Clinical Trial protocol

Combination antibiotic treatment with linezolid for Staphylococcus aureus bacteraemia: a randomised controlled trial

Short title: **Li**nezolid **p**lus **s**tandard of care
Trial acronym: **LIPS**

Study Type:	Clinical trial with Investigational Medicinal Product (IMP)
Study Categorisation:	B
Study Registration:	humanresearch-switzerland.ch, clinicaltrials.gov (NCT06958835)
Study Identifier:	LIPS Trial
Sponsor-Investigator:	PD Dr. Richard Kühl Department of Infectious Diseases University Hospital Basel Petersgraben 4 4031 Basel Switzerland Phone: +41 (0)61 328 66 61 Email: richardalexander.kuehl@usb.ch
Investigational medicinal product:	Linezolid 600 mg tablet Placebo tablet
Protocol Version and Date:	Version 2.1 (dated 24/04/2026)

Confidentiality:
The information contained in this document is explicitly not confidential. We will make the study protocol publicly available as a PDF file on clinicaltrials.gov.

LIST OF PROJECT LEADERS, LOCAL INVESTIGATORS AND OTHER KEY PERSONS INVOLVED IN THE TRIAL

Please refer to the separate document “LIPS list of project leaders” for detailed information on project leaders, local investigators and other key persons involved in the trial including their roles and functions.

Signature Pages

Study number:	ClinicalTrials.gov Identifier: NCT06958835
Study Title:	Combination antibiotic treatment with linezolid for Staphylococcus aureus bacteraemia: a randomised controlled trial (LIPS Trial)

The Sponsor-Investigator and trial statistician have approved the protocol version 2.1 (dated 24/04/2026) and confirm hereby to conduct the study according to the protocol, the current version of the World Medical Association Declaration of Helsinki, the ICH-GCP guidelines and the local legally applicable requirements.

The Sponsor-Investigator has received the ICF and considers it appropriate for use.

Sponsor-Investigator: PD Dr. Richard Kühl

Place/Date	Signature

Co-Principal Investigator: PD Benjamin Speich, PhD

Place/Date	Signature

Co-Principal Investigator: Prof Dr. Nina Khanna

Place/Date	Signature

Trial Statistician: Laura Werlen, PhD

Place/Date	Signature

Trial Manager: Natalie Rose, PhD

Place/Date	Signature

Local Investigator at study site:

I have read and understood this trial protocol version 2.1 (dated 24/04/2026) and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

I have received the ICF and consider it appropriate for use.

Site:

Local investigator:

Place/Date	Signature

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STUDY SYNOPSIS

Sponsor	PD Dr. Richard Kühl Department of Infectious Diseases University Hospital Basel Petersgraben 4 4031 Basel Switzerland Phone: +41 (0)61 328 66 61 Email: richardalexander.kuehl@usb.ch
Study Title:	Combination antibiotic treatment with linezolid for *Staphylococcus aureus* bacteraemia: a randomised controlled trial
Short Title / acronym:	**Li**nezolid **p**lus **s**tandard of care (LIPS)
Protocol Version and Date:	Version 2.1 (dated 24/04/2026)
Trial registration:	ClinicalTrials.gov Identifier: NCT06958835 humanresearch-switzerland.ch: BASEC Nº2025-00655
Study category and Rationale	Risk Category B according to ClinO (Art 2) • Placebo controlled antibiotic treatment with linezolid STADA® authorized in Germany
Clinical Phase:	Phase 3
Background and Rationale:	*Staphylococcus aureus (S. aureus)* is the leading bacterial cause of death in high-income countries. Bloodstream infection (bacteraemia) represents a major manifestation of *S. aureus* affecting 20-30 in 100,000 persons yearly. 90-day mortality rates of 20-30% have remained unchanged over the last decades. Furthermore, *S. aureus* spreads to secondary body sites in 6-44% of cases, causing long-term impairment in up to a third of survivors, with a relapse rate of 4-10%. While more men are affected by *S. aureus* bacteraemia (ratio of approximately 1.5:1), women have 18% higher odds of death (OR 1.18) compared to men. So far, more effective treatments have not been identified. Thus, finding better treatments for patients suffering from *S. aureus* bacteraemia is a high unmet medical need. *S. aureus* expression of virulence factors facilitates the persistence and spread of the bacteria during infection and causes organ damage. We demonstrated the importance of *S. aureus* virulence factors in patho-mechanistic analyses directly from infected patient tissue. This led to our hypothesis that patient outcomes could be improved by adding an antibiotic that inhibits virulence factor expression. Several international guidelines recommend this strategy for toxin-mediated infections. However, due to a lack of evidence from randomised trials, this approach has not become standard clinical practice for bacteraemia with *S. aureus*. Linezolid, an established antibiotic for pneumonia or skin and soft tissue infections, strongly inhibited *S. aureus* virulence factor expression in preclinical studies.
Objectives:	**Primary objective:** To investigate whether early addition of 5-day treatment with linezolid to standard of care improves outcomes at 90 days in participants with *S. aureus* bacteraemia as measured by the desirability of outcome ranking (DOOR). **Secondary objectives:** Secondary objectives include exploring the impact of early addition of 5-day treatment with linezolid to standard of care on a number of secondary outcomes such as physical and mental health, length of hospital stay and safety (full list in section 5 STUDY OUTCOMES). In addition, we aim to explore if potential effects might differ between patient populations based on sex (male vs. female), ICU status at baseline (participants on ICU vs. participants not on ICU), and focus of infection (vascular catheter, skin and soft tissue, endocarditis, osteoarticular, pneumonia, other focus, or focus not identified).

Outcomes:

Primary outcome:

The **Desirability of Outcome Ranking (DOOR)** developed for this study comprises five ranks (Table 1) and is assessed at day 90. The primary outcome will be expressed as the win ratio, i.e., the ratio of the number of times that participants in the intervention group have a lower DOOR compared to those in the control group. In this study, we use the win ratio approach of Pocock et al. (2012), i.e., every participant in the linezolid group is compared with every participant in the control group. When comparing two participants, the winner will be determined by the first component of the DOOR in which the two participants differ, the only exceptions being ties when both participants die or if they do not die but have the same length of hospitalisation (see section 11 STATISTICAL METHODS for details).

Rank	Alive at 90 days	Return to usual level of function by day 90	None of the following complications: • Microbiological or clinical failure leading to treatment change • Serious adverse reaction • Adverse event leading to study drug discontinuation	Hospital length of stay
1	Yes	Yes	Yes (no complications occurred)	Ties will be resolved using the length of hospitalisation
2	Yes	Yes	No (complication occurred)	
3	Yes	No	Yes (no complications occurred)	
4	Yes	No	No (complication occurred)	
5	No	Not applicable	Not applicable	Not applicable

Table 1: Desirability of Outcome Ranking (DOOR) outcome used for the LIPS trial

Secondary outcomes:

Day of randomisation is defined as day 1.

- All-cause mortality at 90 days
- Time to death up to day 90
- Proportion of participants back to their usual level of function at day 90
- Microbiological failure at 14-90 days leading to treatment change
- Early microbiological failure at 5-13 days leading to treatment change
- Clinical failure at 14-90 days leading to treatment change
- Early clinical failure at 5-13 days leading to treatment change
- Hospital length of stay after randomisation
- Time to being discharged alive (assessed by day 90)
- Number of days without being on the Intensive Care Unit (ICU) up to day 90
- Number of days alive and free of antibiotics up to day 90
- Mental health at day 90 (SF-36 questionnaire)
- Physical health at day 90 (SF-36 questionnaire)

- Persistent bacteraemia: *S. aureus*-positive blood culture on day 5
- ≥ 2 systemic inflammatory response syndrome (SIRS) criteria on day 5
- Change in C-reactive protein on day 5
- Development of new antibiotic drug resistance in *Staphylococcus aureus*

Adverse events/safety:

- Serious adverse reactions until day 90
- Adverse events leading to study drug discontinuation
- Adverse events of special interest: clinical signs of serotonin toxicity, laboratory signs of myelosuppression, hyperlactatemia, acute kidney injury, *Clostridioides difficile*-associated diarrhoea within 90 days

Study design: Multi-centric, 1:1 randomised, parallel group, placebo-controlled clinical trial with blinded participants, physicians, and outcome assessors conducted in the acute-care hospital setting.

Inclusion / Exclusion criteria:

Inclusion criteria:

- *S. aureus* grown from at least one blood culture
- Hospitalised at a participating centre
- ≥18 years old
- Written informed consent or fulfilling criteria for an emergency exemption from informed consent requirements

Exclusion criteria:

- Administration of the initial drug treatment not feasible within 72 hours since the collection of the first positive blood culture with *S. aureus*
- Documented history of positive blood cultures for *S. aureus* occurring between 72 hours and 180 days prior to the eligibility assessment
- Necrotising fasciitis
- Currently receiving linezolid or clindamycin
- Use of any monoamine oxidase A or B inhibitor within the last two weeks
- Known hypersensitivity to linezolid or any other ingredients of the study drugs
- Current severe thrombocytopenia (i.e. <30 x 10^9/L)
- Application of study drug not possible (per mouth or per gastric tube)
- Currently breastfeeding
- Local treating team believes that death is imminent and inevitable
- Patient is receiving end of life care and antibiotic treatment is not considered appropriate
- Local treating team believes that participation in the study is not in the best interest of the patient
- Any indication that the patient is unwilling to participate in the study including an advance directive stating such unwillingness

General

Patients taking serotonergic drugs such as selective serotonin reuptake inhibitors (SSRI) or tricyclic antidepressants are not generally excluded. See detailed information on risk assessment and precautions in chapter 8.6 Trial specific preventive measures.

Pregnant women will not be excluded from study participation per se, as linezolid is not formally contraindicated during pregnancy. In the event of pregnancy, the treating physician and the patient (or the patient's next of kin) will assess whether the potential benefits for the patient outweigh the potential risks to the foetus.

Linezolid has been shown to pass into breast milk and accordingly, breastfeeding should be discontinued prior to and throughout administration of linezolid.

Measurements: Infectious disease specialists, serving as the local principal investigators at all participating centres, are routinely involved in the care of patients with *S. aureus* bacteraemia. Hence,

and procedures:	study teams at all participating sites will consider each patient with *S. aureus* bacteraemia for potential inclusion in the LIPS trial. The study team will check inclusion and exclusion criteria, initiate the contact, and inform the patient (or a close relative or an independent physician if patient is incapable of judgement) about this trial. After the written informed consent is obtained, the participant will be randomised to the intervention group (i.e. linezolid 600 mg tablets, twice daily for 5 days in addition to standard of care antibiotic treatment) or the control group (i.e. placebo tablets in addition to standard of care antibiotic treatment). The LIPS trial will mainly use data generated as part of clinical routine during hospitalisation. In brief, baseline data (e.g., date of birth, gender, risk factors), microbiological results (e.g., blood culture results, resistance patterns), laboratory results (e.g., blood count, renal function), and data of concomitant treatments (standard antibiotic, source control procedures) will be collected from the hospital electronic medical records. Participants will be treated and monitored according to clinical routine. If a physician suspects an adverse event (e.g. serotonin toxicity, myelosuppression) they should order any assessments and tests necessary for the detection, as in routine clinical practice. The outcomes “alive at day 90” and "return to usual level of function by day 90" will be assessed through a phone call on day 90 (given that the participant did not die during the hospitalisation). In addition, the participants will receive a questionnaire at day 90 to assess their quality of life (QoL, i.e. physical health and mental health).
Study Product / Intervention:	Participants in the intervention arm will receive linezolid 600 mg tablets (twice a day for 5 days) in addition to standard of care antibiotic treatment.
Control Intervention:	Participants in the control arm will receive oral placebo tablets (twice a day for 5 days) in addition to standard of care antibiotic treatment.
Number of Participants with Rationale:	606 participants (303 in control and 303 in the intervention group) We will use the win ratio to assess if participants in the intervention group have a better overall clinical outcome as defined by the DOOR compared to participants in the control group taking the following domains into considerations: i) survival, ii) participant-reported level of functioning at 90 days compared to the level before the blood infection, iii) treatment change due to persistence or spread of the bacterium within day 14-90 or serious adverse events leading to study drug discontinuation, and iv) hospital length of stay in days. The sample size was calculated using a simulation approach (including missing data in the assumptions), for which 1000 synthetic datasets for each combination of plausible values for the relevant parameters were generated and the intended primary analysis was applied. With a two-sided significance level of α=0.05 and a desired power of 90% (1:1 allocation), an estimated 550 participants will be required to show a significant effect of the intervention. Because of possible post-randomisation withdrawal due to missing retrospective consent, the sample size was increased by 10% to minimise the risk of being underpowered. See section 11 STATISTICAL METHODS for detailed assumptions about (i) occurrence of events and potential effect for each DOOR domain and (ii) about the frequency of missing data for each DOOR domain.
Study Duration:	Estimated duration for the main investigational plan (e.g. from start of screening of first participant to last participant processed and finishing the study): 38 months
Study Schedule:	First patient in: September 2025 Last patient out: October 2028
Local site-Investigators:	Please refer to the separate document “LIPS list of project leaders” for detailed information on local investigators.

Study Centres:	Approximately 12 institutions in Switzerland will be involved in this multi-centric trial. Please refer to the separate document “LIPS trial sites” for the complete list.
Statistical Considerations:	Primary analysis: Intervention and control groups will be compared based on the win-ratio approach as described by Pocock and colleagues: In brief, participants in the intervention group will be compared with participants in the control group. When comparing two participants, the winner will be determined by the first component of the DOOR in which the two participants differ. The following two scenarios will be considered a tie: (i) both participants died within 90 days, or (ii) both participants have the same outcomes for all DOOR elements, including hospital length of stay. The win ratio will be calculated by dividing the number of cases in which participants receiving linezolid win with the number of cases in which participants receiving placebo win. We will reject the null hypothesis that the win ratio is equal to 1 if the *p*-value calculated is less than 0.05. More detailed information and intended approaches for the secondary analyses are listed in section 11 STATISTICAL METHODS. A detailed analysis plan will be written before closing the study database.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, ICH-GCP, as well as all national legal and regulatory requirements.

ABBREVIATIONS

ADL	Activities of Daily Living
AE	Adverse Event
ALT	Alanine Transaminase
Art.	Article
ASR	Annual Safety Report
BASEC	Business Administration System for Ethical Committees, (https://submissions.swissethics.ch/en/)
C. difficile	*Clostridioides difficile*
CA	Competent Authority (e.g. Swissmedic)
CD	Cluster of Differentiation
CEC	Competent Ethics Committee
CI	Confidence Interval
ClinO	Ordinance on Clinical Trials in Human Research *(in German: KlinV, in French: OClin, in Italian: OSRUm)*
CRF	Case Report Form
CRP	C-reactive protein
CTCAE	Common terminology criteria for adverse events
DKF	Department of Clinical Research, University Hospital Basel
DOOR	Desirability Of Outcome Ranking
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
e.g.	For example
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FOPH	Federal Office of Public Health
GCP	Good Clinical Practice
gGT	Gamma-glutamyl Transferase
Hb	Haemoglobin
Ho	Null hypothesis
HR	Heart Rate
HRA	Federal Act on Research involving Human Beings *(in German: HFG, in French: LRH, in Italian: LRUm)*
i.e.	That is
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
ID	Identification
IICT	Investigator-Initiated Clinical Trial
IIT	Investigator-Initiated Trial
IMP	Investigational Medicinal Product
ITT	Intention To Treat
IV	Intravenous
KDIGO	Kidney Disease Improving Global Outcomes
Lc	Leukocytes

LIPS	**Li**nezolid **P**lus **S**tandard of Care
MALDI-TOF	Matrix-Assisted Laser Desorption/Ionization-Time of Flight
MF-DAC	Data Access Committee of the Faculty of Medicine at the University of Basel
MIC	Minimal Inhibitory Concentration
MRSA	Methicillin-Resistant S. aureus
MSSA	Methicillin-Susceptible S. aureus
N/A	Not applicable
OR	Odds Ratio
PCR	Polymerase Chain Reaction
PD	Privatdozent
PI	Principal Investigator
PPI	Patient and Public Involvement
PROM	Patient-Reported Outcome Measure
QoL	Quality of Life
RCT	Randomised Controlled Trial
RR	Respiratory Rate
S. aureus	*Staphylococcus aureus*
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SCTO	Swiss Clinical Trial Organisation
SDV	Source Data Verification
SF-36	Short Form 36 Survey
SIRS	Systemic Inflammatory Response Syndrome
SNAP	*Staphylococcus aureus* Network Adaptive Platform
SNCPT	Swiss National Clinical Trials Portal
SNSF	Swiss National Science Foundation
SOP	Standard Operating Procedure
SMPC	Summary of Product Characteristics
SS	Serotonin Syndrome
SSRI	Selective Serotonin Reuptake Inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
Tc	Thrombocytes
TLS	Transport Layer Encryption
TMF	Trial Master File
US	United States of America
USB	University Hospital Basel
WHO ICTRP	World Health Organisation International Clinical Trials Registry Platform

DEFINITIONS AND TERMINOLOGY

ICU (Intensive Care Unit)

ICU includes all inpatient areas with the capacity for organ support, including invasive or non-invasive ventilation, vasopressors and/or inotropes and higher nursing staff-to-patient ratios than standard hospital wards. Intermediate Care Units that meet these criteria will also be considered ICUs for the purpose of data collection in the LIPS trial.

Local investigator

The physician at a given study site who is responsible for the overall conduct of the trial at that site, including oversight of the study team and ensuring compliance with the protocol, GCP, and applicable regulations.

Study physician

A physician who is a member of the study team, has received trial-specific training, and is delegated trial-related responsibilities by the Local Investigator. The study physician performs study-specific medical assessments, evaluates and reports adverse events, and enters or verifies data in the eCRF.

Study team

Personnel at a study site who are involved in the conduct of the LIPS trial, have received trial-specific training, and are formally delegated trial-related responsibilities by the Local Investigator. Study team members perform study-specific procedures and assessments, enter data into the eCRF, and ensure protocol compliance.

Treating physician

A physician providing routine clinical care to a study participant at a study site who is not part of the study team and is not delegated any study-specific tasks. The treating physician is responsible for the participant's clinical management as part of standard care.

Treating team

Physicians, nurses, or other healthcare professionals providing routine clinical care to a study participant who are not delegated study-specific tasks and have not received trial-specific training. They may administer the IMP and document routine clinical data as part of standard care but are not responsible for study-specific procedures or eCRF data entry.

SUMMARY OF THE REVISION HISTORY IN CASE OF AMENDMENTS

Version Nr, Version Date	Chapter	Description of change	Reason for the change
1.0, 27/03/2025		Initial version	
1.1, 27/06/2025		Minor changes throughout protocol before submission to Swissmedic	Incorporated feedback from competent Ethics committee
1.2, 30/07/2025	7.1, 8.6	Added “Currently breastfeeding” and “Use of any monoamine oxidase A or B inhibitor within the last two weeks” to exclusion criteria, changed wording of hypersensitivity criterion; minor changes in assessment description	Incorporated feedback from Swissmedic’s further information request; close alignment with linezolid SmPC
2.0, 19/03/2026		Various changes, protocol version not approved by ethics committee.	
2.1, 24/04/2026	1.2 and 1.3	The scope of the Data Safety Monitoring Board (DSMB) was defined more clearly. SAEs will be reviewed by an independent physician. The independent outcome assessment board was omitted.	Review of individual SAEs is not within the scope of the DSMB. To ensure SAE assessments are unbiased, the majority of SAEs will be reviewed by an independent physician. After careful consideration, the independent outcome assessment board was deemed unnecessary given the blinded design of the study. Furthermore, limited resources do not permit independent review of all source documents across all study sites or the provision of sufficient resources to sites to anonymise source data (which would be required for independent outcome assessment).
2.1, 24/04/2026	9.1	Data entry scheduled for day 28 was removed from the study schedule.	The required data will be extracted from routine patient charts at each study centre at day 90, making a data entry at day 28 unnecessary.
2.1, 24/04/2026	9.2 and 9.3	Chapters 9.2 and 9.3 have been revised for clarity and structural consistency. Chapter 9.2 now more clearly defines responsibilities for study-specific assessments and specifies which data are to be entered into the eCRF. Chapter 9.3 has been comprehensively restructured to present study-specific procedures by study day. Redundant information previously duplicated from chapter 9.2 has been removed.	Feedback from sites that instructions in the protocol were not clear.
2.1, 24/04/2026	9.3.2.3	For the subproject on molecular mechanisms of *Staphylococcus aureus* bacteraemia, additional blood samples may be collected if culture-negative persistence of *S. aureus* in the blood is suspected.	The sampling timeframe was adapted based on preliminary results indicating that *S. aureus* persists intracellularly for longer than previously anticipated.

2.1, 24/04/2026	10.1.2	The following exemptions from SAE reporting were defined: 1) SAE in the context of pre-existing foci; 2) SAEs in the context of pre-planned procedures	The study population consists of critically ill patients with a high frequency of *S. aureus*-infection–related SAEs. A detailed rationale is provided in chapter 10.1.2.
2.1, 24/04/2026	12.3	Risk-based centralised data monitoring through REDCap® was added in addition to the planned on-site monitoring.	Centralised data monitoring was introduced to enhance the timeliness and quality of data.
2.1, 24/04/2026	N/A	Minor wording changes were made throughout the protocol to improve clarity, including the correction of typographical errors and deletion of redundant information.	The wording changes reflect further clarifications based on feedback from study collaborators.

STUDY SCHEDULE

The study schedule can be found in chapter 9.1 *Study flow chart / table of study procedures and* assessments.

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Monitoring institution

Clinical Trial Unit

Department of Clinical Research, University Hospital Basel

Spitalstrasse 8/12, 4031 Basel

Switzerland

Tel. +41 61 328 51 48

ClinicalTrials@usb.ch

1.2 Data Safety Monitoring Board

The trial will be reviewed by an independent and blinded Data Safety Monitoring Board (DSMB) who assesses safety during prespecified interim analyses. The DSMB will consist of at least two infectious disease experts and one statistician/methodologist, unaware of the treatment assignments and not otherwise involved in the study. In addition, we plan to include at least one patient representative in the DSMB. Members and frequency of meetings are described in the DSMB charter. The DSMB will function independently of all individuals involved in the study, including the investigators at the enrolling sites. The DSMB is primarily responsible for safeguarding the interests of the participants in the LIPS trial. It assesses the safety during the trial and will provide recommendations about stopping, continuing or modifying/amending the trial.

1.3 Independent review of serious adverse events

All reported serious adverse events (SAEs) will be reviewed by the sponsor or a sponsor-delegated independent physician not otherwise involved in the LIPS trial. The independent physician will review the majority of reported SAEs in the electronic Case Report Form (eCRF). The primary responsibilities of the independent physician(s) include:

- Verify completeness and clarity: Ensure the SAE description is understandable and adequately documented. Open queries or contact the recruiting site in case of missing or inadequate information.
- Assess relatedness: Confirm whether the reported relatedness (definitely, probably, possibly, unlikely, not related) is appropriate.
- Assess severity: Confirm whether the reported severity (mild, moderate, severe, life-threatening, death) is appropriate.
- Identify potential Suspected Unexpected Serious Adverse Reactions (SUSAR): Evaluate whether any SAE qualifies as a SUSAR and flag accordingly for the Sponsor-Investigator.

Details of this process are described in the *independent SAE review* charter.

1.4 Any other relevant Committee, Person, Organisation, Institution

1.4.1 Patient and Public Involvement (PPI)

Patient representatives will be involved at all stages of the trial. Detailed information can be found in 6.2 *Patient and Public Involvement*.

1.4.2 IMP Manufacturer

Spital-Pharmazie

Universitätsspital Basel

Spitalstrasse 26

4031 Basel

2. ETHICAL AND REGULATORY ASPECTS

Before the study is conducted, the protocol, the proposed patient information and consent form as well as other study-specific documents shall be submitted to a properly constituted Competent Ethics Committee (CEC) and Swissmedic, in agreement with local legal requirements, for formal approval. The CEC and Swissmedic approval will be communicated to the Sponsor-Investigator in writing before commencement of this study. The study will not start recruiting participants until ethical and regulatory approval has been granted. Any amendment to the protocol will, if legally required, also be approved by these institutions.

2.1 Study registration

This trial will be registered in the following registries before the recruitment of the first participant:

- http://humanresearch-switzerland.ch (BASEC Nº 2025-00655)
- ClinicalTrials.gov: https://clinicaltrials.gov/study/NCT06958835

2.2 Categorisation of study

Category B. A placebo-controlled study using an IMP authorized in Germany. Linezolid STADA® 600 mg tablets have been authorized in Germany, a country with equivalent medicinal product control in accordance with Article 13 Therapeutic Products Act, as a generic of Zyvoxid® 600 mg since 2014. Linezolid STADA® 600 mg is authorized for the treatment of pneumonia and complicated skin and soft tissue infections caused by Gram-positive bacteria. Recommended dose 600 mg twice a day. Recommended treatment duration is 10-14 days, but shorter treatment regimen may be sufficient for certain types of infections. *Staphylococcus aureus* is a Gram-positive bacterium and nearly always susceptible to linezolid. The effectiveness of linezolid in *S. aureus* bacteraemia as an oral continuation treatment after initial intravenous antibiotics is well-documented in observational studies. Drugs containing linezolid as their active ingredient have been approved in Switzerland for over 20 years.

2.3 Competent Ethics Committee (CEC)

The Sponsor-Investigator will submit all Swiss centres for approval to the lead CEC (Ethikkommission Nordwest- und Zentralschweiz, EKNZ) in collaboration with the local Swiss investigators. No changes are made to the protocol without prior sponsor and CEC approval, except where necessary to eliminate apparent immediate hazards to study participants.

The Sponsor-Investigator will report the premature termination, interruption, or resumption of the study, including reasons thereof, to the CEC within 15 days. An interruption lasting more than two years is considered a premature termination. The Sponsor-Investigator will report the first visit of the first participant and the end of the study (defined as the last follow-up visit of the last study participant) to the CEC within 30 days. The final study report will be submitted within one year after study end or premature study termination. Amendments are reported according to chapter 2.10 *Protocol amendments*.

2.4 Swissmedic

The sponsor will obtain approval from Swissmedic before the start of the clinical trial. Reporting duties and timelines are the same as for CEC, except for non-substantial amendments that shall be reported as soon as possible. The application must be submitted to the CEC within two years of approval by the CA (ClinO Art. 23). An application for an extension beyond the two years is a substantial amendment; if this is not complied with, the approval to conduct the study lapses.

Amendments are reported according to chapter 2.10 *Protocol amendments*.

2.5 Ethical Conduct of the Study

The study will be carried out in accordance with the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, and Swiss Law and

Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety reports (ASR) and interim reports and be informed about study stop/end in agreement with local requirements. In addition, the CEC will be informed annually about the general progress of the clinical trial.

2.6 Declaration of interest

There are no potential conflicts of interest to disclose.

2.7 Patient Information and Informed Consent

Patients will be informed about the study by a study physician and consent will be obtained from each patient. Patients who are conscious and capable of making decisions will be approached to give their consent. A study physician will explain the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each patient will be informed that the participation in the study is voluntary, that the patient may withdraw from the study at any time and that withdrawal of consent will not affect the patient's subsequent medical assistance and treatment. The patient will be informed that any questions can be asked, and that consulting family members, friends, their treating physicians, or other experts before deciding about study participation is possible. Enough time will be given before making the decision about study participation. However, it will be noted that the potential effect of the study medication (i.e. linezolid) might be greater if treatment can be started earlier. The patient will be informed that authorised individuals other than their treating physician may examine the patient's medical records.

Due to the nature of *S. aureus* bacteraemia, we expect approximately 10-20% of patients to be unresponsive and incapable of giving informed consent during the acute infection. These patients are particularly at risk of succumbing to the infection and should thus not be excluded from the study. In these emergency situations, consent will be obtained from the patient's next of kin. If no next of kin are present, an independent physician who safeguards the interests of the patient and is not involved in the conduct of the study can confirm participation ("confirmation by independent physician"). If there is any indication that the patient is unwilling to participate in the study including an advance directive stating such unwillingness, the patient will be excluded from participation. After patients regain capacity of judgement, they will be approached about giving retrospective consent.

We will provide the following specific information sheet and consent forms which will enable an informed decision about study participation:

1) Patient informed consent form
2) Next of kin informed consent form
3) Confirmation by Independent physician
4) Retrospective patient informed consent form

Formal consent, using the approved consent form, will be obtained before the patient is subjected to any investigation procedure. The signed consent form is retained as part of the trial records. Consent forms were developed in collaboration with patient representatives.

Detailed information on the informed consent process including revoking of consent can be found in the corresponding SOP and Work Instruction that is provided to the sites.

2.8 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. In particular, anonymity of the participants will be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual participant medical information (i.e. information that would identify an individual participant) obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Participant confidentiality will be further ensured by utilizing participant identification code numbers to correspond to treatment data in the computer files.

The investigator has appropriate knowledge and skills in the areas of data security and data protection or is able to ensure compliance by calling in appropriate expertise (Art. 6, ClinO).

For data verification purposes, authorized representatives of the sponsor, a competent authority (e.g., Swissmedic),

or a CEC may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.9 Premature termination of the study

The Sponsor-Investigator in consultation with the DSMB may terminate the study prematurely before reaching the anticipated sample size of 606 participants according to certain circumstances, for example:

- ethical concerns
- insufficient participant recruitment
- when the safety of the participants is doubtful or at risk, respectively
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise

If the study is terminated earlier than planned, the Sponsor-Investigator notifies the CEC and Swissmedic according to the provisions of ClinO Art. 38.

2.10 Protocol amendments

Suggestions for a protocol amendment can be made to the LIPS trial team by any group member and by all investigators. Should these impact trial specific procedures, additional on-site or web-based training will be provided to all investigators. Substantial amendments are only implemented after approval of the CEC and Swissmedic, respectively. Substantial amendments are changes that affect the safety, health, rights and obligations of participants, changes in the protocol that affect study objective(s) or central research topic, changes of trial site(s) or of trial leader and sponsor (ClinO, Art. 29).

Under emergency circumstances, deviations from the protocol to protect the rights, safety, and wellbeing of human participants may proceed without prior approval of the sponsor and the CEC/Swissmedic. Such deviations shall be documented and reported to the sponsor and the CEC/Swissmedic as soon as possible.

All non-substantial amendments are communicated to Swissmedic and to the CEC within the ASR.

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

Staphylococcus aureus (S. aureus) is the leading bacterial cause of death in high-income countries and estimated second leading bacterial cause of death globally after tuberculosis.[1] Bacteraemia (bacteria in the bloodstream) represents a common manifestation of *S. aureus* infection, affecting 20-30 in 100,000 persons annually.[2-4] These numbers have risen in recent years due to aging of the population and other risk factors such as the use of implantable medical devices.[2 4-6] Approximately 20-30% of patients with *S. aureus* bacteraemia die within 90 days.[7 8] This rate has not significantly changed for decades despite active standard antibiotic therapy[9 10] representing the highest mortality rate among all common bloodstream pathogens.[1] *S. aureus* bacteraemia is reported more often in men than in women.[11-13] Risk factors, as well as diagnostic and therapeutic management can differ between men and women.[13] Women may experience worse outcomes and higher mortality.[11 14-16]

In addition, *S. aureus* bacteraemia spreads to secondary body sites in 6-44% of cases,[17-20] produces prolonged impairment in up to one-third of survivors,[21] and is associated with a relapse rate of 4-10%.[22-24] Despite the magnitude of disease burden with an estimated 2 million people affected yearly worldwide, less than 3000 patients have been included in published randomised controlled trials (RCTs) testing treatments for *S. aureus* bacteraemia.[25] This leaves us with considerable uncertainty about an effective treatment.

Methicillin-susceptible *S. aureus* (MSSA) represents 95% of *S. aureus* antibiotic resistance profiles in Switzerland.[2] The standard management of MSSA bacteraemia consists of an intravenous treatment with an anti-staphylococcal beta-lactam antibiotic such as flucloxacillin or cefazolin for 2-6 weeks and rapid source control if possible.[26-29] Previous studies attempted to increase the antimicrobial efficacy of standard therapy by adding a second antibiotic with evidence of additive or synergistic killing capacity *in vitro*. As identified by a recent systematic review,[30] gentamicin,[31-33] rifampicin,[34 35] levofloxacin,[36] daptomycin,[37] or fosfomycin[38] have been added to standard antibiotics in RCT of bacteraemia with methicillin-susceptible *S. aureus* (Table 2). Unfortunately, none of these RCTs succeeded in demonstrating a significant improvement in clinical outcomes. Several factors may have contributed to the shortcomings of these clinical trials. One possible factor is that the interventions may not have effectively addressed the underlying pathophysiologic factors responsible for the poor outcomes in patients with *S. aureus* bacteraemia. Limitations of the RCTs also include that the sample sizes were generally small, making it difficult to detect small, but relevant differences in mortality. In addition, these RCTs did not prioritise the assessment of other important patient-related outcomes, such as post-infection functional status.

Study (year)	RCT design sample size	Population	intervention	Control	PROM	Primary outcomes
Abrams (1979) [25]	open-label single-centre N=35	*S. aureus* endocarditis in intravenous drug users	Standard **+ gentamicin**	Standard (Beta-lactam)	no	time to defervescence: I: 6.3 days vs. C: 6.6 days mortality/relapse of infection I: 0%. vs. C: 0% **No difference** in primary outcome
Korzeniowski (1982) [26]	open-label multicentre n=78	*S. aureus* endocarditis in drug-addicts and non-addicts	Standard **+ gentamicin**	Standard (nafcillin)	no	cure: I: 60% vs. 65% **No difference** in primary outcome
Van der Auwera (1985) [28]	double-blind placebo-controlled multicentre n=29 (bacteraemia)	*S. aureus* infections (subgroup with bacteraemia)	Standard **+ rifampicin**	Standard (oxacillin / vancomycin) + **placebo**	no	clinical cure: I: 69%, C: 63% **No difference** in primary outcome
Ribera (1996) [27]	open-label single-centre n=90	*S. aureus* right-sided endocarditis	Standard **+ gentamicin**	Standard (cloxacillin)	no	cure (no persistence/relapse/death): I: 86%, C: 89% **No difference** in primary outcome
Ruotsalainen (2006) [30]	open-label multicentre n=381	*S. aureus* bacteraemia	Standard **+ levofloxacin**	Standard (semisynthetic penicillin)	no	28-d mortality: I:14%, C: 14% 90-d mortality: I:18%, C: 21% **No difference** in primary outcome
Thwaites (2018) [29]	double-blind placebo-controlled multicentre n=758	*S. aureus* bacteraemia (MSSA/MRSA)	Standard **+ rifampicin**	Standard (flucloxacillin / vancomycin) + **placebo**	no	failure: (persistence/recurrence/death): I: 17%, C: 18% **No difference** in primary outcome
Cheng (2020) [31]	double-blind placebo-controlled multicentre n=104	*S. aureus* bacteraemia (MSSA)	Standard **+ daptomycin**	Standard (cefazolin/ flucloxacillin) **+ placebo**	no	90-d mortality: I: 18.9%, C: 17.7% Duration of bacteraemia: I: 3.09 d, C: 3.0 d **No difference** in primary outcome
Grillo (2023) [32]	open-label multicentre n=215	*S. aureus* bacteraemia (MSSA)	Standard **+ fosfomycin**	Standard (cloxacillin)	no	7-d treatment success (alive/better qSOFA score/afebrile/negative blood culture): I: 79.8%, C: 74.5% **No difference** in primary outcome

Table 2: Overview of published randomised controlled trials (RCT) testing for superiority in methicillin-susceptible S. aureus bacteraemia (identified by the systematic review by Grillo et al. [30], and Grillo et al [38])
Abbreviations: PROM: patient-related outcome measure; I: intervention group, C: control group, MSSA: methicillin-susceptible S. aureus; MRSA: methicillin-resistant S. aureus

Thus, there is an urgent clinical need to evaluate new therapeutic strategies through high-quality RCTs with the aim of improving patient-relevant outcomes in *S. aureus* bacteraemia.

S. aureus is known for its ability to survive and rapidly adapt to new environments in the human body.[39 40] It employs a wide range of virulence factors, including toxins to attack human (immune) cells[41] and proteases to invade human tissue[42], often eliciting a strong inflammatory response at the site of infection. It can be inferred that most of the damage to the body results from direct and indirect effects of these virulence factors. The impact of indirect damage and physical strain from the infection is evident, as 40-60% of deaths in people with *S. aureus* bacteraemia happen after the initial infection and cause of death cannot be clearly linked to the infection.[17 43] This finding is consistent with prior research involving patients with sepsis.[44] Furthermore, akin to sepsis as a whole, it is imperative to consider not only mortality but also long-term functional and cognitive impairments resulting from the direct and indirect consequences of the infection. This aspect represents a thus far underexplored area of research.[45 46]
The significance of virulence factor expression has been observed in data obtained directly from patient samples as part of our research project within the National Centre of Competence in Research (publication in preparation).
Determining the role of virulence factors becomes even more important considering that standard treatment with a beta-lactam-type antibiotic can augment bacterial toxin production as long as *S. aureus* is not killed.[47] Thus, it has been hypothesised that adding an antibiotic agent inhibiting virulence factor expression could reduce direct and indirect organ damage thereby improving patient outcomes.[48] Linezolid strongly reduced the expression of *S. aureus* virulence factors in preclinical studies,[47] making it an ideal candidate to use clinically. Expert opinion and some guidelines advocate this strategy for severe infections or for *S. aureus* strains with known toxin expression.[49-52] However, evidence from RCTs for this approach is still lacking: our systematic literature search for published or planned RCTs (in PubMed, Embase, and the Cochrane Central Register of Controlled Trials [indexing planned RCTs from clinicaltrials.gov and WHO ICTRP]) that was developed by an information specialist from the University Medical Library yielded 943 hits (search conducted in June 2023). None of those reported RCT results or an ongoing RCT involving an antibiotic combination treatment with linezolid for *S. aureus* bacteraemia.
Currently, an international platform trial called SNAP ("*Staphylococcus aureus* Network Adaptive Platform")[25] compares various treatment options for *S. aureus* bacteraemia including one study domain that assesses open-label adjunctive treatment with clindamycin — a different antibiotic recognised for its toxin-inhibiting properties. Our proposed study, in contrast, will employ linezolid as the adjunctive intervention, thus providing crucial complementary evidence to the findings of the SNAP trial's adjunctive clindamycin.

In summary, effective treatment of *S. aureus* bacteraemia is a high unmet medical need. Our hypothesis suggests that *S. aureus* virulence factors are responsible for these negative outcomes and that early intervention to suppress these factors may lead to improved clinical outcomes. We also consider that the chosen outcomes to date have not covered the whole spectrum of effects associated with the disease. Our goal is to evaluate addition of linezolid to standard of care in a robust RCT with patient-relevant endpoints to achieve better outcomes for patients with *S. aureus* bacteraemia.

3.2 Investigational Medicinal Product (treatment) and Indication

Linezolid STADA® 600 mg tablets and oval placebo tablets (Fagron) will be imported from Germany by Spital-Pharmazie Basel, Spitalstrasse 26, 4031 Basel. Linezolid STADA® 600 mg is authorized for the treatment of pneumonia and complicated skin and soft tissue infections caused by Gram-positive bacteria. Recommended treatment duration is 10-14 days, but shorter treatment regimen may be sufficient for certain types of infections[53].

Packaging and labelling will be performed by Spital-Pharmazie Basel to ensure blinding. A sample of the label will be enclosed to the Swissmedic application.

Detailed information on Linezolid STADA® 600 mg can be found in the provided Summary of Product Characteristics (SMPC).

3.3 Preclinical Evidence

Linezolid inhibits bacterial protein synthesis at an early stage by binding to the 50S subunit of the bacterial ribosome. Animal data revealed enhanced activity of linezolid combined with vancomycin or imipenem in experimental endocarditis models,[54 55] as well as in combination with fosfomycin in a murine peritonitis model.[56] Additionally, linezolid effectively decreased *in vivo* toxin production[57] and was much more effective than vancomycin in protecting animals from dying in pneumonia models.[57-59]

A summary of relevant preclinical data is included in the SMPC.

3.4 Clinical Evidence to Date

Linezolid is an established antibiotic treatment option for skin- and soft tissue infections as well as for pneumonia, especially in case of MRSA due to the low rate of linezolid resistance.[60] Detailed information on pivotal studies of linezolid can be found in the SMPC. For nosocomial MRSA pneumonia, linezolid has been shown to be superior to the commonly administered intravenous vancomycin.[59] For MRSA bacteraemia, linezolid is a safe and effective alternative to standard-of-care glycopeptide (vancomycin/ teicoplanin).[61-63] A trial directly comparing standard-of care beta-lactam therapy with linezolid in MSSA bacteraemia is lacking, since beta-lactam therapy is regarded as most effective for MSSA. Limited clinical data exist regarding combination therapy with linezolid in *S. aureus* bacteraemia. Two observational cohort studies (involving a total of 54 linezolid treated participants) reported favourable outcomes (microbiological response, success rate, mortality) with salvage combination therapy using linezolid and a carbapenem.[64 65] Successful treatment was also observed in a case of MRSA bacteraemia and meningitis with linezolid, daptomycin, and rifampicin.[66] Linezolid may be most effective when started as early as possible according to the open label RCT by Wilkox et al.[67] Even though the study was underpowered, it supports the hypothesis that empirically initiated linezolid might result in better survival. Similarly, a prospective observational single-centre study found significantly improved survival in participants with MRSA bacteraemia empirically receiving linezolid compared to a glycopeptide (adjusted odds ratio for survival 7.7; 95%CI 1.1–53).[68]

The potential clinical impact of toxin inhibition by linezolid is demonstrated in a case report on the successful treatment of a staphylococcal toxic shock syndrome.[69] In addition, a review of 93 cases of *S. aureus* necrotizing pneumonia revealed reduced mortality rates when antibiotic therapy incorporated an anti-toxin agent, such as clindamycin or linezolid.[70] Our systematic search showed that no RCT has assessed the effect of adding linezolid to the standard antibiotic therapy in patients having *S. aureus* bacteraemia.

In summary, linezolid is a valuable antibiotic for various *S. aureus* infections, especially for MRSA cases in which beta-lactams are ineffective. Early use of linezolid, as well as late salvage treatment using linezolid in combination with a beta-lactam for persistent bacteraemia and toxin-mediated infections has been documented. However, no study has evaluated early combined treatment of linezolid with standard therapy for *S. aureus* bacteraemia to mitigate potential toxin-related complications and improve patient relevant outcomes.

3.5 Rationale for the dosage, route, regimen

Linezolid will be applied in addition to the standard antibiotic treatment prescribed by the treating physician.

Linezolid is approved according to the Swissmedic-approved prescribing information of a reference product with marketing authorisation as follows: 600 mg IV or oral twice daily for 10-14 days in case of nosocomial pneumonia and complicated skin and soft tissue infections, and 600 mg IV or oral twice daily for 14-28 days in case of vancomycin-resistant enterococcus infections including enterococcal bacteraemia. Treatment duration is variable and dependent on pathogen, site and severity of infection, as well as clinical response of the patient. The maximum treatment duration is 28 days. Due to linezolid's excellent oral bioavailability of nearly 100%,[71] we selected the oral dosing route for our study. This is in line with patient preferences. It has the additional benefit that participants do not need an intravenous catheter for the study which would increase the risk of catheter-related infections. Moreover, participants are not burdened by the additional administration of fluids, which can have negative cardiovascular effects, especially in patients with heart failure.

We expect the highest therapeutic benefit of linezolid within the first three days following detection of infection. Beyond this early period, we hypothesize that damage caused by the expression of virulence factor has already occurred, leading to decreased potential efficacy and benefit of linezolid. Thus, in line with our hypothesis we have reduced the treatment duration to 5 days which must start within 72 hours after the collection of the first positive blood culture.

3.6 Explanation for choice of comparator

Placebo will be applied in addition to the standard antibiotic treatment prescribed by the treating physician. Some primary outcome measures might be influenced by expectations of physicians and participants. The blinded study design ensures blinding of caregivers (including nurses, treating physicians), the participant, the investigators, and outcome assessors, and mitigates the bias associated with conduct of an open trial.

3.7 Risks / Benefits

Risks

The most commonly reported adverse event of linezolid is gastrointestinal intolerance, occurring in approximately 30-40% of patients when linezolid is administered for a longer duration.[72 73] Within the first 5 days of treatment, gastrointestinal intolerance manifests in approximately 8% leading to early discontinuation in 3%.[73] Myelosuppression, which primarily presents as thrombocytopenia, is another common adverse effect of linezolid that affects up to a third of patients[74-77] and occurs more frequently during treatment durations of ≥10 days.[74 78] Moreover, linezolid is a weak, reversible, and unselective monoamine oxidase inhibitor.[79] Consequently, the combination of linezolid with other serotonergic drugs, such as selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants, can potentially lead to an increase in serotonin activity. The clinical effects of serotonin excess can range from mild serotonin-related side effects to severe serotonin toxicity.[80 81] In the largest meta-analysis involving 2208 patients receiving linezolid and 5058 patients not receiving linezolid, the observed incidence of serotonin toxicity was 0.4% among patients taking linezolid in combination with a serotonergic agent (compared to 0.15% in those taking a serotonergic agent alone).[82] Similarly, in a large cohort of 1135 patients, fewer than 0.5% experienced serotonin toxicity.[83] Further, hyperlactatemia is a rare but potentially severe adverse effect of linezolid documented in various case reports.[72 84 85] The incidence is not well reported, but may be at 1-3% according to retrospective studies.[73 86] Finally, it should be noted that linezolid can potentially cause peripheral and/or optic neuropathy if treatment is administered for more than 28 days.[85 87] Given the short treatment duration of 5 days, we expect a low incidence of these adverse events in our study. Participants will be monitored by their treating team as part of standard clinical care. The treating physician is informed about the participant's enrolment in the trial and that the investigational medicinal product (IMP) is administered in a placebo-controlled design; however, treatment allocation remains blinded.

The treating physician can decide independently to discontinue the study drug at any time if a clinically relevant adverse event potentially related to the study drug is suspected. Whenever possible, the decision to continue or discontinue the study drug should be made jointly by the treating physician and study physician.

Benefits

S. aureus bacteraemia represents a high burden not only on each affected individual person, but also on the community and on the healthcare system in general. [88 89] Even a modest improvement in outcomes resulting from our intervention would yield significant overall benefits, alleviating both the direct and indirect consequences of this still very severe infection. Should our novel approach against *S. aureus* bacteraemia prove effective, it holds the potential to revolutionise the therapeutic management of patients with this condition, not only in Switzerland, but on a global scale. Furthermore, it could serve as a catalyst for both basic and clinical research to explore even more efficacious treatments with an anti-virulence approach.

3.8 Justification of choice of study population

A systematic review from 2022 reported that the median age of patients with *S. aureus* bacteraemia ranged from 62 to 72 years[4] . A retrospective observational study looking at cases of *S. aureus* bacteraemia in Switzerland between 2008 and 2021 found that 92% of all *S. aureus* patients were adults[2]. Overall, mortality seems to be lower in children (2-15%)[90-93] suggesting that the disease may manifest differently in children compared to adults. Due to this difference, we will not include children.

In all participating hospitals, infectious disease specialists serving as the local principal investigators, are routinely involved in the care of patients with *S. aureus* bacteraemia. We will approach all patients with *S. aureus* bacteraemia, regardless of sex or gender, who meet the inclusion criteria and do not meet any exclusion criteria about participating in the LIPS trial. Approximately 10-20% of eligible patients will not be able to provide consent themselves due to their compromised health status caused by the *S. aureus* bacteraemia. These patients stand to benefit the most from improved treatment and should not be categorically excluded from trial participation. Therefore, we will include these patients whenever feasible by obtaining consent from a close relative or confirmation by an independent physician not involved in the study. Once the participant's health improves sufficiently to make an informed decision, delayed consent will be sought directly from the participant. We will follow Swissethics guidelines for obtaining consent in emergency situations.[94]

Patients who are pregnant will not be excluded from study participation per se, as linezolid is not formally contraindicated during pregnancy. Limited data exist on the treatment of pregnant women with linezolid, mainly from clinical trials in treating multidrug-resistant tuberculosis. In 31 recorded pregnancies under linezolid exposure in 7 clinical trials, none reported foetal toxicity.[95] In the event of pregnancy, the treating physician and the patient

(or the patient's next of kin) will assess whether the potential benefits outweigh the potential risks to the foetus. As linezolid has been shown to pass into breast milk,[96 97] breastfeeding should be discontinued prior to and throughout administration of linezolid.

Linezolid is a weak, reversible, and unselective monoamine oxidase inhibitor.[79] Patients whose background medication includes other serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants, can potentially experience an increase in serotonin activity. The clinical effects of serotonin excess range from mild serotonin-related side effects to severe serotonin toxicity.[80 81] In the largest meta-analysis involving 2208 patients receiving linezolid and 5058 patients not receiving linezolid, the observed incidence of serotonin toxicity was 0.4% among patients taking linezolid in combination with a serotonergic agent (compared to 0.15% in those taking a serotonergic agent alone).[82] Similarly, in a large cohort of 1135 patients, fewer than 0.5% experienced serotonin toxicity.[83] Assuming 20% of study participants are on serotonergic drugs, we would expect an additional 0-1 participants with serotonin toxicity in the linezolid arm compared to the placebo arm. In view of the low incidence of clinically relevant serotonin toxicity combined with the study design ensuring adequate monitoring of participants, patients on serotonergic agents are not excluded from study participation. A detailed list of such medications can be found in chapter 8.6 *Trial specific preventive measures*.

3.9 Summary of Background and Data on Linezolid

S. aureus bacteraemia remains a life-threatening condition with high morbidity and a mortality of up to 30% despite antibiotic therapy. Emerging evidence suggests that bacterial virulence factors significantly contribute to organ damage and poor patient outcomes. Linezolid, a well-established antibiotic with anti-virulence factor properties, offers a promising adjunctive treatment option. Preclinical studies demonstrate that linezolid effectively inhibits *S. aureus* virulence factor expression and improves survival in animal models. Clinical data support its safety and efficacy in various *S. aureus* infections, including pneumonia and bacteraemia.

Since its approval more than 20 years ago, the risk profile of linezolid has been well-documented. The approved treatment duration varies from 10-28 days depending on the cause and location of the infection. Notable adverse events of linezolid are myelosuppression, serotonin syndrome, kidney injury, *C. difficile*-associated diarrhoea, lactic acidosis, and neuropathy. Myelosuppression is typically associated with prolonged use (≥10 days) and is reversible upon linezolid discontinuation. Serotonin syndrome is very rare with monotherapy and remains uncommon even with concurrent serotonergic medications. Renal adverse effects including increased creatinine and rare cases of renal failure have been reported with linezolid use. Like many antibiotics, linezolid has been associated with *C. difficile*-associated diarrhoea, which can range from mild diarrhoea to fatal colitis. Lactic acidosis is rare but serious and is linked to extended treatment durations. Neuropathy has been described in patients with treatment durations exceeding the maximum recommendation of 28 days and is thus very unlikely to occur in this trial.

Since linezolid will be administered for only 5 days in the LIPS trial, a favourable safety profile is expected. In addition, hospitalization of study participants facilitates a close monitoring for any adverse events.

Given the significant unmet clinical need and the favourable safety profile of short-term linezolid therapy, the anticipated benefits — including reduction of virulence factor-mediated complications and improvement in patient-relevant outcomes — clearly outweigh the manageable risks. The trial will provide critical evidence on whether early adjunctive treatment with linezolid improves outcomes in *S. aureus* bacteraemia. If linezolid proves to be effective in treating *S. aureus* bacteraemia, it holds the potential to improve the therapeutic management of millions of patients with this condition worldwide.

4. STUDY OBJECTIVES

4.1 Overall Objective

The purpose of the LIPS trial is to evaluate whether the addition of linezolid to standard therapy in participants with *S. aureus* bacteraemia leads to an overall improvement in patient-related outcomes such as mortality, health-related quality of life, complications, and duration of hospitalisation.

4.2 Primary Objective

The primary objective is to investigate whether early addition of 5-day treatment with linezolid to standard of care improves outcomes at 90 days in participants with *S. aureus* bacteraemia as measured by the desirability of outcome ranking (DOOR).[98 99]

4.3 Secondary Objectives

Secondary objectives include exploring the impact of early addition of 5-day treatment with linezolid to standard of care on a number of secondary outcomes such as physical and mental health, length of hospital stay (full list in section 5 STUDY OUTCOMES). In addition, we aim to explore if potential effects might differentiate between patient population based on sex (male vs. female), ICU status at baseline (participants on ICU vs. participants not on ICU), and focus of infection (vascular catheter, skin and soft tissue, endocarditis, osteoarticular, pneumonia, other focus, or focus not identified).

4.4 Safety Objectives

The LIPS study aims to assess the safety of early addition of 5-day treatment with linezolid to standard of care treatment for *S. aureus* bacteraemia in a real-world setting. Details on adverse events of special interests can be found in chapters 5.4 *Safety Outcomes* and 9.2.4 *Assessment of safety outcomes*.

5. STUDY OUTCOMES

5.1 Primary Outcome

The primary outcome utilises the Desirability of Outcome Ranking (DOOR), which has been specifically introduced as a patient-centred outcome for *S. aureus* bacteraemia.[100 101] This hierarchical composite outcome ranking has the advantage that it can incorporate multiple outcomes (both beneficial and harmful) to measure if patients experience better overall outcomes after receiving a specific intervention compared with an appropriate comparator ("*Good Studies Evaluate the Disease While Great Studies Evaluate the Patient*"[100]). In contrast to composite outcomes, the DOOR outcome does not have the limitation that events of different importance are weighted equally.[102] We modified the proposed ranking based on the feedback of our patient representatives and the ongoing SNAP trial.[103] The most important outcome for patient representatives was surviving the infection. The second most important aspect was that they "are the same as before the disease", meaning that they have the same level of function as before the *S. aureus* infection. Patient representatives with a history of *S. aureus* bacteraemia informed us that results of their bacterial blood culture were of highest relevance to them during their hospital stay due to high uncertainty of the progression of the disease. This was particularly important because diagnostic evidence of persistent, relapsing or new *S. aureus* infection results in new diagnostic steps, interventions and/or new exposure to antibiotics with their accompanying toxicities. Therefore, we have implemented the third domain *complications*, including microbiological and clinical failure leading to treatment change, and serious adverse reactions or adverse events leading to study drug discontinuation. Finally, hospital length of stay was included as the fourth DOOR component, since patient representatives mentioned it as an important outcome. We will use outcome definitions consistent with the SNAP trial to facilitate data comparisons.

DOOR comprises five ranks (Table 3). This outcome is assessed at day 90. The overall distribution of rankings can then be compared between the control and intervention arms, with the final treatment effect estimate being the win ratio, i.e., the probability that a participant randomly assigned to the intervention arm has a superior DOOR compared to a participant randomly assigned to the control arm[99] (see section 11 STATISTICAL METHODS).

Rank	Alive at 90 days	Return to usual level of function by day 90	None of the following complications: • Microbiological or clinical failure leading to treatment change • Serious adverse reaction • Adverse event leading to study drug discontinuation	Hospital length of stay
1	Yes	Yes	Yes (no complications occurred)	Ties will be resolved using the length of hospitalisation
2	Yes	Yes	No (complication occurred)	
3	Yes	No	Yes (no complications occurred)	
4	Yes	No	No (complication occurred)	
5	No	Not applicable	Not applicable	Not applicable

Table 3: Desirability of Outcome Ranking (DOOR) outcome used for the LIPS trial

Detailed definitions of DOOR components:

Alive at 90 days: defined as alive at 90 days after randomisation

Return to usual level of function by day 90: defined as return to baseline value (or better score) according to the functional bloodstream infection score introduced by McNamara et al [104]. For this study, the score was modified by adding an intermediate "out-of-hospital" category (level 5: no assistance but some limitation) to increase resolution of out-of-hospital functionality, and by combining the original in-hospital categories ("hospitalised, not in ICU"; "hospitalised in ICU"; "admitted to long-term ventilator unit") into a single in-hospital category (level 2).

Baseline is defined as the best score within the 4 weeks before randomisation. The scores used will be the following:

6: Out of hospital, able to complete daily activities without assistance (no limitations)

5: Out of hospital, able to complete daily activities without assistance but with some limitations (e.g. slow, pain)

4: Out of hospital, unable to complete daily activities without assistance

3: Out of hospital; significant disability; requires a high level of care and assistance daily (this includes residential aged care and nursing homes)

2: Hospitalised (or equivalent)

1: On palliative care in terminal phases of life (in hospital or at home)

Complications:

- Microbiological or clinical failure leading to treatment change, according to the following definitions:
  - Microbiological failure: any positive sterile site culture with *S. aureus* 14-90 days after randomisation. A sterile site means any site of the body where microorganisms are usually absent, i.e. below the outer and inner colonised surfaces of the skin and mucous membranes. Positive sterile sites cultures include deep visceral and musculoskeletal abscesses obtained in a sterile manner.
  - Clinical failure: newly identified focus of *S. aureus* 14-90 days after randomisation as determined by a study physician. This can incorporate clinical, radiological, microbiological and pathological findings.
  - Treatment change: any type of adaptation of the treatment such as additional source control procedures (intervention or surgery), or modification of the antibiotic treatment (re-initiation, change of agent, or prolongation)
- Serious adverse reaction (SAR, see chapter 10.1.1 *Definition and assessment of (serious) adverse events and other safety related events*)
- Any adverse event (irrespective of grade) leading to study drug discontinuation

Hospital length of stay: This corresponds to the duration of the index acute hospital stay from randomisation until the day of hospital discharge. Transfers to another acute care hospital for continuation of acute treatment will be included in the assessment of hospital length of stay. Days after transfer to rehabilitation centres or switch to outpatient parenteral ambulatory treatment will not be included in the acute hospital stay.

5.2 Secondary Outcomes

The secondary outcomes include each part of the DOOR outcome separately as well as additional patient-relevant outcomes and specific outcomes of interest to assess the influence on infection dynamic and control. The secondary outcomes have been aligned to the SNAP trial to allow comparison of the data at a later time point.

Separate parts of the DOOR outcome:

- All-cause mortality at 90 days
- Return to usual level of function at day 90
- Microbiological treatment failure 14-90 days after randomisation leading to treatment change
- Clinical treatment failure 14-90 days after randomisation leading to treatment change
- Adverse events leading to study drug discontinuation
- Hospital length of stay of acute index hospitalisation

Clinical outcomes:

- Time to death up to day 90
- Time to being discharged alive
- Number of days without being on the ICU up to day 90

Infection dynamics and control:

- Persistent bacteraemia: *S. aureus*-positive blood culture on day 5 (±1 day) after randomisation
- Two or more systemic inflammatory response syndrome (SIRS) criteria on day 5 after randomisation

- Change in C-reactive protein (CRP) from day 1 until day 5 (±1 day) after randomisation
- Early microbiological treatment failure 5-13 days after randomisation leading to treatment change
- Early clinical treatment failure 5-13 days after randomisation leading to treatment change
- Development of any new antibiotic drug resistance in *S. aureus* until day 90
- Number of days alive and free of antibiotics in the 90 days

Patient-reported outcomes:

- Physical health at day 90 as assessed by the short form 36 (SF-36) questionnaire.[105-107]
- Mental health at day 90 as assessed by the short form 36 (SF-36) questionnaire.[105-107]

5.3 Other Outcomes of Interest

Additional laboratory outcomes for a subset of participants only in selected centres:

- Linezolid plasma concentrations at day 4 or 5
- Minimal inhibitory concentration (MIC) of linezolid for the respective *S. aureus* strain for patients with linezolid plasma concentration measurements

5.4 Safety Outcomes

Safety outcomes encompass any serious adverse events (SAE) and serious adverse reactions (SAR) until day 90 as well as adverse events of special interest. Definitions can be found in chapter 10.1.1 *Definition and assessment of (serious) adverse events and other safety related events*.

Adverse events of special interest:

(details on how they are assessed is provided in chapter 9.2.4.1 *Adverse events*)

- Clinical signs of serotonin toxicity until day 7
- Laboratory signs of myelosuppression until day 7
- Hyperlactatemia until day 7
- Acute kidney injury
- *C. difficile*-associated diarrhoea within 90 days

Further information on safety outcomes (mortality, SAR, AEs leading to discontinuation of trial intervention) can be found in chapters 5.1 *Primary Outcome* and 5.2 *Secondary Outcomes*.

6. STUDY DESIGN

6.1 General study design and justification of design

LIPS is a pragmatic, multicentre, 1:1 randomised, parallel-group, placebo-controlled, superiority trial with blinded participants, physicians, and outcome assessors in the acute-care hospital setting (see Figure 1).

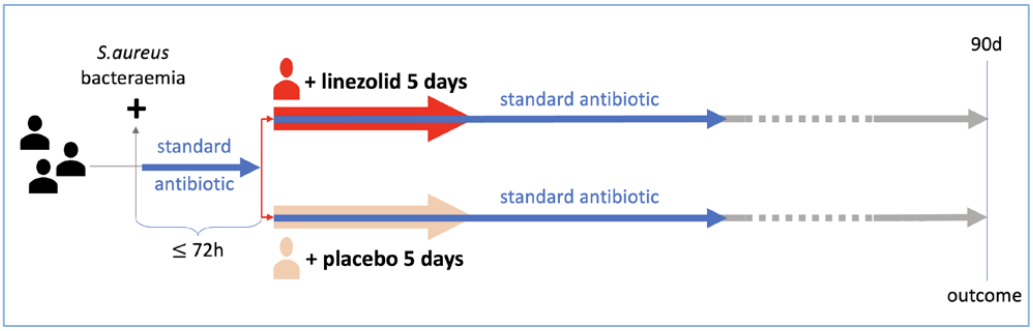


Figure 1: Schematic overview of the trial

The LIPS trial was designed with the involvement of four patient representatives to make sure that the assessed outcomes are patient relevant and that the burden due to the trial remains minimal for the participants. We have chosen a pragmatic trial mainly following routine care (i.e. the majority or outcomes are collected during routine care, and the additional follow-up consists only of one phone call at day 90 and a quality-of-life questionnaire at day 90). However, as the outcomes can be influenced by expectations from participants (i.e. level of function) as well as the treating physicians (i.e. hospital length of stay) we have chosen a blinded study design to eliminate this source of bias.

6.2 Patient and Public Involvement

The following Patient and Public Involvement (PPI) has been and will be conducted to ensure that the trial is highly relevant to patients. We have been collaborating with four PPI representatives (two patient representatives who had complicated *S. aureus* bacteraemias as well as two patient experts) since the preparation of the funding application. These PPI representatives have agreed to lend their expertise for the duration of the trial up to the dissemination of the trial results. Ahead of every meeting, the PPI representatives are briefed on the current stage of the trial and the purpose of the meeting in layman's terms. Before the finalisation of the first protocol and patient informed consent draft, we conducted 3 focus group discussions with the four PPI representatives (2-4 hours/meeting).

6.2.1 PPI activities before receiving approval from authorities

PPI contribution	Outcome
- Advised on the patient relevance of the proposed outcomes. - Informed the researchers about important aspects not covered by the proposed outcomes. - Discussed what the primary outcome should be and help with the exact definition.	- Trial outcomes that are relevant to patients were chosen and ranked in order of importance (DOOR outcome). - PPI representatives advised to include a patient-reported outcome measure on quality of life at day 90.
- Reviewed the eligibility criteria with a focus on inclusivity and making the trial results generalizable.	- Broad inclusion criteria were chosen as recommended by the PPI representatives. - Exclusion criteria focus on safety aspects.
- Provided feedback on how understandable the provided lay summary was.	- Parts of lay summary were flagged as needing further explanation or simplifications and edited accordingly.
- Advised on the chosen time points and if the study visits are useful and patient friendly.	- Outcomes may also be collected by asking the participant's relatives or general practitioner.

- Assessed burden for patients and identified ways to decrease burden, dropout rates and incomplete data selection.	- Burden for participants with the proposed trial design was deemed very low.
- Defined the further study phases during which PPI is critical and what form such involvement should take (guided by SCTO template).	- PPI activities during and after trial conduct were planned (see chapter 6.2.2 *PPI activities after receiving approval from authorities*).
- Provided feedback on draft patient information and informed consent form (ICF) in German. - Some PPI representatives will also assess patient information in other languages	- ICF is concise and comprehensible, giving enough information without frightening patients regarding their diagnosis. - Patient-relevant information on background of the underlying disease, study procedures, risks and adverse events in layman's terms are included.

6.2.2 PPI activities after receiving approval from authorities

Planned PPI contribution	Objective
- Advise on how to approach patients and relatives to inform them about study participation.	- Incorporating PPI feedback into trainings of study sites on how to approach patients and relatives in a sensitive manner.
- Participation in DSMB during prespecified interim analyses	- Including the patient perspective when aggregated trial safety data is discussed in the interim analysis.
- Discussing which of the results/effects are patient relevant and how to best visualise the data.	- We will report all outcomes independent of the assessed effect. The objective of this exchange is to receive feedback which effects are most relevant for patients and how data should be visualised so that they can be understood easily.
- Advise on which form the results should be communicated.	- Assuring that the study results are disseminated to a wide audience.
- Support the communication of results in lay language.	- Ascertaining that the study results can be communicated to participating patients and the general public.
- Discussing the impact and the next steps with the researchers.	- Making sure that appropriate action is taken based on the study results taking into consideration the patient perspective.
- Evaluating the PPI involvement	- Learning how best to involve PPI in future collaborative research projects

6.3 Methods of minimising bias

6.3.1 Randomisation

Participants will be allocated 1:1 to either linezolid or placebo for 5 days using block randomisation with varying random block sizes of 2 and 4 implemented in the data capture system REDCap®. For more details see chapter 7.3 *Assignment to study groups*.

6.3.2 Blinding procedures

The treatment allocation will not be revealed to any study staff or participants (i.e., physicians, study nurses, participants, outcome assessors). Only the unique randomisation number will be visible for blinded personnel. The randomisation list will only be accessible to designated staff from Spital-Pharmazie Basel for manufacturing,

labelling and blinding the study medication, and the data scientist who will prepare the randomisation list and upload it in REDCap®. The study medication will be packaged and dispensed by Spital-Pharmazie Basel to ensure that all participants, treating physicians, clinical investigators and study nurses involved in the study (including outcome assessors) will remain blinded to treatment allocation throughout the study.

6.3.3 Other methods of minimising bias

Not applicable.

6.4 Unblinding Procedures (Code break)

The study medication (10 tablets per container) with a unique randomisation number will be distributed to the study centres. For each unique randomisation number, the study centre will receive a sealed opaque envelope with the information if the container contains linezolid or placebo. The study team will only be allowed to open an envelope if safety concerns require knowing a participant's allocated intervention. All unblinding procedures must be entered within the eCRF. The envelopes will be checked during monitoring visits and after the completion of the study.

7. STUDY POPULATION

7.1 Eligibility criteria

Inclusion criteria:

- *S. aureus* grown from at least one blood culture
- Hospitalised at a participating centre
- ≥18 years old
- Written informed consent or fulfilling criteria for an emergency exemption from informed consent requirements

Exclusion criteria:

- Administration of the initial drug treatment not feasible within 72 hours since the collection of the first positive blood culture with *S. aureus*
- Documented history of positive blood cultures for *S. aureus* occurring between 72 hours and 180 days prior to the eligibility assessment
- Necrotising fasciitis
- Currently receiving linezolid or clindamycin
- Use of any monoamine oxidase A or B inhibitor within the last two weeks
- Known hypersensitivity to linezolid or any other ingredients of the study drugs
- Current severe thrombocytopenia (i.e. $<30x10^9/l$)
- Oral application of study drug not possible (per mouth or per gastric tube)
- Currently breastfeeding
- Local treating team believes that death is imminent and inevitable
- Patient is receiving end of life care and antibiotic treatment is not considered appropriate
- Local treating team believes that participation in the study is not in the best interest of the patient
- Any indication that the patient is unwilling to participate in the study including an advance directive stating such unwillingness

General:

Patients taking serotonergic drugs such as selective serotonin reuptake inhibitors (SSRI) or tricyclic antidepressants are not generally excluded. See detailed information on risk assessment and precautions in chapter 8.6 *Trial specific preventive measures*.

Pregnant women will not be excluded from study participation per se, as linezolid is not formally contraindicated during pregnancy. Limited data exist on the treatment of pregnant women with linezolid, mainly from clinical trials in treating multidrug-resistant tuberculosis. In 31 pregnancies under linezolid exposure, none reported foetal toxicity.[95] In the event of pregnancy, the treating physician and the patient (or the patient's next of kin) will assess whether the potential benefits outweigh the potential risks to the foetus.

Linezolid has been shown to pass into breast milk and accordingly, breastfeeding should be discontinued prior to and throughout administration of linezolid.

7.2 Recruitment and screening

Patients will be recruited during their hospitalisation at participating centres. Patients will be flagged as soon as *S. aureus* is detected in a blood culture. The time required from blood collection to the confirmation of *S. aureus*, typically ranging from 12 to 36 hours, will depend on factors such as the time to positivity and the method employed for *S. aureus* identification.[108] The results will be immediately reported to the study team according to each centre's infrastructure - either via an automated electronic alarm system or via verbal communication from the clinical microbiology laboratory. Infectious disease specialists, serving as the local principal investigators at all participating

centres, are routinely involved in the care of patients with *S. aureus* bacteraemia. Their involvement is well established and recognized for its positive impact on patient outcomes.[109-112] Patients with blood cultures positive for *S. aureus* will be immediately screened for eligibility by the study team using the inclusion and exclusion criteria. Eligible patients will be approached by a study physician as soon as possible. They will be informed about the LIPS trial via verbal and written study information, which consists of a printed summary in lay language including details of the intervention and potentially associated benefits and risks. Each participant will receive a consent form offering sufficient details to enable them to make an informed decision about their participation. For patients unable to give informed consent due to severe illness or other circumstances, it must be checked if a statement of wishes formulated in a state of capacity is available. If no such statement is available, an appropriate substitute (i.e., a close relative or a physician not involved in the research project) may make decisions based on the presumed wishes and the best interests of the patient as recommended by Swissethics.[113] Participants who were included after receiving consent from their next of kin or confirmation by an independent physician will be asked to provide retrospective consent as soon as their health status allows them to make an informed decision.

The randomisation and intervention will start immediately upon the receipt of a formal written consent. Participants will not receive any financial compensation for their participation. The participating centres will receive financial reimbursement for establishing the local trial infrastructure and workflow as well as a reimbursement per participant to compensate for the costs of the study staff and other resources.

The sponsor notifies the CEC and the CA of the first study participant, in accordance with Art. 23a ClinO. If the first participating person is not included in the trial within two years following the issuance of the last authorization, the trial is considered interrupted. The clinical trial may then not be commenced until an application for an extension of the time limit has been approved. The application for the extension is submitted to the CEC, and to CA as a substantial amendment.

7.3 Assignment to study groups

Participants will be allocated 1:1 to either linezolid for 5 days or placebo for 5 days. The randomisation will be stratified by centre and ICU status at time of enrolment and done using block randomisation with varying random block sizes of 2 or 4. The trial statistician will generate the randomisation list outside of the data capture system REDCap®. This list will then be uploaded into the data capture system. The goal is to randomise participants such that the groups are as balanced as possible with respect to study centre and ICU status at time of enrolment.

After informed consent has been obtained and all eligibility criteria have been reviewed and met, the study team enters the minimal required data into REDCap® (i.e., year of birth, if participant is on ICU). The allocation is done by REDCap® which will assign a unique randomisation number to each participant that remains the same throughout the study. Each randomisation number will correspond to a drug container labelled with the same unique randomisation number.

7.4 Criteria for withdrawal / discontinuation of participants

Participants can withdraw from the study at any time without providing a reason. Participants who discontinue the intervention will still be asked to complete follow-up assessments. Reasonable effort should be made to establish the reason for discontinuation while fully respecting the participant's rights so reasons may be analysed. The treating physician can decide at any time to discontinue the study drug administration due to medical reasons. Whenever possible, the decision to continue or discontinue the study drug should be made jointly by the treating physician and study physician. Outcomes of these participants will still be collected, and they remain in the intention-to-treat analysis as randomised.

Participants who were included following consent by their next of kin or confirmation by an independent physician will be asked to provide retrospective consent as soon as their health status allows them to make an informed decision. If the participant refuses to give this retrospective consent, we will not collect any further data. However, we will analyse the data that has been collected up to this timepoint, as excluding these data could bias the analysis.

8. STUDY INTERVENTION

8.1 Identity of Investigational Medicinal Products

8.1.1 Experimental Intervention

The IMP in this study is linezolid 600 mg tablets (Linezolid STADA®) as described in chapter 3.2 *Investigational Medicinal Product (treatment) and Indication*. The IMP will be administered orally twice daily over a 5-day period, with a total of 10 tablets, either from day 1 morning to day 5 evening or from day 1 evening to day 6 morning.

8.1.2 Control Intervention (standard/routine/comparator treatment)

Participants in the control arm will be receiving oral placebo tablets. Procedures regarding route of administration, study treatment duration and treatment phases will be identical in the IMP- and the placebo-group (see chapter 8.1.1 *Experimental Intervention*).

8.1.3 Packaging, Labelling and Supply (re-supply)

Linezolid STADA® and placebo tablets will be provided as trial supplies to the study centres re-packaged in identical opaque containers by Spital-Pharmazie Basel. Each container will contain 10 tablets of either linezolid 600 mg or placebo. The containers will be labelled identically except for the unique randomisation number on each container. The label contains the information required by the authorities. Spital-Pharmazie Basel will be responsible for the labelling, packaging, and shipping of the IMPs. Each centre will be supplied with a minimum number of containers at site initiation.

The trial manager will remotely monitor the recruitment progress of the individual study centres and will inform Spital-Pharmazie Basel if re-supply is needed. Spital-Pharmazie Basel will arrange for the shipment of the re-supply to the centres following instructions by the trial manager.

8.1.4 Storage Conditions

The IMP must be kept in a secure, limited access storage area under the recommended storage conditions (i.e. identical storage conditions apply as for linezolid tablets that are used in routine practice at the study centre).

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention

One linezolid 600 mg tablet will be administered orally twice a day on 5 consecutive days. For hospitalised participants, the study drug will be distributed in the same manner as a participant's other oral medication. The study team will hand over the study drug to the nursing team who will administer the study drug to the participant according to the instructions by the physician and according to the site-specific local procedures. In general, each dose/each tablet will be handed over to the participant separately and only immediately prior to oral administration. If, based on the treating team's assessment, a participant is unable to swallow the study medication, tablets may be crushed and resuspended for easier consumption or for administration via a nasogastric tube according to clinical routine and following site-specific SOPs.

In the unlikely event that participants are discharged home before day 5, they will receive the remaining study medication along with detailed instructions on how and when to take them at home.

8.2.2 Control Intervention

Dosing and administration of the placebo tablets are the same as for participants in the experimental intervention arm.

8.3 Dose modifications

Drug-related AEs leading to discontinuation of the drug are expected to be rare when linezolid is used for 5 days. Discontinuation of IMP may occur in the situations listed in chapter 6.4 *Unblinding Procedures (Code break)* and chapter 7.4 *Criteria for withdrawal / discontinuation of participants*. The study medication will be given twice a day for 5 days (in total 10 administrations) with approximately 12-hour intervals between each administration. If maintaining a fixed 12-hour interval is challenging due to the start time (e.g. if subsequent doses would need to be administered in the middle of the night), the first dosing interval may be adjusted according to standard practice. However, the interval should not be shortened or extended by more than 6 hours. Further dose modifications are not allowed.

8.4 Compliance with study intervention

The treating team will document the administration of the study medication to the participant in the participating hospital's respective clinical information system. The information including date and time of first administration will then be copied into the participant's eCRF. If study drug administration cannot be documented electronically, it will be recorded on paper (which will be later transferred to the eCRF). Any missed doses, along with the reasons for missing them, must also be documented. The participant will receive instructions at the ward for the correct storage and administration of IMP if discharge occurs before completion of the 5-day intervention phase.

8.5 Data Collection and Follow-up for withdrawn participants

Participants can discontinue the trial intervention at any time without providing a specific reason. Participants who wish to withdraw from the study will commonly receive further measurements as part of clinical routine. We will ask these participants if we are allowed to collect the corresponding routine clinical data and/or to contact them on day 90 to assess the primary outcome.

8.6 Trial specific preventive measures

Thrombocytopenia is a common adverse event of linezolid, but it is usually associated with treatment durations of 10 or more days. Given the lifespan of thrombocytes and the short intervention duration of five days in our study, we expect a low risk of linezolid-mediated thrombocytopenia. However, thrombocytopenia is also commonly seen in participants undergoing sepsis. If participants develop severe thrombocytopenia during the intervention, the treating physician should assess, if possible in consultation with the study physician, whether this may be associated with the trial medication and decide on stopping or continuing the intervention for this participant.

Linezolid must not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. the antidepressant moclobemide or the Parkinson's medications rasagiline and safinamide) or within two weeks of taking any such medicinal product.

For participants receiving serotonergic agents, the study physician will provide a recommendation to the treating physician based on available information on linezolid pharmacology, as summarised in the document "LIPS Pharmacology Background" distributed to all study sites. The treating physician will decide if pausing the serotonergic medication for the duration of the interventional phase of the trial (trial day 1-6) is possible, or if the serotonergic agents will be continued under close observation for signs of serotonin toxicity by the treating team. Clinical observation for signs of serotonin toxicity is required for participants taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), directly and indirectly acting sympathomimetic agents (including the adrenergic bronchodilators, pseudoephedrine and phenylpropanolamine), vasopressive agents (e.g. epinephrine, norepinephrine), dopaminergic agents (e.g. dopamine, dobutamine), pethidine or buspirone.

8.7 Concomitant Interventions (treatments)

All participants receive standard of care treatment for *S. aureus* bacteraemia as clinically indicated and according to local and international recommendations. This includes targeted antibiotic treatment for at least 2 to 6 weeks, mostly applied intravenously. The choice of standard of care antibiotic will not be affected by the study. All antibiotic treatment until day 90 will be documented in the eCRF. Concurrent treatment with clindamycin is an exclusion

criterium at the time of randomisation. However, if clindamycin is initiated as part of standard of care after enrolment, participants will remain in the trial.

8.8 Study Drug Accountability

Study drugs will be accurately and adequately monitored from shipment to the site until use or disposal. Dates of receipt/expiry/use/disposal will be recorded.

8.9 Return or Destruction of Study Drug

Study sites will destroy the left-over study medication according to site-specific SOP. In the rare cases that participants are discharged from the hospital before completing the study medication, they will be provided with the necessary tablets to continue their treatment at home until the 5-day course is completed. They will be instructed to return any unused tablets (e.g., if they are unable to take a dose for any reason) to a pharmacy for proper disposal.

9. STUDY ASSESSMENTS

9.1 Study flow chart / table of study procedures and assessments

Study Schedule

	Screening	Enrolment	Intervention phase					In-Hospital Follow-Up (applicable only if participant remains hospitalised)			Close-out
Time point	**0-72h before randomisation**		**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5 (+1 day)**	**Day 7**	**Day 14**	**Discharge day**	**Day 90**
S. aureus positive blood culture	X										
Identification of patient		X									
Eligibility checks		X									
Informed consent		X									
Randomisation			X								
IMP administration			**X**	**X**	**X**	**X**	**X**				
Time point	**0-72h before randomisation**		**Day 1 (-1 day)**	**Day 2**	**Day 3 (±1 day)**	**Day 4**	**Day 5 (±1 day)**	**Day 7 (±1 day)**	**Day 14 (±3 days)**	**Discharge day**	**Day 90 (±7 days)**
Clinical assessments											
Baseline data			X[1]								
SIRS criteria							X				
All-cause mortality			Assessed until day 90								
Clinical failure										X	X
Length of hospital stay										X	
Length of ICU stay										X	X
Antibiotic and/or surgical treatment											X
Laboratory assessments											
Blood cultures				X			X[2]				
Creatinine			X					X	X[3]		
CRP			X					X			
ALT and gGT			X					X	X[3]		
Blood count (Hb, Tc, Lc)			X		X		X	X			
Linezolid trough conc.							X[4]				
Microbiological failure										X	X
New antibiotic resistance											X
Patient-reported outcomes											
Quality of life (SF-36)											X
Return to usual level of function											X
Safety outcomes											
Serotonin toxicity, myelosuppression, hyperlactatemia[5]			X	X	X	X	X	X			
Acute kidney injury[5]								X	X		
C. difficile -associated diarrhoea[5]								X			X
SAE / SAR			Collected until day 90								

Abbreviations: S. aureus – Staphylococcus aureus; SAE – Serious Adverse Event; SAR – Serious Adverse Reaction; SIRS - Systemic Inflammatory Response Syndrome; ICU – Intensive Care Unit; CRP – C-Reactive Protein; ALT – Alanine Transaminase; gGT – Gamma-glutamyl Transferase; Hb – Haemoglobin; Tc – Thrombocytes; Lc – Leukocytes; SF-36 – Short Form-36

[1] Baseline data include: date of hospital admission, index blood culture, linezolid susceptibility, ethnicity, vital signs, comorbidities, standard antibiotic treatment, markers of severity (mechanical ventilation, cardiac arrest, use of vasopressors, ICU), injection drug use, mental health diagnosis.
[2] Assessment of persistent bacteraemia. Only required if day 2 blood culture is positive or recorded if done as part of standard of care.
[3] Choose the result that represents the highest level recorded between day 6-14.
[4] Linezolid trough concentration is only measured in a subset of participants in selected centres.
[5] Adverse events of special interest until day 7 include: serotonin toxicity, myelosuppression, hyperlactatemia; until day 14: acute kidney injury; until day 90: C. difficile-associated diarrhoea.

9.2 Assessments of outcomes

9.2.1 Assessment of primary outcome

The primary outcome utilises the Desirability of Outcome Ranking (DOOR) and is comprised of the following 4 assessments (for definitions of the outcome categories see *Chapter 5.1)*:

i) "Alive on day 90" and ii) "Return to usual level of function by day 90" will be documented by the study team. Participants who did not die during hospitalisation will be called on day 90 (±7 days). If a routine patient visit coincides with this time point, the assessment may be done in person. The participant will be asked to rate their level of function in the 4 weeks prior to their bacteraemia and their current level of function from 6 to 1 according to the modified functional bloodstream infection score[104]: If the participant can't be reached, the study team will make at least 5 attempts at different times of the day to reach the participant. If these fail, reasonable attempt will be made to acquire the information from relatives, caregivers, or the participant's emergency contact or primary care physician.

iii) "Complications" are managed as part of clinical routine by the treating physicians. The corresponding data are accessed from hospital information systems and/or hospital discharge letters, evaluated and entered into the REDCap® database by the study team. Definitive assessment of the complications will be performed by a study physician:

a. Microbiological and clinical failure leading to treatment change will be assessed and documented on day 90 (±7 days). First, any new sterile-site culture positive for *S. aureus* (microbiological failure) or any new focus of infection (clinical failure) occurring between day 14 and day 90 after randomisation will be identified. Subsequently, it will be assessed whether the failure resulted in a change of antibiotic therapy or necessitated any new source-control procedure (surgery or interventional radiology).

b. Serious adverse reactions will be assessed and documented as soon as an investigator becomes aware of the event (see chapter 10.1.1 *Definition and assessment of (serious) adverse events and other safety related events*). In cases where the participant is transferred to another hospital, the study team must contact the new hospital to assess the hospital length of stay and potential SAEs and SARs through information from the discharge letter.

c. Adverse events leading to study drug discontinuation will be assessed and documented on day 7 (±1 day). The study team will review the medical record for any documented reason for study drug discontinuation and assess whether it was due to an adverse event. The reason will be entered into REDCap®, and discontinuation due to an adverse event will be confirmed by selecting the corresponding checkbox.

iv) "Hospital length of stay" will be assessed after discharge of the acute hospital stay, using hospital information system data and/or hospital discharge letters. In case participants are transferred to another acute care hospital, the study team must request this information and a copy of the participant's hospital discharge letter from the consecutive treatment team. Outpatient parenteral antibiotic treatment or transfer to rehabilitation centres are not considered acute hospital stays.

9.2.2 Assessment of secondary outcomes

The secondary outcomes include each part of the DOOR outcome separately as described in chapter 9.2.1 *Assessment of primary outcome* and time to death up to day 90.

Further secondary outcomes will be assessed as follows:

Clinical outcomes:

- Time to being discharged alive (assessed until day 90)

  In the eCRF, the date of hospital discharge is recorded for participants who are discharged alive (see chapter 5.1 *Primary Outcome*). For participants who die before hospital discharge, the date of death is recorded. Time to being discharged alive is derived during data analysis based on these dates. Participants who die during hospitalisation are considered not discharged alive and are censored at day 90.

- Number of days without being on the Intensive Care Unit (ICU) up to day 90 (i.e. number of days alive without being on the ICU between randomisation and day 90).

  We will collect from the hospital information system data how many days the participant spent on the ICU. Together with the available data on mortality, we will calculate the "Number of days without being on the ICU".

Infection dynamics and control:

Information on these outcomes is collected from the hospital information system data.

- Persistent bacteraemia

  Any *S. aureus*-positive blood culture on day 5 (±1 day) after randomisation. If blood cultures obtained on day 2 or 3 are negative for *S. aureus* and no blood cultures are obtained on day 5, the day 5 blood culture will be assumed to be negative.

- Two or more systemic inflammatory response syndrome (SIRS) criteria on day 5 after randomisation.

  This includes: 1. Abnormal body temperature (<36°C or >38°C), 2. tachypnoea or mechanical ventilation (RR >20 breaths per minute), 3. tachycardia (HR >90 beats per minute in an adult, 4. abnormal leukocyte count (from routine blood sampling on day 5 ±1 day, defined as >12.0 x 10^9/L or <4.0 x 10^9/L or >10% of immature (band) forms).

- Change in C-reactive protein (CRP) from randomisation until day 5 (±1 day).

  Day 1 CRP means any blood CRP measurement taken on randomisation day 1 or the calendar day prior to randomisation. If there is more than one measurement, the value recorded is the one taken closest before randomisation. The study team will record all measured CRP levels within the time period.

- Early microbiological treatment failure between 5 and 13 days after randomisation leading to treatment change.

- Early clinical treatment failure between 5 and 13 days after randomisation leading to treatment change.

- Development of any new antibiotic drug resistance in *S. aureus* until day 90.

  This includes any new resistance absent in the *S. aureus* strain isolated from the initial blood culture and detected in any *S. aureus* strain isolated from the participant after the start of the intervention.

- Days alive and free of antibiotics up to day 90

  Any systemic antibiotic therapies received by a participant until day 90 will be recorded in REDCap®, including start and (planned) end days of treatment. Together with mortality data, this endpoint will be calculated during data analysis. Information on antibiotic therapies will be acquired from hospital records. In case participants or their relatives mention previously not documented antibiotic treatment during the day 90 follow up phone call, the information will be verified by requesting the corresponding hospital discharge letter or contacting the responsible primary care physician.

Patient-reported outcomes:

SF-36 questionnaire:[105-107] This represents a validated patient-reported outcome measure and will give more detailed information on the participant's physical, mental, emotional, and social well-being. Participants will receive this questionnaire approximately on day 90 after randomisation either via mail or electronically (based on participant preference). The questionnaire will be available in German, English, French, and Italian. From the SF-36, the following two outcome measures are derived:

- Physical health at day 90 (measured with the SF-36 questionnaire, Mental Component Summary)
- Mental health at day 90 (measured with the SF-36 questionnaire, Physical Component Summary)

9.2.3 Assessment of other outcomes of interest in a subset of participants

The following other outcomes of interest will only be collected at selected study centres and therefore will only be collected from a subset of trial participants.

- Linezolid trough plasma concentration at day 4 or 5
- Linezolid minimal inhibitory concentration of the respective *S. aureus* strain from the blood

Measurement of linezolid trough levels is an established assay that is routinely performed by the USB diagnostic laboratory and can be ordered from the standard catalogue of analyses (see chapter *9.3.5.3 Measurement of trough levels of linezolid in a subset of participants (day 5±1)*).

For the same participants, the minimal inhibitory concentration (MIC, in mg/l) of linezolid for the respective *S. aureus* strain will be measured according to microbiological standard procedures. In general, this will be done by broth microdilution.[114]

9.2.4 Assessment of safety outcomes

9.2.4.1 Adverse events

Adverse events that will be documented by the study team are the following:

Adverse events of special interest:

- Clinical signs of serotonin toxicity until day 7

  Serotonin toxicity will be assessed, diagnosed and documented during clinical routine by treating physicians. In case of clinical signs of serotonin toxicity, the Hunter criteria (including spontaneous or inducible clonus, ocular clonus, tremor, hypertonia and hyperthermia, agitation or diaphoresis, hyperreflexia) and diagnostic algorithm can be provided (see appendix, chapter 18.2 *The Hunter Serotonin Toxicity Criteria: for diagnosing serotonin syndrome*). Evidence of serotonin toxicity will be determined based on the treating physicians' assessment as documented in the participant's EMR. In the absence of such documentation between days 1 and 7, the event will be recorded as "No" in the eCRF.

- Laboratory signs of myelosuppression until day 7

  Laboratory values obtained as part of routine clinical care will be reviewed for evidence of myelosuppression (thrombocytopenia, anaemia, or leukopenia).

  Assessment is based solely on the local laboratory's reference ranges as displayed in the hospital system. If any of the following parameters fall below the laboratory-defined lower limit of normal between days 1 and 7, this will be recorded as "Yes" in the eCRF:

  - Platelet count
  - Haemoglobin
  - Leukocyte count

  Out-of-range values are typically flagged automatically in the hospital laboratory system. No independent clinical grading (e.g. CTCAE classification) is required for eCRF completion.

  If "Yes" is selected, the study team will enter:

  - the date and value of the first out-of-range result within the assessment period,

    and

  - the date and value of the lowest recorded measurement during days 1–7.

  In the absence of any values below the local laboratory reference range, myelosuppression will be recorded as "No".

- Evidence of hyperlactatemia until day 7

  If any lactate measurement exceeds the laboratory-defined upper limit of normal between Days 1 and 7, hyperlactatemia will be recorded as "Yes" in the eCRF.

  If "Yes" is selected, the study team will enter:

  - the date and value of the first elevated measurement,

  and

  - the date and value of the highest recorded lactate value during the assessment period.

  In the absence of values above the local laboratory reference range, hyperlactatemia will be recorded as "No".

- Acute kidney injury until day 14

  Acute kidney injury (AKI) will be defined according to the modified *Kidney Disease: Improving Global Outcomes* (KDIGO) criteria as either:

  - an increase in serum creatinine of ≥ 26.5 µmol/L from baseline (randomisation), occurring at any time from baseline up to study Day 5,

    or

  - an increase in serum creatinine to ≥ 1.5 times the baseline value occurring at any time within 14 days after randomisation.

  Assessment of AKI is based on serum creatinine values obtained as part of routine clinical care. Values will

be extracted from the hospital information system.

For data collection, the study team will record serum creatinine values in the eCRF as follows:

- All available serum creatinine measurements from baseline (randomisation day or the calendar day prior to randomisation) through Day 8 will be entered.
- The highest available serum creatinine value between Day 8 and Day 14 will be recorded.

If a participant is transferred to another acute care hospital before Day 14, reasonable efforts should be made to obtain available serum creatinine results from the receiving institution.

If a participant is discharged home or to residential care/rehabilitation and no routine serum creatinine measurements are performed during the Day 8–14 window, "Not done" may be selected in the eCRF.

No on-site calculation of AKI is required. Determination of AKI according to the protocol-defined KDIGO criteria will be performed during data analysis.

- *C. difficile*-associated diarrhoea within 90 days.

  The treating physicians will assess for *C. difficile* infection based on the centre-specific diagnostic algorithm if clinical suspicion arises due to diarrhoea during antibiotic treatment. *C. difficile* infection will be evaluated on day 90 by reviewing the participant's electronic health records. If a participant reports severe diarrhoea during a 90-day follow-up phone call, occurring after discharge and managed outside the centre, the responsible physician may be contacted to determine if a *C. difficile* infection was diagnosed.

9.2.4.2 Serious Adverse Events

Serious adverse events (SAEs) will be identified by the study team based on documentation in the participant's EMR and hospital discharge summaries. A study physician will assess whether any SAEs have occurred in accordance with the protocol-defined criteria. Detailed information on SAE definitions, grading, and reporting obligations is provided in section 10 SAFETY.

9.2.5 Laboratory parameters

Blood sampling will be done according to clinical routine. Laboratory-specific adverse events will be measured as part of the clinical routine as outlined above. No additional tissue sampling or body fluids are necessary.

9.2.6 Vital signs

Vital signs are measured according to clinical routine. No additional study-specific vital sign measurements are necessary.

9.2.7 Assessments in participants who prematurely stop the study

Participants who withdraw from the study will receive further treatment and clinical examinations by the treating team as part of clinical routine. This includes all relevant assessments of adverse events.

9.3 Procedures at each visit

This clinical trial is largely embedded in routine clinical care and includes no scheduled study-specific on-site patient visits during hospitalisation. Participants are hospitalised patients receiving standard clinical care, and no additional examinations or procedures are performed for study purposes, with the exceptions outlined below.

Data entry into the electronic case report form (eCRF) is performed by trained and delegated study staff at predefined timepoints based on routine clinical documentation rather than study visits.

Study-specific procedures consist of:

- Obtaining of informed consent
- Randomisation

- Administration of the investigational medicinal product embedded into routine clinical care
- Collection of outcome data from the electronic medical record (EMR)
- A follow-up telephone call on Day 90
- A quality-of-life questionnaire (SF-36) filled out by participants at home on paper or electronically.
- Collection of a blood sample on Day 4 or 5 for assessment of linezolid trough levels at selected sites
- Only at University Hospital Basel: For patients who consented to subproject Intra-SA: Collection of blood samples up to once daily from day 1 until end of index hospital stay.

9.3.1 Within 72h after drawing of first positive blood culture with *S. aureus*

9.3.1.1 Screening and identification of patients

Screening and eligibility assessments are performed by the study team based on routinely collected clinical data documented in the electronic patient record. No study-specific screening examinations or procedures are performed. Eligible patients will primarily be identified via regular and timely review of the results of blood culture results sent to the diagnostic microbiology laboratory of each centre. The study team will then review the patient's EMR and check whether all inclusion criteria and no exclusion criteria are met.

Each centre will implement centre-specific procedures to ensure prompt notification of a positive blood culture result with *S. aureus.* This can occur through an electronic alert system or through other communication channels, depending on what is available and practical. Infectious diseases specialists of each centre are routinely involved in all patients with *S. aureus* bacteraemia. The goal is to identify potential participants as quickly as possible. Any microbiological identification method to identify *S. aureus* used in routine practice can be applied to positive blood cultures: PCR (polymerase chain reaction) results as well as other methods (e.g., MALDI-TOF: Matrix-Assisted Laser Desorption/Ionization-Time of Flight) are acceptable. PCR results are typically available about 3 hours after detecting growth in the blood cultures; without PCR, pathogen identification is usually available within 24 hours.

9.3.1.2 Enrolment of participants

Eligible patients are approached for informed consent by a study physician. The patient will be informed about the study and asked if they wish to participate. The patient should be given time to discuss any questions or concerns they may have. The patient will receive the informed consent form along with written explanations about the purpose and procedures of the study. Once the patient agrees to participate in the study, they must provide written consent by signing the appropriate form.

If a patient is unable to give informed consent due to medical reasons (e.g., lack of consciousness due to severity of illness), informed consent may be provided by a family member or confirmed by a study-independent treating physician on behalf of the patient. If the patient can be included, the patient's representative must sign the corresponding informed consent form. After the participant regains the ability to make decisions, the study inclusion will be discussed with them by the study team, and the participant will be asked to provide written informed consent. The participant may choose to withdraw from the study at any point.

The study team must inform the treating team about the participant's participation in the study. Each centre will establish its own process on how to communicate this information.

9.3.2 Day 1

9.3.2.1 Randomisation and assessment of baseline data

Once a participant is enrolled via informed consent, the participant will be randomly assigned to a study arm through electronic randomisation within the REDCap® database. This will be initiated and coordinated by the study team.

Sites should collect baseline data as per the eCRF on the day of randomisation using information available in the electronic medical record (EMR). When more than one laboratory result is available on day 1, the result closest to randomisation should be used. The study team of each site should check if all relevant information is available and – if necessary – will add the missing information by contacting the treating team or the participant directly. Ethnicity should be recorded as reported by the participant or, if not available, as assessed by the study physician who obtained the participant's consent.

If the participant is receiving concomitant medication with potential interactions with linezolid, the study team must inform the treating team and advise appropriate monitoring (e.g. for serotonin syndrome).

9.3.2.2 *IMP administration*

Once a participant has provided written informed consent and has been assigned a randomisation number, the study team will hand over the IMP labelled with the corresponding randomisation number and the participant's first and last name to the participant's treating team for administration over the 5-day intervention period. The IMP will be stored in a designated location according to the centre's guidelines and prespecified workflow for the study.

The IMP will be administered by the treating team as part of routine clinical care and documented in the hospital's medication administration system, as for all other medications. The treating team will document time of IMP administration, any missed or withheld doses and the corresponding reasons in the same system.

The study medication should be administered as soon as possible once a participant has been enrolled and randomised. Thus, the first dose may also be given at night or at any time during the day. The study medication will be administered twice daily for a total of five days (10 administrations). Depending on the time of the first dose, treatment will start either on Day 1 in the morning and end on Day 5 in the evening or start on Day 1 in the evening and end on Day 6 in the morning.

Doses will be administered at approximately 12-hour intervals. If maintaining a fixed 12-hour interval is not feasible due to the start time (e.g. when subsequent doses would need to be administered during the night), the dosing interval may be adjusted in accordance with standard clinical practice. However, the interval should not be shortened or extended by more than 6 hours.

Patient transfer to another hospital ward or to another hospital is a critical time point associated with an increased risk of discontinuation of IMP administration. Therefore, the study team may perform a regular review of the EMR during the IMP administration period to allow early identification of patient transfers and to verify that the IMP has been administered as scheduled. If the IMP administration is stopped without documented reason or notification of the study team, the study team should promptly reach out to the participant's treating team to understand the reason and take appropriate action where necessary.

9.3.2.3 *Day 1 until end of hospital stay: Only for patients at University Hospital Basel who consented to the subproject Molecular mechanisms of S. aureus bacteraemia (IntraSA)*

This applies only to patients included at the University Hospital Basel, Switzerland. Blood will be used to determine the location of *S. aureus* in the blood (intra- or extracellular). For this purpose, a maximum of one additional 7.5 ml EDTA tube of blood per day will be collected.

Depending on the type of consent, the following procedures apply:

- For patients who have provided consent informed consent for additional blood sampling and analysis of *S. aureus* in their blood, either personally or via a legally authorised representative, daily blood samples will be collected until blood cultures have remained negative for 48 hours. If no routine blood collection is performed on an eligible day within this period, an additional blood draw will be performed to obtain the required sample. After blood cultures have remained negative for 48 hours, additional blood samples may be collected if culture-negative persistence of *Staphylococcus aureus* in the blood is suspected. These additional study samples will only be collected as part of routine clinical blood draws, and no study-specific venipuncture will be performed.
- For patients enrolled via the confirmation of an independent physician under emergency exemption from informed consent requirements, blood samples will only be collected during routine blood drawing if venipuncture is required. If blood can be obtained via a central venous or arterial catheter, blood samples will be collected daily until blood cultures have remained negative for 48 hours. Thereafter, blood samples will only be collected during routine blood draws if culture-negative persistence of *Staphylococcus aureus* in the blood is suspected.
- For patients who refused to consent to further analysis in the blood, no additional blood samples for the subproject will be taken.

9.3.3 Day 2

9.3.3.1 *IMP administration*

If feasible, the study team may briefly verify the administration of the IMP in the participant's EMR.

9.3.3.2 *Follow-up blood cultures*

Follow-up blood cultures performed every 24 – 48 hours until clearance of bacteraemia are part of routine clinical practice in patients with *S. aureus* bacteraemia. For study purposes and to ensure standardization, the treating team is advised to obtain follow-up blood cultures on Day 2. If these are not performed, blood culture results obtained on other days as part of routine clinical practice will be used for study assessment.

9.3.4 Day 3 and 4

If feasible, the study team may briefly verify the administration of the IMP in the participant's EMR.

9.3.5 Day 5

9.3.5.1 *IMP administration*

If feasible, the study team may briefly verify the administration of the IMP in the participant's EMR.

9.3.5.2 *Follow-up blood cultures*

If day 2 blood cultures remain positive, then further follow-up blood cultures are mandated on day 5 (±1) and will be part of the clinical routine as outlined above.

9.3.5.3 *Measurement of trough levels of linezolid in a subset of participants (day 5±1)*

Selected centres will collect one 7.5 ml Monovette® Li-Heparin from participants day 5±1 after randomisation for a representative linezolid trough measurement. Plasma sampling may be combined with the routine blood draw but should be timed immediately before the next study drug dose.

Plasma will be isolated by centrifugation. Samples should be frozen as soon as possible after blood draw, but no later than 6 hours, and stored at -80°C until analysis, or linezolid trough levels should be analysed immediately by the diagnostic laboratory of the University Hospital Basel. Leftover aliquots will be stored in the LIPS biobank.

9.3.6 Day 8 – Clinical data collection for data from days 1-7

The study team will review the participant's EMR including routine laboratory results and enter any study relevant data into the eCRF as indicated.

No additional blood draws should be ordered to obtain laboratory tests solely for the purpose of completing the study database.

9.3.6.1 *Review of safety events:*

A study physician should check the EMR for any signs that the participant experienced an SAE. Any SAE must be assessed by a study physician according to the applicable SOP and reported to the Sponsor via REDCap® within 24 hours of awareness.

9.3.7 Day 14 – Clinical data collection for data from days 8-14

If the participant is still hospitalised, the study team will review the participant's EMR including routine laboratory results and enter any study relevant data into the eCRF as indicated.

For participants transferred to another acute care hospital, the study team should make reasonable efforts to obtain missing data from the receiving institution.

Any data of Day 8 –14 can also be assessed on Day 90.

9.3.7.1 *Review of safety events*

A study physician should check the EMR for any signs that the participant experienced an SAE. Any SAE must be assessed by a study physician according to the applicable SOP and reported to the Sponsor via REDCap® within 24 hours of awareness.

9.3.8 Day of acute index hospital discharge

Once the study team becomes aware that a participant has been discharged from the recruiting hospital, data required per the eCRF will be collected.

If a participant is transferred to another acute care hospital before completion of the Day 90 follow-up period, the receiving hospital will be contacted to obtain the participant's discharge letter and any outstanding laboratory results required for eCRF completion.

9.3.8.1 Review of safety events

A study physician should check the EMR and any available discharge letters for any signs that the participant experienced an SAE. Any SAE must be assessed by a study physician according to the applicable SOP and reported to the Sponsor via REDCap® within 24 hours of awareness.

9.3.9 Day 83 – For participants who chose to receive the SF-36 per post

The study team will print the SF-36 in the language as indicated in the eCRF and label it with the participant's name. They will then mail the SF-36 questionnaire along with a short cover letter and a pre-addressed, prepaid return envelope to the participant.

9.3.10 Day 90±7

9.3.10.1 Participant follow-up

The study team will attempt to contact the participant by telephone to complete the follow-up assessment. If the participant has a scheduled hospital visit during the Day 90 follow-up window, the assessment may be conducted in person.

The follow-up must be conducted using the most current approved version of the Day 90 follow-up worksheet. Detailed instructions on contact attempts, procedures if the participant cannot be reached, and required actions based on participant responses are provided in the worksheet and must be followed.

9.3.10.2 Data collection

Data will be collected as indicated in the eCRF using the EMR and any available hospital discharge letters, as well as information gathered from the participant during the follow-up phone call.

9.3.10.3 Review of safety events

A study physician should check the EMR and any available discharge letters for any signs that the participant experienced an SAE until day 90 (see chapter 10.1.2 *Reporting of serious adverse events (SAE) and other safety related events*). SAEs must be assessed by a study physician according to the applicable SOP and reported to the Sponsor via REDCap® within 24 hours of awareness.

If the participant reports an event meeting the SAE criteria within the SAE reporting period, the study team will contact the treating physician, as necessary, to obtain the information required for SAE assessment and reporting.

Any ongoing or previously unresolved SAEs must be followed up, and follow-up reports must be submitted in REDCap® until resolution, stabilisation, or study end, as applicable.

9.3.11 Day 90 until return of SF-36 questionnaire

The study team will collect returned SF-36 questionnaires and transcribe the participant's responses into the eCRF. Completed questionnaires will be archived in accordance with site-specific SOPs, either as the original paper version or as a certified electronic copy.

10. SAFETY

10.1 Drug studies

All adverse events potentially qualifying as serious adverse event (SAEs) will be collected, investigated and documented in source documents by the treating physicians and nursing staff as part of routine clinical care. Trial investigators will assess all events to determine whether they meet the criteria for a SAE and document any SAEs occurring from the first administration of IMP until day 90 in the case report form (CRF). Exemptions from SAE reporting are defined in chapter 10.1.2 *Reporting of serious adverse events (SAE) and other safety related events*. Predefined adverse events of special interest (AE) critical to the safety evaluation will be assessed as outlined in the study protocol. Study duration encompasses the time from when the participant signs the informed consent form until the last protocol-specific procedure has been completed, including a safety follow-up period.

10.1.1 Definition and assessment of (serious) adverse events and other safety related events

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. [ICH E6 1.2]

A **Serious Adverse Event (SAE)** is classified as any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. [ICH E2A]

SAEs should be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination (including safety follow-up visit) will be further followed up until recovery or until stabilisation of the disease after termination.

Assessment of Causality

Both Investigator and Sponsor make a causality assessment of the event to the study investigational medicine product, based on the criteria listed in the ICH E2A guidelines:

Relationship	Description
Definitely	Temporal relationship Improvement after de-challenge* Recurrence after re-challenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after de-challenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out

*Improvement after de-challenge only taken into consideration if applicable to reaction

A causal relationship will be suspected for all SAEs reported with a relationship of “probably” or “definitely”.

Unexpected Adverse Drug Reaction

An “unexpected” adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator’s Brochure for drugs that are not yet approved and Product Information for approved drugs, respectively). [ICH E2A]

Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Sponsor evaluates the SAE that has been reported regarding seriousness, causality and expectedness. If the event is related to the investigational medicinal product and is both serious and unexpected, it is classified as a SUSAR.

Assessment of Severity

Severity of any SAEs will be graded by the local Investigator as well as the Sponsor-Investigator based on the following criteria according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 published November 27, 2017 [116].

Severity	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A semi-colon indicates ‘or’ within the description of the grade. ADL: Activities of Daily Living

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

10.1.2 Reporting of serious adverse events (SAE) and other safety related events

Reporting of SAEs

Except for the exemptions listed below, all SAEs must be reported immediately and within a maximum of 24 hours of becoming aware of the SAE to the Sponsor-Investigator of the study. The Sponsor-Investigator or a sponsor-delegated physician will review the SAE report in a separate eCRF form and provide feedback to the site in case of discrepancies. In addition, aggregated SAEs will also be evaluated by the DSMB during the interim analyses (including external experts as well as patient and public representatives; see also chapter *11.4.4 Interim analysis*).

Exemptions from SAE reporting

The LIPS trial includes patients who at the time of randomisation are already in a life-threatening condition due to *S. aureus* bacteraemia. Participants are included early in the course of their infection to assess whether prompt administration of linezolid improves patient outcomes. Therefore, the diagnostic work-up to determine the aetiology of *S. aureus* bacteraemia, as well as the therapeutic management, is often not completed at the time of randomisation.

1. **Not reported as SAEs in the context of pre-existing infectious foci**
   An infectious focus that is clinically apparent at the time of study inclusion shall not be recorded as an SAE, irrespective of the timing of its formal diagnostic confirmation.

   Examples:

   - Clinical picture of septic arthritis of the knee at the time of study inclusion; puncture and culture of joint fluid one day later confirm the clinical diagnosis.

- Severe back pain and fever at the time of study inclusion; MRI confirms the diagnosis of spondylodiscitis two days later.
- High fever, prosthetic cardiac valve in place and 6/6 blood cultures positive for *S. aureus* at the time of inclusion; Echocardiography confirms the diagnosis of endocarditis one day later.

2. **Not reported as SAEs in the context of pre-planned procedures**

   Any therapeutic procedure documented as planned at the time of study inclusion shall not be considered an adverse event.

   Examples:

   - Participant with septic arthritis of the knee, and surgical debridement is planned for one day after study inclusion.
   - Participant with spondylodiscitis, and surgical debridement is planned for three days after study inclusion.
   - Participant with endocarditis, and a valve replacement is planned for several days after study inclusion.

SAE reporting period

SAEs will be assessed using medical records, recorded and reported from administration of the first IMP dose until 90 days after randomisation.

If an investigator becomes aware of an SAE with a suspected causal relationship to the IMP that occurs after the end of the SAE reporting period or after the end of the clinical trial, the investigator shall nevertheless report the SAE to the sponsor.

Reporting of SUSARs

A SUSAR must be reported by the Sponsor to the Ethics Committee (via BASEC) and to Swissmedic within 7 days of becoming aware of the SUSAR if the event is life-threatening or fatal. For all other SUSARs, the report must be made within 15 days.

The reporting obligations of SUSAR also apply if the Sponsor becomes aware of a suspected case after termination of the clinical trial.

Reporting of immediate safety and protective measures

All suspected new risks and relevant new aspects of known adverse reactions that require immediate safety-related measures, must be reported to the Sponsor within 24 hours of becoming aware of the new risks. The Sponsor must report these measures within 7 days to the Ethics Committee via BASEC and to Swissmedic.

The Sponsor must immediately inform all participating Investigators about the immediate safety and protective measures.

Reporting and Handling of Pregnancies

In the event of pregnancy, the treating physician and the participant (or the participant's next of kin) will determine whether the potential benefits for the participant outweigh the potential risks to the foetus. The course and outcome of the pregnancy should be followed up carefully, and any abnormal outcome regarding the mother or the child must be documented and reported.

Periodic reporting of safety and general progress of the clinical trial.

Once a year, the Sponsor-Investigator submits to the CEC and Swissmedic a list of the safety events including the severity of the events, their causality to the intervention and the safety of the study participants. This report also includes an update on the general progress of the study.

The safety and general progress reports encompass the time from the date of the sponsor's first authorisation to conduct the clinical trial in any country worldwide until the Last Patient Last Visit in Switzerland.

The safety and general progress report is submitted yearly to the CEC and to Swissmedic throughout the duration of the clinical trial in Switzerland, and the last submission of the safety report will cover the Last Patient Last Visit

in Switzerland.

10.1.3 Follow up of (Serious) Adverse Events

SAEs occurring during hospitalisation will be followed up until they are resolved during the hospital stay. If any study personnel become aware of an SAE outside of hospital, they must conduct regular follow-ups until the SAE is resolved. If the participant cannot be reached for follow-up, reasonable attempt will be made to acquire the information from relatives, caregivers, or the participant's emergency contact or primary care physician.

10.2 Assessment, notification and reporting on the use of radiation sources

Not applicable.

10.3 Exemption from the documentation requirements of AE

10.3.1 Exemption from the documentation requirements of AE due to pharmacological arguments

Not applicable.

10.3.2 Exemption from the documentation requirements of AE due to clinical arguments

Not applicable.

11. STATISTICAL METHODS

11.1 Hypothesis

Primary research hypothesis: Inhibition of virulence factor expression by early 5-day treatment with linezolid (600 mg twice daily) in addition to treatment with standard antibiotics will result in superior outcomes at 90 days compared to placebo in participants with *S. aureus* bacteraemia.

11.2 Determination of Sample Size

We collected retrospective data on the DOOR components from all *S. aureus* bacteraemia patients treated at the University Hospital Basel in 2022 (n=119). Our assumptions for the sample size are based on these data along with what is known from the literature to derive plausible estimates for the DOOR components. Patients who died in the first three days after a *S. aureus* bacteraemia diagnosis were excluded so that we do not overestimate the mortality of the planned trial (of note, most of these patients would probably have died before they could have been included in our study (n = 8)). Following extensive consultations with patient representatives, we have established that, for mortality at 90 days, a trial should demonstrate a meaningful relative difference of 10% (equating to an absolute difference of 2.2%). Meanwhile, for the remaining domains, the following relative reductions were deemed acceptable: 15% for level of function and 20% for complications and length of hospital stay).

The sample size was calculated using a simulation approach, for which 1000 synthetic datasets for each combination of plausible values for the relevant parameters were generated. We calculated the p-value of the win ratio for each of the simulated datasets and tested for statistical significance at $\alpha = 0.05$ using the unmatched win-ratio approach described in Pocock et al.[117]. The final sample size is based on the following specific assumptions:

- The statistical tests are conducted at a two-sided significance level of $\alpha=0.05$, and the desired power is 90%
- The two treatment arms are equal in size (1:1 allocation)
- The proportion of deaths within 90 days in the control group is expected to be 22.5% and 20.3% in the linezolid group (relative reduction of 10%; absolute reduction of 2.2%)
- The proportion of participants with worse level of function in the control group is expected to be 25.0% [21], and 21.3% in the linezolid group (relative reduction of 15%; absolute reduction of 3.7%)
- The proportion of participants with any complications (defined DOOR component) will be 6.3% in the control group and 5.0% in the linezolid group (relative reduction of 20%; absolute reduction of 1.3%).
- We modelled hospital length of stay using a log-normal model with any of the complications listed in the definition above as an independent variable; the parameters for this model were derived from the retrospective USB data, and the expected 20% relative reduction in hospital length of stay due to the intervention was applied to the mean of the log-transformed data when generating synthetic datasets.
- Missing data were accounted for in the simulations (i.e., 10% for worse level of function and only 3% for all other components as these data will be available from routinely collected data). In case of missing DOOR components, the comparison among participants was made with the following DOOR domain.

Under the assumptions listed above, 550 participants are required to show a significant effect of the intervention. Since it is possible that some patients themselves or their next of kin withdraw consent post-randomisation, we increased the target sample size by 10% to minimise the risk of being underpowered. Hence, we plan to include 606 participants (303 participants in each study arm).

11.3 Statistical criteria of termination of trial

Not applicable. In brief, we do not have statistical criteria of early termination of the trial. Safety will be monitored by the independent DSMB (which includes patient representatives). If the DSMB observes a major safety concern (i.e. which would also be unacceptable if linezolid is superior to compared to standard of care) the DSMB will provide recommendations on whether the trial should be continued as planned, modified, or terminated for safety reasons.

11.4 Planned Analyses

11.4.1 Datasets to be analysed, analysis populations

Analyses will be performed on the full analysis set (i.e., all randomised participants) and the per protocol dataset

(i.e., those who received at least 7 out of 10 doses of linezolid or placebo). The primary estimand to be calculated in this study is the effect (summarised as the win ratio) of being randomly assigned to treatment with linezolid in the patient population (i.e., equivalent to an intention-to-treat analysis). We will also estimate the treatment effect among the treated participants (i.e., the per protocol dataset).

A detailed analysis plan will be written before closing the study database. Of note, we are currently conducting a systematic scoping review, assessing current practices how to analyse a hierarchical composite outcome. These results will inform our pre-specified analysis plan. Furthermore, we will consider further developments in risk-score classifications for *S. aureus* bacteraemia (e.g. for a potential use of a matched win-ratio versus unmatched win-ratio). The statistical analysis plan will be made publicly available (on clinicaltrials.gov). Currently we intend to conduct the following analyses:

11.4.2 Primary Analysis

Treatment and placebo will be compared on the basis of the win-ratio approach as described by Pocock and colleagues:[117] In brief, each participant in the treatment group will be compared with each participant in the placebo group. When comparing two participants, the winner will be determined by the first component of the DOOR in which the two participants differ. The following two scenarios will be considered as a tie: (i) when both participants died within 90 days, or (ii) when participants have the same outcomes for all DOOR elements, including length of hospital stay. The win ratio will be calculated by dividing the number of cases in which participants receiving linezolid win compared with the number of cases in which participants receiving placebo win. We will reject the null hypothesis that the win ratio is equal to 1 if the *p*-value is less than 0.05.

Subgroup analyses: For the primary outcome and for all DOOR components separately, we will assess if treatment effects differ by sex (male vs. female), ICU status at baseline (participants on ICU vs. participants not on ICU) and focus of infection (vascular catheter, skin and soft tissue, endocarditis, osteoarticular, pneumonia, other focus, or focus not identified). All subgroup analyses will be exploratory in nature.

11.4.3 Secondary Analyses

We intend to conduct the following analyses for the secondary outcomes:

Logistic regression

- Returning to usual level of function by day 90
- Microbiological treatment failure 14-90 days after randomisation
- Early microbiological treatment failure 5-13 days after randomisation
- Clinical treatment failure 14-90 days after randomisation
- Persistent bacteraemia defined as positive blood culture on day 5 after randomisation
- Meeting two or more SIRS criteria simultaneously on day 5 after randomisation

Log-normal linear regression

- Length of hospital stay of acute index inpatient hospitalisation (in days)

Poisson regression

- Number of days without being on the Intensive Care Unit (ICU) up to day 90
- Number of days alive and free of antibiotics up to day 90

Cox proportional hazards model

- Time to death up to day 90

Fine & Gray competing risk model

- Time to being discharged alive (assessed until day 90)

The models listed above will include sex, ICU stay at baseline, and centre as adjustment factors (will be further pre-specified in separate data analysis plan).

Wilcoxon-Mann-Whitney test

- Physical health at day 90 as assessed by the short form 36 (SF-36) questionnaire
- Mental health at day 90 as assessed by the short form 36 (SF-36) questionnaire

Subgroup analyses: We will conduct the following subgroup analyses on the primary outcome to assess if treatment effects differ by sex (male vs. female), ICU status at baseline (participants on ICU vs. participants not on ICU), and dominant focus of infection (vascular catheter, skin and soft tissue, endocarditis, osteoarticular, pneumonia, other focus, or focus not identified).

11.4.4 Interim analyses

After follow-up for the first 50 recruited participants has been completed, and again after 200 participants, the independent Data and Safety Monitoring Board (DSMB, including external clinical experts, an independent statistician, as well as patient and public representatives) will meet to discuss summary statistics about safety outcomes (see section 10 *SAFETY*). In addition, the adherence to treatment will be assessed in these interim analyses. If the proportion of non-adherence is above 10% (i.e., more than 10% of participants received fewer than 7 of the planned 10 doses), the study team will assess the reasons why doses were missed and implement actions (e.g., additional training) to increase adherence.

11.4.5 Safety analysis

The following adverse events and safety outcomes will be analysed descriptively by study group:

- Serious adverse reactions or serious adverse events in the 90 days following study entry
- The following adverse events of special interest until 7 days after study entry during the index hospital stay:
  - Clinical signs compatible with serotonin syndrome
  - Laboratory signs of myelosuppression
- Acute kidney injury defined using modified Kidney Disease Improving Global Outcomes (KDIGO) criteria, modified according to SNAP trial:
  - Increase in serum creatinine by 26.5 µmol/l or more at any time from baseline entry to day 5

    OR
  - Increase in serum creatinine by 1.5 times or more the level at study entry (baseline) within 14 days of study entry
- *Clostridioides difficile*-associated diarrhoea

11.4.6 Deviation(s) from the original statistical plan

If substantial deviations of the analysis as outlined in these chapters are needed for whatever reason, the protocol will be amended. All deviations of the analysis from the protocol or from the detailed analysis plan will be listed and justified in a separate chapter of the final statistical report.

11.5 Handling of missing data and drop-outs

The primary analysis will be performed on the data available (complete cases). In the sample size calculation, we have included expected proportions of missing data for the individual DOOR components. To keep as many participants as possible in the analysis, we will use the components of the DOOR that are not missing in cases where not all components are missing. For the secondary outcomes, we will consider multiple imputation if the proportion of excluded participants is larger than 5% (the imputation strategy will be pre-specified for each outcome in a separate data analysis plan).

12. QUALITY ASSURANCE AND CONTROL

Written standard operating procedures (SOPs) and manuals of operation will be issued to all sites and adherence to guidance is monitored during site visits.

12.1 Data handling and record keeping / archiving

12.1.1 Electronic Case Report Forms (eCRF)

Relevant clinical study data for each enrolled study participant, i.e., observations, tests and assessments specified in the protocol, are recorded in eCRFs via the web-based electronic data capture (EDC) system implemented in REDCap® at the study centres. The participant's name and address will not be recorded. The EDC system includes guidance for study sites on how to perform data entry and will also be used for query handling.

Local investigators and study team members will be authorized for the eCRF entries of study participants enrolled at the site. Study teams will be trained to use the EDC system. The investigators ensure the accuracy, completeness, and timeliness of the data recorded and provide answers to data queries, as specified in the study protocol and in accordance with additional instructions. The identity of the study team member entering data, and date and time of data entry will be recorded as meta-data in the study database.

12.1.2 Specification of source documents

Source data will include all study documents (e.g. informed consent forms, patient data in hospital information system). Source data will be available at all sites and may be found in paper or electronic form. For selected data elements, REDCap® will serve as the primary source document. This applies to participants' ethnicity and to SF-36 questionnaire data when completed electronically by participants (via SMS or email).

When the SF-36 questionnaire is completed on paper (postal delivery), the original paper questionnaire will constitute the primary source document, with data subsequently transcribed into REDCap®.

For safety reporting, serious adverse event (SAE) data will be captured using electronic SAE forms in REDCap®.

Depending on site-specific processes, REDCap® may serve as the primary source document for SAE reporting. At sites where SAEs are first documented in local source systems, these documents will constitute the primary source, with SAE data entered or reconciled in REDCap® accordingly.

Each study site will maintain an up-to-date Source Data Location List specifying the location and format of primary source documents, which will be available for monitoring and audit purposes.

12.1.3 Record keeping / archiving

The sponsor retains all data relating to the clinical trial for at least twenty years after completion or premature termination of the clinical trial. The local investigators retain all documents necessary for the identification and follow-up of the trial participants and all other original data for at least twenty years after completion or discontinuation of the clinical trial. Data will be stored in the REDCap study database located on servers of the University of Basel. Any study relevant paper documents will be archived at each site for a minimum of 20 years.

12.2 Data management

12.2.1 Data Management System

Study data will be captured via the web-based electronic data capture system REDCap®. The system is developed by Vanderbilt University, US and licensed and hosted by the Department of Clinical Research of the University Basel. The REDCap® software installation and periodical updates are validated by the Department of Clinical Research. All data is stored on servers of the University Hospital Basel in Switzerland. Password protection and user-right management safeguard access, ensuring that only authorized personnel can view or modify the data.

Patients will be entered into REDCap® with a unique study ID. Patient data entry in REDCap® is facilitated by manually entering the unique hospital identification number, which is used to locate and input data at predefined time points. Using data-access groups in REDCap® will ensure that study personnel can only access data from their own centre. To enhance data security and confidentiality, the unique hospital identification number is designated as an identifier field in REDCap®, preventing its inclusion in exported datasets. In these exports only

the unique study ID of each participant will be included. To ensure that patients can still be correctly identified, each centre will maintain a separate key list that also serves as a site screening and enrolment log file. All data collected is entered into study specific case report forms. An audit trail maintains a record of initial entries and any changes made; time and date of entry; and username of person authorizing entry or change.

12.2.2 Data security, access, and back-up

Data is encrypted at rest and protected by advanced threat detection software according to the security policy of the University Hospital Basel. REDCap® is accessible via a standard browser on devices with internet connection. The data transfer between clients and servers is encrypted using Transport Layer Encryption (TLS) cryptography protocol. Password protection and user-right management ensure that only authorized study investigators, monitors, data managers and local authorities (if necessary) will have access to the data during and after the study. User administration and user training is performed by the Department of Clinical Research (DKF) Basel according to predefined processes. The built-in audit trail will register any unplanned deviations from the study protocol.

Backup of the REDCap® database is performed daily according to established processes.

12.2.3 Analysis and archiving

REDCap® database will be locked after all data has been monitored and cleaned, and all raised queries have been resolved. Data will be archived by the Sponsor for a minimum of 20 years.

12.2.4 Electronic and central data validation

The data managers of the DKF Basel will implement validation rules in REDCap®. When data gets saved in a case report form, it will be validated for discrepancies. The data will be reviewed by the responsible investigator as well as an independent monitor. The monitor will raise queries using the query management system implemented in REDCap®. The study team must respond to the query and confirm or correct the corresponding data. Thereafter the monitor can close the query.

12.3 Monitoring

The Department of Clinical Research of the University of Basel will perform the monitoring of this trial. According to the scope of the monitoring plan, the monitor will visit the trial site during the study or perform remote monitoring visits, regularly if necessary, and after closing. The monitor will verify the adherence to the protocol, completeness, consistence, and accuracy of the data being entered on eCRF and will thus require access to all patient medical records including laboratory test results and surgery, pathology and radiology reports and supporting documents. The study team should collaborate with the monitor. They must ensure that source data verification forms, source data and documents are made accessible to the study monitor, and they should answer questions by the Study Monitor in detail to ensure that any problems detected during these visits are resolved. Open action items will be listed and explained by the monitor in follow-up letters and are expected to be resolved in reasonable time. In addition, the sponsor team will perform risk-based centralised monitoring through REDCap® by systematically reviewing key aspects of the data, including study drug administration, primary outcome measures, and close-out visits for all participants. If missing or inconsistent data are identified, the sponsor team will raise queries in REDCap® and contact the respective local study team for clarification.

12.4 Audits and Inspections

Authorized representatives of the CEC and CA may perform inspections during the course of the study. The local investigators ensure that source data and study documentation are made accessible to auditors and inspectors and answer their questions. All involved parties must keep the participant data strictly confidential.

12.5 Confidentiality, Data Protection

Direct access to source documents will be permitted for purposes of monitoring, audits and inspections.

Study data entered into the eCRF is only accessible to authorized personnel. Once all data is entered into the REDCap platform and monitoring is completed, the database will be locked and closed for further data entry. The complete dataset is then exported and transferred to the study statistician as well as the principal investigator through a secure channel.

12.6 Storage of biological material and related health data

For selected sites only: Plasma samples used for linezolid trough measurement will be coded for analysis. If applicable, samples will be stored locally at the centre until shipment to the sponsor site (University Hospital Basel). Any leftover samples will be stored in the LIPS biobank. Detailed information can be found in the LIPS biobanking regulation.

13. PUBLICATION AND DISSEMINATION POLICY

The trial results will be published in a peer-reviewed open access journal. Results will also be published if they are negative or if the trial was discontinued. The full protocol will be made publicly available on clinicaltrials.gov. A detailed analysis plan will be written before closing the study database. The statistical analysis plan will be made publicly available on clinicaltrials.gov. Furthermore, we will consider publishing a short peer-reviewed version of the trial protocol. Authorship to publications will be granted according to the rules of the International Committee of Medical Journal Editors (ICMJE). After publication of the main results, the full dataset will be submitted to the Data Access Committee of the Faculty of Medicine (MF-DAC) at the University of Basel. Other researchers interested in re-using the study data may then contact the independent MF-DAC to request data access.

The sponsor will enter and publish a summary of the trial results in a public registry in accordance with ClinO Art. 65a within one year of completion or premature termination of the trial. An interruption lasting more than two years is considered a premature termination of the trial.

The sponsor also ensures that a lay summary of the trial results in German, French, and Italian is entered in BASEC within one year of completion or premature termination of the trial.

The local study teams may provide each study participant with the lay summary of the trial results upon request and inform them where they can find the study results.

14. FUNDING AND SUPPORT

14.1 Funding

The LIPS trial is funded by the Swiss National Science Foundation (SNSF) under the investigator-initiated clinical trials (IICT) funding call (SNSF ID: 221668).

15. INSURANCE

Insurance with a policy value in accordance with ClinO Annex 2 will be provided by the Sponsor University Hospital Basel. A copy of the certificate is filed in each investigator site file and the trial master file. The certificate will be provided as soon as ethics approval has been obtained.

16. TRIAL SUB-PROJECT(S)

16.1 Molecular mechanisms of *S. aureus* bacteraemia (IntraSA)

Hypothesis: *S. aureus* uses intracellular survival inside immune cells as a main survival strategy in the blood for persistence of infection.

Objective: Identification of human cells harbouring *S. aureus* in bacteraemia.

Background: Despite extensive research, the mechanisms underlying *S. aureus* persistence in the bloodstream for more than 48 hours despite active antibiotic therapy remain unclear[8 9]. The associated stark increase of mortality and risk of metastatic spread[18] in these courses of infection underline the importance of further research. Current investigations are limited to *in vitro* and animal studies, lacking sufficient predictive power for the relevant patient setting. Based on these previous findings, *S. aureus* can survive and proliferate within human neutrophils and monocytes[118] and could, as hypothesized[119], use the intracellular niche as a crucial way of evading antibiotic exposure. The existence and relevance of intracellular *S. aureus in* bacteraemia in humans has not yet been shown.

Methods: Blood samples will be drawn daily in routine or study-specific blood draws and sent to the research facility as described in 9.3.2.3 until the end of hospital stay Samples will be divided to perform several analyses: i) Quantification of intracellular and extracellular viable bacteria will be achieved by plating of serum respectively plating of lysed cells on agar plates for counting of colony forming units ii) blood smears stained with fluorescent vancomycin derivate VAN-JF669[120] for intracellular bacterial staining and other standard stainings (e.g. RAB5, RAB7, fibrinogen) will be analysed on a Nikon Ti2 confocal microscope iii) Flow cytometry analysis will be performed on a subsection of blood cells. Using Percoll separation, specific blood cell types are obtained and stained with VAN-JF669 and for cell type markers (e.g. CD14, CD16, CD68). Cells will be analysed using spectral flow cytometry (Cytek Aurora) or image flow cytometry (Amnis ImageStreamX Mark II).

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18. APPENDICES

Documents that are periodically updated and may be updated during the course of the study, are listed here and provided separately.

18.1 Linezolid Stada® Summary of Product Characteristics

Provided separately.

18.2 The Hunter Serotonin Toxicity Criteria: for diagnosing serotonin syndrome

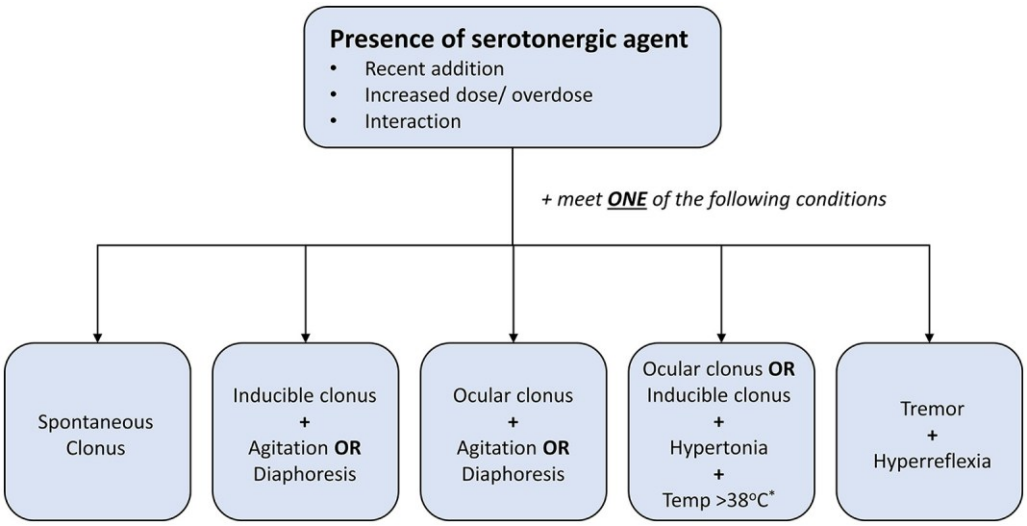


Figure 2: The Hunter Serotonin Toxicity Criteria

*Note the requirement for the presence of some form of neuromuscular excitation, the sine qua non for a diagnosis of serotonin syndrome. *The presence of temperature ⩾38.5°C and/or marked hypertonia or rigidity (especially truncal) indicates severe SS with a risk of progression with respiratory compromise.*

Taken from: Scotton, William J et al. 2019[121]