BMJ Open

Temocillin versus meropenem for the targeted treatment of bacteraemia due to third-generation cephalosporin-resistant *Enterobacterales* (ASTARTÉ): protocol for a randomised, pragmatic trial

Alicia Marín-Candón,[1] Clara M Rosso-Fernández,[1] Natalia Bustos de Godoy,[2,3] Lorena López-Cerero,[2,3] Belén Gutiérrez-Gutiérrez,[2,3] Luis Eduardo López-Cortés,[2,3] Lydia Barrera Pulido,[2,3] Irene Borreguero Borreguero,[1] María José León,[1] Vicente Merino,[4,5] Manuel Camean-Fernández,[4] Pilar Retamar,[2,3] Elena Salamanca ,[2,3] Alvaro Pascual,[2,3] Jesús Rodriguez-Baño,[2,3] On behalf of ASTARTÉ Study Group

To cite: Marín-Candón A, Rosso-Fernández CM, Bustos de Godoy N, *et al*. Temocillin versus meropenem for the targeted treatment of bacteraemia due to third-generation cephalosporin-resistant *Enterobacterales* (ASTARTÉ): protocol for a randomised, pragmatic trial. *BMJ Open* 2021;**11**:e049481. doi:10.1136/bmjopen-2021-049481

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-049481).

Received 26 January 2021
Accepted 06 September 2021

For numbered affiliations see end of article.

Correspondence to
Dr Elena Salamanca;
elesalamanca@hotmail.com

ABSTRACT

Introduction Alternatives to carbapenems are needed in the treatment of third-generation cephalosporin-resistant *Enterobacterales* (3GCR-E). Temocillin is a suitable candidate, but comparative randomised studies are lacking. The objective is to investigate if temocillin is non-inferior to carbapenems in the targeted treatment of bacteraemia due to 3GCR-E.

Methods and analysis Multicentre, open-label, randomised, controlled, pragmatic phase 3 trial. Patients with bacteraemia due to 3GCR-E will be randomised to receive intravenously temocillin (2 g three times a day) or carbapenem (meropenem 1 g three times a day or ertapenem 1 g once daily). The primary endpoint will be clinical success 7–10 days after end of treatment with no recurrence or death at day 28. Adverse events will be collected; serum levels of temocillin will be investigated in a subset of patients. For a 10% non-inferiority margin, 334 patients will be included (167 in each study arm). For the primary analysis, the absolute difference with one-sided 95% CI in the proportion of patients reaching the primary endpoint will be compared in the modified intention-to-treat population.

Ethics and dissemination The study started after approval of the Spanish Regulatory Agency and the reference institutional review board. Data will be published in peer-reviewed journals.

Trial registration number NCT04478721.

Strengths and limitations of this study

- The design of this randomised study has limitations, including the open design, the heterogeneity of oral alternatives for switching and the exclusion of patients with septic shock.
- One of the strengths is its pragmatic design which we hope will allow the appropriate representation of patients with the target infections.
- The multicentre participation and the short time limit to recruit the patients once the bacteraemia is diagnosed are other strengths of this study.

INTRODUCTION

Infections due to antimicrobial-resistant pathogens are recognised as a worldwide public health problem. The problem is especially severe among Gram-negative bacteria. In fact, third-generation cephalosporin-resistant *Enterobacterales* (3GCR-E), either caused by extended-spectrum β-lactamases (ESBLs) or high production of AmpC enzymes, were the leading cause of invasive infections (estimated, 365 000) and attributable deaths (estimated, 12 700) among antibiotic-resistant bacteria in the European economic area in 2015.[1] Also, 3GCR-E have a very important impact in the use of antibiotics; a very important increase in carbapenems consumption (the drugs of choice for invasive infections due to 3GCR-E) has followed these bacteria spread[2] and it is contributing to the subsequent explosive spread of carbapenems resistance.

Therefore, alternative treatments for 3GCR-E are desperately needed. One of the alternatives is piperacillin-tazobactam, but its efficacy compared with carbapenems is controversial.[3 4] The cephamycins may be active against ESBL-producers, but not against AmpC-producers, and their efficacy is doubtful.[5] Fosfomycin and aminoglycosides may be an empirical option in some cases, but they are only useful in urinary tract infection

(UTI).[6 7] Finally, new β-lactams (ceftolozane-tazobactam, ceftazidime-avibactam) might be reserved for other multidrug-resistant pathogens.[8]

Temocillin is a β-lactam drug which is stable against ESBLs and AmpC enzymes, and therefore is active against a high proportion of 3GCR-E.[9] This drug is only approved in a few countries for the treatment of septicaemia, urinary tract and lower respiratory tract infections when susceptible Gram-negative bacilli are suspected or confirmed (standard dosing, 2 g two times a day intravenously; for severe infections, 2 g three times a day is recommended). The pharmacokinetic and pharmacodynamic properties of temocillin have recently been reviewed.[10]

The objective of this article is to describe the hypothesis, objectives, design, variables and procedures for a pragmatic randomised controlled trial comparing the efficacy of temocillin and meropenem in bacteraemic infections caused by 3GCR-E. To the best of our knowledge, no randomised trials have been published with temocillin in these infections.

METHODS AND ANALYSIS

Hypothesis and objectives of the trial

The hypothesis of the study is that temocillin is non-inferior to carbapenems for the targeted treatment of bacteraemia due to 3GCR-E. The primary objective of the trial is to demonstrate the non-inferiority of temocillin in terms of efficacy and safety. Secondary objectives include providing specific comparative data about the efficacy and safety of temocillin and carbapenems in subgroups of patients (eg, different sources of bacteraemia, elderly, renal insufficiency and other underlying conditions), providing data about the pharmacokinetics and pharmacodynamics of temocillin, and about the distribution of the minimum inhibitory concentrations (MIC) of temocillin according to the mechanisms of resistance.

Trial design, sites and study period

ASTARTÉ is a multicentre, open-label, randomised, controlled, pragmatic phase 3 trial. A 36-month recruitment period is planned. The study is coordinated from Hospital Universitario Virgen Macarena (HUVM) under the auspices of the Spanish Network for Research in Infectious Diseases, the Andalusian Network for Clinical Research in Infectious Diseases and the Spanish Clinical Research Network (SCReN). The trial is funded by Instituto de Salud Carlos III, Spanish Ministry of Science and Innovation; the drug is kindly provided by Belpharma SA (Luxemburg) under an agreement with states that Belpharma SA will be informed about the results of the study but cannot influence the analyses or publication of the results. Thirty-one public Spanish hospitals will participate.

Selection and enrolment

Hospitalised adult patients (≥18 years) with monomicrobial bacteraemia due to *Enterobacterales* (including *Escherichia coli, Klebsiella* spp, *Proteus* spp, *Morganella* spp, *Salmonella* spp, *Enterobacter* spp, *Serratia* spp, *Providencia* spp and *Citrobacter* spp) showing resistance to ceftriaxone, cefotaxime and/or ceftazidime and susceptibility to temocillin and carbapenems are eligible. Inclusion and exclusion criteria are detailed in table 1. Participation in the study is voluntary and patients can withdraw from the study at any time. Subjects will be withdrawn from the study if they experience a major protocol violation, in case of clinical failure or according to safety criteria. Patients will be randomised once inclusion and exclusion criteria are checked (therefore, once the isolate is known to be susceptible to study drug), and informed consent is signed; randomisation must be performed in <96 hours after the blood cultures were obtained and in <48 hours of the availability of susceptibility results.

Randomisation

Candidates will be detected from the daily review of positive blood cultures. Patients with all inclusion criteria but

Table 1 Inclusion and exclusion criteria for participating in ASTARTÉ trial

Inclusion criteria	Exclusion criteria
1. Adult hospitalised patients with monomicrobial bacteraemia due to *Enterobacterales*. 2. The micro-organism is resistant to cefotaxime, ceftriaxone (MIC >2 mg/L) and/or ceftazidime (MIC >4 mg/L). 3. The micro-organism is susceptible to temocillin (MIC ≤8 mg/L) and meropenem (MIC ≤2 mg/L). 4. Duration of intravenous treatment is planned to be at least 4 days. 5. The patient signed informed consent.	1. Age <18 years. 2. Pregnancy or breast feeding. 3. Patients under palliative care. 4. Allergy to beta-lactam drugs. 5. Polymicrobial bacteraemia. 6. Meningitis. 7. Infections typically needing >14 days of therapy (eg, endocarditis, prosthetic joint infection, vascular graft infection, empyema, chronic prostatitis). 8. Severe neutropenia (<500 cells/µL). 9. Septic shock at recruitment. 10. Empirical treatment with an in vitro active drug for >96 hours after initial blood culture extraction.

MIC, minimum inhibitory concentrations.

Table 2 Dose adjustment of study drugs according to renal function

Creatinine clearance (mL/min)	Dose	Frequency
Temocillin (intravenous)		
30–60	1 g	Every 12 hours
10–30	1 g	Every 24 hours
<10	500 mg–1 g	Every 24–48 hours
Meropenem (intravenous)		
26–50	1 g	Every 12 hours
10–25	500 mg	Every 12 hours
<10	500 mg	Every 24 hours
Ertapenem (intravenous)		
<30	1 g	Every 24 hours
<30	Not recommended	
Ciprofloxacin (oral)		
>60	500 mg	Every 12 hours
30–60	250–500 mg	Every 12 hours
<30	250–500 mg	Every 24 hours
Amoxicillin-clavulanic acid (oral)		
10–30	500/150 mg	Every 12 hours
<10	500/125 mg	Every 24 hours
Trimethoprim-sulfamethoxazole (oral)		
>30	160/800 mg	Every 12 hours
15–30	80/400 mg	Every 12 hours
<15	Not recommended	Not recommended

with some exclusion criteria will be considered screening failures. Those signing informed consent will be randomised centrally using an online automatic system with a 1:1 randomisation. Randomisation will be stratified according to empirical treatment (in vitro active or not) and suspected source (urinary tract or other) in order to assure that these variables will be balanced between the study arms. The automatic randomisation system is integrated in the electronic case report form (e-CRF) of the study.

Interventions and study treatment

Patients will be allocated to one of the following arms: Arm A (experimental group), in which patients will receive 2 g of temocillin intravenously every 8 hours in 30–40 min infusion; and Arm B (control group), in which patients will receive 1 g of meropenem intravenously every 8 hours in 15–30 min infusion. Ertapenem 1 g per day can be used instead of meropenem except in patients with sepsis, if MIC ≤0.5 mg/L.

Dosing will be adjusted in patients with renal insufficiency according to official labels (table 2). Duration of intravenous therapy will be decided by the treating physician, but should be at least four full days; then, patients can be switched to an oral regimen if the infection is controlled, the source of infection has been drained/removed/solved, the patient tolerates the oral route and the isolate is susceptible to appropriate drugs as follows: ciprofloxacin 500 mg every 12 hours; trimethoprim-sulfamethoxazole 160–800 mg every 12 hours and amoxicillin-clavulanic acid, 875–125 mg every 8 hours. Recommended duration of total active therapy is 7–14 days. In monomicrobial bacteraemia in which a polymicrobial infection is suspected (eg, intra-abdominal infection), addition of metronidazole (only in patients assigned to temocillin), vancomycin or linezolid (for resistant Gram-positive organisms) or an antifungal agent are allowed.

Concomitant treatment with any other systemic antibiotic with intrinsic activity against isolated enterobacteria from blood culture is not permitted. The use of one of these antibiotics during the phase of treatment will be deemed as failure and a withdrawal criterion. There are no absolute contraindications for the use of any other drugs during the study.

Since temocillin is not approved in Spain, Belpharma SA will ship the vials to the Pharmacy Service at HUVM, where they will be relabelled and delivered to the sites. The drug traceability will be ensured. The other study drugs are officially approved in Spain, and they will be used through the normal provision of each Hospital Pharmacy at every participating site. The lot number, expiration dates and the number of vials used will be recorded.

Study endpoints

The primary endpoint will be a clinical success in the modified intention-to-treat (mITT) population (see below), and includes all of the following: (1) clinical success at test of cure (TOC); (2) survival at day 28; (3) no need to stop or change the assigned drug because of an adverse event, perceived failure during treatment or occurrence of a superimposed infection; (4) no need to prolong therapy beyond 14 days and (5) no recurrence until day 28. The TOC will be performed 7–10 days after the last day of antibiotic therapy. Clinical success is defined as resolution of the new signs or symptoms related to the infection.

To control potential investigator's bias, the outcome will be checked through: (1) collection of objective clinical data at day 0 and TOC, including temperature, blood pressure, respiratory and heart rates, Glasgow score and specific examination signs and (2) calculation of the SOFA score (Sequential Organ Failure Assessment) on all visits. A blinded investigator will assess their concordance with the outcome classification provided by the local investigator. Secondary endpoints are shown in table 3.

Follow-up of participants

Patients will be followed until day 28; all visits and procedures to be performed at each one are specified in table 4. The day of blood culture is considered 'Day 0' of

Table 3 Endpoints in ASTARTÉ

Endpoint	Description	Time of evaluation
Primary endpoint		
Clinical success	Proportion of patients with all of the following: (1) clinical cure at TOC (see below); (2) alive at day 28; (3) no need to stop the study drug because of adverse event, failure or intercurrent infection; (4) no need to prolong treatment after 14 days and (5) no recurrence of the infection at day 28	Test of cure (7–10 days after end of treatment)
Secondary endpoints		
Clinical cure	Proportion of patients showing resolution of the new signs/symptoms related to the infection	Test of cure (7–10 days after end of treatment)
Mortality	Proportion of dead patients	Day 28
Length of hospital stay	Average time from randomisation to hospital discharge	Hospital discharge
Adverse events	Proportion of patients with any adverse event from first dose of study drug; also of severe adverse events (standard definition)	Day 28
Development of resistence	Proportion of patients with new isolation of the causative micro-organism in follow-up cultures showing resistant to temocillin or meropenem	Day 28
Recurrence	Proportion of patients with development of signs/symptoms of the infection caused by the same micro-organism after clinical response has been reached	Day 28
Reinfection	Proportion of patients with occurrence of a new infection caused by a different micro-organism	Day 28
Change in SOFA score (descriptive endpoint)	Average change in SOFA score	All follow-up visits
Temocillin serum concentrations (descriptive endpoint; only one site)	Distribution of temocillin serum concentration	See text
Temocillin MIC according to mechanisms of resistance (descriptive endpoint)	Distribution of temocillin MIC according to the mechanisms of resistance to cephalosporins	See text

MIC, minimum inhibitory concentrations; SOFA, Sequential Organ Failure Assessment; TOC, test of cure.

the study. After discharge, patients will be provided the means to attend the face-to-face visits.

Microbiological procedures

Blood samples will be performed using standard clinical practice. Blood cultures and bacterial identification will be performed at local laboratories using standard microbiological procedures; the isolates will be preserved and sent to HUVM. Temocillin susceptibility will be studied in 3GCR-E at local laboratories by gradient strips; those with MIC value >8 mg/L will be considered resistant according to British Society of Antimicrobial Chemotherapy breakpoint for susceptibility. Susceptibility to meropenem and other drugs will be studied using routine protocols and interpreted according to the European Committee on Antimicrobial Susceptibility Testing recommendations. Identification and susceptibility in all isolates to all study drugs will be checked later at HUVM using Matrix-Assisted Laser Desorption Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF) and broth microdilution methods, respectively.

Pharmacokinetic and pharmacodynamic studies

Free temocillin plasma levels will be determined on days 1 and 3 in the first 20 patients allocated to the temocillin recruited at HUVM. Blood samples will be obtained 1, 4, 6 and 8 hours after the administration of temocillin; free temocillin plasma concentrations will be measured using HLPC-DAD.[11] The method will be validated according to the FDA Bioanalytical Method Validation Guidance for Industry.[12] For the population pharmacokinetic analysis, one-compartment and two-compartment linear models will be fitted to the temocillin plasma concentrations-time data. Covariate model building will be performed using sequential assessment of biologically plausible clinical parameters. Monte Carlo models will be built the calculate the probability of target attainment (PTA) ≥50% of the time over the MIC for different MIC values (PTAs for >50% $fT_{>MIC}$) and simulated dosing schemes (2 g of temocillin administered in 30 min and in 4 hours, every 8 or 12 hours). Dose adjustments will be simulated in patients with decreased renal clearance.

Table 4 Schedule of follow-up visits and procedures

Assessment	Day 0	Visit 1 selection (Day 1)	Visit 2 (Day 3)	Visit 3 End of treatment (Days 7–14),	Visit 4 Test of cure (14–24)	Visit 5 Day 28 (±5)	Unscheduled visit
Randomisation		X					
Informed consent		X					
Inclusion/exclusion criteria		X					
Pregnancy test		X					
Clinical history		X	X	X	X	X	X
Physical examination		X	X	X	X	X	X
SOFA scale		X	X	X	X		X
Haematology/chemistry		X	X	X	X		X
Coagulation		X					X
Urinalysis		X			X		X
Blood culture	X		X	X			X
Concomitant medication		X	X	X		X	X
Dispensing control		X	X	X			
Adverse events			X	X	X	X	X

*Day 0 is the day of blood culture. Day 1 must not exceed 96 hours after blood culture was drawn.
†If applicable.
‡The visit can be done by telephone if patient is not hospitalised. In this case, physical examination, blood extraction and SOFA scale are not needed.
§If applicable.
¶If it has not been realised in the previous 72 hours.
**Only in urinary tract infection.
††Only if fever persists since visit 2. Repeat it in 48 hours if positive.
‡‡Between 7 and 14 days from the start of the antibiotic treatment.
§§Day 28 (±5 days) since randomisation.
¶¶7–10 days after the end of the treatment.
SOFA, Sequential Organ Failure Assessment.

Sample size

We estimated an 85% success rate with meropenem and with temocillin. In order to reject the null hypothesis with 80% power and a 5% one-sided significance level for a 10% non-inferiority margin with a 1:1 assignment, with 5% of missing patients, a total of 167 patients in each study arm are needed (total, 334 patients).

Statistical analysis

For the primary analysis, the absolute difference in the proportion of patients reaching the primary endpoint in the two study arms will be compared in the mITT population, which includes all randomised patients who received at least one dose of the study drug, but in which those incorrectly included or randomised will be excluded. The one-sided 95% CI for the difference will be calculated.

As secondary analyses, all secondary endpoint will be analysed in the mITT population, in the per-protocol population (those receiving at least 4 days of the study drugs) and in the clinically evaluable population (patients evaluated at TOC). Absolute difference with 95% CI will be calculated for categorical endpoints, and Mann-Whitney test for length of hospital stay. The primary endpoint will also be analysed in the following subgroups: according to the source of bloodstream infection (BSI); age groups patients with cancer; mechanism of resistance to third-generation cephalosporins; species of *Enterobacterales*; temocillin MIC <4 versus 4–8 mg/L; appropriate vs inappropriate empirical therapy; nosocomial versus non-nosocomial episodes and INCREMENT score <7 or ≥8. Analysis considering the site effect will also be performed by using a random effects model. Finally, multivariate analysis will be performed in order to control the potential effect of variables other than randomised antibiotic therapy on the primary outcome using logistic regression and on mortality by Cox regression. Key outcome determinants including age, Charlson, delay in administering an active drug, specific sources, micro-organism, Pitt score, SOFA and renal insufficiency will be considered for inclusion in the models, and will be selected using a stepwise backward process; the variable study arm will be forced in the models.

Safety and adverse event reporting

Pharmacovigilance activities are delegated from the sponsor to the Clinical Trials Unit of University Hospital Virgen del Rocío (CTU-HUVR). Follow-up of adverse events (AE) will be done according to standard procedures and the European Medicine Agency regulation; all potential AE will be recorded and classified according to severity and potential relation with the trial drugs. Any adverse event must be recorded in the e-CRF and all serious AE will be notified in less than 24 hours to CTU-HUVR. The CTU-HUVR personnel are responsible for the reception, recording and resolution of queries and for the identification of any serious unexpected adverse event (SUSAR). SUSAR will be evaluated to communicate them in less than 15 days to Regulatory Authorities, Ethics Committees and Investigators. Safety annual reports will be reported to regulatory Authorities and Ethics Committees by these personnel. A safety monitor from the CTU-HUVR, will coordinate the activities in collaboration with the SCReN.

Data and safety monitoring

Data collection activities will be assessed by an individual responsible of the CTU-HUVR, in contact with the investigators for the revision and verification of data according to a monitoring plan. Subject data will be anonymised and collected using the e-CRF.

An external independent Data Safety Monitoring Board (DSMB) formed by three expert members not participating as investigators in the project will be selected. Interim analyses will be performed after the first 50 and after the first 150 first patients are recruited. Reports with recommendations from the DSMB will be obtained for both interim analyses. A conditional power ≤20% calculated using Mehta and Pocock method after the inclusion of the first 150 patients will be considered low enough to recommend termination of the trial on the basis of futility. Detailed description of rules for decision-making from the committee will be agreed at the time of the agreement of the independent members.

Ethics and dissemination

Ethics

An approved informed consent (version 1.2, dated 6 May 2020) form must be signed before any study specific procedures is performed. The study is approved by the Spanish Regulatory Agency and by the Hospitales Universitarios Virgen Macarena and Virgen del Rocío Ethic Committee. The trial will be carried out according to the principles of the Declaration of Helsinki and the legal Royal Decree RD 1090/2015 applicable in Spain for the performance of clinical trials and European Regulation (EU) n° 536/2014 for all the EU countries.

The results of the study will be submitted for publication to a scientific journal following the Consolidated Standards of Reporting Trials recommendations.

Patient and public involvement

Patient/public involvement will not be involved in the design, or conduct, or reporting, or dissemination plans of our research.

DISCUSSION

Temocillin, because of its in vitro activity, is a potential alternative to carbapenems for the treatment of infections caused by 3GCR-E and might help to reduce the consumption of these drugs.[13–15] As comparative clinical data for temocillin is scarce, ASTARTÉ is expected to provide evidence for the use of this drug in the setting of BSI due to 3GCR-E, which represents a substantial proportion of all BSI caused by *Enterobacterales*.

Because carbapenems are highly efficacious for the treatment of bacteraemia due to 3GCR-E and the objective is to find alternatives which can help in reducing their use, a non-inferiority approach is proposed. The use of an alternative drug might have additional benefits for the patient or the population by reducing the selective pressure of carbapenems for multidrug-resistant organisms. A superiority trial could be done by using a composite primary outcome including colonisation and/or superinfection by multidrug resistant bacteria, but a very high sample size would be needed, making it unfeasible for an investigator-driven clinical trial with public funds.

It is well known that classical randomised clinical trials (RCT) may not be adequately adapted to daily practice; they are frequently performed in selected sites with highly experienced investigators and selected participants, and the population included might not be representative of most patients to whom the results would be extrapolated, so overestimation of benefits and underestimation of harms can be present for special populations normally not included in RCT. This led to the idea that more pragmatic trials showing the real-world effectiveness of the intervention in broader patient groups, are required.[16] This may be particularly important in the evaluation of antibiotics as the outcome of the infection do not only depends on the treatment itself but on features of the patients, the source and severity of the infection, the micro-organism and different aspect of the clinical management (source control, support therapy). Therefore, ASTARTÉ was designed as a pragmatic trial trying to mimic clinical practice.

The inclusion of patients with bacteraemia was decided because this is a frequent situation, in which the aetiology is perfectly identified and for which the predictors for outcome have been well studied, also by our group[17]; the problem of bacteraemia is that it includes different sources of infection, but the experience in previous trials indicates that this can be adequately controlled in the analysis.[4] The use of a composite primary endpoint was decided to include both a very relevant and hard variable such as mortality plus clinical success as recommended in a consensus document for trials in bacteraemia.[18]

Meropenem as comparator was chosen because carbapenems are considered the drugs of choice for invasive infections caused by ESBL producers.[19] The use of ertapenem (1 g per day) is accepted except in patients with sepsis if MIC ≤0.5 mg/L.[20] In order to approach standard clinical practice, switching to oral therapy when possible is included in the protocol. First option to oral therapy continuation is ciprofloxacin. Trimethoprim-sulfamethoxazole can be used as second option, only in UTI. Third approved option, in case of allergy or resistance to previous treatment described, is amoxicillin-clavulanic acid.

The expected impact of the study is a change in clinical practice allowing temocillin to be used in many patients and contributing to a reduction in the consumption of carbapenems highly needed in the actual situation of resistances.

Strengths and limitations of this study

The design of this randomised study has limitations, including the open design, the heterogeneity of oral alternatives for switching, and the exclusion of patients with septic shock. Some strengths are its pragmatic design which we hope will allow the appropriate representation of patients with the target infections, the multicentre participation and the short time limit to recruit the patients once the bacteraemia is diagnosed.

Trial status

- Funding for the study communicated on November 2019, available for study expenses in January 2020.
- Authorisation from the Spanish Regulatory Authority obtained on 9 September 2020.
- Approval for the Ethic Committee for the 32 sites included obtained on 5 May 2020.
- First patient inclusion for the study occurred on December 2020.

Author affiliations
[1]Unidad de Investigación Clínica y Ensayos Clínicos (CTU), Hospital Universitario Virgen del Rocio, Sevilla, Spain
[2]Unidad de Enfermedades Infecciosas y Microbiología, Hospital Universitario Virgen Macarena, Sevilla, Spain
[3]Departamentos de Medicina y Microbiología, Universidad de Sevilla, Sevilla, Spain
[4]Unidad Clínica de Farmacia, Hospital Universitario Virgen Macarena, Sevilla, Spain
[5]Departamento de Farmacología, Facultad de Farmacia, Universidad de Sevilla, Sevilla, Spain

Twitter Pilar Retamar @PilarRetamar and Elena Salamanca @ElenaSalamancaR

Acknowledgements ASTARTÉ Study Group: Virgen Macarena University Hospital, Sevilla Dr Rodriguez-Bano (IP), Dr Alvaro Pascual Hernández; Dr Vicente Merino Bohorquez; Dr Carmen Lupión Mendoza; Dr Elena Salamanca Rivera; Dr Lorena López Cerero; Dr Dolores Martín Sierra; Dr Belén Gutiérrez Gutiérrez; Dr Marina de Cueto López; Dr Luis Eduardo López Cortés; Dr Fernando Docobo Pérez; Dr Natalia Bustos de Godoy; Red Ancraid; Lydia Barrera Pulido, Enriqueta Tristán Clavijo; CTU; Irene Borreguero Borreguero. María José León León Virgen del Rocío University Hospital, Sevilla; Dr Manuel Enrique Jiménez Mejías; Dr José Antonio Lepe Jiménez, Dr Clara María Rosso-Fernández. University Hospital Reina Sofía, Córdoba; Dr Angela Cano Yuste; Dr Julian de la Torre Cisneros; Dr Pilar Egea Miranda; Dr Juan José Castón; Dr Clara Natera Kindelán; Dr Fuensanta Gavilán; Julián de la Torre Gimenez. University Hospital Marqués de Valdecilla, Santander; Dr Francisco Arnaiz de las Revillas; Dr Jorge Calvo Montes; Dr María del Carmen Fariñas Álvarez; Dr Claudia González. University Hospital Ramón y Cajal, Madrid; Dr Rosa Escudero; Dr Vicente Pintado García; Dr Ana María Sánchez Díaz. University Hospital del Mar, Barcelona; Dr Juan Pablo Horcajada Gallego; Dr Eduardo Padilla León; Dr Silvia Gómez-Zorrilla Martín; Dr Inmaculada López Montesino; Dr Joan Gómez Junyent; Dr María del Mar Arenas Miras; María Fernández Ferrer (N); Dr Mercé Espona Quer; Dr María de la Soledad Escolano Martínez. University Hospital A Coruña (CHUAC); Dr Maria Dolores Sousa Regueiro; Dr Enrique Míguez Rey; Dr Germán Bou Arévalo. C H San Millán-San Pedro de la Rioja; Dr José Antonio Oteo Revuelta; Dr José Manuel Azcona Gutiérrez; Dr Jorge Alba Fernández. University Hospital Clínic, Barcelona; Dr Celia Cardozo Espínola; Dr Laura Morata Ruíz; Dr José Antonio Martínez Martínez; Dr Alex Soriano Viladomiu; Dr Yuliya Zboromyrska; Antonio Moreno Martínez (SC); Montserrat Solà Vidal (SC). University Hospital Son Espases, Mallorca; Dr María Peñaranda Vera; Dr Xavier Mulet Aguilo; Dr Helem Vilchez. Parc Taulí Hospital, Sabadell; Dr Oriol Gasch Blasi; Dr Mateu Espasa Soley. University Hospital Santa Creu i Sant Pau, Barcelona; Dr Joaquín López-Contreras González; Dr María Alba Rivera Martínez; Dr Virginia Pomar Solchaga; Pablo Pascual Alonso (SC). Hospital Mútua de Terrassa; Dr Esther Calbo Sebastian; Dr Emma Padilla Esteba; Dr Lucía Boix Palop; Dr Beatriz Dietl Gómez-Luengo; Dr Mariona Xercavins Valls; Cristina Badía Martí; Dr Genís Catells Lao. University Hospital Vigo; Dr Maria Teresa Pérez

Rodríguez; Dr Francisco José Vasallo Vidal; Dr Adrián Sousa Domínguez. Lozano Blesa University Hospital, Zaragoza; Dr Jose Ramón Paño Pardo; Dr Cristina Pilar Seral García. University Hospital Virgen de Valme, Seville; Dr Juan Corzo Delgado; Dr Ana Isabel Aller García. University Hospital La Princesa, Madrid; Dr Ana Barrios Blandino; Dr Laura María Cardeñoso Domingo; Dr M Carmen de las Cuevas Torresano; María Auxiliadora Semiglia; Dr Aresio Sancha; Dr Javier Bernardo Pérez Serrano; Dr Ángela Gutiérrez Liarte. CUN Clínica Univesitaria de Navarra, Dr Jose Ramón Yuste Ara; Dr José Leiva León. Hospital general de Alicante; Dr Esperanza Merino de Lucas; Dr Adelina Gimeno Gascón. University Hospital Jerez, Cádiz; Dr Salvador López Cárdenas; Dr María Dolores López Prieto. Complejo Hospitalario de Jaén; Dr Carmen Herrero Rodríguez; Dr Carolina Roldán Fontana. University Hospital Torrecárdenas, Almería; Dr M Angeles Esteban Moreno; Dr Waldo Sánchez-Yebra Romera. University Hospital Clinico San Cecilio, Granada, Dr Andrés Ruiz Sancho; Dr Natalia Chueca Porcuna. University Hospital Lucus Augusti, Lugo; Dr Mª José García País; Dr Fernando García Garrote; Dr Eva María Romay Lema; Dr Ramón Rabuñal Rey. University Hospital Puerto Real, Cádiz; Dr Alberto Romero Palacios; Dr Ignacio Correa Gómez; Dr Carolina Freyre Carrillo. University Hospital Juan Ramón Jiménez, Huelva; Dr Francisco Javier Martínez Marcos; Dr Francisco Franco. University Hospital Santiago de Compostela; Dr María Jesús Domínguez Santalla; Dr Gema Barbeito Castiñeiras; Dr María Teresa Rodríguez Jato. University Hospital Gregorio Marañón, Madrid; Dr María Olmedo Samperio; Dr Emilia Cercenado Mansilla. University Hospital Virgen de la Victoria, Málaga; Dra. Carmen Pérez López; Dr Guillermo Ojeda Burgos; Dr María Victoria García López. University Hospital Regional Málaga; Dr Lucía Valiente de Santis; Dr Alexandra Halbardier Carretero; Dr José María Reguera Iglesias; Dr Juan Diego Ruíz Mesa; Dr Antonio Plata Ciézar; Dr Beatriz Sobrino Díaz; Dr Ignacio Márquez Gómez; Dr Inés Pérez Camacho. University Hospital Las Paz, Madrid; Dr Marta Mora Rillo; Dr Emilio Cendejas Bueno. University Hospital Virgen de las Nieves, Granada; Dr Miguel Ángel López; Dr Fernando Cobo Martínez; Dr Concepción Fernández; Dr Carmen Hidalgo; Dr Rosario Javier; Dr Concepción López Robles; Dr Juan Pasquau. Spanish Clinical Research Network (SCReN) funded by Spanish Ministry of Health, Instituto de Salud Carlos III has acted with local support for the study start-up and monitoring activities coordinated and directed from CTU-HUVR (PT17/0012).

Contributors JR-B and AP were responsible for formulating the overall research question and the methodological design of the study. CMR-F, LL-C and ES collaborated in the submission of the project for the Spanish funding. AM-C, CMR-F and ES wrote the first draft of the manuscript and also collaborated in the methodological aspects of the study. JR-B is the PI of the study; NBdG is the study coordinator. CMR-F is responsible for the CTU-HUVR and the Pharmacovigilance monitor, IB, LBP and MJL contributed to the organisation and setting-up of the study. NBdG, LL-C, ES, BG-G, PR and LEL-C participated in its design and supervised the project. VM and MC-F collaborated in all the aspects related with IMP management and PK/PD detailed. All authors read and approved the final manuscript.

Funding ASTARTÉ study is funded by grant (ICI19/00093) and Plan Nacional de I+D+i 2013-2016 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Ministerio de Ciencia, Innovación y Universidades, Spanish Network for Research in Infectious Diseases (REIPI RD16/0016/0001, 0002, 0004, 0008, 0009, 0010, 0011, 0013, 0015), cofinanced by European Development Regional Fund 'A way to achieve Europe', Operative Program Intelligence Growth 2014-2020. The sponsor is Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla (FISEVI).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Elena Salamanca http://orcid.org/0000-0001-8605-7611

REFERENCES

1 Cassini A, Högberg LD, Plachouras D, *et al*. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European economic area in 2015: a population-level modelling analysis. *Lancet Infect Dis* 2019;19:56–66.
2 Klein EY, Van Boeckel TP, Martinez EM, *et al*. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci U S A* 2018;115:E3463–70.
3 Tamma PD, Rodriguez-Bano J. The use of Noncarbapenem β-lactams for the treatment of extended-spectrum β-lactamase infections. *Clin Infect Dis* 2017;64:972–80.
4 Harris PNA, Tambyah PA, Lye DC, *et al*. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with E coli or Klebsiella pneumoniae bloodstream infection and ceftriaxone resistance: a randomized clinical trial. *JAMA* 2018;320:984–94.
5 Gutiérrez-Gutiérrez B, Rodríguez-Baño J. Current options for the treatment of infections due to extended-spectrum beta-lactamase-producing *Enterobacteriaceae* in different groups of patients. *Clin Microbiol Infect* 2019;25:932–42.
6 Rosso-Fernández C, Sojo-Dorado J, Barriga A, *et al*. 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. *BMJ Open* 2015;5:e007363.
7 Palacios-Baena ZR, Gutiérrez-Gutiérrez B, Calbo E, *et al*. Empiric therapy with Carbapenem-Sparing regimens for bloodstream infections due to extended-spectrum β-lactamase-producing *Enterobacteriaceae*: results from the increment cohort. *Clin Infect Dis* 2017;65:1615–23.
8 Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Machuca I, *et al*. Treatment of infections caused by extended-spectrum-beta-lactamase-, AmpC-, and carbapenemase-producing *Enterobacteriaceae*. *Clin Microbiol Rev* 2018;31:pii: e00079-17.
9 Livermore DM, Hope R, Fagan EJ, *et al*. Activity of temocillin against prevalent ESBL- and AmpC-producing *Enterobacteriaceae* from south-east England. *J Antimicrob Chemother* 2006;57:1012–4.
10 Alexandre K, Fantin B. Pharmacokinetics and pharmacodynamics of Temocillin. *Clin Pharmacokinet* 2018;57:287–96.
11 Miranda Bastos AC, Vandecasteele SJ, Tulkens PM, *et al*. Development and validation of a high performance liquid chromatography assay for the determination of temocillin in serum of haemodialysis patients.. *J Pharm Biomed Anal* 2014;90:192–7.
12 U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM). FDA Bioanalytical method validation guidance for industry, 2018. Available: https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf
13 Mischnik A, Baumert P, Hamprecht A, *et al*. Susceptibility to penicillin derivatives among third-generation cephalosporin-resistant Enterobacteriaceae recovered on hospital admission. *Diagn Microbiol Infect Dis* 2017;87:71–3.
14 Balakrishnan I, Awad-El-Kariem FM, Aali A, *et al*. Temocillin use in England: clinical and microbiological efficacies in infections caused by extended-spectrum and/or derepressed AmpC β-lactamase-producing *Enterobacteriaceae*. *J Antimicrob Chemother* 2011;66:2628–31.
15 Laterre P-F, Wittebole X, Van de Velde S, *et al*. Temocillin (6 G daily) in critically ill patients: continuous infusion versus three times daily administration. *J Antimicrob Chemother* 2015;70:891–8.
16 Ford I, Norrie J. Pragmatic trials. *N Engl J Med* 2016;375:454–63.
17 Palacios-Baena ZR, Gutiérrez-Gutiérrez B, De Cueto M, *et al*. Development and validation of the INCREMENT-ESBL predictive score for mortality in patients with bloodstream infections due to extended-spectrum-β-lactamase-producing Enterobacteriaceae. *J Antimicrob Chemother* 2017;72:dkw513–13.
18 Harris PNA, McNamara JF, Lye DC, *et al*. Proposed primary endpoints for use in clinical trials that compare treatment options for bloodstream infection in adults: a consensus definition. *Clin Microbiol Infect* 2017;23:533–41.
19 Rodríguez-Baño J, Cisneros JM, Cobos-Trigueros N, *et al*. Diagnosis and antimicrobial treatment of invasive infections due to multidrug-resistant Enterobacteriaceae. guidelines of the Spanish Society of infectious diseases and clinical microbiology. *Enfermedades Infecciosas y Microbiología Clínica* 2015;33:337.e1–337.e21.
20 Gutiérrez-Gutiérrez B, Bonomo RA, Carmeli Y, *et al*. Ertapenem for the treatment of bloodstream infections due to ESBL-producing Enterobacteriaceae: a multinational pre-registered cohort study. *J Antimicrob Chemother* 2016;71:1672–80.