A Randomized Controlled Multicenter Trial on Albumin Replacement in Septic Shock

ZKSJ0112 ARISS

Statistical Analysis Plan

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Contents

List of Abbreviations

ITT	Intention-to Treat
FAS	Full Analysis Set
PPS	Per-Protocol Set
LOS	Listing Only Set
ICU	Intensive Care Unit
SAP	Systolic Blood Pressure
MAP	Mean Arterial blood Pressure
DAP	Diastolic Blood Pressure
CVP	Central Venous Pressure
CO	Cardiac output
LOCF	Last observation carried forward
GCS	Glascow Coma Scale
AE	Adverse Event
DSUR	Data Safety Update Report
SMC	Study Monitoring Committee

1 Study Background

1.1 Study Objective

To investigate whether the replacement with albumin and the maintenance of its serum level above 30 g/L for 28 days improve survival in the patients with septic shock compared to resuscitation and volume maintenance without albumin.

1.2 Study Design

Randomized Controlled Multicenter

1.3 Protocol Version and Amendments

Final 3.0 from 18JUL2019

2 Analysis Sets

2.1 Full Analysis Set (FAS)

The FAS includes all patients randomized, who have at least one data point after randomization. Patients will be analyzed as randomized (Intention-to Treat, ITT, principle) The primary efficacy analysis will be performed in the FAS. All data assessed will be analyzed in the FAS.

2.2 Per-Protocol Set (PPS)

The Per-Protocol-Set includes all patients of the ITT without additional albumin application other than study medication, who have no *major* protocol deviations.
A protocol deviation is defined as major, if it substantially influences the primary efficacy parameter 90 day mortality.
In particular, application of albumin in addition to the study medication leads to exclusion from PPS, although allowed according study protocol for reasons of patient's safety.
Primary efficacy analysis will be repeated in the PPS as a sensitivity analysis.
In case of differences between treatment randomized and applicated, a further sensitivity analysis will be performed „as treated".

2.3 Safety

The safety analysis will be performed for FAS, but patients will be analyzed as treated.

2.4 Listing Only Set (LOS)

Patients, excluded from FAS (screening failures) will be listed as far as available. Reasons for exclusion/non-inclusion will be analyzed as far as available.

2.5 Predictable Major Protocol Deviations

Application of albumin in addition to the study medication leads to exclusion from PPS, although it is no protocol deviation. It is allowed according study protocol for reasons of patient's safety, but substantially influences the study objective.

3 Study Centers

40-50 Centers. Centers will be listed with number of recruited patients in the statistical report.

4 Study Variables

4.1 Population Characteristics and Baseline Data

- Eligibility and consent
- Age, weight, height, sex, type of admission, residence before admission to ICU and other demographic data
- Diagnoses, comorbidities, data on infection,
- Lactate
- APACHE II-Score, SAPS-II-Score und SOFA-Score
- Treatment application and compliance, albumin application in addition to study medication

4.2 Primary Endpoint

- 90-day-mortality

4.3 Secondary Endpoints

- 28- and 60-day-mortality
- Mortality rate at ICU and in-hospital mortality
- SOFA score
- Duration of stay on ICU and duration of hospitalization,
- Days not requiring artificial respiration, days without vasopressors
- Assessment of amount of albumin applicated, other colloids and crystalloids
- Overall fluid intake, overall fluid balance

4.4 Safety Variables

4.4.1 Adverse Events

- AEs, SAEs and sepsis related events

4.4.2 Laboratory Parameters

- Microbiology
- Routine laboratory: hemoglobin, creatinine, bilirubin, C-reactive protein, procalcitonin, leukocytes, thrombocytes, lactate, arterial blood gas (paCO2, paO2, FiO2, SO2, pH, ScO2)

4.4.3 Other Safety Data

- Clinical parameters: body temperature, respiratory rate, hemodynamic parameters (SAP, MAP, DAP, CVP, CO)
- Anti-infective therapy
- Adjunctive sepsis therapy
- Intensive care (intubation, central venous catheter, arterial catheter, renal replacement therapy, ventilation, ECMO, hemodynamic monitoring)

5 Handling of Missing Values and Outliers

5.1 Missing Values

Single day missing values in GCS (up to 3 consecutive) will be replaced by LOCF for evaluation of daily SOFA score.
All other missing values will be treated as such and not replaced by estimates. Missing values for the primary efficacy parameter 90 day mortality will be respected in Kaplan Meier analysis of mortality.

5.2 Outliers

No special procedures for outliers are planned.

5.3 Other Data Rules

Amount of albumin applicated is defined as sum of volume therapy (human albumin 4% or 5%*0.05 + Human albumin 20%*0.2) and study medication (Albutein® 200g/L OR Plasbumin 20 *0.2) over 24h.

Overall fluid intake, output and balance are defined as follows:
Overall fluid intake
= enteral fluid intake [24 h] + parenteral fluid intake [24 h] + volume therapy [24 h] + study medication application volume sum for the respective 24 h
Overall fluid output [1]
= urine output [24 h] + other fluid loss (Feces, vomiting, stomach tube, perspiration, other).
If perspiration is missing in more than 10% of visits in patients, the following definition [2] excluding perspiration will be used for main analysis. Analysis in subgroup with perspiration available will be performed as additional sensitivity analysis.
Overall fluid output [2]
= urine output [24 h] – other fluid loss (Feces, vomiting, stomach tube, other).
Overall fluid balance
= Overall fluid intake - Overall fluid output

If values are given for a differing time frame, they will be normed to 24 h
(value * 24 / [given different time frame]).
Values of the time window 6 h after randomization will be normed to 6 hours analogously.

Physiological data: Baseline values assessed at randomization time frame will be compared to values assessed at time frame 6h ± 1 after randomization
SOFA: Baseline values assessed 24h before randomization time frame will be compared to treatment days.

Note:

MAP can be used only as given in CRF. Evaluation from Systolic and diastolic blood pressure is not possible, since worst values are assessed, hence values do not reflect same time point

6 Statistical Methodology

6.1 Sample Size Considerations

1412 evaluable patients, 706 per arm planned. For details of sample size planning see study protocol.

6.2 General Principles

All available data will be analyzed at least descriptively. Descriptive analysis includes at least number of available and missing data, mean, standard deviation, minimum, quartiles including median and maximum for metric data and number and % of patients per category for non-metric data. Day-wise descriptive statistics will include at least number of available data, mean, minimum, median and maximum
All analyses will be performed by treatment group and in total.

6.3 Population Characteristics and Baseline Data

Descriptive analysis

6.4 Previous and Concomitant Diseases and Therapies

Frequency analysis

6.5 Exposition to Therapy / Compliance

Descriptive analysis

6.6 Primary Analysis

The primary efficacy variable 90 day mortality will be analyzed with a Generalized mixed model with fixed effects SAPS II score, baseline lactate, baseline-albumin-serum value, type of admission (surgical/non-surgical) and treatment group and random effect center; descriptive statistics will be presented. The primary analysis will take place in FAS according to ITT-principle; an additional sensitivity analysis in PPS will be performed.
In addition, descriptive analysis of 90-day mortality in subgroups with respect to baseline-lactate, baseline albumin, baseline SOFA, SAPS II und APACHE II will be performed.

6.7 Secondary Analyses

28- and 60-day-mortality, mortality rate at ICU and in-hospital mortality will be analyzed descriptively. Overall mortality will be described by Kaplan Meier methods.
SOFA score will be analyzed descriptively over time, for organ subscores frequency analysis will be presented. Number and % of patients with organ dysfunction defined as any subscore > 2 and number of patients with organ failure defined as any subscore >3 will be given.
Duration of stay on ICU and duration of hospitalization, days not requiring artificial respiration and days without vasopressors will be analyzed descriptively.
Amount of albumin applicated, other colloids and crystalloids will be analyzed descriptively over time.
Overall fluid intake and overall fluid balance will be analyzed descriptively over time.
Definition [1] for overall fluid output will be used, if 90% of perspiration values are given If perspiration is missing in more than 10% of visits n patients, definition [2] excluding perspiration will be used for main analysis. Analysis in subgroup with perspiration available will be performed as additional sensitivity analysis.

6.8 Safety and Tolerability Analyses

6.8.1 Adverse Events

For sepsis related AEs, frequency analysis with respect to categories cardiovascular / respiratory / hepatic / renal / hematological / neurological, will be presented.
Respective entries of AEs possibly related to study medication in AE data base will be selected and presented separately.
All AEs and serious AEs will be presented by incidence analysis of the pre-specified categories as well as intensity, relationship to study medication, measures with respect to study medication as well as other measures and outcome. Events of category “Other” will be listed.
For infections, frequency analysis over types, grade and origin will be provided.
Analysis of daily assessed data will be performed over the following time frames: Screening / 6h after randomization / Day 1 / Day 2-7 / Day 8-28.

6.8.2 Laboratory Parameters

For microbiological analysis, incidence of pathogen by source and in total will be evaluated.
For routine laboratory, descriptive analysis will be performed. Analysis of daily assessed data will be performed over the following time frames: Screening / 6h after randomization / Day 1 / Day 2-7 / Day 8-28.

6.8.3 Other Safety Data

Descriptive analysis
Clinical parameters: body temperature, respiratorical frequency, hemodynamic parameters (SAP, MAP, DAP, CVP, CO) will be analyzed descriptively over time.
For anti-infective therapy and adjunctive sepsis therapy, incidence analysis will be performed.
For intensive care measures (intubation, central venous catheter, arterial catheter, renal replacement therapy, ventilation, ECMO, hemodynamic monitoring), frequencies will be presented.
Analysis of daily assessed data will be performed over the following time frames: Screening / 6h after randomization / Day 1 / Day 2-7 / Day 8-28.

6.9 Subgroup Analysis

Descriptive analysis of 90 day mortality and Kaplan Meier analysis will be given in subgroups for
Baseline-albumin (0..< 20g/l, 20..<25 g/l, 25..<30 g/l, ≥ 30g/l)
Baseline-lactate (< / ≥ 8mmol/l, stratum of randomization)
SOFA baseline value (0..<10, 10..<15, ≥15)
SAPS II baseline value (0..<40, 40..<80, ≥80)
APACHE II baseline value (0..<10, 10..<20, 20..<30, ≥30)

If predefined cuts lead to any small subgroups (less than 10 patients), analysis using quartiles of study population for subgroup definition will be added for the respective parameter.

6.10 Interim Analysis

Not planned

6.11 Deviation from Protocol and Amendment

Corresponding to recommendations of reviewers, subgroups with respect to SOFA, SAPS II and APACHE II baseline values are prespecified instead of using quartiles.

7 Software and Validation

Analysis will be performed with SAS Version 9.4 or higher.

Validation plan:
All programs will be validated on either a basic or an enhanced validation level. Basic validation level means validation by the programmer according ZKS Jena SOP Bi06 and includes check of program code, check of log-file and check of output. Enhanced validation will be performed by an independent programmer and includes enhanced check of program code, log-file and output. Primary efficacy analysis will be validated by independent duplicate programming. Results of adverse events analysis will be cross-checked with the contents of the safety data base.
Programms for DSUR and SMC reports will be validated on basic validation level by the respective programmer.

Analysis	Validation level
Population characteristics and baseline data	basic
Previous and concomitant diseases and therapies	basic
Exposition to therapy / compliance	basic
Primary analysis	enhanced
Secondary analyses	basic
Adverse events	basic
Laboratory parameters	basic
Other safety data	basic