Study Plan of

PROSPECTIVE, RANDOMIZED, CONTROLLED, DOUBLE-BLIND, MULTI-CENTRIC, INTERNATIONAL STUDY ON THE EFFICACY AND SAFETY OF AN EARLY TARGET CONTROLLED PLASMA VOLUME REPLACEMENT THERAPY WITH A BALANCED GELATIN SOLUTION VS A BALANCED ELECTROLYTE SOLUTION IN PATIENTS WITH SEVERE SEPSIS / SEPTIC SHOCK

GENIUS (GELATIN IN ICU AND SEPSIS)

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STUDY OVERVIEW

Title of Study	PROSPECTIVE, RANDOMIZED, CONTROLLED, DOUBLE-BLIND, MULTI-CENTRIC, INTERNATIONAL STUDY ON THE EFFICACY AND SAFETY OF AN EARLY TARGET CONTROLLED PLASMA VOLUME REPLACEMENT THERAPY WITH A BALANCED GELATIN SOLUTION VS A BALANCED ELECTROLYTE SOLUTION IN PATIENTS WITH SEVERE SEPSIS / SEPTIC SHOCK
Acronym	GENIUS (**GE**LATIN I**N** **I**C**U** AND **S**EPSIS)
Investigational Products (IPs)	Investigational test product (gelatin group): Gelaspan (plasma adapted gelatin solution for infusion) ● To be administered in combination with background medication (i.e. open-label Sterofundin ISO; a plasma adapted electrolyte solution) in a ratio of 1:1 (gelatin:electrolyte) Investigational reference product (crystalloid group): Sterofundin ISO (plasma adapted electrolyte solution) ● To be administered in combination with background medication (i.e. open-label Sterofundin ISO; a plasma adapted electrolyte solution) in a ratio of 1:1
Background Medication	Open-label Sterofundin ISO (plasma adapted electrolyte solution)
Phase	IV
Study Design	Prospective, controlled, randomized, double-blind, international, multi-centric study with two parallel groups
Number of Sites & Countries	Multi-centric, international (Participating countries: Austria, Czech Republic, France, Germany, Spain) Up to 15 sites
Sample Size	2 x 304 patients (in total 608 patients) Sample size re-calculation after 2 x 200 (in total 400) patients.
Indication	Hypovolaemia in Severe Sepsis / Septic Shock
Primary Objective	Investigate the efficacy of early goal directed fluid management of a combination of a gelatin and crystalloid regime in comparison to a pure crystalloid regime in achieving haemodynamic stability (HDS) in patients with severe sepsis / septic shock.
Primary Variable	Time until first / initial HDS is achieved (in minutes). Time measurement will start with first administration of IPs and will be continued until first HDS is achieved.
Secondary Objectives	Investigation of safety and efficacy parameters of the applied fluid regimes.
Secondary Variables	● **Safety** *Renal function* ▪ Serum creatinine (SCr) ▪ Serum blood urea nitrogen (BUN) ▪ Estimated glomerular filtration rate (eGFR) ▪ Need and indication of renal replacement therapy (RRT)

	▪ Urine output ▪ Kidney Disease Improving Global Outcome (KDIGO) score *Coagulation* ▪ Prothrombin time (PT) ▪ Activated partial thromboplastin time (aPTT) ▪ International norm ratio (INR) Site specific measurements (Innsbruck): ▪ Fibrinogen ▪ Antithrombin (AT) ▪ Platelets absolute *Hepatic function* ▪ Bilirubin *Adverse Events* ▪ (Serious) adverse events ((S)AEs) / reactions ((S)ARs) *Other* ▪ Number of red blood cell (RBC) units ▪ Number of fresh frozen plasma (FFP) units ▪ Number of other blood products ▪ Vasopressor therapy ▪ Inotropic therapy • **Efficacy** *Fluid administration according to the volume algorithm* ▪ Volume needed to achieve first / initial HDS ▪ Total volume until 48 h after randomization ▪ Administered bottles *Additional administered crystalloid solutions for further volume treatment* ▪ Drug and volume *Fluid balance* ▪ Fluid intake ▪ Fluid output ▪ Fluid balance *Haemodynamics* ▪ Volume responsiveness upon passive leg raising (PLR) or exogenous fluid challenge ▪ Haemodynamic readings as required by the volume algorithm and haemodynamics from 48 h after randomization until ICU discharge or day 28, whatever occurs first *Tissue oxygenation and acid base balance* ▪ Arterial blood gas analyses (BGA)

	▪ Serum electrolytes ▪ Base excess (BE) ▪ Lactate / lactate decrease ▪ Central venous BGA ▪ Arterial oxygen content ▪ Oxygen delivery • **Outcome** ▪ Length of stay (LOS) in the intensive care unit (ICU) ▪ Hospital LOS ▪ Days on RRT ▪ Number of infection free days ▪ Number of antibiotic free days ▪ Number of ventilator free days ▪ Number of vasopressor free days • **Follow-up** ▪ Last available SCr (day 28) ▪ Colloid therapy (day 28) ▪ Mortality & cause of death (if applicable) (day 28 & day 90) ▪ Health-related quality of life (HRQoL) (day 90) ▪ New RRT / kidney disease (day 90) • **Other variables** *Demographic data* ▪ Age ▪ Gender ▪ Height ▪ Weight ▪ Race ▪ Type of patient (e.g. trauma patient, surgical patient) *Anamnesis* ▪ APACHE II & SOFA score ▪ Temperature ▪ Fluid input in the 24 h prior to randomization ▪ Origin of sepsis ▪ Procalcitonin (optional) ▪ Causative organism of infection ▪ Medical history *Concomitant medication* ▪ Antibiotic therapy ▪ Nephrotoxic therapy ▪ Contrast agents ▪ Anticoagulation therapy *Study termination*

Patient Inclusion / Exclusion Criteria	Inclusion criteria: • Male or female patients ≥ 18 years of age • Women of child bearing potential must test negative on standard pregnancy test (urine or serum) • Patients with body weight ≤ 140 kg • Patients diagnosed severe sepsis / septic shock (refer to section **Fehler! Verweisquelle konnte nicht gefunden werden.** for definitions) at admission on ICU who can be enrolled within 90 min after admission OR patients diagnosed severe sepsis / septic shock during ICU stay who can be enrolled within 90 min after diagnosis • Patients where antibiotic therapy has already been started (prior to randomization) • Patients who are fluid responsive. Fluid responsiveness is defined as increase of > 10% in mean arterial pressure (MAP) after PLR or fluid challenge (max. 250 ml crystalloid solution) • Signed informed consent by patient, legal representative or authorized person or deferred consent Exclusion criteria: • Administration of HES, dextrane solutions or > 500 ml of Gelatin solutions within the 24 h prior to randomization • Death expected within the next 48 h (moribund patients as defined by ASA ≥ class V) • Patients with confirmed acute SARS-CoV-2 (COVID-19) infection (as available from routine medical records/ patient chart) • Patients for whom the need of pressure infusions are expected • Requirement for renal support (either continuous or discontinuous techniques, including intermittent haemodialysis, haemofiltration and haemodiafiltration) • Patients receiving therapeutic heparin medication due to chronic coagulation disease / anticoagulation medication (i.e. partial thromboplastin time > 60 sec) • Acutely burned patients (refer to section **Fehler! Verweisquelle konnte nicht gefunden werden.**) • Renal failure with oliguria or anuria • Severe general oedema • Severe congestive cardiac failure • Hypersensitivity to the active substance or ingredients of the IPs • Hypersensitivity to galactose-α-1,3-galactose (alpha-Gal) or known allergy to red meat (mammal meat) and offal • Hypervolaemia / hyperhydration • Hyperkalaemia • Hypercalcaemia • Metabolic alkalosis

	• Simultaneous participation in another interventional clinical trial (drugs or medical devices studies)
Investigational Test Product	Gelaspan: Plasma adapted gelatin solution for infusion Composition (1000 ml solution contain): Succinylated gelatin (= modified fluid gelatin) 40.0 g Sodium chloride 5.55 g Sodium acetate trihydrate 3.27 g Potassium chloride 0.30 g Calcium chloride dihydrate 0.15 g Magnesium chloride hexahydrate 0.20 g Excipients for pH-adjustment: Sodium hydroxide 40% 0 – 0.133 g Hydrochloric acid 20% 0 – 0.182 g Electrolyte concentrations Sodium 151 mmol/l Chloride 103 mmol/l Potassium 4 mmol/l Calcium 1 mmol/l Magnesium 1 mmol/l Bicarbonate as Acetate 24 mmol/l Molecular weight, weight average: 30 000 Dalton Molecular weight, number average: 23 200 Dalton Theoretical osmolarity: 284 mOsm/l
Investigational Reference Product	Sterofundin ISO: Plasma adapted electrolyte solution for infusion Composition (1000 ml solution contain): Sodium chloride 6.80 g Potassium chloride 0.30 g Calcium chloride dihydrate 0.37 g Magnesium chloride hexahydrate 0.20 g Sodium acetate trihydrate 3.27 g Malic acid 0.67 g Electrolyte concentration Sodium 145.0 mmol/l Potassium 4.0 mmol/l Calcium 2.5 mmol/l Magnesium 1.0 mmol/l Chloride 127.0 mmol/l Acetate 24.0 mmol/l Malic acid 5.0 mmol/l pH: 5.1 – 5.9 Theoretical osmolarity: 309 mOsmol/l
Fluid Administration	Method of Administration The administration of IPs and background medication is performed intravenously. Dosage

	Dosing of IPs is individualized to the patient's volume needs. Blinded IP volume applied should not exceed 30 ml/kg/day. In addition background medication is applied alternating with IPs in a ratio of 1:1. Fluids are administered according to the volume algorithm as long as the patient is fluid responsive. Fluid responsiveness is defined as an increase of 10% of MAP and / or stroke volume index (SVI) after endogenous or exogenous fluid challenge. An endogenous fluid challenge is achieved by means of PLR. An exogenous fluid challenge is achieved by infusing 500 ml of fluid in 15 min. Refer to protocol section **Fehler! Verweisquelle konnte nicht gefunden werden.** for details on the fluid management strategy. Duration of Treatment Treatment with IPs starts directly with randomization and discontinues with the achievement of HDS, achievement of maximum daily dose (30 ml/kg) or 48 h after randomization, whatever occurs first.
Visit Schedule	<u>Prior randomization - 90 min window:</u> • Verification of in- / exclusion criteria • RBC and antibiotic therapy prior randomization • Demographic data including pregnancy test in women of childbearing potential • Anamnesis & medical history <u>At randomization</u> • Blood samples for laboratory evaluations (renal function, coagulation, hepatic function, lactate, scores) - immediately before first IP administration <u>Randomisation until 48 h thereafter:</u> • Set of catheters (e.g. arterial line, central-venous line) • Set of urinary catheter • Assessment of HDS and primary endpoint 'time to first / initial HDS' (lactate, urine production, $ScvO_2$) • SCr (every 6 h until 48 h after randomization) • Urine output (every 6 h until 48 h after randomization) • Blood samples for laboratory evaluations (renal function, coagulation, hepatic function) • Vasopressor therapy • Inotropic therapy • Fluid administration (i.e. IP and background medication acc. to volume algorithm) • Administered crystalloids for further volume treatment • Fluid intake & fluid output • Fluid responsiveness upon PLR or exogenous fluid challenges as required by the volume algorithm • Haemodynamic readings as required by the volume algorithm

	• Tissue oxygenation and acid base balance (BGA within the first 6 h every 2 h, then every 12 h until 48 h after randomization) • (Serious) adverse events / reactions • Applied blood products • Concomitant medications • SOFA score, temperature • Fulfilment of ICU discharge criteria • RRT including indication • Invasive mechanical ventilation <u>48 h after randomization until ICU discharge or day 28 (whatever occurs first):</u> • Blood samples for laboratory evaluations (renal function, coagulation, hepatic function) • Severe sepsis / septic shock (second, third,… hit) • Vasopressor therapy • Inotropic therapy • Administered crystalloids for further volume treatment • Fluid intake & fluid output • Urine output • Haemodynamic readings (minimum and maximum daily) • Tissue oxygenation and acid base balance • (Serious) adverse events / reactions • Applied blood products • Concomitant medications • SOFA score, temperature • Fulfilment of ICU discharge criteria • RRT including indication • Invasive mechanical ventilation • Several outcome parameters (hospital LOS, ICU LOS, number of ventilator free days, number of infection free days, number of antibiotic free days, number of vasopressor free days, days on RRT) • Study termination <u>Day 28:</u> • Last available SCr documented from ICU discharge until hospital discharge or day 28, whatever occurs first • Colloid therapy from ICU discharge until hospital discharge or day 28, whatever occurs first • Mortality & cause of death if applicable <u>Day 90:</u> • Mortality & cause of death if applicable • New RRT / kidney disease

	• HRQoL questionnaire & appendix (if applicable)
Duration of Study per Patient	Start of study: With randomization Treatment period (administration of fluids according to the volume algorithm): • Start of administration: With randomization • Duration of administration: ▪ Treatment with fluids according to the volume algorithm discontinues with the achievement of HDS or 48 h after randomization, whatever occurs first ▪ Treatment with additional crystalloid solutions for further volume treatment only starts after achievement of HDS, achievement of max. daily dose or 48 h after randomization until ICU discharge or day 28, whatever occurs first End of study: ICU discharge or day 28, whatever occurs first Follow ups: day 28 & day 90
Study Schedule	Planned start: Q1 / 2016 Planned recruitment time: 5.5 years Planned last patient out: Q4 / 2021
Statistical Methods	Sample size will be based on assumption of difference between the gelatin and the crystalloid group.
Randomization / Blinding	Randomized with the following strata: • Site • RBCs pre-treatment within 24 h prior to randomization Double-blinded
Data Safety Monitoring Board (DSMB)	A DSMB is appointed.