# STUDY PROTOCOL AMENDMENT NO. 1

To the Study Protocol:
Final version 2.0 from 15.09.2017
Replaces study protocol final version 1.0 from 21.03.2016

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| **Amendment version, date:** | Final version 1.0, 15.09.2017 |
| **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.** |
| **Acronym:** | Target |
| **Study code ZKS Jena:** | ZKSJ0085 |
| **Protocol version, date:** | Final version 2.0 from 15.09.2017 |
| **EudraCT number:** | 2016-000136-17 |
| **Sponsor:** | Friedrich Schiller University Jena |
| **Sponsor's Representative and Principal Investigator:** | Stefan Hagel, M.D., M.Sc.<br>Center for Sepsis Control and Care<br>Institute for Infectious Diseases and Infection Control<br>Jena University Hospital<br>Am Klinikum 1<br>07747 Jena<br>Phone: +49 (0) 3641-9324590<br>Fax: +49 (0) 3641-9324652 |
| **Biometricians:** | Prof. Dr. Peter Schlattmann<br>Institute for Medical Statistics, Informatics and Documentation (IMSID)<br>Jena University Hospital<br>Bachstraße 18<br>07743 Jena<br>Tel.: +49 (0) 3641 9-34130<br>Fax: +49 (0) 3641 9-33200 |

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## 1. Changes in the study protocol

| Chapter | |
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| Cover page | Final version 2.0 from 15.09.2017 |
| Address<br>Authorized Sponsor<br>and<br>Clinical trial manager (LKP) | Am Klinikum 1<br><br>*Address was updated* |
| 1.1 Synopsis<br>Exclusion criteria | New: Therapy restriction or cessation (old: DNR order)<br><br>Deleted: *Renal insufficiency (acute or chronic) with renal replacement therapy or need for renal replacement therapy expected within 6 hours of randomization* |
| 1.1 Synopsis<br>Schedule | Recruitment period: approx. 3 years<br><br>Inclusion first patient: January 2017<br><br>Inclusion of last patient: 4th quarter 2019<br><br>End of examination last patient: 4th quarter 2019<br><br>Closing of the database: 1st quarter 2020<br><br>End of statistical analysis: 2nd quarter 2020<br><br>Integrated Final Report: 3rd quarter 2020<br><br>*Schedule has been updated* |
| 1.1 Synopsis<br>Number of test centers | 10-15 |
| 1.1 Synopsis<br>statistical methods | 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); |
| 1.2 Organizational structure<br>Addresses | Jena University Hospital<br>Am Klinikum 1<br>07747 Jena<br><br>*Addresses have been updated* |
| 1.2 Organizational structure | Sandra *Fiedler*<br><br>*Name change* |

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| 1.6 Clinical trial schedule/visit plan - legend | EOT: End of therapy (PipKons and PipTDM) |
| 2.5 Technical literature | 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 |
| 4.3 Patient recruitment | *Determination of the number of centers deleted* |
| 4.4 Timing and recruitment | The recruitment phase will be approximately 3 years. |
| 4.4 Timing and recruitment | Daily data collection per patient covers 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 visit to be recorded on day 28 of the study patient ("last patient out") and is expected at the end of the 4th quarter of 201 9. This will be followed by the evaluation phase, which is expected to end in Q2 2020. The end of the evaluation phase is planned for the second quarter of 2020. |
| 5.3 Exclusion criteria | New: Therapy restriction or cessation (old: DNR order)<br><br>Deleted: *Renal insufficiency (acute or chronic) with renal replacement therapy or need for renal replacement therapy expected within 6 hours of randomization* |
| 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. |
| 6.2 Instruction for dosage | *Clarification:*<br>Dose adjustment always takes 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 is comprehensible. |

| Chapter | |
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| 6.8 Side effects | Serious side effects were rarely observed according to the technical information. |
| 7.1.5 Measures to prevent participation in further intervention study | *Change formatting* |
| 7.2 Description of the individual visits Notes | 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. |
| 7.2 Description of the individual visits | Visit EOT (day of discontinuation of therapy with piperacillin/tazobactam).<br>*Specification for both treatment groups* |
| 10.4 Audits and inspections | It is possible that audits will be conducted. |
| 11.3Statistical methods | The change of the exclusion criteria (1st amendment) allows the inclusion of patients with renal insufficiency (acute or chronic) and renal replacement therapy or an 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. In the primary model, the presence of this condition (yes/no) at baseline is therefore considered as a further cofactor. |
| 11.3Statistical methods<br>Subgroup evaluations | The following subgroups are considered:<br>Patients with renal replacement therapy vs. other patients |
| Appendix | |

## 2. Implications for study participants

The exclusion criterion "renal insufficiency (acute or chronic) with renal replacement therapy or need for renal replacement therapy expected within the following 6 hours after randomization" is deleted as part of the amendment. The background for the deletion of this exclusion criterion is the results of a recent study on the pharmacokinetics of pipercillin/tazobactam in patients with renal insufficiency in whom a continuous renal replacement procedure was used (Roger C, Cotta MO, Muller L, et al. Impact of renal replacement modalities on the clearance of piperacillin-tazobactam administered via continuous infusion in critically ill patients. *Int J Antimicrob Agents*. 2017;50(2):227-231. doi:10.1016/j.ijantimicag.2017.03.018. The authors conclude that determination of piperacillin concentration is also recommended in patients on continuous renal replacement. The change has no impact on the risks to study participants.

The changes have no impact on patients previously treated in the study.

Due to the delay in the start of the study that has already occurred, the schedule will be updated. With the extension of the study duration as well as the change of the exclusion criteria, the general conditions for reaching the recruitment target will be optimized.

## 3. Signatures to the test plan amendment

### Signatures

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

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| Dr. Stefan Hagel | | |
| Sponsor Representative / LKP | Date | Signature |
| Prof. Dr. Peter Schlattmann | | |
| Biometrician | Date | Signature |