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Epirubicin for the Treatment of Sepsis and Septic Shock (EPOS-1): study protocol for a randomised, placebo-controlled phase IIa dose-escalation trial

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ABSTRACT

Introduction Sepsis remains the major cause of death among hospitalised patients in intensive care. While targeting sepsis-causing pathogens with source control or antimicrobials has had a dramatic impact on morbidity and mortality of sepsis patients, this strategy remains insufficient for about one-third of the affected individuals who succumb. Pharmacological targeting of mechanisms that reduce sepsis-defining organ dysfunction may be beneficial. When given at low doses, the anthracycline epirubicin promotes tissue damage control and lessens the severity of sepsis independently of the host–pathogen load by conferring disease tolerance to infection. Since epirubicin at higher doses can be myelotoxic, a first dose–response trial is necessary to assess the potential harm of this drug in this new indication.

Methods and analysis Epirubicin for the Treatment of Sepsis and Septic Shock-1 is a randomised, double-blind, placebo-controlled phase 2 dose-escalation phase IIa clinical trial to assess the safety of epirubicin as an adjunctive in patients with sepsis. The primary endpoint is the 14-day myelotoxicity. Secondary and explorative outcomes include 30-day and 90-day mortality, organ dysfunction, pharmacokinetic/pharmacodynamic (PK/PD) and cytokine release. Patients will be randomised in three consecutive phases. For each study phase, patients are randomised to one of the two study arms (epirubicin or placebo) in a 4:1 ratio. Approximately 45 patients will be recruited. Patients in the epirubicin group will receive a single dose of epirubicin (3.75, 7.5 or 15 mg/m^2 depending on the study phase. After each study phase, a data and safety monitoring board will recommend continuation or premature stopping of the trial. The primary analyses for each dose level will report the proportion of myelotoxicity together with a 95% CI. A potential dose-toxicity association will be analysed using a logistic regression model with dose as a covariate. All further analyses will be descriptive.

Ethics and dissemination The protocol is approved by the German Federal Institute for Drugs and Medical Devices. The results will be submitted for publication in peer-reviewed journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Epirubicin for the Treatment of Sepsis and Septic Shock-1 is the first randomised, placebo-controlled, double-blind trial that pharmacologically targets a disease tolerance mechanism.
⇒ Epirubicin will be repurposed with another concentration in a new indication.
⇒ This trial is not powered to assess an effect on mortality.
⇒ Patients are included up to 48 hours after sepsis diagnosis. While this time window was long enough to decrease disease severity in mice, it is not clear whether it will be sufficient in humans.
⇒ Protective effects were shown for bacterial sepsis in previously healthy young animals. Comorbidity and age on epirubicin metabolism in sepsis could influence the effects of epirubicin in patients with sepsis.

Trial registration number NCT05033808.

INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] Despite improvement in outcomes mortality still ranges from 15% to 25% and can be as high as 50% in case of septic shock.[2] Treatment relies on infection control by antibiotics and source control and supportive therapy, for example, by fluid resuscitation, vasopressors, respiratory support or dialysis. Sepsis mortality rates have not decreased substantially over the recent years, and new treatment strategies are scarce. Targeting the immune system has mainly failed,[3] potentially due to the syndromic nature of sepsis and the wide variety of clinical presentations. Immunophenotyping[4] and subsequent personalised immunotherapy are

currently deployed in clinical trials that include patients presenting only with extreme phenotypes such as immunosuppression or hyperinflammation.[5–7] Yet, for the common sepsis denominator, that is organ dysfunction,[8] no effective sepsis-specific treatments are established in clinical practice.[2 9] Noteworthy, the strategies that have been deployed to decrease specifically infectious disease mortality all share the same mode of action, that is the reduction of pathogen burden. This strategy is essentially also used by the immune system and in this context referred to as 'resistance to infection'.[10–12] Another defence strategy termed 'disease tolerance to infection' has not been explored pharmacologically in medicine.[13] In experimental models, this defence strategy has been shown to decrease disease severity by supporting host homeostasis by limiting the extent of tissue damage associated with infection and promoting its repair.[10 11 14] It is achieved using genetically encoded and evolutionarily conserved stress and damage response mechanisms.[14] Anthracyclines, a class of drugs used in chemotherapy for over 30 years,[15–18] have been shown to enhance disease tolerance when given in low doses.[19]

Notably, it has been shown that epirubicin increases survival in animal models of sepsis. This effect was not associated with a decrease in pathogen loads of the infected organism.[19] This indicates that the application of epirubicin would act in a way to enforce disease tolerance mechanisms. Further data show that epirubicin activated the DNA damage response pathways in cells, rendering them less susceptible to infection-associated stress.[19] Survival benefits prevailed when epirubicin was administered 24 hours after sepsis induction.[19] This makes epirubicin a potential candidate for a new therapeutic option in sepsis. We are not aware of any studies or case reports that applied anthracyclines for this indication. Epirubicin has been used at doses up to 30 mg/m^2 without toxicity in earlier studies with cancer patients.[20] This is a higher dosage than what is intended in the Epirubicin for the Treatment of Sepsis and Septic Shock (EPOS-1) trial. Based on the existing preclinical evidence, we designed the EPOS-1 trial to test the hypothesis that low-dose epirubicin is safe in patients with sepsis.

METHODS AND ANALYSIS

EPOS-1 is a randomised, placebo-controlled dose-escalation phase IIa trial to assess the safety of a single low dose of epirubicin as an adjunctive therapy for patients with sepsis. Sepsis is defined following the Sepsis-3 criteria as infection-associated organ dysfunction, represented by an increase in the Sequential Organ Failure Assessment (SOFA) score of 2 points or more.[1] The primary endpoint of the study is myelotoxicity at day 14 after application of epirubicin. Secondary and exploratory endpoints are the rate and level of organ dysfunction, the pharmacokinetic/pharmacodynamic of epirubicin, the concentration of cytokines in plasma and the DNA damage in leucocytes and mortality.

Box 1 Inclusion and exclusion criteria of the Epirubicin for the Treatment of Sepsis and Septic Shock-1 trial.

Inclusion criteria

⇒ Patients > 18 years old with sepsis or septic shock, currently hospitalised at the intensive care unit or intermediate care unit regardless where the sepsis was first diagnosed.
⇒ Sepsis diagnosis within 48 hours prior to screening regardless of the site of infection.
⇒ (defined as an increase Sequential Organ Failure Assessment (SOFA) score of >2 points).
⇒ Informed consent of the patient or their legal representative or if not possible a statement by an independent physician.

Exclusion criteria

⇒ Leucopenia/Neutropenia/Thrombocytopenia-prior or on inclusion (Leucocyte count<4000/µL; Neutrophil/Thrombocyte count below lower limit of normal).
⇒ Weight > 135 kg/BMI > 45.
⇒ Ongoing or history of chemotherapy.
⇒ Hypersensitivity to epirubicin.
⇒ History of bone marrow or solid organ transplantation.
⇒ Immunosuppressive therapy.
⇒ Acute severe infection within 4 weeks prior to admission (hospitalisation for an infection or in case of hospital-acquired infection transfer to a higher level of care due to the infection).
⇒ Chronic infection.
⇒ Cardiomyopathy with a documented ejection fraction<30% or implantable cardioverter-defibrillator implantation.
⇒ Acute liver failure following the European Association for the Study of the Liver definition as International Normalised Ratio (INR) > 1.5 and elevation of transaminases > 3 times of the upper normal limit.
⇒ Pregnancy during all trimester/breast-feeding.
⇒ Chronic mechanical ventilation dependency.
⇒ Cystic fibrosis.
⇒ Concomitant medication with Verapamil or Cimetidine.
⇒ Prior enrolment in this study.
⇒ Participation in another clinical intervention trial.

Study design and setting

The trial will recruit sepsis patients admitted to intensive care (ICU) and intermediate care units (IMC) in German university hospitals. Patients will be randomised subsequently to three study phases with increasing doses of epirubicin or placebo in a 4:1 ratio. After each study phase, a safety analysis will occur before the trial with new patients proceeds to the next higher dose.

Study population

The study population consists of adult patients ≥ 18 years of age with sepsis or septic shock, currently hospitalised at the ICU or IMC regardless of where the sepsis was first diagnosed in one of the five participating centres. There are no sex restrictions or bias. Screening will be performed daily at the respective trial centres to assess whether eligible subjects are present in the ICU or IMC. Pregnant or breastfeeding women are not eligible for participation in this clinical trial. All inclusion and exclusion criteria are listed in box 1. Accounting for a mortality of 30% of

the study participants, we will include approximately a total of 15 participants in each phase, corresponding to 3 patients receiving placebo and 12 the study drug. This will allow for a primary endpoint assessment up to day 14 of two patients in the placebo group and eight patients in the study drug group. Patients will be recruited in five centres in order to assure adequate enrolment.

Trial management

The trial is led by the sponsor representative and coordinating investigator (SW) and his deputy (DT-R). They are supported by the Center for Clinical Studies of Jena University Hospital (Center for Clinical Studies) (project manager CH), which is responsible for trial management and monitoring the source data. Biosamples are analysed at the laboratory of the coordinating investigator and in the laboratories of cooperating partners.

The data and safety monitoring board (DSMB) is composed of three external experts (an intensive care physician, an oncologist and a statistician). The DSMB is regulated by a standardised operating procedure. The main function of the DSMB is to monitor the safety of the study. All Suspected Unexpected Serious Adverse Reaction and all cases fulfilling the primary endpoint definition of myelotoxicity will be reported to the DSMB. Data for interim analysis will be processed and prepared for presentation and reported to the DSMB if at least two patients in the placebo group and at least eight patients in the respective epirubicin group have completed the 14-day follow-up. The DSMB will convene meetings in the context of interim analysis and additional ad hoc meetings if necessary. Following each meeting, the DMSB will recommend continuation, modification or discontinuation of the study based on observed toxicities.

Randomisation and study procedures

The local pharmacies at each trial site have access to a web-based central randomization service, which is available 24 hours / 7 days. The randomization list is prepared by an independent statistician via a computer-based algorithm and is stratified by a study centre. For each study phase, patients are randomised to one of the two study arms (epirubicin or placebo) in a 4:1 ratio. A unique patient ID is generated for data collection throughout the trial (figure 1). Patients in the epirubicin group will receive a single dose of epirubicin. The amount of epirubicin is determined by the study phase. The epirubicin dosage in phase 1 is 25% of the dosage applied in the mouse models, that is, 3.75 mg/m^2, which corresponds to approximately 4% of the epirubicin dosage applied in a single course of chemotherapy. If this dose is safe, it will be escalated to 7.5 mg/m^2 and finally 15 mg/m^2, which corresponds to approximately 16% of the dosage applied in chemotherapy. It equals the dose that showed benefit in the mouse model and would be the dose to use in a future phase III trial. We expect that none of the applied dosages of epirubicin will increase toxicity in patients with sepsis. We expect that none of the applied dosages of epirubicin will increase toxicity in patients with sepsis. The highest dose corresponds to the amount that had beneficial effects in mice.[19]

The study medication is prepared in the hospital pharmacies of the trial sites by unblinded personnel and then delivered to the ICU/IMC. Since epirubicin has a typical red colour, the study medication is delivered blinded in coloured bags already connected to coloured infusion systems. In addition, the bags will be covered by an opaque light protection pouch. At the trial site, the infusion system is prefilled with NaCl solution via a side port before connection to the patient's central line. The transparent parts of the central line are then covered by an opaque towel before the application of the Interventional Medical Product (IMP) is started. After administration of the IMP the infusion system is flushed by normal saline to remove all residues of the IMP before the towel

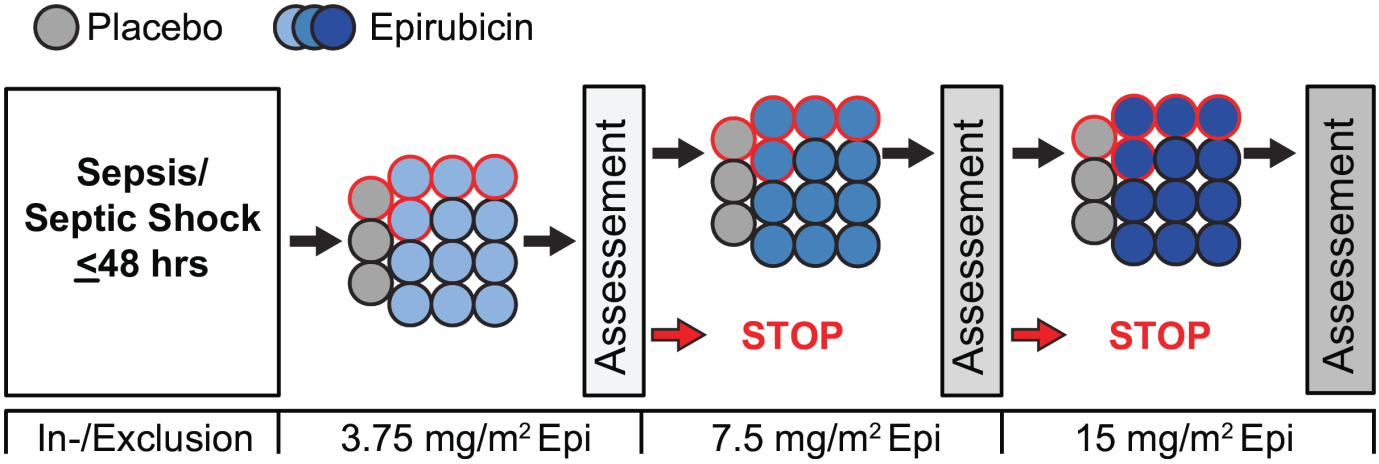

Figure 1 Study design of the EPOS-1 trial. Black-bordered circles indicate minimal participants for the safety analysis. Red-bordered circles indicate patients who were randomised and received the study drug or placebo are expected not to reach the 14-day safety endpoint considering sepsis-related mortality of up to 30%. The assessment indicates a safety assessment of the data and safety monitoring board and a study continuation or stops following their recommendation. Epi, epirubicin; EPOS-1, Epirubicin for the Treatment of Sepsis and Septic Shock-1.

is removed and the infusion system is disconnected from the patient's infusion line.

An overview of the study procedures and assessments is provided in online supplemental table 1. Acute physiology data will be documented directly before and at seven visits up to 24 hours after the IMP administration. Plasma will be centrifugated and stored at −80°C for further analysis. Peripheral blood monocytic cells (PBMCs) will be isolated at the trial site using a commercially available kit (MACSprep PBMC Isolation Kit, Miltenyi Biotec).

Primary endpoint

The general toxicity profile of anthracyclines is well-known and has extensively been studied in tumour patients.[15–18] Epirubicin (4′-Epi-Doxorubicin) is a less toxic derivate from doxorubicin and differs structurally only in the epimerization of the OH group in position 4 of the amino-sugar moiety.[15] Myelosuppression—which is also used as the toxicity read-out in EPOS-1—is the major acute dose-limiting toxicity of epirubicin and consists predominantly of leucopenia and to a lesser extent in thrombocytopenia.[15 16] This would put patients at risk of developing severe infections. In cancer studies, myelotoxicity is a commonly used outcome parameter.[21–23] In early studies, no toxicity was observed when epirubicin was administered as a single dose of 10, 20 or 30 mg/m^2.[20] The maximum tolerated single dose of epirubicin in tumour patients is suggested to be 150 mg/m^2. At lower doses of 120 mg/m^2 only grade 2 myelotoxicities were observed.[24] The nadir of myeloid toxicity occurs between 10 and 14 days after treatment. Therefore, we will closely monitor myelotoxicity.[16 17]

Safety, as assessed by myelotoxicity until day 14 after epirubicin application, is the primary endpoint. It will be determined by automated or manual differential blood count in the respective clinical chemistry departments. Blood count will be measured directly before study drug administration; 24 hours, 2, 3, 5, 7, 10, 12 and 14 days, days after administration of verum/placebo.

Assessing myelotoxicity in sepsis patients can be complicated since leucopenia, neutropenia and thrombocytopenia[25–28] are all being observed in a relevant proportion of sepsis patients. In rare cases, this might be a sign of sepsis-induced myelosuppression, but in most cases, this is caused by increased consumption or sequestration. Immature platelet fraction (IPF) is a parameter reflecting megakaryocyte activity and is therefore reflecting platelet production.[29] Thrombocytopenia with a normal or elevated IPF is indicative of increased consumption and turnover with a normal bone marrow function and is a common finding in sepsis.[29 30] In contrast, thrombocytopenia with a decreased IPF is indicative of a bone marrow depression. Leucopenia and neutropenia in sepsis are typically present early in the disease and are followed by normal or elevated leucocyte counts, while neutropenia due to myelotoxicity is prolonged. Neutropenia and thrombocytopenia in sepsis are not closely correlated with each other, as the pathophysiological processes are different, while myelosuppression normally affects all cell types.

Table 1 Grading of neutropenia and thrombocytopenia

	Neutropenia (acute neutrophil count)	Thrombocytopenia (platelets)
Grade 1	<Lower limit of normal–1500/µL	<Lower limit of normal–75 000/µL
Grade 2	<1500–1000/µL	<75 000–50 000/µL
Grade 3	<1000–500/µL	<50 000–25 000/µL
Grade 4	< 500/µL	< 25 000/µL

To differentiate the best possible way between sepsis-associated alterations and 'real' Epirubicin-induced myelotoxicity, the primary safety endpoint of myelotoxicity is defined as follows:

Neutropenia of grade 3 or 4 (table 1) at two consecutive study visits up to day 14 or thrombocytopenia of grade 3 or 4 (table 1) at two consecutive study visits up to day 14 accompanied by neutropenia or thrombocytopenia of grade 2, 3 or 4 at both study visits and accompanied by an IPF below 2.5% at one or two of the consecutive study visits (figure 2).[31]

Secondary endpoint

Secondary endpoints for safety are cardiotoxicity, assessed by transthoracic echocardiography 7 days after epirubicin application, the frequency of other typical side effects (diarrhoea, mucositis, alopecia, nausea and vomiting) and the overall rate of adverse and severe adverse events. In addition, we will assess the inflammatory response by measuring serum cytokines, procalcitonin (PCT) and C-reactive protein (CRP). A 'success' rate defined as a decrease of PCT serum concentration by 80% or more of its intra-individual peak value or to 0.5 µg/L or lower within 72 hours after randomization (following the 'Stop Antibiotics on Procalcitonin guidance Study' by de Jong *et al*[32] will be assessed. For organ function, SOFA on days of assessment, mean total SOFA and SOFA changes over time in the participants will be assessed. We will further assess fluid balance, urine output, need for renal replacement therapy, paO_2/FiO_2 ratio, need for respiratory support, and catecholamines and inotropes. Mortality will be assessed at days 14, 28 and 90 after randomisation, quality of life will be assessed at day 90 in survivors by 'Short Form 36 Health Questionnaire'. Explorative objectives include pharmacokinetics and pharmacodynamics of epirubicin, by measuring DNA damage. Effects on inflammatory response will be further assessed by measuring additional cytokines and additional molecular markers for organ damage will be analysed. For better characterisation of immune cell composition, thrombocyte numbers and bone marrow function flow cytometry of PBMCs, anti-PF4 antibodies and reticulocytes will be assessed.

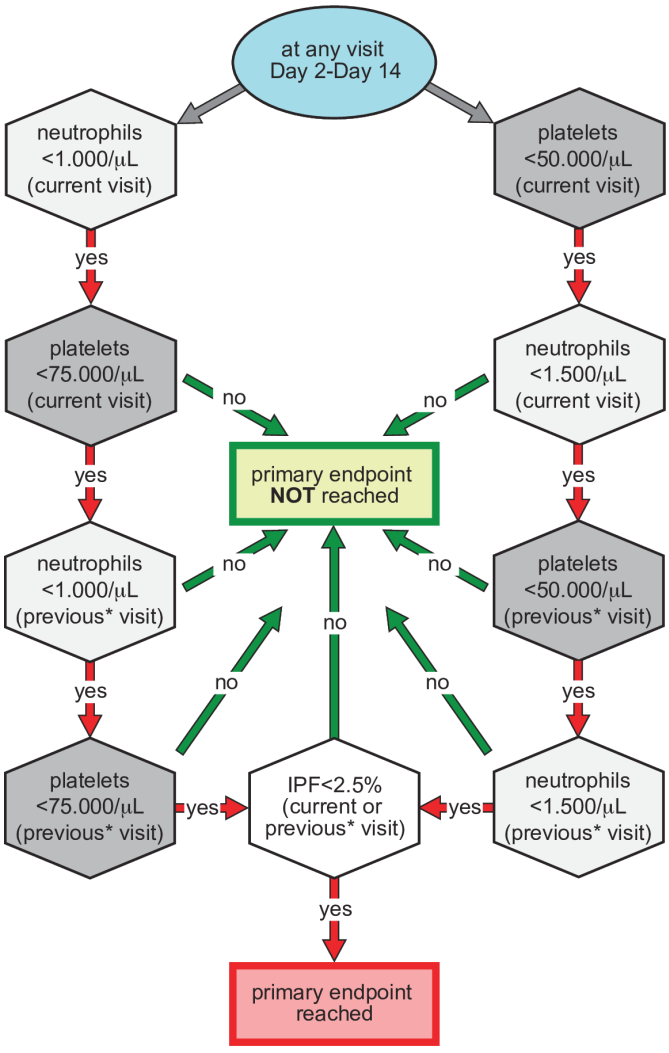

Figure 2 Flow chart that is used to determine the primary endpoint, that is, myelotoxicity in the EPOS-1 trial. * for visit day 2 the previous visit to be considered is day 0–24 hours. EPOS-1, Epirubicin for the Treatment of Sepsis and Septic Shock.

Sample size and power considerations

This is an exploratory trial to test safety of low-dose epirubicin in sepsis. It will serve as a pilot study for a subsequent larger phase II/III trial, in case epirubicin is safe in this indication.

Since sepsis patients are potentially more susceptible to side effects and altered drug toxicity, we base our sample size calculations on data from cancer patients. These receive four times higher doses of epirubicin.[17 33] Myelotoxicity was observed in cancer patients that received repetitive courses of epirubicin. Herait *et al* reported grades 3–4 leucopenia in approximately 20% of patients that were treated every 3–4 weeks using a dose of 85–90 mg/m^2 epirubicin.[33] In another trial, myelotoxicity grades 3–4 using the WHO classification was reported in 14% of patients receiving 71–75 mg/m^2 every 3 weeks.[17]

Based on the assumption that the probability of a myelotoxicity is 18% the probability of observing at least one myelotoxicity out of eight verum-treated patients equals 79.6% based on a binomial distribution. Thus, a total of 30 (8 × verum vs 2× placebo from each phase) patients that reach the 14-day safety endpoint is required. Assuming a mortality of sepsis patients of 30%, it is anticipated that approximately 12 patients in the epirubicin group and three patients in the placebo group per phase will need to be included in the study. Dropouts until day 14 will be replaced until necessary numbers are reached (see figure 1).

Data collection/data management

Data will be collected on an electronic case report form using OpenClinica (OpenClinica, LLC, Waltham, MA, USA) by a trained investigator or study assistant at each respective trial centre. Monitoring will be performed by the Center for Clinical Studies, Jena to its local standard operating procedures. Monitoring, in general, will be performed on-site. All serious adverse events, whether related or not related to study medication, must be reported until 90 days after administration of IMP/control. Patients or relatives are contacted on days 28 and 90 after randomization to obtain the survival status of the participants.

The recommendation will be brought to the attention of the competent higher federal authority and the leading ethics committee as part of the annual safety report or as an urgent safety measure, if necessary.

Statistical analysis

The primary analyses for each dose level will report the proportion of myelotoxicity together with a 95% CI. A potential dose-toxicity association will be analysed using a logistic regression model with dose as covariate. All further analyses for this study will be descriptive. Data analyses will be provided by treatment and overall if applicable. After first and second phase, the DSMB will meet and recommend whether the study will be stopped, or the next higher dose phase can be initiated. The DSMB will be provided with the necessary pre-analysed and raw data. The major stopping rule of the trial will consist of increased toxicity in epirubicin groups as assessed by myelotoxicity.

Ethics and dissemination

The sponsor of the trial is Friedrich Schiller University, Jena, Germany. The trial was approved by the ethics committee of the Jena University Hospital on 20 December 2021 (2021-2440-AMG-ff) and the German Health Authorities (BfArM) on 8 November 2021. In addition, the local ethics committees at each site approved the study protocol and the study competence of each site. Written informed consent is obtained from all patients or their legal representatives. If this is not possible before enrolment in due time, the ethics committees have approved a deferred consent process where the inability to provide consent is confirmed by an independent physician, and the patient is enrolled without informed consent. As soon as the legal representative of the patient is available,

written informed consent is immediately obtained; otherwise, the patient is withdrawn from the study and all study procedures are ended.

The trial is governed by the international standards for Good Clinical Practice developed by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, the Directive 2001/20/EC for clinical trials and General Data Protection Regulation 679/2016 (EC). Results of the trial will be published in a peer-reviewed journal and reported on clinicaltrials.org. All publication will be available in open access.

Patient and public involvement

Patients or the public were not involved in the design of the EPOS-1 trial. The trial design was endorsed by the Deutsche Sepsis Gesellschaft.

DISCUSSION

Despite tremendous research efforts during the last decades, no specific therapy for sepsis exists that targets sepsis-associated organ dysfunction.[2] Instead, treatment relies on the timely administration of broad-spectrum antibiotics, mechanical organ support, along with source control and if necessary organ replacement therapy. Increasing rates of antimicrobial resistance and lack of innovation of new antimicrobials further add to the problem.[2 9] Therefore, new therapeutic approaches are urgently needed. In this study for the first time, we will pharmacologically intend to manipulate disease tolerance to infection, a molecular mechanism that lessens disease severity by enforcing tissue damage control.[34–36] Presumably, manipulation of tissue damage control mechanisms will not impose selection pressure on the pathogens and therefore should not cause antimicrobial resistance to the applied drugs.[14 37] The primary aim of this study is to demonstrate the safety and tolerability of a low dose of epirubicin in sepsis patients. This drug has recently been shown to induce disease tolerance and tissue damage control in animal models of sepsis.[19 38]

With this randomised-controlled, multicentre trial, we aim to investigate whether the administration of low-dose epirubicin is safe in patients with sepsis and septic shock. If this approach proves to be successful, we will be able to provide a sepsis-specific therapy for the first time; that is, targeting the deleterious organ failure. This might ultimately also decrease the rate of antibiotic consumption in the critically ill and improve the antimicrobial resistance rates. In addition, if epirubicin proves to be safe and beneficial for patients with sepsis, it might also extend treatment options for patients living in areas with limited resources and high antimicrobial resistance rates such as in African countries or the Indian subcontinent, among others in which assessment of causing pathogens, determination of antimicrobial resistance patterns is not available for the majority of patients and in which expensive antibiotics cannot be applied. The overall treatment algorithm of patients participating in the clinical trial follows the standard practice for this condition and is in accordance with current guidelines for the treatment of such patients.

A drug licensed for chemotherapy will be applied to a highly vulnerable group, that is, patients with sepsis. Intuitively, this seems to be contraindicated. However, our approach is not intended to use its chemotherapeutic potency. Instead, its potential to induce damage response mechanisms will be applied.[19] Drug dosages are significantly lower than when applied in a single chemotherapeutic cycle. Therefore, relevant toxicity is not expected. Close safety monitoring will be performed, and the major stopping rule of the trial will consist of increased toxicity in the groups that receive epirubicin. As such, in our opinion, the benefits substantially outweigh the potential risks in this trial. The first study site was initiated in June 2022 and the first patient was randomised on 19 October 2022. Five centres can recruit patients since June 2023. Recruitment is planned to finish by the end of 2024.

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Contributors All authors fulfil the ICMJE recommendations for authorships. The roles and contributions of the individual authors are as follows: sponsor representative/principal and coordinating investigator: SW; deputy coordinating investigator: DT-R; project manager: CH; protocol writing and planning of the study: SW, DT-R, FMB, MB, PS, CH, A-JH and LFM; acquisition of funding: SW, FMB and MB; formulation of initial hypothesis: SW and LFM; trial statistician, sample size calculation and statistical analysis plan: PS; molecular analysis: LFM, MGrä and TK; study centre coordinators and recruitment of patients: JE, TR, PM, MGrü and HS. All authors contributed to, read and approved the final manuscript and contributed to the writing.

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Competing interests LFM is an inventor on an international patent (WO 2013/036153) related to the use of anthracyclines for sepsis treatment. All other authors report no competing interests.

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 Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

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