Study protocol for clinical trial according to the German Medicines Act (AMG)

Target

Prospective, randomized, multicenter clinical trial on the impact of therapeutic drug monitoring (TDM) of piperacillin on organ function and survival in patients with severe sepsis or septic shock.

EudraCT-Nummer:	2016-000136-17
Study code ZKS Jena:	ZKSJ0085
Protocol version, date:	Final version 2.0 from 15.09.2017

For the purpose of easier readability, gender-specific differentiation, such as patient, is not used throughout the protocol. Corresponding terms apply to both genders for the purpose of equal treatment.

Document was translated in Englisch using DeepL

Table of contents

1 General

1.1 General overview of the clinical trial (synopsis)

Study title	Prospective, randomized, multicenter clinical trial on the impact of therapeutic drug monitoring (TDM) of piperacillin on organ function and survival in patients with severe sepsis or septic shock.
Study Acronym	Target
Sponsor	Friedrich Schiller University Jena *represented by the* Dean of the Faculty of Medicine Bachstraße 18 07743 Jena
Authorized Sponsor **and** **Clinical trial manager (LKP)**	Stefan Hagel, M.D., M.S. Center for Sepsis Control and Care (CSCC). Institute for Infectious Diseases and Infection Control Jena University Hospital At the clinic 1 07747 Jena Phone: +49 (0) 3641-9324590 Fax: +49 (0) 3641-9324652 E-mail: stefan.hagel@med.uni-jena.de
EudraCT number	2016-000136-17
Target population	Patients with severe sepsis or septic shock
Study design/methodology	Prospective, multicenter, single-blind, randomized controlled treatment optimization study in a parallel-group design. Randomization: 1:1 according to computer-based algorithm, stratified by treatment center. Blinding: Physician open, patient blinded Experimental group: patients with severe sepsis or septic shock with TDM of piperacillin. Control group: patients with severe sepsis or septic shock without TDM of piperacillin.

	Follow-up: 28 days after randomization
Study phase	Phase III
Goals of the clinical trial	Primary objective of the audit: Testing the impact of the intervention on morbidity. Secondary objectives of the audit: Investigation of the influence of the intervention on: • Mortality • Benefit for individual organ systems (lungs, circulation, liver, kidney, central nervous system, hemostasis). • antibiotic consumption, - duration of therapy • Hospital and intensive care unit length of stay • Intervention security
Target figures	Primary Target: SOFA score (individually averaged from day 1 after randomization until discharge from ITS or death, but not exceeding day 10). Secondary targets: • SOFA subscores analogous to the primary endpoint. • 28-day mortality • Duration and cumulative dose of antibiotic therapy. • Number of dose adjustments/therapy cycle • Antibiotic-free days up to a maximum of day 14 • Length of stay in intensive care unit up to maximum day 28 • Hospital stay up to a maximum of day 28 • Days without vasopressors until day 14*. • Days without renal replacement procedure until day 28* • Days without mechanical ventilation until day 28* • Safety (side effects) • Antibiotic therapy costs Other target figures (not relevant for the regulatory earnings report) • Cure of infection ("Clinical Cure") on day 3, 5, 7, 10, 14 after randomization and at end of therapy with piperacillin. • Remediation of microbiological findings ("Microbiological Cure") on day 3, 5, 7, 10, 14 after randomization and at the

	end of therapy with piperacillin. • Incidence of antibiotic-resistant bacteria by day 28. • Re-infection with the same pathogen by day 28 • Superinfection with another pathogen by day 28. • Neurologic outcome (ICDSC) days 7, 10, and 14 and at the end of therapy with piperacillin. • PK/PD indices (including antibiotic concentration >4x MIC 100% (fT>4MIC)). * Only primary ITS/ hospital stay leading to study inclusion.
Number of patients	suitable (eligible): n=920 included (allocated): n=276 analyzed (analyzed): n=234 (2x117) Assumptions: Difference SOFA score 1.4 points, standard deviation 3.8 points, power 80%, two-sided significance level 5%, 2-sample t-test, dropout rate 15%.
Inclusion criteria	• Presence of severe sepsis or septic shock • Onset of severe sepsis or septic shock no longer than 24 hours prior to randomization. • Antimicrobial therapy with piperacillin planned or started. • Age ≥18 years • Written declaration of consent by the patient or his/her legal guardian or authorized representative (or initial consent by the consultant in the case of patients who are incapable of giving consent).
Exclusion criteria	• Pregnancy / Lactation • Anamnestic known hypersensitivity to ß-lactam antibiotics or to any of the other components of the test substance. • Pretreatment with piperacillin (in combination with tazobactam) >24h before randomization. • Patient's participation in another interventional clinical trial • Previous study participation (target) • Therapy restriction or cessation • impaired liver function (Child-Pugh C) • Life expectancy < 28 days due to secondary diseases • Piperacillin measurement not possible within 24 hours after

	randomization
Investigational product	Active ingredient: Piperacillin (in combination with tazobactam) - different trade names (depending on local availability).
Treatments/treatment plan	A) ***PipTDM*** study arm (Individual Dosing): - *Patients **without** pretreatment with piperacillin*: Rando-mization is followed by bolus administration of piperacillin/tazobactam (4.5g) over 30 minutes and immediately followed by continuous intravenous infusion of piperacillin/tazobactam, depending on current renal function at the following dosage (run rate perfusor, 4.5g/50ml NaCl 0.9%): • eGFR ≥ 20 ml/min 13.5g/24 h (6.3 ml/h) • eGFR < 20 ml/min 9g/24 h (4.2 ml/h). Starting on day 1 after randomization, daily determination of the piperacillin concentration is performed, followed by individual dose adjustment based on the minimum inhibitory concentration (MIC) of the sepsis pathogen. - *Patients **with** pretreatment with piperacillin within the last 24 hours*: Bolus administration is omitted; after randomization, continuous intravenous infusion of piperacillin/tazobactam is given, depending on current renal function at the following dosage (run rate perfuser, 4.5g/50ml NaCl 0.9%): • eGFR ≥ 20 ml/min 13.5g/24 h (6.3 ml/h) • eGFR < 20 ml/min 9g/24 h (4.2 ml/h). Starting on day 1 after randomization, the daily determination of the piperacillin concentration is performed with subsequent individual dose adjustment based on the minimum inhibitory concentration (MIC) of the sepsis pathogen. Optionally, a determination of the piperacillin concentration with subsequent dose optimization can already be performed on day 0. B) ***PipKon*** study arm (control group): - *Patients **without** pretreatment with piperacillin*: After randomization, bolus administration of piperacillin/tazobactam (4.5g) for 30 minutes is followed immediately by continuous intravenous infusion of piper-acillin/tazobactam, depending on renal function, at the following dosage (run rate perfuser, 4.5g/50ml NaCl 0.9%): • eGFR ≥ 20 ml/min 13.5g/24 h (6.3 ml/h) • eGFR < 20 ml/min 9g/24 h (4.2 ml/h). - *Patients **with** pretreatment with piperacillin*: bolus administration is omitted; after randomization, continuous intravenous infusion of

	piperacillin/tazobactam is performed, depending on renal function, at the following dosage (run rate perfuser, 4.5g/50ml NaCl 0.9%): • eGFR ≥ 20 ml/min 13.5g/24 h (6.3 ml/h) • eGFR < 20 ml/min 9g/24 h (4.2 ml/h). If renal function changes during the further course of therapy, the dosage of piperacillin/tazo-bactam is adjusted in the control group according to the following guidelines: • eGFR ≥ 20 ml/min or cont. RRT: 13.5g/24 h (6.3 ml/h) • eGFR < 20 ml/min or iHD: 9g/24 h (4.2 ml/h).
Audit-related procedures and laboratory tests	Determination of piperacillin concentration by HPLC (high performance liquid chromatography) or LC-MS/MS (liquid chromatography-mass spectrometry/mass spectrometry).
Timetable (duration of study)	**Audit-related** Recruitment period: approx. 3 years Inclusion first patient: January 2017 Inclusion last patient: 4th quarter 2019 End of examination last patient: 4th quarter 2019 Closing of the database: 1st quarter 2020 End of statistical analysis: 2nd quarter 2020 Integrated Final Report: 3rd quarter 2020 **Patient-related study duration** Intervention duration: treatment duration with test substance as determined by the treating physician, intervention maximum 10 days Follow-up duration: 28 days after randomization.
Number of test centers	10-15
Statistical methods	Primary analysis population: intention-to-treat. Primary analysis SOFA score: mixed linear model; fixed factors are intervention as well as SOFA score and renal insufficiency/renal replacement therapy at the time of randomization (baseline); random factor is the study center (random intercept); Secondary analyses (exploratory) according to the scaling of the secondary outcome measures: Chi2 test / Fisher's exact test, T test, Mann-Whitney U test, logrank test, generalized mixed linear models for further follow-up data; frequencies and incidences of

	adverse events.
Funding	Federal Ministry of Education and Research (BMBF) Funding code: 01EO1502

1.2 Organizational structure

Function/ Qualification	Name/Facility	Address, Phone number, net mail address
Sponsor according to the German Medicines Act	Friedrich Schiller University Jena	P.O. Box 07737 Jena
Authorized Sponsor	Stefan Hagel, M.D., M.Sc.	Center for Sepsis Control and Care (CSCC). Institute for Infectious Diseases and Infection Control Jena University Hospital At the clinic 1 07747 Jena Phone: +49 (0) 3641-9-324590 Fax: +49 (0) 3641-9-324652 E-mail: stefan.hagel@med.uni-jena.de
Head of the clinical trial (LKP) according to the AMG		
Representative of the LKP	PD Frank Bloos, MD, PhD	Center for Sepsis Control and Care (CSCC). Clinic for Anesthesiology and Intensive Care Medicine Jena University Hospital At the clinic 1 07747 Jena Phone: +49 (0) 3641-9-323289 E-mail: frank.bloos@med.uni-jena.de
Statistician/ Biometrician	Prof. Dr. Peter Schlattmann Dr. Heike Hoyer	Institute for Medical Statistics, Informatics and Documentation (IMSID) Jena University Hospital Bachstraße 18 07743 Jena Tel.: +49 (0) 3641 9-34130 Fax: +49 (0) 3641 9-33200 E-mail: peter.schlattmann@med.uni-jena.de E-mail: heike.hoyer@med.uni-jena.de
Contact for analytics and sample bank	PD. Dr. Dr. Michael Kiehntopf	Institute for Clinical Chemistry and Laboratory Diagnostics Jena University Hospital At the clinic 1 07747 Jena Tel.: +49 (0) 3641 9-325000 Fax: +49 (0) 3641 9-325002 E-mail: michael.kiehntopf@med.uni-jena.de

Function/ Qualification	Name/Facility	Address, Phone number, net mail address
Manufacturer/supplier of the investigational medicinal product	According to the specification of the local pharmacy of the respective test center	
Project Management	Sandra fiddler	Center for Clinical Studies Jena University Hospital Salvador Allende Square 27 07747 Jena Tel.: +49 (0) 3641 9-396620 Fax: +49 (0) 3641 9-399969 E-mail: sandra. fiedler@med.uni-jena.de
Data Management	Cornelia Eichhorn Monique Philipp	Center for Clinical Studies Jena University Hospital Salvador Allende Square 27 07747 Jena Tel.: +49 (0) 3641 9-396653 +49 (0) 3641 9-323583 Fax: +49 (0) 3641 9-399969 Email: cornelia.eichhorn@med.uni-jena.de / E-mail: monique.philipp@med.uni-jena.de
Monitoring	Dr. Andrea Rößler Anke Braune	Center for Clinical Studies Jena University Hospital Salvador Allende Square 27 07747 Jena Tel.: +49 (0) 3641 9-396664 +49 (0) 3641 9-323573 Fax: +49 (0) 3641 9-399969 E-mail: andrea.roessler@med.uni-jena.de Email: Anke.braune@med.uni-jena.de
Pharmacovigilance (Safety Management)	Manja Schein	Center for Clinical Studies Jena University Hospital Salvador Allende Square 27 07747 Jena Tel.: +49 (0) 3641 9-396693 Fax: +49 (0) 3641 9-399969 E-mail: manja.schein@med.uni-jena.de
Data and Safety Monitoring Board (**DSMB**)	Angela Huttner, MD	Infection Control Program University Hospitals of Geneva 4, rue Gabrielle-Perret-Gentil CH-1211 Genève 14 E-mail: angela.huttner@hcuge.ch Tel.: +41 79 553 33 96 Fax: +41 22 372 39 87
		Research Center Charlottenburg for Outpatient Studies (RCCOS)

Function/ Qualification	Name/Facility	Address, Phone number, net mail address
	Prof. Dr. med. Hartmut Lode	Reichsstrasse 2 At Theodor-Heuss-Platz 14052 Berlin-Charlottenburg (Westend) E-mail: haloheck@zedat.fu-berlin.de Phone: +49 (0)30 - 88 71 97 92 Fax: +49 (0)30 - 88 71 97 93
	Prof. Dr. Walter Lehmacher	Institute for Medical Statistics, Informatics and Epidemiology - IMSIE Kerpener Street 62, 50937 Cologne, Germany E-mail: walter.lehmacher@uni-koeln.de Phone: +49 (0)221 478-6500 Fax: +49 (0)221 478-6520
Lead Ethics Committee	Ethics Committee of the Friedrich Schiller University Jena	Bachstraße 18 07740 Jena Phone: +49 (0)3641-933770 Fax: +49 (0)3641-933771 E-mail: ethikkommission@med.uni-jena.de
Responsible higher federal authority	Federal Institute for Drugs and Medical Devices (BfArM)	Kurt-Georg-Kiesinger-Allee 3 53175 Bonn Tel: +49 (0)228-99-307-30 Fax: +49 (0)228-99-307-5207
Laboratories	Local laboratory that performs the determination of piperacillin concentration at the respective test center.	
Pharmacy	Local pharmacy of the respective test center	
Financial support/co-financing of the study, material and other support	Federal Ministry of Education and Research (BMBF) Funding code: 01EO1502	Federal Ministry of Education and Research, Health Research Division 11055 Berlin Tel.: 030 1857-0 Fax: 030 1857-5503

1.3 Signatures

The following persons agree to the content of the clinical trial and indicate this with their signature.

_____

Dr. Stefan Hagel, LKP, Sponsor Representative Date

_____

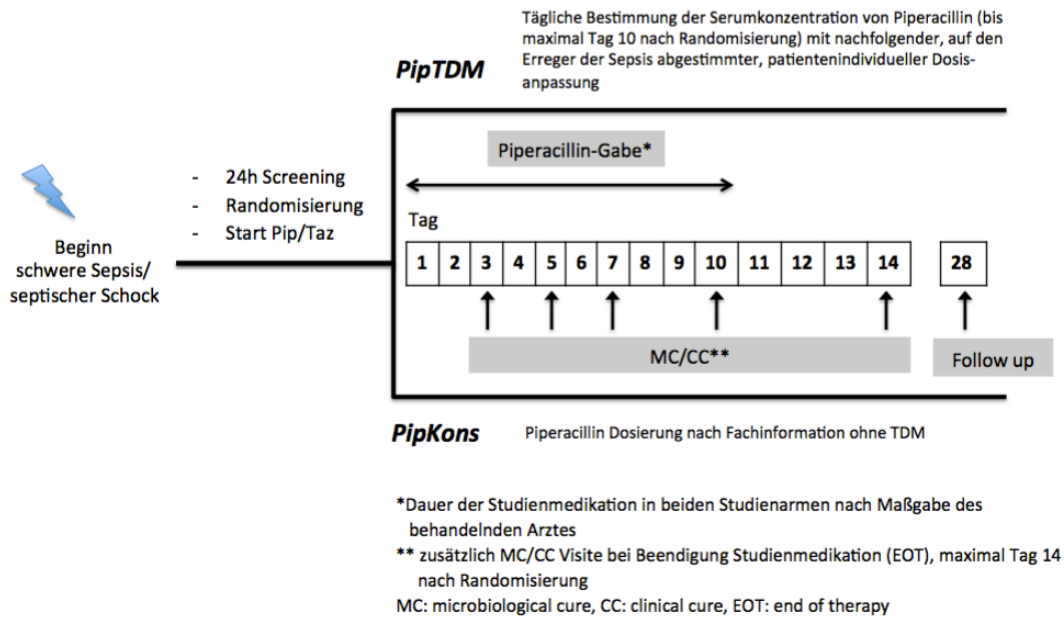
Prof. Dr. Peter Schlattmann, Biometrician Date

1.4 List of abbreviations

Abbreviation	Meaning
AE	Adverse event
AMG	Medicines Act
APACHE	Acute Physiology And Chronic Health Evaluation
BfArM	Federal Institute for Drugs and Medical Devices
respectively	respectively
CC	Clinical cure
CPIS	Clinical pulmonary infection score
CRF/e-CRF	Case Report Form, survey form; electronic survey form.
CSCC	Center for Sepsis Control and Care
CTC	Common Toxicity Criteria
DSMB	Data and Safety Monitoring Board
EK	Ethics Commission(s)
Possibly	possibly
FI	Specialized information
FPFV	First Patient First Visit, 1st visit of the 1st included patient.
GCP	Good Clinical Practice
GCP-V	GCP Regulation
if necessary	if necessary
ICDSC	Intensive Care Delirium Screening Checklist
IFB	Integrated research and treatment center
IHD	Intermittent hemodialysis
ISF	Investigator Site File, Investigation Center Folder
ITS	Intensive Care Unit
KH	Hospital
LC-MS/MS	Liquid chromatography-mass spectrometry/ mass spectrometry/ Liquid chromatography-mass spectrometry/ mass spectrometry
LKP	Head of the clinical trial, study director
LPLV	Last Patient Last Visit, last visit of the last included patient.
MC	Microbiological cure
MHK	Minimum inhibitory concentration
MIC	Minimal Inhibitory Concentration = Minimum inhibitory concentration
PI	Principal Investigator, Study Director, LKP

PK/PD	Pharmacokinetics/ Pharmacodynamics
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event, serious adverse event
SAP	Statistical Analysis Plan
SOFA	Sequential Organ Failure Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction, suspected case of a serious unexpected adverse reaction.
TDM	Therapeutic Drug Monitoring
TMF	Trial Master File, central trial folder
z. B.	for example

1.5 Flowchart of the clinical trial process



*Dauer der Studienmedikation in beiden Studienarmen nach Maßgabe des behandelnden Arztes
** zusätzlich MC/CC Visite bei Beendigung Studienmedikation (EOT), maximal Tag 14 nach Randomisierung
MC: microbiological cure, CC: clinical cure, EOT: end of therapy

1.6 Clinical trial schedule/visit plan

		Days after randomization																
	S	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	EOT	E	28
Inclusion/exclusion criteria	X																		
Declaration of consent		X																	
Randomization		X																	
Demographics		X																	
Blood cultures		X																	
Diagnoses		X																	
APACHE II, SAPS II score		X																	
Capture surgical Interventions		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[1]	
SOFA score		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[1]	
Sepsis criteria		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Recording of concomitant		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[1]	
Routine laboratory		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[1]	
Capture surgical Drainage		X	X	X	X	X	X	X	X	X	X	X					X	X[1]	
Clinical cure					X		X		X			X				X	X	X[1]	
Microbiol. cure					X		X		X			X				X	X	X[1]	
CPIS		X			X		X		X			X				X	X	X[1]	
PCT, CRP		X			X		X		X			X					X		
ICDSC									X			X				X	X	X[1]	
Collecting urine		X			X			X											
Survival status																X	X	X[1]	X
Study inter - vention		X	X	X	X	X	X	X	X	X	X	X							
Administration of piperacillin[2]		X	X	X	X	X	X	X	X	X	X	X							
TDM[3]		X	X	X	X	X	X	X	X	X	X	X							
Documentation of adverse events[4]		X	X	X	X	X	X	X	X	X	X	X	X						
Serum and plasma sample[5]		X	X	X	X	X	X	X	X	X	X	X							

S: screening; EOT: end of therapy (PipKons) or end of intervention (PipTDM); E: Discharge from ITS; [1] If discharge from ITS before day 14; [2] As determined by the treating physician; [3] Determination of piperacillin concentration occurs in both study arms, but in the *PipKon arm the* result is not reported to the treating physician; [a] Optional, exclusively in patients who were pretreated with piperacillin within 24 h before randomization; [4] Documentation of adverse events up to 24 h after last administration of study medication; 5Heparin plasma and EDTA plasma (9 ml monovette each) for central sample bank will be frozen at -80°C, provided that informed consent for this sample collection has been obtained.

2 Question and background

2.1 Background

The cause of sepsis is a systemic inflammatory reaction caused by an infection. (1) The primary and secondary mediators released significantly determine the pathophysiological consequences of sepsis. The multifactorial impairment of tissue oxygenation, increased apoptosis, and direct tissue damage by released oxygen radicals from activated leukocytes are ultimately responsible for the development of multiple organ dysfunction syndrome (MODS), the progression of which is the most common cause of death in patients with sepsis.

Since 2005, mandatory criteria have been deposited in the ICD-10 GM (International Classification of Diseases, www.dimdi.de) that make sepsis codable. In a recent query of the ICD-10-GM codes sepsis (R65.0!), severe sepsis (R65.1!) and septic shock (R57.2!) for the year 2011, an incidence of 106/100,000 population for sepsis, 84/100,000 for severe sepsis and 23/100,000 for septic shock could be determined. (2) When cases less than 20 years of age are excluded, the incidence increases to 121/100,000 for sepsis, 101/100,000 for severe sepsis, and 28/100,000 for septic shock. The incidence of severe sepsis and septic shock is thus 107/100,000 population, extrapolating to a total of 88,000 cases/year in Germany. Hospital mortality was 10.5% for sepsis, 42.8% for severe sepsis, and 60.5% for septic shock. Respiratory infections were the most common sources of infection (sepsis: 7.8%; severe sepsis: 48.2%; septic shock: 60.2%), followed by soft tissue/bone infections (17.4, 20.4, and 25.7%), and intra-abdominal infections (11.4, 18.1, and 25.9%). The most common sepsis pathogens were *S. aureus* (26.8%), *E. coli* (44.7%), and *Streptococcus spp.* (18.7%). *Pseudomonas spp.* were causative agents of sepsis in only 4.6%. These current results are thus relatively consistent with the data of the German SepNet prevalence study from 2003-2004. (3) Thus, an average of 150 patients die daily from sepsis throughout Germany, comparable to deaths from acute myocardial infarction (175/day) and more than from breast cancer (49/day) or colorectal cancer (55/day). With approximately 60,000 deaths, septic diseases represent the third leading cause of death. Based on data from a large German insurance company (13 million insured), the hospital-related costs for patients with severe sepsis (R65.1!) were determined in the current epidemiological study. Accordingly, the median cost per case is € 59,118 for a surviving patient and € 52,101 for a non-surviving patient. Based on current epidemiological case numbers, direct costs in adults over 20 years of age amount to approximately € 3.8 billion annually in Germany. Following the human capital approach, the indirect costs due to premature death alone amount to an additional € 2.43 billion.

The persistently high incidence of this disease, which is associated with high mortality and high costs, necessitates the use of more efficient therapeutic procedures. However, it has become apparent that a so-called "magic bullet" - i.e., a single therapeutic procedure that determines the prognosis - does not exist in the treatment of sepsis. Rather, the treatment of severe sepsis and septic shock consists of a mosaic that must be implemented consistently and in all its facets. Intensive care treatment of sepsis is based on causal therapy- (antimicrobial chemotherapy, focal decontamination), supportive therapy- (rapid circulatory stabilization, mechanical ventilation, renal replacement therapy, correction of disturbed metabolic homeostasis), and adjunctive therapy- interventions to be implemented in addition to and in parallel with the above measures under appropriate circumstances. While the selection and timing of antibiotic therapy in sepsis patients has received considerable attention in recent years, the evaluation of optimal dosages and their monitoring strategies are not yet mature. However, several studies have shown that in more than half of sepsis patients, under the standard recommended dosage according to the professional information, the serum concentration of antibiotics is too low and this is associated with

a worse outcome. (4) In addition, these subtherapeutic antibiotic concentrations have been shown to drive the development of antibiotic-resistant bacteria. (5) However, no study to date has investigated whether determining antibiotic concentration with individual dose adjustment improves outcome in sepsis patients.

This study aims to optimize antimicrobial therapy by adjusting the dose of piperacillin to the individual sepsis pathogen. This could contribute to a substantial improvement in the prognosis of patients with severe sepsis or septic shock. To date, no study results are available on this issue.

2.2 Question and justification of the project

Adequate antibiotic therapy is a critical factor in the survival of patients with severe sepsis and septic shock. (6) The most important determinants of adequate antibiotic therapy are the minimum inhibitory concentration (MIC) of the pathogen to the chosen agent and the localization of the infection. Inadequate antimicrobial therapy is characterized, among other things, by the fact that at the site of infection the MIC of the pathogen is not reached by the achieved drug concentration. This results in uncontrolled multiplication of the pathogens. The unit doses recommended in the technical information and sensitivities shown in antibiograms (sensitive, intermediate or resistant tested) are based on the assumption that the pharmacokinetics (PK) of the drug corresponds to that of a "normal patient" and results in adequate antibiotic therapy. In fact, however, drug distribution and excretion capacity are highly variable and difficult to predict, especially in patients with severe sepsis or septic shock. (7,8) Thus, in the early phase of sepsis, very high doses may be necessary in patients with preserved good organ function to ensure adequate antibiotic therapy, as there may be a substantial increase in renal clearance ("augmented renal clearance"), especially for the hydrophilic β-lactam antibiotics, in the context of the hyperdynamic circulatory situation. (9) In the context of septic shock, a so-called "capillary leak" also develops and a considerable proportion of the antibiotic substance is distributed into a "deep compartment" as a result. There is a risk that, as a consequence, sufficiently high tissue concentrations of the antibiotic are not reached at the site of infection. Intensified volume therapy also leads to a temporary increase in the distribution volume and can cause a reduction in the antibiotic concentration at the site of action. In addition to these pathophysiologic effects of sepsis, hypoalbuminemia is often present and may result in decreased plasma protein binding of antibiotics. This increases the free antibiotic concentration in the serum, which in turn may lead to increased renal clearance. In contrast, if organ failure occurs later in the course of the disease, a significant dose reduction to relatively low doses may be necessary to avoid unnecessarily high concentrations resulting in undesirable side effects. For example, β-lactam antibiotics can have a neurotoxic effect via interactions with GABA receptors, particularly in the case of overdose, and can lead to a reduction in vigilance or seizures, up to and including nonconvulsive status epilepticus or coma. (10,11) Similarly, in the context of simultaneous administration of various drugs via enzyme induction, a significant dose increase may be required.

The test substance piperacillin selected for this study has already been shown in several studies to be underdosed in the majority of patients with severe sepsis or septic shock. For example, in a study by *Taccone et al.* in the early phase of severe sepsis or septic shock, sufficient piperacillin serum concentrations could be measured in only 12 of 27 patients (44%), i.e., concentrations above the required target level (>50%fT > 4×MHK pseudo-monas) in more than half the time of a dose interval. (12) In a study by *Blondiaux et al*, a continuous infusion of piperacillin/tazobactam was administered to patients with sepsis, after administration of a bolus. The piperacillin/tazo-bactam dose was adjusted when the concentration fell to less than 4 times the MIC of the causative pathogen for the infection or when toxic concentrations were reached (defined in the study as >150mg/L). With the initial dosing

recommendations implemented according to the drug label, only 50% of patients had adequate serum piperacillin concentrations. After dosage adjustment, the proportion increased to as high as 75%. (13) The same conclusion was reached by *Roberts et al.* when they prospectively studied serum concentrations of ß-lactam antibiotics in 236 critically ill patients in the intensive care unit. Dose adjustments were required in 74% of patients, with dose increases required in 50% of cases. (14) *Patel et al.* studied serum concentrations of ß-lactam antibiotics in 50 burn patients. Here, only 40% of patients had antibiotic concentrations above the MIC (100% fT> MIC) over the entire dose interval and only 18% of patients reached concentrations >4x MIC (100% fT> 4x MIC). In addition, it was shown that shorter antibiotic therapy was required in those patients with adequate antibiotic concentrations. (15) In a recent work, it was also shown that piperacillin serum concentrations showed wide variations in 11 critically ill patients studied (4.9 mg/l - 98 mg/l) and, in addition to this inter-individual variation, strong intra-individual concentration variations were also evident. (16) *Carlier et al.* further demonstrated that 37% of patients with augmented renal clearance (glomerular filtration rate >130ml/min) did not reach the target 50% fT>MHK. (17) In a review of 57 studies, the authors concluded that the pharmacokinetics of ß-lactam antibiotics in critically ill patients is highly heterogeneous and unpredictable in most cases. In addition to these data on underdosing in critically ill patients, studies show that adequate dosing of antibiotics can also reduce the risk for the emergence of antibiotic-resistant bacteria. In the context of underdosing, eradication of highly sensitive pathogens results in concomitant selection of less sensitive pathogens in the context of subinhibitory/bactericidal serum concentrations of antibiotics. (5)

Against the background of pathophysiological changes in pharmacokinetics (PK) and pharmacodynamics (PD), individual dosing and therapeutic drug monitoring appear to be useful, especially in critically ill patients, to ensure adequate anti-infective therapy. However, routine concentration determination for anti-infectives, which are frequently used in intensive care units, has so far only been an accepted standard for aminoglycosides, vancomycin and voriconazole. For these substances, target concentrations for valley and maximum concentrations have been established; here, TDM makes a decisive contribution to finding the appropriate dose and avoiding toxicity.

A recently published randomized controlled trial by *De Wale et al. evaluated* the effect of therapeutic drug monitoring in 41 patients receiving piperacillin/tazobactam or meropenem therapy. The study demonstrated that only 21% of patients had adequate serum piperacillin concentrations on the first day after initiation of therapy. In the TDM intervention group, 76% of patients required dose adjustment. By the third day after treatment initiation, 58% of patients with TDM had reached the target concentration (100% fT> 4xMHK). In contrast, this was the case in only 16% of the patients in the group without TDM. Patients in the control group without TDM also had lower median baseline concentrations than patients receiving TDM-assisted therapy (26 vs. 40mg/l). (18)

Thus, the following reasons argue for TDM of anti-infectives in the intensive care setting: (19)

- Disease- (and pharmaco-) therapy-related changes lead to relevant inter- and intraindividual variations of pharmacokinetic variables (Cl; Vd; t1/2) of antibiotics in critically ill ICU patients, which may require dose adjustment, to avoid underdosing and treatment failure.
- Established PK/PD models for anti-infectives demonstrating clear relationships between serum concentrations achieved and safe therapy.
- The lack of reliable parameters to assess the success of therapy in the crucial first 24-48 h of therapy.
- The lack of therapeutic alternatives with the increasing incidence of multidrug-resistant pathogens.
- Differences in gender, age, height, body weight and concomitant diseases.

2.3 Justification of treatment and examination procedures, benefit-risk assessment.

Given the continued high mortality of severe sepsis or septic shock, the increasing prevalence of multidrug-resistant pathogens, and the lack of new antibiotics, optimal use of existing agents is imperative. As stated in the previous section, under the recommended unit doses according to the professional information, over- or underdosing of antibiotics occurs in more than half of the patients with severe sepsis or septic shock, due to multiple physiological changes in the course of the disease. Underdosing is associated with a worse outcome and promotes the emergence of resistant bacteria. Excessive antibiotic concentrations, in turn, increase the risk of adverse events (e.g., neurotoxicity). Due to inter- and intraindividual variations in concentration, patient-specific dosing of antibiotics seems to be a promising approach to achieve the best possible clinical treatment outcome while minimizing toxicity and avoiding the development of resistance. However, no study results are available to date on this issue. The chosen test substance is piperacillin, a ß-lactam antibiotic of the ureidopenicillin group, which contains a four-membered lactam ring in its structural formula and is used for the intravenous treatment of bacterial infectious diseases. Piperacillin is administered almost exclusively as a combination preparation with the ß-lactamase inhibitor tazobactam. Piperacillin is bactericidal, and its effects are based on inhibition of cell wall synthesis. Tazobactam is a ß-lactamase inhibitor and extends the spectrum of activity of piperacillin. The spectrum of activity of the piperacillin/tazobactam combination includes Gram-positive (including non-oxacillin-resistant staphylococci and *E. faecalis*) and Gram-negative germs (including Pseudomonas, Proteus, *E. coli*, ß-lactamase formers) and anaerobes. Piperacillin/tazobactam is among the substances recommended for empiric antibiotic therapy in the German S3 guideline on prevention, diagnosis, therapy, and follow-up of sepsis of the German Sepsis Society and the German Interdisciplinary Association for Intensive Care and Emergency Medicine (20) and is the most frequently prescribed substance in this indication in Germany. (21)

In the intervention group, bolus administration is followed by continuous intravenous infusion of the test substance with regular determination of the serum concentration of piperacillin, followed by patient-specific dose adjustment of piperacillin/tazobactam according to the sepsis pathogen. Determination of piperacillin serum concentration alone is sufficient after it has been shown that piperacillin and tazobactam are subject to linear pharmacokinetics (thus, inadequate dosing of piperacillin is associated with inadequate dosing of tazobactam and *vice versa*). (22) For patients in the intervention group, the immediate benefit is an individualized, pathogen-adapted dose adjustment of the test substance in the context of antimicrobial therapy for sepsis. Over- or underdosing of the test substance can thus be detected and intervened at an early stage.

In the control group, bolus administration is followed by continuous intravenous infusion of the test substance at the recommended dose according to the technical information. In case of renal insufficiency, the dosage is adjusted according to the technical information. Since in the control group the measures performed correspond to the standard of regular medical care, no ethical concerns are apparent.

In both study groups, a continuous infusion of the test substance is chosen as the mode of administration, since this is associated with a simpler determination of the pharmacokinetics (time-independent determination of the concentration). In a recently published randomized controlled trial in patients with sepsis, no inferiority was found for continuous administration compared with intermittent administration, so that this mode of administration can be regarded as equivalent to intermittent infusion. (23) In order to achieve the best possible clinical treatment outcome or safety for the study participants, a combination of the test substance with other antimicrobial substances is possible in both treatment groups, as determined by the treating physician. In case of microbiological evidence or clinical suspicion of ineffectiveness of the test substance, the treating physician can also change the antibiotic therapy at any time. Blood samples are taken daily from the study participants over several days for piperacillin

concentration determination and for the central biomaterial bank. This measure is harmless. The amount of blood obtained poses no risk to the patient. Puncture of blood vessels is not necessary, since the blood samples can be collected via vascular catheters that are already in place anyway as part of the intensive medical treatment. The blood samples obtained in this study are subject to strict measures to ensure data protection.

2.4 Assessment of the transferability of the expected study results to practice.

If the benefit of a TDM for piperacillin in patients with severe sepsis or septic shock is proven in the study, it can be assumed that the treatment concept will be widely used in everyday clinical practice. This is against the background that mortality in this clinical picture remains unacceptably high and alternative treatment concepts are currently not available. It should be noted, however, that a validated method for determining the piperacillin concentration is not yet available in all laboratories. However, as mass spectrometry becomes more widespread in many laboratories, a validated method is expected to be available in many clinics in the near future.

2.5 Literature

1 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med. 1992 Jun;20(6):864-74.

2. Heublein S, Hartmann M, Hagel S, Brunkhorst F. Epidemiology of sepsis in German hospitals-an analysis of administrative data. INTENSIV-News. 2013;(4).

3 Engel C, Brunkhorst FM, Bone H-G, Brunkhorst R, Gerlach H, Grond S, et al. Epidemiology of sepsis in Germany: results from a national prospective multicenter study. Intensive Care Med. 2007 Apr;33(4):606-18.

4 Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, et al. DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current β-Lactam Antibiotic Doses Sufficient for Critically Ill Patients? Clin Infect Dis Off Publ Infect Dis Soc Am. 2014 Apr;58(8):1072-83.

5 Abdul-Aziz MH, Lipman J, Mouton JW, Hope WW, Roberts JA. Applying pharmacokinetic/pharmacodynamic principles in critically ill patients: optimizing efficacy and reducing resistance development. Semin Respir Crit Care Med. 2015 Feb;36(1):136-53.

6. MacArthur RD, Miller M, Albertson T, Panacek E, Johnson D, Teoh L, et al. Adequacy of early empiric antibiotic treatment and survival in severe sepsis: experience from the MONARCS trial. Clin Infect Dis Off Publ Infect Dis Soc Am. 2004 Jan 15;38(2):284-8.

7. Roberts JA, Lipman J. Antibacterial dosing in intensive care: pharmacokinetics, degree of disease and pharmacodynamics of sepsis. Clin Pharmacokinet. 2006;45(8):755–73.

8 Sinnollareddy MG, Roberts MS, Lipman J, Roberts JA. β-lactam pharmacokinetics and pharmacodynamics in critically ill patients and strategies for dose optimization: a structured review. Clin Exp Pharmacol Physiol. 2012 Jun;39(6):489-96.

9. Udy AA, Lipman J, Jarrett P, Klein K, Wallis SC, Patel K, et al. Are standard doses of piperacillin sufficient for critically ill patients with augmented creatinine clearance? Crit Care. 2015 Jan 30;19(1):28.

10. Beumier M, Casu GS, Hites M, Wolff F, Cotton F, Vincent JL, et al. Elevated beta-lactam concentrations are associated with neurological deterioration in ICU septic patients. Minerva Anestesiol. 2014 Sep 15;

11 Mattappalil A, Mergenhagen KA. Neurotoxicity with antimicrobials in the elderly: a review. Clin Ther. 2014 Nov 1;36(11):1489-511.e4.

12. Taccone FS, Laterre P-F, Dugernier T, Spapen H, Delattre I, Wittebole X, et al. Insufficient β-lactam concentrations in the early phase of severe sepsis and septic shock. Crit Care. 2010 Jul 1;14(4):R126.

13. Blondiaux N, Wallet F, Favory R, Onimus T, Nseir S, Courcol RJ, et al. Daily serum piperacillin monitoring is advisable in critically ill patients. Int J Antimicrob Agents. 2010 May;35(5):500-3.

14. Roberts JA, Ulldemolins M, Roberts MS, McWhinney B, Ungerer J, Paterson DL, et al. Therapeutic drug monitoring of beta-lactams in critically ill patients: proof of concept. Int J Antimicrob Agents. 2010 Oct;36(4):332-9.

15. Patel BM, Paratz J, See NC, Muller MJ, Rudd M, Paterson D, et al. Therapeutic drug monitoring of beta-lactam antibiotics in burns patients--a one-year prospective study. Ther Drug Monit. 2012 Apr;34(2):160-4.

16. Carlier M, Carrette S, Stove V, Verstraete AG, De Waele JJ. Does consistent piperacillin dosing result in consistent therapeutic concentrations in critically ill patients? A longitudinal study over an entire antibiotic course. Int J Antimicrob Agents. 2014 May;43(5):470-3.

17. Carlier M, Carrette S, Roberts JA, Stove V, Verstraete A, Hoste E, et al. Meropenem and piperacillin/tazobactam prescribing in critically ill patients: does augmented renal clearance affect pharmacokinetic/pharmacodynamic target attainment when extended infusions are used? Crit Care Lond Engl. 2013 May 3;17(3):R84.

18. De Waele JJ, Carrette S, Carlier M, Stove V, Boelens J, Claeys G, et al. Therapeutic drug monitoring-based dose optimisation of piperacillin and meropenem: a randomised controlled trial. Intensive Care Med. 2014 Mar;40(3):380-7.

19 Roberts JA. Using PK/PD to optimize antibiotic dosing for critically ill patients. Curr Pharm Biotechnol. 2011 Dec;12(12):2070-9.

20 Reinhart K, Brunkhorst FM, Bone H-G, Bardutzky J, Dempfle C-E, Forst H, et al [Prevention, diagnosis, treatment, and follow-up care of sepsis. First revision of the S2k Guidelines of the German Sepsis Society (DSG) and the German Interdisciplinary Association for Intensive and Emergency Care Medicine (DIVI)]. Anaesthesist. 2010 Apr;59(4):347-70.

21. Bloos F, Thomas-Rüddel D, Rüddel H, Engel C, Schwarzkopf D, Marshall JC, et al. Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: a prospective observational multi-center study. Crit Care Lond Engl. 2014 Mar 3;18(2):R42.

22 Auclair B, Ducharme MP. Piperacillin and tazobactam exhibit linear pharmacokinetics after multiple standard clinical doses. Antimicrob Agents Chemother. 1999 Jun;43(6):1465-8.

23. Dulhunty JM, Roberts JA, Davis JS, Webb SAR, Bellomo R, Gomersall C, et al. A Multicenter Randomized Trial of Continuous versus Intermittent β-Lactam Infusion in Severe Sepsis. Am J Respir Crit Care Med. 2015 Jul 22;

24. Roger C, Cotta MO, Muller L, Wallis SC, Lipman J, Lefrant JY, Roberts JA. Impact of renal replacement modalities on the clearance of piperacillin-tazobactam administered via continuous infusion in critically ill patients. Int J Antimicrob Agents. 2017 Aug;50(2):227-231

3 Goals of the clinical trial

The primary objective of the study is to determine whether optimization of antimicrobial therapy by means of patient-specific dose adjustment of the test substance piperacillin has a beneficial effect on organ function in severe sepsis or septic shock and is superior to dosing according to the technical information. This will be investigated using a global morbidity measure (mean total SOFA score).

3.1 Primary objective of the trial and primary endpoint

To determine whether and to what extent TDM-based piperacillin therapy provides a benefit to patient organ function. The primary endpoint is the *Sequential Organ Failure Assessment* (SOFA) score. It will be included in the analysis as an individual mean score over the course from day 1 after randomization until discharge from the ITS or death, but not exceeding day 10.

3.2 Secondary targets and secondary endpoints

The secondary study objectives will examine the impact of the intervention on:

Secondary targets:

- SOFA subscores analogous to the primary endpoint.
- 28-day mortality
- Duration and cumulative dose of antibiotic therapy.
- Number of dose adjustments/therapy cycle
- Antibiotic-free days up to a maximum of day 14
- Length of stay in intensive care unit up to maximum day 28
- Hospital stay up to a maximum of day 28
- Days without vasopressors until day 14*.
- Days without renal replacement procedure until day 28*
- Days without mechanical ventilation until day 28*
- Safety (side effects)
- Antibiotic therapy costs

Other target figures (not relevant for the regulatory earnings report)

- Cure of infection ("Clinical Cure") on day 3, 5, 7, 10, 14 after randomization and at end of therapy with piperacillin.
- Remediation of microbiological findings ("Microbiological Cure") on day 3, 5, 7, 10, 14 after randomization and at the end of therapy with piperacillin.
- Incidence of antibiotic-resistant bacteria by day 28.
- Re-infection with the same pathogen by day 28
- Superinfection with another pathogen by day 28.
- Neurologic outcome (ICDSC) days 7, 10, and 14 and at the end of therapy with piperacillin.
- PK/PD indices (including antibiotic concentration >4x MIC 100% (fT>4MIC)).

* Only primary ITS/ hospital stay leading to study inclusion.

3.3 Scientific accompanying program or studies accompanying the examination

As part of the biobanking, heparin plasma and EDTA plasma will be collected in all participating study centers from study participants who have provided informed consent for additional sample collection. In the study center "University Hospital Jena", residual material from routinely collected samples such as cerebrospinal fluid, ascites or pleural punctate, which are not further used for routine diagnostics, can be preserved (e.g. for the determination of the concentration of piperacillin). The collected material will be used in particular in the context of research on sepsis and related disorders, but may also be used for other research questions if appropriate consent forms have been obtained. All samples will be stored pseudonymously in the biomaterial bank of the University Hospital Jena. A separate consent of the patient is necessary for this. For study participants from the study center "University Hospital Jena", exhalate can additionally be collected within the framework of an accompanying study (SMART-Dose) of the Institute for Clinical Chemistry and Laboratory Diagnostics (PD Dr. Dr. Michael Kiehntopf) to determine the antibiotic concentration in the respiratory gas condensate, in order to enable a conclusion to be drawn about the pulmonary drug concentration. For this purpose, the patient or caregiver will be informed separately. Consent to participate in Target is a prerequisite for participation in SMART-Dose, but not vice versa.

4 Study design and schedule

The study will be conducted as a multicenter, prospective, randomized, single-blinded treatment optimization study.

4.1 Study design /Description of the clinical trial

Each patient is randomized to one of two treatment arms. In the experimental arm (***PipTDM*),** patients without prior treatment with piperacillin will be randomized to receive a bolus of piperacillin/tazobactam (4.5 g) over 30 minutes followed immediately by a continuous intravenous infusion of piperacillin/tazobactam at a dose dependent on renal function. If the patient has already been treated with piperacillin within the 24 hours prior to study inclusion, the bolus is omitted. For patients with piperacillin pretreatment, optional TDM with dose adjustment may be performed on the day of randomization (Day 0). The decision is up to the investigator. Starting on day 1 after randomization up to and including day 10 or termination of therapy with piperacillin, daily determination of the serum concentration of piperacillin will be performed for all patients in the intervention arm with subsequent individual dose adjustment adjusted to the minimum inhibitory concentration of the sepsis pathogen. The target concentration for piperacillin is 4 times the Minimum Inhibitory Concentration (MIC), after it was shown that this concentration is associated with maximal bactericidal activity of ß-lactam antibiotics. (De Waele JJ et al (18))

In the control group (***PipKon***), patients without prior treatment with piperacillin will be randomized to receive a bolus of piperacillin/tazobactam (4.5g) over 30 minutes followed immediately by a continuous intravenous infusion of piperacillin/tazobactam at a dose dependent on renal function. If the patient has already been treated with piperacillin within the last 24 hours prior to study inclusion, the bolus is omitted. If renal function changes during the course of therapy, the dosage of piperacillin/tazobactam will be adjusted according to the technical information.

In both treatment groups, the piperacillin concentration is determined by taking a daily blood sample as part of the routine blood collection between 4:00 and 8:00 am. In the control group (***PipKon***), however, the result of the measurement must not be reported to the treating physician. If this cannot be safely guaranteed for logistical reasons (e.g. in case of automatic transmission of results in the laboratory information system), it is recommended to perform the determination collected after the end of the

intervention (maximum day 10 or end of piperacillin therapy). In this case, the sample must be frozen at a minimum of -80°C immediately after collection.

4.2 Discussion of the study design

Randomization of study participants is required to avoid bias. The randomization ratio for the two treatment arms is 1:1, with stratification according to the participating centers. Blinding of the treating physicians in the experimental study arm is not intended. The study physician will receive the result of the piperacillin concentration measurement from the laboratory or will take this from the local laboratory information system. In the control group, the piperacillin concentration is measured without reporting the result or at a later time (see point 4.1).

4.3 Patient recruitment

As calculated in section "11.1Sample size planning", 276 participants are to be included in the study. The study centers are both university hospitals and academic teaching hospitals in central care, each with many years of study experience in the field of intensive care medicine.

4.4 Timetable and duration of study

The recruitment phase will be approximately 3 years. The duration of the intervention (TDM with dose adjustment) will be based on the administration of piperacillin/tazobactam, but not longer than day 10 after randomization, provided the patient is in the ICU for this time. The same applies to patients in the control group. However, at the discretion of the treating physician, the administration of piperacillin/tazobactam may be continued after the end of the intervention, i.e., day 10 after randomization. Daily data collection per patient will include 14 days in the ICU plus a follow-up on day 28 after randomization. The end of the study will be reached with the last remaining visit to be collected on day 28 of the study patient ("last patient out") and is expected at the end of Q4 2019. This will be followed by the evaluation phase, which is expected to end in Q2 2020.

5 Participation in the clinical trial

5.1 Selection of study participants

The target population in the study is adult patients with severe sepsis or septic shock treated in the intensive care unit.

5.2 Inclusion criteria /definitions

All inclusion criteria must be met for inclusion in the clinical trial:

- Presence of severe sepsis or septic shock
- Onset of severe sepsis or septic shock no longer than 24 hours prior to randomization.
- Antimicrobial therapy with piperacillin planned or started.
- Age ≥18 years
- Written declaration of consent by the patient or his/her legal guardian or authorized representative, or initial consent by the consultant in the case of patients who are unable to consent (for more details, see Chapter 7.1).

Definition of severe sepsis

Severe sepsis is present when both of the following criteria are met:

- **Evidence of an *infectious* origin of the inflammation** *(for this, at least one of the following criteria must be met):*
    - Microbiologically confirmed infection
    - clinically confirmed infection
- **Sepsis-associated organ dysfunction within the last 24 hours** *(for this, at least one of the following criteria must be met):*
    - **Acute encephalopathy** (reduced vigilance, agitation, disorientation, delirium without Influence by psychotropic drugs).
    - **Thrombocytopenia** (platelets ≤100,000/µl *or* platelet drop >30% in 24 hr, thrombocytopenia due to acute bleeding or immunological causes must be excluded).
    - **Arterial hypoxemia** (paO2 <10 kPa (75 mmHg) below room air, paO2/FiO2 ≤33kPa (250 mmHg) without manifest pulmonary or cardiac disease as cause).
    - **Arterial hypotension** (systolic arterial blood pressure ≤90 mmHg or mean arterial blood pressure ≤70 mmHg for at least 1 hour despite adequate volume delivery in the absence of other causes of shock).
    - **Renal dysfunction** (urine output ≤0.5 ml/kg/hour for at least one hour despite adequate volume substitution *and/or* increase in serum creatinine ≥2× above the reference range of the respective laboratory).
    - **Metabolic acidosis** (base deficit ≥5.0 mmol/l or a plasma lactate concentration ≥1.5× above the reference range of the respective laboratory).

Definition of septic shock

Septic shock is present when the following criteria are met:

- **Evidence of an *infectious* origin of the inflammation** *(this requires at least one of the following criteria must be met):*
    - Microbiologically confirmed infection
    - clinically confirmed infection
- **Septic shock:** Despite adequate volume therapy-and not explained by any other form of shock-sustained for at least 2 hours systolic blood pressure ≤90 mmHg or mean arterial blood pressure ≤65 mmHg, which necessitates the use of vaso-pressors (dopamine ≥5 µg kg-1 min-1; norepinephrine or epinephrine ≥0.05 µg kg-1 min-1; phenylephrine or vasopressin at any dosage) to maintain systolic blood pressure >90 mmHg or mean arterial pressure >65 mmHg

5.3 Exclusion criteria

- Pregnancy / Lactation
- Anamnestic known hypersensitivity to ß-lactam antibiotics or to any of the other components of the test substance.

- Pretreatment with piperacillin (in combination with tazobactam) >24h before randomization.
- Patient's participation in another interventional clinical trial
- Previous study participation (target)
- Therapy restriction or cessation
- impaired liver function (Child-Pugh C)
- Life expectancy < 28 days due to secondary diseases
- Piperacillin measurement not possible within 24 hours after randomization

5.4 Explanation of the gender distribution of the study population.

There is no influence on the gender distribution in the group of affected persons within the scope of the study.

5.5 Participating test centers/requirements for the test centers

The basic requirement for participation in the study is the possibility to perform the piperacillin concentration determination (at least from Monday-Friday, exception: public holidays) with result notification on the same working day. The determination of the piperacillin concentration is performed by means of the validated measurement method HPLC (high performance liquid chromatography) or LC-MS/MS (liquid chromatography-mass spectrometry/mass spectrometry) available at the study center or its local laboratory or partner laboratory. The test center is responsible for quality assurance measures regarding its used laboratory method within the framework of Good Laboratory Practice (GCLP).

Before the start of the clinical trial, each trial site receives the protocol and confirms by signature that the infrastructure for conducting the clinical trial is available at the trial site. The qualifications of the trial site and the investigators are recorded on a form prior to the start of the clinical trial. The investigational site director must be a physician experienced in the treatment of severe sepsis or septic shock and intensive care medicine and must regularly treat patients with this condition. The head of the trial center must be familiar with and observe the statutory and legal provisions, as well as the principles of GCP. According to § 40 AMG (1a), the investigator shall appoint appropriately qualified members of the study group. He must instruct and supervise them and provide them with the information required for their activities in the course of the clinical trial, in particular the protocol and the investigator's brochure. The investigator must appoint at least one deputy with comparable qualifications.

The patient data are recorded in an electronic case report form. For this purpose, the study sites require a PC with Internet connection. In addition, it must be ensured that the study is conducted in accordance with GCP requirements. Furthermore, due to legal regulations to ensure data quality and to monitor the study conduct at the trial site, the investigators, deputies and medical members of the study group are obliged to guarantee authorized third parties access to the patient files (source data). This includes monitors, auditors and other representatives of the client, employees of the responsible supervisory authority or the higher federal authority. These persons are sworn to secrecy. In the run-up to the clinical trial, the participating centers receive training on the contents of the clinical trial, working instructions and the data entry system.

6 Investigational product

Piperacillin is an approved drug. It is a ß-lactam antibiotic of the ureidopenicillin group, which contains a four-membered lactam ring in its structural formula and is used for the intravenous treatment of bacterial infectious diseases. Piperacillin is administered almost exclusively in combination with the ß-lactamase inhibitor tazobactam. Piperacillin, a broad-spectrum semisynthetic penicillin, exerts bactericidal activity by inhibiting both septal and cell wall synthesis. Tazobactam, a ß-lactam related in structure to penicillins, is an inhibitor of many ß-lactamases that often lead to resistance to penicillins and cephalosporins, but it does not inhibit AmpC enzymes or metallo-ß-lactamases. Tazobactam broadens the antibiotic spectrum of piperacillin to include many ß-lactamase-producing bacteria that have developed resistance to piperacillin alone. The spectrum of activity of the piperacillin/tazobactam combination includes Gram-positive (non-oxacillin-resistant staphylococci) and Gram-negative germs, specifically Pseudomonas, Proteus, E. coli, ß-lactamase-forming bacteria, and anaerobes. Piperacillin/tazobactam is one of the substances recommended for empirical antibiotic therapy in the guideline for prevention, diagnosis, therapy and follow-up of sepsis of the German Sepsis Society and the German Interdisciplinary Association for Intensive Care and Emergency Medicine and is the substance most frequently prescribed in this indication in Germany. The study medication will be provided by the local pharmacy of the study center as part of the regular medical care.

Generic name	Piperacillin/tazobactam
Commercial preparation / Manufacturer	Different manufacturers/trade preparations
Provision	Local pharmacy of the respective study center
Pharmaceutical form used	1 vial contains piperacillin (as sodium salt) corresponding to 4 g and tazobactam (as sodium salt) corresponding to 0.5 g List of other ingredients: none
Container	Penetration bottle with 4.5 g powder
Storage	Dry storage at room temperature
Production of the application mold	Dissolve the powder in 50 ml of 0.9% sodium chloride solution for injection.
Storage and shelf life of the application form	Chemical and physical stability of the reconstituted solution (piperacillin/tazobactam) was demonstrated according to the technical information at 25°C for 24 hours, and in studies even at 35°C for 24 hours. [1]

[1] *Stability of antibiotics in portable pumps used for bronchial superinfection: guidelines for prescribers, Arlicot et al. Pediatrics. 2007 Dec;120(6):1255-9.*

6.1 Interactions with other medicinal products and other interactions

According to the expert information, the following interactions with other drugs and other interactions are described:

Non-depolarizing muscle relaxants.

Prolongation of neuromuscular blockade of vecuronium has been observed when piperacillin is used together with vecuronium. Because of the similar mechanisms of action of these drugs, it is hypothesized that neuromuscular blockade may be prolonged by a non-depo- larizing muscle relaxant in the presence of piperacillin.

Oral anticoagulants

With concomitant administration of heparin, oral anticoagulants, and other substances that affect the blood coagulation system, including platelet function, appropriate coagulation tests should be performed more frequently and monitored regularly.

Methotrexate

Piperacillin may reduce the excretion of methotrexate; therefore, serum concentrations of methotrexate should be monitored to avoid toxicity from the drug.

Probenecid

As with other penicillins, concomitant use of probenecid and piperacillin/tazo bactam results in a longer half-life and lower renal clearance of piperacillin and tazobactam; however, the maximum plasma concentrations of the two agents are not affected.

Aminoglycosides

Piperacillin, alone or in combination with tazobactam, has no significant effect on the pharmacokinetics of tobramycin in patients with normal renal function or mild to moderate renal impairment. The pharmacokinetics of piperacillin, tazobactam, and the M1 metabolite were also not significantly altered by tobramycin use. Inactivation of tobramycin and gentamicin by piperacillin was demonstrated in patients with severe renal insufficiency. Because of the inactivation of aminoglycosides by ß-lactam antibiotics observed in vitro, it is recommended that the test compound and the aminoglycoside be administered separately.

6.2 Instruction for dosage

A) PipTDM study arm (individual dose adjustment).

Saturation dose	Patients **without** piperacillin/tazobactam administration within the last 24 h before randomization: 4.5g piperacillin/tazobactam as a short infusion over 30min intravenously (irrespective of any renal function impairment) Patients **with** piperacillin/tazobactam administration within the last 24 h before randomization: not applicable
Maintenance dose Start with infusion end of the saturation dose Dosage depending on renal function	eGFR ≥ 20 ml/min 13.5g/24h (*6.3 ml/h). eGFR < 20 ml/min 9g/24h (*4.2 ml/h). (*Run rate Perfusor, 4.5g/50ml NaCl 0.9%)
Dose adjustment	Starting on day 1 after randomization up to and including day 10 or termination of therapy with piperacillin, the daily determination of the serum concentration of piperacillin is performed with individual dose adjustment based on the minimum inhibitory concentration of the sepsis pathogen (see table Target concentration). The blood sample is taken between 4:00 a.m. and 8:00 a.m. as part of the routine blood collection. In patients with a piperacillin pre-therapy in the past 24 hours, a determination of the serum concentration with dose adjustment can optionally be performed already on day 0. In case of a piperacillin concentration of >150 mg/l a dose reduction is recommended.

Table Target concentration Piperacillin

Pathogen (MIC)	**Mean target concentration** [Range]*
Unknown pathogen *or* Detection of pathogens with MIC ≤16 mg/l and > 8mg/l	80 mg/l [64-96 mg/l] (16/0.81 * 4 = 79 mg/l)
Detection of pathogens with MIC ≤8 mg/l and >4mg/l	40 mg/l [32-48 mg/l] (8/0.81 * 4 = 40 mg/l)
Detection of pathogens with MIC ≤4 mg/l	20 mg/l [16-24 mg/l] (= 4/0.81 * 4 = 20 mg/l)

*Piperacillin population data: t1/2 = 1 h, Vd = 18 l, Cl = 12.5 l/h, "free fraction" (free, non-protein bound fraction) = 0.81, target concentration piperacillin: 4 x minimum inhibitory concentration.

Due to the linear kinetics of the test substance, dose adjustment is performed by means of a ratio equation, i.e. double dose = double concentration. The calculation of the new perfusion rate is based on the following formula:

$$\textbf{New perfusor run rate} = \frac{\textbf{Target serum concentration}}{\textbf{Actual serum concentration}} \times \textbf{Perfuser run rate}$$

z. E.g. Current perfusor run rate = 6.3 ml/h; Actual piperacillin concentration = 42 mg/l; Target piperacillin concentration = 80 mg/l New run rate: 80/42 x 6.3 = 12 ml/h

The dose adjustment is always made taking into account other clinical parameters, e.g. start of renal replacement therapy or recovering renal function. I.e. the new perfusion rate results from the calculation via the above formula AND consideration of the clinical parameters. The dose adjustment must be documented in the patient's file in such a way that it can be traced.

B) PipKon study arm (control group).

Saturation dose	Patients **without** piperacillin/tazobactam administration within the last 24 h before randomization: 4.5g piperacillin/tazobactam as a short infusion over 30min intravenously (irrespective of any renal function impairment) Patients **with** piperacillin/tazobactam administration within the last 24 h before randomization: not applicable
Maintenance dose Start with infusion end of the saturation dose Dosage depending on renal function	eGFR ≥ 20 ml/min 13.5g/24h (*6.3 ml/h). eGFR < 20 ml/min 9g/24h (*4.2 ml/h). (*Run rate Perfusor, 4.5g/50ml NaCl 0.9%)
Dose adjustment	The piperacillin/tazobactam dosage is adjusted daily according to the current degree of renal function (or type of renal replacement procedure) in accordance with the technical information. For this purpose, the daily calculation of the eGFR is performed according to Cockroft-Gault. • eGFR ≥ 20 ml/min or cont. RRT: 13.5g/24h (6.3 ml/h) • eGFR < 20 ml/min or iHD: 9g/24h (4.2 ml/h).

6.3 Application

Piperacillin/tazobactam should not be mixed with other drugs in a syringe or infusion bottle because compatibility is not assured. Intravenous administration of the test substance should be performed via a separate catheter lumen. If this is not possible and other drugs besides the test substance are infused simultaneously via the same catheter lumen, the compatibility of the infusion solutions must be ensured. Due to the inactivation of aminoglycosides by ß-lactam antibiotics observed in vitro, it is recommended to administer the test substance and the aminoglycoside separately.

6.4 Combination therapy

The implementation of a combination therapy with additional antimicrobial substances is permitted within the scope of the study. The decision on the implementation is incumbent on the treating physician.

6.5 Escalation/de-escalation of antimicrobial therapy.

Escalation or de-escalation of antimicrobial therapy is permitted at any time during the study. The decision to implement is the responsibility of the treating physician.

6.6 Therapy duration

The decision on the duration of treatment with piperacillin/tazobactam is the responsibility of the treating physician. The duration of the intervention (TDM) is based on the administration of

piperacillin/tazobactam, but *up* to and including day 10 after randomization. However, at the discretion of the treating physician, the administration of piperacillin/tazobactam may be continued after the end of the intervention.

6.7 Investigational device management (drug accountability) and labeling

Piperacillin/tazobactam (different manufacturers) is a drug approved by the competent higher federal authority and is intended for use in the clinical trial described here without additional manufacturing measures. Therefore, according to § 5 paragraph 8 GCP-V, special markings on the containers and the outer wrappings of the investigational medicinal products are not required. The preparation is used in the approved indication. The test substance is provided by the respective hospital pharmacy of the test center.

6.8 Adverse events

Serious adverse events have rarely been observed according to the SmPC. According to the expert information, the following known adverse events exist:

Organ system	Frequent	Occasionally	Rare	Very rare
Infections		Candida superinfection		
Diseases of the blood and lymphatic system		Leukopenia, neutropenia, thrombocytopenia	Anemia, hemolytic anemia, purpura, epistaxis, prolonged bleeding time, eosinophilia.	Agranulocytosis, pancytopenia, prolongation of activated partial thromboplastin time, prolongation of thromboplastin time, positive direct Coombs test, thrombocythemia.
Diseases of the immune system		Hypersensitivity	anaphylactic/anaphy-lactoid reactions (including shock)	
Metabolic and nutritional disorders				Hypokalemia, reduced blood glucose levels, albumin levels, total blood proteins
Diseases of the nervous system		Headache, insomnia		
Vascular diseases		Hypotension, thrombophlebitis	Hot flashes	
Diseases of the gastrointestinal tract	Diarrhea, vomiting, nausea	constipation, dyspepsia, icterus, stomatitis	Pseudomembranous colitis, abdominal pain	
Liver and bile diseases		Increase of alanine aminotransferase and aspartate aminotransferase	Hepatitis, hyperbilirubinemia, elevation of blood alkaline phosphatase, elevated GT	
Diseases of the skin	rashes, including	Urticaria, pruritus	Erythema multiforme,	Toxic epidermal

and subcutaneous tissue	maculopapular rashes		bullous dermatitis, exanthema	necrolysis, Stevens-Johnson syndrome
Skeletal muscle, connective tissue and bone disorders			Arthralgia, Myalgia	
Diseases of the kidneys and urinary tract		Increased creatinine blood level	Renal failure, tubulointerstitial nephritis	Elevated blood urea levels
General diseases and complaints at the place of administration		Pyrexia, reactions at the injection site	Chills	

In case of overdose of piperacillin/tazobactam, increased neuromuscular excitability or convulsions have been reported in case reports. In the event of (epilepsy-like) seizures, the usual appropriate emergency measures are indicated. At the first signs of severe hypersensitivity reactions, immediate interruption of the infusion and treatment according to the severity of the anaphylactic reaction must be given.

6.9 Concomitant medication, therapy and concomitant diseases

There are no restrictions regarding concomitant medication during the study. Should the study participant require renal replacement therapy during the course of the study (day 1-10), only a continuous procedure should be used. This is due to the different influence of intermittent (iHD, SLEDD) and continuous (CVVH, CVVHD) procedures on the pharmacodynamics of the test substance. Comparability or interpretation of piperacillin concentrations is thus hampered. However, the decision on the choice of renal replacement procedure is ultimately the responsibility of the treating physician.

6.10 Compliance

The patient's compliance with the medication regimen does not need to be monitored, as the medication is always administered by the attending physician or nurse or is monitored by these persons and documented in the medical record.

7 Clinical trial procedure

7.1 Description of the individual phases of the study process

7.1.1 Screening

Patients treated in intensive care units at the study center will be screened for the presence of the inclusion criteria, taking into account the exclusion criteria.

7.1.2 Patient information and consent

Patient information and consent must be provided verbally and in writing using the forms provided. The signed consent form must be submitted in duplicate. One copy (original) remains at the study center and is to be kept in the investigator's folder. The second copy is given to the consenting party together with the patient information.

7.1.2.1 Patients capable of giving consent

Patients who are able to give consent must be informed orally and in writing by the investigator or a medical member of the study team about the objectives, duration, procedure, benefits and all risks and side effects of the study before the study begins. The investigator will satisfy himself/herself that the patient has understood the information provided. After informed consent, each patient will be given sufficient time and opportunity to clarify any unanswered questions and to decide whether to participate. Each patient will sign and date their consent to participate in the study in writing on the informed consent form. If a patient is unable to personally sign the consent form, an independent witness must be present during the informed consent process. This witness confirms the patient's verbal information and consent by date and signature. A copy of the "Information for Patients" must be given to the patient. In the informed consent form, the patient not only consents to participate in the clinical trial, but also authorizes inspection of his or her original medical records by the monitor and other authorized persons (auditors, inspectors). The patient's consent must also explicitly refer to the collection and processing of health information. Therefore, the patient must be explicitly informed about the purpose and scope of the collection and use of personal data, especially health data.

7.1.2.2 Patients not capable of giving consent

It can be assumed that, due to the severity of the disease, most of the patients to be included in the study are incapable of giving consent. In this case, it will not be necessary to obtain oral or written informed consent from the patient prior to the start of the study. In this case, consent to participate in the clinical trial will be obtained in accordance with Section 41 (3) No. 2 AMG. In patients with severe sepsis or septic shock, early intervention is crucial for the prognosis of these patients. A therapeutic benefit can probably only be demonstrated if the clinical trial is started within the first hours after diagnosis.

In the case of incapacitated **patients who have appointed a proxy by means of a living** will, **care proxy or health care proxy,** consent to participation in the clinical trial may be given by the appointed proxy**,** taking into account the presumed will of the patient.

In the case of **incapacitated patients who have not appointed a proxy,** the written consent of a legal representative (health care responsibilities) of the patient should be obtained. The inclusion of incapacitated patients is done according to the recommendations of the local ethics committee:

- Inclusion can be effected by immediately asking the patient's relatives, by telephone if

necessary, for the patient's voluntary will to participate in the study. If a provisional consent to the clinical trial is given, this is recorded in writing. The information about the patient's presumed will is immediately forwarded to the competent court, which promptly appoints a legal representative. Subsequently, if provisional consent has already been given, the subsequent written consent of the appointed legal representative must be obtained. If the discussion with the relatives reveals that there is no consent or no presumed will to participate in the study, the patient may not be included in the clinical trial.

- It can be assumed that a declaration of consent from a legal guardian often cannot be obtained in time. Since, according to international guidelines, an early start of therapy is an essential standard therapy for severe sepsis and septic shock, it appears justified in trial centers without a specific agreement with the responsible local/guardianship court for the inclusion of incapacitated patients to start the clinical trial as an emergency indication, if necessary, without a declaration of consent from the legal guardian. According to the AMG, study inclusion is legally possible even without a declaration of consent if consent cannot be obtained due to an emergency situation (Section 41 (1) AMG). In this case, the examination of an independent consultant physician must confirm the patient's inability to consent and the urgency of study participation with possible benefit for the patient. Thereafter, provisional inclusion of the patient is possible. The consultant physician must not be involved in the clinical trial, or be a member of the department conducting the study, and must not be a member of the patient's care team. The consultant physician must provide professional written justification for his or her decision. The consultant physician must have specialist status and experience of at least 6 months in the care of intensive care patients. Immediately and no later than 72 hours after inclusion in the clinical trial, the investigator must initiate the establishment of legal guardianship. Subsequent informed consent must be obtained from the legal representative. However, if the patient dies before a guardian can be appointed, the investigator has nevertheless arranged everything necessary. It would also be ethically questionable to exclude this patient from the clinical trial and the analysis, because the information that a group is associated with premature death may be lost.

- If necessary, further procedures according to the specifications of the local ethics committees

The study centers should maintain their locally established procedure for the inclusion of patients who are not able to give consent. If the appointment of a legal representative is required, this must be done as soon as possible. It is the responsibility of the investigator to arrange for the identification of a suitable person and the appropriate application to the appropriate court. If an objection is received from the legal representative, the patient's participation in the clinical trial will be terminated immediately. In this case, data collection will be terminated immediately and all blood samples collected will be destroyed. The data stored up to this point may continue to be used to the extent necessary to

(a) detect an influence of the intervention,

b) ensure that the patient's interests worthy of protection are not impaired.

The aim is to inform the patient subsequently about the clinical trial and to obtain consent, provided that the patient's state of health during the hospital stay permits this. If the patient, who is primarily incapable of giving consent, decides at a later point in time that he/she does not wish to participate in the study, he/she can arrange via the investigator to have all available laboratory samples destroyed at any time until the database is closed.

7.1.3 Withdrawal of consent

Patients or, in the case of non-consenting patients, the person giving consent (authorized representative or guardian) may withdraw their consent and discontinue participation in the study at any time and without giving reasons. In such a case, the patient or authorized representative or caregiver will be asked to state the reason for discontinuation, but will be advised that this is not required. However, information on when and into which study arm a patient was randomized, and that and at what time he or she withdrew consent, must be documented. The patient or authorized representative or caregiver must be informed that in the event of withdrawal of consent, study-related measures will no longer be performed and the stored data may continue to be used to the extent necessary to:

- To determine effects of the intervention,
- ensure that interests of the data subject that are worthy of protection are not impaired.

7.1.4 Randomization

Randomization is performed by an automated internet-based service provided by the Center for Clinical Studies Jena (ZKS) Jena. Usage statistics of the randomizations performed can be generated at any time by IT staff of the ZKS Jena.

7.1.5 Measures to prevent participation in further intervention study.

The study site must ensure that the enrolled patient is not included in any other interventional clinical study during the course of the study. The regular end of the patient's participation in the Target study is reached on day 28.

7.1.6 Subsequent determination of violations of the inclusion and exclusion criteria.

Violation of inclusion and exclusion criteria is generally not a reason for discontinuation of the clinical trial in the patient concerned. If it is subsequently determined that a violation of the inclusion and exclusion criteria existed at the time of randomization, the sponsor's authorized representative must be informed as soon as possible. The sponsor's authorized representative will decide on the patient's continued participation in the study. Documentation and intervention will continue according to the protocol until a decision is made. The patient's documentation will continue regardless of the decision.

7.1.7 Treatment phases

The decision on the duration of treatment with piperacillin/tazobactam is the responsibility of the treating physician. The duration of the intervention (TDM) is based on the administration of the test substance, but up to a *maximum of* 10 days after randomization. However, at the discretion of the treating physician, the administration of piperacillin may be continued after the end of the intervention.

7.2 Description of the individual visits

Notes:

1. Blood samples for determination of piperacillin concentration will be collected only if the patient is (a) treated with piperacillin and (b) in the intensive care unit, but not more than day 10 after randomization.
2. Blood samples for the Central Specimen Bank will only be collected if the patient is treated in the ICU, but not later than day 10 after randomization.
3. With the exception of the "Day 28" and "Visit E" rounds, the rounds are only to be performed if the patient is still being treated in the ICU. If the patient is discharged from the ITS and continues to be treated with piperacillin/tazobactam, the EOT visit is omitted.
4. If the patient is discharged from the intensive care unit before day 14, "Visit E" must be performed in addition to the regular visit of the day. The subsequent rounds are omitted according to point 3.
5. Documentation of AEs, SAEs, SUSARs must occur during therapy with piperacillin, including 24 h after cessation of therapy.

Visit Day 0: Day of inclusion in the clinical trial (baseline).

- Inclusion and exclusion criteria
- Result of randomization
- Onset of severe sepsis / septic shock
- Sepsis criteria
- Collection of demographic data
- APACHE-II, SAPS-II and SOFA Score (see appendix)
- Acceptance blood cultures
- Survey of diagnoses, secondary diagnoses, surgical interventions.
- Survey of physiological parameters
- Renal replacement procedures
- Vasopressors, inotropics
- Mechanical ventilation
- Acquisition of surgical drains
- Survey of the parameters for calculating the Clinical Pulmonary Infection Score (CPIS) in the presence of pneumonia (see appendix).
- Concomitant medication
- Antimicrobial therapy (type, dose, timing of administration).
- Survey of routine laboratory, PCT & CRP, collected urine.
- Microbiological results
- Collection of blood samples for the Central Sample Bank
- Collection of blood samples for determination of piperacillin concentration (Optional, in case of prior therapy with piperacillin/tazobactam within 24h before study inclusion).
- AEs

Visit Day 1 & 2

- Collection of blood samples for the determination of the piperacillin concentration
- Collection of blood samples for the Central Sample Bank
- Antimicrobial therapy (type, dose, timing of administration).
- Concomitant medication
- Vasopressors, inotropics

- Mechanical ventilation
- Renal replacement procedures
- surgical interventions
- Parameters for the calculation of organ functions using the SOFA score (see appendix).
- Sepsis criteria
- AEs
- Survey of the routine laboratory
- Acquisition of surgical drains
- Microbiological results
- Survey of physiological parameters

Visit day 3

- Collection of blood samples for the determination of the piperacillin concentration
- Collection of blood samples for the Central Sample Bank
- Antimicrobial therapy (type, dose, timing of administration).
- Concomitant medication
- Vasopressors, inotropics
- Mechanical ventilation
- Renal replacement procedures
- surgical interventions
- Parameters for the calculation of organ functions using the SOFA score (see appendix).
- Sepsis criteria
- AEs
- Survey of the routine laboratory
- Collecting urine
- Acquisition of surgical drains
- Microbiological results
- Survey of physiological parameters
- Clinical Cure
- Microbiological Cure
- ICDSC
- Survey of the parameters for calculating the Clinical Pulmonary Infection Score (CPIS) in the presence of pneumonia (see appendix).

Visit day 4

- Collection of blood samples for the determination of the piperacillin concentration
- Collection of blood samples for the Central Sample Bank
- Antimicrobial therapy (type, dose, timing of administration).
- Concomitant medication
- Vasopressors, inotropics
- Mechanical ventilation
- Renal replacement procedures
- surgical interventions
- Parameters for the calculation of organ functions using the SOFA score (see appendix).
- Sepsis criteria
- AEs
- Survey of the routine laboratory

- Acquisition of surgical drains
- Microbiological results
- Survey of physiological parameters

Visit day 5

- Collection of blood samples for the determination of the piperacillin concentration
- Collection of blood samples for the Central Sample Bank
- Antimicrobial therapy (type, dose, timing of administration).
- Concomitant medication
- Vasopressors, inotropics
- Mechanical ventilation
- Renal replacement procedures
- surgical interventions
- Parameters for the calculation of organ functions using the SOFA score (see appendix).
- Sepsis criteria
- AEs
- Survey of the routine laboratory
- Determination PCT, CRP
- Acquisition of surgical drains
- Microbiological results
- Survey of physiological parameters
- Clinical Cure
- Microbiological Cure
- Survey of the parameters for calculating the Clinical Pulmonary Infection Score (CPIS) in the presence of pneumonia (see appendix).

Visit day 6

- Collection of blood samples for the determination of the piperacillin concentration
- Collection of blood samples for the Central Sample Bank
- Antimicrobial therapy (type, dose, timing of administration).
- Concomitant medication
- Vasopressors, inotropics
- Mechanical ventilation
- Renal replacement procedures
- surgical interventions
- Parameters for the calculation of organ functions using the SOFA score (see appendix).
- Sepsis criteria
- AEs
- Survey of the routine laboratory
- Collecting urine
- Acquisition of surgical drains
- Microbiological results
- Survey of physiological parameters

Visit day 7

- Collection of blood samples for the determination of the piperacillin concentration
- Collection of blood samples for the Central Sample Bank

- Antimicrobial therapy (type, dose, timing of administration).
- Concomitant medication
- Vasopressors, inotropics
- Mechanical ventilation
- Renal replacement procedures
- surgical interventions
- Parameters for the calculation of organ functions using the SOFA score (see appendix).
- Sepsis criteria
- AEs
- Survey of the routine laboratory
- Determination PCT, CRP
- Acquisition of surgical drains
- Microbiological results
- Survey of physiological parameters
- Clinical Cure
- Microbiological Cure
- ICDSC
- Survey of the parameters for calculating the Clinical Pulmonary Infection Score (CPIS) in the presence of pneumonia (see appendix).

Visit Day 8 & 9

- Collection of blood samples for the determination of the piperacillin concentration
- Collection of blood samples for the Central Sample Bank
- Antimicrobial therapy (type, dose, timing of administration).
- Concomitant medication
- Vasopressors, inotropics
- Mechanical ventilation
- Renal replacement procedures
- surgical interventions
- Parameters for the calculation of organ functions using the SOFA score (see appendix).
- Sepsis criteria
- AEs
- Survey of the routine laboratory
- Acquisition of surgical drains
- Microbiological results
- Survey of physiological parameters

Visit day 10

- Collection of blood samples for the determination of the piperacillin concentration
- Collection of blood samples for the Central Sample Bank
- Antimicrobial therapy (type, dose, timing of administration).
- Concomitant medication
- Vasopressors, inotropics
- Mechanical ventilation
- Renal replacement procedures
- surgical interventions
- Parameters for the calculation of organ functions using the SOFA score (see appendix).

- Sepsis criteria
- AEs
- Survey of the routine laboratory
- Determination PCT, CRP
- Acquisition of surgical drains
- Microbiological results
- Survey of physiological parameters
- Clinical Cure
- Microbiological Cure
- ICDSC
- Survey of the parameters for calculating the Clinical Pulmonary Infection Score (CPIS) in the presence of pneumonia (see appendix).

Visit day 11 to 13

- Antimicrobial therapy (type, dose, timing of administration).
- Concomitant medication
- Vasopressors, inotropics
- Mechanical ventilation
- Renal replacement procedures
- surgical interventions
- Parameters for the calculation of organ functions using the SOFA score (see appendix).
- Sepsis criteria
- AEs (if medication until day 10)
- Survey of the routine laboratory
- Microbiological results
- Survey of physiological parameters

Visit day 14

- Antimicrobial therapy (type, dose, timing of administration).
- Concomitant medication
- Vasopressors, inotropics
- Mechanical ventilation
- Renal replacement procedures
- surgical interventions
- Parameters for the calculation of organ functions using the SOFA score (see appendix).
- Sepsis criteria
- Survey of the routine laboratory
- Acquisition of surgical drains
- Microbiological results
- Survey of physiological parameters
- Clinical Cure
- Microbiological Cure
- ICDSC
- Survey of the parameters for calculating the Clinical Pulmonary Infection Score (CPIS) in the presence of pneumonia (see appendix).
- Survival status

Visit EOT (day of discontinuation of therapy with piperacillin/tazobactam).

- Antimicrobial therapy (type, dose, timing of administration).
- Concomitant medication
- Vasopressors, inotropics
- Mechanical ventilation
- Renal replacement procedures
- surgical interventions
- Parameters for the calculation of organ functions using the SOFA score (see appendix).
- Survey of the routine laboratory
- Determination PCT, CRP
- Acquisition of surgical drains
- Microbiological results
- Survey of physiological parameters
- Clinical Cure
- Microbiological Cure
- ICDSC
- Survey of the parameters for calculating the Clinical Pulmonary Infection Score (CPIS) in the presence of pneumonia (see appendix).
- Survival status

Visit E (discharge from intensive care unit)

- Antimicrobial therapy (type, dose, timing of administration).
- Concomitant medication
- Vasopressors, inotropics
- Mechanical ventilation
- Renal replacement procedures
- surgical interventions
- Parameters for the calculation of organ functions using the SOFA score (see appendix).
- Survey of the routine laboratory
- Acquisition of surgical drains
- Microbiological results
- Survey of physiological parameters
- Clinical Cure
- Microbiological Cure
- ICDSC
- Survey of the parameters for calculating the Clinical Pulmonary Infection Score (CPIS) in the presence of pneumonia (see appendix).
- Survival status

Visit day 28

- Whereabouts
- Survival status, date of death if applicable
- Intensive care unit length of stay
- Hospital length of stay
- Re-infection with the same pathogen
- Frequency, duration Renal replacement procedures
- Frequency, duration of mechanical ventilation

7.3 Description of laboratory analytics and other examinations

7.3.1 Laboratory measurement methods

The piperacillin concentration is determined using the validated measurement method available at the respective study center, which is based on either an HPLC (high performance liquid chromatography) method or LC-MS/MS (liquid chromatography-tandem mass spectrometry). Prior to the start of the study, the measurement methods validated in-house at the test centers are compared between the test centers via an interlaboratory comparison. The quality of the measurement methods is verified by repeated interlaboratory comparisons within the scope of this study. Basically, the investigations are performed according to the laboratory guideline of the European Medicines Agency (EMA) in the form of the "Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples" (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/05/WC500127124.pdf) and the recommendations of the FDA (Food and Drug Administration) "Guidance for Industry / Bioanalytical Method Validation" (http://www.fda.gov/downloads/Drugs/Guidances/ ucm070107.pdf), which provide for a mean deviation of +/- 15% in the course of method validation.

7.3.2 Research methods

7.3.2.1 Assessment of Clinical Cure (CC)

The Clinical Cure assessment will be performed by a local physician from the study team on Day 3, 5, 7, 10, 14, and the day of discontinuation of study medication, depending on the time of discontinuation of study medication, if the patient is still in the ICU. If the patient is discharged from the ICU prior to Day 14, then the "Clinical Cure" assessment will also occur on the discharge day. On these days, the patient will be evaluated according to the criteria listed below (see Table).

Healing	1) Recovery of general clinical signs and symptoms of infection. 2) No additional antibiotic treatment (exception: de-escalating targeted therapy) for the disease under investigation. 3) No initiation of antibiotic treatment for the disease under investigation within 48 h after cessation of the test substance.
Improvement	1) General clinical signs and symptoms of infection have improved. 2) No additional antibiotic treatment (exception: de-escalating targeted therapy) for the disease under investigation. 3) No initiation of antibiotic treatment for the disease under investigation within 48 h after cessation of the test substance.
Therapy failure	General clinical signs and symptoms of infection persist or intensify compared to baseline, or additional antibiotic treatment becomes necessary for the condition under investigation.

7.3.2.2 Assessment of Microbiological Cure (MC)

The Microbiological Cure assessment will be performed on Day 3, 5, 7, 10, 14, and the day the study medication is discontinued, depending on the time of discontinuation. If the patient is discharged from

the ICU prior to day 14, then the "Microbiological Cure" assessment will also be performed on the discharge day. On these days, microbiological samples are taken from the original site of infection (tracheal secretions, wound swabs, blood culture, etc.), if possible, and routinely tested.

Documented microbiological eradication	No culture detection of the original pathogen from the original site of infection
Suspected microbiological eradication	Patient is clinically cured and suitable culture material from the original site of infection is not available.
Documented microbiological persistence	Culture detection of the original pathogen from the original site of infection.
Suspected microbiological persistence	Patient is considered a treatment failure according to Clinical Cure Visit and appropriate culture material from the original site of infection is not available.
Relapse	Documented infection by culture detection from the original site of infection within 14 days of randomization in a patient classified as microbiologically eradicated (microbiologically documented or clinically suspected).
Superinfection	Any patient classified as a treatment failure according to Clinical Cure Visit or clinically improved in whom antibiotic therapy has isolated a pathogen that is different from the original pathogen.
Colonization	Isolation of an organism different from the causative pathogen in a patient who has been classified as clinically cured.
indeterminate	Any patient who does not fit into one of the above categories.

7.3.2.3 Clinical Pulmonary Infections Score

Pneumonia is defined as a *Clinical Pulmonary Infections Score* (modified CPIS; see Appendix) of at least 6 points with concomitant presence of pulmonary infiltrates on chest radiograph. The CPIS will be collected depending on the time of discontinuation of the investigational medication and will be collected on day 3, 5, 7, 10, 14, and the day of discontinuation of the investigational medication. If the patient is discharged from the ICU before day 14, then the CPIS will also be collected on the discharge day.

Healing	1.) Pulmonary infiltrates no longer detectable on chest x-ray and a CPIS ≤1 2.) No additional antibiotic necessary for treatment of pneumonia (exception: de-escalating targeted therapy).
Improvement	1.) Pulmonary infiltrates on X-ray chest image regressed and a CPIS between 2 and 5. 2.) No additional antibiotic necessary for treatment of pneumonia (exception: de-escalating targeted therapy).
Therapy failure	Pulmonary infiltrates on chest x-ray not regressing or a CPIS ≥6 or new antibiotic needed to treat pneumonia.

7.4 Sample collection for biomaterial banks

The patient has the option to participate in the clinical trial itself, but to decline data use and sample collection for the biomaterial bank. Sample collection (see visit plan item 1.6) is performed according to the established sample collection scheme at the trial centers. The monovettes required for this purpose will be provided to the study centers together with a special request form. To avoid confusion, a request document with a unique order number (=sample number) is assigned to each sample collection. From this order slip, the barcodes provided for the corresponding samples (heparin plasma and EDTA plasma) are to be affixed to the corresponding monovettes after sample collection. In addition, the date and time of collection should be noted on the request slip. The samples for central sample determination should then be centrifuged immediately and processed further according to Manual. Here, too, the start and duration of centrifugation as well as the time of sample freezing at -80°C should be recorded. Samples for heparin plasma and EDTA plasma preparation will be shipped to the central sample bank on dry ice every three months by a specially contracted courier service. Samples received from the test centers and tested according to the above criteria are identified by barcode and read into the sample database via an automated barcode reader in the laboratory information system. The samples are then sorted while frozen. After sorting the samples, all heparin plasma and EDTA plasma samples from a patient are thawed under defined conditions, aliquoted and stored again at -80°C/-150°C until later use of the aliquots.

In addition, the residual material from routinely collected samples such as cerebrospinal fluid, ascites or pleural punctate, which is not further used for routine diagnostics, can be preserved at the test center "University Hospital Jena".

7.5 End of study participation

The regular end of study participation for each participant will occur on Day 28.

7.6 Premature withdrawal of a patient (discontinuation criteria)

Discontinuation of investigational medication for individual patients

Discontinuation of study therapy should be avoided as it may significantly affect the quality of the study. The administration of the study medication must be stopped:

- in case of toxicity of the test medication
- In the event of withdrawal of the declaration of consent
- if the declaration of consent had not been obtainable within a reasonable period of time
- by medical decision, including when the investigational medication is appropriate for the treatment of the

underlying infection proves to be unsuitable. This may be the case if:

(a) the underlying infection is caused exclusively by pathogens,
that are resistant to the investigational drug

or

(b) there is clinical evidence that the underlying infection has not been
improves or even worsens

or

c) the attending physician wishes to de-escalate the therapy

The discontinuation of the study medication is documented by the study center caring for the patient with the date (or the most precise possible indication of the time) and with details of the circumstances and reasons. In principle, the follow-up and study documentation must also be carried out after premature termination of the study therapy. Only in case of withdrawal of consent and if the declaration of consent could not be obtained within a reasonable period of time, study documentation will be stopped in addition to study-related measures, except for the recording of adverse events.

Termination of follow-up for individual patients

Follow-up of patients must take place, as 28-day mortality and other parameters (see visit plan point 1.6and 3.2) are secondary study objectives. Follow-up can only not take place if the patient withdraws consent to the study or contact with the patient can no longer be established (Lost to Follow-Up). Any discontinuation of follow-up will be documented by the study center caring for the patient with the date (or the most precise possible indication of the time) and, if possible, with an indication of the circumstances and reasons.

7.7 Plan for further treatment

Specific follow-up care is not required. The study interventions are intensive medical measures without consequence for the subsequent medical care. According to current knowledge, there is no evidence for the occurrence of late effects after therapy with the study medication. Antibiotic treatment will be reported to the continuing physician in the transfer report. On day 28, the patient or his authorized representative/legal guardian will be contacted to clarify the study objectives.

7.8 End of the clinical trial

7.8.1 Regular end of study

The regular end of the study is defined as the date on which the last patient has completed the follow-up (Last Patient Out - LPO). According to GCP-V § 13, the sponsor informs the competent authority, the competent higher federal authority and the competent ethics committee within 90 days about the termination of the clinical trial. The sponsor shall provide the competent higher federal authority and the competent ethics committee with a summary of the clinical trial report covering all essential results of the clinical trial within one year after termination of the clinical trial.

7.8.2 Termination of the study in a trial center

The study may be terminated at an investigational site if.

- it does not meet the technical requirements of the test plan
- the study execution does not comply with the protocol
- the data quality is insufficient
- the patient recruitment rate is inadequate
- unforeseeable circumstances have arisen at the respective trial center that do not permit continuation of the clinical trial (e.g., lack of personnel, equipment capacities; necessary logistics can no longer be provided)

The LKP/sponsor representative decides on the exclusion, if necessary in consultation with his contractually appointed representative and the biometrician. Investigators or study centers that no longer participate in the study must immediately inform the sponsor representative of their decision. Reasons for the decision must be provided. If the discontinuation of the clinical trial was initiated by the study center, the latter must state the reasons for the discontinuation in writing to the sponsor.

7.8.3 Premature interruption/termination of the entire clinical trial

The sponsor is entitled to terminate the clinical trial prematurely due to relevant medical and administrative reasons. The reasons for stopping the trial will be documented in detail. Participants who are still receiving treatment at the time of trial termination will be followed up until Day 28 after randomization and data will be collected and documented as described in Section 7.2If an investigator/deputy/medical member of the study group has ethical concerns regarding the continuation of the clinical trial, this must be reported immediately to the LCP.

The sponsor has the right to terminate the entire clinical trial early if:

- the patient recruitment rate is inadequate

- grave, unresolvable problems occur with the quality of the collected data

- unacceptable risks and toxicities have occurred (decision after new risk-benefit assessment)

- new scientific findings during the term of the trial do not allow the continuation of the same

- there could be a risk to patient safety

- business considerations require this

Since the study is being conducted in accordance with the requirements of the German Medicines Act, it is also possible for the competent higher federal authority (BfArM) to withdraw approval or terminate the study. The data available up to the premature termination must be evaluated and a final report of the trial must be prepared. If the clinical trial has been discontinued or interrupted by the sponsor, the competent state authority, the competent higher federal authority (BfArM) and the competent ethics committee must be informed within 15 days, stating the reasons for the discontinuation or interruption by the sponsor, in accordance with GCP-V § 13 (8). Study participants whose participation in the study has not yet ended must also be informed immediately of any interruption or premature termination of the study. Adequate follow-up must be ensured. The date and time of study treatment as well as the date and reason for interruption or early study termination must be documented in the patient records or CRFs.

8 Safety, Adverse Events and Pregnancy

8.1 Evaluation of the safety of the test therapy

The test medication is an antibiotic for which extensive safety and tolerability data have been available for many years. These data are presented in the product information. In this respect, safe and known use of piperacillin/tazobactam can be assumed for the study. Nevertheless, safety management will ensure patient safety. To this end, adverse events observed during the course of the study will be recorded and evaluated and regularly reviewed by an independent Data Safety and Monitoring Board.

8.2 Adverse event (AE)

According to the GCP-V §3 (6), an adverse **event (AE)** is any adverse occurrence that happens to an affected person who has been administered an investigational product and that is not necessarily causally related to this treatment. According to ICH -GCP, this may include illness, signs of illness (including, for example, abnormal laboratory values), clinically significant laboratory values, or symptoms that are temporally associated with the use of an investigational product. This is independent of whether the event is considered causally related to the investigational product or not.

Severe sepsis and septic shock are among the most acutely life-threatening conditions. According to the prevalence study of the Competence Network Sepsis, the ITS mortality rate is 47%. A large proportion of patients require mechanical ventilation and about half of patients suffer acute renal failure. Parameters of other organ function, such as liver and metabolism, are almost always altered depending on the severity of sepsis. Previous studies investigating severe sepsis or septic shock, such as MAXSEP (EudraCT 2006-006984-21) and SISPCT (EudraCT 2007-004333-42), have used selective AE acquisition for this reason, which has proven successful and will be continued here in the Target study. Because laboratory values and symptoms in sepsis patients are altered in many ways due to the underlying disease and change constantly during the course of the disease, the AE definition is restricted in the Target study as follows:
An Adverse **Event (AE) in the Target Study** is any adverse event that occurs to an individual who has been administered an investigational product and that is not necessarily causally related to that treatment. This may include illnesses, signs of illness (including, for example, abnormal laboratory values), clinically significant laboratory values, or symptoms that are temporally associated with the use

of an investigational product, **unless they can be plausibly explained by the underlying diagnosed sepsis and the investigator considers an association with the administration of the investigational products to be unlikely or even excluded.**
These cases that can be plausibly explained by sepsis are recorded as sepsis-related clinical outcomes in the CRF as a quantitative severity of multiorgan dysfunction (SOFA) score during daily rounds and are not counted as AEs. This rule applies to the following clinical outcomes:

- Death caused by severe sepsis/septic shock
- Cardiovascular event: necessary administration of vasoactive substances or hypotension
- Respiratory events: drop in PaO2/FiO2 ratio, mechanical ventilation, hypoxia, ARDS, acute pulmonary dysfunction.
- Hepatic incident: liver failure or liver dysfunction resulting in elevation of bilirubin/transaminases compared to baseline acquisition.
- Renal occurrence: renal failure, renal insufficiency, or renal failure resulting in an increase in creatinine value compared to baseline acquisition
- Hematologic/coagulation events: Coagulopathy, DIC, thrombocytopenia, thrombocytosis.
- Tachypnea, hypopnea, leukocytosis, leukopenia, hypothermia, hyperthermia, tachycardia, or bradycardia.
- Delirium, confusion

This also applies to the side effects mentioned in 6.8, which may also be typical symptoms or consequences of sepsis. They are therefore not classified as AE/SAE per se, but must be documented in the CRF as clinical outcomes.

Any sepsis-related clinical outcome must be documented in the CRF, even if no association with the administration of the investigational medication is apparent. The investigator assesses the clinical outcome with regard to an association with the investigational medication and classifies this as "possible" or "not possible". The clinical result is only documented as AE if the investigator suspects a connection with the administration of the investigational medicinal product.

However, the following potential side effects of the investigational medication may occur in a **compound-specific manner** and must be documented as AEs in any case:

- pseudomembranous colitis
- cerebral seizure
- allergic reactions; Steven-Johnson syndrome, etc.

8.2.1 Documentation of adverse events

All AEs and sepsis-related clinical outcomes will be recorded in a timely manner by the investigational sites in the CRF during the course of the study. Safety-related clinical outcomes, independent of the safety database data, are regularly provided to the DSMB listed for peer review and safety assessment. Therefore, just prior to retrieval of safety data from the database, a request is made to sites to review and complete these data. This occurs at least once per year or upon request by the sponsor representative, DSMB, or an agency. Medical or surgical procedures are not documented as AEs, but rather the condition that led to the necessary intervention. If the intervention is a result of a medical condition expected in the context of sepsis, the corresponding medical event is documented in the CRF

as a sepsis-related clinical outcome during each visit, rather than as an AE. Also, daily fluctuations in the clinical picture as well as a usual progression of the disease severity of sepsis are not recorded as AEs. Conditions that are pre-existing prior to inclusion in the study will not be counted as an adverse event, but as a concomitant condition. Clinically relevant worsening of a preexisting condition not related to sepsis is considered an adverse event. An adverse event does not include an intervention to treat a pre-existing condition that was already planned prior to inclusion in the study. All other adverse events not listed here, and therefore unexpected, will be recorded as AEs as defined in 8.112. These include the occurrence of a new disease known to be unrelated to sepsis and events unrelated to sepsis.

The recording of AEs starts with the first administration of the study drug after randomization. Due to the pharmacological properties of the study drug, in particular its short plasma half-life of one hour, the recording of possible AEs ends 24 hours after administration of the last study drug.

For AEs, a designation (medical term), onset, end, severity/intensity, causality, measures for handling the test medication and the event, and the outcome are documented. Each AE must be checked for the criteria of an SAE and, if necessary, the SAE reporting procedure must be followed (see chapter 8.4).

Sepsis-related clinical results are collected under the respective visit with indication of the specific parameters. The investigator assesses the clinical outcome with regard to a relationship with the study medication and classifies this as "possible " or "not possible" In the study center, it must be ensured that all persons involved in the treatment of the study participants are adequately informed about the responsibilities in the event of the occurrence of adverse events.

8.2.2 Intensity of the adverse event

The intensity of adverse events is graded according to the following 3-point scale (adapted from Common Toxicity Criteria (CTC) table).

- **1=mild (mild)**: clinical symptom or sign that is well/mildly tolerated, usually requires no intervention
- **2=moderate (moderate)**: clinical symptom or sign sufficient to interfere with normal/daily activity = affects daily activities, intervention may be needed
- **3=severe**: clinical symptom or sign resulting in severe impairment, inability to work, or inability to perform daily activities = daily activities/work not possible, treatment or intervention usually needed

If the intensity of an event changes, only the higher intensity should be documented on the corresponding AE page. If an adverse event loses intensity, the previous classification should not be changed. A mild, moderate, and severe adverse event may or may not be "serious" (=SAE). These terms describe the intensity (medical severity) of certain events (e.g., a mild, moderate, or severe heart attack). However, the event may also be of secondary medical relevance (e.g., a severe headache) and it is not necessarily "serious." "Seriousness," for the purposes of the law, serves as a definition for more extensive reporting requirements.

8.2.3 Causality - relationship of the AE to the investigational product.

For each adverse event, an assessment is made as to whether or not an association with the investigational product can be suspected. The nature and pattern of the reaction, temporal relationship to administration, clinical status of the patient, concomitant medication, and other relevant clinical parameters must be considered.

The following classification is used to assess causality:

1 = yes - possible

- there is a substantiated causal relationship between study medication and event
- Event responds to discontinuation of study medication
- Event appears on readmission (if clinically feasible).
- Information on discontinuation of study medication is missing or unclear

2 = no - unlikely

- There is a temporal relationship to the administration of the study medication, but no substantiated causal relationship between the study medication and the event
- There is no temporal connection with the administration of the study medication (too early, too late, study medication was not taken) or there is a causal connection between another medication, a concomitant disease or other circumstances and the event
- there is a clear alternative explanation or a non-plausibility (e.g. patient is hit by a car and it is ensured that the study medication did not cause disorientation that could have triggered the event; cancer a few days after the first administration of the study medication)

following factors should be considered in the assessment:

- temporal relationship (event should occur after administration of study medication)
- Response to discontinuation and reproduction of study medication.
- Underlying concomitant/basic diseases
- Concomitant medication or non-drug treatment
- Pharmacodynamics/pharmacokinetics of the study medication.

8.2.4 Measures to be taken in the event of an adverse event

A) Measures with the investigational medicinal product

Handling of the investigational product with respect to an AE must be documented as follows:

- Treatment interrupted - temporary or permanent
- Dose reduction
- Dose increase
- No dose change
- Not applicable, since intervention already ended

B) Measures on the patient

If the patient requires treatment due to the adverse event, this must be carried out according to the current state of medical research in order to restore the patient's health. Due to the study-related intensive care setting, any emergency treatment can be performed at the study center at any time. Treatment of the AE and handling of the investigational drug will be documented as follows:

- No measures taken
- drug treatment
- additional intensive medical care
- other measures

8.2.5 Outcome of an adverse event s

The outcome of an adverse event is classified as follows:

- 1 = restored
- 2= restored with sequelae
- 3= improved
- 4= unchanged
- 5= worsened
- 6= lethal
- 7= unknown

8.3 Serious adverse event

According to the GCP-V § 3 (8), a Serious Adverse Event **(SAE)** is any adverse event that is fatal or life-threatening, requires hospitalization or prolongation of hospitalization, or results in permanent or serious disability or incapacity, or results in a congenital anomaly or birth defect.

An SAE may also be an event that is medically significant for other reasons (event in which medical intervention was required to prevent an outcome as serious) or that meets a comparable criterion (as determined by the evaluating investigator/substitute/medical member of the study group or his/her medical judgment). The term "life-threatening" refers to an event that poses a lethal risk to the patient at the time of the response. It does not refer to a reaction that could hypothetically result in death if it had progressed to a higher severity and possibly resulted in complications.

If an adverse event documented according to the study-specific criteria in 8.2.1judged to be serious, this will be documented in the CRF on the AE sheet and an SAE report will be made.

8.4 Reporting of serious adverse events

The documentation and notification obligations according to GCP-V §12 (4) - (6) must be complied with.

8.4.1 Duties of the tester/s tell representative

The investigational site will **immediately (i.e., within 24 hours of becoming aware of the event)** inform the sponsor's designated Clinical Study Center (CCS) of the occurrence of any serious adverse event, excluding events that are not required to be reported immediately by the protocol, and will then submit a detailed written report using an SAE form that will be made available to investigational sites in the ISF.
This form is sent by fax to:

SAE reporting form to ZKS
JenaFax
: +49 (0) 36419399946

If further information on the SAE is available at a later date, this must also be reported immediately to the ZKS Jena. The auditor's report is checked for completeness and plausibility and, if necessary, queries are made and followed up.

For all reports, personal data must be pseudonymized before transmission using the identification code of the person concerned. It must be possible to assign the primary report and all subsequent reports to each other by means of a patient identification number or similar.

8.4.2 Duties of the sponsor

For SAEs submitted by the trial site, a second assessment of the medical content by an experienced specialist is performed by the sponsor with regard to the criteria "serious", "causal relationship" and "expectedness". If the second assessment results in a SUSAR (Suspected Unexpected Serious Adverse Reaction), the report to the BfArM, Ethics Committee and investigator is initiated by the ZKS Jena with the assistance of the second assessment of the sponsor representative. Suspected **Unexpected Serious Adverse Reaction (SUSAR)** is a suspected adverse **reaction that is** both serious and unexpected (not consistent in nature or severity with the available information on the investigational product, i.e. a SmPC for the drug combination piperacillin/tazobactam).
The sponsor representative is responsible for the continuous review of the benefit-risk assessment of the clinical trial. Occasions for a renewed benefit-risk assessment as well as measures to protect against immediate danger are reported in accordance with the law within the specified deadlines.
With the involvement of a Data and Safety Monitoring Board, the safety of the study is monitored. The expert board receives all safety-relevant data and information once a year, or as the occasion arises, in order to conduct an independent assessment of the safety of the study. These results are brought to the attention of the authority as part of the annual safety report, the DSUR, or as the occasion arises.
The responsibilities, information paths and deadlines are defined in the SAE Manual

8.5 Pregnancy

Pregnant and breastfeeding women are excluded from participation in the clinical trial. Due to the severity of the underlying disease and the duration of the study, pregnancy is excluded from this study. Therefore, no explicit information about contraceptive measures will be provided.

9 Documentation and data management

9.1 Patient Identification List

In this document, all patients included in the study are recorded with their full name, date of birth and gender, and their patient identification number (pseudonym) is assigned. The patient identification number is generated according to a special algorithm. This list must not leave the study center and must be filed in the investigator's folder. This list is necessary to be able to identify the patient for later inquiries by the documentation center. The participation of the person concerned in the clinical trial must be noted in the patient file with reference to the investigational product, patient number/randomization number, start and end of the trial. The patient identification list must be archived for **at least ten years** after the end of the trial.

9.2 List of responsibilities

It must be ensured that each person responsible for documentation in the CRF can be identified. A list with signature and abbreviation of the persons who are allowed to make entries in the CRF (Signature/Responsibility Log) is filed in the trial center folder (ISF) and in the central trial folder (TMF). This overview also identifies other persons involved in the clinical trial with their names, signatures and abbreviations as well as their responsibilities and authorities.

9.3 Data Collection Form (CRF)

Source data in the sense of ICH guideline E6 are all routinely collected data and laboratory reports as well as special CRFs for the documentation of the study. The majority of data to be collected will be routinely collected from ICU patients and entered directly into the regular patient record. Data relevant to the study will be collected via RDE (Remote Data Entry - electronic data entry). For this purpose, the data are entered by the investigator or an authorized member of the study group at an online connected workstation computer into special masks, which represent an electronic CRF. Via the electronic CRF, the data are directly transferred to the study database of the study center at the Center for Clinical Studies Jena. It is the responsibility of the investigators to ensure that all data collected during the trial are entered correctly and completely into the database created specifically for this trial. Corrections in the eCRF may only be made by authorized persons or by the responsible investigator/deputy/medical member of the study group and must be justified. Corrections will be recorded so that the old entry can still be retrieved. All data and corrections are automatically logged with date, time and the person making the entry. The CRF consists of individual sections. These are:

- Inclusion and randomization
- Baseline
- Visits in the course of the clinical trial
- AE / SAE
- End of intervention and dropout
- Subsequent consent and withdrawal of consent
- Follow-Up

The items to be recorded in each section will be specified in more detail during the preparation of the CRF. A paper-based sample CRF will be provided to the trial sites as part of the trial site binder.

9.4 Test Center Folder

The investigational site folder (ISF) contains those documents that are required for the clinical trial and, in particular, represent the clinical trial at the respective study center. It contains the essential documents, such as the protocol, protocol amendments, CRFs and query forms, a sample of the patient information and patient consent form, the approval of the competent higher federal authority, the consenting assessment of the competent ethics committee, the notification to the competent state authorities, the curricula vitae of the investigators/deputies, the document regulating responsibilities, as well as correspondence and other relevant documents. As part of the monitoring process, the ISF is reviewed for timeliness and completeness in accordance with the regulations.

9.5 Data processing and data management

The data collection serves scientific purposes. The data are generated in the participating centers. All collected medical data are entered by the corresponding staff in the centers in a computer-based online data entry system and immediately transferred to the servers at the Center for Clinical Trials Jena.

Data collection is performed via web application on the servers of the ZKS of the University Hospital Jena using the study management software "OpenClinica®". The software fulfills the regulatory requirements (GCP, 21CFRPart11). The data are collected via an encrypted data connection (HTTPS) in input masks via web browser. To ensure pseudonymized data analysis, a unique patient identification number is assigned to each patient. The study management software "OpenClinica®" is also used for data management. Range, validity and consistency checks are used to verify the accuracy of the data. Non-plausible or missing data are queried at the study center. Every change to the data, e.g. due to the incorporation of answered queries, is documented in the database via an automatic change tracking (audit trail). The use of a hierarchical, role-based access concept makes unauthorized access to the study data impossible.

9.6 Retention of data, archiving of study documents

The investigator must maintain a confidential list of patients (patient identification code list) in which the patient ID, name and date of birth must be documented in order to be able to identify each patient at any time. The list is part of the ISF and must be archived together with the ISF for at least 10 years after completion of the study.
The Center for Clinical Studies at Jena University Hospital is also appointed as a documentation center for data storage. The backup of electronic data happens regularly. The data storage facilities are located in a locked, central room to which only system administrators have access.

9.6.1 Retention obligations of the sponsor

The following documentation and notification obligations exist for the sponsor according to GCP-V § 13 (10): The sponsor ensures that the essential documents of the clinical trial, including the trial forms, are retained for at least ten years after the trial is terminated or discontinued. Other regulations regarding the retention of medical records remain unaffected. All records must be kept in a secure place and kept confidential. Documents should be retained beyond the above period if necessary (e.g., due to regulatory requirements or by agreement with the sponsor). It is the responsibility of the sponsor to inform the appropriate persons when the documents no longer need to be kept and how to deal with them.

9.6.2 Retention obligations of the test center

Records and documents related to the trial, e.g. patient identification list, (copies of) data collection forms, informed consent forms and other relevant documents such as administrative documents (amendments, correspondence with ethics committee, monitoring authority, sponsor/trial management, study center) must be appropriately retained for **at least 10 years** (or longer if required by law) according to GCP-V § 13 (10).
The patient identification list is kept separately from other clinical trial documentation at all trial sites.

Medical records and other original data must be retained for the **longest possible period** permitted by the hospital, institution, or private practice (in accordance with the archival period applicable to the trial sites and in accordance with local practices and premises), but **not less than 10 years.** The investigator must take precautions to prevent accidental or premature destruction of these documents.

9.7 Privacy

The study serves a scientific objective with considerable clinical relevance. To achieve the study objective, it is necessary to collect and process medical data from individual patients. Data collection takes place in the study centers participating in the study. All collected medical data will be entered in the study centers using a computerized online data collection system and transmitted directly to the documentation center located at the Center for Clinical Studies of the University of Jena (ZKS). Identification of specific patients by name by the documentation center is not required at any time during the study. Therefore, during data collection and data processing, all necessary measures should be taken at the earliest possible time to establish **de facto anonymization.**

The transfer of patient-related medical data from the study centers to the documentation center takes place using a pseudonym. No characteristics are transferred that allow direct identification of specific patients in the documentation center. However, an assignment of the pseudonym to a specific study center by the documentation center is necessary to carry out queries in the context of ongoing monitoring of documentation quality.

In the event of a revocation of consent by the patient, the extent to which the stored data is still required is checked. Data that is no longer required will be deleted immediately.

Data entry, processing and analysis, which takes place at the Center for Clinical Studies Jena (ZKS), complies with the provisions of the Data Protection Act. Only employees of the study have access to all study data. These persons are bound to secrecy. The data are protected against unauthorized access.

Privacy statement

According to § 7 para. 2 no. 15 GCP-V, it is declared that the persons concerned are informed about the disclosure of their pseudonymized data within the framework of the documentation and notification obligations according to § 12 and § 13 of the GCP-V to the recipients named therein. Subjects who do not consent to the disclosure of their pseudonymized data will not be included in the clinical trial. The relevant data protection regulations are complied with.

10 Quality assurance

10.1 Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) is an independent study committee consisting of a group of persons (two independent scientists and one statistician) with relevant experience. It makes recommendations for continuation, modification, or even discontinuation of the clinical trial. In the context of the annual safety reports, the DSMB will make an assessment of the safety-related parameters based on the data specified in the DSMB Manual and make a recommendation on the further course of the study. Responsibilities and details are described in the DSMB Manual.

10.2 Standardization and validation

Within the framework of quality assurance, the measuring methods for determining the piperacillin concentration that have already been validated for routine use in the respective study centers or that are still to be validated are compared according to corresponding acceptance and evaluation criteria. For this purpose, interlaboratory tests are carried out in advance and, if necessary, measures are taken to standardize the measurement methods.

10.3 Monitoring - control of the study process and data quality

According to ICH-GCP E6, continuous monitoring of a clinical trial or the trial conduct is an indispensable quality assurance tool. The purpose of clinical trial monitoring is to ensure that the clinical trial is conducted in accordance with the approved protocol and that the regulatory requirements and standards are met. The sponsor commissions the ZKS Jena with this task. The monitoring includes an initiation for training and briefing of the investigator group prior to the start of recruitment and regular on-site visits as well as a final visit to close the trial site properly. The monitoring will be performed according to the standard operating procedures of the ZKS Jena. Detailed information on the scope, procedure and contents of the monitoring as well as procedures to ensure data quality and necessary measures in case of protocol violations are described in a monitor manual to be released by the sponsor. The investigator shall provide the monitor with direct access to the original data and documents for trial-related monitoring. The monitor is required to maintain the confidentiality of all information and to uphold the study participants' fundamental right to integrity and privacy. The monitor reports to the sponsor in writing on the course and outcome of his on-site visits.

10.4 Audits and inspections

It is possible that audits will be carried out. Inspections as part of the monitoring of ongoing or already completed clinical trials are carried out by the competent higher federal authority in accordance with Section 64 (1) of the German Medicines Act.

The inspection conducted by the competent authority shall be carried out according to written procedures and a pre-established plan.

The sponsor and all participating trial sites undertake to support inspections by competent authorities and, in this context, to grant the authorized persons access to the original documents.

11 Statistical methods and determination of the number of cases

11.1 Caseload planning

The basis for the calculation of the number of cases is the primary outcome measure SOFA score. Superiority of the study intervention is shown when the null hypothesis of equal expected values is rejected in favor of the alternative hypothesis. Data from the VISEP and MAXSEP trials of the SepNET Study Group (N Engl J Med 2008; 358:125-39, JAMA 2012; 307:2390-2399) have shown that a 1.4-point lower SOFA score in the intervention group would be clinically relevant. Assuming a standard deviation of 3.8 points (SepNet data), this results in an effect size of 0.368 standard deviations. To show this effect with a power of 80% using a 2-sample t-test at a two-sided significance level of 5%, 117 patients per study arm are required (software: nQuery Advisor 7.0 Statistical Solutions). Based on the experience of the SepNet studies, a dropout rate of 15% is expected, so that a total of 276 (2x138) patients need to be randomized to reach the number of cases required for the analysis.

11.2 Randomization

The study biometrician generates a computer-based list that realizes blockwise 1:1 randomization stratified by study center. Based on this list, the ZKS-Jena generates an internet-based algorithm for the allocation of patients to the respective study arm.

11.3 Statistical methods

Evaluation population

Primary and secondary outcome measures will be evaluated in the intent-to-treat population, which includes all randomized patients according to their randomly assigned group membership.

Statistical analyses

Baseline data and target variables are described group-specifically by suitable statistical parameters (mean, standard deviation, 25th, 50th, 75th percentile, interquartile range, absolute and relative frequencies).

The primary outcome measure is the SOFA score. It enters the analysis as an individual mean over the course from day 1 after randomization until discharge from the ITS or until death, but at most until day 10. The difference between intervention arms is evaluated confirmatorily using a mixed linear model. Fixed factors are intervention and SOFA score at the time of randomization (baseline). The change in exclusion criteria (1st amendment) allows inclusion of patients with renal insufficiency (acute or chronic) and renal replacement therapy or expected renal replacement therapy within the following 6 hours after randomization. This affects the SOFA score (kidney subscore 4 each for patients with renal replacement therapy) and may bias the intervention effect if unevenly distributed. Therefore, in the primary model, the presence of this circumstance (yes/no) at baseline is considered as an additional cofactor. As a random factor, the study center is modeled as a random intercept. The main effect of the intervention is tested at the two-sided significance level of 5%.

All secondary and further target variables are exploratively analyzed according to their scaling:

Chi2 test or Fisher's exact test for binary data:

- 28 days mortality
- Incidence of antibiotic-resistant bacteria by day 28.
- Re-infection with the same pathogen by day 28.

- Superinfection with another pathogen by day 28.

2-sample t-test or Mann-Whitney U-test for metric data:

- SOFA subscores of each organ system averaged over day 1 to day 10 after randomization.
- Duration and cumulative dose of antibiotic therapy.
- Number of dose adjustments/therapy cycle
- Antibiotic-free days until day 14
- Days without vasopressors until day 14
- Days without mechanical ventilation Day 28
- Days without renal replacement therapy until day 28
- Antibiotic therapy costs

Kaplan-Meier curves / logrank test for right-censored time-to-event data:

- Intensive care unit length of stay up to a maximum of day 28
- Hospital stay up to a maximum of day 28

Generalized linear mixed effects models for binary history data:

- Cure of infection ("Clinical Cure") on day 3, 5, 7, 10, 14 after randomization and at end of therapy with piperacillin.
- Remediation of microbiological findings ("Microbiological Cure") on day 3, 5, 7, 10, 14 after randomization and at the end of therapy with piperacillin.

Generalized linear mixed effects models for ordinal history data:

- Neurological outcome (ICDSC) days 7, 10, and 14 after randomization and at the end of therapy.

Indices resulting from analysis of pharmacokinetics (PK) and pharmacodynamics (PD) (including antibiotic concentration >4x MIC 100% (fT>4MIC)) are compared using appropriate methods mentioned above.

The frequency and incidence of adverse events are reported on a group-specific basis.

Appropriate effect measures with 95% confidence intervals are provided for the target variables.

Missing Data

For the primary endpoint, in case of a relevant number of missing values, appropriate imputation procedures will be applied in the context of a sensitivity analysis. The secondary endpoints will be evaluated exploratively based on the available data.

Interim evaluations

An interim evaluation with statistically justified termination criteria is not planned. Pre-specified safety-relevant data will be submitted to the DSMB at regular intervals, on the basis of which recommendations for the continuation of the study will be made (see item 10.1).

Subgroup evaluations (not relevant for regulatory report on results)

Exploratively, for the primary outcome measure and selected secondary outcome measures, appropriate statistical models will be used to examine whether there are differential intervention effects in patient subgroups. The following subgroups are considered:

- Patients with renal replacement therapy vs. other patients
- Patients with infections with germs that have a high minimum inhibitory concentration (MIC) vs. other patients.

- Patients with increased renal clearance (defined by creatinine clearance >130 ml/min per 173m2) vs. other patients.
- Patients with different infection focus (pulmonary, bloodstream, intra-abdominal, bone/soft tissue infections).

Differences will be statistically assessed using the Intervention*Subgroup Characteristic interaction term.

In addition, the primary outcome measure and selected other outcome measures will be analyzed in the population of all patients surviving at least 48 hours.

Details of statistical analyses are written in a Statistical Analysis Plan (SAP) before the study database is closed.

Presentation of results

The final statistical report is guided by the CONSORT statement checklist for publication of randomized controlled trials in parallel-group design (BMJ 2010; 340:c332) and regulatory requirements.

12 Ethical, regulatory and administrative aspects

12.1 Regulations

The clinical trial will be conducted in accordance with this protocol and the applicable versions of the German Law on the Marketing of Medicinal Products (AMG) and the Regulation on the Application of Good Clinical Practice in the Conduct of Clinical Trials of Medicinal Products for Human Use (GCP-V), as well as the principles published in the ICH GCP Guideline and the ethical principles set forth in the Declaration of Helsinki as the recognized ethical basis for clinical trials, as amended in 2008. The Declaration of Helsinki and the GCP-V are attached to the trial site binder.

12.2 Responsibilities

12.2.1 Duties of the auditor and responsibilities

According to § 4 AMG, the investigator is usually a physician responsible for conducting clinical trials in humans at an investigational site or, in justified exceptional cases, another person whose profession qualifies him or her to conduct research in humans because of its scientific requirements and the experience in patient care that is a prerequisite for its practice.

Thus, the respective investigator assumes responsibility for the conduct of the clinical trial at the trial site.

Pursuant to Section 40 AMG, the investigator shall appoint appropriately qualified members of the trial team. He must instruct and supervise them and provide them with the information required for their activities in the course of the clinical trial, in particular the protocol and the investigator's brochure. The investigator must appoint at least one deputy with comparable qualifications.

A list shall be maintained at the trial site of all persons to whom the investigator has delegated trial-related tasks (list of responsibilities).

12.2.2 Test contract/test center contract

The investigator's or trial site's obligations are set forth in a separate agreement signed by the sponsor and investigator.

12.2.3 Ethics Committee

According to Section 40 AMG, the clinical trial of a medicinal product in humans may only be started by the sponsor if the competent ethics committee has given its approval in accordance with Section 42 (1). In the case of multicenter clinical trials that take place in more than one investigational site within the scope of the AMG, each additional EC responsible for an investigator under state law (participating EC) receives a copy of the application and the documents from the sponsor or the sponsor's authorized representative at the same time. Submission of the documents to the responsible ethics committee and the involved ethics committees is carried out by the head of the clinical trial and the Center for Clinical Trials Jena. Each investigator receives a copy of the consenting assessment from the applicant for the trial site folder. Changes in the protocol and/or the patient information and consent form are submitted to the Ethics Committee for consideration. They must be evaluated approvingly by the Ethics Committee before implementation.

12.3 Competent authorities

12.3.1 Federal Higher Authority

For clinical trials according to the AMG, the Federal Institute for Drugs and Medical Devices (BfArM in Bonn) or the Paul Ehrlich Institute (PEI in Langen) is the competent higher federal authority.
According to Section 40 AMG, the clinical trial of a drug in humans may only be started by the sponsor if the competent higher federal authority has approved it in accordance with Section 42 (2). Each investigator receives a copy of the approval for the trial center folder from the applicant.

12.3.2 State Authority

According to § 67 AMG, there is a general obligation to notify the competent authority for each registered investigator/deputy investigator. According to § 12 GCP-V, the investigator can delegate the execution of the notification to the competent authority to the sponsor and has to document this. In the context of the present study, the notification to the competent authority is carried out by the sponsor or his deputy and the Center for Clinical Studies Jena.
Responsible for a clinical trial are in each case the government authorities or the competent authorities in the states in which a trial center is located. If the sponsorship is taken over by the Friedrich Schiller University Jena, the notification is made at the Thuringian State Office for Food Safety and Consumer Protection (TLLV) in Bad Langensalza. The state notification is to be filed in the trial center folder. A copy of all trial site notifications belongs in the TMF.

12.3.3 Federal Office for Radiation Protection

No radiological examinations, outside of standard clinical care, are planned as part of the study.

12.4 Subsequent changes (amendments)

Amendments requiring approval must be applied for by the sponsor in accordance with Section 10 (1) GCP-V and are only valid after a positive evaluation by the responsible EC, insofar as they concern the information and documents according to Section 7 (2), (3) or (3a), and if they have been approved by the responsible higher federal authority, insofar as they concern the information and documents

according to Section 7 (2) or (4). This does not apply to changes that are necessary to avert immediate danger to the persons concerned (Section 11 GCP-V). These must be implemented immediately. The sponsor immediately informs the responsible BOB and arranges for the responsible EC to be informed of these new circumstances. The consenting evaluation is to be applied for at the responsible ethics committee, the approval is to be applied for at the responsible higher federal authority. The application shall be justified. The competent higher federal authority must also be notified of changes that only require approval by the competent ethics committee. In order to ensure largely comparable conditions in all study centers as well as in the interest of a flawless data evaluation, a change or addition to the agreed study conditions laid down in the study plan (e.g. of study design, study procedure or evaluation method) is not intended.

12.5 Registration

The study will be registered in the WHO-approved German Clinical Trials Registry (DRKS; www.drks.de) before randomization of the first study patient. The present study will be registered and continuously maintained jointly by the ZKS and the LKP.

12.6 Patient information (education) and consent form

Patient information and consent form are submitted to the relevant ethics committee.
With the consent, the patient must have declared that he/she consents to the recording of data occurring within the framework of the clinical trial and its review by the responsible monitoring or federal authority (access to or disclosure of personal or pseudonymized data within the framework of the documentation and notification obligations according to § 12 and § 13 GCP-V to the recipients named therein), as well as authorized third parties (information on data protection). Individuals who do not consent to the transfer of their data cannot be included in the clinical trial.

12.7 Data protection, collection and use of personal data

The collection, transfer, storage and analysis of personal data within this clinical trial will be carried out in accordance with legal requirements (Thuringian Data Protection Act, Federal Data Protection Act). A prerequisite for this is the voluntary consent of the participating persons or the legal guardian within the framework of the declaration of consent prior to participation in the clinical trial. It must be ensured that all study material and data are adequately pseudonymized in accordance with data protection regulations prior to scientific exploitation. The subjects are informed about the transfer of their pseudonymized data within the scope of the documentation and notification obligations according to § 12 and § 13 GCP-V to the recipients mentioned there. Subjects who do not consent to the disclosure cannot be included in the clinical trial.

12.8 Insurance

A proband insurance will be concluded for all included patients according to § 40 AMG within the framework of the proband annual contract of the Friedrich Schiller University Hospital Jena with HDI Gerling Industrie Versicherung AG, 30659 Hannover. Seat, policy no., telephone and fax number of the insurance company will be included in the patient information. Patients are to be informed about their rights and obligations in connection with the insurance. Each participant in the clinical trial will be handed out the insurance conditions.

12.9 Funding

The study is funded by the German Federal Ministry of Education and Research (BMBF) within the framework of the Integrated Research and Treatment Center Sepsis - and Sepsis Consequences at the University Hospital Jena. Details on financial aspects with the study centers will be regulated in separate contracts.

12.10 Reports, reporting of study results

All information concerning this clinical trial must be treated confidentially. According to AMG § 42 b, the sponsor is obliged to publish the results of clinical trials within certain time limits and in compliance with certain requirements.

The sponsor's representative/lead investigator is responsible for the preparation of the final report.

12.11 Publications

The aim is to publish the results of this study in a renowned international medical journal. Therefore, the study will be registered in the Registry of Clinical Studies (DRKS; www.drks.de). registered. Authorship will follow the guidelines of the *New England Journal of Medicine* (http://www.icmje.org/). This implies that each author has made such a contribution to the study and publication that he or she can publicly accept responsibility for the integrity of the entire paper. Therefore, authorship should be chosen according to the following criteria:

- Substantive contribution to study design, data collection or analysis, and interpretation.
- Significant intellectual contribution in the manuscript preparation or proofreading process.
- Final assessment and comment on the manuscript version to be published.

Authors should have contributed substantially in all three aspects. The *Acknowledgement section of the* publication will list the names of all responsible personnel involved in the study at the study centers. The study centers are entitled to the scientific use of the data generated in this study. After consultation with the study steering committee, the study centers may use these data to address their own scientific questions and publish them under their own name (naming the study group).

13 General literature

1. *ICH Topic E 8 General Considerations for Clinical Trials - Note for Guidance on general considerations for clinical trials (CPMP/ICH/291/95)*. 1998, European Medicines Agency: London.
2. *ICH Topic M 3 (R2) Note for Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (CPMP/ICH/286/95)*. 2009, European Medicines Agency: London.
3. *Ordinance on the Application of Good Clinical Practice in the Conduct of Clinical Trials of Medicinal Products for Human Use (GCP Ordinance, GCP-V) of 9.8.2004* 2004, BGBl. I 2004 p. 2081 last amended by Article 8 of the Act of 19 October 2012 (BGBl. I p. 2192).
4. *Law on the marketing of medicinal products (Medicinal Products Act - AMG): Medicinal Products Act in the version published on December 12, 2005 (BGBl. I p. 3394), as last amended by Article 1 of the Ordinance of July 16, 2012 (BGBl. I p. 1534).*
5. *Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (ENTR/CT 3).* 2006, European Commission Enterprise and Industry Directorate-General, Consumer goods, Pharmaceuticals.
6. *4. notice on the notification of adverse drug reactions and misuse of medicinal products pursuant to Section 63b (1) to (8) of the* German Medicines Act (*AMG) of April 29,* 2005 2005, Federal Institute for Drugs and Medical Devices and Paul Ehrlich Institute Federal Office for Sera and Vaccines, Federal Gazette 2005, vol. 57, issue 97 of May 28, 2005, p. 8029, supplement.
7. *ICH Topic E 2 D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting*. 2003.
8. *ICH Topic E 6 (R1) Guideline for Good Clinical Practice, Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)*. 2002, European Medicines Agency (EMEA).
9. *Ordinance on Protection against Damage Caused by X-rays (Röntgenverordnung -RöV) of January 8, 1987, as amended by the announcement of April 30, 2003 (BGBl. I p. 604)*. 2003.
10. *Ordinance on Protection against Damage Caused by Ionizing Radiation (Radiation Protection Ordinance - StrlSchV) of July 20, 2001 (BGBl. I p. 1714; 2002 I p. 1459), last amended by Article 2 of the Act of August 29, 2008 (BGBl. I p. 1793)*. 2008.
11. *ICH Topic E 3 Structure and Content of Clinical Study Reports*. 1995.
12. *ICH Topic E 9: Statistical Principles for Clinical Trials* 1998.
13. Schulz, K.F., D.G. Altman, and D. Moher, *CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials.* BMJ. **340**: p. c332.
14. World Medical Association, *Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects* 2008, 59th WORLD MEDICAL ASSOCIATION General Assembly: Seoul, South Korea.
15. *Directive 2001/20/EC of the European Parliament and of the Council of 04 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 . .* 2001, Official Journal of the European Communities, 01.05.2001 (German version).
16. *Re-announcement of the Thuringian Data Protection Act (ThürDSG) of October 10, 2001 (GVBl. p. 276), based on Article 2 of the First Act to Amend the Thuringian Data Protection Act of September 14, 2001 (GVBl. p. 248), the text of the Thuringian Data Protection Act of October 29, 1991 (GVBl. p. 516), in the version applicable from September 28, 2001, is published below.* 2001.

17. *Federal Data Protection Act (BDSG) in the version published on January 14, 2003 (BGBl. IS. 66), as last amended by Article 1 of the Act of August 14, 2009 (BGBl. I p. 2814)*. 1990.

Appendix

SOFA score

Organ dysfunction is defined according to the SOFA score variables. The worst parameter value of each day is included in the CRF score.
The parameters of the SOFA score are determined exclusively in the intensive care unit until day 14 after randomization. The SOFA score is calculated from the sum of the assessment points of the individual organ systems listed below. The parameters used to calculate the SOFA Sub Score are also part of the CRF. The assessment points of the individual organ systems range from 0 to 4. The SOFA Score is calculated in the data management center. The sub-scores of the SOFA Score are determined as follows:

Cardiovascular system

Mean arterial pressure and catecholamine delivery determine the number of assessment points. The lowest MAP value of the past 24 h is part of the CRF. The highest catecholamine dose > 1 h of 1 h1 h

Score	*Circulation situation*
0	MAP ≥ 70 and no vasopressors
1	MAP < 70 and no vasopressors
2	Dopamine ≤ 5 µg/kg/min or dobutamine (any dose).
3	Dopamine >5 - < 15 µg/kg/min or (**nor)**epinephrine < 0.1 µg/kg/min.
4	Dopamine >15 µg/kg/min **or (**nor)adrenaline >0.1 µg/kg/min

Respiratory system

The PaO2/FiO2 ratio determines this sub-score. If the blood gas analysis is not available for the day in question or the patient in question is no longer intubated but is dependent on oxygen therapy, conversion tables are used.

Score	*PaO2/FiO2*
0	> 400 mmHg (> 53.2 kPa)
1	301-400 mmHg (39.9-53.1 kPa)
2	201-300 mmHg (26.6-39.8 kPa)
3	101-200 mmHg (13.3-26.5 kPa)
4	≤ 100 mmHg (< 13.3 kPa)

Coagulation system:

The platelet count determines this subscore. The lowest platelet count of the past 24 hours is part of the CRF.

Score	*Platelet count*
0	≥ 150 ×103/mm3
1	100-149 $103/mm3_{\times}$
2	50-99 $103/mm3_{\times}$
3	20-49 $103/mm3_{\times}$
4	<20 103/mm3×

Renal system:

Serum creatinine and urine output determine this subscore. The worst value is part of the CRF.

Score	*Serum creatinine and urine excretion*
0	<1.2 mg/dl (<110 µmol/l)
1	1.2-1.9 mg/dl (110 -170 µmol/l)
2	2.0-3.4 mg/dl (171- 299 µmol/l)
3	3.5-4.9 mg/dl (300-440 µmol/l) **or** urinary output - <500 ml/24h
4	> 5.0 mg/dl (> 441 µmol/l) or urinary output <200 ml/24h

Liver:

The total bilirubin determines this value. The worst value is part of the CRF.

Score	*Total bilirubin*
0	<1.2 mg/dl (< 20 µmol/l)
1	1.2-1.9 mg/dl (20-32 µmol/l)
2	2.0-5.9 mg/dl (33-101 µmol/l)
3	6.0-11.9 mg/dl (102-204 µmol/l)
4	> 12 mg/dl (> 205 µmol/l)

Central Nervous System (CNS):

CNS is assessed by the Glasgow Coma Scale (GCS).

Score	*Glasgow Coma Scale*
0	15
1	13–14
2	10–12
3	6–9
4	< 5

Glasgow Coma Scale

The Glasgow Coma Scale is a scoring system for neurological assessment that is composed of three individual assessments that are then summed.

	Score		*Score*
Open eyes spontaneous Upon request On pain stimulus None	 4 3 2 1	**Best motor response** Upon request On pain stimulus Targeted Normal bending defense Flexion synergisms Stretch synergisms None	 6 5 4 3 2 1
Best verbal response Conversational Oriented disoriented Inadequate utteranceunintelligible soundsno	 5 4 3 2 1		

Apache II score

Point value	4	3	2	1	0	1	2	3	4
Rectal temperature	≥41	39–40,9		38,5–38,9	36–38,4	34–35,9	32–33,9	30–31,9	≤29,9
Type. Medium pressure (mmHg)	≥160	130–159	110–129		70–109		50–69		≤49
Heart rate (/min)	≥180	140–179	110–139		70–109		55–69	40–54	≤39
Respiratory rate (/min) *Spontaneous o. ventilated*	≥50	35–49		25–34	12–24	10–11	6–9		≤5
Oxygenation (mmHg) a) FiO2 ≥0.5: AaDO2 b) FiO2<0.5: PaO2	≥500	350–499	200–349		<200 >70	61–70		55–60	<55
Arterial pH	≥7,7	7,6–7,69		7,5–7,59	7,33–7,49		7,25–7,32	7,15–7,24	<7,15
Sodium (mmol/l)	≥180	160–179	155–159	150–154	130–149		120–129	110–119	<110
Potassium (mmol/l)	≥7	6–6,9		5,5–5,9	3,5–5,4	3–3,4	2,5–2,9		<2,5
Creatinine (mg/dl)[1]	≥3,5	2–3,4	1,5–1,9		0,6–1,4		<0,6		
Hematocrit (%)	≥60		50–59,9	46–49,9	30–45,9		20–29,9		<20
Leukocytes ($^{103/mm3}$)	≥40		20–39,9	15–19,9	3–14,9		1–2,9		<1
Glasgow Coma Scale	Score=15 minus GCS								
Venous HCO3 (mmol/l)[2]	≥52	41–51,9		32–40,9	22–31,9		18–21,9	15–17,9	<15

[1] In acute renal failure ×2
[2] only if arterial blood gases are absent

New Simplified Acute Physiology Score (SAPS II)

The value of the first 24 hours that deviates the most from the norm is included.

Parameter	*Findings*	*Point value*
Age (years)	<40	0
	40–59	7
	60–69	12
	70–74	15
	75–79	16
	≥80	18
Heart rate (/min)	<40	11
	40–69	2
	70-119	0
	120–159	4
	≥160	7
Systolic blood pressure (mmHg)	<70	13
	70–99	5
	100–199	0
	≥200	2
Body temperature (°C)	<39	0
	≥39	3
PaO2/FiO2 (with ventilation or CPAP) (mmHg)	<100	11
	100–199	9
	≥200	6
Diuresis (l/24h)	<0,5	11
	0,5–0,999	4
	≥1,0	0
Urea (mg/dl) [mmol/l]	<28 [4,6]	0
	≥84 [13,9]	10
Leukocytes ($^{103/mm3}$)	<1,0	12
	1,0–19,9	0
	≥20	3
Potassium (mmol/l)	<3,0	3
	3,0–4,9	0
	≥5,0	3
Sodium (mmol/l)	<125	5
	125–144	0

	≥145	1
Bicarbonate (mmol/l)	<15	6
	15–19	3
	≥20	0
Bilirubin (mg/dl) [µmol/l]	<4,0 (68,4)	0
	4,0–5,9 (68,4–102,5)	4
	≥6,0 (102,5)	9
Glasgow Coma Score (see p. 72)	<6	26
	6–8	13
	9–10	7
Chron. Diseases	Metastatic carcinoma	9
	Hematologic malignancy	10
	AIDS	17
Assignment type	Planned surgery	0
	Medical cause	6
	Emergency surgery	8

Conversion tables

PaO2/FiO2 Ratio

The following conversion table is used when blood gas analyses are not available to determine PaO2/FiO2:

O2 saturation Conversion table	
SO2 (%)	Calculated PaO2 (mmHg)
80	44
81	45
82	46
83	47
84	49
85	50
86	52
87	53
88	55
89	57
90	60
91	62
92	65
93	69
94	73
95	79
96	86
97	96
98	112
99	145

FiO2 for oxygen therapy

Method	***O2 flow (l/min)***	***Estimated FiO2 (%)***
Nasal probe, nasal cannula	1 2 3 4 5 6	24 28 32 36 40 44
Nasopharyngeal catheter	4 5 6	40 50 60
Face mask	5 6–7 7–8	40 50 60
Face mask with reservoir	6 7 8 9 10	60 70 80 90 95

Clinical Pulmonary Infection Score (CPIS)

	0	1	2
Tracheal secretion	Little (not purulent)	Abundant (not purulent)	Purulent
Pulmonary infiltrates	None	Diffuse	localized
Fever (°C)	36,5 – 38,4	38,5 – 38,9	>38.9 or <36
Leukocytosis	4,0 – 11,0	<4.0 or >11.0	<4.0 or >11.0 and left shift
PaO2/FiO2	>240 or ARDS	---	≤240 and no ARDS
Microbiology	Negative		positive