Trial Description

Title

Therapeutic drug monitoring-based dose optimisation of piperacillin in patients with severe sepsis or septic shock to investigate effects on organ functions and survival: a prospective, multicenter, randomized controlled trial

Trial Acronym

Target

URL of the trial

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Brief Summary in Lay Language

Antibiotic therapy is one of the most important measures in sepsis treatment. Increasing evidence indicates that antibiotic dosing in critically ill patients is inadequate with fixed-dose regimens. Hence, the primary study goal is to investigate whether a daily therapeutic drug monitoring (TDM) - based dose optimization of piperacillin positively affects outcome in patients with severe sepsis or septic shock.

Brief Summary in Scientific Language

Administration of antibiotics active against the infecting organism is a cornerstone of effective sepsis management. Management is however complicated by increasing antimicrobial resistance with shortage of new antimicrobial substances. Given the paucity of new antibacterial agents to optimize antimicrobial use and bring out the best of the currently available agents is indispensable. Increasing evidence indicates however that antibiotic dosing in critically ill patients is inadequate with fixed-dose regimens. Pharmacokinetic (PK) and pharmacodynamic (PD) studies during pharmaceutical registration trials are usually conducted in healthy, normal weighted young adults in most instances. However, critically ill patients have a gross physiological derangement, which profoundly impacts PK. Patients with sepsis are known to become hyperdynamic, causing increased clearance of ß-lactams; end-organ dysfunction can lead to impaired drug clearances and capillary leak syndrome results in increased interstitial fluid volumes. Inadequate concentrations, however, negatively affect infection-related patient outcomes and promote the development of antibiotic resistance. Methods to optimize administration of ß-lactam antibiotics in these patients are urgently required. The primary study goal is to investigate whether an optimisation of antimicrobial therapy by individual dose adjustment of the test substance Piperacillin has a beneficial impact on organ function in severe sepsis or septic shock and whether it is superiour to dosage following prescribing information. This should be examined on the basis of global morbidity measurement (mean total SOFA-score).

Do you plan to share individual participant data with other researchers?

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[---]*

Description IPD sharing plan

[---]*

Organizational Data

- DRKS-ID: **DRKS00011159**
- Date of Registration in DRKS: **2016/10/10**
- Date of Registration in Partner Registry or other Primary Registry: **[---]***
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **4825-06/16 , Ethikkommission der Friedrich-Schiller-Universität Jena an der Medizinischen Fakultät**

Secondary IDs

- EudraCT-No.
  (for studies acc. to Drug Law): **2016-000136-17**

Health condition or Problem studied

- ICD10: **R65.1 - Systemic Inflammatory Response Syndrome of infectious origin with organ failure**
- ICD10: **R57.2 - Septic shock**

Interventions/Observational Groups

- Arm 1: **Daily measurement of piperacillin blood concentration with individual dosing based on the minimal inhibitory concentration of the infecting organism beginning on 1st day after randomization**

  optional: Measurement of the blood concentration of piperacillin and individual drug dosage already on day of randomisation (day 0)

  duration of therapy with piperacillin/tazobactam is at the discretion of the treating physician, intervention (TDM + dose adjustment) for a maximum of 10 days

- Arm 2: **standard piperacillin/tazobactam therapy, dosing based on summary of product characteristics**

Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: **[---]***
- Allocation: **Randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **patient/subject**
- Control: **Active control (effective treament of control group)**
- Purpose: **Treatment**
- Assignment: **Parallel**
- Phase: **III**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **Yes**

Primary Outcome

It should be investigated whether TDM-based piperacillin therapy results in a benefit regarding patient`s organ function.

primary Endpoint: mean total SOFA (Sequential Organ Failure Assessment) Score – from 1st day after randomization until ICU discharge or death, but only until day 10 after randomization

Secondary Outcome

• SOFA-Subscores
• 28-day mortality
• duration and cumulative dosage of antibiotic therapy
• number of dose adjustment / therapy cycle
• days without antibiotic, maximum day 14
• Length of ICU stay, maximum day 28
• Length of hospital stay, maximum day 28
• days without vasopressor, maximum day 14
• days without renal replacement therapy until day 28
• days without mechanical ventilation until day 28
• safety (side effects)
• antibiotic therapy costs

Countries of recruitment

- DE **Germany**

Locations of Recruitment

- University Medical Center **Integriertes Forschungs- und Behandlungszentrum Sepsis und Sepsisfolgen (CSCC) Zentrum für Infektionsmedizin und Krankenhaushygiene, Jena**
- University Medical Center **Charité Universitätsmedizin Berlin, Klinik für Anästhesiologie mit Schwerpunkt operative Intensivmedizin, Berlin**
- Medical Center **Klinikum Heidenheim, Klinik für Anästhesie, operative Intensivmedizin und spezielle Schmerztherapie, Heidenheim**
- University Medical Center **Universitätsklinikum Hamburg-Eppendorf, Klinik für Intensivmedizin, Hamburg**
- University Medical Center **Universitätsklinikum Heidelberg, Klinik für Anaesthesiologie, Heidelberg**
- University Medical Center <style fontName='DejaVu Sans' isBold='true'>Universitätsklinikum Köln, Klinik für Anästhesiologie und Operative Intensivmedizin & Klinik und Poliklinik für Kardiologie, Pneumologie, Angiologie und internistische Intensivmedizin – Klinik III für Innere Medizin , Köln</style>
- Medical Center **Zentralklinik Bad Berka, Zentrum für Anästhesie, Intensiv- und Notfallmedizin, Bed Berka**
- University Medical Center **Ev. Krankenhaus Bielefeld, Klinik für Anästhesiologie, Intensiv-, Transfusions-, Notfallmedizin und Schmerztherapie (AINS), Bielefeld**
- University Medical Center **Universitätsmedizin Greifswald, Klinik für Anästhesiologie, Greifswald**
- Medical Center **Klinikum Sindelfingen-Böblingen, Klinik für Anästhesie und Intensivmedizin Sindelfingen, Sindelfingen**
- University Medical Center **Universitätsmedizin Mainz, I. Medizinische Klinik und Poliklinik, Mainz**
- University Medical Center **Universitätsklinikum Ulm, Klinik für Anästhesiologie, Ulm**

Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2017/01/26**
- Target Sample Size: **276**
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **no maximum age**

Additional Inclusion Criteria

• Patients with severe sepsis or septic shock
• onset of severe sepsis or septic shock not longer than 24 hours prior to randomization
• Antimicrobial therapy with piperacillin planned or started
• age ≥18 years
• written informed consent of the patient or legal representative

Exclusion criteria

• pregnant or breast-feeding women
• anamnestic known hypersensitivity against beta-lactam antibiotics or another part of the investigational medicinal product
• previous treatment with piperacillin (in combination with tazobactam) > 24 hours before randomization
• participation in another interventional clinical trial
• previous participation (TARGET)
• limits of therapy or cessation
• impaired liver function (Child-Pugh C)
• life expectancy < 28 day due to accompanying illnesses
• piperacillin-measurement impossible within 24 hours after randomization

Addresses

■ **Primary Sponsor**

Friedrich-Schiller-Universität Jena
Postfach
07737 Jena
Germany

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■ **Contact for Scientific Queries**

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■ **Contact for Public Queries**

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- **Collaborator, Other Address**

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  Fax: **36419323379**
  E-mail: **cscc at med.uni-jena.de**
  URL: **http://www.cscc.uniklinikum-jena.de**

Sources of Monetary or Material Support

- **Public funding institutions financed by tax money/Government funding body (German Research Foundation (DFG), Federal Ministry of Education and Research (BMBF), etc.)**

  Bundesministerium für Bildung und Forschung Dienstsitz Bonn
  Heinemannstr. 2
  53175 Bonn
  Germany

  Telephone: **[---]***
  Fax: **[---]***
  E-mail: **[---]***
  URL: **www.bmbf.de**

Status

- Recruitment Status: **Recruiting complete, follow-up complete**
- Reason, if "Recruitment stopped after recruiting started" or "Recruiting withdrawn before recruting started": **[---]***
- Reason, if Reason for Recruiting Stop "Other": **[---]***
- Study Closing (LPLV): **2020/12/06**
- Number of Participants in Germany after Recruiting complete: **254**
- Total Number of Participants (all Sites worldwide) after Recruiting complete: **254**

Trial Publications, Results and other documents

- Approval of ethics comm. (mandatory for transfer to Studybox) **Ethikvotum**
- trial protocol (mandatory for transfer to Studybox) **Prüfplan**
- Trial results **Ergebnisbericht**

* *This entry means the parameter is not applicable or has not been set.*

*** *This entry means that data is not displayed due to insufficient data privacy clearing.*