STATISTICAL ANALYSIS PLAN

Title:	A Double-Blind, Placebo-Controlled, Randomized, Multicenter, Proof of Concept and Dose-Finding Phase II Clinical Trial to Investigate the Safety, Tolerability and Efficacy of ADRECIZUMAB in Patients with Septic Shock and Elevated Adrenomedullin
Short Title:	Treatment of patients with septic shock and bio-ADM concentration > 70 pg/mL with ADRECIZUMAB
Version / Date:	Final 1.0 / 05-Feb-2020
Protocol No.:	ADR-02
EudraCT-No:	2016-003883-38
NCT:	NCT03085758

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: ADR-02 (ADRENOSS-2)

CONFIDENTIAL

A Double-Blind, Placebo-Controlled, Randomized, Multicenter, Proof of Concept and Dose-Finding Phase II Clinical Trial to Investigate the Safety, Tolerability and Efficacy of ADRECIZUMAB in Patients with Septic Shock and Elevated Adrenomedullin

Sponsor: ADRENOMED AG
Neuendorfstr. 15a
D-16761 Hennigsdorf
Germany

Author Jenni Reifenberger
M.A.R.C.O. GmbH & Co.KG
Schirmerstr. 71
D-40211 Duesseldorf
Phone: +49 (0)221/ 97793-579
Email: jenni.reifenberger@marco-institut.de

Version: 1.0

Date: 05th February 2020

The undersigned have discussed the topics of this document and agree on the content.

Dr. Jens Zimmermann, M.D., M.Sc. Chief Medical Officer ADRENOMED AG	Date
Dr. Oliver Hartmann Senior Principal Statistician ADRENOMED AG	Date
Jenni Reifenberger Statistical Analyst M.A.R.C.O.	Date

The undersigned have discussed the topics of this document and agree on the content.

Dr. Jens Zimmermann, M.D., M.Sc.
Chief Medical Officer
ADRENOMED AG

Date

Dr. Oliver Hartmann
Senior Principal Statistician
ADRENOMED AG

Date

J. Reifenberger

Jenni Reifenberger
Statistical Analyst
M.A.R.C.O.

05 FEB 2020

Date

The undersigned have discussed the topics of this document and agree on the content.

Dr. Jens Zimmermann, M.D., M.Sc.
Chief Medical Officer
ADRENOMED AG

05-FEB-2020
Date

Dr. Oliver Hartmann
Senior Principal Statistician
ADRENOMED AG

Date

Jenni Reifenberger
Statistical Analyst
M.A.R.C.O.

05 FEB 2020
Date

The undersigned have discussed the topics of this document and agree on the content.

Dr. Jens Zimmermann, M.D., M.Sc.
Chief Medical Officer
ADRENOMED AG

Date

Dr. Oliver Hartmann
Senior Principal Statistician
ADRENOMED AG

6/2/2020
Date

Jenni Reifenberger
Statistical Analyst
M.A.R.C.O.

05 FEB 2020
Date

Table of contents

Listing of tables

Listing of abbreviations and definition of terms

ADM	Adrenomedullin
AE	Adverse event
AUC	Area under the curve
ATC	Anatomic therapeutic class
Bio-ADM	Biologically active Adrenomedullin, measured by Sphingotec bio-ADM assay
BLLOQ	Below lower limit of quantification
BMI	Body mass index
CCC	Clinical Coordinating Center for central evaluation
CL	Systemic clearance
C_{max}	Maximum concentration
CV	Coefficient of variation
DPP3	Dipeptidyl-Peptidase 3
ECG	Electrocardiogram
eCRF	Electronic case report form
FAS	Full analysis set
gCV	Geometric coefficient of variation
ICU	Intensive care unit
IMP	Investigational medicinal product
ITT	Intention-to-Treat
LLOQ	Lower limit of quantification
MAP	Mean arterial pressure
Max	Maximum
MedDRA	Medical dictionary for regulatory activities
Min	Minimum
N	Number of non-missing values
NLOQ	Number of values > lower limit of quantification
PCT	Procalcitonine
PK	Pharmacokinetic(s)
POD	Persistent organ dysfunction
PP	Per-protocol
PT	Preferred term
Q1	Lower quartile
Q3	Upper quartile
QoL	Quality of life
SAP	Statistical analysis plan
SD	Standard deviation
SOFA Score	Sequential Organ Failure Assessment Score
$t_{1/2}$	Elimination half-life
V	Volume of distribution

VAS	Visual Analogue Scale

1. Background and scope

As a general rule:
All text copied from the protocol is set in italics type in this statistical analysis plan (SAP).

This SAP is based on:

- trial protocol (version 4.1/version 4.2, 07 January 2019/28 August 2019)

This SAP covers:

- final statistical analysis of the study

The following accompanying documents are part of the SAP:

- Data review plan (AdrenOSS2_DRP)
- Table shells (AdrenOSS2_Table_shells)

An interim analysis was planned and conducted after 28-day follow-up of the first 150 patients was completed. The statistical analysis plan for the interim analysis is not covered in this SAP, but in a separate document.

2. Study objectives

Primary objective(s):

- *To investigate the safety and tolerability of ADRECIZUMAB in patients with early septic shock and elevated bio-ADM (concentration of > 70 pg/ml) in treatment arm A (2 mg/kg) and in treatment arm B (4 mg/kg) over the 90 days study period.*

Secondary objective(s):

- *To obtain first data on efficacy of ADRECIZUMAB in patients with early septic shock and a bio-ADM concentration of > 70 pg/mL in the treatment arms compared with placebo.*
- *To study the PK of free-ADRECIZUMAB with a focus on plasma accumulation and elimination.*

3. Study design

3.1. Main characteristics of study design

Number of centers: 30 centers in the European Union
Randomized: yes
Blinded: double-blind
Dosing: intravenous infusion (single i.v. dose) over approximately 1 hour
Placebo controlled: yes
Treatments: single i.v. dose of 2 mg/kg Adrecizumab (treatment arm A)
single i.v. dose of 4 mg/kg Adrecizumab (treatment arm B)
single i.v. dose of Placebo (control group)
Randomization ratio: 1:1:2 (treatment arm A : treatment arm B : control group)
PK profile days: Pre-dose
Day 1 (30 min ± 10 min)
Day 2 (24 hours ± 10 hours)
Day 3 (48 hours ± 10 hours)
Day 5 (96 hours ± 10 hours)
Day 7 (144 hours ± 10 hours)
Day 28 (648 hours ± 3 days)

Table 1 Treatment groups and sample sizes

Treatment	N
Treatment arm A: 2 mg/kg Adrecizumab	75
Treatment arm B: 4 mg/kg Adrecizumab	75
Control group: Placebo	150
Total (randomization ratio 1:1:2)	300

For a flow chart of planned study procedures, please refer to the study protocol.

3.2. Sample Size Determination / Power Analysis

If n=300 early septic shock patients are randomized 1:1 (we assume that both doses can be combined) to placebo and ADRECIZUMAB and assuming that delta SSI is >10%, the power is > 80% to demonstrate an improvement of delta SSI of > 0 with at least 80% probability. The lower bound of the confidence interval will be determined based on the non-parametric Wilcoxon test.

The probability of achieving our primary objective, i.e. that the delta SSI is > 0 with at least 80% probability, is 0.87 without interim analysis and 0.85 with the planned interim futility stop.

3.3. Hypotheses

The null-hypothesis is that there is no difference between the Adrecizumab group (both doses combined) and the Placebo group with regard to the primary efficacy endpoint SSI (14 days).
The alternative hypothesis is that the median difference ("delta SSI": Placebo minus Adrecizumab) is larger than zero.

Since confirmative testing is not intended in this phase II trial, a significance level has not been defined.

The study is judged to show a positive result if the lower bound of the two-sided non-parametric 60% confidence interval for delta SSI (Placebo – Adrecizumab) exceeds zero.

4. Patient population

The main inclusion criteria are defined as:

- *Written informed consent by patient or legally designated representative (according to country-specific regulations)*
- *Male and female patient, age ≥ 18 years*
- *Body weight 50 kg - 120 kg*
- *Bio-ADM concentration > 70 pg/ml*
- *Patient with early septic shock (start of vasopressor therapy < 12 hours)*
- *Women of childbearing potential must have a negative serum or urine pregnancy test before randomization*
- *Highly effective method of contraception must be maintained for 6 months after study start by women of childbearing potential and sexually active men*
- *No care limitation*

5. Endpoints for primary and secondary objectives and exploratory endpoints

5.1. Endpoints for primary objectives

Safety analysis:

The endpoints for the primary objective are to determine over the 90 days study period:

- *Mortality*
- *Interruption of infusion*
- *Severity and frequency of treatment-emergent adverse events*

5.2. Endpoints for secondary objectives

Efficacy analysis:

The primary efficacy endpoint of this study is the

- *Sepsis Support Index (SSI) defined as: days with organ support or dead within 14 day follow-up*
  More precisely: In the time frame of 14 day follow-up, each day on support with vasopressor and/or mechanical ventilation (defined as ventilation received on this day, independent from the duration of mechanical ventilation), and/or renal dysfunction (defined as renal SOFA = 4), or not alive, is counted as 1. The sum over the follow-up period is defined as SSI.

Secondary efficacy endpoints (exploratory) *include:*

- *Sepsis Support Index (SSI) at 28 day follow-up*
- *Penalized Sepsis Support Index (pSSI) at 14 and 28 day follow-up, defined similar to the SSI with the exception that patients who die get penalized by assigning the maximum value, i.e. the pSSI is set to 14 or 28, respectively*
- *Persistent organ dysfunction or death at 14 and 28 day follow-up*
- *Day 28 and day 90 mortality rate*
- *SSI and pSSI excluding renal component*
- SSI weighted for mortality
- *Individual Sepsis Support Index components (hemodynamic, respiratory and renal failure) with and without mortality*
- *Sequential Organ Failure Assessment (SOFA) Score*
  - *Mean/maximum/total daily SOFA score during stay at ICU*
  - *Delta SOFA score, defined as maximum versus minimum SOFA during ICU stay*
  - *Change in SOFA score within 48 hours*

- *SOFA-3 (score limited to cardiovascular, respiratory and renal function)*

- *Improvement in renal function as change in penKid and creatinine (day 3 – day 1, day 7 – day 1)*
- *Duration of stay at ICU/hospital*
- *Changes of functional parameters and other parameters during stay at ICU (MAP, creatinine, PaO2/FiO2, blood lactate, MP-pro ADM, inflammatory markers PCT, IL6, DPP3)*
- Fluid balance
- *Vasopressor use (drug, highest/lowest dose, duration)*
- *Quality of Life by Euro-QoL-5 (day 28 and day 90)*
- *Vital signs (heart rate, blood pressure)*

Endpoints for Pharmacokinetics:

In sub-study to determine key PK parameters, including:

- *peak plasma concentrations (C_{max})*
- time to C_{max} (t_{max})
- *systemic exposure (AUC)*
- *volume of distribution (V)*
- *systemic clearance (CL)*
- *elimination half-life ($t_{1/2}$)*

5.3. Exploratory endpoints

Not applicable.

6. General conventions

6.1. Treatment groups

If not otherwise specified, the following treatment groups will be considered for analysis where applicable and meaningful:

- Adrecizumab 2 mg/kg
- Adrecizumab 4 mg/kg
- Adrecizumab overall (i.e. both Adrecizumab doses)
- Placebo
- Total (i.e. both Adrecizumab doses and Placebo)

6.2. Layout of tables

For numbering of tables, listings and figures, please refer to section 11. Nevertheless, in order to facilitate programming, this numbering might be slightly changed in the final outputs.

Table 2 Layout of tables

Issue	Specification
Basic layout of end-of-text tables and listings (header, footnote)	Titles for all tables, figures, listings: • Study: AdrenOSS-2 (ADR-02) Footnotes for all tables, figures, listings include: • Program: xxx.sas • Generation date: DDMMMYYYY • Page X of Y
Font and font size for end-of-text tables and listings	Arial 9 for Tables/Graphs Arial 8 or 9 for Listings Titles in bold and using Arial 10 for Tables and Graphs / Arial 9 or 10 for listings.
Text (Title, footnotes, organizational variables and column headers, contents of table)	Case-sensitive, the first letter should be capitalized
Subject or Patient as label?	Patient
Patient identification numbers	SUBJID (as recorded in eCRF)
Categorical Variables	Display of all possible categories (even if a category is not present in the data) In order to increase readability, large tables may also be presented with only the categories observed (e.g. frequency tables for adverse events by primary system organ class, preferred term and severity).

Issue	Specification
In case a category does not occur	Display absolute frequency as “0”
Display of percentages in tables:	Aligned by decimal point, one decimal place: • 20.3% • 9.3% • 0.0% • 100.0%
Display of units	Presentation case-sensitive and in square brackets, e.g. Concentration [mg/mL]

6.3. General calculation rules

Data will be listed with the observed number of decimal places. Summary statistics will be presented to the same number of decimal places as the observed data, apart from the means and medians (to one more decimal place), and standard deviations (two more decimal places). Calculated data and summary statistics of calculated data will be presented with an appropriate number of decimal places.

The complete set of summary statistics will be given in case that the number of patients is at least three. For one or two patients, summary statistics will only comprise minimum and maximum.

In case of replicate measurements (e. g. three determinations of a parameter at one planned time-point), means of these measurements will be calculated and will be used for summary statistics without any prior rounding.

Data from unscheduled assessments will only be listed and not presented in summary statistics.

Relative study times and dates will be calculated with respect to the start time and date of the administration of study drug.

Calculation of relative days from onset of adverse events:

The relative day for onset of an adverse event is calculated as “day of onset” minus “day of start of treatment”.

Duration of adverse events:

The duration of an adverse event (expressed in days) is calculated as “stop date” minus “start date” plus 1.

If parts of the start/stop date of an adverse event are missing (day, month, or year), the relative day for onset and/or the duration of the adverse event are not calculated.

In order to determine if an adverse event or the worsening of an adverse event is a treatment-emergent event, the following rules will be used as a worst case scenario:

- If the date (and time) of onset or change is completely known, the adverse event is considered as treatment-emergent, provided the day (and time) of onset or change is after or on the same day (and time) as first study treatment.
- If the time of onset or change is missing, but the day, month and year is known, the adverse event is considered as treatment-emergent, provided the day of onset or change is after or on the same day as first study treatment, unless other information (e.g. stop date/time) suggest otherwise.
- If the time and day of onset or change is missing, but the month and year is known, the adverse event is considered as treatment-emergent, provided the month of onset or change is after or in the same month as first study treatment, unless other information (e.g. stop date) suggest otherwise.
- If the time, day and month of onset or change is missing, but the year is known, the adverse event is considered as treatment-emergent, provided the year of onset or change is after or in the same year as first study treatment, unless other information (e.g. stop date) suggest otherwise.
- If the time and date of onset or change is completely missing, the adverse event is considered as treatment-emergent, unless other information (e.g. stop date) suggests otherwise.

Calculation of absolute changes from baseline:

- post-dose value - baseline value

Calculation of relative changes from baseline:

- (post-dose value - baseline value)/baseline value

Frequencies / percentages for qualitative data:

- Number of observations (frequency)
- Percent
  Percentages will be calculated as “frequencies” divided by the number of patients in the population the analysis is based on (i.e. this may include missing data in the denominator).

6.4. Descriptive statistics

Basic descriptive statistics for continuous data comprise:

- Number of observations (N)
- Arithmetic mean
- Standard deviation (SD)
- Minimum (Min)
- Lower quartile (Q1)
- Median
- Upper quartile (Q3)
- Maximum (Max)

Descriptive statistics for continuous variables assumed as log-normally distributed (e. g. PK parameters):

- Number of observations (N)
- Number of observations ≥ LLOQ (NLOQ)
- Arithmetic mean
- Arithmetic SD
- Arithmetic coefficient of variation (CV)
- Geometric mean
- Geometric SD
- Geometric CV(%) (gCV)
- Q1
- Median
- Q3
- Min
- Max

7. Analysis sets and data review criteria

7.1. Data sets for analysis

For the determination of patient populations, please refer to the data review plan and the data review protocol. A general definition of data sets for analysis will be:

Safety analysis set
The safety analysis set includes all patients who

- have received study medication.

Full analysis set (FAS) (based on intent-to-treat (ITT) principle)
The full analysis set includes all patients who

- have received study medication.

FAS analyses will be done based on the actual treatment (“as treated”).

Per-protocol (PP) analysis set
The per-protocol analysis set includes all patients who

- are part of the full analysis set
- did receive the study medication according to the protocol with minor deviations only (refer to the Data Review Plan for details)
- satisfy major entry criteria (refer to the Data Review Plan for details).

.

Pharmacokinetic analysis set (PKS)
The pharmacokinetic analysis set includes all patients who

- received at least one dose of study medication
- showed sufficient compliance concerning medication, i.e. received the full dose of study medication
- have sufficient concentration PK data to calculate reliable estimates of at least one PK parameter
- are without any protocol violation that would interfere with the interpretation of the PK data.

7.2. Protocol violations/data review

For an overview of checks for identification of protocol violations and data review, please refer to the data review plan.

8. Data analysis

8.1. Statistical software

Statistical analysis will be performed using SAS version 9.3 (or higher) on a Windows 7 (or higher) personal computer. The calculation of pharmacokinetic parameters will be performed with WinNonlin version 8.1.

8.2. Definitions, derived variables and handling of missing data

8.2.1. Definitions of time points / time windows

Baseline will be defined per parameter and will be the value/measurement at the following visits:

Parameter for	Visit
Demographics	Screening 1
Vital signs	Screening 2
ECG	Screening 2
Plasma bio-ADM concentration*	Screening 1
Local laboratory assessment	Screening 2
Arterial blood gas analysis	Screening 2
Biomarker	Day 1
SOFA score	Screening 2

* locally measured at study site

8.2.2. Derived variables

Extent of exposure:

Extent of exposure will be defined as total exposure in mg and calculated as:

$$total\ exposure\ [mg] = 20\ \frac{mg}{ml} * IMP\ volume\ [ml] * factor$$

where IMP volume is the body weight adjusted IMP volume before addition of NaCl and factor equals 1 for treatment group 4 mg/kg Adrecizumab and ½ for treatment group 2 mg/kg Adrecizumab. Total exposure will not be calculated for the Placebo treatment group.
In case of premature termination of the infusion, total exposure will additionally be multiplied by $\frac{volume\ administered\ [ml]}{50\ ml}$ in order to account for only partly administration of study drug.

Exposure per kg body weight will be calculated as:

$$Exposure\ per\ kg\ body\ weight\ \left[\frac{mg}{kg}\right] = \frac{total\ exposure\ [mg]}{body\ weight\ [kg]}$$

Body mass index (BMI):

$$BMI = \frac{Weight\ [kg]}{Height\ [m]^2}$$

Sepsis Support Index:

SSI is defined as days with organ support or dead within 14-day follow-up. Organ support days are defined as days with vasopressor, on mechanical ventilation (defined as any mechanical ventilation received on this day, independent from the duration of mechanical ventilation on this day), or need for renal organ support (defined as renal SOFA = 4 (creatinine concentration > 5 mg/dl or > 440 µmol/l or urine output < 200ml) due to expected heterogeneity in treatment for renal failure).

The SSI is calculated as follows: In the time frame of 14-day follow-up, each day on support with either vasopressor, and/or mechanical ventilation, and/or need for renal organ support, or not alive, is counted as 1. Patients discharged from the ICU are treated as not receiving any organ support for the days following discharge (unless the patient dies after discharge from ICU: then all days from death to the end of the follow-up period are counted as 1). The sum over the follow-up period is defined as SSI and ranges from 0 to 14.
SSI describes the effect of a given therapy in a pre-defined patient population with septic shock.

SSI calculation will be based on the eCRF entries for Sepsis Support Index (dataset XS). The date of death and the date of discharge from ICU will be derived from the dataset DS (disposition events) and information included for the calculation of the SSI.

Other versions of the SSI:

- A penalized version of the SSI (pSSI) is defined as above, but including a penalty for patients who die within 14 days: the pSSI is set to 14 for all deaths within 14-day follow-up.
- The individual SSI components will also be compared in the time frame of 14-day follow-up:
  - cardiac component (= sum of days on support with vasopressor)
  - respiratory component (= sum of days with mechanical ventilation)
  - renal failure component (= sum of days with creatinine concentration > 5 mg/dl or > 440 µmol/l or urine output > 200 ml)

- death component (= sum of days not alive)

For the cardiac, respiratory and renal failure component patients will only be considered if they survived the respective time period of 14 days.

- A SSI version excluding the renal component will also be evaluated separately in the time frame of 14-day follow-up, so each day on support with either vasopressor, and/or mechanical ventilation, or not alive will be counted as 1.
- A penalized version of the SSI excluding the renal component as defined above.
- A version of the SSI where mortality is given extra weight: Patients being alive during the 14 days' follow up will have an SSI ranging up to 14 (as defined above), while patients who died within that period will be assigned a score of "14 plus the number of days not being alive". Thus the weighted SSI score may range between zero and 28.

The SSI and all other versions of the SSI will also be analyzed for the 28-day follow-up in addition to the 14-day follow-up except for the SSI where mortality is given extra weight (this will only be calculated for the 14-day follow-up).

Persistent organ dysfunction (POD) or death:

A novel, composite outcome measure for critical care trials was defined by Heyland et al. (2011):
"We define POD as the persistence of organ dysfunction requiring life-sustaining technologies and it is present when a patient has an ongoing requirement for vasopressors, dialysis, or mechanical ventilation at the outcome assessment points."

Defining renal organ support as renal SOFA = 4 instead of dialysis, the assessed aspects for this endpoint are the same as for the SSI, but at a specific time point instead of within a period.

- Did the patient receive any vasopressor on the outcome assessment day?
- Was patient's creatinine concentration > 5 mg/dl or > 440 µmol/l or was the patient's urine output < 200 ml on the outcome assessment day?
- Did the patient receive mechanical ventilation on the outcome assessment day?
- Was the patient dead at the end of the outcome assessment day (or had the patient already died before)?

The outcome assessment time points will be day 14 and day 28. If one of the questions above is answered with 'Yes' at day 14 or day 28, respectively, the endpoint POD or death will be evaluated as 'Yes' for that patient. If all questions are answered with 'No' or if the patient had already been discharged from ICU, the endpoint will be evaluated as 'No' for that patient, unless the patient died after discharge from ICU.

Sequential Organ Failure Assessment (SOFA) Score:

The SOFA score will be evaluated daily for all patients over the entire stay on ICU (until day 28) or discharge (whatever comes first).

An overview for the determination of the SOFA score can be found Section 13.

For day 1, the last data prior to the treatment has to be used. For this baseline SOFA score only, the renal component will be based on creatinine only (and not on urine output).
In the calculation of the score, if multiple values are available within a 24-hour period, the worst value for each parameter will be used, i.e. values resulting in a higher SOFA score will be taken into account. Additionally, parameter values that fall between two scoring intervals will be rounded (e.g. creatinine values to one decimal place) prior to assignment to the categories.

Missing data will not be replaced, i.e. if a single missing value in one of the components occurs, the SOFA score will be set to missing.

Deceased patients will be assigned the maximum SOFA score of 24. In case the patient has been discharged from ICU, the SOFA score will be set to 0 for all days following.

For the cardiovascular system domain, in order to check for vasopressor therapy, the standardized term as allocated during the blinded data review meeting will be used.
In case dose information is missing for vasopressor therapy, a dose that would result in the highest SOFA score for the cardiovascular system domain will be assumed.

The change in SOFA score is defined as:

$$SOFA_{change} = SOFA_{48\ hours\ post\ admission\ (Visit\ 3)} - SOFA_{baseline}$$

The total SOFA score will be calculated as the sum of daily SOFA scores during the ICU stay for each patient (baseline SOFA will not be considered here).

The mean SOFA score is defined as the total SOFA score divided by the length of stay in the ICU with non-missing SOFA score. The mean score will also be limited to the first 7 days after admission.

The highest SOFA score recorded during the ICU stay will also be recorded. The delta-SOFA score is defined as the difference between the maximum and minimum SOFA score during ICU hospitalization. For these endpoints, the imputed SOFA value for deaths and transferred patients will not be used. Additionally, only non-missing scores will be taken into account in this context. Again, the baseline SOFA will not be considered here.

Similar to the full SOFA score, the SOFA-3 score, limited to the cardiovascular, respiratory and renal function, will be calculated including 48 h change, maximum, total, mean and delta (as defined for the full SOFA score).

Improvement in renal function:

Improvement in renal function will be determined by analyzing the change in creatinine and penKid at the visits as described below. The following changes will be analyzed for both parameters separately:

- Change from baseline to day 3 (i.e. “Visit 3”)
- Change from baseline to day 7 (i.e. “Visit 7”)

Missing data due to patient discharge or death will be replaced by carrying the last observation forward, in addition to the analysis using recorded data only.

Measurements will additionally be categorized at baseline and at day 3, respectively, as follows:

Parameter	Low	High
Creatinine [mg/dL]	≤ 1.2	> 1.2
penKid [pmol/L]	≤ 100	> 100

Patients discharged from ICU or dead will be grouped into the low and high-risk category, respectively.

Duration of stay at ICU/hospital:

The duration of stay at ICU will be calculated as:

$$Duration_{(ICU)} = \text{Date of discharge from ICU} - \text{Date of ICU admission} + 1$$

The duration of hospital stay will be calculated as:

$$Duration_{(hospital)} = \text{Date of discharge from ICU} - \text{Date of hospital admission} + 1$$

In case of missing values, no replacement will be performed.

Changes of functional parameters and other parameters during stay at ICU:

The change from baseline to the last observed (non-missing) value will be analyzed for the following parameters:

- MAP
- PaO_2/FiO_2
- Blood lactate
- MR-pro ADM
- PCT
- IL6
- DPP3

The last observed (non-missing) value for fluid balance (calculated as fluid input – fluid output and expressed as absolute value) will be analyzed. In addition, measurements for fluid balance will be categorized as follows:

Parameter	Low	High
Fluid balance [ml/day]	≤ 1000	> 1000

Vasopressor use:

Vasopressor use will be analyzed as frequency tables by drug (ATC code) and number of vasopressors used, highest and lowest dose (per ATC code) as well as mean duration of vasopressor use expressed as days and summarized by treatment group and ATC code using descriptive summary statistics. In case of ongoing vasopressor use, the end date will be replaced by the date of discharge from ICU or the date of death (whatever occurs first).
In case dose information of vasopressor use is given in different units, it will be converted to one common unit. The conversion factors are discussed during the blinded data review meeting.

Quality of Life by Euro-QoL-5:

Quality of Life will be measured by Euro-QoL-5 questionnaire and analyzed for discharge from ICU, follow-up day 28 and follow-up day 90, respectively.

In addition to the possible answers (i.e. level 1-5), the single dimensions will be dichotomized into ‘no problems’ (i.e. level 1) and ‘problems’ (i.e. level 2-5).

Change in quality of life expressed by visual analogue scale (VAS) will be defined as:

- VAS at discharge from ICU – VAS at day 90
- VAS at day 28 – VAS at day 90.

The VAS will be analyzed by treatment group and visit in addition to the changes as defined above.

Vital signs:

The change in vital signs (heart rate, systolic and diastolic blood pressure as well as MAP) will be analyzed for the visits as described below. The following changes will be analyzed for the mentioned parameters separately:

- Change from baseline to day 3
- Change from baseline to day 7

Missing data due to patient discharge or death will be replaced by carrying the last observation forward, in addition to the analysis using reported data only.

Measurements will additionally be categorized at baseline and at day 3, respectively, for MAP and heart rate as follows:

Parameter	Low	High
MAP [mmHg]	≤ 65	> 65
Heart rate [bpm]	≤ 100	> 100

Missing values for patients discharged from ICU or dead will be grouped into the low and high-risk category, respectively.

APACHE II score

For an overview of the single items for the derivation of the APACHE II score, please see Section 13.

The item ‘Temperature’ should be measured rectal according to the scoring table, but is only available as oral/tympanic in this study. Nevertheless, it will be used without applying a correction factor for this item.

The parameter A-a Gradient is needed to score the item 'Oxygenation'. As it was not recorded in this study, it will be derived as:

A-a $_{O2}$ Gradient = [(FiO_2) × (Atmospheric Pressure - H_2O Pressure) - ($PaCO_2$/0.8)] – PaO_2

The following reference values will be used to calculate the A-a $_{O2}$ Gradient:
Atmospheric pressure: 760 mmHg
H_2O pressure: 47 mmHg
$PaCO_2$: 40 mmHg

In case the calculation for the A-a $_{O2}$ Gradient results in a negative value, it will be set to 0.
The single item score for 'Serum creatinine' needs to be doubled for acute renal failure. In this context, all patients with 'Chronic Renal Disease' or 'Hemodialysis' marked 'Yes' on the medical history (non cardiovascular co-morbidities) page in the eCRF will be defined as no acute renal failure patients (i.e. the score will be doubled for all other patients).

For all parameters used to derive the APACHE II score, the value measured/determined at Screening will be used. Only in case this value is missing, the value of Day 1 will be taken into account irrespective of if it was measured/determined before or after IMP administration (as this sometimes is not obvious from the data recorded). This is justified by medical experience stating that values do not vary significantly within such a short time frame (around 24 hours).

Values that fall between two single item scores will be rounded to the number of decimals specified for the respective item and classified accordingly.

The APACHE II score ranges from 0 to 71.

<u>PaO_2/FiO_2 ratio</u>

The PaO_2/FiO_2 ratio as recorded in the eCRF will not be used in any analyses due to unclear unit information. It will be recalculated based on the recorded values for PaO_2 and FiO_2 as follows:

$$\frac{PaO_2}{FiO_2}[mmHg] = \frac{PaO_2\ [mmHg]}{\left(\frac{FiO_2\ [\%]}{100}\right)}$$

This applies to all visits where only a single value is recorded. No recalculation will be performed for visits where minimum and maximum values had to be documented. The (recalculated) value for the ratio will be set to missing in this case.

In case FiO_2 < 1 was recorded, this value will be multiplied by 100 to achieve % values, irrespectively of the unit provided by the sites.
PaO_2 values recorded in kPa will be multiplied by 7.5 in order to obtain values in mmHg.

8.2.3. Handling of missing values

If not already specified in section 8.2.2 for the single endpoints, the following rules for handling of missing values will be applied:

If the SSI is already well-defined despite missing data, i.e. the SSI contribution for a specific day is 1 despite a missing component (e.g. creatinine is missing, but patient received mechanical ventilation), it will not be treated as missing. However, all missing data within each component will be discussed during the blinded data review.

Other replacement of missing values will not be performed.

Data from patients who prematurely terminate the trial will be used to the maximum possible extent.

8.3. Sensitivity analyses

Sensitivity analyses will be performed for the following sub-populations of FAS:

a) exclusion of the first 2 patients from every center (according to the date of dosing)
b) inclusion of centers who had randomized at least 4 patients
c) inclusion of patients with a DPP3 concentration ≤ 70 ng/mL at baseline.

The following endpoints will be analyzed for these subgroups: SSI (follow-up until Day 14), mortality at Day 28 and Day 90 using FAS.

8.4. Disposition

An overview of all patients who entered the study, who were randomized and who completed the study will be provided by treatment group and overall. Reasons for all post-randomized discontinuations will be given by treatment group.
Furthermore, an overview of all patients who are in the different analysis sets will be provided by treatment group.

8.5. Demographic data and baseline characteristics

Demographic data and baseline characteristics will be summarized for the safety analysis set.

Demographic data and baseline characteristics

Summary statistics will be presented for age, weight, height, BMI, vital signs at screening (body temperature, heart rate, MAP, systolic and diastolic blood pressure, respiratory rate), creatinine, blood lactate, SOFA score, APACHE II score, bio-ADM concentration. Frequency tables for qualitative data (gender, ethnic origin, origin of sepsis, location before ICU admission) will be provided.

In order to check structural comparison of the three treatment groups, the Kruskal-Wallis test will be performed for continuous baseline characteristics.
Categorical variables will be compared using the Chi² test for contingency tables.

Medical history

Frequency tables of medical history data by treatment group will be provided using MedDRA coding (Version 22.1) and differentiating between past and ongoing diseases as well as between cardiovascular and non-cardiovascular co-morbidities and other medical history present at inclusion.

Prior and concomitant medications

Frequency tables for prior and/or concomitant medications will be presented by treatment group taking WHO classification into account. Prior medications are medications which started and ended prior to study drug administration. Concomitant medications are defined as all recorded medications not classified as prior medication.

Physical examination

Results of the physical examination (normal, clinically significant, clinically not significant) will be presented as frequency tables by treatment groups.

Diagnosis of early septic shock

MAP [mmHg] before and after fluid resuscitation, volume administered [ml] for fluid resuscitation and plasma bio-ADM concentration [pg/ml] will be analyzed in the context of diagnosis of early septic shock by descriptive summary statistics.
Refractoriness to fluid resuscitation (yes, no) will be presented using frequency tables.

8.6. Analysis of primary endpoints

The analyses of the endpoints for safety and tolerability will be performed on the safety analysis set.
All efficacy analyses will be performed on the full analysis set. In addition, analyses will be presented for the per-protocol set.

Severity and frequency of treatment-emergent adverse events:

The absolute number of treatment-emergent adverse events as well as the number of patients with treatment-emergent adverse events will be analyzed using frequency tables by treatment group. An analysis by Primary System Organ Class (SOC) and Preferred Term (PT) will be given as well. These frequencies will be given for all treatment-emergent adverse events as well as by severity grade (mild (grade 1), moderate (grade 2), severe (grades ≥ 3)).
95% confidence intervals will be calculated for adverse event incidences by treatment group applying the Clopper-Pearson method for each SOC and each PT.

Mortality:

All-cause mortality for 90-day follow-up will be evaluated using Kaplan-Meier plots comparing Adrecizumab (doses combined) vs. Placebo, and Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg vs. Placebo (each with log-rank test without adjustment).

In addition, frequency tables will be provided for all-cause mortality by treatment group. Separate tables will be provided for all-cause mortality during 28-day and 90-day follow-up.

Interruption of infusion:

The number of patients with at least one interruption of infusion as well as the number of interruptions will be analyzed using frequency tables. In case the infusion was stopped prematurely, this will be given as a separate category in the frequency tables.
The three treatment groups will be compared by the Chi² statistic with regard to the categories “complete infusion” and “infusion interrupted at least once or stopped prematurely”.

Sepsis Support Index (SSI) within 14 days:

The primary analysis for efficacy will be based on combining both Adrecizumab doses and comparing the treated groups versus the Placebo group and performed on the FAS. A second-line analysis will compare the two doses separately versus Placebo for differences in efficacy.

For the primary efficacy endpoint, a non-parametric 60% confidence interval will be calculated for the difference between Adrecizumab (doses combined) and Placebo using the Hodges-Lehmann estimator. Testing for differences between treatment groups will be performed by applying the Kolmogorov-Smirnov test. The empirical cumulative distribution functions will be graphically displayed.

The analysis described above will also be applied for comparing Adrecizumab 2 mg/kg vs. Placebo, and Adrecizumab 4 mg/kg vs. Placebo.

Summary statistics of the SSI by treatment group and histograms for each group will also be prepared.

8.7. Analysis of secondary endpoints

All efficacy analyses will be performed on the full analysis set. In addition, analyses will be presented for the per-protocol set.

Mortality:

All-cause mortality 28-day follow-up will be evaluated using Kaplan-Meier plots comparing Adrecizumab vs. Placebo and Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg vs. Placebo (each with log-rank test without adjustment).

An additional analysis will include Cox regression modelling concerning 28-days as well as 90-days mortality, uni- and multivariate, including covariates to adjust for potential confounders. Potential confounders comprise baseline characteristics with a p-value < 0.1 determined during the analyses for structural comparison of baseline characteristics.
If not otherwise specified, baseline values of the above mentioned covariates will be used and it will be assumed that covariates do not vary during follow-up time.

In this context, the following models with only one covariate will be fitted (SAS syntax):

```
PROC PHREG DATA=[…];
        CLASS treatment cat_var;
        MODEL days*survive(0) = treatment <cat_var or cont_var>;
RUN;
```

where days is the survival time in days, survive is the censoring variable with 0 indicating censoring, treatment is the treatment group (1= Adrecizumab, 0=Placebo), cat_var or cont_var is the respective categorical or continuous covariate.

The proportional hazards assumption will be checked graphically by plotting log(-log(S(t))) vs. t, i.e. by looking for parallelism with regard to treatment group and categorical covariates. The survival curve S(t) is estimated by the Kaplan-Meier method.

Multivariate modelling will include all covariates mentioned above as well as treatment:

```
PROC PHREG DATA=[…];
        CLASS treatment cat_vars;
        MODEL days*survive(0) = treatment all_vars;
RUN;
```

with treatment (1= Adrecizumab, 0=Placebo) and with all_vars representing all categorical and continuous variables mentioned above.

Other versions of the SSI:

The other versions of the SSI will be analyzed using the same methods and procedures as described for the primary efficacy endpoint.

Persistent organ dysfunction or death at 14- and 28-day follow-up:

This dichotomous endpoint will be analyzed via cross-tables (2 by 2) for Adrecizumab vs. Placebo including Chi² test. In addition, 2 by 3 tables for Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg vs. Placebo will be presented together with the results of a Cochran-Armitage test for trend.

SOFA score:

Descriptive summary statistics will be presented for the SOFA score and SOFA-3 score by time point as well as for the defined endpoints: $SOFA_{change}$, total score, mean score (over entire ICU stay), mean score (over first 7 days of ICU stay), maximum SOFA score during ICU stay, delta-SOFA score (the difference between the maximum and minimum SOFA score during ICU stay).

The Kruskal-Wallis test will be applied for the defined endpoints to compare Adrecizumab 2mg/kg vs. Adrecizumab 4 mg/kg vs. Placebo. Pairwise comparison (each Adrecizumab dose vs. Placebo) will be carried out using the Wilcoxon test.

Improvement in renal function:

Improvement in renal function will be analyzed using descriptive summary statistics. Analyses for absolute values as well as the changes as defined above will be presented in this context.

The following endpoints are considered:
Change in penKid (day 3 – day 1), change in penKid (day 7 – day 1),
Change in creatinine (day 3 – day 1), change in creatinine (day 7 – day 1)

The Kruskal-Wallis test will be applied for these endpoints to compare Adrecizumab 2mg/kg vs. Adrecizumab 4 mg/kg vs. Placebo. Pairwise comparison (each Adrecizumab dose vs. Placebo as well as Adrecizumab (combined doses) vs. Placebo) will be carried out using the Wilcoxon test.

Duration of stay in ICU/hospital:

The duration of stay in ICU as well as the duration of stay in hospital will be analyzed using descriptive summary statistics.
The Kruskal-Wallis test will be applied to compare Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg vs. Placebo. Pairwise comparison (each Adrecizumab dose vs. Placebo) will be carried out using the Wilcoxon test.

Changes of functional parameters and other parameters during stay at ICU:

MAP (minimum, maximum), creatinine, PaO2/FiO2 (minimum, maximum), blood lactate, fluid balance, bio-ADM, MR-proADM, PCT, IL6, penKid, DPP3, vr-hGH) will be evaluated using descriptive summary statistics by treatment group and time point (Day 1, Day 2, Day 3 etc.).

Vasopressor use:

Continuous variables for vasopressor use will be analyzed by descriptive summary statistics; categorical variables analyses will be carried out using frequency tables.

Quality of Life by Euro-Qol-5:

The VAS for Euro-Qol-5 will be analyzed by descriptive summary statistics. The change from discharge from ICU and from follow-up day 28 to the assessment at 90-day follow-up will also be analyzed by descriptive summary statistics.

The single dimensions of the questionnaire (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) will be presented using frequency tables for all possible answers.

Vital signs:

Vital signs as described in section 8.2.2 will be analyzed using descriptive summary statistics and frequency tables.

8.8. Pharmacokinetic data analyses

PK samples from 80 patients will be collected at designated sites participating in the PK sub-study.
The analyses of Adrecizumab plasma concentrations and derived PK parameters will be performed on the PKS.
The PK parameters will be analyzed by descriptive summary statistics.

8.8.1. Pharmacokinetic parameters

The following parameters will be determined from the individual plasma concentration-time profiles of Adrecizumab using noncompartmental methods based on actual relative sampling times:

Definitions of pharmacokinetic parameters

$AUC_{0\text{-last}}$	Systemic exposure, i.e. area under the observed concentration-time curve from time zero up to the last time point with quantifiable plasma concentration (t_{last}). The area will be calculated according to the linear up/log down trapezoidal rule.
$AUC_{0\text{-144h}}$	Area under the observed concentration-time curve from time zero up to 144 h. The area will be calculated according to the linear up/log down trapezoidal rule.
C_{max}	Observed maximum concentration
t_{max}	Observed time of maximum concentration C_{max}
C_{last}	Last observed concentration
t_{last}	Time of last observed concentration C_{last}
$t_{1/2}$	Terminal elimination half-life

CL	Systemic clearance
V	Volume of distribution

Single concentration data will be shown with the significant number of decimal places as provided by the analytical lab. Derived parameters, as far as they do not present single concentrations such as C_{max}, will be listed with an appropriate number of significant digits (at least 3).

Exposure parameters (C_{max} and $AUC_{0\text{-}last}$) will also be dose-normalized (i.e. divided by dose) for the investigation of dose-dependency.

8.8.2. Analysis of pharmacokinetic endpoints

Not applicable.

8.8.3. Descriptive pharmacokinetic analyses

The PK analysis will be performed for both active treatment groups.

The individual time courses of the plasma concentrations of Adrecizumab will be listed and summarized descriptively by treatment group and time point.
Summary statistics by time point will be calculated including only those samples which were taken according to the pre-defined sampling schedule, i.e.: 30 min ± 10 min, 24 h ± 10 h, 48 h ± 10 h, 96 h ± 10 h, 144 h ± 10 h, 28 d ± 3 d.

For the calculation of summary statistics a data point below the lower limit of quantification (LLOQ) will be substituted by an estimated value of half the lower limit of quantification (½ LLOQ). However, means, standard deviations and coefficients of variation at any time-point will only be calculated if at least 2/3 of the individual data had been measured and were above the lower limit of quantification. In tables showing mean values, where values below LLOQ are included in the calculation of mean values, these means will be marked.

Individual plasma concentration-time profiles will be plotted for Adrecizumab (up to 8 profiles in one plot) for each dose group considering all patients with available PK concentration data even if not included in the PKS using actual relative sampling times. Geometric means of Adrecizumab plasma concentrations including one SD range will be plotted for both active treatment groups in one plot (for PKS). Individual and geometric mean concentration versus time curves will be plotted using both linear and semi-logarithmic scaling.

Summary statistics will be calculated for each pharmacokinetic parameter by dose group based on PKS.

8.9. Pharmacodynamic data analyses

There are no study variables specifically classified as pharmacodynamics endpoints.

8.10. Evaluation of relationships between endpoints

The Cox regression model will be applied to investigate the effects of potential confounders on 90-days mortality. Details are described in Section 8.7.

8.11. Safety analysis

All safety analyses described below will be based on the Safety Analysis Set and will only be exploratory.

8.11.1. Extent of exposure

Total exposure [mg] and relative exposure [mg/kg] will be analyzed by descriptive summary statistics.

8.11.2. Adverse events

An overview over all adverse events (original term as well as SOC and PT) will be generated as patient data listings, including onset relative to start of treatment, duration, intensity, seriousness and relationship to the study drug, action taken and outcome.

The incidence of treatment-emergent adverse events as well as number of patients with treatment-emergent adverse events will be summarized by SOC, PT and relationship to the study drug (certain, probable/likely, possible, unlikely, unrelated) for all treatment groups.

Treatment emergent events are adverse events not present at baseline, or adverse events that worsened after start of treatment even if they were present at baseline.

Deaths and serious adverse events will be listed separately (if applicable).

8.11.3. Clinical laboratory

Complete listings for laboratory values (hematology, biochemistry) will be generated. Laboratory values outside the normal range will be marked.

Only values ≥ 0 will be included in statistical evaluations.

Results from laboratory tests will be summarized by treatment group and time point using descriptive summary statistics including changes from baseline. Since different local labs were involved in this trial with different normal ranges, the laboratory results will be standardized to the normal range prior to analysis, i.e. a value X will be transformed to:
Y = (X – LLN) / (ULN – LLN), where LLN and ULN denote lower limit of normal and upper limit of normal, respectively.
Extreme relative changes (for original laboratory values) from baseline to follow-up visits (post minus baseline) will be categorized as:
Maximum increase from baseline: (maximum value post – baseline) / baseline
≥ 1.5, ≥ 2.0
Maximum decrease from baseline: (baseline - minimum value post) / baseline
≥ 0.5
A frequency table by treatment will be generated for these categorized changes.

In addition, changes from “from within normal range to above normal range” will be evaluated and categorized as:
“changes to at least 1.5-time upper limit normal”, “changes to at least twice upper limit normal”.
A frequency table by treatment will be generated for these categorized changes from normal at baseline.

8.11.4. Vital signs and body temperature

Minimum and maximum values for vital signs assessed within one day will be analyzed using descriptive summary statistics (including changes from baseline) by treatment group and time point (Day 1, Day 2, Day 3 etc.), i.e. concerning body temperature, heart rate, systolic and diastolic blood pressure as well as respiratory rate and MAP.
Only values > 0 will be included in summary statistics.

8.11.5. ECG

Frequencies of overall interpretation (normal, abnormal and clinically not significant, abnormal and clinically significant) will be tabulated by treatment group and time point.

8.11.6. Biomarker

Biomarker results will be analyzed by descriptive summary statistics for the different scheduled determination time points as well as expressed as changes from baseline.

8.11.7. Other assessments

For all other safety data (e.g. echocardiography) listings will be generated.
Patient data listings will also be provided in case derived variables are used for analysis (e.g. for SSI score, SOC and PT for medical history terms or duration of adverse events). A detailed overview of listings to be provided in this context can be found in section 11.

9. Changes to the protocol

“SSI weighted for mortality” has been defined as additional secondary endpoint.

In addition, the Kolmogorov-Smirnov test will be performed for the primary efficacy endpoint.

10. Changes to the SAP after finalization

Not applicable.

11. Contents of statistical tables and figures

			14 Tables and figures referred to but not included in the text
			14.1 Demographic data and general study information
*	Table	14.1-1	Overview of patients
	Table	14.1-2	Reasons for post-randomized discontinuations
*	Table	14.1-3	Patients in the different analysis sets
	Listing	14.1-4	Patients in the different analysis sets
*	Table	14.1-5	Demographic data (descriptive summary statistics)
	Table	14.1-6	Structural comparison of baseline characteristics (continuous variables)
*	Table	14.1-7	Demographic data (frequency tables)
	Table	14.1-8	Structural comparison of baseline characteristics (categorical variables)
	Table	14.1-9	Medical history (frequency tables)
	Listing	14.1.10	Overview of medical history
	Table	14.1-11	Prior and concomitant medications (frequency tables)
	Listing	14.1.12	Overview of prior and concomitant medications
	Table	14.1-13	Physical examination (frequency tables)
	Table	14.1-14	Diagnosis of early septic shock (descriptive summary statistics)
	Table	14.1-15	Diagnosis of early septic shock (frequency tables)
			14.2 Analysis of primary and secondary endpoints
			14.2.1 Analysis of primary endpoints
			14.2.1.1 Mortality
*	Figure	14.2.1.1-1	Kaplan-Meier plot for 90-day follow-up by treatment group (Placebo vs. Adrecizumab)
*	Figure	14.2.1.1-2	Kaplan-Meier plot for 90-day follow-up by treatment group (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)
			14.2.1.2 Interruption of infusion
	Table	14.2.1.2-1	Frequencies for interruption of infusion
	Table	14.2.1.2-2	Comparison of treatment groups for interruption of infusion
			14.2.1.3 Severity and frequency of treatment-emergent adverse events
	Table	14.2.1.3-1	Frequencies for treatment-emergent adverse events by SOC, PT and severity
	Table	14.2.1.3-2	Clopper-Pearson confidence interval for treatment-emergent adverse events
			14.2.1.4 Sepsis Support Index (SSI) within 14 days
	Listing	14.2.1.4-1	Sepsis Support Index (incl. different variations of SSI)
*	Table	14.2.1.4-2	SSI evaluation (incl. different variations of SSI)
*	Table	14.2.1.4-3	Descriptive summary statistics for SSI within 14 days

*	Figure	14.2.1.4-4	Histogram for SSI within 14 days (Placebo vs. Adrecizumab)
*	Figure	14.2.1.4-5	Histogram for SSI within 14 days (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)
			14.2.2 Analysis of secondary endpoints
			14.2.2.1 Mortality
*	Figure	14.2.2.1-1	Kaplan-Meier plot for 28-day follow-up by treatment group (Placebo vs. Adrecizumab)
*	Figure	14.2.2.1-2	Kaplan-Meier plot for 28-day follow-up by treatment group (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)
	Table	14.2.2.1-3	Cox regression
			14.2.2.2 Other versions of the SSI
	Table	14.2.2.2-1	Descriptive summary statistics for SSI within 28 days
	Figure	14.2.2.2-2	Histogram for SSI within 28 days (Placebo vs. Adrecizumab)
	Figure	14.2.2.2-3	Histogram for SSI within 28 days (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)
*	Table	14.2.2.2-4	Descriptive summary statistics for pSSI within 14 days
*	Figure	14.2.2.2-5	Histogram for pSSI within 14 days (Placebo vs. Adrecizumab)
*	Figure	14.2.2.2-6	Histogram for pSSI within 14 days (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)
	Table	14.2.2.2-7	Descriptive summary statistics for pSSI within 28 days
	Figure	14.2.2.2-8	Histogram for pSSI within 28 days (Placebo vs. Adrecizumab)
	Figure	14.2.2.2-9	Histogram for pSSI within 28 days (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)
*	Table	14.2.2.2-10	Descriptive summary statistics for SSI cardiac component within 14 days
*	Figure	14.2.2.2-11	Histogram for SSI cardiac component within 14 days (Placebo vs. Adrecizumab)
*	Figure	14.2.2.2-12	Histogram for SSI cardiac component within 14 days (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)
	Table	14.2.2.2-13	Descriptive summary statistics for SSI cardiac component within 28 days
	Figure	14.2.2.2-14	Histogram for SSI cardiac component within 28 days (Placebo vs. Adrecizumab)
	Figure	14.2.2.2-15	Histogram for SSI cardiac component within 28 days (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)
*	Table	14.2.2.2-16	Descriptive summary statistics for SSI respiratory component within 14 days
*	Figure	14.2.2.2-17	Histogram for SSI respiratory component within 14 days (Placebo vs. Adrecizumab)
*	Figure	14.2.2.2-18	Histogram for SSI respiratory component within 14 days (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)
	Table	14.2.2.2-19	Descriptive summary statistics for SSI respiratory component within 28 days
	Figure	14.2.2.2-20	Histogram for SSI respiratory component within 28 days (Placebo vs. Adrecizumab)

	Figure	14.2.2.2-21	Histogram for SSI respiratory component within 28 days (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)
*	Table	14.2.2.2-22	Descriptive summary statistics for SSI renal failure component within 14 days
*	Figure	14.2.2.2-23	Histogram for SSI renal failure component within 14 days (Placebo vs. Adrecizumab)
*	Figure	14.2.2.2-24	Histogram for SSI renal failure component within 14 days (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)
	Table	14.2.2.2-25	Descriptive summary statistics for SSI renal failure component within 28 days
	Figure	14.2.2.2-26	Histogram for SSI renal failure component within 28 days (Placebo vs. Adrecizumab)
	Figure	14.2.2.2-27	Histogram for SSI renal failure component within 28 days (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)
*	Table	14.2.2.2-28	Descriptive summary statistics for SSI death component within 14 days
*	Figure	14.2.2.2-29	Histogram for SSI death component within 14 days (Placebo vs. Adrecizumab)
*	Figure	14.2.2.2-30	Histogram for SSI death component within 14 days (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)
	Table	14.2.2.2-31	Descriptive summary statistics for SSI death component within 28 days
	Figure	14.2.2.2-32	Histogram for SSI death component within 28 days (Placebo vs. Adrecizumab)
	Figure	14.2.2.2-33	Histogram for SSI death component within 28 days (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)
*	Table	14.2.2.2-34	Descriptive summary statistics for SSI within 14 days excl. renal component
*	Figure	14.2.2.2-35	Histogram for SSI within 14 days excl. renal component (Placebo vs. Adrecizumab)
*	Figure	14.2.2.2-36	Histogram for SSI within 14 days excl. renal component (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)
	Table	14.2.2.2-37	Descriptive summary statistics for SSI within 28 days excl. renal component
	Figure	14.2.2.2-38	Histogram for SSI within 28 days excl. renal component (Placebo vs. Adrecizumab)
	Figure	14.2.2.2-39	Histogram for SSI within 28 days excl. renal component (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)
*	Table	14.2.2.2-40	Descriptive summary statistics for pSSI within 14 days excl. renal component
*	Figure	14.2.2.2-41	Histogram for pSSI within 14 days excl. renal component (Placebo vs. Adrecizumab)
*	Figure	14.2.2.2-42	Histogram for pSSI within 14 days excl. renal component (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)
	Table	14.2.2.2-43	Descriptive summary statistics for pSSI within 28 days excl. renal component

	Figure	14.2.2.2-44	Histogram for pSSI within 28 days excl. renal component (Placebo vs. Adrecizumab)
	Figure	14.2.2.2-45	Histogram for pSSI within 28 days excl. renal component (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)
*	Table	14.2.2.2-46	Descriptive summary statistics for SSI within 14 days where mortality is given extra weight
*	Figure	14.2.2.2-47	Histogram for SSI within 14 days where mortality is given extra weight (Placebo vs. Adrecizumab)
*	Figure	14.2.2.2-48	Histogram for SSI within 14 days where mortality is given extra weight (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)
			14.2.2.3 Persistent organ dysfunction or death at 14- and 28-day follow-up
	Table	14.2.2.3-1	Persistent organ dysfunction or death (Placebo vs. Adrecizumab)
	Table	14.2.2.3-2	Persistent organ dysfunction or death (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)
			14.2.2.4 SOFA score
	Table	14.2.2.4-1	Descriptive summary statistics for SOFA score
	Table	14.2.2.4-2	Descriptive summary statistics for SOFA-3 score
			14.2.2.5 Improvement in renal function
	Table	14.2.2.5-1	Descriptive summary statistics for improvement in renal function
	Table	14.2.2.5-2	Frequency tables for improvement in renal function
			14.2.2.6 Duration of stay in ICU/hospital
	Table	14.2.2.6-1	Descriptive summary statistics for stay in ICU/hospital
			14.2.2.7 Changes of functional parameters and other parameters during stay at ICU
	Table	14.2.2.7-1	Descriptive summary statistics for functional and other parameters during stay at ICU
	Table	14.2.2.7-2	Frequencies tables for fluid balance
			14.2.2.8 Vasopressor use
	Table	14.2.2.8-1	Frequency tables for vasopressor use
	Table	14.2.2.8-2	Descriptive summary statistics for vasopressor use
			14.2.2.9 Quality of Life by Euro-Qol-5
	Table	14.2.2.9-1	Frequency tables for quality of life (single dimensions)
	Table	14.2.2.9-2	Frequency tables for quality of life (dichotomized single dimensions)
	Table	14.2.2.9-3	Descriptive summary statistics for quality of life (VAS)
			14.2.2.10 Vital signs
	Table	14.2.2.10-1	Descriptive summary statistics for vital signs
	Table	14.2.2.10-2	Frequency tables for vital signs
			14.3 Safety analysis
			14.3.1 Extent of exposure

	Table	14.3.1-1	Descriptive summary statistics for extent of exposure
			14.3.2 Adverse events
	Table	14.3.2-1	Frequencies for adverse events
	Table	14.3.2-2	Frequencies for treatment-emergent adverse events by SOC, PT and causality
	Listing	14.3.2-3	Overview of adverse events
	Listing	14.3.2-4	Deaths and serious adverse events
			14.3.3 Clinical laboratory
	Table	14.3.3-1	Descriptive summary statistics for laboratory values
	Listing	14.3.3-2	Overview of laboratory values
			14.3.4 Vital signs
	Table	14.3.4-1	Descriptive summary statistics for vital signs
			14.3.5 ECG
	Table	14.3.5-1	Frequency tables for ECG overall interpretation
			14.3.6 Biomarker
	Table	14.3.6-1	Descriptive summary statistics for biomarker results
			14.3.7 Other safety assessments
	Listing	14.3.7-1	Echocardiography
	Listing	14.3.7-2	Pregnancy test
	Listing	14.3.7-3	Arterial blood collection
	Listing	14.3.7-4	Assessments for APACHE II score
	Listing	14.3.7-5	Assessment for evaluation of organ dysfunction (SOFA score)
	Listing	14.3.7-6	Daily fluid balance
	Listing	14.3.7-7	Vasopressor therapy
			14.4 Pharmacokinetic data analysis
	Table	14.4-1	Descriptive summary statistics for PK parameters
	Table	14.4-2	Frequency tables for PK parameters
	Listing	14.4-3	Individual time courses of Adrecizumab
	Figure	14.4-4	Individual time courses for 2 mg/kg Adrecizumab (linear scale)
	Figure	14.4-5	Individual time courses for 4 mg/kg Adrecizumab (linear scale)
	Figure	14.4-6	Individual time courses for 2 mg/kg Adrecizumab (semi-log. scale)
	Figure	14.4-7	Individual time courses for 4 mg/kg Adrecizumab (semi-log. scale)
	Figure	14.4-8	Geometric means of Adrecizumab (linear scale)
	Figure	14.4-9	Geometric means of Adrecizumab (semi-log. scale)
			14.5 Sensitivity analyses
			14.5.1 SSI within 14 days
	Table	14.5.1-1	SSI evaluation
	Table	14.5.1-2	Descriptive summary statistics for SSI within 14 days
	Figure	14.5.1-3	Histogram for SSI within 14 days (Placebo vs. Adrecizumab)
	Figure	14.5.1-4	Histogram for SSI within 14 days (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)

			14.5.2 Mortality
	Figure	14.5.2-1	Kaplan-Meier plot for 90-day follow-up by treatment group (Placebo vs. Adrecizumab)
	Figure	14.5.2-2	Kaplan-Meier plot for 90-day follow-up by treatment group (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)
	Figure	14.5.2-3	Kaplan-Meier plot for 28-day follow-up by treatment group (Placebo vs. Adrecizumab)
	Figure	14.5.2-4	Kaplan-Meier plot for 28-day follow-up by treatment group (Placebo vs. Adrecizumab 2 mg/kg vs. Adrecizumab 4 mg/kg)

* will be provided in the context of topline analysis

12. Contents of appendices

16 Appendices

16.1.9 Documentation of statistical methods
16.1.9-1 Non-parametric Wilcoxon test for SSI within 14 days
16.1.9-2 Non-parametric Wilcoxon test for SSI within 28 days
16.1.9-3 Non-parametric Wilcoxon test for pSSI within 14 days
16.1.9-4 Non-parametric Wilcoxon test for pSSI within 28 days
16.1.9-5 Non-parametric Wilcoxon test for SSI cardiac component within 14 days
16.1.9-6 Non-parametric Wilcoxon test for SSI cardiac component within 28 days
16.1.9-7 Non-parametric Wilcoxon test for SSI respiratory component within 14 days
16.1.9-8 Non-parametric Wilcoxon test for SSI respiratory component within 28 days
16.1.9-9 Non-parametric Wilcoxon test for SSI renal failure component within 14 days
16.1.9-10 Non-parametric Wilcoxon test for SSI renal failure component within 28 days
16.1.9-11 Non-parametric Wilcoxon test for SSI death component within 14 days
16.1.9-12 Non-parametric Wilcoxon test for SSI death component within 28 days
16.1.9-13 Non-parametric Wilcoxon test for SSI within 14 days excl. renal component
16.1.9-14 Non-parametric Wilcoxon test for SSI within 28 days excl. renal component
16.1.9-15 Non-parametric Wilcoxon test for pSSI within 14 days excl. renal component
16.1.9-16 Non-parametric Wilcoxon test for pSSI within 28 days excl. renal component
16.1.9-17 Non-parametric Wilcoxon test for SSI within 14 days where mortality is given extra weight
16.1.9-18 Cox regression for day 28 mortality
16.1.9-19 Cox regression for day 90 mortality

16.2 Patient data listings

Raw data listings will be generated and numbered appropriately.

13. Definition of Scores

13.1. SOFA Score

SOFA Score		0	1	2	3	4
Organ system	**Parameter**					
Respiratory system	PaO_2 / FiO_2 (mmHg)	≥ 400	< 400	< 300	< 200 **and** mechanically ventilated	< 100 **and** mechanically ventilated
Nervous system	Glasgow Coma Scale	15	13 to 14	10 to 12	6 to 9	< 6
Cardiovascular system	Mean arterial pressure OR administration of vasoactive agents required	No hypotension	MAP < 70 mmHg	dopamine ≤ 5 µg/kg/min or dobutamine (any dose)	dopamine > 5 µg/kg/min OR epinephrine ≤ 0.1 µg/kg/min OR norepinephrine ≤ 0.1 µg/kg/min	dopamine > 15 µg/kg/min OR epinephrine > 0.1 µg/kg/min OR norepinephrine > 0.1 µg/kg/min
Liver	Bilirubin (mg/dL) [µmol/L]	< 1.2 [< 20]	1.2 to 1.9 [20 to 32]	2.0 to 5.9 [33 to 101]	6.0 to 11.9 [102 to 204]	≥ 12.0 [> 204]
Coagulation	Platelets $x10^3$/µl	≥ 150	100 to < 150	50 to < 100	20 to < 50	< 20
Kidneys	Creatinine (mg/dL) [µmol/l] or urine output	< 1.2 [< 110]	1.2 to 1.9 [110 to 170]	2.0 to 3.4 [171 to 299]	3.5 to 4.9 [300 to 440] or urine output < 500 ml/day	≥ 5.0 [> 440] or urine output < 200 ml/day

13.2. APACHE II Score

A. Total Acute Physiology Score (sum of points for the 12 variables below)

	Physiologic Variable	High Abnormal Range					Low Abnormal Range			
		+4	+3	+2	+1	0	+1	+2	+3	+4
1	Temperature – rectal (°C)	≥ 41	39 to < 41		38.5 to < 39	36 to < 38.5	34 to < 36	32 to < 34	30 to < 32	<30
2	Mean Arterial Pressure (mmHg)	> 159	> 129 to 159	> 109 to 129		> 69 to 109		> 49 to 69		≤ 49
3	Heart Rate (bpm)	≥ 180	140 to < 180	110 to < 140		70 to < 110		55 to < 70	40 to < 55	< 40
4	Respiratory Rate (breaths/min)	≥ 50	35 to < 50		25 to < 35	12 to < 25	10 to < 12	6 to < 10		< 6
5	Oxygenation:									
	if FiO_2 < 50% record PaO_2					> 70	61 to 70		55 to 60	< 55
	otherwise use A-a gradient	> 499	350 to 499	200 to 349		< 200				
6	Arterial pH (preferred)	≥ 7.7	7.6 to < 7.7		7.5 to < 7.6	7.33 to < 7.5		7.25 to < 7.33	7.15 to < 7.25	< 7.15
7	Serum Sodium (mmol/L)	≥ 180	160 to < 180	155 to < 160	150 to < 155	130 to < 150		120 to < 130	111 to < 120	< 111
8	Serum Potassium (mmol/L)	≥ 7	6 to < 7		5.5 to < 6	3.5 to < 5.5	3 to < 3.5	2.5 to < 3		< 2.5
9	Serum creatinine (mg/dl) *double point score for acute renal failure	≥ 3.5 *	2 to < 3.5 *	1.5 to < 2 *		0.6 to < 1.5		< 0.6		
10	Hematocrit (%)	≥ 60		50 to < 60	46 to < 50	30 to < 46		20 to < 30		< 20
11	White Blood Count (total/mm^3 in 1000s)	≥ 40		20 to < 40	15 to < 20	3 to < 15		1 to < 3		< 1
12	Glasgow Coma Scale (GCS)	15 – GCS Score								

B. Age points

Age (years)	Points
≤ 44	0
45 – 54	2
55 – 64	3
65 -74	5
≥ 75	6

C. Chronic Health Points

If the patient has a history of severe organ system insufficiency or is immunocompromised as defined below, assign points as follows:
5 points for nonoperative or emergency postoperative patients
2 points for elective postoperative patients

Definitions: The following defines "chronic organ insufficiency" and immunocompromised:

- **Liver insufficiency –** biopsy proven cirrhosis, documented portal hypertension, episodes of past upper GI bleeding attributed to portal hypertension, prior episodes of hepatic failure/encephalopathy/coma
- **Cardiovascular –** New York Heart Association Class IV Heart Failure
- **Respiratory –** Chronic restrictive, obstructive or vascular disease resulting in severe exercise restriction (i.e., unable to climb stairs or perform household duties), documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (> 40 mmHg), respirator dependency
- **Renal –** receiving chronic dialysis
- **Immunosuppression –** the patient has received therapy that suppresses resistance to infection (e.g., immunosuppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukemia, lymphoma, AIDS)

Total APACHE II Score: add together the points from A, B and C

14. References

[1] Heyland et al.; Persistent organ dysfunction plus death: a novel, composite outcome measure for critical care trials. Critical Care 2011, 15

[2] https://www.mdcalc.com/sequential-organ-failure-assessment-sofa-score#next-steps
(last checked 27-NOV-2019)

[3] https://www.mdcalc.com/apache-ii-score#evidence
(last checked 27-NOV-2019)