Clinical Trial Protocol

Title	**E**fficacy **a**nd **s**afety of SP16 in pr**e**venting **A**cute **K**idney **I**njury in at-risk subjects with chronic kidney disease undergoing elective cardiac surgery using the heart-lung-machine: A prospective, randomized, double-blind, placebo-controlled clinical trial (EASE-AKI)
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ABBREVIATIONS

AE	Adverse Event
ACEi	Angiotensin Converting Enzyme Inhibitor
ADL	Activities of Daily Living
AF	Atrial Fibrillation
AI	Aortic (valve) Insufficiency / aortic (valve) Regurgitation
AKD	Acute Kidney Disease
AMG	Arzneimittelgesetz / German Medicinal Products Act
AKI	Acute Kidney Injury
ALT (GPT)	Alanine Aminotransferase (glutamate-pyruvate-transaminase)
AMI	Acute Myocardial Infarction
ANP	Atrial Natriuretic Peptide
API	Active Pharmaceutical Ingredient
AR	Adverse Reaction
ARB	Angiotensin II Receptor-1 Blocker
AS	Aortic Stenosis
ASA	Acetylsalicylic Acid
AST (GOT)	Aspartate aminotransferase (glutamate-oxaloacetate-transaminase)
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
CAD	Coronary Artery Disease
CABG	Coronary Artery Bypass Graft
CeBE	Central Biobank Erlangen
CCS	Canadian Cardiovascular Society
CCS	Center for Clinical Studies Erlangen
CK	Creatine Kinase
CK-MB	Creatine Kinase MB
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COPD	Chronic Oobstructive Pulmonary Disease
CPB	Cardiopulmonary Bypass (heart-lung-machine)
CRP	C-reactive Protein

CSA	Cardiac Surgery Associated
CTCFG	Common Terminology Criteria for Adverse Events
CTFG	Clinical trial facilitation group of the Heads of Medicines Agencies
CTIS	Clinical Trial Information System
CTP	Clinical Trial Protocol
CTR	Clinical Trials Regulation
D	Day
dl	Deciliter
DO2i	Oxygen Delivery Index
DOAC	Direct Oral Anticoagulants
DRKS	Deutsches Register Klinischer Studien
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylene Diamine Tetraacetic Acid
EF	Ejection Fraction
eGFR	Estimated Glomerular Fitration Rate
EMA	European Medicines Agency
EoS	End of Study
EU	European Union
FEV1	Forced Expiratory Volume per Second
FFP	Fresh Frozen Plasma
FPFV	First Participant First Visit
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
h	Hour
HCG	Human Chorionic Gonadotropine
HF	Heart Failure
HMA	Heads of Medicines Agencies
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors

ICU	Intensive Care Unit
IG	Immature Granulocytes
IGFBP-7	Insulin-like Growth Factor-binding Protein 7
IgG	Immunoglobuline G
IL	Interleukin
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IPD	Important Protocol Deviation
ISF	Investigator Site File
IT	Information Technology
i.v.	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes [organization] (Global non-profit foundation; Belgium)
kg	Kilogram
KIM-1	Kidney Injury Molecule-1
l	Liter
LDH	Lactate Dehydrogenase
L-FABP	Liver Fatty Acid-binding Protein
LOS	Length of Stay
LPFV	Last Participant First Visit
LPLV	Last Participant Last Visit
LRP	Low-density Lipoprotein Receptor-related Protein
LV-EF	Left Ventricular Ejection Fraction
LV	Left Ventricle
MAKE	Major Adverse Kidney Event
MedDRA	Medical Dictionary for Regulatory Activities
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
mg	Milligram
min	Minutes
ml	Milliliter
mmol	Millimol
MI	Mitral (valve) Insufficiency / Mitral (valve) Regurgitation

MS	Mitral Stenosis
MSc	Member State Concerned
N/A	Not Applicable
NAC	N-acetyl Cysteine
NGAL	Neutrophil Gelatinase-Associated Lipocalin
NSAID	Nonsteroidal Antiinflammatory Drug
NT-proBNP	N-Terminal Pro-B-Type Natriuretic Peptide
NYHA	New York Heart Association
PA	Pulmonary Artery
PAD	Peripheral Artery Disease
PBMC	Peripheral Blood Mononuclear Cell
PK	Pharmacokinetics
PRBC	Packed Red Blood Cells
PTT	Partial Thromboplastin Time
pi-GST	Pi-glutathione S-transferase
pO2	Oxygen Saturation
POCT	Point of Care Testing
RA	Right Atrium
RBC	Red Blood Cell Count
RDW	Red-Cell Distribution Width
RSI	Reference Safety Information
RRT	Renal Replacement Therapy
RV	Right Ventricle
OP	Surgery
PRBC	Packed Red Blood Cells
QM	Quality Management
RIPC	Remote Ischemic Preconditioning
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sPAP	Systolic Pulmonal Arterial Pressure
SAR	Serious Adverse Reaction
s.c.	Subcutaneous
SCr	Serum Creatinine

ScvO2	Central Venous Oxygen Saturation
SEE	Systemic Embolic Event
SOP	Standard Operating Procedure
SpS	Special Situation
SR	Sinus Rhythm
STEMI	ST-Segment Elevation Myocardial Infarction
STIKO	Ständige Impfkommission
SUSAR	Suspected Unexpected Serious Adverse Reaction
SV	Stroke Volume
TAPSE	Tricuspid Annular Plane Systolic Excursion
TEE	Transesophageal Echocardiography
TIA	Transient Ischemic Attack
TIMP-2	Tissue Inhibitor of Metalloproteinases 2
TMF	Trial Master File
TOM	Technical and Organisational Measures
TRV	Tricuspid Regurgitant Velocity
TTE	Transthoracic Echocardiography
TXA	Tranexamic Acid
UNS	Unscheduled
Urine-NGAL	Urine Neutrophil Gelatinase-associated Lipocalin
USAR	Unexpected Serious Adverse Reaction
V	Visit
VTE	Venous Thrombembolism
WBC	White Blood Cell count (leucocytes)
WOCBP	Women of Childbearing potential

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol full title	Efficacy and safety of SP16 in preventing Acute Kidney Injury in at-risk subjects with chronic kidney disease undergoing elective cardiac surgery using the heart-lung-machine: A prospective, randomized, double-blind, placebo-controlled clinical trial
Short titel	EASE-AKI
Protocol code	UKER-SP16-AKI-01
EU CT number	2025-522491-89-00
Investigational medicinal product (IMP), dose and route of administration	SP16-3M or placebo, solution for injection, subcutaneous use; administered subcutaneously at two different timepoints, at first shortly before the start of cardiac surgery and then 9±1 h after the first administration. Each administration of a single dose of 6 mg is divided into two injections of 2 ml SP16-3M (1,5 mg/ml) or resembling placebo. Total dose per participant: 12 mg
Indication	Participants with chronic kidney disease undergoing elective cardiac surgery using the heart-lung-machine
Trial design	Phase II, single center, interventional, prospective, randomized, double-blind, placebo-controlled
Trial objectives	**Primary Objective** To evaluate the safety of SP16 administration and its ability to prevent CSA AKI as defined by KDIGO criteria, in participants with CKD 2-3b undergoing planned cardiac surgery. **Secondary Objectives** To evaluate the effect of SP16 on • The severity of post-surgical CSA-AKI (according to KDIGO stages 1-3). • The duration of post-surgical CSA-AKI. • Necessity of RRT. • Duration of RRT. • The cardiac left and right ventricular function. • The composite of major adverse kidney events (MAKE) that include death, need of dialysis, or sustained impaired renal function within 90±7 d after index surgery (MAKE90). • The incidence of AEs and SAEs.
Trial endpoints	**Primary safety endpoint** Frequency of AEs and SAEs within 72 h after index surgery. **Primary efficacy endpoint** Number of participants who develop CSA AKI during hospital stay defined by KDIGO stage 1 or higher. If at least one of the following criteria is observed in the interval since end of index surgery and the 7 day assessment, a participant will be considered to have developed CSA AKI:

	• Increase in SCr by ≥0.3 mg/dl (>26.5 µmol/l) within 168±4 h after index surgery (defined as the period since CPB was terminated and systemic circulation resumed). • Increase in SCr to ≥1.5 times the baseline value, using the highest SCr value within 168±4 h after index surgery. • Decrease in urine output <0.5 ml/kg/h for more than 6 hours within 168±4 h after index surgery. **Secondary endpoints** • Highest CSA AKI stage value according to the stage classification of the KDIGO-AKI in the 7 day period after the index surgery. • Number of days after post-surgical onset of CSA AKI until re-achievement of baseline level of serum creatinine (defined as a return of creatinine to <0.3 mg/dl above baseline value) or discharge from hospital, whichever comes first. • Necessity of RRT (yes/no). • Duration of RRT measured by starting date [yyyy-mmm-dd] and end date [yyyy-mmm-dd]. • Cardiac function on Day 90±7 d after cardiac index surgery compared to pre surgical assessment (Visit 1) assessed by echocardiography (TTE). • Cardiac function on Day 0 post-surgery (Visit 3), Day 1, and on Day 5 after index surgery assessed by point of care echocardiography (TTE) compared to pre surgical assessment (Visit 1). • NT-proBNP level on Day 1, Day 7, and Day 90±7 d after index surgery compared to pre-surgical assessment on Day 0 (Baseline; Visit 2). • Central venous oxygen saturation (ScvO2) on Day 1, Day 5 and Day 7 after index surgery compared to pre-surgical assessment on Day 0 (Baseline; Visit 2). • All cause death within 90±7d (3 months) after cardiac index surgery. • Sustained impaired renal function defined as ≥ 25% increase in SCr at Day 90±7 d compared to baseline. • Sustained impaired renal function requiring at least one dialysis during the post-surgical interval until Day 90±7 d (end of observation period). • Frequency of AE and SAE within 7 days after cardiac index surgery. • Frequency of AE and SAE during the observation period. • Number of participants with at least one SAE during the observation period.
Main inclusion criteria	1. Individual aged ≥18 years. 2. Male or female. 3. Scheduled for CABG OR aortic valve surgery (aortic valve replacement or repair alone, with or without aortic root repair) OR mitral valve surgery OR aortic/mitral valve surgery combined with CABG. 4. Use of the CPB during surgical intervention expected. 5. Written informed consent obtained from the participant.

	6. Understanding of study procedures and willingness to abide by all procedures during the course of the clinical trial. 7. CKD Stage 2–3b with eGFR ≤90 and ≥30 ml/min/1.73 m2 (according to 2021 CKD-EPI equation) known for ≥ 3 months prior to enrolment 8. BMI ≥19 kg/m² to ≤40 kg/m². 9. Contraceptive measures for female and male participants.
Main exclusion criteria	1. CKD stages 4-5 with eGFR <30 ml/min/1.73 m2 pre-surgery as determined by CKD EPI. 2. Previous cardiac surgery. 3. Person has a kidney transplant or another solid organ transplant. 4. Person is scheduled for intermittent or continuous renal replacement therapy (dialysis). 5. Known diagnosis of dementia or other clinical signs of mental illness that will prevent full understanding. 6. Known diagnosis of severe COPD (Gold 3) and/or FEV1 < 1 l/s. 7. Heart failure with severity of symptoms according to NYHA IV. 8. Heart failure with impaired cardiac pump function (LVEF <35%). 9. Acute onset or ongoing sepsis - sepsis is defined as the presence of a confirmed or putative infection, along with a dysregulated systemic immune reaction leading to organ dysfunction. 10. Clinical signs of a currently active infection including endocarditis requiring antibiotic treatment. 11. Clinical signs of an acute viral infection. 12. Serious underlying disease(s) or very poor general medical condition, so that in the investigator's judgment the person is not expected to survive ICU or hospital stay. 13. Patient who has an active (requiring treatment) malignancy or history within 5 years prior to enrolment in the study, of solid, metastatic or hematologic malignancy with the exception of basal or squamous cell carcinoma of the skin that has been removed. 14. Administration of iodinated contrast agent within 24 hours prior to cardiac surgery 15. Recent (discontinued in the last 14 days before V1a or V1b) or current treatment with immunosuppressive drugs, including, but not limited to, high dose corticosteroids [> 1 mg/kg of prednisone equivalent], tumour necrosis factor alpha blockers, or ciclosporin. 16. Current regular use of anti-inflammatory drugs such as NSAID, with discontinuation not possible. (However, if these medications are discontinued in the last 10 days before V2, the participant is eligible to participate). ASA up to 100 mg per day is allowed. 17. Systemic corticosteroid therapy (any dose). 18. Known active chronic inflammatory disease (including, but not limited to, rheumatoid arthritis or systemic lupus erythematosus). 19. Known allergy to SP16 or to other ingredients of the IMP.

	20. Person who is not willing to use highly effective contraceptive measures (according to CTFG recommendations v1.2). 21. Pregnant women. 22. Breastfeeding women. 23. Current participation in another interventional clinical study (register studies or non-interventional, observational studies excluded). 24. Employee or direct relative of an employee of the study site, the CRO, or the Sponsor.
Trial procedures	Potential participants will be screened for eligibility within a time window of 54 to 2 days prior to the elective surgery. Eligible patients will receive the first dose of study drug shortly prior to surgery and the second dose post-surgery within 9±1 h after the first administration. After the Screening Visit (Visit 1a), Randomization (Visit 1b) and the Baseline Visit (Day 0) prior to surgery participants will complete 9 visits during hospitalization until discharge followed by a telephone follow-up on Day 30±3 d and the Final Visit (EOS) on Day 90±7 d. Unscheduled Visits may be performed as deemed necessary by the investigator.
Number of visits	14
Total number of participants	120
Trial periods/duration	Overall trial duration: approximately 38 months Per participant trial duration: around max. 5 months
Statisical analysis methods	The aim is to show superiority of the intervention compared to placebo in the primary efficacy endpoint. Three blinded interim analyses are planned after 30, 60 and 90 patients (four analyses in total).

2 TRIAL ADMINISTRATION

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3 INTRODUCTION

3.1 Background

The majority of cardiac surgical interventions is commonly operated using an extracorporeal cardiopulmonary bypass (CPB), also called heart-lung machine, for maintaining blood and oxygen circulation throughout the body while bypassing the heart and lungs. The use of the CPB is not without risk, and there is a high number of associated problems, among them cardiac surgery-associated acute kidney injury (CSA-AKI).

3.1.1 Incidence of cardiac surgery-associated acute kidney injury

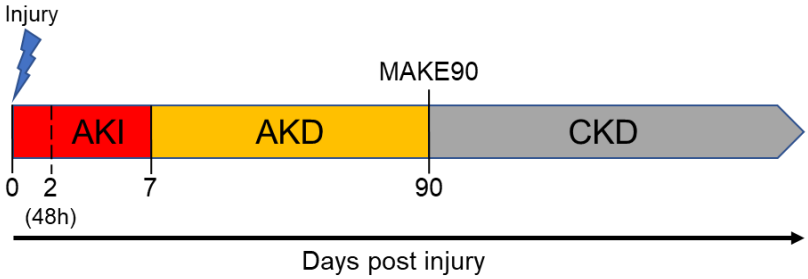
Maintenance of renal blood flow is achieved by maintaining adequate CPB pump flow throughout CPB to minimize the risk of CSA-AKI. Nevertheless, about 19% - 45% of all patients undergoing cardiac surgery are suffering from CSA-AKI (Kuitunen et al., 2006; Haase et al., 2009; Robert et al., 2010; Bastin et al., 2013; Thiele et al., 2015; Landoni et al., 2024). The rate is elevated to 50% in patients with a preexisting chronic kidney disease (CKD) (Schley et al., 2015). Severe AKI requiring renal replacement therapy (RRT) occurs in 2% - 6% (Kuitunen et al., 2006; Haase et al., 2009; Robert et al., 2010; Bastin et al., 2013). Besides, AKI is significantly associated with the induction of or progression to CKD, but also with increased rates of heart failure events and death (Abel et al., 1973; Ikizler et al., 2021). Even after full recovery of renal function, long-term survival is reduced (Hobson et al., 2009). Although the optimization of supportive care according to the KDIGO guidelines is beneficial, the rate of CSA-AKI is still high (Meersch et al., 2017b).

3.1.2 Continuous transition from AKI to acute kidney disease and chronic kidney disease

The continuum of kidney injury includes AKI, acute kidney disease (AKD), and CKD, reflecting a progression from an initial damage to persistent dysfunction. AKI is characterized by a rapid decline in kidney function within 7 days, while CKD is defined as kidney disease persisting for more than 90 days. AKD represents the intermediate phase, involving acute or subacute kidney damage and/or dysfunction lasting between 7 and 90 days after the initial AKI event.

Typically, recovery from AKI within 48 h signals rapid reversal. However, unresolved AKI may transition into AKD with increasing risk of progression to CKD. In patients with preexisting CKD, an AKI event may exacerbate their renal condition, with AKD superimposed on CKD. This overlap heightens the risk of further decline in kidney function, making patients with AKD and preexisting CKD particularly vulnerable to disease progression.

Figure 1: Timeline of acute kidney injury, acute kidney disease and chronic kidney disease



Modified from Acute Dialysis Quality Initiative 16; www.adqi.org, (Chawla et al., 2017).

3.1.3 Possible factors in the pathomechanism of CSA-AKI in connection with CPB

The genesis of CSA-AKI is mainly prerenal, caused by reduced intraoperative oxygenation/perfusion via the CPB. The CPB pump generates an average CPB pump flow index of about 2.4 l/min/m^2 which is below the lower limit of the physiological normal range (2.5 – 4.0 l/min/m^2) (Bennett et al., 2013; Condello et al., 2020).

Additionally, CPB is known to activate the coagulation cascade and stimulate inflammatory mediators, leading to hemolysis and coagulopathies. This problem worsens as complement proteins build on the membrane oxygenators. The CPB pump therefore requires anticoagulation but also hemodilution to avoid clotting, resulting in a 30% reduction of the oxygen transporter hemoglobin to ~8.5 g/dl (normal value 13.5 - 17.5 g/dl for males, 12.0 - 16.0 g/dl for females) (Bennett et al., 2013) which is directly associated with AKI (Barbu et al., 2024). This causes a significant reduction of the average oxygen delivery (DO_{2i}) to ~ 280 l/min/m^2 (normal value 450 − 550 l/min/m^2), which may result in an increase of lactate as a marker of general hypoxia (Ranucci et al., 2006; Condello et al., 2020). The intraoperative lactate correlates with postoperative increase of creatinine (Ranucci et al., 2006; Condello et al., 2020). As a consequence, CPB is only used during the period a cardiac surgery may take.

Besides this intraoperative renal hypoxia, multifactorial cardiac complications may result in a temporarily reduced cardiac output post-surgery. Diastolic dysfunction has been found in the large majority of cardiac surgery patients (McKenney et al., 1994; Metkus et al., 2018) and is caused by cardiac ischemia reperfusion injury that is unavoidable in all patients receiving CBP. It is characterized by elevated cardiac filling pressures and reduced cardiac output, which increases the risk of AKI (Metkus et al., 2018).

In addition, cardiac surgery induces systemic hypertension with peripheral vasoconstriction that leads to elevated plasma renin activity as a marker for renal hypoperfusion (Roberts et al., 1977), which is a predictor of acute cardiovascular instability and AKI (Küllmar et al., 2021).

Additionally, CPB induces systemic inflammatory response syndrome (SIRS) by contact of the blood cells with the artificial surface of the bypass circuit, ischemia–reperfusion injury, endotoxemia and operative trauma itself (Paparella et al., 2002). This leads to release of inflammatory mediators including interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and interleukin-8 (IL-8) (Orime et al., 1999).

For example, TNF-α induces glomerular fibrin deposition, cellular infiltration, and vasoconstriction, leading to a reduction in glomerular filtration rate (GFR), but causes myocardial apoptosis and dysfunction as well (Meldrum and Donnahoo, 1999).

3.2 Therapeutic approaches to prevent or attenuate CSA-AKI

Supportive treatment. The *PrevAKI* study (Meersch 2017a) applied supportive treatment (optimization of volume status and hemodynamics, avoidance of nephrotoxic drugs, and prevention of hyperglycemia) according to the KDIGO guidelines for the prevention of AKI in high risk cardiac surgery patients (defined as the product of [TIMP-2] x [IGFBP7] in urine >0.3), reducing the AKI rate, but remaining on a very high risk level (55.1% vs. 71.7% in the control group). In contrast, the subsequent *PrevAKI-Multicenter Randomized Controlled Trial* including cardiac surgery patients in general did not show a significant difference in the AKI rate (46.3% vs 41.5% in the control group) but a reduction of moderate and severe AKI (14.0% vs 23.9% in the control group).

A meta-analysis conducted in 2023 included 86 trials (25,855 patients) evaluating 10 non-pharmacological interventions to reduce the incidence of CSA-AKI (Hariri 2023). However, only two non-pharmacological interventions (goal-directed perfusion and remote ischemic preconditioning) were likely to reduce CSA-AKI incidence, with moderate quality of evidence.

Several pharmacologic therapies have been investigated for the prevention and treatment of AKI but have not demonstrated significant benefits:

Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Blockers (ARBs): Long-term medication with ACEIs and ARBs did not increase the incidence of CSA-AKI, but perioperative discontinuation remains controversial. Some studies present hints that stopping ACEIs/ARBs before cardiac surgery might lower AKI incidence, while others indicate that postoperative AKI rates are not affected with continuous administration (Arora 2008; Ouzounian 2012).

Sodium Bicarbonate: A meta-analysis published in 2014, which included five RCTs with 1,079 patients, found that sodium bicarbonate does not reduce the incidence of AKI associated with cardiac surgery (Tie 2014). However, it prolonged ventilation duration and ICU length of stay (LOS) while increasing the risk of alkalemia. An individual patient data meta-analysis also showed that alkalinization of urine with sodium bicarbonate infusion does not significantly reduce the overall risk of AKI in cardiac surgery patients (Bailey 2015).

Statins: While some studies suggest that statins may aid in early recovery from post-vascular surgery kidney injury and are associated with a lower incidence of AKI (Welten 2008; Billings 2010), other RCTs and cohort studies have failed to validate statin treatment as effective in reducing CSA-AKI, AKI requiring RRT, or hospital mortality (Argalious 2010; Prowle 2012).

Fenoldopam: The antihypertensive drug fenoldopam showed promise for renal protection in a preliminary trial (Ranucci et al., 2010), but was associated with hypotensive episodes and turned out to not affect RRT initiation, ICU/hospital LOS, or overall survival in a large multicentric RCT (Zangrillo 2012). It did not prevent AKI progression to RRT initiation nor did

it have an effect on mortality or secondary outcomes. Fenoldopam induced greater hypotension than placebo (Bove 2014).

Mannitol: Studies have indicated that mannitol can increase urine flow, renal blood flow, and decrease renal vascular resistance (Bragadottir 2012). However, its role in preventing CSA-AKI has not been tested in RCTs.

Atrial Natriuretic Peptide (ANP) and B-type Natriuretic Peptide (BNP): Both ANP and BNP have favorable physiological profiles. A meta-analysis in 2011 found that BNP infusion reduces ICU/hospital LOS but does not affect RRT incidence or mortality. While BNP showed a 10% reduction in AKI incidence in a systematic review, no RCTs have tested this intervention (Patel 2011).

N-Acetylcysteine (NAC): NAC is an antioxidant with various biological actions and has been studied for AKI prevention. However, there is no solid evidence that prophylactic administration of NAC prevents AKI or reduces mortality after cardiac surgery (Ashworth and Webb, 2010; Lameire and Kellum, 2013).

Remote Ischemic Preconditioning (RIPC): Zarbock and colleagues examined RIPC effects on AKI rates and severity in cardiac surgery patients (Zarbock 2015). In a multicenter trial involving 240 high-risk patients, RIPC significantly reduced AKI incidence compared to a sham control. However, this small study's findings have been contradicted by another study (Young 2012) and a meta-analysis (Pilcher 2012).

Recently, the PROTECTION trial (ClinicalTrials.gov number, NCT03709264) showed a protective renal effect of intravenous amino acids in cardiac surgery patients, but the AKI rate still remained high (26,9% vs. 31,7%) and there were no differences between the two groups in secondary outcomes (Landoni 2024).

Thus, renal protection and prevention of CSA-AKI to CKD progression is yet of high interest in cardiac surgery patients depending on CBP.

3.2.1 Novel therapeutic approach with the LRP1-agonist SP16

Serpins are a superfamily of proteins that were first identified for their serin-protease inhibition activity and are found in all kingdoms of life. They irreversibly inhibit target proteases by inducing steric protein changes that alter the active cleavage site and are involved in inflammation and coagoulation. Important serpins are antithrombin, alpha1-antitrypsin (AAT), c1-inhibitor, or plasminogen activator inhibitor-1. A small segment of the serpin molecule is cleaved after serpin binding to the target protease. This polypeptide is composed of both anti-inflammatory and pro-inflammatory sequences and is secreted into the blood.

Many permanent serpin target protein complexes are cleared from circulation by the low-density lipoprotein receptor-related protein (LRP) which is a membrane receptor and binds to these complexes and, thus, induces cellular uptake.

SP16 acts as an LRP1 agonist and initiates the immunomodulatory cascade. SP16 is a short peptide consisting of 17 amino acids derived from AAT and contains only the anti-inflammatory

amino acid sequence. Therefore, SP16 is highly potent in overturning and reining in an acute inflammatory response, e.g. caused by myocardial reperfusion after acute myocardial infarction (AMI) or renal reperfusion after prerenal AKI.

LRP1 is a scavenger receptor with regulatory function that also initiates a cytoprotective and anti-inflammatory process. LRP1 is upregulated in the myocardium upon myocardial infarction (Toldo 2017).

The ubiquitously expressed LRP1 protein contributes to Wnt/β-catenin signaling and cholesterol metabolism, for example in macrophages and T-cells. LRP1 upregulates Wnt5a that reduces intracellular cholesterol accumulation (El Asmar et al., 2016), connecting LRP1 to another damaging factor of AKI – the intracellular accumulation of cholesterol.

Local immune cells, in particular macrophages and T-cells, are involved in the pathophysiology of AKI by regulating renal repair but may also induce the transition to CKD (Han et al., 2019; Dellepiane et al., 2020). Others have shown that macrophage LRP1 is a survival factor (Yancey et al., 2010). LRP1 agonism may increase the proportion of regulatory T cells (Kedzierska et al., 2021) which is a beneficial effect in AKI recovery and prevents transition to CKD (Dellepiane et al., 2020).

In our preclinical experiments using an AKI mouse model we found a comparable upregulation of LRP1 in mouse kidneys suffering from renal ischemia-reperfusion injury. We could show that SP16 treatment in both cell culture and zebrafish models reduced the damage of renal tubular cells (own data). In addition, an external collaborator could show a renoprotective effect of SP16 in mice with proteinuric kidney disease, reducing proteinaceous casts and matrix accumulation in a podocyte-specific knock-out mouse model (personal communication).

In a randomized, double-blind placeo-controlled first-in man phase I safety trial in 24 healthy volunteers (NCT03651089) (Wohlford et al., 2021) SP16 was administered as a one time treatment with subcutaneous injection in three dose-cohorts with dose levels of 0.0125, 0.05 and 0.2 mg/kg body weight, capped at a maximum dose of 12 mg. Participants requiring a volume greater than 2 ml had the dose split into two equal volume injections that were sequentially administered separately on opposite sides of the abdominal wall. Dose selections were made in accordance with US FDA guidance for estimating the maximum safe starting dose and based on data obtained in rat and dog animal models. In rats, doses of 60 mg/kg SP16 were administered without any observed toxicity. When the FDA human equivalent dose conversion factor of 6.2 and FDA safety factor of 10 were applied, a dose of 0.97 mg/kg was estimated to present acceptable safety. The dose for the first cohort (0.0125 mg/kg) exceeded the FDA standards with a calculated safety factor of 77.4.

Participants received SP16 or placebo in a 3:1 ratio. Safety monitoring included vital signs, laboratory examinations (including hematology, coagulation, platelet function, clinical chemistry, and myocardial toxicity) and electrocardiography (to measure effect on PR interval, duration of QRS complex, and the corrected QT interval). Importantly, SP16 administration was not associated with serious adverse events. Main adverse event was injection site pain in 15 out of 16 patients in the SP16 group and 3 out of 6 patients in the placebo group ($p = 0.07$) with values of 3.5 (SD 2.5) vs. 1.5 (SD 2.1) in the placebo arm using a 11-point pain scale (0-10). Higher SP16 concentrations correlated with greater pain scores. Pain was transient over

a short period as no participant reported injection pain beyond 1/10 after 30 minutes. 22 patients (92%) reported no injection site pain after 12 h (maximum pain after 12 h = 1/10) and all patients (100%) reported no pain after 24 h. There were no significant differences in vital signs, laboratory examinations, and electrocardiography between both groups. The authors mentioned the small number of cases and the short follow-up as limitations of the study. Pharmacodynamic effects could not be evaluated in healthy participants with presumably low levels of systemic inflammation.

The single subcutaneous injection of up to 12 mg (if necessary, distributed to two injection sites) was considered safe and well tolerated.

In a single-armed open label Phase Ib/IIa clinical trial in 38 patients with acute STEMI (NCT04225533), 10 participants received a single subcutaneous administration of SP16 (0.2 mg/kg). They were compared to 28 historical placebo-treated controls who had participated in another clinical trial (Van Tassell et al.,2018; Abate et al., 2020) with similar enrollment criteria. (Van Tassell et al., 2022). SP16 administration was again safe and very well tolerated, with no infection, local or systemic adverse reactions after SP16 injection. In addition, no significant changes in systemic blood pressure, heart rate, or oxygen saturation were observed. Two (20%) patients in the SP16 group experienced transient heart failure (HF) symptoms (<48 h) shortly after reperfusion. Neither had a pre-existing diagnosis of HF, both had evidence of elevated left ventricular end-diastolic pressure at the time of cardiac catheterization, and both received loop diuretics. No patients in the SP16 treated group experienced any HF events after discharge, developed persistent HF symptoms, or experienced HF hospitalization during the 12-month follow-up. One patient had a stroke 69 days after the index event, and one patient had an AMI after 363 days. All these events were not unexpected and considered not to be related to the investigational treatment by the trial investigators. The limitations of the trial were the low number of cases and the lack of a paralleled control group with a randomized double-blind design. However, this study again showed good tolerability of SP16 administration and a trend towards a reduction in the inflammatory response and infarct size.

3.3 Trial rationale

Patients undergoing cardiac surgery with CPB are at high risk of developing CSA-AKI, particularly with pre-existing CKD (Schley 2015). Various efforts are still being made to reduce the high incidence of CSA-AKI. To date, none of the measures tested have led to a relevant breakthrough, so there is still a high clinical need for renal protection in this vulnerable patient cohort.

It has been shown that an inflammatory reaction is a key factor in the development of AKI. A promising therapeutic approach could be to trigger immunomodulatory cascades via LRP1. Experimental data showed both renal and myocardial protective effects by treatment with the LRP1-agonist SP16. SP16 was well tolerated in the two previous clinical trials, one study already showing a trend towards a reduction of inflammatory response. Based on the physiological mechanism of action, promising preclinical and preliminary clinical data, SP16 will be investigated to evaluate preventive effects on the incidence of CSA-AKI by reducing the inflammatory reaction after hypoxia and reperfusion caused by the use of the CPB pump during cardiac surgery. In addition, this study will provide further safety data in this larger placebo-

controlled study collective. Reduction of post-surgical end-organ damage to both kidney and heart is expected to lead to a significant decrease in the rate and severity of AKI and a faster or more pronounced myocardial recovery.

3.4 Risks and benefits

There are the general non-study related risks of cardiac surgery with extracorporeal circulation (CPB), which will not be discussed in detail here.

3.4.1 Risks

SP16 is a drug at an early stage of development, and currently only a small number of people (healthy volunteers and patients) have received the active substance. The risk profile of SP16 can therefore not be conclusively assessed yet. In the clinical trials conducted to date, SP16 has been administered as a single treatment with a maximum dose of 0.2 mg/kg or 12 mg (split into two injection sites where necessary). SP16 was well tolerated, with only transient low to moderate pain at the injection site and no other reported adverse events. In this clinical trial SP16 is administered for the first time twice at intervals of 9±1 hours. Since the total dose of 12 mg per participant is not exceeded and is also divided in two doses of 6 mg per time point the drug-associated risk is considered to be the same or even lower than in the two previous studies due to the lower single-dose. Both injections will be administered under full anesthesiological monitoring, the first in the area of the operating theatre, the second in the ICU. Without injection site pain (patients are planned to be under anesthesia at both injection time points), SP16 appears to have a favorable safety profile. Overall, the drug-related risk is therefore considered to be low, even in the elderly participants.

Risk due to age. Patients aged 65 years and older with no upper limit may also be enrolled in this clinical trial because the necessity of CABG or valve replacement surgery with the underlying condition under investigation occurs with particular frequency in this age group. A relevant increased risk solely due to age is not expected, because there is a wealth of experience with routine cardiac surgery, particularly for this older patient group. To further mitigate the risk only, patients who are considered to be suitable candidates for surgery with CPB by cardiac surgeons will be included. The study teams possess extensive expertise in the clinical management of geriatric patients. Moreover, the routinely planned stay in the intensive care unit ensures continuous post-administration monitoring following the delivery of the investigational medicinal product.

Risks due to study related assessments. All study-related assessments are essentially routine examinations with little or no risk. For asservation in the central biobank (CeBE) and later use for research analyses (such as biomarkers), blood samples with a maximum volume of 25-27 ml per blood draw will be drawn at seven occasions during the study. This translates into a maximum of about 170 ml of blood drawn for study-specific purposes. Since blood will be sampled at all visits during the hospital stay for routine assessments, no additional invasive procedure is required for study-specific blood sampling, with the sole exception of the End of Study (EOS) examination on Day 90±7 d, which is performed as an outpatient visit with

additional blood draw. The risk associated with study-specific blood sampling, such as blood loss, is considered to be very low.

3.4.2 Benefits

In this clinical trial, all participants receive standard treatment. Half of the participants are given the opportunity of additionally receiving SP16, a potentially preventive medication that is thought to reduce their risk or even avoid the development of CSA-AKI.

The other half of the participants randomized to the control group will receive placebo. They are not expected to gain any individual benefit over standard treatment by participating in the clinical trial.

3.4.3 Risk-benefit balance and conclusion

The overall risks associated with the study participation appear small in relation to the development of CSA-AKI.

The Sponsor therefore considers the benefit-risk balance of this study to be positive.

4 TRIAL OBJECTIVES AND ENDPOINTS

4.1 Primary objective

To evaluate the safety of SP16 administration and its ability to prevent CSA-AKI as defined by KDIGO criteria, in participants with CKD 2-3b undergoing planned cardiac surgery.

4.1.1 Primary safety endpoint

Frequency of AEs and SAEs within 72 h after index surgery.

4.1.2 Primary efficacy endpoint

Number of participants who develop CSA-AKI during hospital stay defined by KDIGO stage 1 or higher. If at least one of the following criteria is observed in the interval since end of index surgery and the 7-day assessment, a participant will be considered to have developed CSA-AKI:

- Increase in SCr by ≥0.3 mg/dl (>26.5 µmol/l) within 168±4 h after index surgery (defined as the period since CPB was terminated and systemic circulation resumed).
- Increase in SCr to ≥1.5 times the baseline value, using the highest SCr value within 168±4 h after index surgery.
- Decrease in urine output <0.5 ml/kg/h for more than 6 hours within 168±4 h after index surgery

4.2 Secondary objectives

To evaluate the effect of SP16 on

- The severity of post-surgical CSA-AKI (according to KDIGO stages 1-3).
- The duration of post-surgical CSA-AKI.
- Necessity of RRT.
- Duration of RRT.
- The cardiac left and right ventricular function.
- The composite of major adverse kidney events (MAKE) that include death, need of dialysis, or sustained impaired renal function within 90±7 d after index surgery (MAKE90).
- The incidence of AEs and SAEs.

4.2.1 Secondary endpoints

- Highest CSA-AKI stage value according to the stage classification of the KDIGO-AKI in the 7-day period after the index surgery.

- Number of days after post-surgical onset of CSA-AKI until re-achievement of baseline level of serum creatinine (defined as a return of creatinine to <0.3 mg/dl above baseline value) or discharge from hospital, whichever comes first.
- Necessity of RRT (yes/no)
- Duration of RRT measured by starting date [yyyy-mmm-dd] and end date [yyyy-mmm-dd]
- Cardiac function on Day 90±7 d after cardiac index surgery compared to pre surgical assessment (Visit 1) assessed by echocardiography (TTE).
- Cardiac function on Day 0 post-surgery (Visit 3), Day 1, and on Day 5 after index surgery assessed by point of care echocardiography (TTE) compared to pre-surgical assessment (Visit 1).
- NT-proBNP level on Day 1, Day 7, and Day 90±7 d after index surgery compared to pre-surgical assessment on Day 0 (Baseline; Visit 2).
- Central venous oxygen saturation (ScvO2) on Day 1, Day 5 and Day 7 after index surgery compared to pre-surgical assessment on Day 0 (Baseline; Visit 2).
- All-cause death within 90±7d (3 months) after cardiac index surgery.
- Sustained impaired renal function defined as ≥25% increase in SCr at Day 90±7 d compared to baseline.
- Sustained impaired renal function requiring at least one dialysis during the post-surgical interval until Day 90±7 d (end of observation period).
- Frequency of AE and SAE within 7 days after cardiac index surgery.
- Frequency of AE and SAE during the observation period.
- Number of participants with at least one SAE during the observation period.

4.3 Other objectives

- To investigate the effect of SP16 on AKI-specific biomarkers.
- To assess the impact of SP16 on the duration of the treatment in the intensive care unit (ICU LOS).
- To assess the impact of SP16 on the duration of hospitalization (hospital LOS).
- To assess the impact of SP16 on the need and duration of post-surgical mechanical ventilation.
- To investigate the potential impact of impaired renal function on the pharmacokinetics of SP16.

4.3.1 Other endpoints

- Blood and/or urine levels of AKI-specific biomarkers, such as cystatine C, urine-NGAL; IL-6, IL-10, TIMP2 and IGFBP7 at defined post-surgical time points within 7 days after index surgery compared to pre-surgical assessment at baseline (Visit 2).
- Time [hours] of the ICU stay.

- Time [days] of inpatient stay in the primary hospital (stay in rehab clinic not included).
- Need and total time [date, hours] of post-surgical mechanical ventilation.
- Pharmacokinetic parameters of SP16 based on serum levels of SP16.

4.4 Accompanying research program

Biospecimens of the participants will be collected and transferred to the local biobank CeBE of the Universitätsklinikum Erlangen and the Medical Faculty of the FAU for later analysis. The analyses may include various parameters in connection with the area of disease to be investigated and be performed after the end of the trial.

5 TRIAL DESIGN

5.1 Description of trial design

This is a prospective, randomized, two-armed, parallel-group, double-blind, placebo-controlled clinical trial to investigate efficacy and safety of SP16 in preventing CSA-AKI in adult at-risk subjects with chronic kidney disease KDIGO CKD stage G2-3b undergoing elective cardiac surgery using CPB.

The investigational medicinal product (SP16 in a dose of 6 mg or placebo) will be administered subcutaneously at two different timepoints, at first shortly before the start of cardiac surgery and then 9±1 h after the first administration. The total dose of 12 mg SP16 within 12 h corresponds to the recommendations of the SERPIN based on previous findings from clinical trials. SP16 has been used in a placebo-controlled phase I dose escalation trial in healthy volunteers with increasing dose levels of 0.0125, 0.05, and 0.2 mg/kg bodyweight with a maximum dose of 12 mg. In a small single armed, open-label phase IIa clinical trial, 10 participants with STEMI received SP16-3M in a single dose of 0.2 mg/kg bodyweight per s.c. administration. Single doses of up to 12 mg administered in the Phase I and Phase Ib/IIa study were well tolerated. Due to solubility properties of the API the maximum concentration is limited. As the drug is intended for subcutaneous administration, the maximum injectable volume at one injection site is also limited. Therefore, the total dose of 12 mg is divided into two doses of 6 mg each, which are then administered at two injection sites per injection time.

Since pharmakokinetic parameters are currently only available for a limited number of humans, (i.e. 8 patients with myocardial infarction) all of whom with normal renal function, a series of PK parameters from 12 participants who received IMP and 3 placebo controls will be evaluated to identify possible influencing factors due to altered kidney function. The PK analyses will be performed in a randomized manner among the first cohort of approximately 30 participants until the first interim analysis, with the data being blinded to the investigators. The PK results and preliminary pharmacodynamic effects, as well as safety data will be reviewed to confirm dose appropriateness and considered by the sponsor for the further course of the clinical trial.

Biological samples collected in this trial may be stored for future research that is consistent with the participants' informed consent and applicable ethical and regulatory requirements. The pharmacokinetic samples will be transferred to and processed in laboratories outside the European Union, namely in the USA, subject to appropriate safeguards for data protection and ethical oversight. Long-term storage, governance procedures, and permitted future uses will follow EU Regulation 536/2014, ICH-GCP E6(R3), and the WMA Declaration of Taipei.

5.1.1 Justification for the placebo-controlled trial design

The clinical trial will be randomised, double-blinded and placebo-controlled to ensure an even distribution of known and unknown influencing factors across both study groups. This is particularly relevant because, in the patient group under investigation, which is planned to undergo heart surgery, cardiopulmonary bypass and subsequent short-term intensive care,

the influencing factors can be extensive and make it difficult to detect signals relating to the test medication. A preventive effect on CSA-AKI cannot be investigated in any other setting.

The study-related pharmacological intervention will be carried out as an ‘add-on’, in addition to the standard inpatient therapy in the two study arms. Neither the efficacy of SP16 in this patient population has yet been proven nor any other pharmacotherapy is established as standard therapy in the prevention of AKI in patients at risk undergoing CSA. A placebo arm has been introduced to the study to enable a double-blinded design and avoid a potential bias of the investigator in the evaluation of safety and tolerability. Thus, the control in the form of a placebo group is deemed appropriate in this Phase II clinical trial, ethically justifiable and in line with the Declaration of Helsinki 2024-10, No. 33.

As both treatment arms receive standard treatment, the placebo-group is not posed to an additional risk due to withholding any treatment but is also not expected to gain any individual benefit over standard treatment. Thus, the risk-benefit ratio of the placebo-group is expected to be equivalent to the standard treatment.

5.2 Number of participants

A total of 120 evaluable participants, randomized 1:1 to the two study arms.

5.3 Trial sites

This is a single center clinical trial at the Universitätsklinikum Erlangen, Germany.

5.4 Trial duration

The period from the first visit of the first participant (FPFV) to the last visit of the last participant (LPLV) is expected to last around 38 months. Each participant will participate in the clinical trial for a maximum of 151 days. The recruitment period is expected to last around 35 months.

After the Screening Visit (Visit 1a), Randomization (Visit 1b) and the Baseline Visit (Visit 2) participants will complete 9 visits during hospitalization until discharge followed by a telephone follow-up on Day 30±3 d and the Final Visit (EOS) on Day 90±7 d.

5.4.1 Start of the trial

The trial begins with the first participant consenting to participate in this trial (first consent form signed).

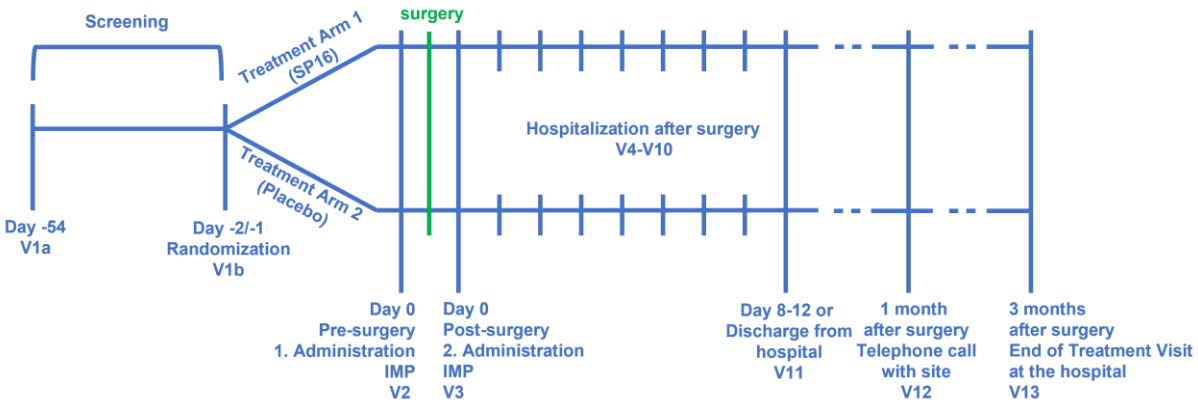
5.4.2 End of the trial

The end of the trial is defined as the date when the last participant has completed V13 (Day 90±7 d; EOS) or the date of the last visit of the last participant should that participant drop out earlier for other reasons, respectively.

5.5 Access to trial intervention after end of trial and post-trial provisions

The administration of SP16 is planned only short-term with preventative intention during a surgical procedure that is routinely performed as part of standard care. It is not intended as a long-term therapy, continued access to this medication after the end of the study is therefore not foreseen.

5.6 Study schematic



6 TRIAL POPULATION

6.1 Selection of trial population

This phase II clinical trial will enroll adult persons with CKD Stage 2-3b, who are scheduled to undergo elective cardiac surgery using CPB.

Gender distribution

Data from patients with coronary heart disease who are candidates for a coronary artery bypass graft (CABG) indicate a preponderance of the male gender (about 70:30), whereas for patients with diseased aortic valve or mitral valve no relevant gender difference is observed. Therefore, no measures to influence gender distribution in study enrollment will be taken.

6.2 Inclusion criteria

A participant meeting all inclusion criteria will be considered eligible for study enrollment.

Inclusion criteria	**Screening Visit (Day -54 to -2)**
1. Individual aged ≥18 years.	X
2. Male or female.	X
3. Scheduled for CABG **OR** aortic valve surgery (aortic valve replacement or repair alone, with or without aortic root repair) **OR** mitral valve surgery **OR** aortic/mitral valve surgery combined with CABG.	X
4. Use of the CPB during surgical intervention expected.	X
5. Written informed consent obtained from the participant.	X
6. Understanding of study procedures and willingness to abide by all procedures during the course of the clinical trial.	X
7. CKD Stage 2–3b with eGFR ≤90 and ≥30 ml/min/1.73 m^2 (according to 2021 CKD-EPI equation) known for ≥ 3 months prior to enrollment	X
8. BMI ≥19 kg/m^2 to ≤40 kg/m^2.	X

Inclusion criteria	Screening Visit (Day -54 to -2)
9. Contraceptive measures: Female participants must fulfil at least one of the following criteria of highly effective contraception (according to CTFG recommendations v1.2) during and up to 3 months after the end of study participation: • Menopause (at least 12 months of natural amenorrhoea or 6 months of amenorrhoea with serum FSH >40 mU/ml) OR • Condition after bilateral ovariectomy or hysterectomy for at least 6 weeks prior to the screening appointment (Visit 1a, Day -54 to -2) OR • Regular, correct and reliable use of a contraceptive method with an error rate ≤1% per year: a) Inhibition of ovulation by estrogen and progesterone combination preparations (oral, intravaginal, or transdermal) or b) Inhibition of ovulation by progesterone monopreparations (oral, per injectionem [depot injections], or implant) or c) Intrauterine device, hormone coil OR • Bilateral tubal ligation OR • Vasectomy of all partners OR • Sexual abstinence. Male participants must fulfill at least one of the following contraceptive criteria during and up to 3 months after the end of participation in the study: • Vasectomy OR • Regular, correct, and reliable use of condoms	X

6.3 Exclusion criteria

A person meeting any of the following criteria will not be included in the clinical study:

Exclusion criteria	Screening Visit (Day -54 to -2)	Randomization (Day -2 to -1)
1. CKD stages 4-5 with eGFR <30 ml/min/1.73 m^2 pre-surgery as determined by CKD-EPI.	X	X
2. Previous cardiac surgery.	X	
3. Person has a kidney transplant or another solid organ transplant.	X	
4. Person is scheduled for intermittent or continuous renal replacement therapy (dialysis).	X	
5. Known diagnosis of dementia or other clinical signs of mental illness that will prevent full understanding.	X	

Exclusion criteria	Screening Visit (Day -54 to -2)	Randomization (Day -2 to -1)
6. Known diagnosis of severe COPD (Gold 3) and/or FEV1 < 1 l/s.	X	
7. Heart failure with severity of symptoms according to NYHA IV.	X	
8. Heart failure with impaired cardiac pump function (LVEF <35%).	X	
9. Acute onset or ongoing sepsis - sepsis is defined as the presence of a confirmed or putative infection, along with a dysregulated systemic immune reaction leading to organ dysfunction.	X	X
10. Clinical signs of a currently active infection including endocarditis requiring antibiotic treatment.	X	X
11. Clinical signs of an acute viral infection.	X	X
12. Serious underlying disease(s) or very poor general medical condition, so that in the investigator's judgment the person is not expected to survive ICU or hospital stay.	X	X
13. Patient who has an active (requiring treatment) malignancy or history within 5 years prior to enrollment in the study, of solid, metastatic or hematologic malignancy with the exception of basal or squamous cell carcinoma of the skin that has been removed.	X	
14. Administration of iodinated contrast agent within 24 hours prior to cardiac surgery		X
15. Recent (discontinued in the last 14 days before V1a or V1b) or current treatment with immunosuppressive drugs, including, but not limited to, high-dose corticosteroids [> 1 mg/kg of prednisone equivalent], tumour necrosis factor alpha blockers, or ciclosporin.	X	X
16. Current regular use of anti-inflammatory drugs such as NSAID, with discontinuation not possible. (however, if these medications are discontinued in the last 10 days before V2, the participant is eligible to participate). ASA up to 100 mg per day is allowed.	X	X
17. Systemic corticosteroid therapy (any dose).	X	X
18. Known active chronic inflammatory disease (including, but not limited to, rheumatoid arthritis or systemic lupus erythematosus).	X	
19. Known allergy to SP16 or to other ingredients of the IMP.	X	

Exclusion criteria	Screening Visit (Day -54 to -2)	Randomization (Day -2 to -1)
20. Person who is not willing to use highly effective contraceptive measures (according to CTFG recommendations v1.2).	X	
21. Pregnant women.	X	X
22. Breastfeeding women.	X	
23. Current participation in another interventional clinical study (register studies or non-interventional, observational studies excluded).	X	
24. Employee or direct relative of an employee of the study site, the CRO, or the Sponsor.	X	

6.4 Lifestyle considerations

None considered necessary.

6.5 Screening failure

A screening failure is defined as a participant who signed informed consent but did not fulfill all inclusion criteria or fulfill at least one exclusion criterion and has also not yet received study medication. All participants who gave informed consent and have been screened, but did not enter the study, will be listed on the participant screening/enrollment log.

6.6 Drop-out

A drop-out is defined as a participant who signed the consent form, fulfills all inclusion criteria and no exclusion criterion, and received study medication at least once, and for whatever reason prematurely discontinued the study participation.

7 TREATMENT

7.1 Description of the study medication (investigational medicinal products)

7.1.1 SP16-3M

The medicinal product with the active pharmaceutical ingredient SP16-3M, which has not yet been authorized in the EU, is used as the investigational medicinal product (IMP).

The synthetic peptide drug SP16 is a polypeptide of 17 aminoacids [redacted] acting as an LRP1 agonist.

Name of IMP	SP16 (Serpin Peptide 16)
Product type	Peptide
API	SP16-3M
List of excipients	Dextrose 5%, water for injection
Pharmaceutical form	Liquid; solution for s.c. injection
Appearance	Clear liquid
Strength per dose	1.5 mg/ml
Packaging	Sterile glass vials VIAL EZ-FILL® VB 8mL, 22x1x40, ISO8362-1-A-6R, NE48 (Stevanato Group S.p.A) Plastic cap with stopper (A Raymond; Manufacturer's Cat/Part No 259346002)
Content	Fill volume 4.5 ml ± 5% by weight
Dose	Single dose 6 mg
Route of administration	Subcutaneous injection
Manufacturer	[redacted] (contract manufacturer for Serpin Pharma Inc)
Developer/(future) Marketing Authorization Holder	Serpin Pharma,Inc [redacted] USA
MAH Number	Not authorized yet
Storage condition	To be stored at -20±5° C

	Before injection the product may be thawed and stored for up to 1 week at 2-8° C or for 24 h at room temperature before being injected

7.1.2 Placebo

Name of placebo	Dextrose 5%
Product type	Solvents and diluents including rinsing solutions
ATC code	V07AB
API	N/A
List of excipients	5% dextrose, water for injection
Pharmaceutical form	Liquid; solution for injection or infusion
Appearance	Clear liquid
Strength per dose	50 mg/ml
Packaging	Sterile glass vials VIAL EZ-FILL® VB 8mL, 22x1x40, ISO8362-1-A-6R, NE48 (Stevanato Group S.p.A) Plastic cap with stopper (A Raymond; Manufacturer's Cat/Part No 259346002)
Content	Fill volume 4.5 ml ± 5% by weight
Dose	4 ml
Route of administration	Subcutaneous injection
Manufacturer	[redacted] (contract manufacturer for Serpin Pharma Inc)
Storage condition	no specific storage conditions required

7.2 Dosing and administration

In the SP16 group, the IMP is injected subcutaneously at two different time points.

- The first administration will take place pre-surgically, in the area of the operating theatre, when the participant is under anesthesia.
- The second administration will be performed post-surgically, 9±1 h after the first administration.

At each of the two injection timepoints, a fixed dose of 6 mg SP16 (4 ml out of one vial) is divided and slowly (over about 30 seconds) administered by two s.c. injections of 2 ml (concentration 1.5 mg/ml) each at two different injection sites.

In the placebo group, placebo (dextrose 5%) is injected subcutaneously at the same timepoints as the IMP, each time slowly (over about 30 seconds) at a fixed volume of 2 ml each at two different injection sites.

For safety reasons, the study participants will be closely monitored for a period of approximately 1-2 h after completion of the injection. The monitoring is ensured by continuous intraoperative monitoring after the first IMP administration and by monitoring in the ICU after the second IMP administration.

7.3 Emergency treatment

If peracute systemic allergic reactions occur during the application of the IMP at the trial site, the injection is stopped immediately. In these cases as well as in the case of delayed reactions after the injection has already been fully administered, appropriate anti-allergic medication (e.g. glucocorticoids,antihistamines, epinephrine) has to be administered to the participant as an immediate measure at the discretion of the investigator depending on the severity of the reaction and according to the standard treatment of the hospital. If necessary, the participant can be admitted immediately to the ICU.

7.4 Treatment of overdose

Upon request of the study site, the hospital pharmacy will ship the exact number of vials of study medication needed for administration to the participant. The study medication is not handed over to the participant. The treating physician controls the exact dose of the application. Nevertheless, in the event of overdosing the participant concerned would receive symptom-adapted treatment according to hospital standard.

Any overdose must be separately recorded in the relevant section of the eCRF as a special situation (SpS) and reported to the Pharmacovigilance Department of the Sponsor in an expedited manner using the SpS reporting form.

Any case of overdose leading to an adverse reaction (AR) or a serious adverse reaction (SAR) must additionally be recorded in the corresponding AE/SAE sections of the eCRF and, in case of an SAR, be reported to the Pharmacovigilance Department of the Sponsor in an expedited manner using the SAE reporting form.

7.5 Handling, labelling, and accountability of study medication

7.5.1 Handling of study medication

The study medication is supplied as ready-to-use solutions for injection by the manufacturer SCINAI to the hospital pharmacy of the Universitätsklinikum Erlangen in different preliminary labelled bulk containers containing either verum or placebo vials.

The study medication is stored separately from other medications, protected from light and frozen at -20±5° C in the hospital pharmacy of the Universitätsklinikum Erlangen until delivered to the trial site.

IMP delivery from the hospital pharmacy of the Universitätsklinikum Erlangen to the trial site is requested separately for each participant by the trial site by e-mail. The type of study medication, IMP or placebo, and the number of vials needed are then chosen by an unblinded pharmacist (or delegated pharmacy staff) according to the randomization list available at the hospital pharmacy. The study medication will be thawed and labeled as such by the hospital pharmacy. Further, the required number of vials for each participant will be packed into a secondary packaging which will be provided with a secondary label. The IMP is then delivered to the trial site in compliance with the local in-hospital medication transport rules and and handed over to the investigator or an authorized person. The handover is confirmed in writing by the investigator or the authorized person.

The thawed study medication may be stored at the trial site refrigerated at 2-8° C for up to 7 days (168 h) or at room temperature for less than 24 h before administration to the participant.

The investigator or a member of the trial team authorized by the principal investigator is responsible for the proper handling of the study medication at the trial site and the corresponding documentation. The persons who have access to the study medication must be listed by name and area of responsibility in the list of personnel involved in the trial. The storage temperature needs to be checked and documented (continuous temperature monitoring, documented for both the period in the refrigerator and at room temperature) at the trial site.

With transport to the operating theatre the study medication may be stored at room temperature until the second administration 9±1 h after the first administration.

7.5.2 Labelling of study medication

The primary package (glass vial) of the study medication taken from the bulk container and the secondary package (bag or container) will be labelled as study medication by the hospital pharmacy of the Universitätsklinikum Erlangen in accordance with the requirements of the EU Regulation 536/2014 Annex VI and the Delegated Regulation 2022/2239.

7.5.3 Accountability of study medication

The issue and return as well as the application of the study medication are documented in the so-called Drug Accountability Log (for example: Identification of the study participant via code, date and quantity of solution administered).

The study personnel safely store the empty vials, the secondary packaging and the accompanying documents at the trial site for the traceability of the drug accountability of the study medication. After control by the monitor, the empty vials and the secondary packaging are disposed of properly at the trial site. Ready-to-use but not administered study medication is returned by the investigator to the hospital pharmacy of the Universitätsklinikum Erlangen

for destruction. The process should be documented in the investigator site file (ISF) (date and quantity of the returned trial medication).

7.6 Participant assignment, randomization

The participants are assigned to one of the two treatment arms, either IMP or placebo by means of 1:1 randomization. The randomization will be stratified by gender. The randomization list will be kept strictly confidential until unblinding and will not be accessible to anyone involved in the clinical trial with the exception of the responsible employees of the hospital pharmacy and the biobank CeBe of the Universitätsklinikum Erlangen.

7.7 Blinding, unblinding

The clinical trial will be conducted in a double-blind design. The investigators and study staff with patient contact at the trial site (e.g. study nurse) as well as the trial participants will be blinded. Further, the biostatistician and the person doing the pharmacovigilance will be blinded, too. The blinding will be maintained at least until the last participant last visit (LPLV) has been performed (or until the participant's last visit if the participant dropped out earlier), data have been monitored and cleaned and the data base has been closed.

Each envelope will be labeled with the patient number, as provided by the EDC system. The envelope will list "male" and "female" according to stratification and the treatment group for each stratum (e.g.: Stratum: female - Verum; Stratum: male – Placebo). To unblind the study, the study team/pharmacovigilance must check the sex of the patient to be unblinded. One complete set of emergency envelopes is sent to the trial site and one set is deposited with the person responsible for pharmacovigilance.

Unblinding of individual study participants before this time will only take place in the following cases:

- The participant experiences a medical emergency the treatment of which requires mandatory knowledge of the identity of the administered study medication. In this case, the participant's emergency envelope will be opened by the investigator or an appropriately authorized member of the study team. This person notes the date and time of opening on the envelope and signs it. The result of the unblinding is documented in the eCRF together with the date and time of opening.
- An SAE occurs in a participant that is assessed by the investigator or Sponsor as possibly causally related to the IMP and in addition assessed by the Sponsor as unexpected according the information given in the Reference Safety Information section of the valid version of the Investigator´s Brochure. Prior to a potential supected unexpected serious adverse reaction (SUSAR) report (or prior to interruption of the entire clinical trial, see Section 8.3), the participant's emergency envelope is opened by the person responsible for pharmacovigilance of the clinical trial on behalf of the Sponsor. This person notes the date and time of opening on the envelope and signs it. The result of the unblinding is documented on the corresponding SAE Assessment Sheet.

After completion of the clinical trial, all emergency envelopes are returned to the Sponsor for archiving.

7.8 Trial intervention compliance

The study medication is administered subcutaneously twice in total, at each occasion by authorized study personnel, and not handed out to the participant. This ensures compliance to the study intervention to the highest degree.

7.9 Concomitant intervention (cardiac surgery)

As a central component of the definition of the patient collective of interest, at least one elective open heart surgery using CPB, also named the index surgery, is performed on all participants. The surgery is clinically indicated and would be performed regardless of the patient's participation in the study. It caneither be a CABG or a repair/replacement of the mitral and/or aortic valve or a combination of aortic/mitral valve surgery with CABG. The individual surgery is performed according to local hospital standards and current guidelines. The entire surgical procedures are therefore not study related for the participant in this clinical trial.

7.10 Concomitant medication

Unless already listed below, the medication to be administered as part of the cardiac surgery falls entirely under the permitted concomitant medication in the clinical trial.

7.10.1 Prohibited concomitant medication

The administration of the following drugs is prohibited during study participation:

- Corticosteroids at any dose during a period of 7 days after first dose of study medication.
- Interleukin inhibitors (IL-1 receptor antagonist anakinra, IL-6 antagonist tocilicumab)
- NSAIDs (e.g. ibuprofen, diclofenac, naproxen, ASA >100 mg/day)
- Aminoglycoside antibiotics.
- Further prohibited concomitant medication which is not listed above, but, at the discretion of the investigator, is necessary to ensure patient safety, might be included and will be documented accordingly.

If a clinical condition requires treatment with renally excreted drugs for which dose adjustment is recommended, or drugs known to alter renal function in a relevant manner, the dosage and timing of administration should be adjusted at the discretion of the investigator. Drugs should be documented accordingly.

7.10.2 Permitted concomitant medication

The medicinal products listed below are permitted as concomitant medication for study participants during participation in the study, provided they are not listed in Section 7.10.1. The

list contains medications usually administered after heart surgery, but is not exhaustive. Other medications may be administered at the discretion of the attending physicians depending on clinical necessity.

- Intra- and post-surgical treatment in heart surgery with cardiopulmonary bypass (CPB) according to hospital standard. The therapy can be initiated prior to operation, in the intraoperative post-bypass period and continued during admission to the ICU or during the participant's subsequent inpatient stay:
    - For cardiovascular management to treat left and/or right ventricular dysfunction and/or vasoplegia (low vascular resistance): Inotropic agents and vasopressor (e.g. ephedrine, norepinephrine, epinephrine, dopamine, dobutamine, vasopressin, isoproterenol), beta-blocking agents (e.g. esmolol, metoprolol), calcium channel blockers (e.g. nicardipine), or direct vasodilators (e.g. hydralazine, nitroglycerin).
    - Diuretics (e.g. for volume control, against potassium overload).
    - For heart rhythm control to treat arrhythmias: E.g. beta-blocking agents, amiodarone.
    - For analgesia: Opioids, e.g. fentanyl, sufentanil, hydromorphone, morphine, remifentanil, methadone.
    - For sedation: e.g. propofol, ketamine, dexmedetomidine, midazolam, lorazepam, diazepam, clonidin, lormetazepam.
    - Oxygen.
    - For hemostasis, coagulopathy: e.g. clotting factors, transfusion of red blood cells, platelets, or fresh frozen plasma (FFP), fibrinogen, cryoprecipitate, tranexamic acid (TXA), desmopressin.
    - For VTE prophylaxis: DOAC, low molecular weight heparin, unfractionated heparin (in advanced age patients [< 80 years] who are at risk of renal insufficiency), argatroban.
    - For systemic embolic events (SEE) prophylaxis if post-surgical cardiac surgery-associated atrial fibrillation persists for more than 48 h: DOAC (e.g. apixaban), phenprocoumon (Marcumar®), warfarin, heparin, argatroban.
- Any prescribed medication for the treatment of chronic underlying diseases such as antihypertensive drugs, anti-arrhythmic drugs (e.g. beta-blockers, amiodarone), diuretics, antidiabetics, statins, anticoagulants, platelet inhibitors (e.g. ASA up to a dose of 100 mg/day, clopidogrel and its analoga).
- Any medication for the treatment of acute illnesses (e.g. antibiotics for intercurrent acute bacterial infections).
- Acetaminophen (paracetamol) or metamizole for headache, fever etc.
- Any non prescription therapy for concomitant diseases.
- Necessary vaccinations as recommended by the STIKO.

The medicines can be used at the discretion of the attending physician.

7.10.3 Measures in case of relevant deterioration of kidney function

If a participant experiences a clinically relevant acute deterioration in postoperative renal function, this is considered a non-response requiring targeted treatment (rescue therapy). The participant concerned should receive appropriate drug treatment and/or hemodialysis according to the trial protocol. The measures taken should be properly documented in the eCRF. Affected participants are followed until the final study visit.

Indications for RRT are:

1. Refractory hyperkalemia with serum potassium >= 6.0 mmol/l
2. Refractory AKI-associated metabolic acidosis with pH <7.20
3. Refractory volume overload
4. Uremia (e.g. urea >200 mg/dl)
5. Other, with consultation of a nephrological investigator.

7.10.4 Standard rehabilitation program after surgery

As all patients who have undergone heart surgery, the study participants are usually referred to a post-surgical cardiac rehabilitation program by the surgical department starting 10 to 14 days after surgery. This takes place during the observation period of the clinical trial prior to the EOS Visit.

8 TERMINATION OF THE TRIAL

8.1 Premature discontination of a participant by an investigator

If it is determined at Randomization (V1b) or Baseline (V2), that circumstances have arisen in the participant since the Screening Visit (V1a) that lead to a violation of the inclusion or exclusion criteria, the participant will be withdrawn from the clinical trial before the application of any study medication. Premature discontinuation is documented in the eCRF as an unscheduled visit.

Other reasons for an individual participant to discontinue the study participation may include

- Serious violation of the protocol with impact on the reliability of the data.
- Any situation, disease, or clinically relevant change in laboratory values that, in the opinion of the investigator, would jeopardize the participant's health and would not justify further participation in the clinical trial.
- Second cardiac surgery within the observation period of 7 days after the index surgery (prior to the assessment of the primary efficacy endpoint).

After application of at least one injection IMP, the participant should be followed until the final visit. In the case of serious protocol violations relevant to the quality of the data the participant should be excluded from the per protocol analysis or, if necessary, at the discretion of the Sponsor, from all other data analyses.

8.2 Premature discontinuation of the clinical trial by a participant

In accordance with the Declaration of Helsinki participants can withdraw from the clinical trial at any time at their own request without any disadvantages for their further treatment. The reason for the participant's withdrawal from the trial will be documented in the eCRF, if communicated. All participants who withdraw prematurely from the clinical trial at their own request should be asked to undergo a final examination in an Unscheduled Visit at the earliest possible date, the results of which are documented in the eCRF. If they have already received the first administration of study medication, their data recorded until the time of withdrawal will be included in the biostatistical analysis.

8.3 Temporary halt of the clinical trial

The clinical trial should be halted temporarily by the Sponsor for safety review as soon as three SAEs suspected to be causally related to the IMP (meaning a Serious Adverse Reaction, SAR) occur. The Sponsor will first unblind the affected trial participants. If it is confirmed that the participants have been treated with SP16, recruitment of further patients will be suspended until the suspected causal relationship of the SAEs with SP16 has been clarified. The Sponsor shall notify the Member State concerned about the temporary halt and, where applicable, the resumption of the clinical trial within 15 d of the interruption and the resumption, respectively, via the EU portal, CTIS. Resumption after temporary halt constitutes a substantial modification requiring approval by the competent authority.

8.4 Premature termination of the entire clinical trial

The Sponsor is authorized to terminate the trial prematurely for relevant medical or administrative reasons. The statutory reporting obligations prescribed for this are complied with.

The Sponsor will terminate the clinical trial prematurely if

- the patient recruitment rate is inadequate.
- serious, unresolved problems arise with the quality of the data collected.
- unforeseeable circumstances have arisen at the trial site that do not allow the clinical trial to continue.
- unacceptable risks and side effects have arisen (decision following a new risk-benefit assessment).
- new scientific findings, e.g. new insights from other clinical trials, during the term of the trial, that could affect the patient's safety so that the benefit-risk assessment is no longer positive, do not permit its continuation.
- the license to manufacture or import the IMP is withdrawn.
- in the event of death or permanent occupational disability, the maximum sum insured can no longer be considered sufficient and cannot be adjusted to cover the compensation provided for in accordance with Article 76 of the Regulation (EU) No. 536/2014 i.c.w. Section 40a, Sentence 1, No. 3, lit. b) of the German Medicinal Products Act.

The reasons for premature discontinuation of the trial are documented in detail. Participants who are still in the treatment or observation phase at the time the trial is discontinued must undergo a final examination as an Unscheduled Visit which is documented in the eCRF.

If the investigators have ethical concerns regarding the continuation of the trial, they must notify the Sponsor immediately.

8.4.1 Further treatment of participants after discontinuation of the clinical trial

After premature discontinuation of the clinical trial, the participant will receive standard treatment by the hospital's attending physicians during the inpatient stay, followed by regular treatment by the attending general practitioner or specialist (e.g. cardiologist, nephrologist).

9 TRIAL ASSESSMENTS AND PROCEDURES

9.1 Description of procedures

As part of the clinical trial, study participants are monitored in a standardized manner using the following tests and study related procedures. The times at which the procedures are performed can be found in the visit schedule (Section 10.1).

9.1.1 Informed consent

Informed consent comprises providing written and verbal information to a potential participant and obtaining their consent to participate in the clinical trial. Every person must be fully informed about the planned study prior to enrollment into the clinical trial. The information is provided in writing in the study-specific patient information leaflet and in person by an investigator. Only after all of the participant's questions have been clarified will they be asked to sign and personally date the informed consent form (ICF).

The original of the ICF remains at the trial site and is filed in the ISF. A photocopy is filed in the patient record. The study participant will receive a second original of the ICF and a copy of the participant insurance certificate. Upon request, a copy of the general terms and conditions of the trial participant insurance will be provided.

9.1.2 Medical history

As part of the medical history the following items should be inquired from the patient (disease known/present and since when, current medication):

- Coronary artery disease (vascular status [main stem stenosis, single-vessel, 2-vessel, 3-vessel disease, small vessel disease]).
- Canadian Cardiovascular Society (CCS-Grade 1-4).
- Previous acute myocardial infarction (AMI) (yes/no; yes: number of AMI, localization [anterior, posterior, septum, apical]).
- Heart rhythm: SR or AF.
- Heart valve disease (affected valve [aortic valve, mitral valve], stenosis/regurgitation, AS grade 1-3, MS grading mild/moderate/severe, AI grading mild/moderate/severe, MI grading mild/moderate/severe).
- Severity of illness: Heart failure (NYHA class I-III; EF).
- Comorbidities:
    - Chronic kidney disease (CKD stage 2, 3a, 3b).
    - Hypertension (yes/no, since when, treated/untreated).
    - Diabetes type 1 or type 2.
    - COPD (yes/no, stage according to the GOLD criteria).

- Peripheral artery disease (PAD) (yes/no, yes (type of PAD [pelvis, thig, lower leg, upper extremity], symptomatology according to Fontaine stages I-IV).
- Previous cerebral ischemia (yes/no, yes (stroke/TIA).

- Smoking status (current/never/former), for current and former smokers: pack years.
- Alcohol consumption frequency (yes, often [daily, almost daily], yes, occasionally [approximately once a week], yes, rarely [less than once a week], no).
- Use of NSAIDs (yes, often [daily, almost daily], yes, occasionally [approximately once a week/every 2 weeks], yes, rarely [less than once a month], no)
- Liver disease/hepatitis
- Liver cirrhosis (CHILD-Pugh-classification Grade 1-3)
- Malignancy
- Immunocompromised state (chemo-, radiation-, high dose steroid therapy, advanced leukemia, lymphoma, or AIDS)
- Any other known/present disease (name of disease)

9.1.3 Demographic data

The following demographic data should be recorded: Age (year of birth), gender (male/female, national/geographical origin (participant's self-idenfication), type of heart surgery (CABG, valve surgery, or combined CABG and valve surgery). Patients with combined valve and CABG surgery are grouped into one of both categories according to echocardiography and coronary examination.

9.1.4 Physical examination

The physical examination comprises an orientating examination of the skin, the thoracic organs (auscultation of heart and lungs), the abdominal organs, the extremities and a roughly orientating examination of the nervous system (gait, muscle tone, musculature in lateral comparison, finger-nose test, strength [handshake, holding test], balance [one-legged stand], selective reflex test).

9.1.4.1 Targeted physical examination

For V1b-V10, the physical examination is limited to auscultation of the heart and lungs and re-examination of other organs and functional systems if pathological findings were made in the previous examination (targeted physical examination).

9.1.4.2 Body-Mass Index

For BMI calculation height [in centimeters] is determined once during the Screening Visit (V1a), the weight [in kilograms] is determined at the Screening Visit (V1a) and at the Final Visit (V12).

9.1.5 Vital signs

During the ICU stay, the following vital parameters are recorded daily at 3 defined timepoints: In the morning (between 08h00 and 09h00), at midday (between 13h00 and 14h00), and in the evening (between 19h00 and 20h00). The highest and lowest value within this timeframe should be recorded.

- Systolic and diastolic blood pressure [mmHg].
- Pulse rate in beats per minute [bpm].
- Oxygen-saturation (SpO2) in percent [%], determined by pulse oximetry.
- Body temperature [° C].

During the stay in the normal hospital ward vital signs should be determined three times a day a day according to ward routine.

9.1.6 ECG

The standard 12-lead ECG should comprise

- rhythm (SR/AF).
- heart rate [bpm].
- Axis of the heart (normal, axis deviations: left, right, extreme).
- PQ interval [ms].
- QRS interval [ms].
- QTc interval (Fridericia formula for QT interval correction: $QTc = QT/RR^{0.33}$) [ms].
- Morphologic pattern of the QRS complex, ST-segment, T-wave.
- R/S transition zone

9.1.7 Echocardiography

A transthoracic echocardiogram (TTE) for highly accurate and non-invasive quick assessment of the function of the heart is performed according to hospital standard at the trial site. The following selection of parameters should be recorded as a minimum in the eCRF for Visit 1a and Visit 13:

<u>Left ventricle (LV) and atrium (LA)</u>

- LV-EF (ejection fraction) [%] with biplane determination by Simpson´s method
- LV diameter systolic/diastolic
- Valve stenoses and/or insufficiencies
- SV (stroke volume) [ml]
- LV kinetics (dyskinesia [yes/no], hypokinesia [yes /no], akinesia [yes/no])

- Tissue doppler analysis
- Strain analysis of the LV
- Area of the LA

Right ventricle (RV) and atrium (RA)

- TAPSE [mm]
- 3D-RV-EF
- RVEDD
- Tricuspid insufficiency
- TRVmax [m/s]
- Systolic pulmonalarterial pressure (sPAP)
- Strain analysis of the RV
- Area of the RA

All other point of care transthoracic echocardiograms (TTE) at Visit 3, Visit 4, and Visit 8 the following selection of parameters should be recorded as a minimum in the eCRF:

Left ventricle (LV) and atrium (LA)

- LV-EF (ejection fraction) [%] with biplane determination by Simpson´s method
- LV diameter systolic/diastolic
- Valve stenoses and/or insufficiencies
- SV (stroke volume) [ml]
- LV kinetics (dyskinesia [yes/no], hypokinesia [yes /no], akinesia [yes/no])
- Area of the LA

Right ventricle (RV) and atrium (RA)

- TAPSE [mm]
- RVEDD
- Tricuspid insufficiency
- Systolic pulmonalarterial pressure (sPAP)
- Area of the RA

The echocardiographic data are evaluated separately in the two subgroups of CABG and heart valve surgery patients.

9.1.8 Assessment of nephrotoxic agents

In the first 7 days, nephrotoxic agents administered are daily assessed:

- ACEi
- Aciclovir
- Amikacin
- Amphotericine liposomal
- Amphotericin B
- ARB
- Carboplatin
- Cefotaxime
- Ceftazidime
- Cefuroxime
- Cidofovir
- Cisplatin
- Colistimethate/Colistin
- Ciclosporine
- Foscavir
- Gadopentetate dimeglumine (Gadolinium)
- Gadoextate disodium (Primovist)
- Ganciclovir
- Lithium
- Mesalamine
- Methotrexate
- Piperacillin/Tazobactam
- Radio contrast media
- Sirolimus
- Tacrolimus
- Tobramycin
- Valaciclovir
- Valganciclovir
- Vancomycin

9.1.9 Laboratory tests

The following laboratory tests should be carried out:

9.1.9.1 Lab 1 (safety)

Hematology:

- Hemoglobin
- Hematocrit
- RBC
- MCH
- MCV
- MCHC
- WBC
- Platelets
- Differential blood count (neutrophils/eosinophils/basophils/lymphocytes)
- Immature Granulocytes (IG)
- Monocytes
- RDW

Clinical chemistry:

- Sodium
- Potassium
- Calcium
- Chloride
- Creatinine
- eGFR
- Urea
- Anorganic phosphate
- IL-6
- IL-10
- AST (GOT)
- ALT (GPT)
- γ-GT
- Bilirubin

- LDH
- Alkaline phosphatase
- Lipase
- Lactate
- Creatine kinase (CK)
- Creatine kinase-MB (CK-MB)
- Troponine I (high-sensitive)
- Total protein
- Albumin
- CRP
- Uric acid
- Calcium Phosphate Product
- Corrected Calcium (Albumin)

Coagulation:

- Thromboplastin time as Quick value [%]
- Thromboplastin time as INR
- pTT [s]

Urine (if available):

Specific gravity, pH, erythrocytes, leukocytes, bilirubin, proteins (quantitative), creatinine, albumin, IgG, transferrin, alpha-1-microglobulin will be determined in an urine sample (as far as appropriate volume available) by the local lab. Total protein and albumin will be analyzed in relation to creatinine level (in gram or mmol).

9.1.9.2 Lab 2 (biomarkers for AKI)

For special AKI diagnostics venous blood samples of 7.5 ml each and a urine sample are taken at the following timepoints: Pre-surgery and 240±30 min, 24±1 h, 72±2 h, 7 d±6 h post-surgery. The following biomarkers are determined:

- Cystatin C
- Cystatin C-GFR
- NGAL (urine)

9.1.9.3 Lab 3 (biomarker for cardiac function)

Venous blood samples should be drawn for determination of NT-proBNP, a diagnostic biomarker of the cardiac function. Serum levels correlate well with the severity of acute heart failure. Frequency of sampling according to the visit schedule.

9.1.9.4 Lab 4 (accompanying research program)

Experimental biomarkers of AKI will be determined for research purposes. Venous blood samples of 7.5 ml (EDTA tube) and a 7.5 ml sample (serum tube) as well as urine samples should be collected during study participation at the following timepoints: 7.5 ml EDTA and 7.5 ml serum tube: Pre-surgery and 120±30 min, 240±30 min, 24±1 h, 72±2 h, and 7 d±6 h and on Day 90±7 d post-surgery.

The analyses include, but are not limited to, the following parameters:

- Plasma NGAL
- Urine KIM-1
- Urine L-FABP
- Urine TIMP-2
- Urine IGFBP7
- Urine TIMP-2*IGFBP7 (calculated)
- Urine IL-18
- Urine pi-GST

Another 10 ml venous blood sample in an EDTA tube to collect PBMC for immunocellular diagnostics should be taken at the following time points: pre-surgery (V2), 24 h (V4), 3 d (V6) 7 d (V10) and 90±7 d (V13) post-surgery.

The samples are stored in CeBE and can be analyzed at a later stage after the end of the trial.

Overview of sample volume for scientific analyses, storage for later analyses and pharmacokinetics:

Specification	pre-OP	2 h post-OP	4 h post-OP	24 h post-OP	3 d post-OP	7 d post-OP	90 d post-OP	No. of samples	Total blood volume
7,5 ml EDTA	1	1	1	1	1	1	1	7	52,5
7,5 ml Serum	1	1	1	1	1	1	1	7	52,5
10 ml EDTA	1	0	0	1	1	1	1	5	50
10 ml Urine	1	0	0	1	1	1	1	5	
2 ml PK	Time points see 9.1.11							7	14*
									155 -169* ml

*From 15 participants only (see below)

9.1.9.5 Pre-Randomization Lab

Selected blood samples will be drawn to support the review of exclusion criteria prior to randomization

- Serum creatinine with eGFR
- CRP
- Hematology (WBC)

9.1.9.6 Urine output

The urine output [ml/kg/h] will be determined at least every 6 h (starting at 12:00 am) by urinary catheter within 24 h post surgery or during the ICU stay. Thereafter urine output will be determined for routine control of volume balance every 12 h (starting at 12:00 am). If urine output is measured multiple times over a 6- or 12-hour period, the measured volumes are added together and recorded in the patient's medical record.

9.1.10 Pregnancy test

The pregnancy test (determination of HCG through urine or blood test) is only necessary for women of childbearing potential; this is determined by questioning about individual contraceptive measures. If the test at V1a was carried out more than 72 h before Baseline, then it must be repeated at V1b. A new pregnancy test must be carried out one month after the administration of the IMP and at EOS (V13) or at the last visit if participation is terminated prematurely.

9.1.11 Blood sampling for pharmacokinetics

For the analysis of pharmacokinetic parameters of the active substance SP16-3M blood samples of 2 ml (with a minimum of 1 ml) using K2 EDTA Monovette (Sarstedt) or a comparable system should be taken from an unused line of the central venous catheter or from separate peripheral venous canula at the following time points:

Visit	Sampling time point	Sample volume
V2 (D0 Baseline)	Within 1 h before 1st injection of study medication	2 ml
V3 (D0 post op) trough level	Within 30 min before 2nd injection of study medication	2 ml
V3 (D0 post op)	15±2 min after 2nd injection of study medication	2 ml
V3 (D0 post op)	30±3 min after 2nd injection of study medication	2 ml
V3 (D0 post op)	60±6 min after 2nd injection of study medication	2 ml
V3 (D0 post op)	90±9 min after 2nd injection of study medication	2 ml
V3 (D0 post op)	180±18 min after 2nd injection of study medication	2 ml

PK samples will be collected from 12 participants in the IMP group and 3 participants in the placebo group. To maintain the blinding of the study team at the study site, appropriately flagged tubes for PK sampling will be provided to the study team by an unblinded delegate party.

PK samples must be collected from the arterial catheter. If not possible, the participant can be replaced by another participant to achieve the number of PK samples required.

9.1.12 AKI assessment according to KDIGO criteria

Acute kidney injury is defined by the KDIGO* criteria:

Stage	Serum creatinine level	Urine output
1	1.5 to 1.9 times baseline within 7 d OR ≥ 0.3 mg/dl (≥ 26.5 µmol/l) increase within 48 h	< 0.5 ml/kg/h for 6 h
2	2.0 - 2.9 times baseline	< 0.5 ml/kg/h for ≥ 12 h
3	3.0 times baseline OR increase to ≥ 4.0 mg/dl (≥ 353.6 µmol/l) OR Initiation of renal replacement therapy	< 0.3 ml/kg/h for ≥ 24 h OR anuria for ≥ 12 h

*Reference: https://kdigo.org

9.1.13 Recording of perioperative conditions and cardio-pulmonary bypass

Inflammatory mediators released during CPB may interact with the potential anti-inflammatory effects of the IMP. The perioperative conditions and information on the CPB use should be recorded to be considered in the data analysis to investigate the potential impact on the efficacy of SP16. The following data should be collected:

-
- Duration of surgery
- Duration of CPB and aortic cross-clamping. Timepoint of start of the CPB and the time at which the technician switches the pump off again [date; hh:mm].
- Intra-operative urine output [ml/h] is measured to monitor the development of oliguria (< 0.5 ml/h). The bladder catheter should be checked for kinking or disconnection or other problems with the bladder at the investigator's discretion.
- Necessity [yes/no] as well as dose and duration [dd:hh] of extraordinary dosing of vasopressor support (defined as >1 mg/h norepinephrine).
- Necessity for and dose of inotropes (dobutamine, epinephrine, norepinephrine, milrinone, levosimendan).
- Necessity for more than one vasopressor.

- Minimal temperature during CPB.
- Usage of hypothermic circulatory arrest.
- Use of hemofiltration (for hemoconcentration) during CPB [yes/no].
- Presence and duration of intra-operative prolonged hypotension during CPB, defined as mean arterial pressures <50 mmHg for more than 10 min.
- Presence and duration of low pump flow rate. Determined by oxygen delivery index DO2i.

9.1.14 Recording of post-surgical data (during ICU and hospital stay)

The following data during ICU and hospital stay should be collected:

- Necessity and duration of inotropic and vasopressor support on ICU.
- Necessity and duration of post-surgical hemodialysis (RRT).
- Hemodynamic data (If available, only when participant has PA catheter) at the time of ICU admission (Day 0), Day 1, Day 2, Day 3: Cardiac index, systemic pressure, pulmonary pressure, central venous pressure, wedge pressure, central venous oxygen saturation).
- Duration of mechanical ventilation.
- ICU LOS [calculated from date (yyyy-mmm-dd) of start and end of ICU stay].
- Hospital LOS [calculated from date (yyyy-mmm-dd) of start and end of hospital stay].
- Post-surgical complications [yes/no]: Atrial fibrillation, ventricular fibrillation, reintubation, bleeding, need of non-invasive respiratory support, post-surgical delirium, post-surgical stroke, post-surgical myocardial infarction [STEMI], wound infection.
- Necessity and volume of blood products use (PRBC, FFP, platelets).
- Death in ICU.
- Death in hospital (all-cause death).

9.1.15 Study diary

During the last visit before discharge from hospital, the participants are given a study diary to record any AEs in the period up to V13 (Day 90±7 d) or time of prematurely termination of study participation.

10 VISITS

The standardized evaluation and monitoring of the participants is carried out using the examinations listed below.

The day of baseline with the first administration of trial medication and the index surgery is designated as Day 0.

The pre-surgical visit on Day 0 (V2) is defined as baseline.

A visit day is defined by calendar day, which lasts from 00.00 h until 23.59 h.

Note: If a study participation ends prematurely, the last visit should be performed and documented as an Unscheduled Visit (and not as EOS!).

10.1 Visit schedule

Table 01: Visit schedule

	Screening	Randomization	Baseline	OP	Hospitalization												For details click link to CTP section
	Visit 1a	Visit 1b	Visit 2		Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12 (by phone)	Visit 13 /regular EoS	unsche-duled Visit[1] /Early termination	
	Day -54 to -2	Day -2 to -1	Day 0 pre-op		Day 0 post-op	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 10[2]±2	Day 30±3	Day 90 ±7		
Informed Consent	✓																9.1.1
Inclusion/Exclusion criteria	✓	✓															6.2 6.3
Demographics	✓																9.1.3
Medical history	✓																9.1.2
Body-Mass-Index (BMI)	✓														✓	✓	9.1.4.2
Physical examination	✓												✓		✓	✓	0

[1] Unscheduled Visits may be performed more frequently if medically indicated at the investigators discretion or if a participant's participation is prematurely terminated

[2] or discharge from hospital whichever comes first

	Screening	Randomization	Baseline	OP	Hospitalization											For details click link to CTP section
	Visit 1a	Visit 1b	Visit 2		Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12 (by phone)	Visit 13 /regular EoS	unsche-duled Visit[1] /Early termination	
	Day -54 to -2	Day -2 to -1	Day 0 pre-op		Day 0 post-op	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 10[2]±2	Day 30±3	Day 90 ±7		
Targeted physical examination		✓[3]			✓	✓	✓	✓	✓	✓	✓	✓					9.1.4.1
Vital signs	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	9.1.5
ECG [4]	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	9.1.6
Echo	✓				✓	✓				✓					✓		9.1.7
Randomization		✓															
CPB parameters					✓												9.1.13
IMP Administration			✓		✓												7.2
Pre-Randomization Lab		✓[3]															9.1.9.5
Lab 1 - Safety Laboratory	✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	9.1.9.1

[3] tests only need to be performed if, in the opinion of the investigator, the values collected in V1a are too far apart to be used for randomization of the patient.

[4] on ICU at least one ECG-recording should be taken after surgery (Day 0) and the next day (Day 1).

	Screening	Randomization	Baseline	OP	Hospitalization											For details click link to CTP section
	Visit 1a	Visit 1b	Visit 2		Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12 (by phone)	Visit 13 /regular EoS	unsche-duled Visit[1] /Early termination	
	Day -54 to -2	Day -2 to -1	Day 0 pre-op		Day 0 post-op	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 10[2]±2	Day 30±3	Day 90 ±7		
Lab 2 - Biomarkers kidney function			✓		✓	✓		✓				✓					9.1.9.2
Lab 3 – Biomarker cardiac function			✓			✓						✓			✓	✓	9.1.9.3
Lab 4- accompanying research			✓		✓	✓		✓				✓			✓		9.1.9.4
PK sampling			✓		✓												9.1.11
Urine output / volume balance					✓	✓	✓	✓	✓	✓	✓	✓					9.1.9.6
Pregnancy test if applicable in WOCBP [5]	✓	✓[6]												✓	✓	✓	9.1.10
AKI assessment (KDIGO criteria)			✓		✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	0

[5] according to CTFG [clinical trial facilitation group of the Heads of Medicines Agencies] recommendations for contraception and pregnancy testing in clinical trials v1.2 for WOCBP

[6] only if the test at V1a was carried out more than 72 h before the start of V2.

	Screening	Randomization	Baseline	OP	Hospitalization											For details click link to CTP section
	Visit 1a	Visit 1b	Visit 2		Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12 (by phone)	Visit 13 /regular EoS	unsche-duled Visit[1] /Early termination	
	Day -54 to -2	Day -2 to -1	Day 0 pre-op		Day 0 post-op	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 10[2]±2	Day 30±3	Day 90 ±7		
Post-surgical data													✓				9.1.14
Concomitant medication	✓	✓[3]			✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	
Nephrotoxic agents					✓	✓	✓	✓	✓	✓	✓	✓					9.1.8
AE assessment			✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Study Diary dispense/control													✓		✓	✓	9.1.15

10.2 Visit 1a (Screening) Day -54 to -2

- Informed consent.
- Check of inclusion and exclusion criteria.
- Medical history.
- Demographics.
- Recording of current concomitant medication.
- Physical examination.
- Height [measured or declared by participant] and weight. Calculation of BMI.
- Vital signs.
- 12-lead ECG.
- Full cardiologic echocardiography (TTE) (at echocardiography laboratory).
- Urine pregnancy test (only for women of childbearing potential [WOCBP]).
- Blood and urine samples for laboratory tests:
  - Lab 1: Hematology, clinical chemistry, coagulation, urine.

10.3 Visit 1b (Randomization; Day -2/-1)

- Review of selected exclusion criteria (see Section 6.3) before randomization.
- The following tests only need to be performed if, in the opinion of the investigator, the values collected in V1a are too far apart to be used for randomization of the patient.
  - Pre-Randomization Lab to support the review of selected exclusion criteria.
  - Targeted physical examination.
  - Recording of current concomitant medication.
- Urine pregnancy test (only for WOCBP), and only if the test at V1a was carried out more than 72 h before the start of V2.
- Vital signs: Body temperature, blood pressure, pulse rate, oxygen saturation [pulse oximeter]).
- Randomization

10.4 Visit 2 (Baseline; Day 0 pre-surgery)

- Vital signs: Body temperature, blood pressure, pulse rate, oxygen saturation [pulse oximeter]).
- Blood and urine samples for laboratory tests:
  - Lab 1: Hematology, clinical chemistry, coagulation, urine.
  - Lab 2: Biomarkers.

- Lab 3: Biomarker(s) for comorbiditites.
- Lab 4: Research samples.

- PK sample pre-surgery and before administration of the study medication (blank value).
- AKI assessment (KDIGO criteria).
- 1st administration of study medication (s.c. injection).
- AE assessment.

Note: Blood samples should be taken from the arterial catheter (first choice), an unused line of the central venous catheter or from separate peripheral i.v. cannula.

10.5 Visit 3 (Day 0 post-surgery)

- Targeted physical examination.
- Vital signs: Body temperature, blood pressure, pulse rate, oxygen saturation [pulse oximeter]).
- 12-lead ECG.
- Documentation of CPB parameters (recording of perioperative conditions and CPB).
- POCT-Echocardiography (TTE).
- Blood and urine samples for laboratory tests:
  - Lab 1: Hematology, clinical chemistry, coagulation, urine.
  - Lab 2: Biomarkers; time point 240±30 min post-surgery.
  - Lab 4: Research samples; time points: 120±30 min, 240±30 min post-surgery.
- PK sample post-surgery at timepoint within 30 min before 2nd administration of study medication (trough level). **Note**: PK samples to be drawn only from selected participants with flagged tubes!
- 2nd administration of study medication (s.c. injection).
- PK samples post-surgery at timepoints 15±2 min, 30±3 min, 60±6 min, 90±9 min, and 180±18 min after administrationof study medication. **Note**: PK samples to be drawn only from selected participants with flagged tubes!
- Urine output in ml/kg/h.
- AKI assessment (KDIGO).
- Recording of current concomitant medication.
- Recording and assessment of nephrotoxic agents (list provided in section 9.1.8)
- AE assessment.

Note: Blood samples should be taken from the arterial catheter (first choice), an unused line of the central venous catheter or from separate peripheral i.v. cannula.

10.6 Visit 4 (Day 1)

- Targeted physical examination.
- Vital signs: Body temperature, blood pressure, pulse rate, oxygen saturation [pulse oximeter]).
- 12-lead ECG.
- POCT-Echocardiography (TTE).
- Blood and urine samples for laboratory tests:
  - Lab 1: Hematology, clinical chemistry, coagulation, urine.
  - Lab 2: Biomarkers; time point: 24±1 h post-surgery.
  - Lab 3: Biomarker(s) for comorbiditites.
  - Lab 4: Research samples; time point: 24±1 h post-surgery.
- Urine output in ml/kg/h.
- AKI assessment (KDIGO).
- Recording of current concomitant medication.
- Recording and assessment of nephrotoxic agents (list provided in section 9.1.8).
- AE assessment.

Note: Blood samples should be taken from the arterial catheter (first choice), an unused line of the central venous catheter or from separate peripheral i.v. cannula.

10.7 Visit 5 (Day 2)

- Targeted physical examination.
- Vital signs: Body temperature, blood pressure, pulse rate, oxygen saturation [pulse oximeter]).
- 12-lead ECG.
- Blood and urine samples for laboratory tests:
  - Lab 1: Hematology, clinical chemistry, coagulation, urine.
- Urine output in ml/kg/h.
- AKI assessment (KDIGO).
- Recording of current concomitant medication.
- Recording and assessment of nephrotoxic agents (list provided in section 9.1.8).
- AE assessment.

Note: Blood samples should be taken from the arterial catheter (first choice), an unused line of the central venous catheter or from separate peripheral i.v. cannula.

10.8 Visit 6 (Day 3)

- Targeted physical examination.
- Vital signs: Body temperature, blood pressure, pulse rate, oxygen saturation [pulse oximeter]).
- 12-lead ECG.
- Blood and urine samples for laboratory tests:
  - Lab 1: Hematology, clinical chemistry, coagulation, urine.
  - Lab 2: Biomarkers; timepoint: 72±2 h post-surgery.
  - Lab 4: Research samples; timepoint: 72±2 h post-surgery.
- Urine output in ml/kg/h.
- AKI assessment (KDIGO).
- Recording of current concomitant medication.
- Recording and assessment of nephrotoxic agents (list provided in section 9.1.8).
- AE assessment.

Note: Blood samples should be taken from the arterial catheter (first choice), an unused line of the central venous catheter or from separate peripheral i.v. cannula.

10.9 Visit 7 (Day 4)

- Targeted physical examination.
- Vital signs: Body temperature, blood pressure, pulse rate, oxygen saturation [pulse oximeter]).
- 12-lead ECG.
- Blood and urine samples for laboratory tests:
  - Lab 1: Hematology, clinical chemistry, coagulation, urine.
- Urine output in ml/kg/h.
- AKI assessment (KDIGO).
- Recording of current concomitant medication.
- Recording and assessment of nephrotoxic agents (list provided in section 9.1.8).
- AE assessment.

Note: Blood samples should be taken from the arterial catheter (first choice), an unused line of the central venous catheter or from separate peripheral i.v. cannula.

10.10 Visit 8 (Day 5)

- Targeted physical examination.

- Vital signs: Body temperature, blood pressure, pulse rate, oxygen saturation [pulse oximeter]).
- 12-lead ECG.
- Echocardiography (TTE).
- Blood and urine samples for laboratory tests:
- Lab 1: Hematology, clinical chemistry, coagulation, urine.
- Urine output in ml/kg/h.
- AKI assessment (KDIGO).
- Recording of current concomitant medication.
- Recording and assessment of nephrotoxic agents (list provided in section 9.1.8).
- AE assessment.

Note: Blood samples should be taken from the arterial catheter (first choice), an unused line of the central venous catheter or from separate peripheral i.v. cannula.

10.11 Visit 9 (Day 6)

- Targeted physical examination.
- Vital signs: Body temperature, blood pressure, pulse rate, oxygen saturation [pulse oximeter]).
- 12-lead ECG.
- Blood and urine samples for laboratory tests:
  - Lab 1: Hematology, clinical chemistry, coagulation, urine.
- Urine output in ml/kg/h.
- AKI assessment (KDIGO).
- Recording of current concomitant medication.
- Recording and assessment of nephrotoxic agents (list provided in section 9.1.8).
- AE assessment.

Note: Blood samples should be taken from the arterial catheter (first choice), an unused line of the central venous catheter or from separate peripheral i.v. cannula.

10.12 Visit 10 (Day 7)

- Targeted physical examination.
- Vital signs: Body temperature, blood pressure, pulse rate, oxygen saturation [pulse oximeter]).
- 12-lead ECG.

- Blood and urine samples for laboratory tests:
  - Lab 1: Hematology, clinical chemistry, coagulation, urine.
  - Lab 2: Biomarkers; time point: Day 7±6 h.
  - Lab 3: Biomarker(s) for comorbiditites.
  - Lab 4: Research samples; time point: Day 7±6 h.
- Urine output in ml/kg/h.
- AKI assessment (KDIGO).
- Recording of current concomitant medication.
- Recording and assessment of nephrotoxic agents (list provided in section 9.1.8)
- AE assessment.

Note: Blood samples should be taken from the arterial catheter (first choice), an unused line of the central venous catheter or from separate peripheral i.v. cannula.

10.13 Visit 11 (Day 10±2 d or discharge)

- Physical examination.
- Vital signs: Body temperature, blood pressure, pulse rate, oxygen saturation [pulse oximeter]).
- 12-lead ECG.
- Blood and urine samples for laboratory tests:
  - Lab 1: Hematology, clinical chemistry, coagulation, urine.
- AKI assessment (KDIGO).
- Recording of current concomitant medication.
- AE assessment.
- Recording of post-surgical data.
- Handover and explanation of the study diary.
- Hand over of an urine pregnancy test (only for women of childbearing potential [WOCBP]). The test should be performed by the participant under own management at the time of 1 month after baseline.

Note: Blood samples should be taken from the arterial catheter (first choice), an unused line of the central venous catheter or from separate peripheral i.v. cannula.

10.14 Visit 12 (Day 30±3 d)

This visit is performed by a telephone or video call. At least two attempts should be made to reach the participant.

- AE assessment.

- Reminder to complete the study diary regularly and carefully.
- Asking for the result of the urine pregnancy test, only of women of childbearing potential.

10.15 Visit 13 (End of Study; Day 90±7 d)

- Physical examination.
- Weight. Calculation of BMI.
- Vital signs: Body temperature, blood pressure, pulse rate, oxygen saturation [pulse oximeter]).
- 12-lead ECG.
- Full cardiologic echocardiography (TTE) (at echocardiography laboratory).
- Blood and urine samples for laboratory tests:
  - Lab 1: Hematology, clinical chemistry, coagulation, urine.
  - Lab 3: Biomarker(s) for comorbiditites.
  - Lab 4: Research samples.
- Urine pregnancy test (only for women of childbearing potential [WOCBP]).
- AKI assessment (KDIGO).
- Recording of current concomitant medication.
- AE assessment.
- Collecting study diary.

10.16 Unscheduled Visit

- Physical examination.
- Weight. Calculation of BMI.
- Vital signs: Body temperature, blood pressure, pulse rate, oxygen saturation [pulse oximeter]).
- 12-lead ECG.
- Blood and urine samples for laboratory tests:
  - Lab 1: Hematology, clinical chemistry, coagulation, urine.
  - Lab 3: Biomarker(s) for comorbiditites.
- Urine pregnancy test (only for women of childbearing potential [WOCBP]).
- AKI assessment (KDIGO).
- Recording of current concomitant medication.
- AE assessment.
- Collecting study diary.

Note: Blood samples should be taken from an arterial catheter (fist choice), an unused line of the central venous catheter or from separate peripheral i.v. cannula.

11 SAFETY ASSESSMENTS

11.1 Definition of adverse event and serious adverse event

Adverse Event (AE) means any untoward medical occurrence in a participant to whom an IMP is administered and which does not necessarily have a causal relationship with this treatment. [Regulation (EU) No. 536/2014]

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

Clinically significant abnormal laboratory findings are considered AEs, however abnormal laboratory findings may not be considered as AEs if there is no change compared to baseline values.

Adverse Reaction (AR) "is any noxious and unintended response to a medicinal product related to any dose of the product." [Q&A-CTR, Regulation (EU) No 536/2014 Questions & Answers]. In accordance with ICH E2A the definition of an adverse reaction implies a reasonable possibility of a causal relationship between the event and the IMP.

Special Situation (SpS). Although not always defined as an AE by regulatory definition the following safety information associated with an IMP must be documented by the investigator in the eCRF and reported to the Sponsor: overdose, abuse, misuse, occupational exposure, medication error and potential medication error, unintended benefit and suspect drug interaction. The reporting procedure is the same as for SAEs as described in Section 11.4.

Serious Adverse Event (SAE) means any untoward medical occurrence or effect (independent of whether there is a suspected causal relationship to the IMP or not) that at any dose

- requires inpatient hospitalization or prolongation of existing hospitalization.
- results in persistent or significant disability or incapacity.
- results in a congenital anomaly or birth defect.
- is life-threatening[7].
- results in death. [Regulation (EU) No. 536/2014]
- consists of any other important medical event[8]. [Q&A, Regulation (EU) No. 536/2014]

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7 The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

8 According to ICH E2A, CPMP/ICH/377/95: "Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic

Events not considered to be SAEs in this clinical trial are hospitalizations for elective treatments that may require hospitalization planned before screening and which are documented in the participant's source data. It also covers the hospitalizations due to the planned rehab after cardiac surgery.

Serious Adverse Reaction (SAR) is an AR which results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect. [Regulation (EU) No. 536/2014 → Directive 2001/83/EC]

Unexpected Serious Adverse Reaction (USAR) means a SAR, the nature, severity or outcome of which is not consistent with the RSI. [Regulation (EU) No. 536/2014]

Suspected Unexpected Serious Adverse Reaction (SUSAR) during the clinical trial is an AE which is possibly related to the IMP, fulfills at least one of the criteria of seriousness listed above and is unexpected.

11.2 Recording of adverse events

The investigator is responsible to evaluate and document all AEs arising from the scheduled (and unscheduled) visit assessments from the time of IMP administration at Baseline Visit, Day 0 (Visit 2) till the end of observation period, Day 90±7 d (Visit 13).

Pre-existing conditions that do not worsen during the course of the study are not reportable as AEs. To determine whether a condition has worsened, it is compared to the condition of the participant at the Screening Visit (Visit 1a), Day -54 to -2.

Elective treatments planned before screening and which are documented in the participant's source data are usually not regarded as AEs.

Data pertaining to AEs will be collected during each study visit based on the participant's spontaneous description, through investigator inquiry, or discovered in the course of examinations done during the visit. The investigator will assess and record any AE in detail in the participant's file and on the eCRF AE report form.

An AE will be monitored until the event has resolved, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the investigator, until there is a satisfactory explanation for the changes observed, or until the participant is lost to follow-up.

11.3 Assessment of adverse events

11.3.1 Required information

The following information needs to be recorded in the participant's file and on the source data sheets:

bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse."

- AE diagnosis (if possible) or main symptom.
- Date and time (if relevant) of onset.
- Severity (maximum observed); see Section 11.3.2.
- Causal relationship with the IMP; see Section 11.3.4.
- Seriousness; see Section 11.1.
- Action(s) taken with the study medication; see Section 11.3.6.
- Any other action required for treatment (discontinuation, concomitant medication, etc.).
- Outcome; see Section 11.3.7.
- Stop date and time (if relevant).

11.3.2 Severity

The clinical severity of an AE will be classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 as:

Grade I	**Mild**	**Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.**
Grade II	**Moderate**	**Minimal, local or non-invasive intervention indicated; limited age-appropriate instrumental activities of daily living*.**
Grade III	**Severe**	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living**.**
Grade IV	**Life-threatening**	**Life-threatening consequences; urgent intervention indicated.**
Grade V	**Fatal**	**Death related to AE.**

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The definitions above are difficult to apply for some data (e.g. clinically relevant laboratory values that are documented and evaluated on the eCRF AE report form). In such situations, the investigator should make a judgment based on personal experience.

11.3.3 Seriousness

The **seriousness** will be assessed by the investigator and the Sponsor. The seriousness criteria are described in Section 11.1.

11.3.4 Causal relationship

The **causal relationship** of an AE to the IMP being studied is usual assessed by the investigator and in case of an SAE by both the investigator and by the Sponsor.

The causality assessment given by the investigator shall not be downgraded by the Sponsor. If the Sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the Sponsor shall be provided with the report.

An AE is considered to be related if there is at least a "reasonable possibility" of establishing a causal relationship between the IMP and the event based on the analysis of available evidence. Otherwise, the relationship should be considered as "not reasonable possible". [Annex III 2.1, Regulation (EU) No. 536/2014]

11.3.5 Expectedness

Section 7.4 in the current version of the Investigator´s Brochure serves as the Reference Safety Information (RSI) for the assessment of the **expectedness** of SARs.

The assessment of expectedness should always be done by the Sponsor from the perspective of events previously observed, not on the basis of what might be anticipated from the pharmacological properties of the IMP.

11.3.6 Actions taken with the IMP

Action(s) taken with the IMP are as follows:

- Drug withdrawn.
- Dose reduced.
- Dose increased.
- Dose not changed.
- Unknown.
- Not applicable.
- Drug withdrawn temporarily.

11.3.7 Outcome

The reportable **outcomes** and/or sequelae of an AE are as follows:

- Resolved/recovered.
- Recovering/resolving.
- Resolved/recovered with sequelae.
- Not resolved/not recovered (ongoing).
- Fatal.

- Unknown.

If there is more than one AE, only the AE leading to death will be attributed with a “fatal” outcome.

11.4 Reporting of serious adverse events

Until Day 90±7 d (Visit 13) any SAE, whether considered to be related to the IMP or not, has to be reported by the investigator to the Pharmacovigilance Department of the Sponsor without undue delay, but not later than within 24 h of obtaining knowledge of the event.

The investigator must complete a paper-based SAE report form which are provided in the EDC or in the ISF.

Although all information required for completion of an SAE report form may not be available within the specified time period, an “initial report” should be submitted if the following minimal information is available:

- An identifiable participant (participant ID).
- A suspected product.
- An identifiable reporting source (investigator/study site identification).
- An event or outcome that can be identified as serious.

The address for SAE reporting is

Universitätsklinikum Erlangen
Center for Clinical Studies (CCS)
Pharmacovigilance Department
Krankenhausstr. 12
91054 Erlangen Germany

Phone: [redacted]
Fax: [redacted]
Email: [redacted]

The investigator must supply further supporting information within 3 days of knowledge of the SAE, and a detailed SAE description is an integral part of this supporting information.

Follow-up reports should be sent immediately to the CCS Erlangen by a SAE report form (marked as a “follow-up” report) and accompanied by appropriate supporting documentation (e.g., hospital reports). The SAE has to be followed up until a final outcome and date are available.

If after Day 90±7 d (Visit 13) the investigator becomes aware of an SAE that occurs in a study participant with a suspected causal relationship to the IMP, the investigator should report this SAR without undue delay to the Sponsor to the same address listed above.

11.5 Second SAE assessment by the Sponsor

The Pharmacovigilance Department will inform the Sponsor of all SAEs immediately (within 24 hours after receipt) and request a second assessment of all SAEs.

The Sponsor`s contact details are:

[redacted]Sponsor Designee / Medical Expert)
Universitätsklinikum Erlangen, Medizinische Klinik 4
Phone:[redacted]
Email:[redacted]

The Sponsor is responsible for the reassessment of seriousness and relatedness of all SAEs and at least the assessment of expectedness of all SARs.

11.6 SUSAR reporting by the Sponsor

In the case of a SUSAR, the Sponsor should report all relevant information about the SUSAR to the Agency via EudraVigilance. The timeline for reporting of a SUSAR is based on the seriousness criteria of the concerned AEs and is defined as follows:

- A SUSAR that is fatal or life-threatening must be reported as soon as possible, in any case **no later than 7 calendar days** after the Sponsor or one of the Sponsor's delegates first becomes aware of it. Follow-up information must be reported within an additional 8 days.
- All other SUSARs must be reported as soon as possible, in any case **no later than 15 calendar days** after the Sponsor or one of the Sponsor's delegates first becomes aware of it. In the case of a SUSAR which was initially considered to be non-fatal or non-life-threatening but which turns out to be fatal or life-threatening, the SUSAR must be reported as soon as possible, in any case not later than 7 days after the Sponsor became first aware of the reaction being fatal or life-threatening.

The Pharmacovigilance Department of the CCS Erlangen is commissioned by the Sponsor to ensure the timely reporting of all relevant SUSARs to the Agency via EudraVigilance according the timelines described above.

Before submitting a potential SUSAR to the Agency, the blinded treatment of the concerned study participant must be unblinded by the Sponsor. The participant´s emergency envelope is opened by the person responsible for pharmacovigilance on behalf of the Sponsor.

Only SUSARs of patients treated with the IMP will be reported to the Agency (see Section 7.7).

Information for reporting of SUSARs shall at least include:

- EU CT number.
- Sponsor study number.
- An identifiable coded participant.
- An identifiable reporter.

- SUSAR description.
- Suspected IMP including active substance name or code.
- Causality assessment.

In addition, in order to properly process the report electronically, the following administrative information shall be provided:

- Sender's (case) safety report unique identifier.
- Receipt date of the initial information from the primary source.
- Receipt date of the most recent information.
- Worldwide unique case identification number.
- Sender identifier.

If an initial report of a SUSAR is incomplete (e.g., investigator has not provided all the information within 7 days), the Sponsor shall submit a completed report based on the initial information within an additional 8 days. If significant new information on an already reported case is received by the Sponsor, the information shall be reported as a follow-up report within 15 days.

11.7 Other reporting obligations relevant for participant´s safety

11.7.1 Annual safety report

Once a year or if requested, the Sponsor will submit to the Agency via the EU portal, CTIS, a report on the safety of each IMP used in the clinical trial. In accordance with Guideline ICH E2F, the annual report will be written in the format of a Development Safety Update Report (DSUR). The report will contain aggregated and anonymized safety data only. [Article 43, Regulation (EU) No. 536/2014]

The date to start the annual reporting is the anniversary of the Sponsor´s first authorization to conduct the clinical trial.

11.7.2 Unexpected events which affect the benefit-risk balance

The Sponsor will notify the Agency via the EU portal, CTIS, of all unexpected events which affect the benefit-risk balance but are not SUSARs as described in Section 11.6.

The notification will be sent without undue delay, but not later than 15 days from the date the Sponsor became aware of this event.

11.7.3 Urgent Safety measures

Where an unexpected event is likely to affect the benefit-risk balance of the clinical trial, the Sponsor and the investigator shall take appropriate urgent safety measures to protect the participant´s safety in the clinical trial. [Article 54, Regulation (EU) No. 536/2014]

The Sponsor will notify the Agency via the EU portal, CTIS, of the event and the measures taken. The notification will be done without undue delay, but not later than 7 days after the measures have been taken.

11.8 Pregnancy

Each pregnancy that becomes known during the clinical trial in a female participant or in a female partner of a male participant must be reported by the investigator without undue delay, but not later than **within 24 hours** of obtaining knowledge of its occurrence to the addressee mentioned above (see Section 11.4) and followed up until 8 weeks post-partum. If applicable, a separate consent for collection of data after birth will be collected from both legal guardians. Pregnancies and pregnancy follow-up should be reported on a Pregnancy Monitoring Form. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous discontinuation; details of the birth; the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications, and their relation to the IMP or trial procedures performed. Additionally, the investigator should report pregnancy follow-up as an SAE, if the outcome of the pregnancy includes:

- A spontaneous, therapeutic abortion or voluntary termination.
- Stillbirth.
- Neonatal death (all neonatal deaths that occur within 28 days of birth without regard to causality).
- Presence of birth defects or congenital anomaly (including that in an aborted fetus, stillbirth or neonatal death).
- Any other complication in mother or child that fulfils at least one seriousness criterion.

The participant who is confirmed to be pregnant has to discontinue the treatment with the IMP permanently.

12 STATISTICS

12.1 Sample size estimation

This is a blinded, 1:1 randomized superiority study with two parallel arms.

The primary efficacy endpoint is the occurrence of CSA-AKI within 7 days after surgery (see Section 4.1.2). This is a binary variable. The rate of CSA-AKI in the control arm is expected to be 50% (see (Schley et al., 2015), Table 1, row CKD 3). The rate of CSA-AKI in the treatment arm is expected to be 25%. Alpha is set to 5% and beta to 20%. A formula for a sample size estimation for a two-sided test can be found in equation 1 of Friede and Kieser, 2004.

Three interim analyses are planned (four analyses in total) according to a Group Sequential Method described by Wang and Tsiatis (see section 8.3 in (Chow et al., 2007)). This increases the sample size by a factor of 2.4% (see table 8.2.2 of (Chow et al., 2007)).

Drop-outs are not expected up to day 7 as the patients are in an ICU after heart surgery. The rate of death within 7 days after surgery is minimal.

This yields a sample size of 120 participants (60 per arm) and interim analyses at 30, 60 and 90 evaluable participants.

12.2 Recruitment

Between 2019 and 2024 the Dept. of Cardiac Surgery at the Universitätsklinikum Erlangen treated approximately 240 patients who suffered from CKD stages 2-3b and underwent aortic valve, mitral valve, bypass surgery, or a combination of these procedures using a heart-lung machine.

It is therefore assumed that the planned number of 120 patients for this study will be reached within the planned 38-month study period from the patient pool of the Dept. of Cardiac surgery.

12.3 Blinding

See Section 7.7. The interim analyses of the primary efficacy endpoint will not break the blind.

12.4 Randomization

The randomization sequence is created according to the Maximal Procedure described in (Berger et al., 2003) with the randomizeR software (Uschner et al., 2018).

The randomization will be stratified by gender.

12.5 Estimand for the primary efficacy hypothesis

The estimand framework is described by the EMA in their document “ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials”.

The estimand for the primary hypothesis is:

A. Population: All randomized participants.

B. Endpoint: Participant has CSI-AKI within 7 days after index surgery.

C. Intercurrent events are the administrations of various other drugs, in particular for the heart surgery, which could also affect the kidney and thus CSI-AKI occurrence.

D. Population level summary is the difference of the relative frequency of CSI-AKI of the two arms.

Intercurrent events are addressed with the treatment policy strategy (i.e. the occurrence of intercurrent event is irrelevant for the analysis) and with the principal stratum strategy (i.e. subgroup analysis for the administered drugs and generalized linear models with various drugs as covariates).

12.6 Analysis sets

For the analysis of the primary efficacy variable no missing values are expected (see Section 12.1). Non-compliance is also unlikely to occur.

Three additional analyses sets are defined:

- Complete case analysis (participants with available data on the primary efficacy variable only).
- Intention-to-treat analysis with imputation (all randomized participants; missing values of the primary efficacy variable CSA-AKI are imputed via carrying forward the worst observation of the individual AKI-asssessments. Another method of imputation is: if any of the individual AKI-asssessments is missing the worst case is imputed.).
- Per protocol analysis (participants with available data on the primary efficacy variable and no major protocol deviations only).

12.7 Other variables for statistical analysis

Other endpoints of the study are listed in Section 4.2.1.

The null hypotheses for these variables are the same as for the primary efficacy variable: The variables and the study arms are independent. Appropriate statistical tests are chosen to test these hypotheses in the complete case population.

For the primary safety endpoint “Frequency of AE and SAE within 72 hours after index surgery”, the number of these events are counted per arm and compared with Poisson test. The number of participants with at least one of these events is also counted. This is a binary variable.

12.8 Interim analyses

See Section 12.1 for a description of the interim analyses.

13 REGULATORY, ETHICAL, AND TRIAL OVERSIGHT

This trial will be conducted in accordance with the protocol, the ethical principles derived from international guidelines including the Declaration of Helsinki, ICH guideline E6, Clinical Trials Regulation 536/2014 (CTR), and all applicable national laws and regulations governing the conduct of clinical studies.

13.1 Regulatory requirements

Prior to the start, the clinical trial must be authorized by the competent authority (authorities) and ethics committee(s) in the Member State(s) concerned (MSc). To obtain authorization of the clinical trial, essential documents in accordance with CTR (and with national regulation) must be submitted via the EU portal, CTIS (Clinical Trials Information System). The clinical trial shall only be started after authorization of the MSc has been obtained. In addition, any substantial modification will only be implemented after authorization. The sole exception are appropriate urgent safety measures to protect the participants when an unexpected event is likely to seriously affect the benefit-risk balance. Those urgent safety measures shall be notified to the MSc through CTIS immediately after the event and the measures taken.

The principal investigator of each trial site is responsible for ensuring compliance with the clinical trial protocol, requirements of the CTR, and all applicable national laws at their site. The required notifications of all investigators to the Sponsor or Sponsor's designee are listed in the Investigator's Agreement.

The Sponsor/Sponsor's designee must continuously update the trial information in the EU database and notify the MSc of the following:

- The start or restart of the clinical trial, the first visit of the first participant, the end of recruitment of participants, the temporary halt, the early termination, or the end of clinical trial within 15 days of the respective event.
- A serious breach (see Section 14.2.4) of the CTR or of the version of the protocol applicable at the time of the breach without undue delay but not later than 7 days of becoming aware of that breach.
- All unexpected events which are likely to seriously affect the benefit-risk balance of the clinical trial, but are not SUSARs, and the urgent safety measures taken without undue delay but no later than 7 days from the date the measures have been taken.

The Sponsor is responsible for achiving the trial master file for at least 25 years after the (premature) end of the clinical trial and ensure that its content is readily available and accessible upon request.

The investigator/institution of participating sites should maintain the essential trial documentation as specified in ICH-GCP E6 such as source records, medical records, laboratory results, informed consent documents, safety reports, and other pertinent data. The investigator/institution should retain the essential records and the ISF for the required retention period of 25 years in accordance with the CTR. Medical files of participants should be archived in accordance with the national law. Trial documents should not be destroyed prior to the end

of the retention period and without the prior written consent of the Sponsor. The investigator should keep the Sponsor informed of the person responsible for archiving the essential documents.

13.1.1 Results reporting

A summary of results and a summary for laypersons, irrespective of the outcome of the clinical trial, will be submitted within one year after the end of the clinical trial in accordance with CTR and made available in the EU database. The end of this clinical trial is defined as mentioned in Section 5.4.2.

13.2 Informed consent process

Informed consent means a person's free and voluntary expression of willingness to participate in a particular trial.

The Sponsor will provide the investigator with an appropriate sample ICF which will include all elements required by ICH guideline E6 and applicable regulatory requirements and adhere to the ethical principles that have their origin in the Declaration of Helsinki. Any participant included in a clinical trial should receive the relevant information related to the clinical trial as required by the CTR as well as the information according to Article 13 of the General Data Protection Regulation [Regulation (EU) No. 2016/679, GDPR], in particular the legal basis for data processing.

Prior to obtaining informed consent, the investigator must ensure that potential participants are clearly and fully informed about the nature, objectives, significance, potential risks, and other critical issues regarding the trial. The potential participants should have the opportunity to ask questions at any moment, and adequate time should be provided to consider participation in the trial.

Potential participants who are unable to give informed consent are excluded from study participation.

Prior to participation in the trial, the written ICF must be personally signed and dated by the potential participant and by the investigator who conducted the informed consent discussion. As part of the informed consent process, participants must consent to direct access to their medical records for trial-related monitoring, auditing, and inspections. A second original of the signed ICF and a copy of the insurance conditions must be provided to the participant. The investigator must document details of the informed consent discussion and confirm in the participant's medical record that informed consent was obtained prior to the performance of any trial-related procedures. The investigator should maintain a coded log of all participants who signed the ICF and document whether the participant received trial-related treatment or why not. In addition, the investigator or a member of the investigating team will attribute a participant code to the participant (see Section 13.6.2).

If a substantial modification to the protocol is required or whenever important new information becomes available that are relevant to the participant's consent, the ICF may need to be revised and submitted via the EU portal, CTIS, for obtaining approval prior to its use. After

approval, the revised ICF will be used to inform all participants and potential new participants. All participants must sign the revised form to express their willingness to further participate in the trial. Participants who have already completed their last study visit need to sign new ICF versions only that relate to their basic rights and obligations (e.g. data sharing) and do not relate to the study procedures.The participant's right to withdraw their consent to participate in the trial at any time must be respected.

13.3 Insurance

Throughout the duration of the clinical trial, each participant will be insured against any health-related issue occurring as a result of participation in this clinical trial as per the laws and regulations of the MSc in which this clinical trial is conducted. The participant will be informed by the investigator and through the participant's ICF about the existence of this insurance and the associated obligations. The insurance conditions will be handed over to the participant as required by local law. Any medical deviation from the protocol that is deemed to have occurred attributable to the participant's actions is not covered by this insurance. The Sponsor is usually not liable for injuries/cases of death that occur solely as a consequence of the participant's underlying disease or condition, or from diagnostic or therapeutic measures not specifically required by the approved protocol. The Sponsor is also usually not liable for events resulting from negligence of the investigator(s), members of the investigating team, and/or other facilities, including failure to act according to ICH guideline E6 or to comply strictly with the agreed protocol.

13.4 Financing

This clinical trial is funded by Serpin Pharma, LLC (Manassas, VA, USA) by providing the study medication and funds to conduct the trial. Neither investigators nor study participants receive any personal financial compensation for their work or participation in the clinical trial, respectively. The collection, administration, analysis, and interpretation of data is the responsibility of the Sponsor, Universitätsklinikum Erlangen.

13.5 Publication policy

The results of this clinical trial and any discoveries related to this trial, regardless of whether they have technical or medical character, are the property of the Sponsor, Universitätsklinikum Erlangen. Therefore, the Sponsor has the right to decide on publication of results that are not already required by law or regulation (Section 13.1.1).

The clinical trial may additionally be registered with a public trial register (such as DRKS, ClinTrials.gov) before recruitment begins.

The results of this trial will be submitted for publication in a peer-reviewed, international journal of appropriate aim and scope. The principal investigator together with the biostatistician will draft and circulate manuscripts for discussing with co-authors. The authorship will follow the criteria developed by the International Committee of Medical Journal Editors (ICMJE), including those that distinguish authors from other contributors.

The ICMJE recommends that authorship be based on the following 4 criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, AND
- Drafting the work or revising it critically for important intellectual content, AND
- Final approval of the version to be published, AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All those designated as authors should meet all 4 criteria for authorship, and all who meet the 4 criteria should be identified as authors. Those who do not meet all 4 criteria can be acknowledged in the manuscript.

The scientific use of data resulting from this trial by local trial sites is ruled by the site contracts between the Sponsor and the local trial sites. Generally, sites might use data for own scientific questions (independent from the questions discussed in this trial protocol) and publication after consultation with the Sponsor. Publications concerning study results must be approved in advance by the Sponsor in writing.

13.6 Data protection

All data collection and processing during this clinical trial will be performed in accordance with Regulation (EU) No. 2016/679 (General Data Protection Regulation, GDPR) and all applicable national data protection requirements.

This single center clinical trial will be conducted at the Universitätsklinikum Erlangen, which is the Sponsor of this clinical trial and the "*controller*" in accordance with Art. 4(7) of the Regulation (EU) No. 2016/679.

The legal basis for the processing of the personal data is the informed consent of the participant (see Section 13.2) in accordance with Art. 6(1)a and Art. 9(2)a GDPR in conjunction with §40b(6) AMG. Prior to trial participation each participant must be informed in written and by the investigator about the purpose and extent of the collection and use of personal data, particularly medical records and their rights according to GDPR. Furthermore, the participants are asked to give consent to direct access to their medical records for trial-related monitoring, auditing and inspections. Eligible participants who do not consent to the processing of data will not be included in the clinical trial.

Clinical monitors appointed by the Sponsor will visit the trial sites regularly and check the participants' ICF. Data will not be used for analysis until the monitor has verified that the participants has given unambiguous consent to participate and to have data collected, transferred, and analyzed in the trial. In the event of withdrawal of consent, the necessity for storing data will be evaluated. While the GDPR strengthens personal data protection rights, encompassing the right to access, rectification, and withdrawal of data, it also specifies the situations when restriction on those rights may be imposed. The withdrawal of informed consent should not affect the results of activities already carried out, such as the storage and use of data obtained on the basis of informed consent before.

13.6.1 Technical and organisational measures (TOM) for data protection

In principle, targeted criminal cyberattacks can never be completely avoided or ruled out. Within the means available to an academic institution, the Sponsor as well as the participating cooperation partners (“joint controllers”) and their contracted service providers (“processors”) are using several technical and organisational measures (TOMs) to protect the data.

In order to ensure data confidentiality and to prevent data misuse, the following TOMs are taken:

- Pseudonymisation of participants’ data (see Section 13.6.2).
- Encryption during data transmission in the eCRF with SSL (Secure Socket Layers) connections.
- Access control by central user administration.
    - Implementing access restriction to premises and data processing facilities where personal data are processed or biological samples are stored and processed (door can only be opened with key/card transponder system; administrative instructions on locking obligations).
    - Restricting access to protected personal data, data processing systems, study documents, patient files (e.g. password protection, service ID, log-in to clinical workstation, firewall, antivirus software).
    - Ensuring that only authorized and trained persons can access the data corresponding to their access authorisation (e.g. by means of a rights and roles concept, user accounts according to trial-specific delegation log).
- Dissemination control are measures to ensure that personal data cannot be processed without authorization during electronic transmission or during their transport or storage on data carriers, and that it is possible to check and determine the location to which a transfer of personal data is intended (encrypted connection during data transmission, audit trail in the eCRF).
- Modification control as any change or correction to the eCRF is only permitted by authorized personnel in accordance with the provisions of ICH guideline E6 and must be traceable and recognisable (audit trail in EDC system, correction with date and signature on paper-based documents).
- Loss control by taking regular backups for digital data, audit trail and orderly filing of documents. Employees involved in the study are instructed by those responsible on the duty of confidentiality and trained in the handling of personal data and samples.
- Quality management (QM) system based on Standard Operating Procedures (SOPs) and manuals for conducting the clinical trial.
- Strict separation between information technology (IT) infrastructures that process personal data and structures that do not.
- Strict requirements for the maintenance/updating of the systems, including requirements for the prompt installation of security-relevant patches and updates.

- Strict guidelines for mobile working, including guidelines for the use of external storage media.

13.6.2 Pseudonymization/anonymization

Pseudonymization is the processing of personal data in such a way that it can no longer be assigned to a specific person without additional information. Once an eligible participant has given consent to trial participation and data collection, the investigator will assign the participant a unique identification code according to the Sponsor specifications on unique identifier assignment. All clinical data entered into eCRF by the investigator(s) or designated members of the investigating team will be recorded in pseudonymized form (i.e. without participant's name and date of birth) using only the participant identification code. Also any participants' records or datasheets transferred to the Sponsor directly will contain the identifier only. However, *re-identification* by the investigator (e.g. in case of emergencies) must be possible.

As analysis of the PK samples would lead to unblinding, PK samples will, after initial pseudonymisation and prior to analysis, be pseudonymised again.

After expiry of the statutory archiving period of currently 25 years, all study-related data may be stored in anonymized form for scientific use at the discretion of the Sponsor.

13.6.3 Measures in case of data security breaches

A personal data breach means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data transmitted, stored, or otherwise processed (according to Art. 4(12) GDPR). In dealing with data breaches, the legally required documentation obligation and the safeguarding of the rights of the data subjects pursuant to Art. 33 and 34 GDPR will be complied with. Appropriate steps are taken with the responsible data protection officers in accordance with the requirements of the supervisory authority.

If a data breach becomes known within the scope of the clinical trial, the Sponsor/controller (to whom data breaches should be reported) will be informed without delay (see Section 14.2.4). For the Sponsor and the trial sites at the Universitätsklinikum Erlangen, the reporting and procedural instructions for data breaches that are binding for the institution apply. For other participating trial sites or external providers, the instructions for data breaches of respective institution apply.

A report to the supervisory authority is to be made by the responsible data protection officer (in consultation with the Sponsor) , taking into account the internal process regulations of the relevant organization through which the report to the authority is made. The obligation to notify the affected individual depends on whether the breach is likely to result in a high risk to the individuals' rights and freedom. All data breaches are to be documented by the controller. The records need to be maintained.

14 RISK MANAGEMENT AND QUALITY ASSURANCE

14.1 Committees

14.1.1 Data and safety monitoring board (DSMB)

The DSMB consists of three independent experts who are not involved in the operative conduct of the clinical study. A list of its members will be filed in the Trial Master File (TMF).

The DSMB evaluates the data on the IMP's safety and tolerability and advises the Sponsor regarding the continuation, suspension, or early termination of the clinical study. The DSMB's *modus operandi* will be determined in a separate charter.

The DSMB will be set up according to EMEA/CHMP/EWP/5872/03 Corr, EMA/CHMP/470185/2020 Questions and answers on Data Monitoring Committees issues, ICH E9 section 4.6, EMA/CHMP/ICH/135/1995 ICH E6 [R3] Annex 1: 3.6.1, 3.9.7, 3.9.9, 3.16.1 lit. p, 3.16.2 lit. b., 4 lit. d and Appendix B, B.8.2, B.9.2; Essential Records Table, Glossary.

14.2 Data quality assurance

All participant data relating to the trial will be recorded on eCRFs (see Section 14.3.2) developed for this clinical trial. The principal investigator is responsible for verifying the accuracy, completeness, and correctness of data entries by physical (if applicable) and electronical signature. In addition, accurate documentation (source data, see Section 14.3.1) that substantiates the information entered in the eCRF must be maintained. These and further aspects of the trial will be carefully monitored for compliance with applicable regulations related to ICH guideline E6. Audits by the Sponsor or inspection by regulatory authority representatives are possible at any time, even after the end of trial.

14.2.1 Monitoring

In order to verify that the rights, safety, and well-being of participants are protected, that the reported data are reliable and robust, and that the conduct of this clinical trial follows the protocol, the ICH guideline E6, and all applicable national and international laws and regulations, the Sponsor shall adequately monitor the conduct of this clinical trial.

Prior to initiation of trial and enrollment of participants, the Sponsor or delegated monitor will review the protocol, CRF, procedures for obtaining informed consent, record keeping, and reporting of AEs with the investigator(s) and members of the investigating team.

The investigator provides the monitor with access to all trial-related original data and documents relevant for the monitoring of the trial.

The extent and nature of the monitoring is determined by the Sponsor and described in detail in the monitoring plan. In principle, ICFs, adherence to inclusion/exclusion criteria, and documentation of SAEs including the proper recording will be reviewed as part of the monitoring process. In addition, the monitor will review trial records and directly compare them

with source documents (source data verification, SDV), review proper handling of the IMPs, discuss the conduct of the trial with the investigator(s) and members of the investigating team, and verify that the clinical trial site remains acceptable.

Any missing data or data discrepancies will be communicated to the trial site for clarification/resolution. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of the monitoring visits are addressed and resolved and therefore ensures the consistency of the trial with ICH guideline E6 and all applicable national and international laws and regulations.

14.2.2 Audits and inspection

In accordance with ICH guideline E6 this trial may be selected for audits by the Sponsor or for inspection by the regulatory authority to conduct an official review of documents, facility, quality assurance arrangements, and any other resources that are deemed to be related to the clinical trial. The investigator should notify the Sponsor immediately when the regulatory authority announces an inspection.

According to CTR, inspections of the trial sites can be conducted by the local or federal authorities at any time during or after completion of the clinical trial. For audits and inspections, the investigators agree to permit direct access to facility, documents, source data, and records related to the clinical trial. The investigator should make every effort to be available for the audits and/or inspections. The Sponsor shall submit through the EU portal, CTIS, all inspection reports concerning the clinical trial.

14.2.3 Adherence to the protocol

After a participant has been enrolled, the investigator must ensure that the recorded data are documented as per protocol and must avoid non-adherence to the protocol in order to ensure the collection of unbiased data for the trial. Minor variations are inevitable in clinical routine but should be documented together with a justification.

In general, all non-adherence to the approved clinical trial protocol or to Good Clinical Practice must be identified and recorded by the investigator, members of the trial team, and all involved vendors/providers on the corresponding log (**protocol deviation log**).

Protocol deviation is a non-compliance to the approved protocol which may not have significant effect on the participants, e.g. a visit date outside the study visit window.

The investigator documents the deviation, should provide a detailed explanation, and outline actions to prevent recurrence.

The Sponsor/Sponsor's designee regularly reviews the protocol deviations that have occurred, e.g. on the basis of the monitoring reports, and takes appropriate measures (preventive and corrective action) if necessary to prevent recurrence.

Important Protocol deviation (IPD) is a subset of protocol deviations that **might** significantly affect the completeness,accurracy and/or reliability of data or might impacts a participant's

safety, rights, or well-being. IPD are defined by the risk analysis performed before and during trial implementation and will be further detailed in separate documents belonging to the risk assessment/monitoring plan. This list can be augmented in the course of the trial. Some examples of IPD:

- No written informed consent of participant enrolled.
- Enrollment of a participant even though the person does not meet the inclusion/exclusion criteria.
- Incorrect dose or wrong treatment
- Use of excluded concomitant medications.

IPD may be identified during routine monitoring or at a later stage of the trial during data review meeting. The Sponsor/Sponsor's designee will regularly assess protocol deviation for importance (classifiying as IPD) and will take appropriate measures (preventive and corrective action) to prevent recurrence. The Sponsor assesses whether the error meets the threshold for a Serious Breach.

A deviation can be an IPD but escalate to a Serious Breach if the potential harm or data impact is deemed "significant" and the error is **likely** to significantly affect the participants well-beingor the clinical trials reliability.

In addition, the IPD will be documented and discussed with the responsible biostatistician before closing the data base and carrying out the statistical analysis. IPD can lead to exclusion of affected participants from certain statistical populations (e.g. per protocol analyses). IPD are summarized in the CSR.

14.2.4 Recording and reporting of suspected serious breaches

Serious breach means a breach that is **likely** to significantly affect the safety and rights of a participant or the reliability and robustness of the data generated in the clinical trial. [Regulation (EU) No. 536/2014, Art. 52(2)]

If an investigator, a member of the trial team, or an involved vendor/provider becomes aware of a suspected serious breach according to EMA Guideline for the notification of serious breaches of Regulation (EU) No. 536/2014 or the clinical trial protocol (EMA/698382/2021), the information must be reported promptly to the Sponsor/Sponsor's designee and Sponsor-QM of Universitätsklinikum Erlangen so that they can conduct further investigations and assess if the breach qualifies as a serious breach.

The e-mail addresses for suspected serious breach reporting are

[redacted] **AND**

[redacted]
(to be informed in parallel)

The form to be used for reporting will be provided with the ISF *(Suspected Serious Breach Site Report Form)*. Delivery should be confirmed by e.g. reading confirmation option in the e-mail settings. The Sponsor's designee then evaluates the report and initiates further steps for notification to the Agency according to the provisions of the Sponsor. Further information on the reporting obligations will be given in the ISF and by the Sponsor-QM. Completed forms, confirmations, follow-up documents, and relevant correspondence should be filed in the ISF of this clinical trial.

14.3 Data collection and management

All data (except source data) will be recorded, processed, handled, and stored by the Sponsor or investigator and authorized members of the investigating team at the trial site. Source documentation is the responsibility of the investigating team at the trial site, and the principal investigator must ensure the accuracy, completeness, and correctness of the data recorded. The Sponsor must grant access for authorized and trained personnel to the eCRFs for recording data of each participant enrolled. In this trial, data will be recorded into the electronic data capture (EDC) system SecuTrial™.

Data management via SecuTrial™, including programmed quality checking of the data, will be delegated to Medizinisches Zentrum für Informations- und Kommunikationstechnik (MIK) of Universitätsklinikum Erlangen. The MIK is responsible for implementing procedures for the collection, storage, protection, retention, and destruction of data. The MIK has implemented a data safety and security concept according to the requirements of the German Federal Office for Information Security (**www.bsi.bund.de**). Trial sites will be responsible for timely data entry into the EDC system. Data captured by the investigating team will be processed in such a way that it can be accurately reported, interpreted, and verified while the confidentiality of records and the personal data of the participants remain protected. In the event of discrepant data, the delegated monitor or Sponsor will request data clarification from the trial sites which the trial sites will resolve electronically in the EDC system. The MIK will create a Data Validation Specification document (DVP) that describes the quality check to be performed on the data. The eCRF completion and correction history will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the trial data will be in accordance with applicable laws and regulations. At the end of the trial, the investigator will receive trial participant data for their trial site in a readable format that must be kept with the trial records.

Access to non-coded data will be allowed solely to check validity. Access will be strictly limited to authorized individuals such as monitors, auditors, or inspectors from regulatory authorities who are bound to confidentiality.

Each party/service provider involved in this clinical trial will create the record of (categories of) processing activities under its responsibility in accordance with Art. 30 GDPR.

In the event of a potential personal data breach, the trial site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by applicable laws and regulations (see Section 14.2.4 and Section 13.6.3)

14.3.1 Source data

All data of a participant collected in the context of this clinical trial must be entered or filed in the corresponding patient file by authorized members of the investigating team (source documentation).

If source data is generated electronically, a printout of the data will be made, dated and signed by the investigator (or a suitably qualified member of the trial team). If additional source data is generated after the printout, this is entered, dated, and signed on the printout. The same applies to corrections to printed source data.

14.3.2 Case report form

The data collected from each participant will be recorded on electronic Case Report Forms (eCRFs) using the validated Electronic Data Capture (EDC) system SecuTrial™. The trial site personnel will be trained and given personalized access to the eCRF. The principal investigator is responsible for ensuring that all sections of the eCRF are completed correctly and that entries can be verified against the source data. If certain data are not available or not applicable, this will be appropriately noted on the corresponding eCRF. The study monitor reviews the eCRFs and checks them for completeness. (S)AEs and the related concomitant medication have to be documented and the EoS visit has to be completed.

15 DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS

15.1 Definitions

The terms "**after index surgery**" and "**post-surgical**" are defined as follows: The post-surgical observation interval begins at the time when the CPB is terminated by release of aortic cross-clamp and when systemic circulation resumes.

Acute kidney injury. According to the consensus definition (Chawla 2017), AKI 'ends' after day 7; from day 90 onwards, CKD or CKD progression is to be assumed.

Observation period. The planned observation period begins at Baseline (V2) and terminates at the last visit on Day 90±7 d.

Women of childbearing potential (WOCBP) will be included only if they are willing to use highly effective birth control methods during and up to 3 months after the end of study participation. Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods.

Women of non-child-bearing potential are not required to use contraceptives and are defined as:

- Women with premature ovarian failure confirmed by a specialist gynecologist.
- Women who are infertile due to surgical sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).
- Women of at least 50 years of age and at least 12 months of natural amenorrhoea or 6 months of amenorrhoea with serum FSH >40 mU/m.

15.2 Pregnancy testing

Pregnancy testing is performed according to the HMA CTCG *Recommendations related to contraception and pregnancy testing in clinical trials.*

15.3 Country-specific dispositions

Not applicable.

16 REFERENCES

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17 SIGNATURES

17.1 Sponsor Statement

I hereby approve the content of this protocol and declare that the clinical trial will be conducted in accordance with the Regulation (EU) No 536/2014, the ICH guideline E6 and all applicable parts of the local regulations governing the conduct of clinical studies.

In addition, I confirm that the investigators and institutions involved in this clinical trial are to permit clinical trial-related monitoring, audits and regulatory inspections, including provision of direct access to source data and documents.

Furthermore, I confirm that data will be collected and processed in accordance with General Data Protection Regulation (GDPR, Regulation (EU) No 2016/679) and applicable local laws on data protection.

Name: [redacted]

Role: Sponsor's designee

This version of the protocol has been reviewed and approved by the Sponsor and its designee. The approval signature of the Sponsor and its designee is provided on a separate version of this signature page and filed in the TMF of the respective clinical trial.

17.2 Investigator's Agreement

Investigator's Agreement

I confirm that I have read, understood and agree to adhere to all conditions, instructions and restrictions as specified in this clinical trial protocol.

I confirm that I will conduct this clinical trial in compliance with the protocol, with the Regulation (EU) No. 536/2014, with the principles of good clinical practice (GCP) and all applicable parts of the local regulations governing the conduct of clinical studies.

I acknowledge that any changes in the protocol must be approved by the Sponsor/ Sponsor's designee and authorized by the Member State concerned before implementing.

I confirm to obtain informed consent for all participants prior to any investigation-related action performed.

I permit clinical trial-related monitoring, audits and regulatory inspections, including provision of direct access to the medical records of the trial participants (source data) and documents by all authorized third parties. All of these individuals are bound to confidentiality.

I acknowledge that I must report any clinical adverse event that is considered serious to the pharmacovigilance section of CCS Erlangen (Fax: 09131-85-35120) without undue delay but not later than within 24 hours of obtaining knowledge of the event.

I am aware that I must report all unexpected events likely to seriously affect the benefit-risk balance and the measures taken without undue delay but not later than within 24 hours of taking the measures.

I am aware that I must immediately report any suspected serious breach of the Regulation 536/2014 or the clinical trial protocol to the Sponsor/ Sponsor's designee (see 14.2.4).

Trial Site

Universitätsklinikum Erlangen
Medizin 4
Ulmenweg 18
91054 Erlangen

(Principal) Investigator (Printed Name)	Date	Signature