NOVARTIS

Novartis Research and Development

Clinical Trial Protocol Title

A randomized, multi-centric, placebo-controlled, participant and investigator-blinded study to evaluate the safety, tolerability and efficacy of TIN816 in adult patients at risk for acute kidney injury following cardiac surgery

NCT05524051

Clinical Trial Protocol Number: CTIN816A12201

Version Number: v02 (Clean)

Compound: TIN816

Brief Title: A multi-center study to evaluate the safety, tolerability and efficacy of TIN816 in patients at risk for acute kidney injury following a cardiac surgery

Study Phase: IIa

Sponsor Name: Novartis

Regulatory Agency Identifier Number(s): EudraCT 2022-000794-47

Approval Date: 25-Jan-2024 (content final)

Table of contents

List of tables

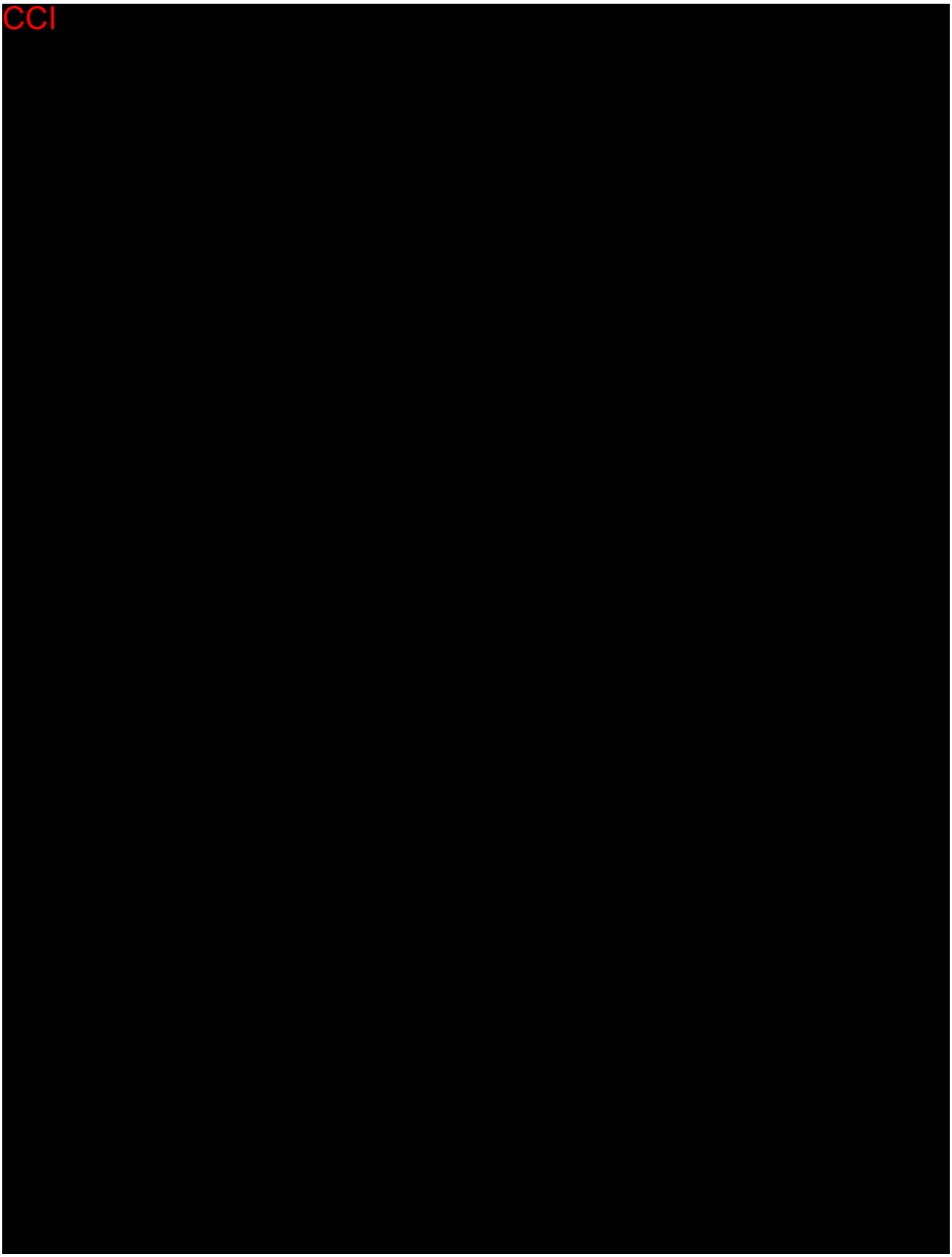
List of figures

Amendment 2 (January 2024)

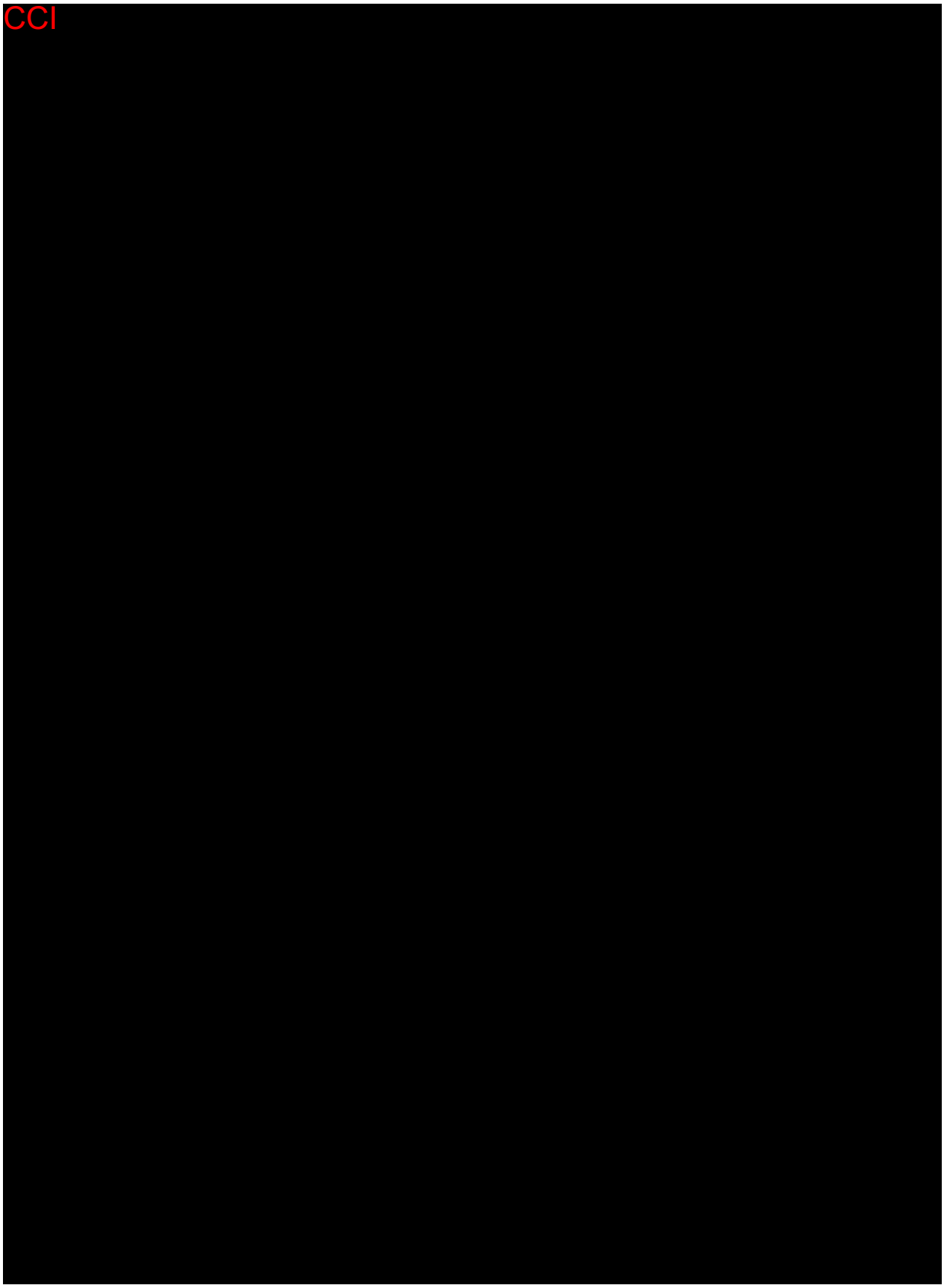
Amendment rationale

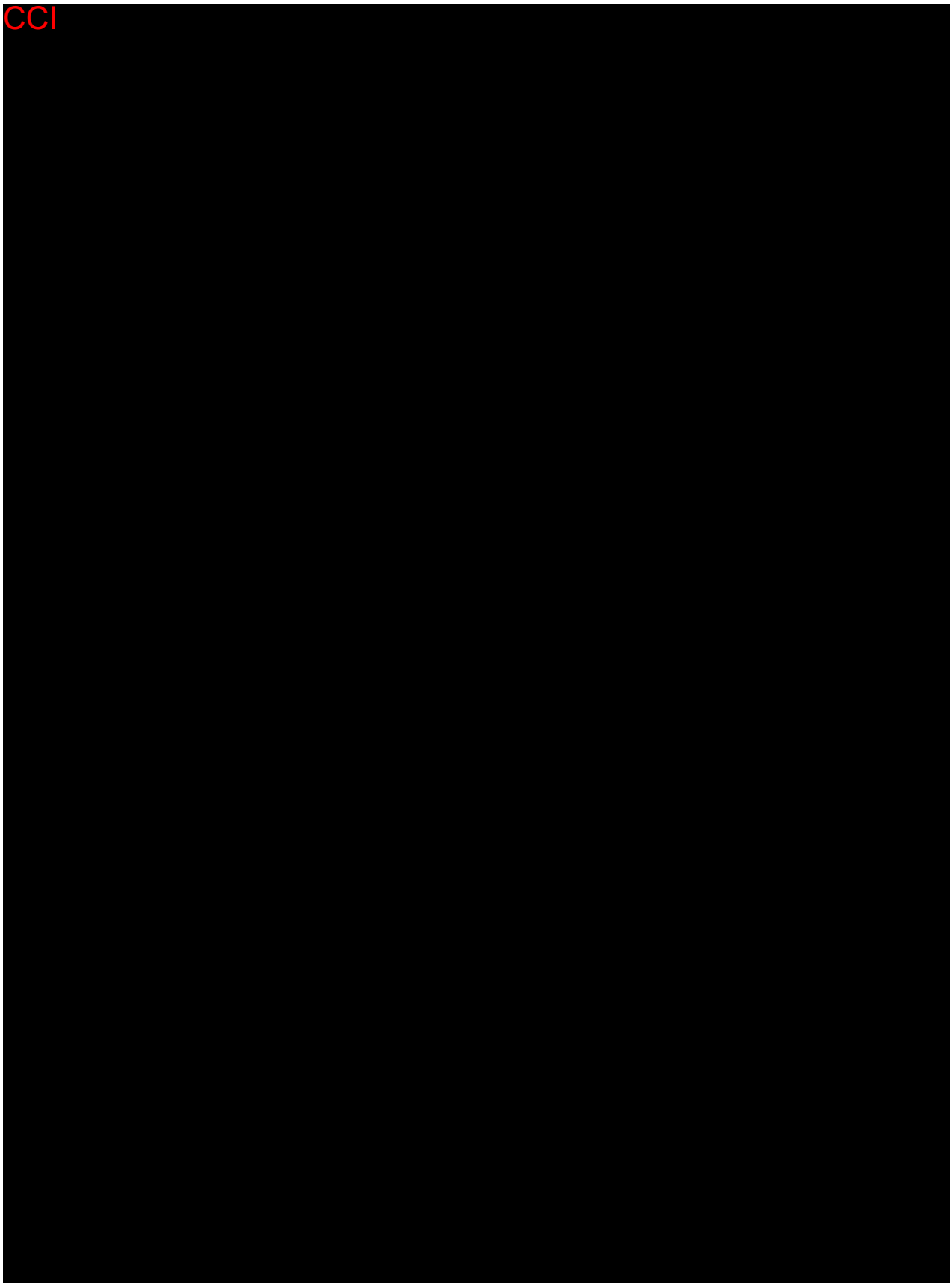
CCI

[redacted]

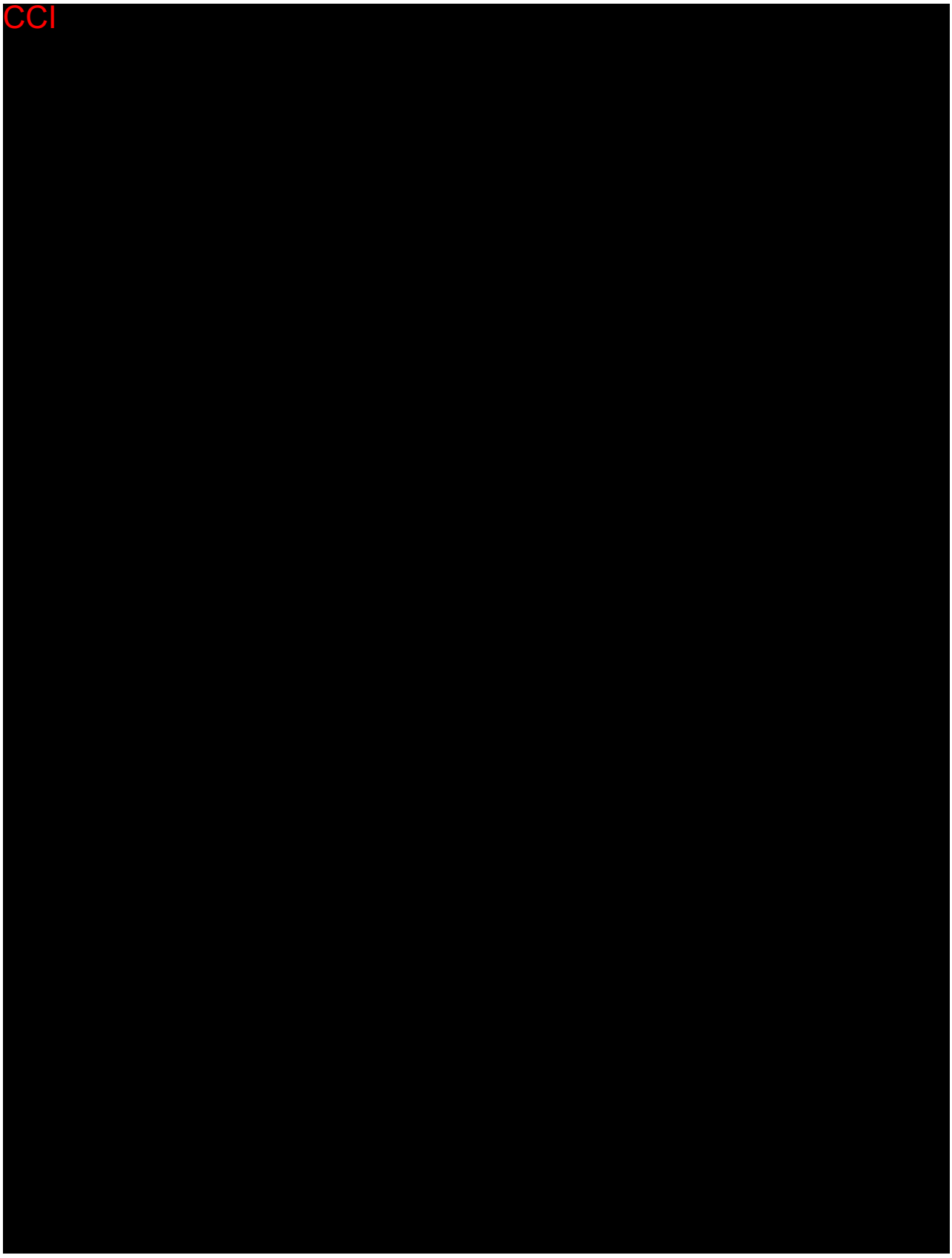

CCI

CCI




CCI

CCI



IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

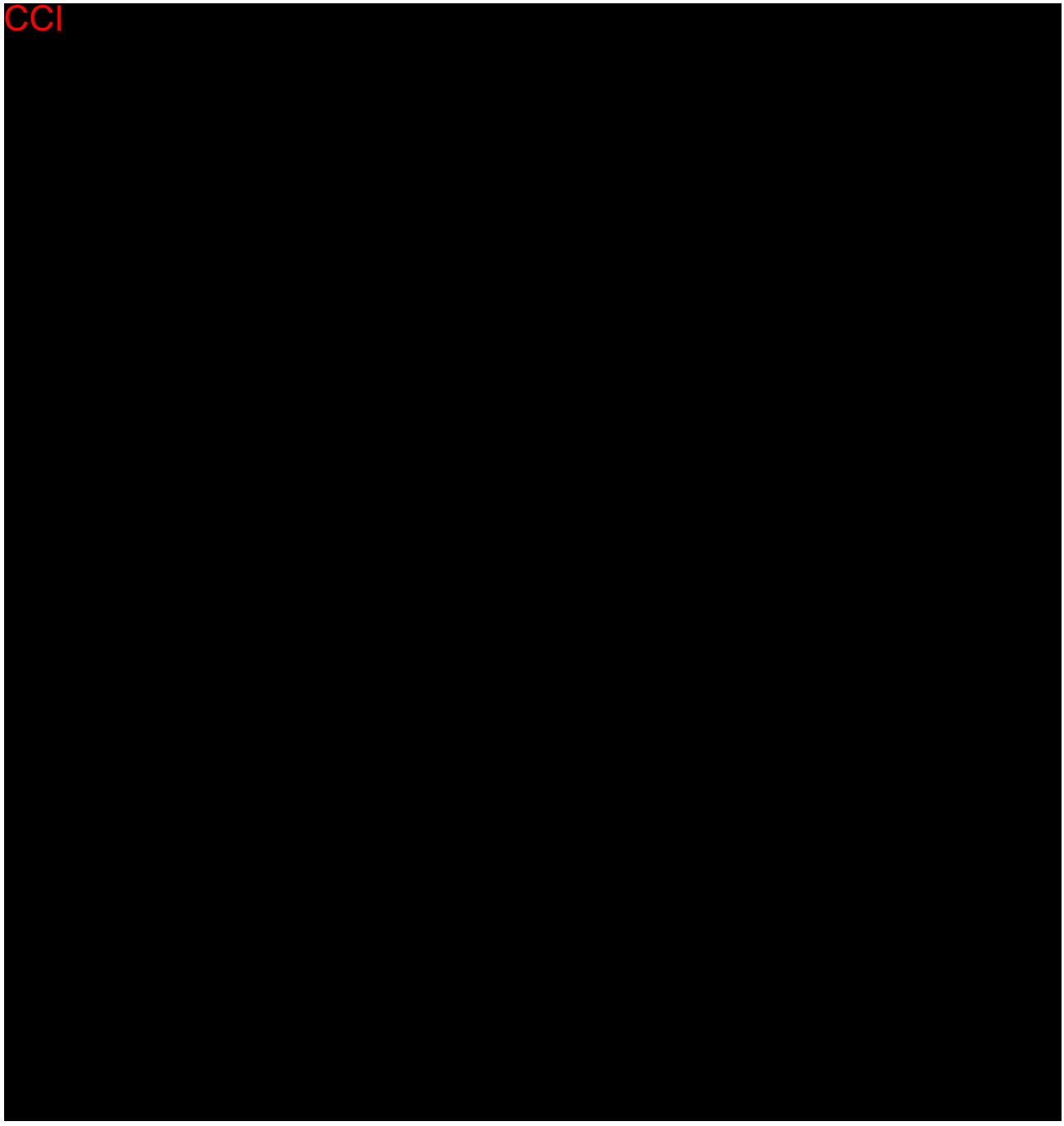
The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval of a revised Informed Consent that takes into account the changes described in this protocol amendment.

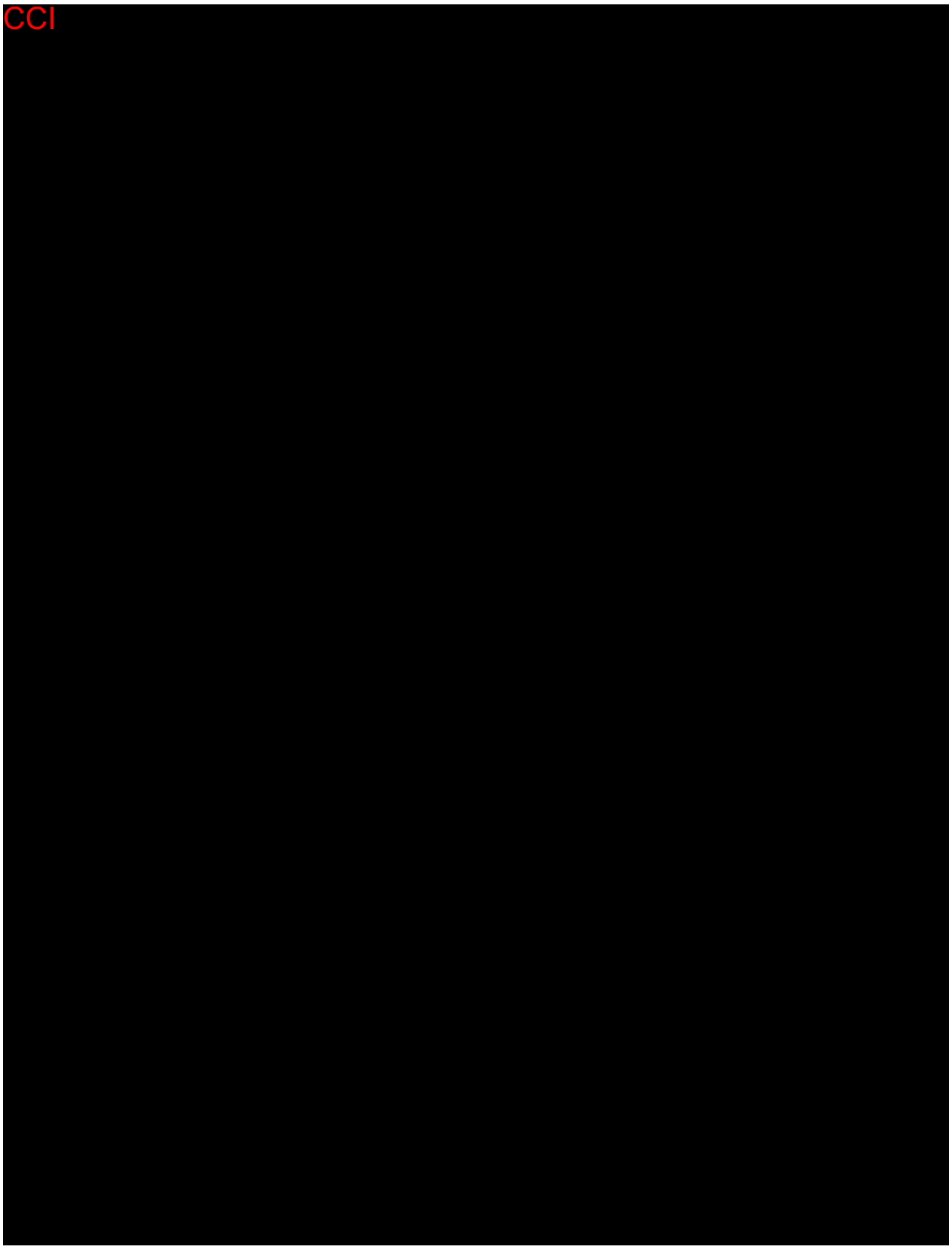
Amendment 1 (April 2023)

Amendment rationale

CCI



CCI



IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval of a revised Informed Consent that takes into account the changes described in this protocol amendment.

1 Protocol summary

1.1 Summary

Protocol Title:

A randomized, multi-centric, placebo-controlled, participant and investigator-blinded study to evaluate the safety, tolerability and efficacy of TIN816 in adult patients at risk for acute kidney injury following cardiac surgery.

Brief Title:

A multi-center study to evaluate the safety, tolerability and efficacy of TIN816 in patients at risk for acute kidney injury following cardiac surgery.

Purpose

This is a phase IIa study to evaluate the safety, tolerability and efficacy of TIN816 in patients at risk for acute kidney injury (AKI) following major cardio-vascular surgery, versus placebo.

Study indication /Medical Condition:

Patients at risk of developing acute kidney injury following cardiac surgery.

Treatment type

A CCI dose of investigational study treatment TIN816 will be administered via an i.v. infusion over CCI .

Study type

Interventional phase IIa study to evaluate the safety, tolerability and efficacy of TIN816

Objectives, Endpoints, and Estimands:

Table 1-1 Objectives and related endpoints

Objectives	Endpoints
Primary	
To assess the effect of TIN816 on serum creatinine levels in patients at high risk for AKI and undergoing major cardio-vascular surgery, versus placebo	Ratio of the highest serum creatinine value (up to and including Study Day 6) versus baseline
Secondary	
To evaluate the safety and tolerability of TIN816	Safety based on vital signs, physical examination, ECGs, laboratory assessments and collection of AEs assessed from baseline until the end of the study visit

Objectives	Endpoints
To assess the effect of TIN816 on the incidence and severity of AKI in patients at high risk for AKI and undergoing major cardio-vascular surgery, versus placebo.	AKI stages 1, 2 and 3 as defined by modified AKI Network (AKIN) criteria for serum creatinine
To assess immunogenicity of TIN816	Anti-drug antibodies against TIN816
To assess the effect of TIN816 on the incidence of acute kidney disease (AKD) in high-risk patients undergoing major cardio-vascular surgery, versus placebo	Occurrence of major adverse kidney events at day 30 (MAKE30) and day 90 (MAKE90) Occurrence of individual components of the MAKE criteria at Days 30 or 90.

Trial Design:

This is a non-confirmatory, randomized, multi-centric, placebo-controlled, participant and investigator-blinded study. Approximatively 120 adult patients at risk for acute kidney injury (AKI) following non-emergent cardiac surgery will be enrolled in the study.

The study consists of a pre-operative period (screening visit), a treatment period (Day 1) and a follow-up period (Day 2 to Day 90). Participants will be followed up daily in the hospital from Day 2 to Day 8 (or at home/nearby accommodation/in a rehabilitation unit if discharged earlier than Day 8), and then as an out-patient until the end of study (Day 30 and Day 90 visits). Participants will receive a CCI i.v. infusion of TIN816 or placebo on Day 1, after wound closure.

CCI

[redacted]

Brief Summary:

AKI is a frequent and serious complication of cardiopulmonary bypass surgery (CPBS), however, there are no effective therapies to prevent or treat AKI. Depending on the definition, AKI occurs in up to 15-40% of adults after CPBS. Of those patients who experience AKI as a complication of cardiac surgery, the odds of death increase from four-fold for mild cases, to greater than fifteen-fold for severe AKI. Severe AKI requires renal replacement therapy in 1-5% of cases and is associated with a mortality rate of up to 70%.

Perioperative organ injury is caused by ischemia and concomitant hypoxia-induced inflammation. During hypoxic or inflammatory disease states, many cells release ATP from their intracellular space toward the extracellular compartment. In the extracellular space, ATP can activate P2 receptors, which have been shown to cause inflammatory activation and organ

injury. CCI [redacted]. In addition, extracellular ATP is a potent inducer of vasoconstriction which can lead to lack of perfusion and no-reflow phenomenon. In conjunction with the activation of P2Y12 via extracellular ADP leading to platelet activation and thrombosis, microvascular occlusions and long-lasting damage can occur. Specifically, the kidney is largely dependent on maximal perfusion, oxygenation, and nutrition. In addition, the unique microvascular system of the kidney and the high demand in the proximal tubular cells makes this organ highly vulnerable to the described pathomechanisms.

CCI [redacted]

Data generated in non-clinical pharmacokinetics, pharmacology, and toxicology studies as well as in the first in human (FIH) clinical study support further testing of TIN816 in patients. The current study will be the first clinical trial in which TIN816 is tested in patients.

This study is designed to assess the safety, tolerability and efficacy of TIN816 in patients at risk of cardiac surgery associated AKI (CSA-AKI). A total of approximately 120 participants will be randomized to TIN816 or placebo.

Participants enrolling into this study will be managed according to current medical and surgical standard of care and as per standard institutional procedures. The study will consist of a pre-operative period (screening visit), a treatment period (Day 1) and a follow-up period (Day 2 to Day 90). Participants will be monitored daily in the hospital from Day 2 to Day 8 (or at home, in a nearby accommodation (e.g., hotel) or in a rehabilitation center if discharged earlier than Day 8), and then as an out-patient until the end of study (Day 30 and Day 90 visits).

On Day 1, the participant will undergo on-pump cardiac surgery. Randomization will be performed at start of surgery based on the leading surgeon or delegate's expectation of a CPB time of at least 60 min. However, TIN816 or placebo will only be administered after the main surgery has been completed and actual CPB time has been confirmed as ≥ 60 min, and also only after the leading surgeon has confirmed that there is no ongoing or active bleeding. CCI [redacted] Efficacy endpoints include assessments of renal function and Major Adverse Kidney Events (MAKE).

Safety assessments, CCI [redacted] immunogenicity (IG) and CCI [redacted] will be assessed starting pre-surgery and up to end of study. Safety assessments will include physical examinations, ECG, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, coagulation parameters, and urinalysis), adverse event and serious adverse event monitoring.

Treatment of interest

TIN816 (human recombinant CCI enzyme).

Number of Participants:

Approximately 120 patients aged 45 years or older with risk factors for acute kidney injury. These patients will be randomly assigned to study intervention or placebo.

Key Inclusion criteria

- Signed informed consent must be obtained prior to participation in the study.

Article I. Participants must be able to communicate well with the investigator and to understand and comply with the requirements of the study.

Article II. Male and female patients ≥45 years at screening

Article III. Participants must weigh at least 50 kg and maximum 150 kg to participate in the study and must have a body mass index (BMI) below 40. BMI = Body weight (kg) / [Height (m)]^2

- At screening, vital signs should be assessed in the sitting or supine position and be within the following ranges:
  a. body temperature between 35.0-37.5 °C
  b. blood pressure (systolic 100-160 mmHg, diastolic < 100 mmHg)
  c. pulse rate (50-100/min) stable with or without medication(s) as per Investigator‘s assessment.

  If vital signs are outside these ranges, the Investigator may obtain two additional readings, so that up to three consecutive assessments are made. At least the last reading must be within the ranges provided above for the participant to qualify.
- Stable renal function with no known increase in SCr of ≥25% at screening visit compared to a previous value obtained within the last 6 months as documented by a local laboratory using standard assay methodology, and no AKI present (any stage) at pre-surgery baseline at discretion of the investigator.

CCI [redacted]

- Non-emergent open chest cavity major cardiopulmonary bypass (CPB) surgery with expected CPB time ≥1 hour, defined by any of the following options:

CCI [redacted]

CCI

[redacted]

Key Exclusion criteria

- eGFR at screening <15 mL/min/1.73 m^2 (calculated using CKD-EPI 2021 equation)
- Receiving renal replacement therapy (RRT) currently or at any time within 3 months prior to screening, or scheduled to start RRT shortly after cardiac surgery.
- Patients with bleeding risk at screening, or identified as such pre-surgery if screening was performed earlier than Day -1. The Investigator should make this determination in consideration of the participant's medical history and/or clinical or laboratory evidence of any of the following:
  - History of bleeding with suspected or confirmed bleeding disorder or any other high risk for bleeding in the opinion of the investigator
  - Thrombocytopenia: platelet count <$100x10^9$/L
  - History of platelet dysfunction e.g., ADP induced platelet aggregation lower than 60%
  - History of coagulation factor deficiencies, including but not limited to fibrinogen ≤ 2.5 g/L or Von Willebrand factor (vWF) ≤ 50 IU/dL.
- Duration of cardiopulmonary bypass (CPB) <60 minutes
- Patient with active bleeding at the end of the surgery as per assessment of the leading surgeon
- Donation or loss of >450 mL of blood or > 200 mL of plasma within four weeks prior to dosing, or longer if required by local regulation

- Scheduled to undergo cardiac surgery off CPB or with hypothermic circulatory arrest or scheduled to undergo TAVI or TAVR only or single vessel, minimally invasive direct coronary artery bypass (MIDCAB) off-pump surgeries or left ventricular assist device (LVAD) implantation.

CCI

Treatment Groups:

Participants will be randomized at visit Day 1 to one of the following treatment arms:

- For participants enrolled under protocol amendment v00 and v01:
  - CCI i.v. infusion of TIN816 CCI mg/kg
  - CCI i.v. infusion of placebo
- For participants enrolling under protocol amendment v02 onwards:
  - CCI i.v. infusion of TIN816 CCI mg/kg
  - CCI i.v. infusion of placebo

For treatment allocation ratio please refer to Section 6.1.2.

Administration of either TIN816 or placebo will occur via CCI intravenous infusion.

Data Monitoring/Other Committee:

Yes, see Section 10.1.4 (Committees Structure)

Key words

Inflammation, CCI acute kidney injury, cardiopulmonary bypass surgery

1.2 Schema

Figure 1-1 Study design

1.3 Schedule of activities (SoA)

The SoA lists all the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

Participants should be seen for all visits/assessments as outlined in the SoA or as close to the designated day/time as possible.

Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue from study should be scheduled for a final evaluation visit if they agree, as soon as possible, at the time all the assessments listed for the final visit will be performed. At this final visit the adverse events and concomitant medications not previously reported must be recorded on the CRF.

The preferred sequence of data collection during study visits is ECG collection first, followed by vital signs, and blood sampling.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the Investigator as the situation dictates. If allowable by a local health authority, national and local regulations and depending

on operational capabilities, phone calls, virtual contacts (e.g., tele consultation) or visits by site staff/ off-site healthcare professional(s) staff to the participant´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 1-2 Assessment Schedule

Period	Screening	Treatment				Post-Treatment Follow-Up								
Visit Name	Screening	Treatment day 1				Follow-up day 2	Follow-up day 3	Follow-up day 4	Follow-up day 5	Follow-up day 6	Follow-up day 7	Follow-up day 8	Follow-up day 30	Follow-up day 90 (EOS)
Visit Numbers[1]	1	100				110	120	130	140	150	160	170	180[2]	1999
Days	-30 to -1	1				2	3	4	5	6	7	8	30 ±3	90 ±7
Time	-	Pre-surgery	Predose 0H[3]	CCI [20]	8h[20]	24h[20]	48h[20]	72h[20]	-	-	-	-	-	-
Informed consent	X													
Genetic consent	X													
Inclusion / Exclusion criteria	X		X[4]											
Demography	X													
Medical history/current medical conditions	X													
HIV, Hepatitis and TB screen[15]	S													
CCI														
Physical Examination	S													S
Body Height	X													
Body Weight	X											X	X	X
Vital signs[10]	X	X	X	X	X	X	X	X		X		X	X	X
Electrocardiogram (ECG)	X				X	X	X	X				X	X	X
CCI														
Surgery related information[7]			X											
CCI														
Urine output[11]			X[9]	CCI										
CCI														

Period	Screening	Treatment				Post-Treatment Follow-Up								
Visit Name	Screening	Treatment day 1				Follow-up day 2	Follow-up day 3	Follow-up day 4	Follow-up day 5	Follow-up day 6	Follow-up day 7	Follow-up day 8	Follow-up day 30	Follow-up day 90 (EOS)
Visit Numbers[1]	1	100				110	120	130	140	150	160	170	180[2]	1999
Days	-30 to -1	1				2	3	4	5	6	7	8	30 ±3	90 ±7
Time	-	Pre-surgery	Predose 0H[3]	CCI [20]	8h[20]	24h[20]	48h[20]	72h[20]	-	-	-	-	-	-
CCI														
CCI Oxygen Saturation)[12] CCI														
CCI														
Drug administration record			X[3]											
Urine dipstick		X[13]		X		X	X	X		X		X	X	X
Urine microscopy/sediment		X[13]		X		X						X		
Urine chemistry	X	X[13]	X	X		X	X	X		X		X	X	X
Full Hematology	X	X[13]				X						X	X	X
Limited Hematology[14]			X	X	X		X	X		X				
CCI														
Full Clinical Chemistry	X	X[13]				X	X			X		X	X	X
Limited Clinical Chemistry				X				X						
Lipids	X													X
CCI														
Immunogenicity		X[13]										X	X	X
CCI														

Period	Screening	Treatment				Post-Treatment Follow-Up								
Visit Name	Screening	Treatment day 1				Follow-up day 2	Follow-up day 3	Follow-up day 4	Follow-up day 5	Follow-up day 6	Follow-up day 7	Follow-up day 8	Follow-up day 30	Follow-up day 90 (EOS)
Visit Numbers[1]	1	100				110	120	130	140	150	160	170	180[2]	1999
Days	-30 to -1	1				2	3	4	5	6	7	8	30 ±3	90 ±7
Time	-	Pre-surgery	Predose 0H[3]	CCI [20]	8h[20]	24h[20]	48h[20]	72h[20]	-	-	-	-	-	-
CCI														
Concomitant medications	as required													
Information on renal replacement therapy	as required													
Information on hospitalization[23]	as required													
Adverse Events	as required													
Serious Adverse Events	as required													
Study completion information														X

Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] Visit structure given for internal programming purpose only.
[2] If the patient is in rehabilitation, this visit can be performed remotely
[3] CCI
[4] Check exclusion criterion # 11 (time on CPB pump) and #12 (active bleeding) before proceeding to study drug administration
[5] CCI
[6] CCI
[7] Date of surgery, type of surgery, start/end time of surgical intervention, start/end time of cardio-pulmonary bypass, concomitant vasopressor medication and dose, any surgical re-assessment for bleeding

CCI

[9] Blood loss, urine output and fluid balance from beginning to end of surgery (before start of TIN816/placebo administration)
[10] Vital signs will include the collection of body temperature (recorded in °C), blood pressure (BP) and pulse measurements.
[11] From collection bag if urine catheter still in place
[12] CCI .
[13] This pre-surgery assessment can be performed on Day-1. If Screening assessment has been done on Day -1, no need to perform a new pre-surgery collection.
[14] Only platelets count, leucocytes, erythrocyte count, hemoglobin, HCT need to be tested
[15] To be performed only if clinically indicated to rule out active infection
[16] CCI
[17] CCI
[18] CCI
[19] CCI
[20] Time post TIN816/placebo infusion start; CCI
[21] CCI
[22] CCI
[23] Duration of ICU stay, duration of overall hospital stay after cardiac surgery (from Day 1 to day of discharge), occurrence/date of any rehospitalization

2 Introduction

2.1 Study rationale

The purpose of this study is to assess the safety, tolerability and efficacy of TIN816 in patients at risk for AKI following cardiac surgery.

2.2 Background

Despite remarkable progress, acute organ injury remains one of the leading causes for morbidity and mortality in surgical and intensive care patients.

Advancements in modern medicine, in emergency and intensive care have led to significant improvements in monitoring capabilities, in safer drugs, and somewhat improved outcomes. Patients who require major surgical interventions - such as cardiothoracic, vascular, general surgery, or solid organ transplantation - may often experience perioperative acute organ injury. For example, acute kidney injury (AKI), Delayed Graft Function (DGF), acute myocardial infarction (AMI), acute ischemic stroke (AIS), intestinal ischemia, reperfusion injury, or lung injury are some of the complications that are among the leading causes of perioperative morbidity and mortality (Eltzschig, Carmeliet 2011, Eltzschig, Eckle 2011). Acute organ injuries represent major cost drivers in the intensive care setting and their prevention is a significant unmet medical need.

AKI is a frequent and serious complication of cardiopulmonary bypass surgery (CPBS), however, there are no effective therapies to prevent or treat AKI. AKI is new or worsened renal insufficiency characterized by a relatively abrupt decrease in glomerular filtration rate (GFR), often accompanied by a reduction in urine output (Mehta, Clarke 2007). AKI usually occurs within the first 7 days after an initial insult, most commonly following an episode of transient hypotension of any cause, but may also occur in response to nephrotoxins or radio-contrast media (Waikar et al 2008, Kellum et al 2013). The clinical incidence of AKI is found in 3-18% of all hospitalized adult patients worldwide, (Hoste et al 2018) and is more common in the context of complex surgery. Depending on the definition, AKI occurs in up to 15-40% of adults after CPBS, (Zanardo et al 1994, Rosner, Okusa 2006). Of those patients who experience AKI as a complication of cardiac surgery, the odds of death increase from four-fold for mild cases, to greater than fifteen-fold for severe AKI (Chertow et al 1998). Severe AKI requires renal replacement therapy in 1–5% of cases and is associated with a mortality rate of up to 70% (Khosla et al 2009).

In many instances, perioperative organ injury is caused by ischemia and concomitant hypoxia-induced inflammation. Hypoxia and inflammation share an interdependent relationship, where inflammatory diseases such as intestinal inflammation or acute lung injury can cause inflamed areas to become severely hypoxic. This typically occurs because of increased metabolic demand of resident and inflammatory cells while metabolic supply is simultaneously decreased.

During hypoxic or inflammatory disease states, many cells release ATP from their intracellular space toward the extracellular compartment. In the extracellular space, ATP can activate extracellular ATP receptors, which are classified as P2 receptors. They function as G-protein coupled receptors (P2Y receptors) or as ligand-gated ion channels (P2X receptors). Activation of P2 receptors has been shown to cause inflammatory activation and organ injury during ischemia or inflammation, and therapeutic strategies to reduce ATP receptor activation have been hypothesized for the treatment of inflammatory diseases (Idzko et al 2007, Colgan, Eltzschig 2012, Gulbransen et al 2012).

CCI [redacted] In addition, extracellular ATP is a potent inducer of vasoconstriction which can lead to lack of perfusion and no-reflow phenomenon. In conjunction with the activation of P2Y12 via extracellular ADP leading to platelet activation and thrombosis, microvascular occlusions and long-lasting damage can occur. Specifically, the kidney is largely dependent on maximal perfusion, oxygenation, and nutrition. In addition, the unique microvascular system of the kidney and the high demand in the proximal tubular cells makes this organ highly vulnerable to the described pathomechanisms.

In contrast to the pro-inflammatory functions of ATP receptors, adenosine receptors have been shown to attenuate hypoxic inflammation (Rosenberger et al 2009), provide metabolic tissue adaptation to increase ischemia tolerance (Eckle et al 2012), and to promote injury resolution (Eckle et al 2008, Grenz et al 2008).

Conversion of extracellular ATP to adenosine is controlled by a two-step enzymatic system. The first step, which is rate limiting, is the conversion of extracellular ATP to adenosine monophosphate CCI [redacted]
The subsequent second step in the extracellular generation of adenosine from AMP is catalyzed by the ecto-5'-nucleotidase CD73. CCI [redacted]

[redacted] has been proven beneficial in preclinical models of acute organ injuries, including mouse models of ischemia-reperfusion induced AKI where TIN816 was dose dependently preserving kidney function. The protection could be shown in terms of kidney structure, kidney inflammation, and acute tubular necrosis, which are also hallmarks of human AKI pathophysiology (Basile et al 2012). In addition, the common biomarkers of kidney injury and repair in the kidney tissue and in the urine of animals undergoing AKI were normalized with TIN816 treatment. CCI [redacted]

CCI [redacted]

Data generated in non-clinical pharmacokinetics, pharmacology, and toxicology studies as well as in the first in human (FIH) clinical study supported further testing of TIN816 in patients. The current phase 2 study (CTIN816A12201) is the first clinical trial in which TIN816 is tested in CS-AKI patients.

CCI [redacted]

2.3 Benefit/Risk assessment

TIN816 has not been previously administered with therapeutic intent to patients undergoing cardiac surgery. No statement can therefore be made at this time regarding the actual clinical benefit of TIN816 in this population. CCI [redacted]

The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures as well as close clinical monitoring and periodic review of safety data by an independent DMC.

CCI

Please refer to the Investigator's Brochure (Section 7) for a full review of potential risks.

2.3.1 CCI

CCI

2.3.2 CCI

CCI

[redacted]

2.3.3 Infusion and hypersensitivity reactions

Injection of a foreign protein into humans may trigger an immune response with or without inflammatory signs and symptoms. Such reactions, if they occur, may be immediate or delayed up to several weeks. CCI

[redacted]

2.3.4 Anti-drug antibody mediated reactions (immunogenicity)

There is a possibility of TIN816 inducing an immune response in human subjects. CCI [redacted] The primary consequence of immunogenicity may be altered CCI [redacted], leading to a potential loss in efficacy. There is also a theoretical possibility of immune-mediated reactions. During the non-clinical studies, presence of anti-drug antibodies (ADA) was noted in one cynomolgus monkey and in some rats and minipigs treated with TIN816 (see Investigator Brochure) but these ADA were not correlated with any safety findings. CCI [redacted], the occurrence of ADA in either species was in the range expected for a human recombinant protein. It is important to note that the occurrence of ADA and resulting ADA-mediated immune reactions in animals are generally not considered predictive of the same response in humans and that severe responses to monoclonal antibodies in humans are rare (Bugelski, Treacy 2004). CCI [redacted]

2.3.5 COVID-19

It is not known whether TIN816 CCI [redacted] can influence the clinical course of an infection with coronavirus SARS-CoV-2 (COVID-19). TIN816 is designed to treat acute organ injuries (Peters et al 2016). Novartis is committed to supporting the safety and well-being of our study participants, investigators, and site staff. All local regulations and site requirements are being applied in the countries that are affected by the COVID-19 pandemic, including COVID-19 testing of participants if applicable. As the COVID-19 situation evolves, investigators must use their best judgement to minimize risk to participants during the conduct of the study.

2.3.6 Drug-drug interactions at pharmacodynamic level

CCI [redacted]

CCI [redacted]

CCI

[redacted]

[redacted]

[redacted]

2.3.7 Blood sample volume

A volume of approximatively 450 mL is planned to be collected over a period of 4 months from each participant as part of the study. Samples collected as part of standard of care will not need to be repeated for the study. The approximate volumes are mentioned in the ICF. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the schedule of activities in Section 1.3.

2.4 Prevention of pregnancy

Since TIN816 has not been tested in reproductive toxicity studies to date, the teratogenicity potential of TIN816 is not known. It is known that monoclonal antibodies can actively cross the placenta and are detectable in the fetus; however, this requires receptor-mediated transcytosis by binding to the neonatal Fc receptor. Proteins for which no specific transport system exists, are not expected to cross the placenta due to their high molecular weight (Tetro et al 2018).

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study, they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any possibility that the participant will not reliably comply, they should not be entered or continue in the study.

CCI [redacted]

3 Objectives, endpoints, and estimands

Table 3-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the effect of TIN816 on serum creatinine level in patients at high risk for AKI and undergoing major cardio-vascular surgery, versus placebo	• Ratio of the highest serum creatinine value up to and including Study Day 6 versus baseline
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the safety and tolerability of TIN816	• Assessment of safety based on vital signs, physical examination, ECGs, laboratory assessments, and collection of AEs assessed from baseline until the end of the study visit
• To assess the effect of TIN816 on the incidence and severity of AKI inpatients at high risk for AKI and undergoing major cardio-vascular surgery, versus placebo	• AKI stages 1, 2 and 3 as defined by modified AKI Network (AKIN) criteria
• To assess immunogenicity (IG) of TIN816	• Anti-drug antibodies (ADA) against TIN816
• To assess the effect of TIN816 on the incidence of AKD in high-risk patients undergoing major cardio-vascular surgery, versus placebo	• Occurrence of major adverse kidney event at Day 90 (MAKE90) • Occurrence of MAKE30 • Occurrence of individual components of the MAKE criteria at Days 30 or 90.
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
CCI [redacted]	

Objective(s)	Endpoint(s)
CCI	[redacted]

Objective(s)	Endpoint(s)
CCI	[redacted]

Objective(s)	Endpoint(s)
CCI	

3.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results.

The primary clinical question of interest is: what is the effect of treatment with TIN816 on serum creatinine levels (up to and including Study Day 6) in adult patients at high risk of developing AKI after undergoing non-emergent CPB surgery regardless of the use of any concomitant medications (such as vasopressors), and factors potentially associated with changes in serum creatinine levels, such as fluid overload and oxygen saturation.

The justification for the primary estimand is that it will capture both the effect of the study treatment and the effect of additional medications/AKI-associated factors, mirroring the conditions in clinical practice.

CCI

3.2 Secondary estimands

Not applicable.

4 Study design

4.1 Overall design

This is a non-confirmatory, randomized, multi-centric, placebo-controlled, participant and investigator-blinded study. Approximatively 120 adult patients at risk for acute kidney injury following non-emergent cardiac surgery will be enrolled in the study.

There will be 3 groups in the study:

- Placebo
- TIN816 CCI mg/kg; subjects enrolling under original protocol and amendment 1
- TIN816 CCI mg/kg from protocol amendment 2 onwards

Participants enrolling into this study will be managed according to current medical and surgical standard of care and as per standard institutional procedures. The study will consist of a pre-operative period (screening visit), a treatment period (Day 1) and a post-treatment follow up period (Day 2 to Day 90).

Participants will be followed up daily in the hospital from Day 2 to Day 8 (or at home, in a nearby accommodation (e.g., hotel) or in a rehabilitation center if discharged earlier than Day 8), and then as an out-patient until the end of study (Day 30 and Day 90 visits).

Patients, who are scheduled to undergo non-emergent open chest cavity or minimally invasive cardiac surgeries with cardio-pulmonary bypass (CPBS), will be informed about the study purpose and provided with study-specific participant information and informed consent.

Participants who have agreed to participate will be asked to sign a study-specific written informed consent and attend a screening visit to determine their eligibility, within 30 days prior to the surgery. The visit will assess the participant's suitability to participate in the study based on study inclusion and exclusion criteria.

During the pre-operative period, eligible participants will have blood and urine collected for safety lab and CCI . The pre-operative values will be considered baseline values.

On Day 1, the participant will undergo cardiac surgery. Randomization will be performed at start of surgery based on the leading surgeon or delegate’s expectation of a CPB time of at least 60 min. However, actual administration of TIN816 or placebo will only be administered once the main surgery has been completed and preparations are ongoing to close the wound, and the leading surgeon has confirmed that there is no active bleeding, and it is safe to proceed with wound closure. CCI

Safety assessments, CCI , immunogenicity (IG) and CCI will be done for up to end of study visit (see Assessment schedules Section 1.3). Blood and urine samples will be collected for these assessments.

During each visit, basic demographic, clinical information and adverse events (AE) will be collected and entered in a Case Report Form (CRF). The collected samples and clinical information will be provided to Novartis in coded form.

Safety assessments will include physical examinations, ECG, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, coagulation parameters, and urinalysis), adverse event and serious adverse event monitoring.

Remote procedures

At the Investigator's discretion and based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option to have certain clinical trial procedures according to Section 1.3 Schedule of Activities performed at a remote location.

Procedures will be performed remotely under the oversight of the Investigator, who retains accountability for the oversight. The Investigator retains accountability for all efficacy and safety decisions with delegation of tasks to an off-site healthcare professional.

The remote procedures will be utilized in certain countries and sites as determined by protocol needs and based on national and local/site regulations.

The off-site healthcare professionals will be provided by the site, or a third-party vendor sourced by Novartis. Where a site wishes to use off-site healthcare professionals from a third-party vendor that is not provided by Novartis this must be agreed with Novartis before use.

In addition to procedures performed by the off-site healthcare professional, the on-site staff may perform certain procedures remotely using tele-visits.

4.2 Scientific rationale for study design

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Targeted study population	The inclusion criteria for this study were chosen following current knowledge on clinical and demographic factors associated with AKI and with a goal to enroll patients at highest risk for developing AKI after cardiac surgery. According to literature, subjects undergoing complex surgeries with long CPB times and patients with pre-existing kidney disease and other comorbidities as well as older individuals in general have a higher risk to develop AKI after the surgery. CCI [redacted] (Delanaye et al 2019).CCI [redacted]

Study Design Aspect	Rationale
	(Pottel et al 2017, CCI [redacted].
Randomization (strata, allocation ratio)	Randomization decreases the chance of imbalance of participant characteristics between groups, thereby facilitating an unbiased assessment of safety, tolerability and efficacy. In addition, randomization prevents selection bias. CCI [redacted]
Blinding	The study is participant- and investigator-blinded until final database lock (except where indicated in Section 6.3) to reduce potential bias in the assessment of readouts.

Study Design Aspect	Rationale
Duration of study periods	The study follow-up duration is 90 days to allow for a meaningful assessment of the safety, tolerability and efficacy of TIN816 in AKI. The incidence and severity of AKI will be assessed through the first week after surgery and the MAKE criteria will be evaluated at Day 30 and 90. CCI [redacted]
Treatment groups	The control group is placebo on top of standard of care because there is no approved treatment for AKI

4.2.1 Participant input into design

Acute kidney injury (AKI) is a silent condition, characterized by a sudden deterioration of kidney function, sometimes with reduced or even complete loss of urine output. Most patients will experience this syndrome during a hospital stay, especially critically ill patients and patients undergoing major surgeries. Recovery from AKI is possible, however, in some patients, kidney function will continue to decline further and remain chronically impaired. Some patients will need at least short-term dialysis or will be left with severe renal impairment and remain dialysis -dependent with the need for a kidney transplant.

Based on an internal review of social information mining data conducted by Novartis in 2021, acute kidney injury patients reported being admitted to the hospital for around 7 days to restore their kidney function. In some cases, patients had to stay longer and required hemodialysis treatment, besides other minor interventions. After the acute kidney injury episode, patients reported feeling exhausted and drained after the hospital stay. Other points of concern were the financial strain from the treatment and the fear of acquiring another unexpected medical emergency/complication.

Many patients described how much their lives changed because of dialysis or transplantation. For instance, they said they had to stop travelling because of dialysis or transplant. Some of them even lost partners or the job they loved because of the many hours they had to spend attached to the dialysis machine. Some of them were also discouraged from becoming pregnant or continuing with a pregnancy because of the high risks involved.

Many patients need to relocate to live close to a hospital where they can undergo dialysis.

Most patients would simply like to avoid dialysis. The most important drug they would like to have is the one that would prevent AKI from progressing into severe AKI or severe kidney dysfunction, and even better, prevent any AKI from developing to begin with.

Since severe AKI is also associated with a high mortality rate in the more severe cases, and no treatment is currently available, all preventive measures should be taken to avoid the heavy burden of this common, but usually overlooked, clinical entity.

4.3 Justification for dose

CCI

In this study, patients will be administered placebo or the study drug at a dose of CCI mg/kg (for patients enrolled under the original protocol and protocol amendment 1) or CCI mg/kg (from protocol amendment 2 onwards) via a CCI intravenous infusion in a double-blinded fashion. Due to the acute nature of AKI and CCI it is believed that CCI at CCI mg/kg should result in a pharmacologically relevant systemic and tissue TIN816 exposure which is CCI . This is based on *in vitro* and *ex vivo* PD assessments in human whole blood and the assumption that close to full inhibition of CCI pathways are required to provide efficacy.

CCI

CCI [redacted]

Dose administration CCI [redacted] provides time to react if unexpected safety related reactions occur during dosing. CCI [redacted]

Patients will be followed up for a total duration of 90 days, CCI [redacted] and safety data used to adapt the dose level at interim analysis and to support the dosing strategy for subsequent studies in this indication.

4.3.1 Rationale for choice of background therapy

Patients undergoing cardiac surgery are sedated and ventilated, and hence medicated with sedatives, anesthetics and analgesics. Moreover, cardiac patients receive anti-platelet therapies due to a generally increased risk of thromboembolic events, plus heparin to prevent clotting within the cardiopulmonary bypass circuits. Caution is required when TIN816 is CCI [redacted] adequate monitoring of respective CCI [redacted] is required as per protocol (see Section 8.4.5). There are no specific medicines currently approved or available for the prevention or treatment of acute kidney injury (AKI), and standard interventions usually consist of fluid management and hemodynamic support. These standards will be followed in this trial for both treatment groups (TIN816 and placebo) as deemed necessary by the study physician and medical team in charge as per local procedures.

4.4 Rationale for choice of control drugs (comparator/placebo) or combination drugs

The comparator treatment in the study will be placebo, in order to provide objective control for the evaluation of safety, clinical efficacy and PD parameters. Since there is no approved treatment for AKI, the use of placebo as comparator is considered justified. Standard background interventions for the prevention as well as treatment of AKI include fluid management and hemodynamic stabilization. These will be applied to both study cohorts, TIN816 and placebo, as part of standard therapy during and after surgery.

4.5 Rationale for public health emergency mitigation procedures

During a public health emergency as declared by local or regional authorities (i.e., pandemic, epidemic or natural disaster), mitigation procedures to ensure participant safety and trial integrity may be implemented: such procedures are listed in the relevant sections. The principal investigator should notify and discuss the public health emergency as declared by local or regional authorities with Novartis before implementation of any such procedures. All procedures adapted to the situation must be submitted, if required as per local regulations, through a protocol amendment (see Section 10.1.8.1) to the competent authorities and ethics committees prior to implementation of mitigation procedures.

4.6 Purpose and timing of interim analyses/design adaptations

CCI

Additional interim analyses may be conducted to support decision making concerning the current clinical study, the Sponsor's clinical development projects in general, or in case of any safety concerns.

Additional information is presented in the interim analysis Section 9.8.

4.7 End of study definition

The end of the study is defined as the date of the last visit of the last participant in the study.

Study completion is defined as when the last participant finishes their last study visit and any repeat assessments associated with this visit have been documented and followed -up appropriately by the Investigator.

5 Study population

The study population will be comprised of approximately 120 patients who are scheduled to undergo non-emergent CPB surgery and are at risk of developing AKI.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. Participants must be able to communicate well with the investigator and to understand and comply with the requirements of the study.
3. Male and female patients ≥45 years at screening.
4. Participants must weigh at least 50 kg and maximum 150 kg to participate in the study and must have a body mass index (BMI) below 40. BMI = Body weight (kg) / [Height (m)]^2.
5. At screening, vital signs should be assessed in the sitting or supine position and be within the following ranges:
   a. body temperature between 35.0-37.5 °C
   b. blood pressure (systolic 100-160 mmHg, diastolic < 100 mmHg)
   c. pulse rate (50-100/min) stable with or without medication(s) as per Investigator assessment

   CCI [redacted]
6. Stable renal function with no known increase in SCr of ≥25% at screening visit compared to a previous value obtained within the last 6 months as documented by a local laboratory using standard assay methodology, and no AKI present (any stage) at pre-surgery baseline at discretion of the investigator.
7. CCI [redacted]

CCI

8. Non-emergent open chest cavity major cardiopulmonary bypass (CPB) surgery with expected CPB time ≥1 hour, defined by any of the following options:

CCI

CCI

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. eGFR at screening <15 mL/min/1.73m^2 (calculated using CKD-EPI 2021 equation).
2. Receiving renal replacement therapy (RRT) currently or at any time within 3 months prior to screening or scheduled to start RRT shortly after cardiac surgery.
3. Patients with bleeding risk at screening (or identified pre-surgery if screening was performed earlier than Day -1). The Investigator should make this determination in consideration of the participant's medical history and/or clinical or laboratory evidence of any of the following:
   - History of bleeding with suspected or confirmed bleeding disorder or any other high risk for bleeding in the opinion of the investigator
   - Thrombocytopenia: platelet count <100x10^9/L
   - History of platelet dysfunction e.g., ADP induced platelet aggregation lower than 60 %
   - History of coagulation factor deficiencies: including, but not limited to fibrinogen ≤ 2.5 g/L or Von Willebrand factor (vWF) ≤50 IU/dL

4. Any emergency surgeries performed less than 30 days before screening, including aortic dissection, and/or major congenital heart defects.
5. Scheduled to undergo cardiac surgery off CPB or with hypothermic circulatory arrest.
6. Scheduled to undergo TAVI or TAVR only or single vessel, minimally invasive direct coronary artery bypass (MIDCAB) off-pump surgeries or left ventricular assist device (LVAD) implantation (Note: See Inclusion Criterion #8).
7. Cardiogenic shock or hemodynamic instability within four weeks prior to surgery, requiring inotropes or vasopressors or mechanical devices such as intra-aortic balloon counter-pulsation (IABP). Current or within four weeks prior to surgery, clinically significant arrhythmias associated with syncope, dyspnea or hemodynamic instability
8. Have required any of the following within four weeks prior to cardiac surgery: defibrillator, mechanical (invasive) ventilation, IABP, LVAD, other forms of mechanical circulatory support (MCS).
9. Have received cardiopulmonary resuscitation (CPR) within 30 days prior to cardiac surgery.
10. CCI [redacted]
11. Duration of cardiopulmonary bypass (CPB) <60 minutes.
12. Patient with active bleeding at the end of surgery as per assessment of the leading surgeon.
13. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or until the expected PD effect has returned to baseline, whichever is longer; or longer if required by local regulations.
14. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes.
16. Patients who are post-nephrectomy.
17. Any significant QT prolongation as per PI judgment and/or concomitant use of agents known to prolong the QT interval unless they can be discontinued or replaced by safe alternative for the duration of study (at the discretion of the investigator).
18. Taking medications prohibited by the protocol (see Table 6-3 (Prohibited medications)).
19. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in-situ* cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
20. Donation or loss of >450 mL of blood or > 200 mL of plasma within four weeks prior to dosing, or longer if required by local regulation.
21. Have a history of any organ or cellular transplant which requires active immunosuppressive treatment which can interfere with kidney function (e.g., calcineurin inhibitors).
22. Have ongoing sepsis or history of sepsis within the past 8 weeks or untreated diagnosed infection prior to screening visit. Sepsis is defined as presence of a confirmed pathogen, along with fever or hypothermia, and hypoperfusion or hypotension.
23. Heart failure stage IV as defined by the New York Heart Association (NYHA) Functional Classification.

24. Left ventricular ejection fraction of < 30% as per most recent echocardiography available.
25. Recent (within the last three years) and/or recurrent history of autonomic dysfunction (e.g., recurrent episodes of fainting, palpitations, etc.).
26. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the participant in case of participation in the study. The Investigator should make this determination in consideration of the participant's medical history and/or clinical or laboratory evidence of any of the following:
    - Inflammatory bowel disease, peptic ulcers, gastrointestinal including rectal bleeding;
    - Pancreatic injury or pancreatitis;
    - Liver disease or liver injury as indicated by abnormal liver function tests: ALT (SGPT), AST (SGOT), GGT, alkaline phosphatase and serum bilirubin will be tested.
    - Evidence of significant urinary obstruction or difficulty in voiding at screening.

    If necessary, laboratory testing may be repeated on one occasion (as soon as possible) prior to randomization, to rule out any laboratory error.
27. History of immunodeficiency diseases or known HIV positive test.
28. Active hepatitis defined as (a) abnormal liver enzymes (Alanine aminotransferase (ALT), Gamma-glutamyl transferase (GGT) and ALP > 3x Upper Limit of Normal (ULN)) or (b) for active hepatitis B or C infection, a positive Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) serology, as per most recent test available, or patients with advanced chronic liver disease, confirmed by a Child-Pugh score of 10–15 (Class C).
29. In patients where medical and travel history, clinical symptoms, or the standard pre-operative chest x-ray (not older than 1 month before screening visit) suggest possibility for active or latent TB, a QuantiFeron tuberculosis test or a purified protein derivative test (PPD, ≥5 mm induration) should be performed, and patient should be excluded if the test result is positive or cannot be done. Patients can be included if treatment for TB is initiated and completed according to local treatment guidelines.
30. History of drug abuse or unhealthy alcohol use[#] within the 12 months prior to dosing, or evidence of such abuse per investigator judgement at screening.

    [#]Unhealthy alcohol use is defined as a history of, or current alcohol misuse/abuse, defined as “Five or more drinks on the same occasion on each of 5 or more days in the past 30 days."
31. Pregnant or nursing (lactating) women.
32. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception while taking study treatment and until the end of study. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, sympto-thermal and post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female bilateral tubal ligation, female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or total hysterectomy at least six weeks

before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

- Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
- Use of oral (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

If local regulations are more stringent than the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age-appropriate history of vasomotor symptoms). Women are considered not of child-bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks prior to enrollment on study. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered to be not of child-bearing potential.

33. Vulnerable participants, e.g., institutionalized due to regulatory or juridical order, dependent on sponsor, site or investigator or not able to consent, respectively.
34. Use of plasma exchange, plasmapheresis, and other extracorporeal filtration techniques within last month prior to screening or if planned to be used during or after the surgery.

5.3 Lifestyle considerations

For the duration of the study, participants should be informed and reminded of the restrictions outlined in this section.

5.3.1 Recreational drugs

No recreational drug use during study through study completion evaluation (i.e., cocaine, marijuana).

5.3.2 Activity

No strenuous physical exercise (e.g., weight training, aerobics, football) from screening until after Study Completion evaluation.

5.4 Screen failures

A screen failure occurs when a participant who consents to participate in the clinical study is subsequently found to be ineligible and therefore not randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized. Data and samples collected from participants prior to screen failure may still be analyzed.

Participants who are eligible to be randomized but fail to start treatment (e.g., participants randomized in error, with CPB time <60 minutes, or ongoing bleeding at end of surgery), will be discontinued and IRT must be notified that no dosing occurred. The reason should be recorded on the appropriate Case Report Form.

Individuals who do not meet the criteria for participation in this study (screen failure) typically may not be rescreened. In the event of a strong rationale to re-screen a participant, the case must be discussed and agreed with Novartis on a case-by-case basis.

In the case where a safety laboratory assessment at screening is outside of the range specified in the eligibility criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified range, the participant must be excluded from the study.

5.4.1 Replacement policy

Participants will not be replaced on study. However, enrollment of additional participants may be considered until at least the minimum number of 120 evaluable participants who have reached Day 6 is achieved.

5.4.2 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is rescreened. The Participant No. consists of the Site Number (Site No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

6 Study treatment(s) and concomitant therapy

The investigational drug, TIN816 or placebo, will be manufactured by Novartis and supplied to the unblinded pharmacist or unblinded qualified site designee. The unblinded pharmacist/ unblinded qualified site designee will prepare the appropriate dosage (detailed instructions will be provided in the Pharmacy Manual).

Details on the requirements for storage and management of study treatment, prescribing/ dispensing, and administration of study treatment are outlined in the Pharmacy Manual.

6.1 Study treatment(s)

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Treatment Form or Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
TIN816 70 mg (lyophilizate in vial)	Powder for Solution for infusion	Intravenous use	Open label patient specific supply; vials	Sponsor (global)
Placebo 1 mL (liquid in vial)	Concentrate for Solution for infusion	Intravenous use	Open label patient specific supply; vials	Sponsor (global)

Drug will be administered as CCI at the clinical site by the study personnel in accordance with the specified study procedures.

6.1.1 Additional study treatments

No other treatment beyond investigational drug and placebo are included in this trial.

6.1.2 Treatment arms/group

For participants enrolled under protocol amendment v00 and v01:

Participants will be randomized at visit Day 1 to one of the following treatment arms in a ratio of CCI (TIN816:placebo)

- CCI i.v. infusion of TIN816 CCI mg/kg
- CCI i.v. infusion of placebo

For participants enrolling under protocol amendment v02 onwards:

Participants will be randomized at visit Day 1 to one of the following treatment arms in a ratio of CCI (TIN816:placebo)

- CCI i.v. infusion of TIN816 CCI mg/kg
- CCI i.v. infusion of placebo

CCI

6.2 Preparation, handling, storage, and accountability

Each study site will be supplied with study treatment in packaging as described under Table 6-1 Investigational and control drugs section (for details on drug preparation please refer to the Pharmacy Manual).

A unique medication number is printed on the study medication label. Unblinded pharmacist/unblinded qualified site designee will identify the study medication kit to be diluted after Investigator or delegated staff has contacted the IRT and triggered the medication number(s) release. The study medication has a 2-part label (base plus tear-off label), before diluting, the unblinded pharmacist/unblinded qualified site designee will detach the outer part of the label from the packaging and affix it to the source document.

6.2.1 Handling of study treatment

Study treatment must be received by an unblinded pharmacist or a qualified site designee, handled and stored safely and properly and kept in a secured location to which only the unblinded pharmacist or a qualified site designee have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The unblinded pharmacist or an unblinded qualified site designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site or remote monitoring visits, and at the completion of the trial. The unblinded pharmacist or an unblinded qualified site designee need to make sure all the materials required for IMP preparation are available at the site and at enough quantities to be used in the trial.

The site may destroy and document destruction of unused study treatment, drug labels and packaging, as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the Investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the Investigator folder at each site.

6.2.2 Handling of other treatment

Not applicable

6.2.3 Instruction for prescribing and taking study treatment

TIN816 or corresponding placebo will be administered to the participant at the study site via i.v. infusion over CCI (see details in the Pharmacy Manual). There should be a period of at least 1 hour after the infusion during which the participant requires close observation. Patient care should be managed as per local medical practice.

6.3 Measures to minimize bias: randomization and blinding

6.3.1 Treatment assignment, randomization

At visit Day 1, all eligible participants for whom the PI expects a CPB time of at least 60 minutes will be randomized via Interactive Response Technology (IRT) to one of the treatment arms at start of the surgery. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and Investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

CCI [redacted]

The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

6.3.2 Treatment blinding

Participants, Investigator staff (except unblinded pharmacist/unblinded qualified site designee) and persons performing the assessments will remain blinded to the identity of the treatment from the time of randomization until database lock.

Unblinding a single participant at site for safety reasons (necessary for participant management) will occur via an emergency system in place at the site.

Open label supply (TIN816 and placebo) will be provided at sites to the unblinded pharmacist/unblinded qualified site designee in order to prepare study treatment and to conceal treatment code from participants and the Investigators staff performing the assessment.

The following unblinded sponsor roles are required for this study:

- Statistician, programmers or delegates who need to prepare safety reports for the DMC and
- Bioanalysts CCI [redacted]

Both will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. They will provide the sample data to the study team under blinded conditions unless otherwise allowed. The study statistician will be able to access the randomization list for interim analyses and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in Table 6-2. For example, unblinded summaries and unblinded individual data can be shared

with the team for interim analyses. Statistical programmers and other personnel involved in study data analysis (e.g., drug supply manager) are allowed to access treatment assignment information for the purpose of data analysis. The clinical trial team is allowed to share unblinded results with other sponsor staff (e.g., decision boards) as required for internal decision making on the study or the project at the time of IAs while the study is ongoing. All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above. The DMC will be provided with unblinded results to facilitate the review of safety information (Table 6-2). More details will be provided in the DMC charter about the unblinding plan and data flow. Following final database lock all roles may be considered unblinded. See Table 6-2 for an overview of the blinding/unblinding plan.

Table 6-2 Blinding and unblinding plan

Role	Time or Event			
	Randomization list generated	**Treatment allocation & dosing**	**Safety event (single subject unblinded)**	**Interim Analysis/ dose escalation/ safety review**
Participants	B	B	UI	B
Site Staff	B	B	UI	B
Unblinded site staff, e.g., pharmacy staff	B	UI	UI	B
Randomization Office	UI	UI	UI	UI
Unblinded Sponsor staff, e.g., for study treatment re-supply, unblinded monitor(s), sample analyst(s)	B	UI	UI	UI
Independent committees used for assessing interim results, if required (e.g., DMC)	UI	UI	UI	UI
All other Sponsor staff not identified above (i.e., project team, management & decision boards, support functions)	B	B	UI	UI
Statistician/statistical programmer/ data analysts CCI [redacted]	B	UI	UI	UI

B Complete blinded

UI Unblinded to individual participant treatment codes

6.3.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to treat the participant safely.

Most often, discontinuation from study treatment and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the Investigator contacts

the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The Investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the Investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The Investigator will provide:

- protocol number
- participant number

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

A participant can continue participation in the study in the event of an unblinding incident.

6.4 Study treatment compliance

A one-time intravenous infusion will be administered in the clinic. This information must be captured in the source document, the appropriate CRF/s and in the Drug Accountability Log. The site personnel should reflect the total dose administered as well as date and time of administration start and end in the eCRF page. Any reason for dose interruption of the IV infusion will also be captured in the source document and the eCRF.

CCI [redacted]

6.4.1 Recommended treatment of adverse events

At present there is insufficient information to provide specific recommendations regarding treatment of AEs. There is also no specific antidote to the IMP. Investigators should use their best clinical judgement and follow local treatment guidelines in treating adverse events.

Medication used to treat AEs must be recorded on the appropriate CRF.

Treatment of acute infusion and/or hypersensitivity reactions

As with most biologic compounds, administration of TIN816 carries the risk of anaphylaxis and/or hypersensitivity-type reactions. In the event of such a reaction, investigators should consider study-specific criteria for treatment interruption (Section 7.1), and the participant should be treated with antihistamines and glucocorticoids. Depending on severity, participants may also require supplemental oxygen, volume expansion, catecholamine administration and transfer to an intensive care setting. Plasmapheresis to decrease the systemic concentration of TIN816 may be considered dependent on the participant's condition. Participants should be observed for at least four hours after resolution of signs and symptoms, and those who have experienced severe infusion reactions should be closely observed for 24 hours after resolution because of the risk for a biphasic episode.

6.5 Dose modification

Investigational treatment dose adjustments are not permitted. Administration could be interrupted in case of adverse reaction (see Section 6.4.1).

6.6 Continued access to study treatment after the end of the study

There will be no treatment following the end of the study.

6.6.1 Post-trial access

Not applicable

6.7 Treatment of overdose

There is no experience with TIN816 overdose. Should an overdose occur, the participant should be carefully monitored for any potential symptoms and changes in laboratory parameters (including coagulation parameters), and if necessary, appropriate supportive care should be provided until the participant has recovered. The use of plasmapheresis may be considered to facilitate more rapid elimination of TIN816 from the peripheral circulation in the case of overdose.

In the event of an overdose, the Investigator should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study treatment should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until TIN816 can no longer be detected systemically.
- Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study treatment if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.

6.7.1 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE. Study treatment errors and uses outside of what is foreseen in the protocol, misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within

24 hours of Investigator's awareness. For more information on AE and SAE definition and reporting requirements, please see the respective sections.

6.8 Concomitant and other therapy

6.8.1 Concomitant therapy

All concomitant therapies (medications, procedures and non-drug therapies, including physical therapy) administered from the day the participant was enrolled into the study until the end of study must be recorded on the appropriate Case Report Forms.

Note:

Volatile anesthetics are not required to be documented in the CRF, all other anesthetics and analgesics should be documented in the CRF for the intra-operative period but can be omitted if given post-operatively. One exception are NSAIDs (non-steroidal anti-inflammatory drugs), which should always be documented in the CRF (including topical use).

Intravenous fluids (crystalloid and colloidal) should be documented in the CRF for the intra-operative period but are not required to be documented in the CRF for the post-operative period.

CCI [redacted]

Significant procedures applied prior to trial enrollment (e.g., previous cardiac surgeries or cancer-related procedures) must be documented in the CRF as appropriate.

Each concomitant drug must be individually assessed against all exclusion criteria and prohibited medication. If in doubt, the Investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.8.1.1 Permitted concomitant therapy requiring caution and/or action

CCI [redacted]

CCI

Refer to Section 2.3.1 and Investigator Brochure for more details.

6.8.2 Prohibited medication

Use of the treatments displayed in the table below are not allowed during the indicated period:

Table 6-3 Prohibited medication/procedures

CCI

Medication	Prohibition period	Action taken
CCI		

6.8.3 Rescue medicine

CCI As with most biologic compounds, administration of TIN816 carries the risk of anaphylaxis and/or hypersensitivity-type reactions. In the event of such a reaction, investigators should consider study-specific criteria for treatment interruption (Section 7.1), and the participant should be treated with antihistamines and glucocorticoids. Depending on severity, participants may also require supplemental oxygen, volume expansion, catecholamine administration and transfer to an intensive care setting. Plasmapheresis to decrease the systemic concentration of TIN816 may be considered dependent on the participant's condition. Participants should be observed for at least four hours after resolution of signs and symptoms, and those who have experienced severe infusion reactions should be closely observed for 24 hours after resolution because of the risk for a biphasic episode. Blood products (packed red blood cells, platelets, plasma, etc.) should be ordered by the site as is standard of care for surgical patients and stored for trial participants to allow for immediate transfusion in case of major bleeding events, if indicated as per Principal Investigator's evaluation and local procedure.

7 Discontinuation of study treatment and participant discontinuation/withdrawal

7.1 Discontinuation of study treatment

The treatment involves CCI i.v. infusion over CCI, and therefore the infusion can be interrupted at any time for the reasons described below.

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study treatment administration, if any) and can be initiated by either the participant or the Investigator.

The Investigator must discontinue study treatment for a given participant if he/she believes that continuation would negatively impact the participant's well-being.

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which continued study participation might result in a safety risk to the participant
- Following emergency unblinding
- Any laboratory abnormalities that in the judgment of the Investigator, prevents the participant from continuing participation in the study
- Severe hypersensitivity reaction occurs, including any of the following: anaphylaxis, fever, chills, urticaria, dyspnea, headache, myalgia, hypotension. Immediate interruption of the infusion to administer study treatment is required in such cases.

If discontinuation from study treatment occurs, the Investigator should make a reasonable effort to understand the primary reason for the participant’s discontinuation from study treatment and record this information.

Participants who discontinue from study treatment are asked to return for the follow-up visits indicated in Section 1.3 Schedule of Activities.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be performed according to the study visit schedule.

After discontinuation from study treatment, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New/concomitant treatments
- Adverse Events/Serious Adverse Events

The Investigator must also contact the IRT to register the participant’s discontinuation from study treatment.

7.2 Participant discontinuation from the study

Discontinuation from study is when the participant prematurely stops receiving the study treatment infusion, and/or further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in Section 1.3 Schedule of Activities.

7.3 Withdrawal of informed consent and exercise of participants' data privacy rights

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be as per local regulations (e.g., in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the Investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

No further assessments must be conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise data privacy rights should be made as detailed in Section 1.3 Schedule of Activities.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

7.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other participants' data privacy rights), the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g., dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

7.5 Study stopping rules

Sponsor will review emergent safety reports on an ongoing basis to react as soon as there is a possibility that a stopping rule could apply. The sponsor will review all SAE as individual cases and will also be able to review summaries of non-serious adverse events for patterns and trends and will first exclude any events determined to be clearly unrelated to study treatments (e.g., SAE which occurred during the pre-treatment screening period, or disease-related SAE expected in the population under study). CCI

CCI

Table 7-1 CCI

CCI

CCI [redacted]

Table 7-2 CCI [redacted]

CCI [redacted]

7.6 Early study termination by the Sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination (but not limited to):

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study treatment development in this indication

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from the study: the participant should come for a final End of Study (EOS) visit. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The Investigator or Novartis depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Study Assessments and Procedures

Study procedures and their timing are summarized in Section 1.3 Schedule of Activities. Protocol waivers or exemptions are not allowed.

- Immediate safety concerns should be discussed with Novartis upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in Section 1.3 Schedule of Activities, is essential and required for study conduct.
- Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Screening

Procedures conducted as part of the participant's routine clinical management/standard of care (e.g., clinical chemistry, hematology, urinalysis) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the

protocol-specified criteria and were performed within the timeframe defined in Section 1.3 Schedule of Activities.

8.1.1 Eligibility screening

Results of below screening evaluation will be available as source data at the study site and will not be recorded within the eCRF.

8.1.1.1 Hepatitis screen, HIV screen, Tuberculosis screen

All participants will be evaluated for active hepatitis (refer to exclusion criterion 28).

Evaluation of history of immunodeficiency diseases or known positive HIV test documented in source data. Notification of state and federal authorities, as required by law, will be the responsibility of the Investigator.

Determination of TB status will be required before administration of study treatment and should be performed as defined by local guidelines (refer to exclusion criterion 29).

8.1.1.2 Alcohol test, drug screen

Participants will be assessed by the Investigator at screening for history of drug abuse and unhealthy alcohol use as described in Exclusion criterion 30. A positive evaluation will lead to the exclusion of the participant.

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and are subsequently found to be ineligible (either pre-surgery, or during or shortly after surgery but prior to IMP infusion) will be considered a screen failure.

The reason for screen failure should be entered on the applicable Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see Section 8.6 Serious adverse events for reporting details).

Participants who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition Case Report Form.

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

Participant demographics: age (in years), sex, race/predominant ethnicity (if permitted) and relevant medical history/current medical conditions (until date of signature of informed consent) will be recorded in the eCRF. Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics. In addition, these data are necessary to assess the diversity of the study population as required by health authorities.

All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented up to 6 months before the study. See also the protocol Section 6.8.1 Concomitant Therapy for further details on what information must be recorded on the appropriate page of the eCRF.

To determine the eligibility for inclusion in the study, serum creatinine, eGFR and surgery information will be collected and recorded in the eCRF.

8.2.1 CCI

CCI

8.3 Efficacy assessments

Planned time points for all efficacy assessments are provided in Section 1.3 Schedule of Activities.

Pharmacodynamic (PD) samples will be collected at the time points defined in Section 1.3 Schedule of Activities. Follow instructions outlined in the Laboratory manual regarding sample collection, numbering, processing, and shipment.

Pharmacodynamic samples will be obtained and evaluated in all participants at all dose levels, including the placebo group.

8.3.1 Serum Creatinine

Serum creatinine is a standard marker to assess renal function and diagnose AKI. Serum creatinine samples will be collected from participants at all visits from baseline to Day 90/EOS.

8.3.2 AKI incidence and severity

AKI incidence over the first week after surgery will be measured using the modified AKIN classification system, based on changes in serum creatinine compared to pre-operative value. Severity of AKI will be assessed using three stages, with stage 1 being the less severe and stage 3 the more severe (see Table 8-1).

CCI

CCI [redacted]

Table 8-1 The modified AKIN classification system of acute kidney injury

Stage	Serum Creatinine/RRT
1	Serum creatinine (SCr) ≥1.5 - <2.0 x baseline within 7 days post-surgery
	Or
	↑ SCr by ≥26.5 µmol/L (≥0.3 mg/dL) within 2 days post-surgery
2	SCr ≥2.0 - <3.0 x baseline within 7 days post-surgery
3	SCr ≥3.0x baseline within 7 days post-surgery
	Or
	↑ SCr to ≥353.6 µmol/L (4.0 mg/dL) AND by ≥44.2 µmol/L (0.5 mg/dL) within 7 days post-surgery
	Or
	[a]Initiation of RRT within 7 days post-surgery

↑ Increase from baseline

[a]Stage 3 includes patients requiring RRT independent of the AKI stage they are in at the moment of RRT initiation.

Adapted from (Barry, James 2015)

Table 8-2 The kidney disease improving global outcomes (KDIGO) classification

Stage	Serum Creatinine/RRT
1	SCr 1.5-1.9 x baseline within 7 days post-surgery
	Or
	↑ SCr by ≥0.3 mg/dL (≥26.5 µmol/L) within 2 days post-surgery
2	SCr 2.0-2.9 x baseline within 7 days post-surgery
3	SCr ≥3.0 x baseline within 7 days post-surgery
	Or
	↑ SCr to ≥4.0 mg/dL (≥353.6 µmol/L) AND by ≥0.5 mg/dL within 7 days post-surgery
	Or
	Initiation of RRT

↑ Increase from baseline

Table 8-3 The RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) classification

Class	Serum Creatinine/GFR
Risk	SCr 1.5 x baseline or ↓ eGFR >25%
Injury	SCr 2 x baseline or ↓ eGFR >50%
Failure	SCr 3 x baseline or ↓ eGFR >75% Or ↑ SCr to ≥353.6 µmol/L (≥4 mg/dL) AND by >44.2 µmol/L(>0.5 mg/dL)
Loss of kidney function	Complete loss of kidney function >4 weeks
End-stage kidney disease	Complete loss of kidney function >3 months

SCr = serum creatinine, eGFR = estimated glomerular filtration rate

↑ Increase from baseline, ↓ decrease from baseline

8.3.3 Major Adverse Kidney Event (MAKE)

The proportion of participants having major adverse kidney event at Day 30 (MAKE30) and 90 (MAKE90) will be assessed using the following components: 1) death, 2) initiation of renal replacement therapy, 3) ≥25% reduction in eGFR.

Information on death such as date of occurrence and cause will be captured in the eCRF.

In case a participant needs to receive renal replacement therapy, information will be collected in the eCRF, such as date, duration, method of dialysis and number of sessions.

eGFR will be calculated as described in Section 8.3.4.

8.3.4 Estimated glomerular filtration rate (eGFR)

The eGFR 2021 CKD EPI creatinine equation that estimates kidney function without a race variable should be used for eGFR calculations during this study. A taskforce of members from the National Kidney Foundation NKF and American Society of Nephrology ASN assessed the accuracy of a new eGFR equation that incorporates creatinine but omits race, and concluded the new equation to be more accurate. Immediate implementation in all US labs was recommended in November 2021.

$eGFR = 142 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012$ [if female]

where: SCr is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.241 for females and -0.302 for males, min indicates the minimum of SCr /κ or 1, and max indicates the maximum of SCr /κ or 1.

The equation does not require weight because the results are reported normalized to 1.73 m^2 body surface area, which is an accepted average adult surface area.

8.3.5 Appropriateness of efficacy assessments

Serum creatinine is a standard marker used to assess renal function and diagnose AKI (Ronco et al 2019).

MAKE is a composite endpoint including death, need for RRT and worsening renal function (eGFR> 25% reduction from baseline). It can be assessed at defined intervals/ timepoints and is increasingly being recognized as an important patient centered outcome from studies in patients who are critically unwell (Billings, Shaw 2014).

8.4 Safety assessments

Safety assessments are specified below with Section 1.3 Schedule of Activities detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to Section 8.6.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

8.4.1 Physical examinations

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

Body mass index (BMI) will be calculated using the following formula:

- BMI = Body weight (kg) / [Height (m)]^2

The Screening Visit height measurement will be used for BMI calculations throughout the study.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.

8.4.2 Vital signs

Vital signs will include the collection of body temperature (recorded in °C), blood pressure (BP) and pulse measurements.

Vital signs should be measured in sitting position whenever possible and measured in supine position if this is not possible especially early after surgery. After the participant has been sitting

for 3 minutes, with back supported and both feet placed on the floor, or just in supine position, systolic and diastolic BP will be measured using an automated validated device, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

If vital signs are at screening (see Inclusion Criteria of the protocol for details), two additional readings can be obtained, so that up to three consecutive assessments are made, with the participant seated quietly for approximately five minutes preceding each repeat assessment. The last reading must be within the ranges provided in the eligibility criteria in order for the participant to qualify.

In case of repeated vital assessments, the eCRF should contain the qualifying results.

8.4.3 Electrocardiograms

The Fridericia QT correction formula (QTcF) must be used for clinical decisions, e.g., at the Screening visit to assess eligibility. The Investigator must calculate QTcF if it is not auto--calculated by the ECG machine.

ECGs will be locally collected and evaluated. Interpretation of the tracing must be made by a qualified physician and documented on the appropriate CRF. Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the appropriate CRF. Clinically significant findings must be discussed with Novartis prior to enrolling the participant in the study. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

The original ECGs and a certified copy on non-heat sensitive paper, appropriately signed, must be archived at the study site.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the Investigator at any time during the study as clinically indicated. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding.

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate.

8.4.4 Oxygen saturation

CCI [redacted]

8.4.5 Clinical safety laboratory tests

Local laboratories will be used for analysis of all safety specimens collected (see Table 8-4).

As per Section 4.5, during a public health emergency as declared by local or regional authorities' i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site for protocol-specified safety lab assessments, an alternative lab (local) collection site may be used.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

In the case where a laboratory range is not specified by the protocol, but a value is outside the reference range for the laboratory at screening and, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator (in consultation with Novartis) and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to randomization.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e. result was/was not clinically significant and/or medically relevant) in allowing or disallowing the participant to continue in the study.

Fresh spot urine should be collected for urine assessments, e.g., urinalysis, CCI [redacted]. For patients with a urine catheter in place, the fresh urine should be obtained from the catheter sampling port. For patients without a catheter, a mid-stream (spot) urine should be collected for the sample (first morning void should be avoided).

Table 8-4 Local Laboratory evaluations

Test Category	Test Name
Full Hematology	Erythrocytes, Erythrocyte indices (MCH - Mean Corpuscular Hemoglobin, MCHC - Mean Corpuscular Hemoglobin Concentration, MCV - Mean Corpuscular Volume, Erythrocyte Morphology*), Hematocrit, Hemoglobin, Free Heme*, Platelets, Platelet indices (Platelet clumps count*, MPV - Mean Platelet Volume*), Leukocytes, Leukocyte Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Band Neutrophils)
Limited Hematology	Leucocytes, Erythrocytes, Platelets, Hematocrit, Hemoglobin
Full Clinical Chemistry	Albumin, Alkaline phosphatase (ALP), Alanine Transaminase (ALT), Amylase (total), Aspartate Transaminase (AST), Bicarbonate (from venous blood), Total Bilirubin, Direct Bilirubin (conjugated), Indirect Bilirubin (unconjugated), Calcium, Chloride, Creatine Kinase (CK), Gamma-glutamyl-transferase (GGT), *Glutamate-dehydrogenase (GLDH), Glucose (fasting or non-fasting**), Lactate dehydrogenase (LDH), Lipase, Magnesium, Phosphate, Potassium, Sodium, Total Protein, Urea Nitrogen (BUN or Urea), Uric Acid, N-terminal pro b-type natriuretic peptide (NT-proBNP#, High-sensitivity C-reactive Protein (hs-CRP)#, high-sensitivity cardiac troponin# (preferentially I (hs-cTnI), but T can be performed if I is not available)
Limited Clinical Chemistry	ALT, AST, Bilirubin total, BUN, hs-CRP#, hs-CTnI (hf-CTnT)#, LDH, NT-proBNP#

Test Category	Test Name
Lipid Panel	HDL Cholesterol, LDL Cholesterol, Total Cholesterol, Triglycerides
CCI	
Urine Chemistry	Urine albumin, urine creatinine, urine protein, urine albumin-creatinine ratio (UACR), urine albumin-protein ratio (UPCR)
*Urine microscopy/sediment (automatic or manual)	Bacteria, Casts (RTEC - Renal Epithelial Cell Casts, GC – Granular Casts, HC – Hyaline Casts, Erythrocyte Casts, - Leucocyte Casts)
Urine dipstick	Macroscopic Panel: Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes (leucocyte esterase), Nitrite, pH, Protein, Specific Gravity, Urobilinogen
CCI	
Hepatitis testing	HBV or HBC serology tests
Liver Event Testing and Liver Follow-Up Testing	Albumin, ALP, ALT, AST, CK, GGT, GLDH, INR, PT, and Total Bilirubin (TBIL), Test for hemolysis (haptoglobin, reticulocytes, unconjugated [indirect] bilirubin. These tests are in addition to routine testing, to be performed only in follow-up to safety events when indicated in Section 10.5 Liver safety monitoring
Pregnancy Test	Serum pregnancy test Urine pregnancy test Confirmatory serum pregnancy required in case of positive urine pregnancy test

*To be performed if the test is available at the local lab.

** Type (fasting/non-fasting) to remain consistent throughout study

In case tests are not available at the local lab, discuss with Novartis regarding analysis of these safety BM parameters by Central Lab.

8.4.6 Pregnancy testing

All pre-menopausal women who are not surgically sterile will have pregnancy testing performed at the timepoint specified in the assessment schedule (see Section 1.3). Additional pregnancy testing might be performed if requested by local requirements.

CCI [redacted]

Assessments of fertility

A woman is considered of childbearing potential from menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

In absence of the medical documentation confirming permanent sterilization, or if the post-menopausal status is not clear, the investigator should use their medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

8.4.7 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population.

Most patients planned for cardiac surgery are at higher risk for thrombotic events and are therefore already under treatment with CCI [redacted]. As per guidance of professional societies, anti-platelets are either continued during surgery (aspirin) or discontinued and quickly re-started after surgery (P2Y12 inhibitors). In addition, anti-coagulants are frequently switched to heparin for the peri-operative period, and heparin is used to prevent clots in circuits during CPB use. Bleeding/Coagulation parameters will be assessed frequently before, during, and after surgery to ensure monitoring of bleeding risk and to allow timely intervention with protamine sulfate, blood or thrombocytes.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Clinician reported outcomes (ClinRO)

CCI [redacted]

8.5.2 Surgery related information

Collection of surgery parameters

Date of surgery, type of surgery, start/end time of surgical intervention on Day 1 will be collected.

Cardiopulmonary bypass information

CCI [redacted]

Vasoactive agents during surgery

CCI [redacted]

8.5.3 Collection of mechanical ventilation information

CCI [redacted]

8.5.4 Information on renal replacement therapy

In case a subject receives renal replacement therapy, information will be collected in the CRF, such as date, duration, method of dialysis and number of sessions.

8.5.5 Information on hospitalization

The following information will be collected on hospitalization:

- Duration of ICU stay after the cardiac surgery in days (date of admission to ICU and date of transfer to regular hospital floor)
- Duration of overall hospitalization after cardiac surgery in days (date of cardiac surgery and date of discharge from the hospital)
- Rehospitalization: record date of any new admission (occurring up to Day 90) and date of discharge

8.5.6 CCI [redacted]

CCI [redacted]

8.5.7 Fluid Balance, urine output, blood loss

Collection intervals for urine output, fluid balance and blood loss are outlined in the assessment schedule (see Table 1-2) and in Table 10-5.

Fluid balance

Fluid balance is the difference between the overall fluid input, e.g., oral liquid foods, beverages and i.v. fluids (including blood transfusions and i.v. medications), and the sum of all bodily fluid losses (e.g., perspiration, urination, loose stools, vomitus, drainage from surgical tubes, blood), and will be recorded for the intervals outlined in the assessment schedule.

Urine output

Urine output as also necessary for fluid balance will be calculated from collection bag(s) if urine catheter still in place, and by measured collections following removal of the catheter.

Blood loss

Estimated blood loss (e.g., from open wounds, drainage, wound dressings) is to be recorded and reported in the CRF.

Please consider if any blood loss meets the definition of an adverse event and report accordingly, as outlined in Section 8.6.

8.5.8 CCI

CCI

8.6 Adverse events (AEs), serious adverse events (SAEs), and other safety reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 8.6.

AEs will be reported by the participant.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 8.6.3.

8.6.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The Investigator has the responsibility for managing the safety of individual participants and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial-related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 8.6.2):

1. CCI [redacted] (version 5 or higher).

If CCI [redacted] grading does not exist for an adverse event, use 1=mild; 2=moderate, 3=severe; and 4=life threatening. CCI [redacted] grade 5 (death) is not used, but is collected in other eCRF (e.g., Study Completion, Death/Survival).

2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates or ongoing) and the outcome must be reported
4. Whether it constitutes a SAE (see Section 8.6.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/permanently discontinued

6. Its outcome

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued until last study visit.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be not recovered/not resolved (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease.

8.6.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect, fetal death or a congenital abnormality or birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the participant’s general condition

- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

- is medically significant, e.g., defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

All reports of intentional misuse and abuse of the product are also considered serious adverse events irrespective of whether a clinical event has occurred.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

8.6.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until last study visit must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site. Information about all SAEs is collected and recorded on the Electronic Serious Adverse Event (eSAE) or Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

Event common in the participant population under study: Investigators will report AEs or SAEs that are commonly seen in the study population, but they will not be unblinded and will not be reported as Suspected Unexpected Serious Adverse Reaction (SUSAR) to regulatory agencies, ECs, or investigators during the study. In clinical trials evaluating treatments for high morbidity and/or high mortality disease states, SAEs that are known consequences of the underlying disease or condition under investigation, or events common in the study population, are anticipated to occur with some frequency during the course of the study, regardless of drug exposure. While the investigator must still report all SAEs, SUSARS considered consistent with the following SAE Preferred Terms (PT) will not be unblinded and reported in an expedited timeframe to regulatory agencies, ECs or investigators during the course of the study. These events will be presented in the clinical study report at the end of the study: acute kidney injury (PT)

If specifically requested by a local Health Authority (HA), pre-specified SAEs that also meet the criteria for SUSARs will be expedited to this HA as blinded reports. Investigator Notification (IN) will not be issued for these events.

OR

Pre-specified SAEs commonly observed in the study population that occur in patients under the jurisdiction of the requesting Health Authority will be expedited to the Health Authority as unblinded reports; INs will be issued for these events.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the Investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the Investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with *EU Guidance 2011/C 172/01* or as per national regulatory requirements in participating countries.

Any SAEs experienced after the last study visit should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

Treatment-emergent elevations in AST or ALT (>3x ULN) in combination with total bilirubin >2x ULN or jaundice in the absence of cholestasis (defined as ALP <2 ULN) or other causes of hyperbilirubinemia can be an indicator of severe drug induced liver injury (Hy's Law). For this reason, a potential Hy's Law case requires expedited reporting, and will be handled as a serious unexpected adverse event (assessing it as medically significant in the absence of any other seriousness criteria). It must be reported as an SAE to the sponsor promptly (i.e., even before all other possible causes of liver injury have been excluded). Reporting should include all available information, especially that needed for evaluating the diagnosis, severity and likelihood that the study treatment caused the reaction. For patient monitoring and to better understand potential etiologies, the investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

8.6.4 Pregnancy

Since TIN816 has not been tested in reproductive toxicity studies to date, the teratogenicity potential of TIN816 is not known. Therefore, if a female trial participant becomes pregnant, the study treatment should be stopped, if still possible, and the pregnancy consent form should be

presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence.

Details of all pregnancies in female participants will be collected after the start of study treatment and until the Day 90 visit.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

Any post study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to Novartis as described in Section 8.6.3. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the Investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

8.6.5 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable.

8.6.6 Adverse events of special interest

CCI

8.7 CCI

CCI

[redacted]

8.7.1 CCI

CCI

[redacted]

CCI

8.8 CCI

CCI

8.9 Immunogenicity assessments

Immunogenicity (IG, production of anti-TIN816 antibodies) serum samples will be obtained and evaluated in all participants at all dose levels including the placebo group as defined in the assessment schedule (Section 1.3). Unscheduled ADA samples may be collected in case of a safety event (Section 8.4) that is potentially immunogenicity related. In case of suspected allergic hypersensitivity, the participant should return to the site and a sample to assess immunogenicity will be collected. Additionally, serum samples should be collected at the final visit from participants who discontinued study treatment or were withdrawn from the study. Details on immunogenicity serum sample collection, numbering, processing and shipment are provided in the Laboratory Manual.

Immunogenicity will be evaluated in serum by a validated three-tiered ligand binding assay approach (MSD bridging assay), details will be outlined in the method validation report.

All samples will be screened for potential anti-TIN816 antibodies. Any positive screen result is confirmed using a confirmatory assay where sample screening signal suppression upon addition of drug in excess is investigated. If a sample is confirmed positive for the presence of anti-TIN816 antibodies it will be further analyzed using a titration assay.

CCI [redacted]

8.9.1 Immunogenicity blood sample collection and handling

Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing, and shipment.

8.9.2 Immunogenicity analytical method(s)

A validated ligand binding assay will be used for the detection of anti-TIN816 antibodies, thereby applying a 3-tired approach. All samples collected for detection of anti-TIN816 antibodies will also be evaluated for TIN816 serum concentration to enable interpretation of the antibody data. Confirmed immunogenicity positive samples will be titrated CCI [redacted]

The detailed methods for immunogenicity assessment will be described in the Bioanalytical Data Report.

8.10 Health economics OR Medical resource utilization and health economics

Health economics OR Medical resource utilization and health economics parameters are not evaluated in this study.

9 Statistical considerations

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

9.1 Analysis sets

For all analysis sets, participants will be analyzed according to the study treatment(s) received.

The safety analysis set will include all participants that received any study treatment.

CCI [redacted] will include all participants with at least one available valid (i.e. not flagged for exclusion) CCI [redacted], who received TIN816 treatment and with no protocol deviations that impact CCI [redacted].

The PD analysis set will include all participants that received any study treatment and had no protocol deviations with relevant impact on PD data.

The IG analysis set will include all participants with at least one available valid (i.e. not flagged for exclusion) IG concentration measurement, who received any study treatment and with no protocol deviations that impact on IG data.

9.2 Statistical analyses

9.2.1 General considerations

Data from TIN816 treatment groups (CCI mg/kg and CCI mg/kg) will not be pooled for the analyses and will be reported separately.

All inferential analyses will use 1-sided tests, 0.1 significance level and 90% confidence intervals.

CCI

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

9.2.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the Safety set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term by treatment group.

9.2.3 Treatments

The Safety set will be used for the analyses below. Data for study drug administration and concomitant medications and significant non-drug therapies will be listed by treatment group and subject.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system and by treatment group.

Additionally, rescue therapy as well as concomitant anti-histamines and glucocorticoids will be summarized by treatment group.

9.3 Primary endpoint(s)/estimand(s) analysis

The primary aim of the study is to assess the effect of TIN816 on serum creatinine level in high-risk patients undergoing major cardio-vascular surgery, versus placebo. This will be evaluated by comparing the serum creatinine level up to and including Study Day 6 vs baseline. This analysis will be performed on the PD analysis set.

9.3.1 Definition of primary endpoint(s)

The primary endpoint of the study is the ratio of the highest serum creatinine value up to and including Study Day 6 versus baseline.

9.3.2 Statistical model, hypothesis, and method of analysis

The log-transformed ratio of the highest serum creatinine value up to and including Study Day 6 vs baseline will be analyzed by a linear model, including log-transformed baseline serum creatinine value, treatment group, age and baseline eGFR as covariates. The estimated mean and 90% confidence interval of the difference in log-transformed ratios vs baseline between each TIN816 treatment group and placebo will be back-transformed to obtain the geometric mean ratio and corresponding 90% confidence interval, which will be reported along with the corresponding 1-sided p-value.

CCI [redacted]

9.3.3 Handling of intercurrent events of primary estimand

CCI [redacted]

9.3.4 Handling of missing values not related to intercurrent event

CCI [redacted]

9.3.5 Sensitivity analyses

Not Applicable

9.3.6 Supplementary analysis

Not Applicable

9.4 Secondary endpoint(s)/estimand(s) analysis

The secondary objectives of the study are provided in Table 3-1.

9.4.1 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period lasts from the date of first administration of study treatment to 90 days (EOS) after the date of actual administration of any study treatment.

Adverse events

All information obtained on adverse events will be displayed by treatment group and participant.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of blinded treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, and other significant adverse events leading to discontinuation.

The number (and proportion) of participants with adverse events of special interest will be summarized by treatment group.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be summarized by treatment group and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment group and visit/time for raw and change from baseline.

12-lead ECG

PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant during the study. CCI [redacted]

Categorical analysis of QT/QTc interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these participants will be produced by treatment group.

All ECG data will be listed by treatment group, participant, and visit/time; abnormalities will be flagged. All ECG data will be summarized by treatment group and visit/time.

Clinical laboratory evaluations

All laboratory data will be summarized by treatment group, and visit/time.

All laboratory data parameters (hematology, biochemistry and Urinalysis) will be listed by treatment group, participant, and visit/time and if normal ranges are available abnormalities will be flagged.

9.4.2 Acute Kidney Injury Network (AKIN) criteria

Proportion of patients developing AKI as defined by the AKIN (Acute Kidney Injury Network) criteria within 7 days post dose using SCr will be summarized by treatment groups and listed by visit, participant and by treatment group.

9.4.3 Immunogenicity

Immunogenicity results will be listed by treatment group, participant and visit/time. The listing will contain ADA status (negative or positive) and for ADA-positive samples a titer and CCI [redacted]. Participants with one or more treatment emergent ADAs are counted as ADA-positive participants and they will be summarized by treatment group to derive an ADA incidence. CCI [redacted] Visualizations overlaying ADA status including characterizations, CCI [redacted] and potentially efficacy read-outs, may be presented.

9.4.4 Acute Kidney Disease (AKD)

MAKE30 is defined as the proportion of patients developing at least one of the following:

1. death through day 30,
2. initiation for renal replacement therapy through day 30, or
3. ≥25% reduction in eGFR from baseline to 30 days after surgery.

MAKE90 is defined as the proportion of patients developing at least one of the following:

1. death through day 90,
2. initiation for renal replacement therapy through day 90, or
3. ≥25% reduction in eGFR from baseline to 90 days after surgery.

Proportion of patients developing the MAKE90 will be summarized by treatment and listened by participant and treatment.

Proportion of patients developing the MAKE30 will be summarized by treatment and listened by participant and treatment.

Similarly, the proportion of patients with occurrence of individual components of MAKE90 and MAKE30 mentioned above will be summarized by treatment and listed by participant and treatment.

9.5 Exploratory endpoint(s)/estimand(s) analysis

9.5.1 CCI

CCI

9.5.2 CCI

CCI

9.5.3 CCI

CCI

Summary statistics will include mean (arithmetic and geometric), standard deviation (SD), CV

CCI

Table 9-1 CCI

CCI

9.6 (Other) Safety analyses

Not applicable.

9.7 Other analyses

Other exploratory endpoints will be presented as appropriately. More details will be provided in the study Statistical Analysis Plan.

9.8 Interim analysis

CCI

[redacted]

9.9 Sample size determination

9.9.1 Primary endpoint(s)

CCI

[redacted]

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, [IDFU], and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments/modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

Signing a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required

Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Inform Novartis immediately if an inspection of the clinical site is requested by a regulatory authority

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC or European Clinical Trial Regulation 536/2014, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

10.1.2 Informed consent process

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional additional research. The Investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant’s agreement to allow any remaining specimens to be used for additional research. Participants who decline to participate in this optional additional research will document this.

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

Information about common side effects already known about the investigational treatment can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant upon obtaining consent and also during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also included:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
- As applicable, Pregnancy Outcomes Reporting Consent for female participants who took study treatment
- CCI [redacted]

The study includes CCI [redacted] component which requires a separate signature if the participant agrees to participate. It is required as part of this protocol that the Investigator presents this option to the participants, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these CCI [redacted] will in no way affect the participant's ability to join the main research study.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

The study includes the option for the participant to have certain study procedures performed off-site by an off-site healthcare professional instead of at the study site, for which a separate signature is required if the participant agrees. It is required as part of this protocol that the Investigator presents this option to the participant, as permitted by national and local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local health authority.

Guidance issued by local regulatory bodies on this aspect prevails and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

10.1.3 Data protection

Participants will be assigned a unique identifier by Novartis. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

10.1.4 Committees structure

10.1.4.1 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site Investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial and safety data, and recommend to Novartis whether to continue, modify, or terminate a trial.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between Novartis and the DMC.

10.1.5 Data quality assurance

Monitoring details describing strategy, including definition of study critical data items and processes (e.g. risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan, contracts.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novartis. No records may be transferred to another location or party without written notification to Novartis.

10.1.5.1 Data collection

Designated Investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the Investigator staff.

The Investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the Investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

10.1.5.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated Investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, randomizations, screen failures, as well as randomization codes and data about all study treatments dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded to those who are blinded in the trial setting and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

10.1.6 Source documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. The Investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant). Definition of what constitutes source data and its origin can be found in the monitoring guidelines.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis / delegated CRO /CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters and provide reports to Novartis clinical teams to assist with trial oversight.

10.1.7 Publication policy

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT or CTIS public website. In addition, after study completion (defined as last participant last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required health authority websites (e.g. Clinicaltrials.gov, EudraCT or CTIS public website, etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial Investigator meetings.

Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

Summary results of primary and secondary endpoints will be disclosed based upon the global Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

10.1.8 Protocol adherence and protocol amendments

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case-by-case basis. Under no circumstances including incidental collection is an Investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the Investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

10.1.8.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

10.2 Appendix 2: Abbreviations and definitions

10.2.1 List of abbreviations

ACCM	American College of Critical Care Medicine
ADA	Anti-Drug Antibodies
ADP	Adenosine diphosphate
AE	Adverse Event
AESI	Adverse Events of Special Interest
AF	Arterial fibrillation
CCI	[redacted]
AKD	Acute kidney disease
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
CCI	[redacted]
AMP	Adenosine monophosphate
aPTT	Activated partial thromboplastin time
ARDS	Acute Respiratory Distress Syndrome
ASA	Acetylsalicylic acid
AST	Aspartate Aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the curve
CCI [redacted]	
BMI	Body Mass Index
CCI [redacted]	
CDS	Core Data Sheet
CHMP	Committee on Human Medicinal Products
CCI	[redacted]
CK	Creatine Kinase
ClinRO	Clinician Reported Outcomes
CLR	Renal clearance
CCI	[redacted]
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization

COA	Clinical Outcome Assessment
CPB	Cardiopulmonary bypass
CPR	Cardiopulmonary resuscitation
CQA	Clinical Quality Assurance
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSA	Cardiac Surgery Associated
CS-AKI	Cardiac Surgery-Associated Acute Kidney Injury
CSR	Clinical study report
CTA	Clinical trial application
CTC	Common Terminology Criteria
CTT	Clinical Trial Team
DBP	Diastolic Blood Pressure
DGF	Delayed Graft Function
DIN	Drug Inducted Nephrotoxicity
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DQF	Data Query Form
DRES	Disease-related events
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
ELISA	Enzyme-linked immunosorbent assay
EOI	End of infusion
EOS	End of study
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
EU	European Union
FDA	Food and Drug Administration
FFP	Fresh frozen plasma
FIH	First in Human
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
GLP	Good laboratory practice
h	Hour
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus

HCP	Host Cell Protein
HCV	Hepatitis C Virus
HED	Human Equivalent Dose
HEOR	Health Economics & Outcomes Research
HIV	Human immunodeficiency virus
HV	Healthy volunteer(s)
IA	Interim analysis
i.v.	intravenous
IABP	Intra-aortic balloon counter-pulsation
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine system
LDH	lactate dehydrogenase
LFT	Liver function test
LPLV	Last patient last visit
LVAD	Left ventricular assist device
MAKE	Major adverse kidney event
CCI	[redacted]
MCS	Mechanical circulatory support
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
CCI	[redacted]
MIDCAB	minimally invasive direct coronary artery bypass
mL	milliliter(s)
MRSD	Standard deviation
CCI	[redacted]
NCDS	Novartis Clinical Data Standards
NOEL	No Observed Adverse Effect Level
NYHA	New York Heart Association
oHCP	off-site Healthcare Professional
PD	Pharmacodynamic(s)
PerfO	Performance Outcomes

CCI	[redacted]
PoC	Proof of Concept
CCI	[redacted]
PPoS	Predictive probability of success
PRO	Patient Reported Outcomes
PSD	Premature Subject Discontinuation
PT	Prothrombin Time
PTT	Partial thromboplastin time
QD	Once a day
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
R Value	ALT/ALP x ULN
RAP	The Report and Analysis Plan
RBC	Red blood cells
REB	Research Ethics Board
RIFLE	Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCr	Serum Creatinine
SD	standard deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SoC	Standard of Care
Society of Critical Care Medicine	SCCM
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAVI	Transcatheter aortic valve implantation
TAVR	Transcatheter aortic valve replacement
TB	Tuberculosis
CCI	[redacted]
ULN	upper limit of normal
ULOQ	Upper limit of quantification
WHO	World Health Organization
WoC	Withdrawal of Consent

10.2.2 Definitions

Acute kidney disease	Subchronic kidney injury longer than 7 days but less than 3 months after AKI with a glomerular filtration rate (GFR) <60 mL/min/1.73m^2, or GFR decrease ≥35% from baseline, or SCr increase ≥1.5 times from baseline
Acute kidney injury	Serum creatinine (SCr) increase ≥1.5 times from baseline within 7 days, or >0.3 mg/dL (25.5 umol/L) increase within 48 hours
Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Adverse event	An unexpected medical problem that happens during treatment with a drug or other therapy. Adverse events may be mild, moderate, or severe, and may be caused by something other than the drug or therapy being given.
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cardiopulmonary Bypass (CBP)	CBP is used to temporarily perform the functions of the heart (circulation of blood) and lungs (gas exchange) during surgical procedures on the heart and great vessels.
Chronic kidney disease	Chronic kidney damage beyond 3 months with a glomerular filtration rate (GFR) <60 mL/min/1.73m^2, or structural kidney damage >3 months
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Concomitant drug	Concomitant drugs are two or more drugs used or given at or almost at the same time.
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based

	applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant
Endpoint	An outcome or event used to objectively measure the effect of a drug or other intervention being studied.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Glomerular Filtration Rate (GFR)	GFR is a measure of how well the kidneys are able to filter waste products
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
In vitro	Describes processes or tests performed or taking place in a test tube, culture dish, or elsewhere outside a living organism.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Investigational Product/ Investigational Medicinal product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference (such as an active comparator) in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Kidney disease improving global outcomes criteria (KDIGO)	Increased creatinine level greater than or equal to 1.5 times the baseline (historical or measured), which is known or presumed to have occurred within the prior seven days. Stage 1: Serum creatinine 1.5–1.9 times baseline or ≥0.3 mg/dl (≥26.5 mmol/l) increase or Urine output <0.5 ml/kg/h for 6–12 hours Stage 2: Serum creatinine 2.0–2.9 times baseline or <0.5 ml/kg/h for ≥12 hours Stage3: Serum creatinine 3.0 times baseline or increase in serum creatinine to ≥4.0 mg/dl (≥353.6 mmol/l) or Initiation of renal replacement therapy or in patients <18 years, decrease in eGFR to

	<35 ml/min per 1.73 m² or Urine output <0.3 ml/kg/h for ≥24 hours or anuria for ≥12 hours
Major adverse kidney event (MAKE)	Clinical outcome defined using the following components: 1) death, 2) initiation of renal replacement therapy, 3) ≥25% reduction in GFR. MAKE is assessed 30 or 90 days after AKI (MAKE30 and MAKE90, respectively)
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study or the participant allocated to an invalid stratification factor
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Off-site healthcare Professional (OHP)	A qualified healthcare professional, such as include those used in the study e.g., Nurse, Phlebotomist, Physician, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e., concomitant or rescue therapy)
Overdose	An excessive and dangerous dose of a drug
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient	An individual with the condition of interest for the study
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Placebo	S substance that has no active ingredient which could cause a therapeutic effect, used as a control in testing new drugs
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.

Randomization number	A unique identifier assigned to each randomized participant
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
Risk, Injury, Failure, Loss and End-stage kidney classification (RIFLE)	RIFLE is an international consensus classification for acute kidney injury. RIFLE defines three grades of increasing severity of acute kidney injury – risk (class R), injury (class I) and failure (class F) – and two outcome classes (loss and end-stage kidney disease)
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Standard of Care (SOC)	Treatment that is accepted by medical experts as a proper treatment for a certain type of disease and that is widely used by healthcare professionals
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of consent	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or biological samples AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.
Withdrawal of study consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

10.3 Appendix 3: Clinical laboratory tests

10.3.1 Clinically notable laboratory values and vital signs

Table 10-1 Clinically notable laboratory values

Parameter	Conventional Alert Value	Conventional Units	SI Alert Value	SI Units
Hematology				
Red Blood Cell Count	>50% increase, >30% decrease	$\times 10E^6/\mu L$	>50% increase, >30% decrease	$\times 10E^{12}/L$
Hemoglobin	>50% increase, 30% decrease, or any value <7	g/dL	>50% increase, >30% decrease, or any value <70	g/L
Hematocrit	>50% increase, >30% decrease	%	>50% increase, >30% decrease	L/L
White Blood Cell Count	>50% increase, >50% decrease	$\times 10E^3/\mu L$	>50% increase, >50% decrease	$\times 10E^9/L$
Platelet Count	>75% increase, >50% decrease	$\times 10E^3/\mu L$	>75% increase, >50% decrease	$\times 10E^9/L$
Chemistry				
BUN	>50% increase	mg/dL	>50% increase	mmol/L
Creatinine	>50% increase	mg/dL	>50% increase	µmol/L
Albumin	<2	g/dL	<20	g/L
Glucose	>50% increase, >50% decrease, or any value <60	mg/dL	>50% increase, >50% decrease, or any value <3.3	mmol/L
Total Bilirubin	>100% increase	mg/dL	>100% increase	µmol/L
CPK	>300% increase	U/L	>300% increase	U/L
AST (SGOT)	>150% increase	U/L	>150% increase	U/L
ALT (SGPT)	>150% increase	U/L	>150% increase	U/L
Alkaline phosphatase	>100% increase	U/L	>100% increase	U/L
Sodium	>5% increase, or any value >150	mEq/L	>5% increase, or any value >150	mmol/L
Potassium	>20% increase, >20% decrease, or any value >5.3	mEq/L	>20% increase, >20% decrease, or any value >5.3	mmol/L

Parameter	Conventional Alert Value	Conventional Units	SI Alert Value	SI Units
Chloride	>10% increase, >10% decrease	mEq/L	>10% increase, >10% decrease	mmol/L
Calcium	>10% increase, >10% decrease	mg/dL	>10% increase, >10% decrease	mmol/L
Uric Acid	>50% increase	mg/dL	>50% increase	mmol/L

10.4 Appendix 4: Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the time points indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Study infographic: AKI Infographic
- Study start and study end Thank You Cards
- Plain language trial summary - after CSR publication
- Individual study results - after CSR publication

10.5 Appendix 5: Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 10-2 in Appendix 5 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 10-2 should be followed up by the Investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 10-3 and Table 10-4. Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

- These liver chemistry repeats should be performed using the local laboratory used by the site. Repeated laboratory test results must be reported as appropriate.
- If the initial elevation is confirmed, close observation of the participant will be initiated.
- Hospitalization of the participant if appropriate.
- Causality assessment of the liver event.
- Thorough follow-up of the liver event should include.
    - These investigations can include based on Investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Exclusion of underlying liver disease, as specified in Table 10-2.
- Imaging such as abdominal US, CT or MRI, as appropriate.
- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

10.5.1 Liver event and laboratory trigger definitions & follow-up requirements

Table 10-2 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers: If ALT, AST and total bilirubin normal at baseline:	ALT or AST > 5 × ULN ALP > 2 × ULN (in the absence of known bone pathology) Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) ALT or AST > 3 × ULN and INR > 1.5 Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) Any clinical event of jaundice (or equivalent term) ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia Any adverse event potentially indicative of a liver toxicity
If ALT or AST abnormal at baseline:	ALT or AST > 3x baseline AND > 5x ULN

Table 10-3 Follow up requirements for liver laboratory triggers - ALT, AST, TBL

ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:			
If normal at baseline: ALT > 5 x ULN for more than two weeks OR ALT > 8 x ULN	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **No change to study treatment** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin and CK in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies.
If elevated at baseline: ALT > 3 x baseline AND > 5x ULN for more than two weeks OR ALT ≥ 5x baseline AND ≥ 8x ULN			
ALT increase with bilirubin increase:			
If normal at baseline: ALT > 3 x ULN	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
If elevated at baseline: ALT > 2 x baseline AND >3x ULN			
If normal at baseline: ALT > 3 x ULN	Normal or elevated*	Severe fatigue, nausea, vomiting, right upper quadrant pain*	
If elevated at baseline: ALT > 2 x baseline AND > 3x ULN			
* This situation suggests liver injury based on (i) elevation of ALT, and (ii) the presence of symptoms of liver injury. Even if bilirubin is normal, the presence of liver symptoms indicates potentially severe liver injury.			

Table 10-4 Follow up requirements for liver laboratory triggers - Isolated Hyperbilirubinemia

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	• Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48-72 hours • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. concomittant medication, medical history, laboratory and imaging investigations) in the appropriate CRF	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	• Hospitalize the participant • Establish causality • Record the AE and contributing factors(e.g. concomittant medication, medical history, laboratory and imaging investigations) in the appropriate CRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion)
Any AE potentially indicative of a liver toxicity	• Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. concomittant medication, medical history, laboratory and imaging investigations) in the appropriate CRF	Investigator discretion

Based on Investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

10.6 Appendix 6: CCI [redacted]

CCI [redacted]

11 References

References are available upon request

CCI [redacted]

CCI [redacted]

Barry R, James MT (2015) Guidelines for Classification of Acute Kidney Diseases and Disorders. Nephron; 131(4):221-6.

Basile DP, Anderson MD, Sutton TA (2012) Pathophysiology of acute kidney injury. Compr Physiol; 2(2):1303-53.

CCI [redacted]

Billings FT, Shaw AD (2014) Clinical trial endpoints in acute kidney injury. Nephron Clin Pract; 127(1-4):89-93.

Bugelski PJ, Treacy G (2004) Predictive power of preclinical studies in animals for the immunogenicity of recombinant therapeutic proteins in humans. Curr Opin Mol Ther; 6(1):10-6.

Chertow GM, Levy EM, Hammermeister KE, et al (1998) Independent association between acute renal failure and mortality following cardiac surgery. Am J Med; 104(4):343-8.

Colgan SP, Eltzschig HK (2012) Adenosine and hypoxia-inducible factor signaling in intestinal injury and recovery. Annu Rev Physiol; 74:153-75.

CCI [redacted]

Eckle T, Faigle M, Grenz A, et al (2008) A2B adenosine receptor dampens hypoxia-induced vascular leak. Blood; 111(4):2024-35.

Eckle T, Hartmann K, Bonney S, et al (2012) Adora2b-elicited Per2 stabilization promotes a HIF-dependent metabolic switch crucial for myocardial adaptation to ischemia. Nat Med; 18(5):774-82.

Eltzschig HK, Carmeliet P (2011) Hypoxia and inflammation. N Engl J Med; 364(7):656-65.

Eltzschig HK, Eckle T (2011) Ischemia and reperfusion--from mechanism to translation. Nat Med; 17(11):1391-401.

CCI [redacted]

CCI [redacted]

CCI [redacted]

Grenz A, Osswald H, Eckle T, et al (2008) The reno-vascular A2B adenosine receptor protects the kidney from ischemia. PLoS Med; 5(6):e137.

Gulbransen BD, Bashashati M, Hirota SA, et al (2012) Activation of neuronal P2X7 receptor-pannexin-1 mediates death of enteric neurons during colitis. Nat Med; 18(4):600-4.

Hoste EAJ, Kellum JA, Selby NM, et al (2018) Global epidemiology and outcomes of acute kidney injury. Nat Rev Nephrol; 14(10):607-625.

Idzko M, Hammad H, van Nimwegen M, et al (2007) Extracellular ATP triggers and maintains asthmatic airway inflammation by activating dendritic cells. Nat Med; 13(8):913-9.

Kellum JA, Lameire N, KDIGO AKI Guideline Work Group (2013) Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care; 17(1):204.

CCI [redacted]

Khosla N, Soroko SB, Chertow GM, et al (2009) Preexisting chronic kidney disease: a potential for improved outcomes from acute kidney injury. Clin J Am Soc Nephrol; 4(12):1914-9.

Mehta TA, Clarke JM (2007) Regarding "Glomerular filtration rate after left renal vein division and reconstruction during infrarenal aortic aneurysm repair". J Vasc Surg; 46(5):1085; author reply 1085.

CCI [redacted]

Peters E, Heuberger JAAC, Tiessen R, et al (2016) Pharmacokinetic Modeling and Dose Selection in a Randomized, Double-Blind, Placebo-Controlled Trial of a Human Recombinant Alkaline Phosphatase in Healthy Volunteers. Clin Pharmacokinet; 55(10):1227-37.

Pottel H, Delanaye P, Weekers L, et al (2017) Age-dependent reference intervals for estimated and measured glomerular filtration rate. Clin Kidney J; 10(4):545-51.

CCI [redacted]

Ronco C, Bellomo R, Kellum JA (2019) Acute kidney injury. Lancet; 394(10212):1949-64.

Rosenberger P, Schwab JM, Mirakaj V, et al (2009) Hypoxia-inducible factor-dependent induction of netrin-1 dampens inflammation caused by hypoxia. Nat Immunol; 10(2):195-202.

Rosner MH, Okusa MD (2006) Acute kidney injury associated with cardiac surgery. Clin J Am Soc Nephrol; 1(1):19-32.

CCI [redacted]

Tetro N, Moushaev S, Rubinchik-Stern M, et al (2018) The Placental Barrier: the Gate and the Fate in Drug Distribution. Pharm Res; 35(4):71.

CCI [redacted]

CCI [redacted]

CCI [redacted]

Waikar SS, Liu KD, Chertow GM (2008) Diagnosis, epidemiology and outcomes of acute kidney injury. Clin J Am Soc Nephrol; 3(3):844-61.

Zanardo G, Michielon P, Paccagnella A, et al (1994) Acute renal failure in the patient undergoing cardiac operation. Prevalence, mortality rate, and main risk factors. J Thorac Cardiovasc Surg; 107(6):1489-95.