Fosfomycin versus meropenem in bacteraemic urinary tract infections caused by extended-spectrum β-lactamase-producing *Escherichia coli* (FOREST): study protocol for an investigator-driven randomised controlled trial

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**ABSTRACT**

**Introduction:** Finding therapeutic alternatives to carbapenems in infections caused by extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL-EC) is imperative. Although fosfomycin was discovered more than 40 years ago, it was not investigated in accordance with current standards and so is not used in clinical practice except in desperate situations. It is one of the so-called neglected antibiotics of high potential interest for the future.

**Methods and analysis:** The main objective of this project is to demonstrate the clinical non-inferiority of intravenous fosfomycin with regard to meropenem for treating bacteraemic urinary tract infections (UTI) caused by ESBL-EC. This is a 'real practice' multicentre, open-label, phase III randomised controlled trial, designed to compare the clinical and microbiological efficacy, and safety of intravenous fosfomycin (4 g/6 h) and meropenem (1 g/8 h) as targeted therapy for this infection; a change to oral therapy is permitted after 5 days in both arms, in accordance with predetermined options. The study design follows the latest recommendations for designing trials investigating new options for multidrug-resistant bacteria. Secondary objectives include the study of fosfomycin concentrations in plasma and the impact of both drugs on intestinal colonisation by multidrug-resistant Gram-negative bacilli.

**Ethics and dissemination:** Ethical approval was obtained from the Andalusian Coordinating Institutional Review Board (IRB) for Biomedical Research (Referral Ethics Committee), which obtained approval from the local ethics committees at all participating sites in Spain (22 sites). Data will be presented at international conferences and published in peer-reviewed journals. **Discussion:** This project is proposed as an initial step in the investigation of an orphan antimicrobial of low cost with high potential as a therapeutic alternative in common infections such as UTI in selected patients. These results may have a major impact on the use of antibiotics and the development of new projects with this drug, whether as monotherapy or combination therapy. **Trial registration number:** NCT02142751. EudraCT no: 2013-002922-21. Protocol V.1.1 dated 14 March 2014.
BACKGROUND

The scarcity of available drugs for the treatment of infections caused by multidrug-resistant (MDR) and extensively drug-resistant pathogens is recognised as a public health problem. Besides the efforts on infection control or facilitating and promoting new drug development,1 old drugs may offer some solutions in the short term. On one hand, some old drugs may be active against some MDR pathogens, offering an alternative for therapy in desperate situations. On the other hand, old drugs may have avoided overuse, unlike other broad-spectrum antibiotics, thus contributing to limit the selective pressure posed by the latter, which facilitates the spread of emerging resistant bacteria. However, because of real, urgent medical needs, some of these old drugs are being used without solid evidence. High-quality clinical research in the MDR field is challenging;2 this is particularly true in the case of old drugs because studies must typically be designed and driven by academic investigators.

Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae and particularly Escherichia coli have been established in the last decade as a common cause of infection worldwide.3 Since carbapenems are considered the drugs of choice for serious infections caused by these microorganisms, consumption of these drugs is increasing,4 which is contributing to the selection and spread of carbapenem-resistant Gram-negative bacilli.5

In this setting, therapeutic alternatives to carbapenems for the treatment of ESBL-producing Enterobacteriaceae are urgently needed. Since these organisms are usually resistant to penicillins, cephalosporins and quinolones, the most plausible alternatives are β-lactam/β-lactamase inhibitor combinations, temocillin (available only in a few countries), aminoglycosides (the limitations of which are well known6) and fosfomycin. Fosfomycin, an antibiotic discovered more than 40 years ago, acts by inhibiting the formation of peptidoglycans during the bacterial cell wall biosynthesis. This antibiotic is frequently active against MDR and extremely resistant Enterobacteriaceae,7 and in particular against ESBL-EC.8

Fosfomycin, in its intravenous formulation (disodium fosfomycin), is approved in Spain, according to a summary of product characteristics (SCP), for clinical use in a wide variety of infections caused by susceptible organisms, including complicated urinary tract infections (UTI) and urinary sepsis (in this case it is advised to be used in combination with other active drugs).9 The recommended dose is 4 g every 6–8 h. It is important to consider that when this drug was developed, the requirements of the regulatory agencies were different from those currently applicable.

A systematic review on the effectiveness of fosfomycin in the treatment of infections caused by MDR Enterobacteriaceae10 was published in 2010; the existing information on the efficacy in systemic infections caused by these microorganisms was virtually non-existent; moreover, they were limited to a few small series of cases in which they were used in combination with other active drugs. Thereafter, not much information has been generated.

The objective of this article is to describe the hypothesis, objectives, design, variables and procedures for a randomised controlled trial with fosfomycin.

METHODS/DESIGN

The FOREST study is a phase 3, randomised, controlled, multicentric, open-label clinical trial to prove the non-inferiority of fosfomycin versus meropenem in the targeted treatment of bacteraemic UTI due to ESBL-EC, designed as a real practice trial. It is a non-commercial, investigator-driven clinical study funded through a public competitive call by Instituto de Salud Carlos III, Spanish Ministry of Economy (PI13/01282). The study is coordinated by investigators from Hospital Universitario Virgen Macarena in Seville, Spain; the sponsorship is performed by Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla (FISEVI), of which the sponsor-scientific responsibilities are delegated to the CTU (Clinical Trial Unit—Hospital Universitario Virgen del Rocío, Seville, Spain).

All participating patients or their relatives must give written informed consent before any study procedures occur, including the withdrawal of biological samples for the study. Informed consent form and patient information sheet are included as online supplementary appendix 1.

STUDY HYPOTHESIS AND OBJECTIVES

The hypothesis to test is that intravenous fosfomycin is not inferior to meropenem for the targeted treatment of bacteraemic UTI caused by ESBL-EC in terms of efficacy. The primary objective of the study is to demonstrate that intravenous fosfomycin is not inferior to meropenem for reaching clinical and microbiological cure 5–7 days after the completion of treatment. Secondary objectives include comparing the early clinical and microbiological response, 30-day mortality, hospital stay, recurrence rate, safety and impact on intestinal colonisation by MDR Gram-negative bacilli, evaluation of the rate of resistance development to fosfomycin and blood level concentration of fosfomycin. The outcome definitions and time frames on which they are measured are described in table 1.

SELECTION AND ENROLMENT

Hospitalised adults (18 years of age or older) with bacteraemic UTI caused by fosfomycin and meropenem susceptible ESBL-EC are candidates to be included in the study. Eligible patients will be detected from the daily review of blood culture results. Inclusion and exclusion criteria are detailed in table 2. The setting for the study will be 22 public and academic hospitals with research groups pertaining to the Spanish Network for Research in Infectious Diseases (REIPI) and/or the Spanish Study
Group of Nosocomial Infections (GEIH) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC).

**RANDOMISATION**

A 1:1 randomisation system allows the assignment of treatment arms, either fosfomycin or meropenem. Randomisation is stratified according to active or non-active previous empirical treatment received for the infection in order to ensure the homogeneous distribution of empirical active treatment. The automatic randomisation system allows the inclusion of patients 24 h a day, 7 days a week, and is integrated in the electronic case report form (e-CRF) of the study. A copy of the randomisation list is in the CTU, so in case of technical problems, data can be easily reached and further randomisation allowed.

**TRIAL INTERVENTION AND CONTROL**

Each patient will enter one of the following treatment branches:

- **Study arm A**: intravenous disodium fosfomycin 4 g/intravenously/6 h in 60 min infusion.

- **Study arm B**: intravenous meropenem 1 g/intravenously/8 h in 15–30 min infusion.

Switch to oral therapy is allowed from the fifth day of treatment with the study medication to complete 10–14 days of therapy if all the following conditions are fulfilled: clinical improvement has been achieved, there is haemodynamic stability, the patient can tolerate oral intake and the isolate is susceptible to one of the following options. For patients in arm A, intravenous fosfomycin can be switched to oral fosfomycin trometamol 3 g/48 h.

For patients in arm B, intravenous meropenem can be switched to one of the following oral drugs in the specified sequence, based on the susceptibility tests.

1. Ciprofloxacin 500 mg/12 h
2. Amoxicillin/clavulanate 500/125 mg/8 h
3. Trimethoprim-sulfamethoxazole 160/800 g/12 h

Treatment assignment is intended for targeted treatment of bacteraemic UTI caused by ESBL-EC. Concomitant treatment with any other systemic antibiotic with intrinsic activity against Gram-negative bacilli is not permitted. The administration of any of these drugs while the patient is receiving the study drug will be deemed as a withdrawal criterion.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Description of outcome variables and time frames</th>
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<tbody>
<tr>
<td><strong>Outcome</strong></td>
<td><strong>Description</strong></td>
</tr>
<tr>
<td>Clinical cure</td>
<td>Complete resolution of infection symptoms present at the day on which blood culture was drawn</td>
</tr>
<tr>
<td>Microbiological cure</td>
<td>Negative blood and urine cultures</td>
</tr>
<tr>
<td>Mortality</td>
<td>Death for any reason</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>Time from randomisation to hospital discharge Development of new symptoms of urinary tract infection in patients with previously clinical and microbiological cure plus positive urine or blood cultures with the same microorganism isolated in the initial cultures</td>
</tr>
<tr>
<td>Relapse</td>
<td></td>
</tr>
<tr>
<td>Reinfecion</td>
<td>Same definition as above but with different strains isolated in cultures</td>
</tr>
<tr>
<td>Emergence of <em>Escherichia coli</em> clinical strains resistant to fosfomycin or meropenem</td>
<td>Isolation of <em>E. coli</em> from urine or blood culture strain showing resistant to fosfomycin or meropenem</td>
</tr>
<tr>
<td>Fosfomycin steady-state plasma concentrations</td>
<td>Plasma concentration of fosfomycin</td>
</tr>
<tr>
<td>Ecological impact</td>
<td>Faecal colonisation by multidrug-resistant Gram-negative bacilli</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Any related adverse event occurring from the informed consent form signature to the end of follow-up</td>
</tr>
</tbody>
</table>

Considering that all the study drugs are officially approved for urinary tract sepsis in Spain, the sponsor will not provide the study drugs; permission for the use of the drugs through the normal provision of each Pharmacy Hospital has been obtained for every site participating in the study. In order to ensure the tracking of the products administered, the lot number and expiration dates will be recorded. This is also required by the Spanish Regulatory Agency.

Dose adjustment is detailed in case of renal dysfunction for all study drugs according to creatinine level clearance as described in Table 3. For this reason, renal function is monitored during the entire duration of antibiotic treatment.

There are no absolute contraindications for the use of any other drugs during the study. However, contraindications, warnings and precautions for their use and possible interactions with the study drugs are to be taken into account. Only drugs used as a consequence of adverse events will be collected in the e-CRF of the study.

FOLLOW-UP SCHEME

Patients included in the study have to be followed for 60 days (±10 days) after the diagnosis of bacteraemic UTI. Follow-up will be organised in six planned visits as: V1, baseline or day 1; V2, day 3; V3, day 5–7; V4, end of treatment or day 12 (±2 days); V5, 5–7 days after treatment completion (test of cure); and V6, day 60 (±10 days). Additionally, data from unplanned visits will be collected with special consideration for the occurrence of any adverse event or recurrence. A flow chart for the study is included in figure 1. Procedures to be performed during those visits are specified in figure 2.

The visit schedule is planned in order to obtain data for clinical status, samples collection, and efficacy and safety variables, including renal and liver monitoring function- ing, and adverse events. At the final evaluation up to 60 days of follow-up, data for all the outcome variables will be gathered.

BIOLOGICAL SAMPLES

All the sites are asked to locally process the blood and urine cultures at the times described in the schedule of

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Inclusion and exclusion criteria</th>
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<tbody>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td><strong>Exclusion criteria</strong></td>
</tr>
<tr>
<td>1. Adults (≥18 years) hospitalised patients with clinically significant monomicrobial bacteraemia due to ESBL- <em>Escherichia coli</em> susceptible to fosfomycin and meropenem, with at least one clinical and one urine analytical criteria and no evidence of other source</td>
<td>1. Polymicrobial bacteraemia</td>
</tr>
<tr>
<td>Clinical criteria</td>
<td>2. In case of renal abscess, lack of early drainage</td>
</tr>
<tr>
<td>▶ Lower UTI symptoms (dysuria, urgency, frequency, suprapubic pain)</td>
<td>3. In case of obstructive uropathy, lacking or early resolution</td>
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<td>▶ Lumbar back pain.</td>
<td>4. Evidence for acute or chronic prostatitis</td>
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<td>▶ Cost-vertebral angle tenderness.</td>
<td>5. Haematogenous infection or other concomitant infection</td>
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<tr>
<td>▶ Presence of a vesical catheter</td>
<td>6. Renal transplant recipients</td>
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<tr>
<td>▶ Altered mental status in patients older than 70 years in the absence of other explanation</td>
<td>7. Polycystic kidney disease</td>
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<tr>
<td><strong>Urine analytical criteria</strong></td>
<td>8. Hypersensitivity and/or previous intolerance to meropenem or fosfomycin</td>
</tr>
<tr>
<td>▶ Urine dipstick test positive for either nitrites or leucocyte esterase</td>
<td>9. Palliative care or life expectancy &lt;90 days</td>
</tr>
<tr>
<td>▶ Isolation of ESBL-<em>E. coli</em> in urine culture</td>
<td>10. Septic shock at time of randomisation</td>
</tr>
<tr>
<td>2. Negative pregnancy test in fertile women</td>
<td>11. New York Heart Association (NYHA) functional class III or IV, liver cirrhosis or renal impairment receiving dialysis</td>
</tr>
<tr>
<td>3. Signed informed consent</td>
<td>12. Empirical treatment active against the isolated bacteria for &gt;72 h</td>
</tr>
<tr>
<td><strong>14. Participation in other clinical trial for the infection</strong></td>
<td>13. Delay in randomisation &gt;24 h after identification of ESBL-<em>E. coli</em> in blood cultures</td>
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<table>
<thead>
<tr>
<th>Table 3</th>
<th>Dose adjustment according to renal functioning</th>
</tr>
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<tbody>
<tr>
<td><strong>Creatinine clearance (mL/min)</strong></td>
<td><strong>Dose</strong></td>
</tr>
<tr>
<td>Disodium fosfomycin</td>
<td></td>
</tr>
<tr>
<td>40–20</td>
<td>4 g</td>
</tr>
<tr>
<td>20–10</td>
<td>4 g</td>
</tr>
<tr>
<td>≤10</td>
<td>4 g</td>
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<tr>
<td>Meropenem</td>
<td></td>
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<tr>
<td>26–50</td>
<td>1 g</td>
</tr>
<tr>
<td>10–25</td>
<td>500 mg</td>
</tr>
<tr>
<td>&lt;10</td>
<td>500 mg</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td></td>
</tr>
<tr>
<td>&gt;60</td>
<td>500 mg</td>
</tr>
<tr>
<td>30–60</td>
<td>250–500 mg</td>
</tr>
<tr>
<td>&lt;30</td>
<td>250–500 mg</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td></td>
</tr>
<tr>
<td>10–30</td>
<td>500/125 mg</td>
</tr>
<tr>
<td>&lt;10</td>
<td>500/125 mg</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td>160/800 mg</td>
</tr>
<tr>
<td>15–30</td>
<td>80/400 mg</td>
</tr>
<tr>
<td>&lt;15</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>
visits, using standard microbiological techniques for the isolation and identification of bacteria; the microbiology laboratories of these centres use the Quality Control system of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). Susceptibility test are to be interpreted according to EUCAST recommendations. The isolated ESBL-EC are to be sent to the central laboratory located in Hospital Universitario Virgen Macarena in Seville in order to confirm the identification, ESBL production, susceptibility testing using reference techniques and ESBL characterisation through PCR and sequencing.

Three hospitals (Hospital Universitario de Bellvitge, Hospital Universitario Vall d’Hebrón, both in Barcelona, and Hospital Universitario Virgen Macarena, Seville) will participate in the study of the rectal carriage of ESBL-producing and carbapenemase-producing Gram-negatives by taking rectal swabs from participants at different times, as set out in the schedule of visits; 60 patients are expected to be included in the rectal carriage study. Additionally, fosfomycin serum concentrations will be measured in a sample size of 20 patients at only one site (Hospital Universitario Virgen Macarena).

All study samples will be anonymised, being identified only by the patient study code, in order to ensure that the association with personal data is not possible. The objective and management of these samples are included in the patient information sheet and informed consent form. Specific details for sample management and procedures are included in online supplementary appendix 2.

**Outcome measures**

The primary efficacy end point is the clinical and microbiological cure at 5–7 days after finalisation of treatment (test of cure, TOC); it will be assessed in the modified intention-to-treat (m-ITT) population, formed by all patients with evaluable microbiological diagnosis of bacteraemic UTI due to ESBL-EC who received at least one dose of intravenous antibiotics. The primary efficacy end point will be evaluated by blinded investigators.

Secondary end points will include early clinical response, early microbiological response, length of hospital stay, impact of study treatment in the colonisation by MDR Gram negatives, relapse rate and reinfection rate, emergence of *E. coli* resistant to fosfomycin or...
meropenem, fosfomycin steady-state plasma concentrations, safety of intravenous fosfomycin in this indication and mortality of any cause for the complete follow-up period (table 1).

Safety will also be evaluated in the m-ITT population. Any adverse event occurring from the informed consent form signature to 28 days after the last dose of study medication will be recorded.

**Sample size calculation**

The sample size calculation was performed on the basis of 80% power to reject null hypothesis with a two-tailed significance level of 5%. Assuming estimated clinical cure rates of 90% in the control group and 85% in the experimental group, for non-inferiority margin of 7%, with an assignment in 1:1 proportion and 5% of lost patients, a total of 198 patients (99 patients in each group) were needed.

Participating centres were selected after a feasibility survey in which data for bacteraemic UTI by ESBL-EC in 2012 were included. All participating centres were committed to include at least 10 patients in the study period, competitively, thereby achieving the guaranteed sample size. Time schedule of enrolment is 24 months from the first patient inclusion.

**Statistical analysis**

The absolute difference, and 95% CI in clinical and microbiological cure rate at TOC between patients in both arms, will be calculated. Multivariate analysis using logistic regression for the main outcome will be performed in order to ensure the independence of the effect of treatment. Special consideration will be taken in the multivariate analysis considering the site origin of the study sample. Absolute difference with 95% CI in early clinical cure rates and early microbiological
cure (5th day of treatment), mortality, rate of adverse events and rectal colonisation with antibiotic-resistant Gram negatives will also be calculated. Also, average hospital stay will be compared between both study arms.

A description of the fosfomycin plasma concentration and its variability among patients will be performed.

Interim analysis
An interim analysis has been planned to be carried out when 50% of cases are recruited. This analysis will include a safety assessment performed by an independent committee of three experts pertaining to REIPI network but not participating in this study.

Definition of analysis population

ITT: all randomised patients.

m-ITT: randomised patients who have received at least one dose of intravenous antibiotics.

Clinically evaluable population (CE): patients who have completed 5 days of intravenous (or who have died after having received at least one dose of intravenous antibiotics) and a total duration of at least 10 days, with at least 75% of the total amount of oral antibiotics if treatment was performed sequentially.

Clinical and microbiologically evaluable population (CME): the population clinically evaluable in whom microbiological tests (blood and urine cultures where applicable) at the indicated follow-up visits were performed.

Safety and adverse event reporting
Pharmacovigilance activities including the registration, reporting and communication of all adverse events occurred within the patients included in the clinical trial are mandatory as part of the legal requisitions applicable in clinical trials. For this reason, the responsibility of performing those activities was derived from the sponsor to the CTU.

In order to recollect all the information related with possible adverse events in the study, every study team is trained during the site initiation visit on the definitions of adverse events and rules for communication. Any adverse event related, or not with the study medication, has to be gathered in the e-CRF, which contains a specific pharmacovigilance module. Serious adverse events (SAE) are mandatorily to be completed with more detailed information comprising SAE description (according to international dictionaries in pharmacovigilance), date of onset and resolution, severity, assessment of causality to study medication, action taken and other concomitant medication/procedures. Any adverse event occurred is followed by initial and follow-up/s communication/s until resolution.

The crucial data related to the adverse event are to be filled in a specific form provided for the study. The SAEs form is centralised in the CTU, the personnel of which are responsible for the reception (by fax or email communication), and registering and resolution of queries to the sites. The identification of any Serious Unexpected Adverse Event (SUSAR) is assessed by a safety medical monitor in order to evaluate if the information is to be communicated to Regulatory Authorities, Ethics Committees and Investigators following Good Clinical Practices (GCPs) rules. In that case, communication through the EudraVigilance system is foreseen. Safety annual reports are issued with all the safety information in the study being reported to regulatory Authorities and Ethics Committees. The safety medical monitor is responsible for any update in safety information of the investigational medicinal product (IMP).

Study organisation
The study coordinating team (SCT) is formed by the scientific group in the coordinating site (Hospital Universitario Virgen Macarena) and the Clinical Trials Unit in Hospital Universitario Virgen del Rocío, the personnel of which are responsible for the entire coordination of the study in the sites involved. These personnel will submit the administrative authorisations for the study, handle regulatory affairs, provide ethics committee contact and response, take up safety monitoring and pharmacovigilance responsibilities of the sponsor, as well as provide logistic coordination and a contact point for all the 22 participating hospitals.

CTU acts as delegation figure of the sponsor (FISEVI, managing foundation for research in Seville) in relevant activities evolved in a multicentre trial. Monitoring activities in Spain are performed by clinical research associates (CRAs) connected with the Spanish Clinical Trial Network in public hospitals. CTU is in close contact with the scientific coordination of the study, acting accordingly and in a parallel manner, so that necessary decisions have been taken after previously having consulted with the study coordination team (SCT). All efforts will be made in order to maintain the recruitment rhythm needed for achieving the sample size through continuous communication with the participant sites.

Data and safety monitoring
The quality of all data collected will be carefully supervised by the CTU; individual responsible for the revision and update of data collection will be in close contact with the investigators, in order to perform a close follow-up of the study procedures, data update and corrections through email or phone contact. Besides this, visits will be organised in order to perform data source verification according to a monitoring plan.

An independent, objective review of all accumulated data from the clinical trial is foreseen. This will be performed at the time of the interim analysis when 50% of the sample has been included. Based on this review, the independent committee (3 independent investigators from REIPI) will advise the sponsor on the appropriateness of continuing the clinical trial as designed.
Ethical considerations

We do not consider having any special ethical considerations beyond those typical for the development of a randomised trial. The study will be carried out according to the principles of the Declaration of Helsinki, and according to the legal norm directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use.

The trial was started after obtaining approval of an Ethics Review Committee, conformity of the Directors of the Institutions, and the authorisation of the Spanish Regulatory Agency (AEMPS, Agencia Española del Medicamento y Productos Sanitarios) and the Institutional Review Boards (IRBs) at each site participating in the trial. A formal contract agreement was signed with each of the institutions and with the sponsor of the study. Any modification to the protocol that could impact on the conduct of the study or potential benefit of the patient, or that may affect patient safety, including changes of study objectives, study design, patient population, sample size, study procedures or significant administrative aspects, will require a formal amendment to the protocol. Such amendment will be agreed on by the study coordinating team (CTU will act as delegation figure of the sponsor) and will be approved by IRBs prior to implementation and notified to the health authorities in accordance with local regulations.

The confidentiality of records that could identify subjects in the FOREST study will be protected in accordance with the EU Directive 2001/20/EC. All the laws that legislate for the control and protection of personal information will be carefully followed. The identity of patients will not be disclosed in the e-CRF; names will be replaced by an alphanumeric code and any material related to the trial as samples will be identified in the same way so that any personal information can be revealed.

SPIRIT 2013 Explanation and Elaboration paper and SPIRIT statement will be followed for the reporting of results to any scientific journal or event.

DISCUSSION

Fosfomycin has been identified as an orphan antibiotic with high potential value in order to be investigated in this era of antibiotic resistance. No studies have been found on fosfomycin for the proposed or similar indication in careful revision of the clinical trials public registries. Therefore, an opportunity to design and conduct a randomised clinical trial to evaluate its efficacy and safety presented itself. In this sense, it seems especially important to take into consideration the new proposed paradigms for investigating new alternatives for antibiotic resistant bacteria through randomised clinical trial designs in order to meet the real clinical needs. The main concern with the use of fosfomycin is the possibility of resistance development during treatment. While it is true that spread of resistant strains in our environment has been linked to increased consumption of drugs for oral treatment of uncomplicated UTI, it seems that the resilience of fosfomycin-resistant enterobacteria has decreased, which would otherwise have permitted it to maintain its activity over time. Even though development of resistance to fosfomycin can occur during treatment, it seems to be much less frequent in E. coli than in Klebsiella spp or Pseudomonas aeruginosa, and specifically in UTI, which provides an adequate background for testing the efficacy of this drug in monotherapy for bacteraemic UTI caused by ESBL-EC. Also, bacteraemic infections with a source in the urinary tract, especially in the absence of urine obstruction, is associated with lower mortality in comparison with other sources; finally, the development of resistance in the course of treatment is less likely in these infections. Therefore, the investigation of fosfomycin efficacy as monotherapy in bacteraemic UTIs by E. coli, at least if there has been an adequate source control if necessary, is justified.

The few pharmacokinetic and pharmacodynamic studies performed to date with fosfomycin indicate that sufficient plasma concentrations are reached for the treatment of systemic infections due to susceptible organisms for at least 4 h following an intravenous dose of 4 g. Since it is excreted unchanged in the urine, its levels in the urine are also suitable for diagnosing these infections. Pharmacokinetic data available to date have been obtained following administration of single doses; however, we intend to determine fosfomycin plasma levels following repeated doses (48 h after treatment).

The Food and Drug Administration (FDA) considers ‘complicated UTI’ to be a syndrome for new therapy evaluation. However, we believe the syndrome definition of the FDA is overly heterogeneous as it includes different clinical situations, from lower UTI in catheterised patients, to pyelonephritis with bloodstream infection in patients with structural of functional problems in the urinary tract. The research group responsible for this trial considers that using such definitions for investigating fosfomycin would not provide valuable results, particularly for patients with bacteraemia; furthermore, the results can be readily transferable to non-bacteraemic UTIs. This is why we decided to include patients with BUTI, who are readily identifiable and for whom clinical decisions are taken every day in real practice.

We decided to use meropenem as comparator because carbapenems are considered the drugs of choice for invasive infections caused by ESBL producers, and there is extensive experience with meropenem. Ertapenem was not considered because treatment of UTIs is not an approved indication for this drug in Europe.
Switching to oral therapy was considered in our study, with the aim of reflecting clinical practice. However, decisions were not easy at this point. Fosfomycin trometamol is an oral formulation of fosfomycin reaching low plasma concentrations but very high urinary concentrations; the results from observational studies suggest that fosfomycin trometamol is useful for the treatment of cystitis and complicated UTIs caused by ESBL-EC. Anecdotal experience from our team with the use of fosfomycin trometamol in this situation has been positive (Rodríguez-Baño J, unpublished data). Therefore, once the bacteraemia and source of infection have been controlled, which is the objective in the first phase of intravenous treatment, the use of oral fosfomycin trometamol is reasonable. For the control arm, and since there are no oral carbapenems available, we needed to look for other alternatives. Because the susceptibility of ESBL-EC to oral drug is heterogeneous, we defined a step-based strategy. Because of the extensive experience with fluoroquinolones in these infections, ciprofloxacin is our first option; however, most ESBL-EC are resistant. The second option is amoxicillin/clavulanate, which is active against a significant proportion of ESBL-EC and has been shown to be effective in observational studies. Finally, trimethoprim-sulfamethoxazole is also recommended for pyelonephritis caused by susceptible strains and is, therefore, included as the third option.

Regarding the safety of disodium fosfomycin, available data suggest it is a very well tolerated drug. Because the sodium content is high (330 mg of sodium per gram of fosfomycin), the Spanish Medicines Agency recommends to take this into account in patients requiring sodium restriction, and therefore we excluded patients with moderate-to-severe heart insufficiency, liver cirrhosis or renal impairment receiving dialysis. Also, determination of plasma sodium and presence of oedema are incorporated in the follow-up visits. However, more data from well-designed studies are clearly needed.

This clinical trial is proposed as an initial step in the investigation of a low cost, orphan antimicrobial with a high potential as a therapeutic alternative for frequent infections caused by MDR E. coli in selected patients. The results may have a major impact in the use of antibiotics and in the development of new projects with this drug, both in monotherapy or in combination therapy.

**Trial status**

- Funding for the study was approved on November 2013 and available for study expenses in January 2014.
- Authorisation from the Spanish Regulatory Authority was obtained on 5 May 2014.
- Approval for the EC for the 22 sites included was obtained on 27 July 2014.
- A total of 15 of 22 sites have been officially opened at the time of manuscript submission.
- First patient inclusion for the study occurred on 1 August 2014.
- Study is approved until August 2017 (recruitment period 2 years).
- Dissemination of results directed to patients will be channelled through the Spanish Clinical Studies Registry (Agencia Española del Medicamento y Productos Sanitarios), of which content is adapted to patients.

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**Contributors**

JR-B and JS-D were responsible for formulating the overall research questions and for the methodological design of the study. CR-F collaborated in the submission of the project for the Spanish funding, wrote the first draft of the manuscript and also collaborated in the methodological aspects of the study. JR-B is the coordinating investigator and leader of the Coordination Team. CR-F is responsible for the CTU and the pharmacovigilance monitor, and AB and LL-A collaborated in the organisation of the study. IL-H and AP contributed in all the microbiological details of the study. VM and MC are responsible of the fosfomycin pharmacokinetics study. JR-B and JS-D participated in its design and supervised the project. All authors read and approved the final manuscript.

**Funding**

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**Competing interests**

JR-B has been the speaker for Pfizer, Merck, Gilead and AstraZeneca, has received unrestricted grants for research from Novartis, and has served as scientific consultant for Merck, AstraZeneca and Roche.

**Patient consent**

Obtained.
REFERENCES


BIOLOGICAL SAMPLES

All the sites are asked to locally process the blood and urine cultures at the times described in the schedule of visits, using standard microbiological techniques for the isolation and identification of bacteria; the Microbiology laboratories of these centers use the Quality Control system of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). Susceptibility test are to be interpreted according to EUCAST recommendations. ESBL-EC isolated are to be sent to the central laboratory located in Hospital Universitario Virgen Macarena in Seville in order to confirm the identification, ESBL-production, susceptibility testing using reference techniques and ESBL characterization through PCR and sequencing.

Three hospitals (Hospital Universitario de Bellvitge, Hospital Universitario Vall d’Hebrón, both in Barcelona and Hospital Universitario Virgen Macarena, Seville) will participate in the study of the rectal carriage of ESBL- and carbapenemase-producing Gram negatives by taking rectal swabs from participants at different times as set out in the schedule of visits; 60 patients are expected to be included in the rectal carriage study. Additionally, fosfomycin serum concentrations will be measured in a sample size of 20 patients in only one site (Hospital Universitario Virgen Macarena).

All study samples will be anonymized, being identified only by the patient study code, in order to ensure that the association with personal data is not possible. Objective and management for these samples are included in the patient information sheet and informed consent form.

The study documentation includes a check list and specific instructions for samples management.
RECTAL SWAPS

Swab to be gathered are to be stored with tube transport medium, Amies, Stuart or Cary-Blair.

To obtain a rectal swab, the swab is inserted slightly surpassing the anal sphincter and gently rotated to take the sample from anal crypts. The swap has to be left between 10 and 30 seconds in order to the microorganisms to be absorbed and then, be removed (the presence of stool in the swab is to be checked).

Insert the swab immediately into the tube containing transport medium and clearly identify the samples with the study ID code.

Bring the sample to sample receiving area of the microbiology laboratory. If transport to the laboratory will be delayed more than two hours the sample should be maintained at 4 °C (refrigerator) until the arrival at the laboratory.

In the centres involved in the study of intestinal colonization (Hospital Virgen Macarena, Bellvitge and Vall d'Hebron) the presence of ESBL-producing enterobacteria or Carbapenemases, or gram-negative bacilli resistant to carbapenems (n = 60 patients) will be determined. Detection will be performed through Mc Conkey with cefotaxime (4 mg / l) or chromogenic medium for Enterobacteriaceae ESBL (ESBL ID Chrom. BioMerieux, France) means. The detected strains, once identified should be frozen at -80 °C following the usual procedure of each centre and sent to the reference by the method described afterwards.
DELIVERY OF MICROBIOLOGICAL ISOLATIONS

1. Pathogens once identified should be frozen at -80 °C following the usual procedure of each centre.

2. Delivery to the central laboratory will be performed every three months.

3. A blood agar plate subculture from the frozen strains has to be performed. Those will be incubated at 37 °C during 18-20h until an adequate bacterial growth is achieved.

4. Microorganisms are to be sent with swab in Amies transport medium or Stuart Cary-Blair medium at room temperature. In order to do so, abundance quantities of microorganisms on the surface of the agar plate subcultured are to be gathered with a sterile swab collect. The swab is to be inserted into the tube incorporating the means of transport. Fit the plug in the tube ensuring a good seal. Identify isolation clearly on the label of each tube using the reference study code.

- Each isolate has to be properly identified and accompanied by the appropriate form (attached) Isolation and antibiogram report copy of the referring centre.

- Samples has to be packed and transported as Category A infectious substances, according to the regulations by WHO (Guidance on regulations for the transport of infectious substances 2011-2012) and BOE # 63 (03/14/2013).

- Contact with the courier services provided for the study.

- Postal address for the central laboratory:  
  Dra. Inmaculada López Hernández  
  Servicio de Microbiología (primera planta)  
  Hospital Virgen Macarena  
  Avda. Dr. Fedriani s/n  
  41009 Sevilla
- Contact the referral centre via email (inlopezh@us.es) indicating in subject "FOREST_Name of the sender SHIPPING hospital" to confirm sending samples indicating in the text of the email:

  a. Institution (Hospital) name.
  b. Date of departure.
  c. Name and contact details (phone number) of the responsible of the delivery.
  d. Number of microorganisms delivered.

2. Confirmation of the specific form included in the delivery.
# ISOLATION FORM

<table>
<thead>
<tr>
<th>REFERENCE NUMBER</th>
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<td><em>(to be filled in by the reference site)</em></td>
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<th>Name of the Hospital (Sender)</th>
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<th>Date of isolation</th>
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<th>Reference number for the institution</th>
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<th>Unit/Department of origin</th>
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<th>Identification method in the reference centre</th>
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<th>Antibiogram method in the reference centre</th>
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**ANTIBIOTIC SENSITIVITY DATA**
*(copy of the report issued in the center of origin is recommended)*
SAMPLES MANAGEMENT FOR FOREST STUDY
EudraCT: 2013-002922-21

**PHARMACOKINETICS**

The pharmacokinetics parameters of fosfomycin will be evaluated solely in the coordinating center (Hospital Universitario Virgen Macarena, Seville). A total of four samples are collected from 20 patients with the evaluation times listed below:

**Sample 1:** just before the initiation of fosfomycin administration.
**Sample 2:** at the time of the initiation of fosfomycin administration.
**Sample 3:** after two hours of the initiation of fosfomycin administration.
**Sample 4:** after four hours of the initiation of fosfomycin administration.

Blood samples will be drawn into a tube with 3 ml EDTA. Each sample has to be centrifuged at 3500 rpm for 5 min, removing the plasma, which is to be frozen at -20°C until analysis (in <30 days).

Fosfomycin determination will be performed through high resolution liquid chromatography linked to a triple quadruple mass spectrometer (LC-MS/MS) by Li et al (J Chromatography B 2007; 856: 171-177). The method validation will be done according to the Bioanalytical Methods Validation Guide of the FDA.
STUDY TITLE: A phase 3, randomized, controlled, multicentric, open-label clinical trial to prove the non-inferiority of fosfomycin vs meropenem in the targeted treatment of bacteraemic urinary tract infection UTI due to Escherichia coli producing extended-spectrum beta-lactamases (ESBLs).

SPONSOR CODE: FOREST

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

INTRODUCCION

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

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

VOLUNTARY PARTICIPATION

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

GENERAL STUDY DESCRIPTION

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

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

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

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

STUDY DESIGN

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

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

You may receive one of the following treatments:

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

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

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

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

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

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

☐ YES I AGREE  ☐ I DO NOT AGREE

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

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

☐ YES I AGREE  ☐ I DO NOT AGREE

**BENEFITS OF YOUR PARTICIPATION IN THE STUDY**

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

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

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

**POSSIBLE RISKS ARISING FROM YOUR PARTICIPATION IN THE STUDY**

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

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

In the case of participation of **women of childbearing potential**, a negative pregnancy test will be required for study inclusion.
Are there side effects associated with the antibiotics used in this study?

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

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

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

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

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

INSURANCE

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

CONFIDENTIALITY

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

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

Access to your personal information is restricted to the study doctor / partners, health authorities (Spanish Agency for Medicines and Health Products), the Ethics Committee
for Clinical Research and persons authorized by the sponsor, when they need to check the data and study procedures, but always maintaining the confidentiality of such data in accordance with current legislation.

**ECONOMIC COMPENSATION**

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

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

**OTHER RELEVANT INFORMATION**

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

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

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

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

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

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

I, ................................................................................................ (Name and Surname)

- I have read the Information leaf facilitated by the medical team
- I have had the opportunity to express my questions and doubts
- I have received sufficient information on the study
- I have spoken with………………………………………………………………..
  (Name of the researcher)

I understand that my participation is voluntary

I understand that I can retire of the study:

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

I freely give my conformity to participate in the study.

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

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

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

Name of of the Investigator