h). The V2 visit requires a different blood sample from the one taken at inclusion. [b] For an assessment of adverse events, the patient should be specifically asked about symptoms/signs of weakness/myalgia or diarrhoea and the skin should be explored to detect allergic reactions. For patients with diarrhoea, a *Cl difficile* test should be carried out, and if there is weakness/myalgia, CPK should be measured urgently. Adverse events of any grade leading to dose modifications/interruption/early discontinuation, grade IV or serious adverse events should be recorded on the clinical chart and e-CRF. [C] This is not mandatory. [#] *S. aureus* isolated prior to screening and in blood cultures taken at V2, V3, V4, V6 and V7 (TOC) must be stored locally and frozen at -70ºC before being sent to the central laboratory (in the Hospital de Bellvitge). Blood cultures are mandatory at V2, V4, V6 and V7 (TOC)

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.

APPENDIX 2

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.

APPENDIX 2

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.

APPENDIX 2

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.

SPONSOR CODE: BACSARM
SPONSOR: Miquel Pujol i Rojo

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:*

APPENDIX 2

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.

SPONSOR CODE: BACSARM
SPONSOR: Miquel Pujol i Rojo

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:*

APPENDIX 2

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.

SPONSOR CODE: BACSARM
SPONSOR: Miquel Pujol i Rojo

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:*

APPENDIX 3

Administrative information

Title

A multicentre, randomised, phase III, open study to assess the efficacy of daptomycin plus fosfomycin versus daptomycin monotherapy for treatment of methicillin-resistant *Staphylococcus aureus* bacteraemia in hospitalised patients

Trial registration

Sponsor protocol code: BACSARM

EudraCT number: 2013-000586-37

Clinical trial registration: NCT01898338

Protocol version

version 4. 30th April 2014

Funding

The trial is supported by grant funding from the National Institute of Health Research, Instituto de Salud Carlos III (ISCIII), Ministerio de Economía y Competitividad. Gobierno de España (Expediente PI12/01907)

Roles and responsibilities

Miquel Pujol. Department of Infectious Diseases. Hospital Universitari de Bellvitge-IDIBELL: study sponsor; study design; recruitment of patients.

Evelyn Shaw. Department of Infectious Diseases. Hospital Universitari de Bellvitge-IDIBELL: study design; review of the protocol; recruitment of patients.

JM Miró. Department of Infectious Diseases. Hospital Universitari Clínic de Barcelona-IDIBAPS: Study design, review of the protocol.

J Carratalà. Department of Infectious Diseases. Hospital Universitari de Bellvitge-IDIBELL: Study sponsor; study design; recruitment of patients

C de la Calle. Department of Infectious Diseases. Hospital Universitari Clínic de Barcelona-IDIBAPS: review of the protocol; recruitment of patients

M Puig-Asensio and C Pigrau. Department of Infectious Diseases. Hospital Universitari Vall d'Hebron, Barcelona: review of the protocol; recruitment of patients

J López-Contreras. Department of Infectious Diseases. Hospital Universitari Santa Creu y Sant Pau, Barcelona: review of the protocol; recruitment of patients

M Montero. Department of Infectious Diseases. Hospital Universitari Parc de Salut Mar, Barcelona: review of the protocol; recruitment of patients

APPENDIX 3

G García-Pardo. Department of Internal Medicine. Hospital Universitari Joan XXIII, Tarragona: review of the protocol; recruitment of patients

F Barcenilla. Unit of Hospital Infection Control. Hospital Universitari Arnau de Vilanova, Lleida: review of the protocol; recruitment of patients

E Calbo. Department of Internal Medicine. Hospital Universitari Mutúa de Terrassa, Barcelona: review of the protocol; recruitment of patients

E Espejo. Department of Internal Medicine. Hospital de Terrassa, Terrassa, Barcelona: review of the protocol; recruitment of patients

O Gasch. Department of Infectious Diseases. Corporació Sanitaria Parc Taulí, Sabadell, Barcelona: review of the protocol; recruitment of patients

B Padilla. Department of Microbiology and Infectious Diseases. Hospital Universitario Gregorio Marañón, Madrid: review of the protocol; recruitment of patients

A García-Reyne. Department of Internal Medicina. Hospital Universitario 12 de Octubre, Madrid: review of the protocol; recruitment of patients

V Pintado. Department of Infectious Diseases. Hospital Universitario Ramón y Cajal, Madrid: review of the protocol; recruitment of patients

J Rodriguez-Baño. Department of Infectious Diseases. Hospital Universitario Virgen Macarena, Sevilla: review of the protocol; recruitment of patients

J Paquau. Department of Infectious Diseases. Hospital Universitario Virgen de las Nieves, Granada: review of the protocol; recruitment of patients

M Montejo. Unit of Infectious Diseases. Hospital Universitario de Cruces, Barakaldo: review of the protocol; recruitment of patients

M Salavert. Department of Infectious Diseases. Hospital Universitario I Politècnic la Fe, Valencia: review of the protocol; recruitment of patients

J Murillas. Department of Internal Medicine. Hospital Universitario Son Espases, Mallorca: review of the protocol; recruitment of patients

M J García-País. Department of Internal Medicine. Hospital Universitario Lucus Augusti, Lugo: review of the protocol; recruitment of patients

Name and contact information of the trial sponsor

Miquel Pujol

Department of Infectious Diseases

Hospital Universitari de Bellvitge-IDIBELL

Feixa Llarga s/n

APPENDIX 3

08907 L'Hospitalet de Llobregat
Barcelona, Spain
Tel. +34 93 260 73 83
Fax. + 34 93 260 72 74
Email: mpujol@bellvitgehospital.cat

Role of study sponsor and funders

The sponsor made the study design. He will take part in interpretation of data and also commits to publishing this data within twelve months of the completion of the study. Results will be analysed and reported in accordance with CONSORT guidelines. He will have ultimate authority over writing of the report and the decision to submit the report for publication.

Funders have no role in the study.

Monitoring committe

An independent monitoring committee will ensure the correct progress of the research and the efficacy of the data towards achieving the goals of the study. This committe depends on Clinical Research Unit (UCICEC)-IDIBELL, in Hospitalet de Llobregat, Barcelona . http://www.idibell.cat/modul/ucicec/en

APPENDIX 4

Microbiological specimens

Blood cultures will be carried out following the protocol of each center and will be processed by the microbiology laboratories of the participating hospitals. MRSA isolation of the first episode of bacteraemia will be stored and all consecutive isolates in successive blood cultures performed, if they were positive. All isolates must be properly maintained (frozen at -20 ° C) until the time of delivery to the coordinating center Microbiology. Microbiology laboratories only will deliver frozen strain (no blood samples). The strain will be identified by a code that only the IP and other study researchers will be able to connect with the patient and their medical history.