TRIAL PROTOCOL

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
Protocol Version / Date:	Final 4.2 / 28-Aug-2019
Protocol No.:	ADR-02
EudraCT-No:	2016-003883-38
NCT:	NCT03085758

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Short Title:	Treatment of patients with septic shock and bio-ADM concentration > 70 pg/mL with ADRECIZUMAB
Protocol Code:	AdrenOSS-2
Protocol No.:	**ADR-02**
EudraCT No.:	2016-003883-38
Protocol Version / Date:	Final 4.2 / 28-Aug-19
Sponsor:	ADRENOMED AG Neuendorfstr. 15a 16761 Hennigsdorf Germany
Emergency Phone No.:	**++49 (0) 17623781763**

This clinical trial will be conducted in accordance with the International Council for Harmonization Good Clinical Practices Guideline

1. TABLE OF CONTENTS

1.1 List of Abbreviations

ADM	Adrenomedullin
AE	Adverse Event
AESIs	Adverse Event of Special Interest
Bio ADM	Biologically active Adrenomedullin, measured by Sphingotec bio-ADM assay
BGA	Blood Gas Analysis
cAMP	cyclic Adenosine Monophosphate
CA	Competent Authority
CCC	Clinical Coordinating Center
CHF	Chronic Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
CRO	Clinical Research Organization
CS	Clinically Significant
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EU	European Union
GCS	Glasgow Coma Scale
GCP	Good Clinical Practice
hCRLR	human Calcitonin Receptor-Like Receptor
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IL6	Interleukin 6
ILMA	Immuno LuminoMetric Assay
IMP	Investigational Medicinal Product
IRB	Institutional Review Board

LPS	Lipopolysaccharide
MAP	Mean Arterial Pressure
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
MR-proADM	Mid-Regional pro-Adrenomedullin
NOAEL	Non Observed Adverse Event Level
PaO2/FiO2	Horowitz Index
PCT	Procalcitonine
penKid	Sphingotec penKid – a novel biomarker for kidney dysfunction
PK	Pharmacokinetic
pSSI	penalized Sepsis Support Index
RAMP3	Receptor Activity Modifying Protein 3
SAE	Serious Adverse Event
SC	Steering Committee
SEM	Stand Error Mean
SOFA Score	Sequential Organ Failure Assessment Score
SSI	Sepsis Support Index
SUSAR	Suspected Unexpected Serious Adverse Reaction

2. PROTOCOL SYNOPSIS

2.1 Protocol Summary

Full 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
Protocol Code:	AdrenOSS-2
Protocol Number:	ADR-02
Phase:	Clinical Trial Phase II – Proof of Concept
Study Centers:	Multicenter study conducted in the European Union
Indication:	Patients with early septic shock and an elevated bio-adrenomedullin (concentration > 70 pg/ml)
Study Objectives:	**Primary Objective:** 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
Sample Size:	300 randomized patients Randomization 1:1:2 to the following treatment arms and placebo (control group): • Treatment arm A: 2 mg/kg (75 evaluable patients) • Treatment arm B: 4 mg/kg (75 evaluable patients) • Control group: Placebo (150 evaluable patients)

Duration of Treatment / Dosing:	Intravenous infusion over approximately 1 hour Single i.v. dose of 2 mg/kg (treatment arm A) Single i.v. dose of 4 mg/kg (treatment arm B) Single i.v. dose of placebo (control group)
Subject Enrollment Period:	24 months
Study Duration per Patient:	The total study duration for primary efficacy endpoint is 14 days, for safety up to 90 days: • Treatment period: single dose as i.v. infusion over approximately 1 hour • Follow-up period: Until 90 days after end of infusion.
Inclusion Criteria:	1. Written informed consent by patient or legally designated representative (according to country – specific regulations) 2. Male and female patient, age ≥ 18 years 3. Body weight 50 kg – 120 kg 4. Bio-ADM concentration > 70 pg/ml 5. Patient with early septic shock (start of vasopressor therapy < 12 hours) 6. Women of childbearing potential must have a negative serum or urine pregnancy test before randomization 7. Highly effective method of contraception must be maintained for 6 months after study start by women of childbearing potential and sexually active men. 8. No care limitation
Exclusion Criteria:	1. Moribund 2. Pre-existing unstable condition (e.g. a recent cerebral hemorrhage or infarct, a recent acute unstable myocardial infarction (all < 3 months), congestive heart failure – NYHA Class IV) 3. Patients that required cardiopulmonary resuscitation in the last 4 weeks prior to evaluation for enrollment 4. Severe COPD with chronic oxygen need at home (GOLD IV) 5. Any organ or bone marrow transplant within the past 24 weeks 6. Uncontrolled serious hemorrhage (≥ 2 units of blood / platelets in the previous 24 hrs.). Patients may be considered for enrollment if bleeding has stopped and patient is otherwise qualified 7. Uncontrolled hematological / oncological malignancies 8. Absolute neutropenia < 500 per µL) 9. Severe chronic liver disease (Child-Pugh C) 10. Systemic fungal infection or active tuberculosis 11. Neuromuscular disorders that impact breathing / spontaneous ventilation 12. Burns > 30% of body surface 13. Plasmapheresis 14. Breastfeeding women 15. Participation in a clinical trial involving another investigational drug within 4 weeks prior to inclusion 16. Unwilling or unable to be fully evaluated for all follow-up visits

Trial Design:	This is a double-blind, placebo-controlled, randomized, multicenter proof of concept and dose-finding phase II study using two doses of ADRECIZUMAB in patients with early septic shock and a bio-ADM plasma concentration at admission of > 70 pg/ml. "***Early" septic shock*** is defined as a life-threatening organ dysfunction due to dysregulated host response to a proven or suspected infection which leads to a decline of MAP < 65 mmHg, which is refractory to fluid resuscitation and requires vasopressors. Early is defined as a maximum of less than 12 hours between onset of the cardiovascular organ-dysfunction and administration of ADRECIZUMAB. Refractoriness to fluid resuscitation is defined as a lack of response to the administration of 30 mL of fluid per kilogram of body weight or is determined according to a clinician's assessment of inadequate hemodynamic results. It is intended to enroll 300 patients from surgical, medical and mixed ICU at multiple centers in Europe. All patients will be treated according to "International Guidelines for Management of Severe Sepsis and Septic Shock". Eligible patients (confirmed by central verification) will be randomized (1:1:2) to ADRECIZUMAB treatment arm A (2 mg/kg) or to ADRECIZUMAB treatment arm B (4 mg/kg) or to placebo as control group. Patients assigned to the treatment arm A or B will be administered a single dose of ADRECIZUMAB as intravenous infusion over approximately 1 hour; patients assigned to the control group will be administered placebo as intravenous infusion over approximately 1 hour. As long as the patients are on the ICU, measurements of clinical signs and laboratory data will be collected for safety reasons and for determination of SOFA score. Additional blood samples for central laboratory analyses will be taken prior to start of IMP infusion (day 1) and 24 hours, 48 hours, 96 hours and 144 hours after end of infusion (+/- 10 hours) or between scheduled assessments, if discharged earlier from the ICU ((whatever comes first) for measurement of biomarkers. The SOFA score and its components will be determined daily for all patients over the entire stay on the ICU (28 days or until discharge whatever comes first) as long as an arterial line is in place. Safety monitoring for each patient will begin at the time of signing the Informed Consent Form and continue for 90 days after end of short-term infusion of study medication. At selected study centers a PK substudy will be performed to determine the profile of ADRECIZUMAB in 80 randomized patients.

	An interim analysis for efficacy is planned after 50% of patients have completed the study day 28 (n=150).
Investigational Medicinal Product (IMP):	**Test Substance: ADRECIZUMAB** ADRECIZUMAB (HAM8101) is a humanized IgG1 mono-clonal antibody (mAb). Dosage form: Solution for injection in 200 mg vials Strength: 10,4 mL HAM8101 protein for an extractable volume of 10 mL Dose: 2 mg/kg single dose or 4 mg/kg single dose Route: i.v. infusion over approximately 1 hour Stored: 2 – 8 °C, protected from light (refrigerator) **Reference Substance: Placebo** Histidine-HCl and Glycine solution in water for injection. Route of administration corresponding to ADRECIZUMAB. Any study medication has to be diluted from the Drug Product Stock solution with sterile NaCl solution 0.9%.
Study Endpoints	**Endpoints for primary objective (safety and tolerability):** • Mortality • Interruption of infusion • Severity and frequency of treatment-emergent adverse events **Endpoints for secondary objectives (efficacy and PK):** • Primary efficacy endpoint: Sepsis Support Index (SSI) defined as: days with organ support or dead within 14 days 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 any 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: Sepsis Support Index (SSI) at day 28 follow-up - Penalized Sepsis Support Index (pSSI) at 14 and 28 day follow-up, defined similar to the SSI with the exception that patients that die get penalized by assigning the maximum value, i.e. the pSSI is set to 14 or 28 day respectively. - Persistent organ dysfunction or death at 14 and 28 day follow-up - Day 28 and day 90 mortality rate - SSI and pSSI excluding the renal component

	- Individual SSI components (hemodynamic, respiratory and renal failure) with and without mortality
	- Sequential Organ Failure Assessment (SOFA) Score
	  o Mean/maximum/total daily SOFA score during stay at ICU
	  o Change in SOFA score within 48 hours
	  o Delta SOFA score, defined as maximum versus minimum SOFA during ICU stay
	  o 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 and other parameters during stay at ICU (MAP, creatinine, PaO2/FiO2, blood lactate, fluid balance, MR-proADM, inflammatory markers PCT, IL-6)
	- 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 sub-study: determine key PK parameters, including
	- peak plasma concentrations (C_{max})
	- systemic exposure (AUC)
	- volume of distribution (V)
	- systemic clearance (CL)
	- elimination half-life ($t_{½}$)

Data and Safety Monitoring Board (DSMB):	The independent Data and Safety Monitoring Board will consist of two clinical experts in the field of sepsis, one statistician and one Pharmacovigilance representative. The DSMB will review and evaluate the safety data monthly during the course of the study and will recommend to the sponsor whether to continue, modify or terminate the study based on the mortality rate.
Steering Committee:	The SC will provide oversight of the conduct of the study to ensure that the study is conducted to the rigorous standards set out in Good Clinical Practice.
Statistical Methods:	A total sample size of 300 patients is needed for the study and assuming that delta SSI is >10%, the power is > 80% to demonstrate an improvement of 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. Power simulations are based on using real patient data on the combined endpoint from the ALBIOS study *[2]*. Simulations were extended to and results confirmed by data from the AdrenOSS observational study.

	An interim analysis with futility stop will be performed when 150 patients (n=150) have completed the study day 28. The study will be stopped if the probability of a positive outcome is below 40% once 50% of patients (n=150) completed study day 28. Power remains > 80% if futility stop is included in the simulation.

Figure 1 Study Flow Chart for Randomized Patients

Visit	Hospitalization and ICU											Follow-up	
	Pre-Treatment		Start of Treatment Day 1	2	3	4	5	6	7	8 - 27 or Discharge*	28	28 **	90 Phone Contact
	Screening	Eligibility Confirmation										+/- 3 days	
Written Informed Consent	X[1)]												
Retrospective Written Informed Consent	(X[2)])	(X[2)])	(X[2)])	(X[2)])	(X[2)])	(X[2)])	(X[2)])	(X[2)])	(X[2)])	(X[2)])	(X[2)])	(X[2)])	
Diagnosis of early septic shock	X												
Information on Hospital and ICU Admission	X[3)]												
Medical History	X[4)]												
Physical Examination	X												
Demography (includes body weight and height)	X												
Vital Signs	X[5)]		X[6)]	X[6)]	X[6)]	X[6)]	X[6)]	X[6)]	X[6)]	X[6)]	X[6)]	X[5)]	
Echocardiography (optional)	(X)												
ECG	X												
Plasma bio-ADM concentration	X[7)]												
Local Laboratory Assessment	X[8)]			X[9)]	X[9)]	X[9)]	X[9)]	X[9)]	X[9)]	X[10)]	X[9)]	X[9)]	
Arterial Blood Gas Analysis			X[11)]	X[12)]	X[12)]	X[12)]	X[12)]	X[12)]	X[12)]	X[12)]	X[12)]		
Pregnancy test (urine or serum)	X										X[13)]	X[13)]	
APACHE II	X												
Central Verification of Inclusion and Exclusion Criteria		X[14)]											
Randomization			X										
IMP administration			X[15)]										
Therapy of special interest (vasopressor)	X[16)]		X[17)]	X[17)]	X[17)]	X[17)]	X[17)]	X[17)]	X[17)]	X[17)]	X[17)]		
Cornerstone Medication and Concomitant Medication	X[18)]		X[18)]	X[18)]	X[18)]	X[18)]	X[18)]	X[18)]	X[18)]	X[18)]	X[18)]	X[18)]	
Fluid Balance				X[19)]	X[19)]	X[19)]	X[19)]	X[19)]	X[19)]	X[19)]	X[19)]		
Evaluation of Organ Dysfunction (SOFA)			X[20)]	X[21)]	X[21)]	X[21)]	X[21)]	X[21)]	X[21)]	X[21)]	X[21)]		
Blood Sampling for biomarkers			X[22)]	X	X	(X[23)])	X	(X[23)])	X				
PK Substudy			X[24)]	X	X	(X[25)])	X	(X[25)])	X		X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life by Euro-QoL-5				X[26)]	X[26)]	X[26)]	X[26)]	X[26)]	X[26)]	X[26)]	X[26)]	X	X[27)]

* (whatever comes first)
** For all patients discharged prior to day 28

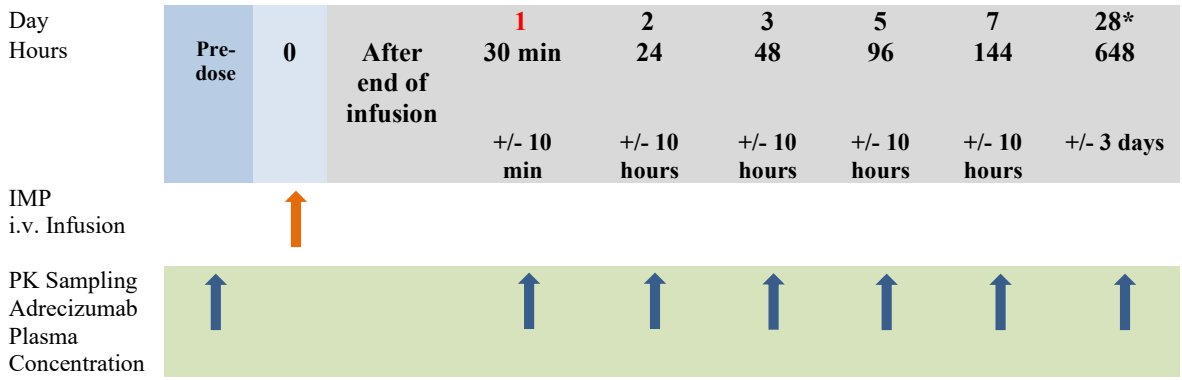
(1) Written informed consent must be obtained prior to any study specific procedures. In case the patient is not able to give informed consent due to the emergency nature of the patient's condition, legally designated representatives according to local law or local regulation should sign informed consent form.
(2) Retrospective consent from the study patient is required to be obtained for continuation with study procedures and should be obtained as soon as the patient is able to provide the written informed consent.
(3) Date, time, location before admission, type of admission, origin of sepsis to be recorded at hospital and ICU admission, start of vasopressor administration if prior to admission.
(4) Document all ongoing conditions and relevant medical history and co-morbidities present or treated within the last year (cardiovascular and non-cardiovascular) and concomitant illnesses present at inclusion.
(5) Vital signs (blood pressure, heart rate, MAP, respiratory rate and oral or tympanic temperature) will be collected as single value.
(6) Vital signs (blood pressure, heart rate, MAP, respiratory rate and oral or tympanic temperature) will be collected as minimal as well as maximal value of the study day.
(7) Plasma bio-ADM concentration of > 70 pg/mL required for enrollment. Measurement is allowed to be repeated in case concentration is < 70 pg/mL and as long as definition of septic shock is still applicable at the time of repeated measurement.
(8) For screening lab values can be used which hav already been analyzed for clinical routine (e.g. routine blood test at ICU) and not for study purposes specifically. However, only documentation from lab analyses should be considered, which is closest to the time point of IMP administration: BUN or urea, sodium, potassium (at screening only). creatinine, total bilirubin, platelet counts, hemoglobin, hematocrit, blood lactate concentration, white blood count, differential blood count (at screening only).

(9) Day 2 to day 7 and day 28 (taken at the morning routine) or discharge from ICU (whatever comes first) and follow-up day 28: BUN or urea, sodium, creatinine, total bilirubin, platelet count, hemoglobin, hematocrit, blood lactate concentration, white blood count.
(10) Day 8 to day 27 or discharge from ICU (whatever comes first): Daily measurement of creatinine . Total bilirubin, platelet count and blood lactate concentration will be measured every other day.
(11) Day 1: PaO2/FiO2 (if arterial line in place) and arterial pH (APACHE II score), prior to IMP administration.
(12) Day 2 to day 28 or discharge from ICU (whatever comes first): PaO2/FiO2 (if arterial line in place) and arterial pH minimal and maximal values.
(13) Pregnancy test will be performed on day 28 (for patients still on ICU) or on follow-up day 28 (for patients discharged from ICU).
(14) Eligibility Confirmation: Inclusion and Exclusion criteria to be sent to Clinical Coordinating Center for central evaluation. Only after receipt of results of central verification, randomization of patient to one of the treatment arms or to the placebo control group possible.
(15) Day 1: Start of treatment within 12 hours after start of vasopressor administration due to septic shock.
(16) Screening: Record start and stop date/time, drug, dose, unit, of the first vasopressor administration due to septic shock.
(17) Day 1 to day 28 or discharge from ICU (whatever comes first): Record start and stop date/time, drug, dose (highest/lowest) and unit.
(18) Concomitant medication and cornerstone medication: Should be recorded from screening to day 28 or discharge from ICU (whatever comes first) as well as on follow-up day 28 if patient was discharged from ICU before day 28.
(19) Fluid balance: Difference between fluid administered (intravenous fluid, blood products, enteral fluids) and fluid lost (ultrafiltrate from renal replacement therapy, urine output for 24 hours, enteral losses, drain losses) in the last 24-h period.
(20) Day 1: Evaluation of Organ dysfunction (SOFA score): Cardiovascular system, respiratory system, kidneys, coagulation, liver, nervous system (Appendix 3) to be performed shortly before IMP administration.
(21) Day 2 to day 28 during stay in ICU: Data for SOFA score to be recorded are always the worst values within 24 hours.
(22) Day 1: Central laboratory assessment to be performed for biomarkers prior to start of IMP infusion.
(23) Day 2 to day 27 in the morning of the sampling day): Central laboratory assessment at 24 hours, 48 hours, 96 hours and 144 hours after end of infusion (+/- 10 hours) or between scheduled assessments, if discharged earlier from the ICU (whatever comes first).

(24) At pre-selected sites only. On day 1 plasma concentration of free ADRECIZUMAB to be determined prior to IMP infusion.
(25) Day 2 to day 7 and day 28 (either during day in ICU or on follow-up day 28, if discharged from ICU prior to day 28): Determination of PK after 30 minutes, 24 hours, 48 hours, 96 hours, 144 hours and 648 hours after end of infusion). (+/- 10 hours) or between scheduled assessments, if discharged earlier from the ICU (whatever comes first).
(26) Only on discharge from ICU.
(27) Completion of paper questionnaire by telephone.

Others:
In the time frame of 14 day follow-up, each day on support with vasopressor, and/or mechanical ventilation (defined as any ventilation received on this day, independent from the duration of mechanical ventilation), and/or renal dysfuncion (defined as renal SOFA = 4), or not alive, is counted as 1. The sum over the follow up period is defined as SSI.

Figure 2 PK Sampling – Substudy



* **Day 28:** Sample to be taken either during stay in ICU or on day 28 follow-up, if patient is discharged from ICU prior to day 28

Biomaker Determination (Central Lab)

- After approval of eligibility of patient by CCC and prior to start of IMP infusion
- After 24 hours +/- 10 hours after end of infusion
- After 48 hours +/- 10 hours after end of infusion
- After 96 hours +/- 10 hours after end of infusion
- After 144 hours +/- 10 hours after end of infusion

or between scheduled assessments, if discharged earlier from ICU (whatever comes first).

Figure 3 Study Flow Chart for Screen Failure Patients

	Hospitalization and ICU	Follow-up	
Day	**1 (Screening) to 14 or Discharge**	**28**	**90**
Sepsis Support Index (SSI) [1)]	X		
Survival / Mortality		X	X

(1) Investigator will be asked to contact the patient on day 14 for calculation of the SSI (screening to day 14) during stay at ICU as well as on follow-up day 28 and day 90 for recording and evaluation of survival / mortality. For assessment of the SSI and for recording and evaluation of survival / mortality data the investigator should seek to obtain the patient's consent.

3. INTRODUCTION AND RATIONALE

3.1 Background Information

3.1.1 Septic Shock

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in 2 total SOFA score points subsequent to the infection. Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP > 65 mm Hg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of 40% *[4, 22]*.

One important factor in the pathogenesis of sepsis and septic shock seems to be Adrenomedullin (ADM), a circulating hormone and a local autocrine/ paracrine mediator. ADM is an autocrine and paracrine hormone where the local ADM concentration (i.e. in the immediate vicinity of endothelial and vascular muscle cells) is assumed to be substantially higher than the plasma concentrations; this applies for healthy conditions, but for sepsis as well. It is therefore assumed that the ADM plasma concentrations are an overspill of local concentrations. Therefore, the exact mechanism of action is difficult to explain based on the plasma concentrations.

In several preclinical and clinical studies ADM was infused to healthy volunteers or CHF patients. The ADM infusion led to an arterial blood pressure decrease, increase of heart rate and cardiac index *[7, 8, 9, 10, 11, 12, 18, 19, 24]*.

Ueda et al. reported that the plasma ADM concentrations in patients with septic shock were more than 10-fold over normal *[25]*. Hirata et al have also shown that an increase of plasma ADM concentrations over time in septic intensive care unit (ICU) patients is associated with fatal outcome, whereas in septic patients who recovered from sepsis ADM concentrations decreased over time *[6]*. Nishio et al. investigated in a prospective clinical trial plasma concentrations of adrenomedullin in patients with septic shock and the potential association of these concentrations with relaxation of vascular tone. The mean plasma concentration of adrenomedullin was markedly higher in patients than in controls (226.1 +/- 66.4 [SEM] vs. 5.05 +/- 0.21 fmol/mL, p <.01). Moreover, these concentrations correlated significantly with cardiac index, stroke volume index, and heart rate values, and correlated significantly with decreases in diastolic blood pressure, systemic vascular resistance index, and pulmonary vascular resistance index. They concluded, that the enhanced production of Adrenomedullin in patients with septic shock may contribute to reduced vascular tone, hypotension, or both *[13]*.

ADM has also an effect on endothelial permeability via the phosphatidyl-Inositol-3-Kinase/ Akt pathway. ADM reduces the endothelial permeabilty by reducing tyrosin-phosphorylation of VE-cadherin (Tyr ^{731}) and enhances the binding of ß-catenin to the cytoplasmic tail of VE-cadherin which leads to enhanced vascular integrity.

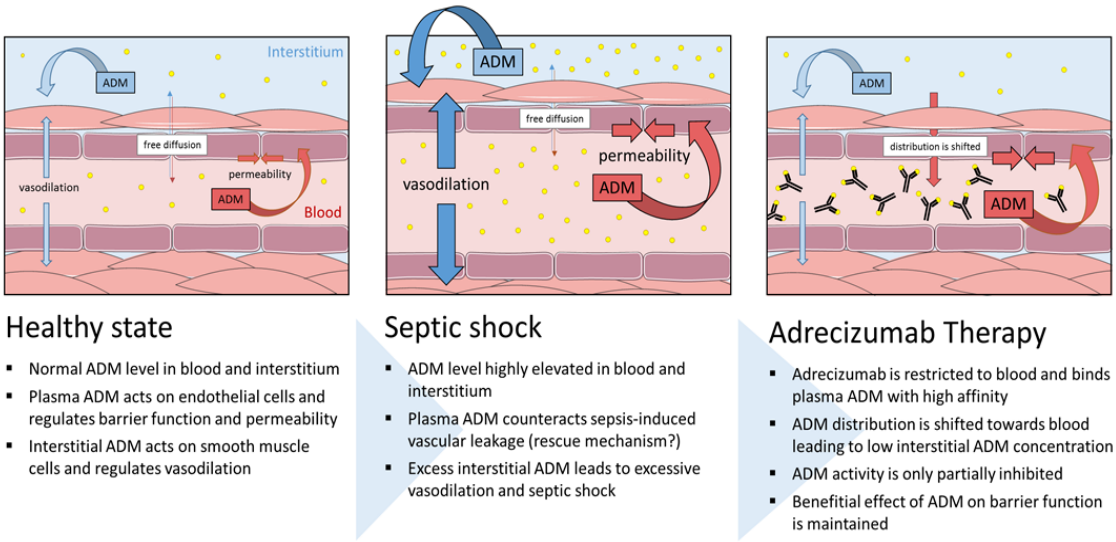
3.1.2 Investigational Medicinal Product

HAM8101 is classified as a biotechnology-derived pharmaceutical falling into the scope of ICH S6(R1). Therefore, the non-clinical development program was based on the ICH S6(R1) guidance and in addition follows recommendations provided during a Scientific Advice Meeting with Paul Ehrlich Institute in November 2012.

Mode of Action

A possible mode of action for the anti-Adrenomedullin antibody Adrecizumab has been developed on the basis of published data, own experimental data and theoretical considerations. The model has been discussed with key opinion leaders in the field (Prof. Hippenstiel, Charité Berlin, Germany, and Prof. Ouafik, University Marseille, France).

The model developed is described here:



ADM is a relatively small peptide comprising 52 amino acids, which is synthesized mainly in endothelial and smooth muscle cells and is secreted from these cells. Several functions of ADM have been described, including vasodilatory activity and stabilization of endothelial permeability. ADM acts in an autocrine/paracrine way but also as a hormone. Due to its small size, ADM is supposed to be able to freely diffuse between the blood circulation and the interstitium. The inner wall of blood vessels is composed of endothelial cells. Smooth muscle cells, on the contrary, have no direct contact to the blood circulation, as they are located distal at the basal site of the endothelial cell layer of arteries. Thus, it can be assumed that ADM located in the blood circulation can act on endothelial cells to stabilize endothelial permeability, but from this compartment cannot directly exert its vasodilatory activity on smooth muscle cells. Rather, smooth muscle cells are accesible for ADM, when it is located in the interstitium.

When the anti-Adrenomedullin antibody Adrecizumab is administered in the blood circulation at high concentrations by far exceeding those of plasma ADM, the compartmental distribution of ADM is altered. Adrecizumab, an IgG with a molecular weight of more than 150 kDa, is too large to freely diffuse from the blood circulation to the interstitium.

With its fast association kinetics Adrecizumab quickly binds to ADM in the blood circulation and „pulls“ ADM, which has been initially located in the interstitium, from this compartment to

the blood circulation. The more Adrecizumab is applied, the stronger is the „pulling“ effect and the higher the resulting concentrations of Adrecizumab-bound ADM in the blood circulation. The increase of Adrecizumab-bound ADM in the blood circulation occurs within 5-15 minutes after administration of Adrecizumab, and no parallel increase of MR-proADM, another peptide derived from the same precursor as ADM, has been observed. Thus, it can be excluded that Adrecizumab leads to an immediate transcriptional activation of the ADM gene or release of a pool of ADM-precursor derived peptides from secretory vesicles, but that it rather induces a translocation of preformed ADM. As a consequence of this redistribution, the ADM concentration in the interstitium decreases, and less ADM is able to act on smooth muscle cells to exert its vasodilatoryactivity. In the progression to septic shock, when it comes to excessive vasodilation and hypotension, administration of Adrecizumab thus can reduce vasodilation by substracting excessive levels of interstitially located ADM.

At the same time levels of Adrecizumab-bound ADM increase in the blood circulation, and it is assumed that this can be functionally relevant: Due to its epitope specificity for the N-terminal moiety of ADM, Adrecizumab is a special anti-Adrenomedullin antibody. While it is a high-affinity antibody, its binding to ADM does not completely block the function of ADM, but rather only partially reduces its capacity to elicit a second messenger response. The net effect of an increase of Adrecizumab-bound ADM in the blood circulation on the one hand, and an only partial functional inhibition of ADM brought about by the binding of Adrecizumab on the other hand, is that more ADM activity is present in the blood circulation after administration of Adrecizumab than without administration of Adrecizumab. The increased net activity in the blood circulation could promote stabilization of endothelial permeability.

An additional effect of binding of Adrecizumab to ADM in the blood circulation could be an – at least partial and/or temporal – protection from otherwise occurring proteolytic decay of ADM. Proteolytic degradation of ADM occurs at its N-terminus. It is exactly this site, where Adrecizumab binds to ADM.

3.1.2.1 Clinical Experience

Prior to investigating ADRECIZUMAB in septic patients, the safety, tolerability and pharmacokinetics/-dynamics of single administrations of ADRECIZUMAB was evaluated in a Phase I study in healthy volunteers, consisting of two parts (Phase Ia and Phase Ib).

In the Phase Ia part healthy male subjects were randomized in a double-blind, placebo-controlled study with single escalating doses of ADRECIZUMAB administered as intravenous (i.v.) infusion in 3 sequential groups of 8 subjects each, 1st group 0,5 mg/kg, 2nd group 2 mg/kg, 3rd group 8 mg/kg (n=6 active, n = 2 placebo for each group).

The main inclusion criteria were written informed consent, age 18 – 35 years, agreement to use a reliable way of contraception and a BMI between 18 and 30 kg/m². Subjects received a single i.v. dose of ADRECIZUMAB (0,5 mg/kg; 2 mg/kg; 8 mg/kg) or placebo by slow infusion over a 1-hour period in a research unit.

As the minimal effect concentration in healthy animals based on studies Safety-01 and Safety-06 is between 0.1 and 0.5 mg/kg, which showed an increase in total plasma ADM concentrations starting at a HAM8101 concentration of 0.5 mg/kg rising upon further increase in dose of applied drug, the starting dose was chosen at 0.5 mg/kg.

The apparent terminal elimination half-life is approximately 14 – 15 days. Due to the slow elimination the mean residence time was also long: ~ 17 days. The small volume of distribution also indicates the weak distribution properties of ADRECIZUMAB. Thus, the administered dose is localized predominantly in the circulation and distributed and eliminated slowly.

This phase 1a study in healthy volunteers has been completed with the result that no SAEs or SUSARs were observed, no clinically significant electrocardiographic abnormalities were observed, normal local tolerability and no obvious abnormalities, vital signs or clinical laboratory values.

A Phase 1b study was conducted to investigate the safety and tolerability of ADRECIZUMAB under inflammatory conditions in healthy volunteers. The experimental human endotoxemia model, in which healthy male volunteers receive a low dose of LPS derived from Escherichia coli, is widely used to study the effects of systemic inflammation in humans in vivo and is considered a safe and highly reproducible method to activate the innate immune system. After induction of the systemic inflammation the study design (ADRECIZUMAB doses and administration and study assessments) were the same as for the Phase Ia study. No clinical relevant AEs/SAEs were observed after administration of ADRECIZUMAB.

After these phase I studies it is intended to start a phase II study in 300 patients with early septic shock.

3.2 Rationale for the Clinical Trial

The importance and the potential clinical relevance of Adrenomedullin in sepsis has also been confirmed in several observational clinical studies with patients with sepsis, severe sepsis and septic shock. It could be demonstrated in a pilot study that in patients who had a bio-ADM concentration < 70 pg/mL there was a significant lower mortality than those with a bio-ADM concentration > 70 pg/mL. Keep in mind that Adrenomedullin has to be amidated when biologically active (please refer to more information to the investigator's brochure). Interesting is the observation that those patients who had a higher bio-ADM concentration > 70 pg/mL and remained high over the next four days had a mortality of around 65%, but of those who had a significant decline of bio-ADM concentration over the next four days 100 % survived *[14]*. This observation was also confirmed by data from Marx et al. in septic patients on a surgical ICU. Patients with a bio-ADM concentration of 97.5 pg/mL had a significantly higher mortality rate than those with a bio-ADM concentration of 42.6 pg/mL. Patients who had a median bio-ADM concentration of around 40 pg/mL did not need any vasopressor support over the entire stay at ICU *[21]*.

In a further observational study, similar observations were made in the FROG-ICU study: ICU patients with severe sepsis on admission (n=61) had a bio-ADM concentration of around 70 pg/mL compared to around 120 pg/mL in septic shock patients who received vasopressor/inotropics on the day of admission *[16, 17]*.

These data indicate that ADM plays an important role in the pathogenesis of sepsis. ADRENOMED AG has developed an epitope–specific antibody for therapeutic use in patients with septic shock.

Aim of a targeted therapy should be to maintain the beneficial effect of ADM, while counteracting an excess of ADM.

Therefore, several mouse monoclonal anti-ADM antibodies were developed which inhibit the ADM function differently depending on their epitopes. While the anti-ADM antibody directed against C-terminal moiety of ADM led to a 100% inhibition of ADM activity, the anti-ADM antibody activity against the N-terminal moiety of ADM led to a inhibition of ADM function of approx. 35% - 50 % *[23]*. Only the antibody leading to a partial inhibition (directed against the N-terminal moiety of ADM) has shown the most benefit in preclinical septic models: Administration of this antibody largely improved survival in CLP mice *[23]*, and in a resuscitated mouse CLP model led to an improvements of hemodynamics (reduced catecholamine demand to maintain MAP > 65 mmHg), increase of creatinine clearance, less positive fluid balance and reduced systemic inflammation *[26]*. Also, the CLP induced deterioration in kidney barrier function, expressed by extravascular albumin accumulation, was significantly reduced *[15]*. Therefore the antibody has been further developed to a humanized variant (ADRECIZUMAB).

The main preclinical results obtained with ADRECIZUMAB can be summarized as follows:
It was shown that the administration of ADRECIZUMAB in a two-hit pig model of systemic bacteremia led to an improvement of renal function, an attenuated inflammatory response and a significant reduction of vasopressor use in acute shock *[20]*. Delayed treatment of CLP rats improved mean arterial pressure *[1]*. Overall, these results illustrate that the administration of ADRECIZUMAB exerts beneficial effects in sepsis models demonstrated by

- reduced edema formation,
- reduced fluid demand,
- improved fluid balance
- improved kidney function,
- improved blood pressure and
- reduced inflammation.

ADRECIZUMAB was tested for safety extensively in mice, rats, dogs and in non-human primates. The NOAEL (none-observed adverse events level) in NHP was 100 mg/kg (max. tested) and the NOAEL in rats is 400 mg/kg (max. tested).

3.2.1 Study Design

This is a double-blind, placebo-controlled, dose-finding, multicenter randomized proof of concept phase II study using two doses of ADRECIZUMAB in patients with early septic shock and a bio-ADM plasma concentration at admission of > 70 pg/ml.

"***Early" septic shock*** is defined as
a life-threatening organ dysfunction due to dysregulated host response to a proven or suspected infection which leads to a decline of MAP < 65mm Hg which is refractory to fluid resuscitation and requires vasopressors. Early is defined as a maximum of < 12 hours between onset of the cardiovascular organ-dysfunction (start of vasopressor use) and administration of

ADRECIZUMAB. Refractoriness to fluid resuscitation is defined as a lack of response to the administration of 30 mL of fluid per kilogram of body weight or is determined according to a clinician's assessment of inadequate hemodynamic results.

In this phase II study 300 patients with early septic shock and a plasma concentration of bio-ADM > 70 pg/mL from surgical, medical and mixed ICU at multiple centers in Europe will be randomized. This concept is based on the observation of the clinical observation study AdrenOSS-1, in which 201 out of 291 patients with septic shock and a bio-ADM concentration > 70 pg/mL had a 28-day mortality rate of approximately 35% compared with 84 out of 291 patients with a bio-ADM concentration < 70 pg/mL who had a 28-day mortality rate of 23 %.

All patients will be treated according to "International Guidelines for Management of Severe Sepsis and Septic Shock" *[3]*.

300 patients with early septic shock will be randomized into two treatment arms and one control group. After informed consent has been signed by patient or legally designated representative and the result from plasma-ADM concentration (> 70 pg/ml) is available, inclusion and exclusion criteria will be checked via a centralized procedure. After fulfilling the inclusion and exclusion criteria patients will be assigned randomly (randomization 1:1:2; four – block randomization per center) to the treatment arms (2 mg/kg or 4 mg/kg) or to the placebo control group.

Patients assigned to the treatment arms will be administered a single dose of ADRECIZUMAB as i.v. infusion over approximately 1 hour; patients assigned to the control group will be administered placebo as i.v. infusion over approximately 1 hour.

Patients will be evaluated for safety and tolerability of the therapy, but also for signs of clinical efficacy. As long as the patients are on the ICU, measurements of clinical signs and laboratory data will be collected for safety reasons and for determination of SOFA score as long as arterial line is in place for determination of PaO2/FiO2.

Additional blood samples for determination of Adrenomedullin (prior to infusion) and the biomarker MR-proADM and inflammatory biomarkers PCT, IL-6 and penKid will be taken prior to start of IMP infusion (day 1) and within the time frame of 24 hours (+/- 10 hours) after end of IMP infusion (day 2). Further blood sampling for biomarker assessment will follow at 48 hours, 96 hours and 144 hours after end of infusion (+/- 10 hours) or between scheduled assessments, if discharged earlier from ICU (whatever comes first).

Patient accrual is expected to be completed within 24 months.

An interim analysis is planned after 50% of patients (n=150) have completed study after day 28 .

3.2.2 Dose Selection

The rationale for the chosen doses of 2 mg/kg or 4 mg/kg is based on model considerations: It was derived from *in vitro* studies (Adrenomedullin-induced cAMP response in CHO cells overexpressing hCRLR/RAMP3) that the local ADM concentration is assumed to be substantially higher than what is found under normal conditions in plasma. This is also true for sepsis and septic shock situations – the local concentration of ADM is likely much higher than what is found in the plasma. It is therefore assumed that the ADM plasma levels reflect an overspill of local concentrations. Since the aim is to provide with a single dose of

ADRECIZUMAB an excess in order to bind all endogenous ADM (systemic and local) for at least 7 days, a dose of 2 mg/kg or 4 mg/kg has been determined as the target doses for Phase II. These thoughts derived from model should be confirmed in this study.

In a phase Ia/Ib study additional doses of ADRECIZUMAB (0.5 mg/kg and up to 8 mg/kg) are tested for safety. No relevant AEs were observed in any of the groups in the Phase Ia study. The Phase Ib study was conducted and completed before start of the Phase II study. Nonclinical safety studies in various animal species have been conducted in order to cover the safety of the target dose. In summary, in all species no adverse events, even at the highest tested dose (in rodents up to 800 mg/kg) were detected.

3.3 Assessment of Potential Risks and Benefits and Risk Management

Primary aim of this phase II study is to demonstrate safety and tolerability as well as efficacy of ADRECIZUMAB in patients with septic shock. The current phase II study is underpowered to detect a relevant reduction of 28-day mortality by ADRECIZUMAB; on the other hand, there is evidence from our animal models that ADRECIZUMAB can improve organ function. The improvement in organ function is measurable using days with relevant organ support (cardiac, renal, respiratory) while on ICU. Therefore, a composite endpoint of days with organ support AND all-cause of mortality will be used: the "Sepsis Support Index" (SSI). Further, it is intended to determine pharmacodynamics and pharmacokinetics of ADRECIZUMAB.

ADRECIZUMAB is a humanized monoclonal antibody. Therefore, there is a general potential risk of an allergic reaction or allergic shock when administered to patients. To minimize this risk strict compliance with the inclusion and exclusion criteria of the conducted clinical trials is necessary. Furthermore, Adrecizumab should be given as an infusion over 1 hour to be able to stop the infusion in case of an allergic reaction AND patients should only be treated under the controlled environment of an ICU. In case of an allergic reaction or allergic shock in a study patient, the local standard treatment should be followed.

During the first administration of ADRECIZUMAB to 36 male, healthy volunteers in the Phase Ia and phase Ib studies ADRECIZUMAB was very well tolerated and no serious adverse events, in particular no allergic reactions/allergic shock, and no clinically relevant adverse events and no clinically relevant disturbances in the ECG were observed. Local tolerability was normal and there were no obvious deviations in the vital signs (blood pressure, pulse and respiratory rate) or in clinical laboratory values.

The side effects of ADRECIZUMAB that occurred were equally distributed across all dosage groups, were only transient and required no medical treatment. The following adverse effects were observed:

- Headache, 13 events;
- Influenza-like symptoms/blocked nose, 27 events;
- Back pain, 3 events;
- Shoulder pain, 4 events;
- Nosebleeds, 2 events;
- Inflammatory skin change (eczema), 2 events.

The following side effects only occurred once: Skin infection (on the toe), skin rash at the infusion site, abdominal pain, blood loss in the rectum (once), dull pain/sensation in the thumb,

sleep-disordered breathing (in the sleep laboratory), bone fracture in the wrist, swelling of the upper eyelid.

ADRECIZUMAB has not been used before in septic patients. Therefore AEs could occur which are not predictable. The administration of ADRECIZUMAB in septic patients will occur after comprehensive preclinical studies have been conducted and after completion of the phase Ia and phase Ib study in healthy volunteers with and without LPS challenge without observation of any relevant side effects. Therefore, the striking effect of ADRECIZUMAB in preclinical testing and excellent safety data from phase Ia and phase Ib study let expect a positive benefit/risk ratio for the treatment in patients with septic shock. Therefore it is considered to launch this phase II proof of concept study.

Additional information can be found in the IB.

4. TRIAL OBJECTIVES AND ENDPOINTS

4.1 Primary Objective

The primary objective of this study is

- 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.

4.2 Secondary Objectives

The secondary objectives of this study are

- 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.

4.3 Endpoints for Primary Objective (Safety and Tolerability)

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

4.4 Endpoints for Secondary Objective (Efficacy)

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 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 *[5]*
- Day 28 and day 90 mortality rate
- SSI and pSSI excluding the renal component
- 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, fluid balance, MR-proADM, inflammatory markers PCT, IL6)
- 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)

4.5 Endpoints for Pharmacokinetics

In sub-study (with 80 patients only) to determine key PK parameters, including:

- peak plasma concentrations (C_{max})
- systemic exposure (AUC)
- volume of distribution (V)
- systemic clearance (CL)
- elimination half-life ($t_{½}$)

5. INVESTIGATIONAL PLAN

5.1 Study Design

This study is designed to evaluate the potential of ADRECIZUMAB as targeted therapy in preselected patient using the biomarker ADM with regard to safety and tolerability, PK and efficacy. Therefore, it is intended to enroll patients with "early" septic shock (start of vasopressor therapy < 12 hours) and ADM level of > 70 pg/ml.

For the purpose of this protocol a total of 300 patients from surgical, medical and mixed ICU will be randomized at multiple centers in the European Union.

For appropriate randomization the central Clinical Coordination Center (CCC) in Brussels will be used to confirm eligible patients prior to randomization to treatment arm A with ADRECIZUMAB 2 mg/kg or to treatment arm B with ADRECIZUMAB 4 mg/kg or to the placebo control group in a 1:1:2 ratio for a single dose intravenous infusion over 1 hour.

As long as the patients are on the ICU, measurements of clinical signs and laboratory data will be collected for safety reasons and for determination of SOFA score as long as arterial line is in place for determination of PaO2/FiO2.

Additional blood samples for determination of ADRECIZUMAB, inflammatory biomarker and cardiac biomarkers will be taken prior to start of IMP infusion (day 1) and within the time frame of 24 hours (+/- 10 hours) after end of IMP infusion (day 2). Further timepoints for blood sampling will follow as specified in Figure 2 at 48 hours, 96 hours and 144 hours after end of infusion (+/- 10 hours) or between scheduled assessments, if discharged earlier from ICU (whatever comes first).

The SOFA score and its components will be determined daily for all patients over the entire stay on the ICU until day 28 or discharge (whatever comes first). Safety monitoring for each patient will begin at the time of signing the Informed Consent Form and continue for 90 days after end of short-term infusion of study medication.

At selected study centers a PK substudy will be performed to determine the profile of ADRECIZUMAB in 80 randomized patients.

Patient accrual is expected to be completed within 24 months.

An interim analysis is planned after 50% of patients (n=150) have completed study day 28.

5.2 Study Population

5.2.1 Selection of Study Population

In this phase II study up to 300 adult male and female patients with "early" septic shock and a bio-ADM concentration at inclusion of > 70 pg/mL will participate.

To qualify for randomization and treatment with the study medication, patients must meet all inclusion criteria and none of the exclusion criteria at inclusion. Eligibility will be re-checked

and confirmed by a central Clinical Coordinating Center (CCC) in Brussels prior to randomization.

No deviation to the following inclusion or exclusion criteria is allowed.

5.2.2 Inclusion Criteria

To participate in the study, patient must meet all of the following inclusion criteria:

1. Written informed consent by patient or legally designated representative (according to country – specific regulations)
2. Male and female patients, age ≥ 18 years
3. Body weight 50 kg – 120 kg
4. Bio-ADM concentration **>** 70 pg/ml
5. Patient with early septic shock *(start of vasopressor therapy < 12 hours)
   * Early septic shock < 12 hours between onset of the cardiovascular organ-dysfunction and administration of ADRECIZUMAB

   Definition:
   *Septic shock is defined as a life-threatening organ dysfunction due to dysregulated host response to a proven or suspected infection which leads to a decline of MAP < 65 mmHg, which is refractory** to fluid resuscitation and requires sustained vasopressors*
   ** *Refractory: Defined as lack of response to the administration of 30 mL of normal saline/kg body weight or according to a clinician's assessment of inadequate hemodynamic results*
6. Women of childbearing potential must have a negative serum or urine pregnancy test before randomization.
7. Highly effective method of contraception must be maintained for 6 months after study start by women of childbearing potential and sexually active men.
8. No care limitation

5.2.3 Exclusion Criteria

A patient who meets any of the following criteria must be excluded from the study:

1. Moribund
2. Pre-existing unstable condition (e.g. a recent cerebral hemorrhage or infarct, a recent acute unstable myocardial infarction (all < 3 months), congestive heart failure – NYHA Class IV)
3. Patients that required cardiopulmonary resuscitation in the last 4 weeks prior to evaluation for enrollment
4. Severe COPD with chronic oxygen need at home (GOLD IV)
5. Any organ or bone marrow transplant within the past 24 weeks
6. Uncontrolled serious hemorrhage (≥ 2 units of blood / platelets in the previous 24 hrs). Patients may be considered for enrollment if bleeding has stopped and patient is otherwise qualified
7. Uncontrolled hematological / oncological malignancies
8. Absolute neutropenia < 500 per µL
9. Severe chronic liver disease (Child-Pugh C)
10. Systemic fungal infection or active tuberculosis
11. Neuromuscular disorders that impact breathing/ spontaneous ventilation

12. Burns > 30% of body surface
13. Plasmapheresis
14. Breastfeeding women
15. Participation in a clinical trial involving another investigational drug within 4 weeks prior to inclusion
16. Unwilling or unable to be fully evaluated for all follow-up visits

5.3 Patient Numbering

Inclusion- and exclusion criteria from patients admitted to the ICU will be verified by the investigator to identify potential patients to be enrolled into the study.

After availability of written informed consent by patient or legally designated representative (or other accepted procedure according to local requirements in case patient is unable to sign informed consent personally due to the emergency nature) patient will be assigned a unique 6-digit patient identification number in ascending order at inclusion which will include country (1 digit), site number (2 digits), patient number (3 digits). For example 1-01-001, 1-02-001, 2-01-001, 2-02-001 etc. This patient identification number will be maintained throughout the study without any reassignment.

The eligibility of each patient, based on assessment of all inclusion- and exclusion criteria including the bio-ADM concentration of > 70 pg/mL, must be confirmed by the central CCC prior to randomization to one of the two treatment arms or to the placebo control group. An overview of the randomization procedure is provided in section 6.5.

5.4 Screen Failure Patients

Patients who sign the informed consent form but fail to meet one or more of the eligibility criteria, or who decline study participation before receiving IMP, will be defined as screen failures. For those patients the investigator will be asked to contact the patient on day 14 for calculation of the SSI during stay at ICU (screening to day 14) as well as on follow-up day 28 and day 90 for recording and evaluation of survival / mortality. For assessment of the SSI (screening to day 14) and for recording and evaluation of survival / mortality data the investigator should seek to obtain the patient's consent.

5.5 Discontinuation of Individual Subjects

Participation in this clinical study is strictly voluntary and any subject may withdraw from the study at any time without providing an explanation. This will not affect his/her right for future medical care.

In the event that a patient withdraws from the study, the investigator must be informed immediately. The date, circumstances and any reason provided will be documented on the withdrawal page of the eCRF. If the patient already received the investigational treatment prior to withdrawal of consent, he/she will be asked to perform the assessments for day 28 or day of discharge and to complete the quality of life questionnaire on day 28. For the completion of the paper telephone Euro-QoL-5 Quality of Life Short Form, the patient will be called from the investigator's site on day 90 of the follow-up period.

No data obtained after withdrawal of consent will be recorded on eCRFs - with the exception of any case of death until 90 days for safety reasons - and will not be evaluated as part of the clinical study. For recording and evaluation of survival / mortality data the investigator should seek to obtain the patient`s consent.

In both arms treatment may be withheld temporarily or stopped definitively at the investigator's discretion at any time. Possible reasons include:

- Serious adverse event (SAE) considered to be related to treatment with the study medication
- Any situation in which, in the investigator's opinion, a continuation of the treatment with the study medication would be harmful to the patient's safety and well-being.

Time, circumstances and reason/s for stopping treatment will be documented in the eCRF. The sponsor must be informed within 24 hours about any treatment discontinuation of a patient including the reason. Patients whose treatment is stopped stay in the study unless they withdraw consent. After the treatment is stopped, patients are followed according to the plan for the follow-up visits.

Patients may be withdrawn from treatment or from the study by the investigator or the sponsor in case of a major protocol deviation considered being relevant by the investigator and/or the sponsor (e.g. deviation of selection criteria) or if new information arise making the continued study participation of a patient unadvisable. Patients withdrawn from the study will be informed about the reasons for withdrawal.

5.6 Stopping of Clinical Trial

All safety signals including suspected unexpected serious adverse reaction (SUSAR) and SAEs will be reviewed on a continuous basis by the Data and Safety Monitoring Board (DSMB) (see section 12.5). The stopping rules defined below apply to any treatment-related AE and clinical laboratory assessments. However for clinical laboratory assessments, the rules apply only if deviations of laboratory parameters relate to the same organ system, indicating clinical significance. A single deviation of a laboratory value without any clinical symptoms will not be considered clinically significant.

The stopping rules are stipulated as follows:

- Following investigation of AEs the DSMB may recommend stopping the study if continuation may pose a substantial risk to subjects.
- The DSMB may recommend stopping the study if previously unknown data become available and raise concern about the safety of the study drug, so that continuation would pose a potential risk to the patients.

The sponsor may terminate the study for other important reasons at his discretion. Such reasons may be external information that impact the risk-benefit assessment for patients or technical or operational reasons such as unexpectedly slow recruitment that may put the scientific value of the study at risk.

If the study is prematurely terminated or suspended, the investigator will promptly inform the patient and assure appropriate therapy and follow-up.

Furthermore, the study can be terminated at any time if the authorization and approval to conduct the study is withdrawn by ethics committee, by regulatory authority decision, insufficient accrual, emergency, new data impacting the scientific value of the study on ethical grounds.

5.7 Concomitant Treatment

Standard medical treatment(s), including all therapies and medications, prescriptions and over-the-counter, being taken by the patient upon entry in the study, maintained throughout the study including any medication to treat AEs or SAEs will be collected. Any changes in concomitant medication must be recorded from screening until day 28 or discharge from ICU, (whatever comes first) as well as on follow-up day 28 if patient was discharged from ICU before day 28.

Recording of treatment for ongoing AEs or SAEs will be continued after day 28 until resolution or until end of study for new AEs or SAEs occurred during the follow-up period.

5.8 Cornerstone Medication - Permitted Concomitant Medication

The main therapy administered according to the international guidelines for treatment of patients with septic shock (Surviving Sepsis Campaign), e.g. enteral / parenteral nutrition, antimicrobiotic therapy (drug, dose, duration), insulin, blood transfusion should be documented on a daily basis from screening to day 28 or discharge from ICU (whatever comes first) as well as on follow-up day 28 if patient was discharged from ICU before day 28.

5.9 Vasopressor Therapy

Vasopressors are provided for patients with septic shock who do not respond to fluid resuscitation.

Use of vasopressors (dopamine, dobutamine, phenylephrine) in combination with catecholamine (adrenaline, noradrenaline*) will be recorded from admission to ICU at time point of diagnosis of septic shock and daily thereafter from day 1 through day 28 or discharge from ICU (whatever comes first) (drug name, highest / lowest dose, starting time and duration of use of vasopressor therapy).

* used equivalent to epinephrine and norepinephrine

5.10 Lost to Follow-up

For patients whose status is unclear because they fail to appear for the follow-up visit on day 28 and fail to have the phone call on day 90 without stating an intention to withdraw, the investigator should show "due diligence" by contacting the subject, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered lost to follow-up until his/her scheduled phone call on day 90 would have occurred.

6. INVESTIGATONAL TREATMENTS

6.1 Investigational Medicinal Product (IMP)

ADRECIZUMAB (HAM8101) is a humanized IgG1 monoclonal antibody (mAb) directed against the N-terminus of adrenomedulling (ADM) and intended for the treatment of sever sepsis and septic shock. The antibody was generated by complementarity determining region (CDR) grafting a murine IgG2a mAB, which was obtained by immunizing female Balb/c mice with the ADM 1-10 peptide (H-YRQSMNQGSC-OH) using a peptide-BSA (bovine serum albumin) – conjugate.

The epitope of ADRECIZUMAB on ADM comprises the first 5 amino acids in the N-terminal region of the peptide hormone, and binding requires the N-terminal tyrosine residue of ADM to be free. This epitope is identical among many mammalian species including mouse, rat, dog, pig and cynomolgus monkey. The binding of ADM to its receptor is achieved via the C-terminus, which is identical across all species tested *[27]*.

The quality control standards and requirements for each study medication are described in separate release protocols/certificates of analysis.

ADRENOMED AG will supply ADRECIZUMAB 2 mg/kg and 4 mg/kg and placebo for intravenous infusion to the investigator as a sterile solution for infusion. Each vial will contain 200 mg ADRECIZUMAB. Excipients contained in ADRECIZUMAB are listed below. The solution will be diluted with NaCl 0,9% up to 50 mL to reach an osmotic strength of < 300 mOsmol/L. The volume has to be adjusted to the infusion volume of 0,5 mL/kg plus the dead volume that will remain in the line for infusion.

Table 1 Composition of the ADRECIZUMAB Drug Product

Name of Ingredient	Function	Quantity (per mL)	Quantity for 10.4 mL filled vials
ADRECIZUMAB protein	Active	18 - 22 mg	187.2 – 228.8 mg
Histidin-HCl monochlorid	Buffer	4.19 mg	43.6 mg
Glycine	Stability	22.5 mg	234.0 mg
Water	Solvent	qs to 1.0 mL	qs to 10.4 mL

Table 2 Composition of the Placebo Product

Name of Ingredient	Function	Quantity (per mL)	Quantity for 10.4 mL filled vials
Histidin-HCl monochlorid	Buffer	4.19 mg	43.6 mg
Glycine	Stability	22.5 mg	234.0 mg
Water	Solvent	qs to 1.0 mL	qs to 10.4 mL

Stability:	The shelf life will be established from the real-time results of the stability testing program, which will monitor stability over 36 months. Expiry date is indicatedon the IMP label.
Storage:	at 2 – 8 °C and protected from light
Manufacturer:	Celonic Deutschland GmbH & Co. KG Czernyring 22 69115 Heidelberg, Germany
Packaging and Labeling:	CSM Clinical Supplies Management Europe GmbH Am Kronberger Hang 3 65824 Schwalbach a.Ts. Germany
QP Release:	Celonic Deutschland GmbH & Co. KG Czernyring 22 69115 Heidelberg, Germany

6.2 Packaging, Labeling and Shipment

ADRECIZUMAB 200 mg solution for infusion and ADRECIZUMAB placebo are in clear Type I glass vials, size 10R, sealed with fluoropolymer coated bromobutyl rubber stoppers and tear-off plain aluminum cover seals.

Clinical supplies are provided in boxes containing 8 vials respectively. Individual vials have a nominal volume of 10 mL (see section 6.3).

The packaging and labeling of the investigational medicinal product (IMP) will be performed by CSM Clinical Supplies Management Europe GmbH, Am Kronberger Hang 3, 65824 Schwalbach a.Ts., Germany according to requirements of ECGuide on GMP, Annex 13 (4).

IMP kits will be supplied by sponsor including a certificate of compliance issued by the European Qualified Person. The IMP boxes will be shipped under controlled and monitored temperature conditions at 2 – 8°C. The receiving center has to confirm the receipt and the condition of the delivery via appropriate study forms. Should the temperature monitoring device indicate that the specific shipment conditions were not maintained during the transport, the IMP kits must be quarantined such they cannot be used unintentionally and the sponsor must be contacted immediately.

All vials and secondary packaging will be labeled for purpose of the clinical study in accordance with applicable regulatory requirements.

The IMP kits will be labelled in local language according to local requirements. The vial-label will contain a tear-off section which, after IMP administration, will be attached in the appropriate field of the Preparation and Dispensing Proecedure Log - IMP.

6.3 Handling, Storage and Preparation

The IMP kits must be stored at temperature between 2°C – 8 °C, protected from light under temperature controlled and restricted access conditions either in the local pharmacy or at the ICU. Any temperature deviation (temperature below +2°C and/or above +8°C) must be reported to the Sponsor for an evaluation if the IMP can be used or not. In case the IMP kit is stored in the local pharmacy one kit of IMP will be ordered according to the processes being in place at the hospital for transportation of the IMP to the ICU under ambient conditions once a patient has been approved for randomization.

The vials will be warmed up to room temperature no longer than 1 hour prior to their use and product is diluted with sterile 0.9% sodium chloride for infusion. IMP administration has to be started within a maximum of 2 hours after its preparation.

In case of interruption of IMP administration (e.g. technical issues), it is allowed to restart the IMP administration as long as the infusion can be completed within 6 hours after IMP preparation. Cave: This patient is not eligible any longer for the PK substudy. No further PK samples should be collected.

Treatment will consist of a body weight adjusted dose of ADRECIZUMAB up to 100 kg body weight or an equivalent amount of placebo. Patients with a body weight of > 100 – 120 kg will get the highest dose of the assigned treatment arm. This is reasonable because the ADRECIZUMAB dose is administered in excess over Adrenomedullin plasma concentrations and sufficient to still elicit increased Adrenomedullin concentration (>25 pg/ml) until seven days after application. Therefore differences will not be expected between different weight groups.

All patients will receive an intravenous infusion using an infusion pump over approximately 1 hour by medically trained personnel who are part of the study team. ADRECIZUMAB 2 mg/kg and 4 mg/kg and placebo will be administered under completely blinded conditions.

Study medication will be provided in boxes according to the 4 –block-randomization list.

Each box contains:

- 1 vial ADREZICUMAB+ 1 vial placebo
- 2 vials ADREZICUMAB
- 2 vials placebo
- 2 vials placebo

If the patient is assigned to one of the two treatment arms or to the placebo group the body weight adjusted dose of study medication is calculated according to the following formula:

$$\textbf{\textit{Infusion volume}} = 20\ \text{mL} - \left(\frac{(100\ \text{kg} - \text{actual BW}) \times 20}{100}\right) \textbf{\textit{added up to 50 mL with 0.9\% NaCl}}$$

For dose calculation, please refer to Appendix 4.

The solution for infusion must be visually inspected prior to use. Only clear, colorless solutions without particles must be used. Should IMP kit fail to meet these criteria the corresponding IMP kit has to be separated and the sponsor has to be contacted immediately.

Aseptic techniques must be strictly observed throughout preparation of IMP kits, since they contain no preservative. Standard laboratory care should be used during handling and preparation ofIMP kits, i.e. use of gloves and other protective clothing to prevent skin contact is recommended.

6.4 Accountability

In agreement with the sponsor, the PI will designate a responsible person for receipt, storage and preparation of the study medication.

Regular study drug reconciliation will be performed throughout the study to document drug assigned, drug administered, and drug remaining, or drug inadvertently damaged. This reconciliation will be documented on the IMP Inventory Log. All study medication supplies and associated documentation will be reviewed and verified by the monitor at regular intervals. Any discrepancies noted will be investigated, resolved and documented prior to return for destruction of unused study drug.

Used IMP vials will be kept at the center for monitoring/ reconciliation before they are discarded according to local requirements. Upon instruction by the sponsor unused IMP kits will be returned to the sponsor or designee for destruction.

6.5 Treatment Assignment

6.5.1 Randomization Procedures

In order to ensure the appropriate number of patients to be enrolled on identifying a potential study patient the investigator is required to ***complete a site authorization worksheet*** for confirming patient eligibility by the central Clinical Coordination Center (CCC). When appropriate investigator will receive confirmation for randomization of patient from the CCC by providing a authorization number.

Patient will then be randomly allocated to treatment arm A, to treatment arm B or to the placebo control group in a 1:1:2 randomization ratio (ADRECIZUMAB 2 mg/kg, ADRECIZUMAB 4 mg/kg and Placebo). Patient is not allowed to be enrolled until this confirmation has been received.

The randomization code list will be generated within the Biometrics Department of the designated CRO by an independent statistician not involved in the study.

6.5.2 Maintenance of the Randomization Code

This study will be performed in a double-blind fashion. The Investigator and site staff, patients, monitors, Sponsor and CRO staff will remain blinded to the treatment assignment until study closure. The investigational drug and its matching placebo are indistinguishable and all study drug kits will be packed in the same way.

The randomization list is kept strictly confidential. It is accessible only to authorized persons who are not involved in the conduct and analysis of the study, until time of unblinding.

Sets of sealed envelopes with the randomization codes will be prepared containing information about treatment and the dose the patient had received (dose of ADRECIZUMAB or placebo) for each patient:

- One set is kept at the clinical study site to be used in case of emergency (during the entire study period)
- One set is kept with the secretary of the DSMB (pharmacovigilance expert)
- One set is kept with the party responsible for reporting of a suspected unexpected serious adverse reaction (SUSAR) as required by the regulatory agencies. The evaluation and decision as to whether a Serious Adverse Event (SAE) qualifies as an SUSAR is the responsibility of the Sponsor or designee.

6.5.3 Emergency Unblinding

Under normal circumstances, the blinding should not be broken. The blinding should be broken only if specific emergency treatment would be indicated by knowing the treatment status of the patient. Whenever a code is broken, the person breaking the code must record the time, date and reason as well as his/her initials in the source documents. Unblinding will result in discontinuation of the patient from the study.

Unblinding will be performed via the emergency envelopes.

In such cases the sponsor must be contacted prior to breaking the code unless an emergency dictates otherwise. In all cases, the investigator is required to notify the sponsor within 24 hours following the code break reporting the reason for the unblinding.

Unblinding will be performed at spm² for reporting of SUSARs as required by CAs.

All codes (whether broken or not) must be kept throughout the study period in the Investigator Site File. Accountability of all broken or unbroken codes will be performed at every monitoring visit until study closure and will be collected at the last monitoring visit by the monitor and forwarded to the sponsor if not otherwise instructed by sponsor.

6.5.4 Routine Unblinding

After completion of the study, locking of the clinical database, and performance of a blinded data review, a routine unblinding will be authorized by the Sponsor.

7. STUDY CONDUCT

7.1 Standards of Study Conduct

This study will be conducted in compliance with applicable regulatory requirements, in particular the EU Clinical Trials Directive and the Declaration of Helsinki. It will be conducted strictly following the study protocol and in compliance with the revised ICH guidance E6, the EU-GCP directive and all applicable national laws and regulations.

This protocol and any amendment will be submitted to the Competent Authorities and to Independent Ethical Committees for formal approval to conduct the study. Informed consent will be obtained by all patients participating in this clinical study as discussed in protocol section 7.2.

7.2 Informed Consent

7.2.1 Patients Able to Provide Consent Personally

Prior to any study-related activity, any patient to be included in this study must give informed consent in accordance with the EU Clinical Trial Directive, the Declaration of Helsinki and with ICH-GCP requirements. The responsibility for obtaining informed consent remains with the investigator. Each investigator will maintain a list of all patients who signed the informed consent form.

The written information addresses the rights of the patient to ask for updated information on what data are recorded, to require corrections of errors, to know who will be responsible for keeping the data and who will have access to them.

The investigator will provide sufficient information about the study orally and with the patient information, to enable the patient to understand the study and any risks in details. Upon receiving this information, the patient will be given opportunity to ask any questions he/she might have and will be given appropriate time to decide on the participation in the study. The voluntary agreement to study participation by the patient will be documented by his personally dated signature on the informed consent form. The written informed consent must be co-signed and personally dated by the person who obtained the informed consent on the Informed Consent Form (ICF). The patient will be provided with copy or second original of the signed ICF.

The patient will be informed in a timely manner of any changes to the conduct of the study or other relevant information that may alter the risk benefit ratio of study participation or that may be relevant to the patient's willingness to continue participating in the study.

It will be guaranteed that personal data are kept confidential and will be used only for study related purposes.

7.2.2 Patients Unable to Provide Consent Personally

For patients unable to give consent due to the emergency nature of the patient's condition the investigator will provide sufficient information about the study to the legally designated representative of the patient, designated according to the applicable national law, local regulations in the involved countries to enable the patient's legally designated representative to understand the study and any risks in detail.

Upon receiving this information, the patient's legally designated representative will be given opportunity to ask any questions he/she might have and will be given appropriate time to decide on the participation in the study on the patient's behalf.

The voluntary agreement to study participation by the patient's legally designated representative will be documented by his personally dated signature on the informed consent form. The written informed consent must be co-signed and personally dated by the person who obtained the informed consent on the Informed Consent Form (ICF). The patient's legally designated representative will be provided with copy or second original of the signed ICF.

Once the patient has recovered and is able to understand the nature of this study a consent will be obtained retrospectively after the patient has been provided information about he study by the investigator in detail and after the patient has been given ample time to consider his/her further participation in the study to take a voluntary decision. After his/her decision in favor of further participation the patient will confirm his/her willingness to continue in this study by personally dated signature on the informed consent form, co-signed and dated by the informing investigator. The patient will be provided with copy or second original of the signed ICF.

Patient and / or the patient's legally designated representatives can withdraw their consent on study participation at any time without necessarily giving a reason and without any penalty or loss of benefits to which they are entitled.

7.2.3 Screen Failure Patients

In case the patient was unable to provide consent personally and information about the study was provided to the the legally designated representative of the patient and informed consent was obtained from the legally designated representative of the patient afterwards, investigator should seek to get a retrospective ICF signed from the patient once the patient has recovered and is able to understand the nature of this study (see also 7.2.2).

7.3 Protocol Amendments

Changes to the protocol during the study will be documented as amendments. The amended protocol will be signed by the relevant personnel at ADRENOMED AG und by the investigator. Depending on the content of the amendment and local legal requirements, the amendment will be submitted to the relevant Independent Ethics Committee (IEC) and, where necessary, to the relevant Competent Authorities.

When a patient is currently undergoing study procedures and is affected by the amendment, then the patient must be asked to consent again using the new information sheet. The new information sheet must be used to obtain consent from new patients before enrollment.

The investigator should not implement any deviation from, or changes to the protocol, without agreement by ADRENOMED AG and prior review and documented approval/favorable opinion of the appropriate IEC and, if legally required, competent authorities, except where necessary to eliminate an immediate hazard to the patients, or when the change(s) that were approved by ADRENOMED AG involve only logistical or administrative aspects of the study.

7.4 Study Visits and Procedures

Study procedures are scheduled for screening, administration of study medication and for assessment of the safety and tolerability of the investigational treatment, as well as until end of study as outlined in the flow-charts (Figure 1, Figure 2 and Figure 3). The procedures on particular study days are described in more detail in the following sections.

7.4.1 Pre-Treatment: Screening

Before starting any screening procedure, patient or legally designated representative must provide written informed consent as described in protocol section 7.2.1 and 7.2.2.

The investigator will keep a log of all screened and randomized patients. For patients who were not entered into the study the reason for no enrolment must be documented.

After providing written informed consent, patient will undergo the following screening assessments including further required documentation:

- Check availability of signed informed consent form
- Assign patient identification number
- Record information on hospital and ICU admission, including date, time and location before admission in ICU (surgical, medical or mixed ICU)
- Record diagnosis of the admission (early septic shock) and origin of sepsis
  Definition:
  *Septic shock is defined as a life-threatening organ dysfunction due to dysregulated host response to a proven or suspected infection which leads to a decline of MAP < 65 mmHg, which is refractory** to fluid resuscitation and requires sustained vasopressors*
  *** Refractory: Defined as lack of response to the administration of 30 mL of normal saline/kg body weight or according to a clinician's assessment of inadequate hemodynamic results*
- Record time from hospital admission to ICU admission
- Record starting time of vasopressor administration due to septic shock
- Document medical history including all ongoing conditions and relevant medical history and co-morbidities present or treated within the last year (cardiovascular and non-cardiovascular) and concomitant illnesses present at inclusion (see section 8.2)
- Record concomitant medication, age, gender and Ethnic origin (see section 5.6, 8.1)
- Conduct physical examination, body weight and height (see section 8.1, 8.3)
- Record vital signs (blood pressure, heart rate, MAP, respiratory rate and oral or tympanic temperature) (see section 8.4)
- Record 12-lead ECG (supine or semi-supine position) (see section 8.7)
- Record Echocardiography (optional) (see section 8.14)
- Blood sampling for laboratory examinations (see section 8.8) of:
- BUN or urea, sodium, potassium creatinine, total bilirubin, platelet counts, hemoglobin, hematocrit, blood lactate concentration, white blood count, differential blood count Perform pregnancy test (urine or serum) (see section 8.8)
- Blood sampling for measurement of bio-ADM plasma concentration by using sphingotest® bio-ADM^{CDx} (see section 8.9.1 - **Cave: In case bio-ADM is ≤ 70 pg/mL patient will not qualify for inclusion)**
- Calculation of APACHE II score (see Appendix 2)
- Evaluation of organ dysfunction by calculation of SOFA score (see section 8.10)

- Check of inclusion / exclusion criteria
- Recording of (S)AEs

7.4.2 Eligibility Confirmation:

For patients who meet all inclusion criteria and do not meet any of the exclusion criteria a site authorization worksheet will be completed and forwarded to the central CCC in Brussels for confirmation of patients' eligibility.

7.4.3 Day 1: Start of Treatment

Permission for randomization for the central CCC granted by receipt of the authorization number. The patient will then be randomized to one of the two treatment arms (A or B) or to the control group (placebo) and the following activities and assessments will be performed:

- Prior to IMP infusion:
  - Blood sampling for central laboratory assessment of MR-proADM and biomarkers (see section 8.9.2) and PK (at designated centers only) (see Figure 2, section 8.11)
  - arterial blood collection for measurement / calculation of PaO2/FiO2 and arterial pH (see section 8.8)
  - Evaluation of organ dysfunction by calculation of SOFA score (see section 8.10)
- IMP administration of body weight adjusted dose (see section 6.3) as intravenous infusion using an infusion pump over approximately 1 hour within 12 hours after start of vasopressor administration due to septic shock
- Recording of vasopressors therapy (drug, highest / lowest dose, duration) (see section 5.9)
- Recording of cornerstone medication and concomitant medication (see section 5.8)
- Start of calculation of daily fluid balance according to baseline body weight (see section 8.6)
- PK blood sampling (at designated centers only) 30 minutes after end of infusion (see Figure 2, section 8.11)
- Recording of vital signs (minimum / maximum valueat)
- Recording of (S)AEs

<u>Day 2 – Day 28 (or discharge, whatever comes first)</u>

Day 2 and all consecutive days will start with the ICU day change (with the next morning routine which starts according to the individual hospital's time schedule). Each hospital follows its own time schedule for the morning routine.

The following activities and assessments will be performed during stay on ICU:

- Daily recordings of vital signs (minimum / maximum values within 24 hours)
- Daily arterial blood sampling for PAO2/FiO2 (if arterial line in place) and arterial pH **until day 7**
- Daily blood sampling for laboratory examinations **until day 7 and on day 28**:
  BUN or urea, sodium, creatinine, total bilirubin, platelet count, hemoglobin, hematocrit, blood lactate concentration, white blood count
- Daily blood sampling for laboratory examinations from **day 8 to day 28** (during stay in ICU):
  - PAO2/FiO2 (if arterial line in place) and arterial pH, creatinine

  - Blood sampling every other day: total bilirubin, platelet count, blood lactate concentration
- Daily recording of vasopressors therapy (drug, highest / lowest dose, duration)
- Daily recording of cornerstone medication and concomitant medication
- Daily calculation of daily fluid balance according to baseline body weight for 24 hours
- Daily evaluation of organ dysfunction by calculation of SOFA score
- Blood sampling for central laboratory assessment for MR-proADM and biomarkers at 24 hours, 48 hours, 96 hours and 144 hours or at discharge (whatever comes first) after end of IMP infusion
- PK blood sampling (at designated centers only) at 24 hours, 48 hours, 96 hours, 144 hours and on day 28 (after 648 hours, in case patient is not discharged from ICU) after end of IMP infusion
- Recording of (S)AEs
- Perform pregnancy test on day 28 (urine or serum for patients not discharged from ICU prior to day 28)
- Completion of Quality of Life Questionnaire Euro-QoL-5 on day 28 (on discharge day whatever comes first)

Patients may be discharged from ICU on day 28 or earlier depending on patients' conditions. It is the investigator's decision to keep patients under medical supervision as long as needed to protect their safety.

7.4.4 Follow-up Period

Day 28 (+/- 3 days)
The following activities and assessments will be performed for all patients already discharged from ICU prior to day 28:

- Recording of vital signs
- Blood sampling for laboratory examinations:
  BUN or urea, sodium, creatinine, total bilirubin,platelet count, hemoglobin, hematocrit, blood lactate concentration, white blood count
- Record cornerstone medication and concomitant medication
- Perform pregnancy test (urine or serum)
- PK blood sampling on day 28 (648 hours) after end of IMP infusion
- Recording of all (S)AEs since discharge from hospital
- Completion of Quality of Life Questionnaire Euro-QoL-5

Patients already discharged from hospital and not returned to perform the required assessments for day 28 in the follow-up period will be contacted by phone to ensure all deaths and hospitalizations and their causes are captured.

Day 90 (+/-3 days)
Follow-up contact by phone will be performed when the patient is not hospitalized anymore. If patient is anticipated to visit the hospital as part of routine follow-up then this can be combined.

All patients will be contacted by phone 90 days after enrollment into the study to ensure all deaths and hospitalizations and their causes are captured. The paper telephone Quality of Life Questionnaire Euro-QoL-5 will be completed by the interviewer with the answers from the

patient on line. Further the patient will be asked if he has experienced any (S)AEs since the last contact including any treatments. In case of a pregnancy, course and outcome will be followed up.

7.4.5 Screen Failure Patients

Patients who did not get permission to be randomized by the central CCC in Brussels after completion of the screening procedures (see 7.4.1) or who decline study participation before receiving IMP will be defined as screen failures.
Additional informed consent from the patient or the legally designated representative of the patient has to be obtained for collection of the following data:

Screening – day 14 (or discharge)
Patients will be contacted by the Investigator for the calculation of the SSI during stay at ICU.

Follow-up Period Day 28 and Day 90
Patients will be contacted by phone for recording and evaluation of the patient's survival or death.

7.5 Premature Discontinuation

All patient have the right to withdraw formal consent without prejudice at any time during the study. If a patient withdraws formal consent, the investigator should make a reasonable effort to determine the cause for withdrawal of consent. For these patients, as well as all other patients who require premature discontinuation due to ADRECIZUMAB, the investigator should make a reasonable effort to complete all trial procedures listed above for day 28 or discharge.

7.6 Visit Window

The study flow chart (see Figure 2.1) must be followed. However, under special conditions, e.g. holidays, weekends, etc. a window of +/- 3 days is allowable for the day 28 follow-up visit as well as for the follow-up phone call on day 90. These visit windows are not applicable for day 1 through day 28 or discharge.

8. STUDY PROCEDURES

8.1 Demography

Demographic data are to be collected at screening and will include age, gender, Ethnic origin as well as body weight and height.

8.2 Medical History

In addition to the diagnosis of early septic shock all ongoing conditions and relevant medical history and co-morbidities present or treated within the last year (cardiovascular and non-cardiovascular) and concomitant illnesses present at inclusion need to be documented. Whenever possible, diagnosis and not symptoms will be recorded.

Cardiovascular co-morbidities:	**Non cardiovascular co-morbidities:**
Chronic Heart Failure	COPD
Hypertension	Chronic Renal Disease
Diabetes Mellitus	Hemodialysis
Blood Lipid Disorder (Dyslipidemia)	Chronic Liver Disease
Obesity	Active / recent malignant tumors
Coronary Artery Disease	Depression
Stroke or Transient Ischemic Attack (TIA)	Anemia
Peripheral Artery Disease	HIV
Congenital Heart Defect	Dystyroidism
Severs valval disease or previous valvar surgery	Chronic Inflammatory Disease
Pulmonary embolism	Cognitive dysfunction
Atrial fibrillation / flutter	Alcohol (> 30g/day for male and > 20g/day for woman)
Pulmonary Hypertension	
LVEF % (if available)	Smoking (active or stopped within the last year)

8.3 Physical Examination

Physical examination including general appearance will be assessed at inclusion into the study.

Physical examination will include the following body systems:

- Mouth, ear, nose, throat
- Thyroid and neck
- Lymph nodes and spleen
- Respiratory system
- Cardiovascular system including blood pressure measurements in sitting position
- Abdomen
- Musculoskeletal system
- Central and peripheral nervous system
- Skin

8.4 Vital Signs and Body Temperature

Vital signs (blood pressure, heart rate, MAP, respiratory rate and oral or tympanic temperature) will be collected at screening and daily from day 1 to day 28 or discharge as well as on the follow-up visit day 28. Vital signs must be assessed as min/max values within 24 hours except at screening and on the follow-up visit day 28.

8.5 Glasgow Coma Scale

GCS will be used for daily assessment of impairment of conscious level in response to define stimuli after confirmation of eligibility on day 1 shortly before IMP administration. Lowest (worst) value of GCS will be recorded daily from day 2 to day 28 or discharge. Observations on patient's current conditions regarding opening eyes, verbal communication and motoric reactions will be assessed.

In the calculation of the score, the worst value for each paramenter in the 24 hours period will be used. When patient is stable, the estimation would be based on clinical experience. In sedated patients, the Glasgow Coma Score Scale at the time of the intubation will be used to evaluate the neurological status. When sedation is removed, the GCS is recorded to actual values. In the rare event that the patient experiences a stroke or bleeding after the initial intubation the GCS estimation of 3 – 4 will be used.

8.6 Fluid Balance

Daily fluid intake will be calculated as the sum of all intravenous and oral fluids. The daily fluid output will be calculated as the sum of the volume of urine output, ultrafiltration fluid, drain fluid, and estimated gastrointestinal losses (including stools only in the presence of profound diarrhea). Insensitive losses will not be taken into account because they are difficult to assess reliably. Daily fluid balance (according to baseline patient weight) will be calculated by subtracting the total fluid output from the total intake. Day 1 is defined with start of IMP infusion (whatever time it is) unil the next ICU day change at the individual hospital. Depending on IMP administration time day 1 can last more or less than 24 hours.

8.7 12-lead ECG

A standard 12-lead ECG will be recorded at screening in supine or semi-supine position, if not already done at any time after diagnosis of septic shock.

The ECG device will compute overall rhythm analysis, heart rate, P wave, PQ interval, QRS duration, QT and QTc intervals. The QT interval will be corrected for heart rate (QTc) using Bazett's and Fridericia´s formula (QTcB and QTcF). Each original ECG recording will be evaluated by the investigator following automated measurement, and the interpretation of the results will follow the categories 'normal', 'abnormal, not clinically significant', or 'abnormal, clinically significant'. ECG results will only be defined as an AE, if they are evaluated as 'abnormal, clinically significant'. The investigator will evaluate and assesst the print out with initials and date. The tracing must then be stored with the patient's source documents.

ECG recording will be printed as an original rhythm strip with at least 5 evaluable ECG complexes (cardiac cycles) for each lead. To avoid any variability caused by relocation, self-adhesive electrodes should be used for ECG recording.

8.8 Local Laboratory Assessments

Laboratory examinations are done locally as part of routine clinical care during stay in ICU and at the day 28 follow-up visit. In order to verify the patient's eligibility for the study during screening, lab values can be used which have already been analysed for clinical routine (e.g. routine blood test at ICU) and not for study purposes specifically. However, only documentation from lab analyses should be considered, which is closest to the timepoint of IMP administration.

A center specific table of the reference ranges for each of the laboratory parameter measured with a description of the methods will be available in the Investigator's Site File and sent to the sponsor before the study starts. Changes in reference ranges or in the methodology during the course of the study are to be communicated to the sponsor by the investigator.

Laboratory values outside the reference ranges require a written comment by the investigator regarding their clinical significance throughout the clinical study. Evaluation and assessment by the investigator will be documented by dated signature or initials. Any lab abnormality assessed as "CS" must be recorded as an AE if not explained by a coexisting condition (documented in the medical history or reported AE during the study).

If clinically relevant abnormal values are obtained at any time during the course of the study additional blood samples for laboratory tests should be taken at the respective clinical unit.

8.8.1 Day 2 through day 7 or discharge (whatever comes first)

Daily blood collection (taken at the morning routine) for assessment of safety laboratory markers (hematology – blood sample up to 2 mL blood, biochemistry – blood sample approximately 2,5 mL) will be performed.

The following parameters will be assessed:
BUN (calculated) or urea, sodium, potassium (at screening only), creatinine, total bilirubin, platelet count, hemoglobin, hematocrit, blood lactate concentration, whith blood count, differential blood count (at screening only).

Blood Gas Analysis (BGA):
PaO2/FiO2, arterial pH: Arterial blood collection (0,1 mL) will be performed for measurement/calculation of PaO2/FiO2 and arterial pH. Recordings are to be performed prior to IMP administration (day 1), minimal value as well as maximal value and each day thereafter (until ICU discharge) or removal of arterial line.

8.8.2 Day 8 through Day 27 or discharge (whatever comes first):

The following parameters will be measured daily: PaO2/FiO2 (if arterial line in place), arterial pH and creatinine. Total bilirubin, platelet count and blood lactate concentration will be measured every other day.

8.8.3 Follow-up Day 28:

For assessment of safety laboratory markers a blood sample (approximately 4,5 mL) will be collected for analysis of BUN (calculated) or urea, sodium, creatinine, total bilirubin, blood lactate concentration, platelet count, hemoglobin, hematocrit, white blood count.

8.8.4 Pregnancy test

Pregnancy test (urine or serum ß-HCG) will be performed in all women to assure that no pregnant women is included in the study. Female patients who are not of childbearing potential due to being postmenopausal (2 years without menstruation) or surgically sterilised (oophorectomy, hysterectomy and/or tubal ligation) do not need a pregnancy test.

Pregnancy test will be performed before randomization and on day 28 (for patients still on ICU) or on day 28 follow-up (for patients discharged from ICU). Inquiry regarding a potential pregnancy will be made by the investigator at Day 90 (no test to be performed).

8.9 Blood Sampling for bio-ADM and Biomarker

8.9.1 Blood Sampling for measurement of bio-ADM (screening)

For measurement of bio-ADM concentation a 5 mL EDTA plasma sample will be collected (derived from EDTA blood). For measurement of bioactive Adrenomedullin in human EDTA-plasma the sphingotest® bio-ADM^{CDx}, a immuno luminometric assay (ILMA) will be used. ADM measurement should be performed **before** randomization. Any ADM measurement performed after randomization will immediately exclude the patient from the study.

Bio-ADM is stable for up to 24 hours in EDTA blood and plasma at room temperature. The sample will be centrifuged, marked with the patient identification number and the sphingotest® assay performed according to the sphingotest® bio-ADM^{CDx} instruction manual. The remaining plasma will be stored at -20 ºC or below at the site until shipment to the central laboratory (Sphingotec GmbH in Hennigsdorf, Germany) for re-evaluation of the bio-ADM concentration.

8.9.2 Blood Sampling for Biomarker for central laboratory

Blood samples for determination of the biomarkers MR-pro-ADM, inflammatory biomarkers PCT, IL-6 and penKid will be taken prior to start of IMP infusion (day 1) and within the time frame of 24 hours +/- 10 hours after end of IMP infusion (day 2). Further timepoints for blood sampling for determination of the biomarkers will follow as specified in Figure 2.

All remainings of the blood samples are stored for future analysis of additional exploratory biomarkers suitable for the safety and efficacy evaluation of the study. Excluded are any genetic analyses.

EDTA blood, 2 samples of 7 mL content (resulting in approximately half the volume of plasma) are collected at each time point.

The samples will be centrifuged within 3 hours of blood collection, marked with the patient identification number and stored at -20 ºC or below (please refer to laboratory manual).

All biological samples to be gained for the measurement of the biomarkers shall be shipped on dry ice to Sphingotec GmbH in Hennigsdorf, Germany. Sphingotec GmbH will be responsible

for organization of shipment and evaluation of samples at Sphingotec GmbH (bio-ADM, PCT, penKid) and at MVZ Gemeinschaftslabor Cottbus in Cottbus, Germany (MR-pro-ADM, IL-6).

Shipments from the site to the central laboratory should be done according to sponsor request, by secure transportation company that will provide boxes and dry ice.

8.10 Organ Dysfunction Characterized by SOFA Score

It is intended to calculate the SOFA score on each day the patient remains in the ICU from day 1 (shortly before IMP administration) and daily from day 2 through day 28 or discharge (whatever comes first) as an expression for organ dysfunction. Therefore, kidney function, Glasgow Coma Score, invasive/non-invasive mechanical ventilation and blood gas, liver function and coagulation system and vasopressor use will be documented daily. The data entered for day 1 must all be pre-treatment in order to calculate the baseline score. Data to be recorded for day 2 to day 28 are always the worst values within 24 hours. Therefore minimum and maximum daily values are collected for vasopressor dose and the laboratory parameters PaO2/FiO2, creatinine, total bilirubin and platelet count.

8.11 Pharmacokinetic Analysis - Substudy

Pharmacokinetic (PK) samples from 80 patients will be collected at designated sites participating in the PK substudy.

Plasma samples for PK analysis from 80 patients receiving either ADRECIZUMAB 2 mg/kg body weight (treatment arm A) or ADRECIZUMAB 4 mg/kg body weight (treatment arm B) or placebo (control group) will be drawn at time points provided in Figure 2 for determination of plasma concentration of free ADRECIZUMAB.

Blood samples (2 mL EDTA blood at each time point) will be obtained prior to IMP dosing and after 30 minutes as well as 24 hours 48 hours, 96 hours, 144 hours and 648 hours after end of infusion (during stay in ICU or on day 28 follow-up, if patient is discharged from ICU prior to day 28).

The allowed time windows for the respective time points are given in Figure 2.. Blood (approximately 2 ml) will be collected in EDTA plasma tubes. The samples will be centrifuged. Separated plasma will be split into two aliquots of at least 0,5 mL and transferred into two tubes labelled with the patient identification number to ensure blinding of the analytical data. The samples will be frozen and stored at -20 °C or below within 2 hours.

One aliquot will be stored as back-up sample at the center up to finalization of laboratory measurements or will be shipped to the laboratory according to the sponsor's decision.
One aliquot will be shipped on dry ice based on an agreed schedule to

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2120 Dunakeszi
Hungary

Details about procedures for collection, processing, labeling, storage, and shipment of PK samples will be provided separately in a laboratory manual.

8.12 Contraception, Pregnancy, Breastfeeding

8.12.1 Contraception

Female patients who are not of childbearing potential due to being postmenopausal (2 year without menstruations) or surgically sterilized (oophorectomy, hysterectomy and/or tubal ligation) do not need to use contraception to be eligible for the study. All other female patients are considered to be of childbearing potential.

Women of childbearing potential and sexually active men must use highly effective contraception after randomization and until 6 months after the end of intravenous infusion. The following contraception methods are considered highly effective:

- Hormonal (estrogen and progesterone) contraception (oral, intravaginal, trans-dermal) associated with inhibition of ovulation
- Progesterone-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation
- Intrauterine deviced (IUD) or intrauterine hormone releasing systems (IUS)
- Bilateral tubal occlusion
- Vasectomy

Women who become pregnant while participating in the clinical study must discontinue immediately. The pregnancy must be reported following procedures detailed in Section 9.3.1. Also any pregnancy that occurs in a female partner of a male study participant must be reported and followed-up for its outcome.

Patients should be informed that taking ADRECIZUMAB may involve unknown risks to the fetus if pregnancy were to occur during the study. In order to participate in the clinical study they must adhere to the contraception requirement (described above) for the duration of the study up to 6 months after the end of intravenous infusion of IMP. If there is any doubt whether a patient will reliably comply with the requirements for contraception, that patient should not be entered into the study.

8.12.2 Pregnancy

The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated.

The outcome of the pregnancy will be reported to the safety department of the sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g. death, abortion, congential anomaly, or other diabling or life-threatening complication to the mother or newborn). The investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the sponsor (see Section 9.4).

8.12.3 Breatfeeding Women

It is unknown whether ADRECIZUMAB is excreted in human milk. Because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for randomization.

8.13 Patient Reported Outcomes

Euro-QoL – 5 Quality of Life Short Form will be completed at the day of discharge from ICU (day 2 to day 28, whatever comes first), and on follow-up day 28. Patients will be called from the investigator's site on follow-up day 90 after end of infusion of study medication for completion of the paper telephone Euro-QoL – 5 Quality of Life Short Form.

8.14 Echocardiography (optional)

If transthoracic or transeosophageal echocardiography is performed at screening , left ventricle end-diastolic diameter, right ventricular end-diastolic diameter, inferior vena cava diameter (and respiratory variation) and left ventricular ejection fraction will be recorded. Each original echocardiography recording will be evaluated by the investigator following automated measurement, and the interpretation of the results will follow the categories "normal", "abnormal, not clinically significant", or "abnormal, clinically significant".

Results from echocardiography evaluated by routine clinical care at the ICU or through retrospective analysis close to IMP administration can also be used.

9. PHARMACOVIGILANCE

9.1 Definitions

9.1.1 Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a patient or clinical study patient administered a product and which does not necessarily have a causal relation-ship with this treatment.

Examples of AEs include one of the following or a combination of two or more of these factors:

- Any unfavourable and unintended sign, symptom, illness, or syndrome
- Abnormal laboratory values, if judged clinically significant in the opinion of the investigator
- Worsening (change in nature, severity or frequency) of a concomitant or pre-existing illness
- An adverse event of the IMP including comparator or concomitant medication
- Drug interactions
- An adverse event of an invasive procedure required by the protocol
- An accident or injury

Any new data that may lead to:

- A re-evaluation of the benefit and risk ratio of the research or product being researched
- Changes in the use of this product, in the research throughout study conduct, or research related to materials, or
- Suspension or discontinuation or modification of the research protocol or similar research (even if the new data occurred in another country).

For trials involving the first administration or use of a health product in persons with no conditions: any serious adverse reactions.

All AEs fall into one of two categories: “non-serious” and “serious” (see Section 9.1.2).

Pre-existing illness or symptoms of the sepsis should only be recorded as AEs if they worsen during the course of the treatment, i.e. either change by one degree of the CTCAE grading from baseline, or significant clinical change in severity (for CTCAE grading, please refer to Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, June 14, 2010).

Surgical procedures or other therapeutic interventions themselves are not AEs, but the condition for which the surgery/intervention is required is an AE and should be documented accordingly.

Planned surgical measures and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the period of observation and did not worsen during the trial. In the latter case the condition should be reported as medical history.

9.1.2 Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that at any dose (including overdose):

- Results in death

- Is life-threatening
  "Life-threatening" means that the patient was at immediate risk of death at the time of the SAE; it does not refer to an SAE that hypothetically might have caused death if it were more severe.
- Requires subject hospitalization or prolongation of existing hospitalization.
  This means that hospital patient admission or prolongation of hospital stay was required for the treatment of the AE, or that they occurred as a consequence of the event. Visits to a hospital by ambulance or to the emergency room without admission will not be regarded as hospitalization unless the event fulfils any other of the seriousness criteria.
- Results in persistent or significant disability or incapacity
  "Persistent or significant disability or incapacity" means a permanent or significant and substantial disruption of a person's ability to carry out normal life functions.
- Is a congenital anomaly or birth defect
- Is an important medical event
  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in patient hospitalization, or the development of drug dependency or drug abuse.
  A diagnosis of cancer/malignant tumor during the course of a treatment should always be considered as medically important.

Clarification of the difference in meaning between "severe" and "serious": The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Other events to be reported on the SAE report form:

- Misuse and overdose:
  Drug misuse and drug overdose should be reported in the same format and within the same timelines as an SAE, even if they may not result in an adverse outcome. If no SAE is associated, the case will be regarded as non-serious.
  An overdose is defined as any dose higher than the assigned treatment dose (i.e. if a patient assigned to a dose > 8 mg/kg body weight, this would qualify as "overdose").
- Exposure to drug during pregnancy or lactation:
  In the unlikely event of a pregnancy occurring during the course of this particular study, the patient should be withdrawn from study, but closely followed up during the entire course of the pregnancy and postpartum period. All recommendations described in the investigational drug brochure during pregnancy and lactation have to be carefully considered.

The sponsor must be notified without delay. Parental and neonatal outcomes must be recorded even if they are completely normal and without Adverse Events. Offspring should be followed up for at least 8 weeks after delivery.

Longer observation periods may be determined by the sponsor if an adverse outcome of the pregnancy was observed.

9.1.3 Recommendations to Treat Overdosing and Intoxication with the Study Medication

No drug-specific antidote is available. Other emergencies will be treated symptomatically according to standard medical practice.

9.1.4 Investigational Product Complaints

Pharmaceutical technical complaints associated with the investigational product must be reported to the sponsor immediately:

ADRENOMED AG
Neuendorfstr. 15a
16761 Hennigsdorf
Germany

The same reporting timelines as for serious adverse events apply.

9.2 Period of Observation

For the purpose of this study, the period of observation for collection of AEs extends from screening until 90 days after end of IMP administration.

If the investigator detects an AE in a study patient after the end of the period of observation, and considers the event possibly related to prior study treatment or procedures, he or she should contact the sponsor to determine how the AE should be documented and reported.

All AEs that occur in the course of a clinical study regardless of the causal relationship must be monitored and followed up until the outcome is known (see also section 9.3.4 and 9.4). There must be documented reasonable attempts to get this information.

It is the responsibility of the investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

9.3 Documentation and Reporting of Adverse Events

9.3.1 Documentation and Reporting of Adverse Events by Investigator

The investigator must document all AEs that occur during the observation period set in this protocol in the eCRF. Additional instructions may be provided in the Investigator Site File and in the eCRFs itself.

The following approach will be taken for documentation:

All AEs (whether serious or non-serious,) must be documented on the “adverse event” page of the eCRF.

If the AE is serious (see Section 9.1.2), the investigator must complete, in addition to the "adverse event" page in the eCRF, a "serious adverse event report form" at the time the SAE is detected. This form must be sent immediately, i.e. within 24 hours from the awareness of the SAE to the safety contact of the sponsor (spm² - safety projects & more GmbH).

The investigator will document the date when any study team member had first been aware of the report and fax all SAE reports (initial and follow-up reports) even if they are incomplete within one working day upon receipt to the safety department of the sponsor:

spm² - safety projects & more GmbH
Aurum 05
Goldbeckstr. 5
69493 Hirschberg a. d. Bergstraße, Germany
Fax: 0049 - 621 - 570 5971
Email: Adrenomed-phv@spm2-safety.com

When an "overdose" or "drug misuse" of the investigational product occurs without an AE or if a "pregnancy is detected *without an adverse outcome*", the investigator should only complete a "serious adverse event report form" and send this to the sponsor's safety contact. It should be clearly stated that no AE was observed. In this case, there is no need to complete the "adverse event" page in the eCRF. The event will not be considered as serious.

Every attempt should be made to describe all AEs in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms should not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

The initial report should be as complete as possible, including details of the current illness and (serious) AE, the reason why the event was considered serious, date of onset and stop date (if applicable), diagnostic procedures and treatment of the event, relevant medical history and concomitant medication and action taken with trial medication.

9.3.2 Assessment of Severity

The investigator will also provide an assessment of the severity of the event and causal relationship between the event and the investigational product or trial procedures.

The basis of assessing severity and causality is described as:

- **Grade 1** - mild event: Causing no limitations of usual activities; the subject may experience slight discomfort
- **Grade 2** - moderate event: Causing some limitation of usual activities; the subject may experience annoying discomfort
- **Grade 3** - severe event: Causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain
- **Grade 4** - life-threatening or disabling event

- **Grade 5** - death related to event

9.3.3 Assessment of Causality

The investigator will use medical judgment to determine whether there is evidence for a causal relationship, including all relevant factors such as temporal course and latency, results from de-challenge or re-challenge, pattern of the reaction, known pharmacological properties of the product, and alternative explanations (e.g. other drugs, medical history, concomitant diseases). The investigator will apply the terms “certain”, “probable/likely”, “possible”, “unlikely” or “unrelated” to determine causality. For regulatory E2B reporting, this assessment will be converted to the binary system of “reasonable possibility” and “no reasonable possibility” (see table below). The expression “reasonable possibility” means to convey in general that there is factual evidence or argument to suggest a causal relationship. The assessment will be documented on the AE and SAE form.

The causality criteria will be used as described in the following.

Table 1: Mapping of Causality Categories to Binary Causality Assessment

Causality term	Assessment criteria*	E2B (EudraVigilance Database / EMA)
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacological or phenomenological (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Re-challenge satisfactory, if necessary	Reasonable possibility
Probable / Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Re-challenge not required	
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear	
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations	No reasonable possibility
Unrelated	• There is no evidence or argument to suggest a causal relationship.	

* All points should be reasonably complied with

9.3.4 Follow-up of Missing Information

Information not available at the time of the initial SAE report (e.g., an end date for the SAE or laboratory values received after the report) must be documented on a "Serious Adverse Event" form, with the box "Follow-up" checked under "Report type".

All subjects who have AEs, whether considered associated with the use of the investigational products or not, must be monitored to determine the outcome. The clinical course of the AE will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up. Should the AE result in death, all efforts should be

exercised to have an autopsy performed and a full pathologist's report should be supplied, if possible.

The sponsor will identify missing information for each SAE report. Requests for follow-up will be sent to the investigators for further processing. spm²will require follow-up information in regular intervals from the investigators until all queries are resolved or no further information can be reasonably expected. All responses to queries and supply of additional information by the investigator should follow the same reporting route and timelines as the initial report.

9.3.5 Determination of Expectedness, Reference Safety Information

Expectedness will be determined by the sponsor according to the designated Reference Safety Information. Any updates or substantial amendments will be considered accordingly. The Reference Safety Information for the investigational medicinal product will be the chapter "Reference Safety Information" of the current IB version for ADRECIZUMAB.

Unexpected:
An AE or suspected adverse reaction is considered unexpected if it is not listed in the Reference Safety Information or is not listed with the specificity or severity that has been observed. Unexpected, as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Reference Safety Information as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

9.3.6 Expedited Reporting of Adverse Events / SUSAR Reporting

All AEs and SAEs will be classified according to severity and causality.The sponsor will report all those serious and unexpected AEs, which are judged by either the investigator or the sponsor as having a reasonable suspected causal relationship i.e. SUSAR, to the Competent Authority, the concerned EC and the investigators according to applicable law without any delay.

Unblinding:
If applicable treatment codes will be broken prior to submission to authorities and concerned IRB/IECs, by the sponsor's safety group, which is an independent entity within the sponsor. The study team will be kept blinded regarding treatment assignment.

Development Safety Update Reports:
The sponsor will prepare and submit development safety update reports to the Competent Authority and concerned EC.

9.4 Follow-up of Adverse Events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow-up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

The Investigator is expected to record any case of unexpected pregnancy throughout the treatment and follow-up periods until 90 days after the end of treatment. With the consent of the patient, the Investigator should monitor any occurring pregnancy until delivery to record any abnormality. The Investigator must immediately communicate any case of pregnancy resulting

in an abnormal outcome (e.g. miscarriage, congenital anomaly, or stillbirth). Any such case is to be managed as SAE and reported within 24 h after awareness.

10. STATISTICAL CONSIDERATIONS

A full statistical analysis plan will be drawn up before the trial database is locked and analyzed. Prior to performing any statistical tests or fitting statistical models, an exploratory analysis of the baseline variables and outcome measures will be completed. The level and pattern of missing data in the baseline variables and outcomes will analyzed and likely causes of any missing values will be investigated.

10.1 Demographic and Other Baseline Characteristics

Demographic characteristics will be listed and summarized.

10.2 Statistical Methods for Safety Parameters

All safety and tolerability assessment will be based on the safety analysis set, which is defined as all patients who have received study medication.

10.3 Handling of Withdrawals, Protocol Deviations and Missing Values

Data from subjects who prematurely terminate the study will be used to the maximum extent possible.

Missing data in the primary efficacy endpoint will be dealt with using sensitivity analysis. Details will be outlined in the statistical analysis plan.
All protocol deviations will be listed. The deviations will be assessed as critical, major or minor with regard to their influence prior to locking the database.

The reasons for exclusion of patients from any of the analysis sets will be listed and, where relevant, the data from these patients will be described separately.

10.4 Safety Analysis

Safety monitoring will begin at the time the Informed Consent Form (ICF) is signed and will continue for 90 days after short-term infusion of study medication.

All AEs will be listed. The number and percent of patients experiencing 1 or more AEs will be summarized by treatment arm / control group, relationship to study drug and severity/grade.

SAE specific listings for each patient population will be generated on reported SAEs, but not as SUSARs .

Endpoints relevant for the primary objective of safety and tolerability are

- Mortality
- Interruption of infusion
- Treatmant-emergent adverse events
- Severity and frequency of adverse events

Demographic and medical background data, secondary endpoints and safety variables are to be analyzed by means of descriptive and exploratory methods.

Continuous variables are to be summarized by the number of patients, mean, SD, median, quartiles and range.

Categorical variables are to be summarized using number and percentage by category.

Medical terms and adverse events are to be coded using the MedDRA Version 19.1 and summarized according to system organ class and preferred term.

Concomitant medications are to be coded using the WHO-Drug Dictionary and summarized to the therapeutically chemical (ATC) terminology.

10.5 Efficacy Analysis

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

For the primary efficacy endpoints, a first analysis will determine whether the improvement due to treatment is > 0 with at least 80% probability, i.e. the lower bound of a 60% confidence interval must be larger than 0. Only if this is achieved, the classical p-value using the described methods will be calculated.

The primary analysis of the primary efficacy endpoint will be done as intention-to-treat, i.e. patients will be analyzed with respect to the group they were randomized to. A per protocol analysis will be performed, excluding patients that did not receive the treatment according to protocol or that did not meet the inclusion criteria. In case patients did not receive the treatment they were randomized to, an analysis based on the actual treatment (as-treated-analysis) will also be performed.

10.5.1 Sepsis Support Index (SSI) and Penalized Sepsis Support Index (pSSI)

SSI as primary efficacy endpoint is defined as days with organ support or dead within 14 day follow up. Organ support days are defined as days with vasopressor, mechanical ventilation or renal replacement therapy (defined as renal SOFA = 4 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 (defined as any mechanical ventilation received on this day, independent from the duration of mechanical ventilation), and/or renal dysfunction, or not alive, is counted as 1. The sum over the follow-up period is defined as SSI. SSI describes the effect of a given therapy in pre-defined patient population with sepsis at risk or septic shock.

A penalized version of the Sepsis Support Index (pSSI) is defined as above, but patients who die get penalized, i.e. the pSSI is set to 14 days. SSI and pSSI will also be evaluated for 28 day follow-up. The individual SSI components (cardiac, respiratory and renal failure), as well as an SSI-Version excluding the renal component, will also be evaluated separately.

The non-parametric Wilcoxon test will be used to test the treatment effect.The effect measure, delta SSI, will be estimated by the Hodges-Lehmann estimator.

A third version of a composite endpoint is also considered: Persistent organ dysfunction or death at 14 and 28 day follow up (as defined by *[5]*).

10.5.2 All-cause Mortality at Follow-up Day 28 and Day 90

All-cause mortality will be evaluated using Kaplan-Meier plots comparing treatment vs. placebo (log-rank test) and Cox regression modelling including covariates to adjust for potential confounders, e.g. severity, age and others.

10.5.3 SOFA Score

The SOFA score will be evaluated daily for all patients over the entire stay on ICU (as long as the arterial line is in place) until day 28 or discharge (whatever comes first).

In the calculation of the score, the worst values for each parameter in the 24 hours period will be used. In sedated patients, the GCS at the time of intubation will be used. When sedation is removed, the GCS is recorded with actual values. In the rare event, that the patient exeriences a stroke or bleeding after the initial intubation the GCS estimation of 3 – 4 will be used. When the patient is stable, the estimation would be based on clinical experience.

When using the SOFA score as an endpoint, patients deceased will be assigned the maximum SOFA score (24). If the patient has been transferred from ICU to another ward and / or home the SOFA score will be set to0.

The total SOFA score will be calculated as the sum of daily SOFA scores during the ICU stay for each patient. The mean SOFA score is defined as the total SOFA score divided by the length of stay in the ICU. 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. The change in SOFA score is defined as the difference between the SOFA score 48h post admission and baseline.

Appropriate parametric and or non-parametric methods will be applied for the various endpoints based on SOFA score.

10.6 Sample Size Determination / Power Analysis for Primary Efficacy Endpoint (SSI within 14 days)

Power simulations are based on using real patient data on the combined endpoint from the ALBIOS study, and underlying assumptions were re-evaluated using results from the AdrenOSS observational study..

- **Details of the simulation:** 1,000 simulations using real patient data from ALBIOS (n=539)
- Simulated sample size: n=150 per group (sampling with replacement)
- Simulated effect size: 10% average reduction in the treated group, irrespective of treatment dose
- p-values, confidence intervals and point estimates [=pseudo-median] based on Wilcoxon rank test
- Simulation includes interim futility stop
- Patients may not have less than 1 day with organ support (as vasopressor is given at day 1 by definition)

Power Analysis Assumptions

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.

Interim Analysis with Futility Stop
An interim analysis is planned after 50% of patients (n=150) completed study day 28. The study will be stopped if the probability of a positive outcome is below 40% once 50% of patients (n=150) completed study day 28. Power remains >80% if futility stop is included in simulation. "Positive outcome" of the study will be defined in the SAP.

Power Considerations Summary
Based on the described simulation, 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 (discontinue if the probability of success is less than 40%). Details will be outlined in the SAP.

10.7 Statistical Methods for Pharmacokinetic Parameters

The analysis plan for PK assessment for the study will be part of the SAP.

PK of ADRECIZUMAB profile is studied after single administration of ADRECIZUMAB 2 mg/kg and 4 mg/kg in order to determine key PK parameters, including peak plasma concentrations (C_{max}), systemic exposure (AUC), volume of distribution (V), systemic clearance (CL), and elimination half-life ($t_{½}$) (in 80 patients only).

10.8 Analysis of Observational Data and Exploratory Analysis

Several post-hoc analyses using all patients included in the study are planned, such as analyzing the association between 28 day mortality rate/ vasopressor use/ ventilation and bio-ADM.

Exploratory post-hoc analysis of efficacy endpoints in patient subgroups defined by severity, other biomarkers, concomitant medication or other clinical data will be performed, as well as interactions with other drugs, in order to identify subgroups which possibly benefit overproportionally from treatment with Adrecizumab.

11. DATA MANAGEMENT and DATA HANDLING

11.1 Data Management

All data management activities will be done according to ICH-GCP as required by regulatory agencies. Responsibility for data management lies with the designated CRO following their internal standard operating procedures (SOPs).

The designated CRO will be responsible for the activities associated with the data management of this study, including the production of an eCRF, setting up a relevant database, along with appropriate validation of data and resolution of queries. All data will be entered into an eCRF. Automated and manual checks will be made against the data to ensure completeness and consistency.

AEs will be standardized for terminology and classification, using MedDRA dictionary. Concomitant medications will be classified by site of action, therapeutic and clinical characteristics using the WHO-DRUG dictionary. Clean data sets will be provided for statistical analysis and reporting.

11.2 Data Handling and Recording of Data

All data collected during the study have to be recorded in an electronic CRF (eCRF) which is provided in an internet portal. This eCRF will be designed by M.A.R.C.O. GmbH & Co. KG (M.A.R.C.O) in the Amedon system. The Amedon system has been validated by Amedon GmbH for use in clinical studies. Validation checks will be implemented in the system or programmed with SAS®, Version 9.1 or higher according to the data validation plan set up by M.A.R.C.O.

Personnel at the site will be trained on the use of the eCRF. All investigator site personnel seeking access must go through training process before they are granted access to the system. Training records are maintained. All access to the internet portal is password protected.

All personnel with access to the system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

The investigator is responsible for ensuring that all sections of each eCRF are completed correctly, and that entries can be verified against source data. If certain data are not available or not applicable this will be indicated as such on the appropriate space on the eCRF. The study monitor will review the eCRFs and check them for completeness. In case of any missing data, inconsistencies, implausible values or other imperfections the data manager or the monitor will supply the site with queries, so that the investigator can correct this. It will also be done within the electronic system.

The system contains a system-generated audit trail that captures any changes made to a data filed, including who made the change and the date and time the change was made.

Addenda of the eCRF (i.e. clinical laboratory reports, ECG printouts) should bear the patient identification number, allocated randomization code, study day and time, and signature of the investigator.

Clinical laboratory parameters will be provided in laboratory print-outs which are to be signed by the investigator. Comments on all clinically significant abnormal values should be given by the investigator on these print-outs and will then be transferred into the eCRF.

11.3 Source Data

Source data is all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, consultant letters, screening and enrollment logs etc.

The investigator is responsible to record all study related source data enabling the sponsor to reconstruct the complete course of the clinical study. Source data will be transcribed to and reported through the eCRF accordingly.

12. ETHICAL CONSIDERATIONS

12.1 Good Clinical Practice

The investigator will ensure that this clinical study is conducted in accordance with the principles of the Good Clinical Practices (GCP), ICH Guidelines, and the Declaration of Helsinki and with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the patient.

12.2 Independent Ethic Committees (IEC) and Competent Authorities (CAs)

The study will only start after approval of the study protocol and all relevant documentation by the IRB/IEC and CA of the participating countries.

In addition, all local national legal requirements for the conduct of a clinical study have to be followed prior to the start and during the study.

The CA and IECs of the participating countries will be informed about any changes in the study protocol, the end of the study, or the premature study termination as appropriate and within the requested time period.

12.3 Subject Insurance

Insurance for patients included in this study will be arranged by ADRENOMED AG as sponsor of the clinical study according to country-specific requirements. A copy of the insurance certification will be held in the study master file at ADRENOMED AG. Patients are to be informed by the investigator of the existence of the insurance, and that they have the right to inspect the terms and conditions of said insurance or may receive a copy, if required per national legislation.

12.4 Steering Committee

The Steering Committee oversees all aspects of the study and during the study will remain blinded to treatment group results. The Steering Committee has the authority to propose protocol amendments to the sponsor based on its monitoring of the progress of the study, including reports or recommendations received from the DSMB.

The Steering Committee will be responsible for approval of the final protocol for the study, the substudy and the publication of study results. The Steering Committee will meet regularly to monitor the progress of the study using blinded tabulations based on all patients. The Steering Committee will also approve the interim and final analysis dates proposed by the DSMB on basis of event accrual. Based on recommendations from the DSMB, the sponsor in conjuction with the Steering Committee has the authority to stop the study for unexpected safety reasons.

Membership will include one coordinating investigator for each involved country and representatives of the sponsor. Chairpersons are Prof. A. Mebazaa, France, Prof. P.F. Laterre, Belgium, Prof. G. Marx, Germany and Prof. P. Pickkers, Netherlands.

12.5 Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) will be established and serves as an independent group responsible for the ongoing review of a clinical trial and for making recommendations to the sponsor concerning the continuation, modification, and termination of the trial throughout the study conduct. The key responsibilities of the DSMB are to ensure patient safety by routine review of overall safety data including all SAEs, SUSARs, all severe AEs, AESIs and AEs leading to drug or study discontinuation and, where applicable, literature cases and information from Competent Authorities (CAs) and by judging the relevance of the events for patients' safety.

The DSMB will operate independently of the Steering Committee and the sponsor.

The specific composition and working procedures are described in the Charter of the DSMB. The DSMB will be comprised two clinical experts in the field of sepsis, a biostatistician and a Pharmacovigilance representative. The DSMB Chair and committee members will be selected by the sponsor and the Steering Committee.

The DSMB will monitor a subset of safety data on monthly intervals during the study. For these monitoring activities data on SAE & SUSAR (including fatal outcome) will be provided aggregated, stratified by treatment groups to the members of the DSMB. The data will be presented in semi-blinded fashion (assignment into group A, B or C). In addition the DSMB will routinely review severe AEs, AESIs and AEs leading to drug or study discontinuation.

Based on the results of these monitoring activities, the DSMB is empowered to recommend to the Steering Committee any change in the design of the study required to ensure the safety of the enrolled patients and the scientific integrity of the study.

13. ADMINISTRATIVE STRUCTURE AND RESPONSIBILITIES

13.1 Study Monitoring

This study will be monitored according to the monitoring plan which will be prepared and filed in the study master file prior to initiation of a study site. The monitor is responsible for routine review of the eCRFs at regular intervals throughout the trial to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered into them. The monitor should have access to any patient records needed to verify the entries on the eCRFs.

The investigator will allocate adequate time for such monitoring activities and ensure that the monitor has adequate space to conduct the monitoring visit. The investigator agrees to assist the monitor in resolving any problem that may be detected during the monitoring visit or data cleaning process.

The investigator will be contacted by the study monitor on a regular basis. The monitor will have the responsibility of reviewing the ongoing study with the investigator to verify adherence to the protocol and to deal with any problems. eCRFs will be checked for completeness and consistency with the source data. At all times, the confidentiality of study-related documents will be maintained.

The investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given direct access to study related facilities (e.g. pharmacy, diagnostic laboratory, etc.) and all the study-related documents (source data) which supports the data on the eCRFs for the study. Direct access is defined as the permission to examine, verify, and reproduce any records and reports that are important for evaluation of a clinical study. Any party allowed direct access to study source data and documents should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identities and sponsor proprietary.

13.2 Investigator Study File

The investigator is responsible for keeping files of essential documents as defined by the ICH guidelines on GCP and local requirements. The Investigator's Study File must be available at monitoring visits and during an audit or inspection.

13.3 Changes in Study Conduct

For any change of the study conduct the sponsor must be contacted and must agree to such change. Substantial changes to the protocol during the study will be documented as protocol amendments. The amended protocol will be signed by the responsible personnel at ADRENOMED AG and the Principal investigator.

Depending on the contents of the amendment and local legal requirements, the amendment will be submitted to the relevant IEC and, where necessary, to the relevant CAs.

13.4 Protocol Compliance

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

13.5 Protocol Deviations

Sponsor does not allow any deviations or exemptions relating to protocol inclusion and exclusion criteria. All protocol deviations will be documented. This study will be conducted as described in this protocol except for emergency situations in which the protection, safety, and well-being of the patient requires immediate intervention based upon the judgment of the Investigator (or a responsible, appropriately trained and credentialed professional(s) designated by the Investigator).

13.6 Drug Accountability

The investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused investigational medicinal product and placebo. This includes acknowledgement of receipt of each shipment of IMP kits (quantity and condition), IMP administration records, and returned or destroyedkits of IMP. IMP records will document quantities received from the sponsor and quantities administered to patients, including date /time of administration, patient identification number and the initials of the person responsible for IMP administration.

All drug supplies and associated documentation will be periodically reviewed and verified by the monitor over the course of the study.

13.7 Audits and Inspections

The investigator will permit study-related audits, and inspections by the IRB/IEC, the sponsor, and regulatory authorities of all study-related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the availability of applicable study-related facilities (e.g. pharmacy, laboratory, etc.) for inspections.

Audits and inspections will be performed in accordance with ICH-GCP, EU Directives, and applicable local regulations to ensure that the clinical study is conducted in compliance with the study protocol requirements.

13.8 Confidentiality

The investigators, designated CRO and ADRENOMED AG and all other involved parties will preserve the confidentiality of all patients taking part in the study, in accordance with ICH-GCP and local regulations. The confidentiality of all patient identities will be maintained, except during source data verification, when monitors, auditors and other authorized agents of the sponsor or its designee, the IECs approving this research, as well as any other applicable regulatory authorities will be granted direct access to the study patients' original medical records. No material bearing a patient's name will be kept on file by designated CRO or ADRENOMED AG.

The data retained from this study will be protected in accordance with all applicable legal requirements. Information about study patients will be kept confidential and managed according to the requirements of the EU Directives 2001/20/EC, 2005/28/EC, and 2003/63/EC and relevant national and local legislations.

13.9 Patient Data and Data Protection

Permission for direct access to patient data will be sought in writing by the investigator and from the patient as part of the informed consent procedure. This gives permission to examine, analyse, verify and reproduce any records and reports that are important to the evaluation of the study. Any party (e.g., domestic and foreign regulatory authorities, clinical research associates and auditors) with direct access must take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of the patient's identity and sponsor's proprietary information.

It is the monitor's responsibility to verify that each patient has consented, in writing, to direct access. It is to be ensured by the investigator that documents that are given to ADRENOMED AG or its representatives do not contain the name or address of the patient, or other information that would affect the anonymity of the patient.

The EU General Data Protection Regulation (GDPR) will also be taken into consideration during the conduct of study.

13.10 Reports

All reports to the sponsor will be written in English. All clinical, analytical and statistical results will be presented in a final clinical study report which will be structured in accordance with ICH Topic E3.

The clinical study report will be the sole property of the sponsor. Publication of the clinical study report or of parts of it may only be allowed when authorized by the sponsor. Independently from the clinical study report, the data obtained in this clinical study will be published.

Short reports to the CA and IEC after study termination will be provided as required by law, i.e. no later than 1 year after study completion defined as last patient last visit.

13.11 Publication of Study Results

The investigator and the institution recognize that all data generated from this study are the proprietary and confidential information of the sponsor, along with all information supplied by the sponsor. The sponsor recognizes the investigator's and the institution's rights and obligations, as an academic partner, to publish the study results. The study results will be published in accordance with the good publication practice guideline of the international society for medical publication professionals. This includes but is not limited to the following principles:

The sponsor confirms the authors' freedom to make public or publish the study results and grants full access to the study data for this purpose. The investigator and the institution agree that they are not permitted to publish data related to the study independent of the sponsor and the other investigators.

The investigator and the institution plan and produce publications in a timely manner and avoid premature release of study information.

The sponsor and the investigator and other individuals who have expertise in the area and who are willing to interpret the data and write or review articles and presentations will form a publication Steering Committee to oversee the preparation of articles and presentations from this study.

Prior to any written or oral presentation of the study results or any part thereof, the investigator or the institution shall send the full text of the proposed disclosure to the sponsor (or, if applicable, the publication steering committee) for review and comments at least 60 business days prior to submission for publication or oral presentation. The sponsor reserves the right to have deleted from the proposed publication any confidential information of the sponsor with the exception for results or data generated on the basis of the study which are of scientific interest to the investigator and which may be published in compliance with this section. During the above mentioned period, sponsor in his sole discretion will take the steps he deems necessary to secure any intellectual property arising from the study results or data, including the filing or substantiating of one or more patent applications. The investigator or the institution shall follow customary principles related to scientific publications in determining and attributing authorship of any proposed publication, provided that any such publication shall acknowledge the sponsorship by the sponsor.

13.12 Study Documents and Record Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be significantly verified. These documents should be classified into two separate categories (although not limited to) the following:
(1) investigator's study file and (2) patient clinical source documents.

The investigator's study file contains the protocol and any amendments, eCRF and query records, IRB/IEC and regulatory approvals including all correspondence, informed consent forms, drug records, staff curriculum vitae and authorizations forms and other appropriate documents and correspondence.

In compliance with GCP guidelines and regulations, the investigator will keep all clinical study documents until at least two years after the last approval of a marketing application in an ICH region (i.e. United States, Europe or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until two years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements or an agreement with ADRENOMED AG.

No data should be destroyed without the consent of ADRENOMED AG.

Should the investigator assign the study records to another party or move them to another location, ADRENOMED AG must be notified in advance. If the investigator cannot guarantee these archiving requirements at the study center for any or all of the documents, special arrangements must be made between the investigator and ADRENOMED AG to store these in sealed containers outside of the center so that they can be returned sealed to the investigator in case of a regulatory audit. Where source documents are required for the continued care of patient, appropriate copies should be made for storage outside of the center.

13.13 Data Archiving

The clinical center is responsible for the secure and restrictive archiving of source data for at least 15 years or until written notification from ADRENOMED AG that the documents are no longer required. During the required period, the clinical center will ensure that archived data and documents will be undamaged, legible and accessible to the sponsor and/or for regulatory purposes, if required.

The study master file, the eCRFs, the code envelopes and other material supplied for the performance of the study will be retained by ADRENOMED AG according to applicable regulations and laws.

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APPENDICES

Appendix 1: Declaration of Sponsor and Investigator

DECLARATION OF SPONSOR

This study protocol was subject to critical review and has been approved by the Sponsor and its representatives. The following signature documents this approval.

Jens Zimmermann, MD, M.Sc.

Chief Medical Officer
ADRENOMED AG
Neuendorfstraße 15a
16761 Hennigsdorf, Germany

Signature

4-SEP-2019
Date

DECLARATION OF INVESTIGATOR

I have read the protocol, including all appendices, and I agree that it contains all necessary details for my staff and me to conduct this clinical study as described. My signature below certifies my agreement with regard to the conduct of the clinical study and the required documentation of data. I agree to comply with the protocol in its entirety and with the applicable regulations and the International Council for Harmonization (ICH) guidelines for Good Clinical Practice (GCP).

I will provide all study personnel under my supervision access to the information provided by ADRENOMED AG. I will discuss this material with them to ensure that they are fully informed about the drugs and the clinical study.

Principal Investigator Name (Printed)

Signature

Date

Center Number: _____

Appendix 2: APACHE II Score

A. Acute Physiology Score:

	PHYSIOLOGIC VARIABLE	HIGH ABNORMAk RANGE					LOW ABNORMAL RANGE			
		+4	+3	+2	+1	0	+1	+2	+3	+4
1	Temperature – rectal (°C)	≥ 41°	39 - 40.9°		38.,5 - 38.9°	36.0 - 38.4°	34 - 35.9°	32 - 33.9°	30 - 31.9°	≤ 29.9°
2	Mean Arterial = (2 x diastolic + systolic)/3	≥ 160	130 - 159	110 - 129		70 - 109		50 - 59		≤ 49
3	Heart Rate (ventricular response)	≥ 180	140 - 179	110 - 139		70 - 109		55 - 69	40 - 54	≤ 39
4	Respiratory Rate (non-ventilated or ventilated)	≥ 50	35 - 49		25 - 34	12 - 24	10 - 11	6 - 9		≤ 5
5	Oxygenation: A-aDO_2 or PaO_2 (mmHg)	≥ 500	350 -- 499	200 - 349		< 200				
	a. FiO_2 > 0.5 record A-aDO2									
	b. FiO_2 > 0.5 record PaO2					> 70	61 - 70		55 - 50	< 5
6	Arterial pH (*If no ABGs record Serum HCO3 below)	≥ 7.7	7.6 - 7.69		7.5 - 7.59	7.33 - 7.49		7.25 - 7.32	7.15 - 7.24	< 7.15
7	Serum Sodium (mMol/L)	≥ 180	160 - 179	155 - 159	150 - 154	130 - 149		120 - 129	111 - 119	≤ 110
8	Serum Potassium (mMol/L)	≥ 7	6 - 6.9		5.5 - 5.9	3.5 - 5.4	3 - 3.4	2.5 - 2.9		< 2.5
9	Serum Creatinine (mg/dl) Double point score for acute renal failure	≥ 3.5	2 - 3.4	1.5 - 1.9		0.6 - 1.4		< 0.6		
10	Hematocrit (%)	≥ 60		50 - 59.9	46 - 49.9	30 - 45.9		20 - 29.9		< 20
11	White Blood Count	≥ 40		20 - 39.9	15 - 19.9	3 - 14.9		1 - 2.9		< 1
12	Glasgow Coma Scale Enter 15 minus actual GCS – see calculations in table below	15-GCS =								
A	Total Acute Physiology Score (APS)	Sum of the 12 individual variable points =								
*	Serum HCO3 (venous-mMol/L) (Not preferred, use if no ABGs)	≥ 52	41 – 51.9		32 – 40.9	22 – 31.9		18 – 21.9	15 – 17.9	< 15

APACHE II Severity of Disease Classification System

Glasgow Coma Score (GCS) (circle appropriate response)		
Eyes open (E)	Motor response (M)	Verbal-Response (V)
4 – spontaneously	6 – to verbal command	5 – oriented and controversed
3 – to verbal command	5 – localizes to pain	4 – confused and disoriented
2 – to painful stimul	4 – withdraw to pain	3 – inappropriate words
1 – no response	3 – decorticate	2 – incomprehensible sounds
	2 – decerebrate	1 – no response
	1 – no response	
GLASGOW COMA SCORE^{+} = E + M + V		
Subjects scoring 3 or 4 have an 85 % chance of dying or remaining vegetative, while scores above 11 indicate 5 to 10 % likelihood of death or vegetative state and 85 % chance of moderate disability or good recovery. Intermediate scores correlate with proportional chances of subjects recovering.		
B. Age Points		
Age	Points	
≤ 44	0	
45 -54	2	
55 – 64	3	
65 – 74	5	
≥ 75	6	
Age points =	_____	
C. Chronic Health Points (CHE)		
If any of the 5 CHE categories is answered with yes give +5 points for nonoperative or emergency postoperative subjects, or +2 points for elective postoperative subjects Liver-Cirrhosis with Portal Hypertension (PHT) or encephalopathy Cardiovascular – NYHA Class IV angina at rest or with minimal self-care activities Pulmonary – chronic hypoxemia or hypercapnia or polycythemia or PHT > 40 mm Hg Kidney – chronic peritoneal dialysis or hemodialysis Immune – immune compromised host Chronic Health Points = _____		
APACHE-II Score is sum of A+B+C		
APS points	A _____	
Age points	+B _____	
Chronic Health Points	+C _____	
Total APACHE-II Score = _____		

Source: Adapted from Knaus WA, Draper EA, Wagner DP, Zimmermann JE (1985). APACHE II: a severity of disease classification system. *Critical Care Medicine* 13 (10): 818-29

Appendix 3: SOFA Score

SOFA Score		1	2	3	4
Organ system	Parameter				
Respiratory system	PaO_2 / FiO_2 (mmHg)	< 400	< 300	< 200 **and** mechanically ventilated	< 100 **and** mechanically ventilated
Nervous system	Glasgow Coma Scale	13-14	10-12	6-9	< 6
Cardiovascular system	Mean arterial pressure OR administration of vasopressors required	MAP < 70 mm/Hg	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]	1.2-1.9 [20-32]	2.0-5.9 [33-101]	6.0-11.9 [102-204]	> 12.0 [> 204]
Coagulation	Platelets $x10^3/\mu l$	< 150	< 100	< 50	< 20
Kidneys	Creatinine (mg/dl) [µmol/l] (or urine output)	1.2-1.9 [110-170]	2.03-3.4 [171-299]	3.5-4.9 [300-440]	> 5.0 [> 440] (or< 200 ml/d)

Use of vasopressors (dopamine, dobutamine, phenylephrine) in combination with catecholamine (adrenaline, noradrenaline*).
* used equivalent to epinephrine and norepinephrin

Appendix 4: IMP Body weight Adjustment

IMP Bodyweight Adjustment

Protocol Code: AdrenOSS-2

Weight range	IMP amount to use from EACH vial of the kit	NaCl amount
kg	ml	ml
50,0 - 50,4	5	40
50,5 - 51,4	5,1	39,8
51,5 - 52,4	5,2	39,6
52,5 - 53,4	5,3	39,4
53,5 - 54,4	5,4	39,2
54,5 -55,4	5,5	39
55,5 - 56,4	5,6	38,8
56,5 - 57,4	5,7	38,6
57,5 -58,4	5,8	38,4
58,5 - 59,4	5,9	38,2
59,5 - 60,4	6	38
60,5 - 61,4	6,1	37,8
61,5 -62,4	6,2	37,6
62,5 - 63,4	6,3	37,4
63,5 - 64,4	6,4	37,2
64,5 - 65,4	6,5	37
65,5 -66,4	6,6	36,8
66,5 - 67,4	6,7	36,6
67,5 - 68,4	6,8	36,4
68,5 - 69,4	6,9	36,2
69,5 - 70,4	7	36
70,5 - 71,4	7,1	35,8
71,5 - 72,4	7,2	35,6
72,5 - 73,4	7,3	35,4
73,5 - 74,4	7,4	35,2
74,5 -75,4	7,5	35

Weight range	IMP amount to use from EACH vial of the kit	NaCl amount
kg	ml	ml
75,5 - 76,4	7,6	34,8
76,5 - 77,4	7,7	34,6
77,5 -78,4	7,8	34,4
78,5 - 79,4	7,9	34,2
79,5 -80,4	8	34
80,5 - 81,4	8,1	33,8
81,5 - 82,4	8,2	33,6
82,5 - 83,4	8,3	33,4
83,5- 84,4	8,4	33,2
84,5 -85,4	8,5	33
85,5 86,4	8,6	32,8
86,5 - 87,4	8,7	32,6
87,5 - 88,4	8,8	32,4
88,5 - 89,4	8,9	32,2
89,5 - 90,4	9	32
90,5 - 91,4	9,1	31,8
91,5 - 92,4	9,2	31,6
92,5 - 93,4	9,3	31,4
93,5 - 94,4	9,4	31,2
94,5 - 95,4	9,5	31
95,5 - 96,4	9,6	30,8
96,5 - 97,4	9,7	30,6
97,5 - 98,4	9,8	30,4
98,5 - 99,4	9,9	30,2
99,5- 120	10	30

Appendix 5: Protocol History

Version	Date	Comment
Version 1.0	01 December 2016	Not submitted
Version 2.0	13 January 2017	Submitted in Germany
Version 2.1	31 May 2017	Not submitted
Version 2.2	14 June 2017	Valid for Germany
Version 3.0	03 July 2017	Valid for Belgium, The Netherlands
Version 3.1 – France	15 March 2018	Valid for France
Version 4.0	19 March 2018	Not submitted
Version 4.1	7-January 2019	