NOVARTIS

Novartis Research and Development

**Clinical Trial Protocol Title:**

# A multicenter, participant and investigator-blinded, randomized, placebo-controlled Phase 2a study to investigate the pharmacokinetics, pharmacodynamics, safety and tolerability of TIN816 in the treatment of patients with sepsis-associated acute kidney injury

**Clinical Trial Protocol Number:** CTIN816B12201 / NCT05507437

**Version Number:** v00 (Original Protocol)

**Compound:** TIN816

**Brief Title:** A multicenter study to evaluate pharmacokinetics, safety and tolerability of TIN816 in patients with sepsis-associated acute kidney injury.

**Study Phase:** IIa

**Sponsor Name:** Novartis

**Regulatory Agency Identifier Number(s):** EUDRACT Number: 2022-000887-23

**Approval Date:** 03-Jun-2022 (content final)

## Table of contents

## List of tables



## List of figures

# 1 Protocol summary

## 1.1 Summary

### Protocol Title:

A multicenter, participant and investigator-blinded, randomized, placebo-controlled phase 2a study to investigate the pharmacokinetics, pharmacodynamics, safety and tolerability of TIN816 in the treatment of patients with sepsis-associated acute kidney injury

### Brief Title:

A multicenter study to evaluate pharmacokinetics, safety and tolerability of TIN816 in patients with sepsis-associated acute kidney injury

### Purpose

This is a phase 2a study to characterize pharmacokinetic (PK)/pharmacodynamic (PD) profile and to evaluate safety and efficacy of TIN816 in hospitalized adult participants in an intensive care setting with a diagnosis of sepsis-associated acute kidney injury (SA-AKI).

### Study Indication /Medical Condition:

Sepsis-associated acute kidney injury

### Treatment type

A single dose of investigational study treatment TIN816 will be administered via an IV infusion.

### Study type

Interventional phase 2a study to evaluate PK/PD, safety and efficacy of TIN816

### Objectives, Endpoints, and Estimands:

**Table 1-1 Objectives and related endpoints**

| Objectives | Endpoints |
|---|---|
| Primary | |
| To assess PK of TIN816 with a single dose of IV infusion | TIN816 concentrations in serum<br>PK parameters: $C_{max}$, $T_{max}$, $T_{1/2}$, Cl, $V_z$, $AUC_{last}$ and $AUC_{inf}$ of TIN816 (See Section 10.2.2 for definitions) |
| Secondary | |
| To assess safety and tolerability of TIN816 vs placebo | Safety evaluations (including adverse events/serious adverse events, safety laboratory parameters, vital signs and immunogenicity) |

## Trial Design:

This is a multicenter, participant and investigator-blinded, randomized, placebo-controlled study to characterize PK/PD profile and to evaluate the safety and the efficacy of TIN816 in hospitalized adult participants with diagnosis of sepsis and acute kidney injury (AKI). Approximately 20 participants will be randomized in the study. The study consists of a screening period (up to 48 hours), treatment period (Day 1), and post-treatment period (Day 2 to 90).

An interim analysis (IA) is planned when approximately 8 participants complete Day 14 visit. The study will continue without modification if a similar PK profile of TIN816 compared to the one in the healthy volunteers (HV) is confirmed. Otherwise, an adaptive design would be implemented with options to add up to two additional arms testing a higher dose, multiple bolus doses, extended infusion dosing regimens or combination of bolus dose and extended infusion.

The adaptive design will be supported by modeling and simulation with data from the preclinical studies, first in human (FIH) study and the IA of the current PK/PD study. Patient recruitment will continue during the IA to enroll up to a cap of 12 patients. In the circumstance that the first IA does not provide sufficient PK data to support phase 2b, an additional IA will be added when all 20 patients complete Day 14 visit.

## Brief Summary:

Approximately 90% of sepsis is caused by bacterial infection and 40-60% of septic patients experience sepsis-associated acute kidney injury (SA-AKI). In the recent decades, the growing knowledge about the physiopathology of sepsis and AKI has suggested that adenosine triphosphate (ATP), adenosine diphosphate (ADP) and adenosine play an essential role as extracellular signaling molecules in both sepsis and AKI. Several lines of evidence have shown the potential benefits of the conversion of extracellular ATP to adenosine in treating sepsis and the related organ injury.

TIN816 is an engineered, highly effective, soluble, and stabilized human recombinant CD39 enzyme. The enzyme hydrolyzes extracellular ATP and ADP to adenosine monophosphate (AMP). TIN816 has been proven beneficial in preclinical models of acute organ injuries. TIN816 has also been studied in healthy volunteers. To date, 32 healthy participants have received either TIN816 (N=24) or placebo (N=8) in the ongoing phase 1 healthy volunteer study (CTIN816A02101). The study results showed that TIN816 was safe and well tolerated. Overall, based on the existing evidence of potential benefits by conversion of extracellular ATP to adenosine in treating sepsis and the related organ injuries, the accumulated data of TIN816 from the preclinical studies; as well as, the FIH study, it is anticipated that therapeutic application of TIN816 will have potent anti-inflammatory and tissue-protective activity in patients suffering from SA-AKI.

This study is designed to assess the PK/PD profile of TIN816 in the participants with SA-AKI. In addition, this study will evaluate safety, tolerability and efficacy of TIN816. Screening will take place during hospitalization in intensive care unit (ICU) or intermediate/high dependency unit (HDU) where potential participants will undergo screening to assess the presence of sepsis and AKI based on sequential organ failure assessment (SOFA) and kidney disease improving global outcomes (KDIGO) scores. A total of approximately 20 participants will be randomized

in the study. Participants will be randomly assigned to receive either TIN816 at 2 milligram (mg)/kg or placebo using a 3:1 allocation ratio (TIN816:placebo). A single dose of the study treatment will be administered via 2-hour intravenous infusion (IV) at the randomization visit in a participant and investigator-blinded fashion. The study treatment must be administered within 48 hours after SA-AKI is first diagnosed, but ideally as soon as possible. PK sample will be taken prior to the study treatment, immediately after the completion of IV infusion at Day 1 and also at Day 2, 3, 5, 8, 14, 30, 60 and 90. All participants will be followed-up for a total duration of 90 days. Safety will be monitored during the entire course of the study; all adverse event (AE) and serious adverse event (SAE) will be collected and reported following standard process and local regulations. [redacted] The data generated from this study will be used to support further development of TIN816 for the indication of SA-AKI.

### Treatment of interest

TIN816 (human recombinant CD39 enzyme)

### Number of Participants:

Approximately 20 participants will be recruited in the study.

### Key Inclusion criteria

- ≥ 18 and ≤ 85 years of age.
- Admitted to ICU or intermediate/HDU.
- Diagnosis of sepsis according to criteria defined by The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) based on:
  - Suspected or confirmed infection
  - SOFA score of 2 or more (excluding renal component)
- Diagnosis of AKI Stage 1 or greater per the following criterion:
  - An absolute increase in serum or plasma creatinine (CR) by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours or presumed to have occurred in the previous 48 hours as compared to the reference creatinine baseline as below:
  - For hospital-acquired AKI, a stable serum creatinine obtained in the hospital prior to AKI should be used as reference baseline, otherwise, baseline serum creatinine in the following order of preference:
    1. Median value within 3 months of the hospital admission. If not available:
    2. Median value between 3 and 6 months prior to hospital admission. If not available:
    3. At hospital admission.

### Key Exclusion criteria

- History of chronic kidney disease (CKD) with a documented estimated glomerular filtration rate (eGFR) < 45 ml/min prior to development of AKI.

- Receiving renal replacement therapy (RRT) or a decision has been made to initiate RRT within 24 hours of admission.
- Presence of AKI for a period longer than 48 hours prior to study drug administration as suggested by clinical manifestations, e.g., prolonged oliguria or severe renal dysfunction (eg., serum creatinine > 4 mg/dL) on admission without a history of CKD.
- Evidence of recovery from AKI based on the investigator's clinical judgement prior to randomization.
- Documented (biopsy proven) or suspected history of acute or sub-acute kidney diseases such as rapidly progressive glomerular nephritis (RPGN) and acute interstitial nephritis (AIN).
- Patients who are on dual antiplatelet therapy.
- Patients who are thrombocytopenic at screening (Platelet count <100,000 microliter) or other high risk for bleeding in the opinion of the investigator.

### Treatment Groups:

Approximately 20 participants will be assigned to one of the following two treatment arms/groups in a ratio of 3:1; TIN816: placebo

- TIN816: 2 mg/kg; intravenous infusion; one-time administration
- Placebo: intravenous infusion; one-time administration

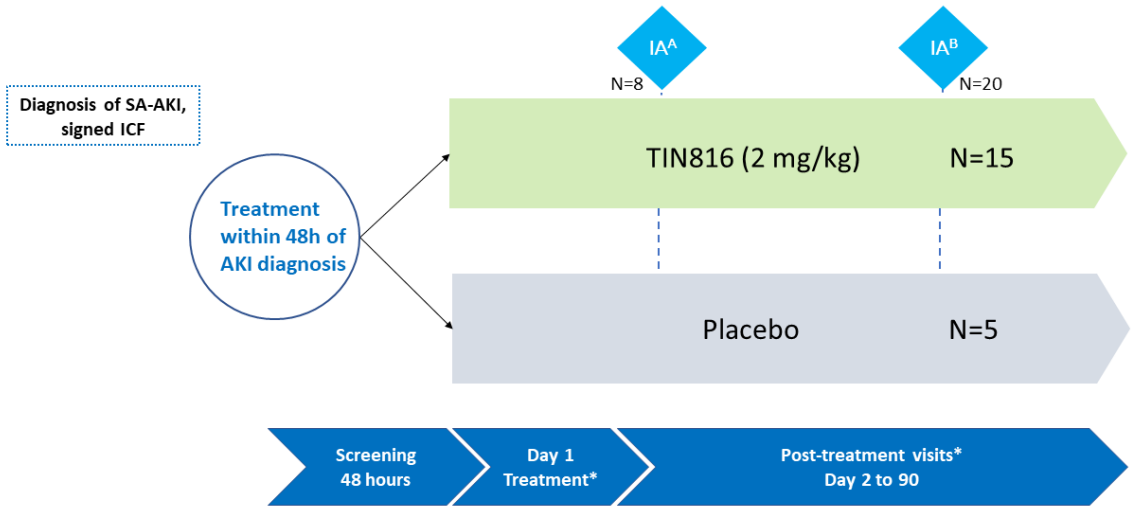
### Data Monitoring/Other Committee: No

### Key words

Sepsis, acute kidney injury, anti-inflammatory, immunosuppression

## 1.2 Schema

**Figure 1-1 Study Design**




[A] interim analysis (IA) based on 8 patients with 14-day data collected from baseline
[B] conditional additional interim analysis (IA) based on 20 patients with 14-day data collected from baseline
* participant-investigator blinded

## 1.3 Schedule of activities (SoA)

The SoA lists all of 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. Unscheduled visits may occur at any time for adverse event/serious adverse event follow-up and/or to repeat any laboratory assessment due to safety and/or technical reasons.

Participants who discontinue from the study should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of 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 electronic case report forms (eCRF).

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 Visits | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Name | Screening | Day 1[2] | | | Day 2 | Day 3 | Day 5 | Day 8 | Day 11 | Day 14 | Day 21 | Day 30 | Day 60 | Day 90/End of Study (EOS) |
| Visit Numbers[1] | 1 | 100 | | | 110 | 120 | 130 | 140 | 150 | 160 | 170 | 180 | 190 | 200 |
| Days | -2 to -1 | 1 | | | 2 | 3 | 5 | 8 | 11 | 14 | 21 | 30 | 60 | 90 |
| Time (post-dose) | - | pre-dose[3] | 0H | 2 H (END of the infusion) [3] | - | - | - | - | - | - | - | - | - | - |
| Informed consent | X | | | | | | | | | | | | | |
| Diagnosis of sepsis | X | | | | | | | | | | | | | |
| Diagnosis of AKI/AKI assessments | X | X | | | | | X | | | X | | X | X | X |
| [redacted] | | | | | | | | | | | | | | |
| Inclusion / Exclusion criteria | X | X | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | |
| IRT/Randomization | X | X | | | X | X | X | X | X | X | X | X | X | X |
| Study drug administration | | | X | | | | | | | | | | | |
| Medical history/current medical conditions | X | | | | | | | | | | | | | |
| Alcohol history | X | | | | | | | | | | | | | |
| Smoking history | X | | | | | | | | | | | | | |
| Physical Examination | S | S | | | | | | | | S | | | | S |
| Body Height | X | | | | | | | | | | | | | |
| Body Weight | X | X | | | | | | | | X | | X | X | X |
| Vital Signs | X | X[4] | | X[4] | X | X | X | X | X | X | X | X | X | X |

| **Period** | **Screening** | **Treatment** | | | **Post-treatment Visits** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | **Screening** | **Day 1[2]** | | | **Day 2** | **Day 3** | **Day 5** | **Day 8** | **Day 11** | **Day 14** | **Day 21** | **Day 30** | **Day 60** | **Day 90/End of Study (EOS)** |
| **Visit Numbers[1]** | **1** | **100** | | | **110** | **120** | **130** | **140** | **150** | **160** | **170** | **180** | **190** | **200** |
| **Days** | **-2 to -1** | **1** | | | **2** | **3** | **5** | **8** | **11** | **14** | **21** | **30** | **60** | **90** |
| **Time (post-dose)** | **-** | **pre-dose[3]** | **0H** | **2 H (END of the infusion) [3]** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** |
| Electrocardiogram (ECG) | S | S | | | | | | | | | | | | |
| Pregnancy and assessments of fertility[5] | X | X | | | | | | | | | | X | X | X |
| Clinical Chemistry[6] | X | X | | | | | X | | | X | | X | | X |
| Hematology[6] | X | X | | | | | X | | | X | | X | | X |
| Coagulation Parameters ( PT, INR, PTT, APTT)[6] | X | X | | | | | X | | | X | | X | | X |
| Hepatitis screen[6] | X | | | | | | | | | | | | | |
| Local lab evaluations[6] | X | X | | | X | X | X | X | X | X | X | X | X | X |
| PK blood collection[3,7] | | X[3] | | X[3] | X | X | X | X | | X | | X | X | X |
| [redacted] | | | | | | | | | | | | | | |
| Serum creatinine, Cystatin C[9] | | X | | | X | X | X | X | X | X | X | X | X | X |
| Immunogenicity[7,10] | | X[10] | | | | | | | | X | | X | | X |
| Urinalysis[6] | X | X | | | | X | X | | | X | | X | | X |
| Urine creatinine[7] | | X | | | X | X | X | X | X | X | X | X | X | |
| [redacted] | | | | | | | | | | | | | | |

| **Period** | **Screening** | **Treatment** | | | **Post-treatment Visits** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | **Screening** | **Day 1[2]** | | | **Day 2** | **Day 3** | **Day 5** | **Day 8** | **Day 11** | **Day 14** | **Day 21** | **Day 30** | **Day 60** | **Day 90/End of Study (EOS)** |
| **Visit Numbers[1]** | **1** | **100** | | | **110** | **120** | **130** | **140** | **150** | **160** | **170** | **180** | **190** | **200** |
| **Days** | **-2 to -1** | **1** | | | **2** | **3** | **5** | **8** | **11** | **14** | **21** | **30** | **60** | **90** |
| **Time (post-dose)** | **-** | **pre-dose[3]** | **0H** | **2 H (END of the infusion) [3]** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** |
| Urine volume ( 6 +/1 hours or 24 hours collection) [11] | | X | | | X | X | X | X | X | X | X | X | X | X |
| Creatinine clearance | | X | | | X | X | X | X | X | X | X | X | X | X |
| [redacted] | | | | | | | | | | | | | | |
| APACHE II Score | | X | | | | | | | | | | | | |
| Concomitant medications | X | X | | | X | X | X | X | X | X | X | X | X | X |
| Surgical and Medical Procedures | X | X | | X | X | X | X | X | X | X | X | X | X | X |
| Adverse Events | X | X | | X | X | X | X | X | X | X | X | X | X | X |
| Serious Adverse Events | X | X | | X | X | X | X | X | X | X | X | X | X | X |
| Disposition | X | X | | | | | | | | | | | | X |
| Study completion information[12] | | | | | | | | | | | | | | X |

X Assessment to be recorded in the clinical database or received electronically from a vendor
1 Visit structure given for internal programming purpose only
2 Day 1 = baseline values and treatment
3 Two samples will be collected on Day 1, one sample pre-dose and one sample (post-infusion) immediately after or within 15 minutes after the two hour study drug infusion
4 At Day 1, vital signs will be monitored before and after study drug infusion, and data will be collected at the following timepoints: a) immediately before the administration of the study drug, and b) immediately after the completion of the administration of the study drug, which includes post-dose saline flushing.
5 Pregnancy test to be performed locally and more frequently if required by local regulations.
6 Scheduled assessments (Clinical Chemistry, Hematology, Urinalysis, Coagulation parameters, Hepatitis screen) as well as follow-up safety labs to be analyzed by

| Period | Screening | Treatment | | | Post-treatment Visits | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Name | Screening | Day 1[2] | | | Day 2 | Day 3 | Day 5 | Day 8 | Day 11 | Day 14 | Day 21 | Day 30 | Day 60 | Day 90/End of Study (EOS) |
| Visit Numbers[1] | 1 | 100 | | | 110 | 120 | 130 | 140 | 150 | 160 | 170 | 180 | 190 | 200 |
| Days | -2 to -1 | 1 | | | 2 | 3 | 5 | 8 | 11 | 14 | 21 | 30 | 60 | 90 |
| Time (post-dose) | - | pre-dose[3] | 0H | 2 H (END of the infusion) [3] | - | - | - | - | - | - | - | - | - | - |

local laboratory and results entered in the eCRF
7 Sample will be shipped and analyzed by the sponsor designated laboratory.
[redacted]
9 During hospitalization, one midpoint serum creatinine sample will be collected during the 6 hour +/-1 urine collection. When participants are discharged from the hospital, one serum creatinine sample will be collected at the end of the 24 hour urine collection period. Dedicated blood samples for serum creatinine and Cystatin C will be analyzed by the central laboratory.
10 Sample should be taken at day1 pre-dose before administering the study drug
[redacted]
12 Study Completion information includes Interactive Response Technology (IRT) completion of last visit

# 2 Introduction

## 2.1 Study rationale

The purpose of this study is to assess the pharmacokinetics, pharmacodynamics and safety profile of TIN816 in patients with SA-AKI to support future phase 2 clinical drug development.

## 2.2 Background

During sepsis, a dysregulated host response to infection leads to a life-threatening multi-organ dysfunction. Sepsis is a leading cause of death and a major public health problem that affects millions of patients worldwide every year (Fleischmann et al., 2016, Rudd et al., 2020). In the United States (US) alone, an estimated 1.7 million adults present to hospital each year with sepsis with up to 270,000 deaths resulting (Rhee et al., 2017). An aging population and an increase in underlying comorbidities have led to continuous growth in the incidence of sepsis (Mayr et al., 2014).

Approximately 90% of sepsis is caused by bacterial infection and 40-60% of septic patients experience sepsis-associated acute kidney injury (SA-AKI ) (Liu et al., 2020, Yu et al., 2021). Acute kidney injury (AKI) refers to an abrupt decrease in kidney function, resulting in the retention of urea and other nitrogenous waste products and in the dysregulation of extracellular volume and electrolytes. It is estimated that ~813,000 patients suffer from SA-AKI in the US, ~793,000 in urban China, ~232,000 in Japan and ~79,000 in Germany (Fleischmann-Struzek et al., 2018, Peters et al., 2018, Tian et al., 2019, Imaeda et al., 2021). Development of AKI in patients with sepsis is associated with significantly increased mortality rate of up to 65%, and survivors are at significantly increased risk of developing chronic kidney disease (CKD) and kidney failure, resulting in a significant health and financial burden for both patient and society (Peerapornratana et al., 2019, Chua et al., 2020, Liu et al., 2020).

SA-AKI is a multifactorial syndrome with inflammatory, nephrotoxic, and ischemic insults occurring simultaneously with other pathophysiological responses rapidly leading to kidney impairment. Over the last 30 years, there were a considerable number of potential drug targets and the development of new therapies to treat sepsis and/or AKI. Attempts were primarily focusing on improving hemodynamics, reducing oxidative stress, and blocking hyper-inflammatory response; however, all of which have failed in clinical trials (Cohen et al., 2015, Kellum et al., 2021). As a result, there are currently no specific pharmacological agents available for the treatment of SA-AKI. Management of patients with SA-AKI relies mainly on targeted antibiotics and supportive treatment including fluid resuscitation, vasoactive agents and renal replacement therapy (RRT).

In the recent decades, the growing knowledge about the pathophysiology of sepsis and AKI has suggested that adenosine triphosphate (ATP), adenosine diphosphate (ADP) and adenosine play an essential role as extracellular signaling molecules in sepsis as well as AKI (Burnstock and Verkhratsky, 2010, Menzies et al., 2017, Dwyer, Kishore and Robson, 2020). Extracellular purines can modulate immune responses, balancing inflammatory processes and immunosuppression. Following an infectious insult, immune cells release intracellular ATP toward the extracellular compartment through various mechanisms. In addition, purine

metabolites released from cell death caused by lytic bacterial or viral toxin or the dysregulated host responses further increase extracellular levels of ATP and ADP (Ledderose et al., 2016). Increased levels of extracellular ATP have been detected in the plasma and peritoneum of animals with sepsis (Sumi et al., 2014, Li et al., 2017). Moreover, extracellular ATP levels correlate with lactate levels and APACHE II scores in severely ill patients with burns or multi organ dysfunction due to post-cardiac arrest syndrome (Sumi et al., 2014).

In the extracellular space, ATP and ADP can activate extracellular purine receptors which are classified as P2 receptors. They function as G-protein coupled receptors (P2Y receptors) or as ligand-gated ion channels (P2X receptors). Extracellular ATP induces activation of P2X7 and downstream inflammasome activation, interleukin-18 (IL-18) and interleukin-1 beta (IL-1β) secretion and cell death. In addition, extracellular ATP is vasoactive. In the kidney, ATP is inducing vasoconstriction which can lead to lack of perfusion and no-reflow phenomenon (Guan and Inscho, 2011). In conjunction with the activation of P2Y12 via extracellular ADP leading to platelet activation and thrombosis, it will result in microvascular occlusions and long-lasting damage to the kidney. Specifically, the kidney is largely dependent on maximal perfusion, oxygenation, and nutrition. The unique microvascular system of the kidney and the high metabolic 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), to 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). In summary, treatment approaches to enhance extracellular ATP conversion to adenosine represents a therapeutic strategy to mitigate and dampen acute organ injury in general (Idzko et al., 2007, Colgan and Eltzschig, 2012, Gulbransen et al., 2012).

Several lines of evidence have shown the potential benefits by conversion of extracellular ATP to adenosine in treating sepsis and the related organ injury. In a septic animal model induced by cecal ligation and puncture (CLP), treatment with apyrase, an ATPase that promotes the enzymatic breakdown of extracellular ATP, diminished the concentration of extracellular ATP in peritoneal lavages and significantly reduced mortality (Li et al., 2017). A clinical study conducted with alkaline phosphatase (ALP) in SA-AKI patients showed that AP improved kidney function determined by a composite endpoint of creatinine clearance, requirement for RRT, and duration of RRT (Pickkers et al., 2012). Alkaline phosphatase is an endogenous enzyme that exerts detoxifying effects through dephosphorylation of endotoxins and extracellular ATP. In a relatively larger clinical study in patients with SA-AKI (N=301), results have suggested a potential mortality benefit with treatment of AP compared to placebo even though the study did not meet its primary endpoint in improving short-term kidney function measured by area-under-the time corrected endogenous creatinine clearance from Day 1 to Day 7 (Pickkers et al., 2018).

TIN816 is an engineered, highly effective, soluble, and stabilized human recombinant CD39 enzyme. The enzyme hydrolyzes extracellular ATP and ADP to adenosine monophosphate (AMP), which is a rate limiting step in conversion of extracellular ATP to adenosine. AMP is further catalyzed by the ecto-5'-nucleotidase CD73 to adenosine. The enzymatic activities of CD39 and CD73 play strategic roles in calibrating the duration, magnitude, and chemical nature of purinergic signals delivered to immune cells, driving a shift from an ATP-driven pro-

inflammatory environment to an anti-inflammatory milieu induced by adenosine. It is becoming increasingly appreciated that rebalancing this equilibrium could change the course and outcome of several pathophysiological events, such as SA-AKI.

TIN816 has been investigated extensively in preclinical models. In human whole blood TIN816 dose dependently inhibited ATP/Lipopolysaccharide (LPS)-induced IL-1β secretion as well as ADP induced platelet aggregation. TIN816 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, Anderson and Sutton, 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. Biomarkers of target engagement and proximal pharmacodynamic extracellular ATP and ADP in the urine of animals after AKI were dose-dependently reduced and extracellular AMP and adenosine were dose-dependently increased (Investigator Brochure).

TIN816 has also been studied in healthy volunteers (HV). To date, 32 healthy participants have received either TIN816 (N=24) or placebo (N=8) in the ongoing phase 1 FIH healthy volunteer study (CTIN816A02101). In this study, single IV doses of TIN816 (0.1, 0.3, 1.0 and 2.0 mg/kg) were administered to healthy participants in four cohorts. In each cohort of eight healthy participants, six received the investigational drug (TIN816) and two received matching placebo. The study results showed that TIN816 was safe and well tolerated. The breakdown of adverse events to different doses of TIN816 does not suggest any pattern or increase of the AE incidence associated with higher doses. There was no increased bleeding/clotting time beyond the normal range compared to placebo; there were no immunogenicity findings. The pharmacokinetic results are fully in line with the previously predicted TIN816 serum concentration. The pathway engagement markers demonstrate dose-dependent and reversible inhibition of (i) *ex vivo* ADP-induced platelet aggregation and (ii) *ex vivo* LPS/ATP-induced IL-1β release in TIN816 treated participants (Investigator Brochure).

Overall, based on the existing evidence of potential benefits by conversion of extracellular ATP to adenosine in treating sepsis and the related organ injuries, the accumulated data of TIN816 from the preclinical studies; as well as, the FIH study, it is anticipated that the therapeutic application of TIN816 will have potent anti-inflammatory and tissue-protective activity in patients suffering from SA-AKI. As a result, a small study of TIN816 is proposed in patients with SA-AKI to generate pharmacokinetic (PK) and pharmacodynamic (PD), safety [redacted] in SA-AKI patients to inform the future phase 2b study.

## 2.3 Benefit/Risk assessment

An expanded risk-benefit summary is provided in the TIN816 IB.

### 2.3.1 Benefits

There is currently no approved pharmacological therapy to treat or prevent AKI. Management of patients with SA-AKI relies mainly on anti-microbial therapies and supportive treatment including fluid resuscitation, vasoactive agents and RRT. The potential benefit of TIN816 in SA-AKI to be assessed in this study is anti-inflammation, anti-coagulation and tissue protection

that could lead to improvement of renal function and reduction of mortality. However, all potential benefits are theoretical and need to be confirmed in a large phase 3 study.

### 2.3.2 Risks

TIN816 has been tested in HV with doses up to 2 mg/kg via intravenous infusion. Although there was no safety signal detected in the FIH study, there are potential risks based on its mechanism of action and the findings from the preclinical studies as listed below (refer also to the Investigator's Brochure for details). The risk to participants in this study will be minimized by compliance with the eligibility criteria, close clinical monitoring, early stopping rules, periodic review of the safety data and guidance for the investigators in the Investigator Brochure (IB).

#### 2.3.2.1 Bleeding

TIN816 ability to decrease ADP levels can reduce ADP and thrombin-induced platelet aggregation; and therefore, is linked to a potential risk of increase in bleeding (see Investigator's Brochure). For this reason, standard coagulation tests (including prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), activated partial thromboplastin time (APTT) will be monitored throughout the acute phase of the study. In addition, patients on dual antiplatelet therapy will be excluded from this study given that an increased risk of bleeding following concomitant administration of TIN816 and antiplatelet/anticoagulant agents cannot be excluded. Caution is required when TIN816 is concomitantly administered with anticoagulant agents, and adequate monitoring of respective coagulation parameters is required.

In the ongoing phase 1 study in healthy volunteers, inhibition of ADP-induced platelet aggregation was seen in the ex vivo whole blood aggregometry assay, but was not associated with any changes in coagulation parameters (such as PT, INR, APTT), and bleeding time nor any bleeding AE (see Investigator's Brochure).

#### 2.3.2.2 Perivascular/vascular mineralization

Minimal to mild perivascular/vascular mineralization in kidney, reproductive tract and thyroid were seen in 2- and 4-week minipig toxicology studies at ≥15 mg/kg/q4d.

In the ongoing phase 1 study in healthy volunteers, no changes were observed in kidney function markers (e.g., eGFR) and no abnormalities were seen in urine dipstick parameters (protein, blood, glucose, ketones, bilirubin, urobilinogen, pH, leukocyte esterase, specific gravity). There was no change in cardiovascular parameters (blood pressure, ECG) or joint AE pointing to mineralization. There was no change in serum calcium. Measurement of PPi levels in serum in cohorts 1-4 from the FIH study (where single doses of 0.1, 0.3, 1 and 2 mg/kg TIN816 were given IV) showed a dose dependent and reversible reduction (cleavage) of PPi with maximum effect reached within hours post dose. PPi data in cohorts 1-4 suggest a similar effect of TIN816 on PPi concentrations compared to the ex vivo IL-1ß assay.

Comparable duration of low PPi levels was observed in minipig at the no observed adverse effect level (NOAEL) while mineralization was only seen following low PPi levels for at least 35 days. Of note, the minipig is considered a highly sensitive species to vascular calcification

compared to rats or cynomolgus monkeys. In the absence of effect on phosphorus and calcium, this low level of PPi for a duration of 2-3 weeks is unlikely to lead to vascular calcification; however, plasma calcium, phosphorus and inorganic pyrophosphate level will be monitored (see Investigator's brochure).

#### 2.3.2.3 Infusion and hypersensitivity reactions

Injection of a foreign protein into humans may trigger immune response with or without inflammatory signs and symptoms. Such reactions, if they occur, may be immediate or delayed up to several weeks. Since TIN816 is a modified version of a naturally occurring human protein, immunogenicity may occur. In the ongoing phase 1 study in HVs, no infusion reaction, nor hypersensitivity, was observed (see Investigator's Brochure).

#### 2.3.2.4 Anti-drug antibody mediated reactions (immunogenicity)

As with other therapeutic recombinant proteins, there is a possibility of TIN816 inducing an immune response in human participants. Presence of host cell proteins in preclinical and clinical TIN816 batches, is also known to enhance the risk of immunogenicity (Vanderlaan et al., 2018). The primary consequence of immunogenicity may be altered PK and PD properties of the drug, leading to a potential loss in efficacy. There is also a theoretical possibility of immune-mediated reactions.

In the ongoing phase 1 study in HVs, no anti-drug antibodies (ADA) were observed in cohort 1-3 until end of study, and in Cohort 4 up to Day 8 (data cut-off). Development of anti-TIN816 antibodies including their potential to neutralize TIN816 or endogenous CD39 will be monitored (see Investigator's Brochure).

### 2.3.3 COVID-19

It is not known whether TIN816 (recombinant CD39) 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, Pickkers et al., 2018). 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.

### 2.3.4 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 question that the participant will not reliably comply, they should not be entered or continue in the study.

Given the very low predicted levels of TIN816 in the semen, the subsequent serum levels of a female sexual partner would be negligible (Scialli et al., 2016). Therefore, given that the likelihood is low that TIN816 would be carried in the semen and result in teratogenicity, no restrictions will be placed on male participants with regard to sexual activity or condom use.

### 2.3.5 Drug-drug interactions

**Concomitant use with antiplatelet agents**

*In vitro* incubation of human whole blood with TIN816 at ≥ 0.8 µg/mL had a strong effect on ADP - and thrombin - (TRAP-6) - induced platelet aggregation. Moreover, an additive PD interaction between TIN816 and antiplatelet agents with respect to platelet aggregation is anticipated since *in vitro* incubation of human whole blood with TIN186 in combination with P2Y12 inhibitors (e.g., ticagrelor or cangrelor) or acetylsalicylic acid (ASA) resulted in dose-dependent increased inhibition of platelet aggregation with lower IC50 but no increase in maximal inhibitory effect, compared to TIN816 or antiplatelet agents alone. However, an increased risk of bleeding following concomitant administration of TIN816 and antiplatelet agents cannot be excluded. If concomitant treatment is indicated, adequate monitoring of respective coagulation parameters is required.

**Concomitant use with anticoagulant agents**

*In vitro* incubation of human whole blood with TIN816 at 1.0 µM had only a minimal effect on clot formation with delayed start of clot formation. In addition, no drug interaction between TIN816 and anticoagulant agents with respect to coagulation cascade (clot formation) is anticipated since *in vitro* incubation of human whole blood with TIN816 in combination with heparin showed absence of additive effect on clot formation. However, concomitant use of TIN816 with anticoagulant agents may increase the bleeding risk. Caution is required when TIN816 is concomitantly administered with anticoagulant agents, and adequate monitoring of respective coagulation parameters is required.

### 2.3.6 Blood sample volume

The approximate volumes are mentioned in the informed consent form (ICF). Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in Section 1.3.

# 3 Objectives, endpoints, and estimands

The following objectives will be evaluated in the study period:

**Table 3-1 Objectives and related endpoints**

| Objective(s) | Endpoint(s) |
|---|---|
| **Primary objective(s)** | **Endpoint(s) for primary objective(s)** |

| **Objective(s)** | **Endpoint(s)** |
|---|---|
| • To assess pharmacokinetics (PK) of TIN816 with a single dose of IV infusion | • TIN816 concentrations in serum<br>PK parameters: $C_{max}$, $T_{max}$, $T_{1/2}$, Cl, $V_z$, $AUC_{last}$ and $AUC_{inf}$ of TIN816 |
| **Secondary objective(s)** | **Endpoint(s) for secondary objective(s)** |
| • To assess safety and tolerability of TIN816 vs placebo | • Safety evaluations (including adverse events/serious adverse events, safety laboratory parameters, vital signs and immunogenicity) |

[redacted]

## 3.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during study conduct which could impact the interpretation of the study results (eg. premature discontinuation of treatment).

The primary clinical question of interest is: What are the pharmacokinetic characteristics (systemic exposure) of TIN816 (IV infusion) in hospitalized adult participants with diagnosis of SA-AKI, who received the complete treatment infusion?

The primary estimand is described by the following attributes:

1. Population: hospitalized adult patients with diagnosis of SA-AKI with complete IV infusion and at least one available valid PK concentration measurement who survived at Day 7.

2. Primary endpoint: PK parameters, including $C_{max}$, $T_{max}$, $T_{1/2}$, Cl, Vz, $AUC_{last}$ and $AUC_{inf}$.

3. Treatment of interest: A single dose of investigational study treatment TIN816 will be administered via an IV infusion.

4. Handling the intercurrent events: PK will be evaluated in patients who remain alive until Day 7.

5. The summary measure: geometric mean and median.

## 3.2 Secondary estimands

As the intention of estimand framework is applied to efficacy endpoints, considering all safety outcomes are the secondary endpoint, the estimand framework for secondary estimands is not further discussed.

# 4 Study design

## 4.1 Overall design

This is a multi-center, participant and investigator-blinded, randomized, placebo-controlled, parallel group study to characterize PK/PD profile and to evaluate safety and efficacy of TIN816 in hospitalized adult participants with diagnosis of sepsis and AKI. The study consists of a screening period, treatment (Day 1) and a post-treatment period for a total duration of 90 days. Refer to Section 1.2 Schema for study design figure.

Screening will take place during hospitalization in ICU or intermediate/HDU care) where potential participants will undergo screening to assess the presence of sepsis and AKI. Pre-identified participants (or their legal representative according to local regulatory requirements) will provide informed consent and undergo screening assessments to determine eligibility. Potential study candidates will be hospitalized patients with a diagnosis of sepsis based on Sepsis 3 criteria with suspected or confirmed infection and SOFA score $\geq 2$ after excluding the renal component, and a diagnosis of AKI stage 1 or greater using the KDIGO serum creatinine-based criteria.

For hospital-acquired AKI, a stable serum creatinine obtained in the hospital prior to AKI should be used as reference baseline, otherwise, baseline serum creatinine in the following order of preference:

1. Median value within 3 months of the hospital admission. If not available:

2. Median value between 3 and 6 months prior to hospital admission. If not available:

3. At hospital admission.

The study will exclude participants whose AKI diagnosis or AKI presence based on investigator's clinical judgement has a period longer than 48 hours prior to study drug administration because of the criticality of an early treatment for patients with SA-AKI.

This study is designed to assess PK profile of TIN816 in the participants with SA-AKI as compared to that observed in HVs. [redacted]

A total of approximately 20 participants will be randomized for the study. After informed consent is obtained from the participant/legal representative and the participants' eligibility is confirmed, study sites will perform the screening and baseline (Day 1) assessments following the assessment schedule (Table 1-2). Participants will be randomly assigned to receive either TIN816 at 2 mg/kg or placebo using a 3:1 allocation ratio (TIN816:placebo). A single dose of the study treatment will be administered via 2-hour IV at the randomization visit in a participant and investigator-blinded fashion. The study treatment must be administered within 48 hours, after SA-AKI is first diagnosed, but ideally as soon as possible. Two PK samples will be taken at Day 1, one prior to study treatment and one immediately after the completion of IV infusion (within 15 minutes), and additional samples will be taken at Day 2, 3, 5, 8, 14, 30, 60 and 90, optimally always at the same time of the day as when dosing of TIN816 started on Day 1. All participants will be followed-up for a total duration of 90 days.

An interim analysis is planned when approximately 8 participants complete Day 14 visit. The study will continue without modification if a similar PK profile of TIN816 compared to that in the HV is confirmed. Otherwise, an adaptive design would be implemented with options to add up to two additional arms testing a higher dose, multiple bolus doses, extended infusion dosing regimens or combination of bolus dose and extended infusion. The adaptive design will be supported by modeling and simulation with data from the preclinical studies, FIH study and the interim analysis of the current PK/PD study. Patient recruitment will continue during the IA to enroll up to a cap of 12 patients. In the circumstance that the first IA does not provide sufficient PK data to support phase 2b, an additional IA will be added when all 20 patients complete Day 14 visit.

## 4.2 Scientific rationale for study design

This study is designed as a multi-center, participant and investigator-blinded, randomized, placebo-controlled study to evaluate the PK/PD profile as well as the safety and efficacy of TIN 816 in patients with SA-AKI. The participant and investigator-blinded design is to control for bias in the assessment of safety, efficacy [redacted] The study design fulfills the purpose of the trial in the assessment of pharmacokinetics in SA-AKI patients, collecting preliminary safety and efficacy data while obtaining operational insights in the acute trial setting. The data generated from this study will be used to support further development of TIN816 for the indication of SA-AKI.

Potential study participants will consist of patients with a recent diagnosis of sepsis (according to the criteria defined by The Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3) with an additional diagnosis of AKI (stage 1 or greater using the KDIGO serum creatinine-based criteria). The patient population is typical for the intended indication without a further enrichment. In addition, patient safety is well considered in the design of inclusion /exclusion criteria.

The primary objective of this study is to evaluate the PK profile in SA-AKI patients. PK sampling schedule and PK parameters including $C_{max}$, $T_{max}$, $T_{1/2}$, Cl, $V_z$, $AUC_{last}$ and $AUC_{inf}$ are considered as standard for PK assessments. [redacted]

The study includes safety and efficacy endpoints. Safety will be monitored during the entire course of the study. All adverse event (AE) and serious adverse event (SAE) will be collected and reported following standard processes and local regulations. [redacted]

Although this study is not powered for evaluation of efficacy of TIN816, inclusion of those efficacy endpoints will help to gain important insights in future phase 2 study design and key clinical data collection.

AKI develops in 40-60% patients with sepsis and progresses during the first few weeks resulting in a reduction in GFR. RRT is often required either temporarily or permanently and morbidity and mortality are high because of the multiple organs affected. Thus, selection of the efficacy endpoints for this patient population aims to assess the presence and severity of the complications of SA-AKI and the potential benefit of TIN816.

The routine renal function test of serum creatinine has limitations in patients who are not in a steady state, and other measures of renal function including GFR measured by iohexol are less feasible in the acute setting (Carlier et al., 2015). As a result, and consistent with previous trials in this area, creatinine clearance has been selected as the endpoint for measuring renal function. Creatinine clearance is a reasonable approximation of GFR, not affected by diet, and calculated from the routine in-hospital collection of serum and urine creatinine with no special collection conditions or assays required. It has the further benefit of mitigating both the lack of steady state conditions during the early period of AKI and the reduced creatinine production that characterizes very ill hospitalized patients (Prowle et al., 2014). As an endpoint, it has the advantage of being a continuous variable that provides sufficient power for a phase 2 study compared with the more clinically relevant but categorical measures in the MAKE-30 and MAKE-90 endpoints (i.e., death, RRT, 25% reduction in eGFR).

To calculate the creatinine clearance in mL/min, urine will be collected at every visit over a 6±1 hour period (during hospitalization) with serum creatinine measurements at the midpoint of the urine collection period. Although 24-hour urine collection periods are the most accurate way to reliably determine creatinine clearance, a 6-hour collection period is expected to be representative of the full 24 hours for that day (Baumann et al., 1987, Pickering and Endre., 2012) 24-hour urine collections will occur at visits after patient is discharged from the hospital; serum creatinine will be collected at the end of the 24-hour collection at the site visit.

## 4.3 Justification for dose

The in vitro potency for TIN816 in whole blood (WB) assays (LPS/ATP induced IL-1β release and ADP-induced platelet aggregation) was demonstrated to be comparable for rat, minipig and human. The similarity in pharmacology across species allowed to predict and explore an exposure range expected to be safe in light of animal safety and pharmacology data and reaching expected therapeutic doses. These PD whole blood assays revealed in-vitro IC90s of approximately 1.66 to 2.66 µg/mL for human.

In a FIH study in healthy volunteers, a starting dose of 0.1 mg/kg and subsequent doses of 0.3, 1.0 and 2.0 mg/kg were selected in accordance

with CHMP (2017) and CDER (2005) guidelines. The administration of 0.1, 0.3, 1.0 and 2.0 mg/kg of TIN816 or placebo as a single IV infusion was well tolerated and did not reveal any safety signals related to the investigational medicinal product (IMP). The effect of TIN816 on purinergic signaling was assessed in two ex-vivo PD assays in whole blood by studying inhibition of LPS/ATP induced IL-1β release and inhibition of ADP induced platelet aggregation. Ex-vivo, an IC90 of 0.25µg/mL was derived for inhibition of ADP-induced platelet aggregation and an IC90 of 7.8µg/mL for inhibition of LPS/ATP-induced IL-1β release. In FIH, exposure was determined systemically and in skin interstitial fluid. Results indicate that TIN816 may attenuate purinergic signaling systemically for roughly three weeks at a dose of 2 mg/kg. This conclusion depends; however, on the PD assay considered (LPS/ATP induced IL-1β release or ADP-induced platelet aggregation, assessed in-vitro or ex-vivo), on the relevance of the determined inhibiting TIN816 concentrations (e.g. IC50s, IC90s) for the clinical situation and on the required exposure in the relevant tissues.

In this study, participants will be administered the study drug at a dose of 2 mg/kg or placebo via a 2-hour intravenous infusion in a participant and investigator-blinded fashion. Dose administration by 2 hour infusion approximately, allows time to react if unexpected safety related reactions occur during dosing. The dose of 2 mg/kg is selected in this study to serve the purpose of evaluation of the PK profile in septic patients. In the FIH study a dose of 2 mg/kg was well tolerated and safe. At 2 mg/kg, the expected exposure systemically and in relevant tissue interstitia is believed to inhibit purinergic signaling and provide a beneficial pharmacological effect. Total exposure ($AUC_{inf}$) of a single dose of 2 mg/kg in human is approximately 10.4-fold lower compared to the NOAEL overall exposure from 4 IV doses of 10 mg/kg TIN816 administered q4d in the 2 weeks minipig study (compared to $AUC_{tau,ss}$ from the 4th dose in minipig at steady state the exposure margin is 2.6-fold) and $C_{max}$ shows a 7-fold margin to the NOAEL exposure. Participants will be followed-up for a total duration of 90 days and PK/biomarker data will be used to support the dosing strategy for subsequent studies in this indication.

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

The choice of placebo as treatment control will allow an objective assessment of safety, tolerability, efficacy and target engagement of TIN816. Placebo is further justified in this SA-AKI participant study given that there is no approved treatment for this disease. Notwithstanding the absence of approved treatment, all participants including those treated with study drug or placebo should be managed and treated as locally appropriate for SA-AKI.

## 4.5 Rationale for public health emergency mitigation procedures

In the event of a public health emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster), mitigation procedures may be required to ensure participant safety and study integrity and are listed in relevant sections of the study protocol. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by local or regional health authorities and ethics committees as appropriate.

## 4.6 Purpose and timing of interim analyses/design adaptations

An IA will be performed at the time when 8 participants have completed Day 14 visit. The intent of this IA is to provide PK concentration data on sepsis AKI participants. Participants will continue to be recruited while this analysis is being completed up to a cap of 12 participants. If a similar PK profile of TIN816 compared to that in the HVs is confirmed, the study will continue without modification. Otherwise, the study design may be amended with options of additional arms for testing a higher dose, multiple bolus doses, extended infusion dosing regimens or combination of bolus dose and extended infusion. The total sample size may increase to provide adequate PK data after dose level and/or dose regimens are changed. In the circumstance that the data from the first IA is not conclusive, an additional IA will be added when all 20 patients have completed Day 14 visit.

## 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 hospitalized male and female patients with a diagnosis of sepsis and AKI. Approximately 20 participants will be enrolled in the study and randomized to receive either TIN816 or placebo.

The investigator must ensure that all participants being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator in order to ensure that the study population will be representative of all eligible participants. Deviation from any entry criterion excludes a participant from enrollment into the study. Replacement participants may be enrolled to replace participants who discontinue the study for reasons other than safety, based on the sponsor's decision.

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

## 5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria at screening assessment, unless otherwise specified at randomization (Day 1) :

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

2. $\geq$ 18 and $\leq$ 85 years of age.

3. Admitted to ICU or intermediate/HDU.

4. Diagnosis of sepsis according to criteria defined by The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) based on:

- Suspected or confirmed infection
- SOFA score of 2 or more (excluding renal component)

5. Diagnosis of AKI Stage 1 or greater per the following criterion at randomization :

- An absolute increase in serum or plasma creatinine (CR) by ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hours or presumed to have occurred in the previous 48 hours as compared to the reference creatinine baseline
- For hospital-acquired AKI, a stable serum creatinine obtained in the hospital prior to AKI should be used as reference baseline, otherwise, baseline serum creatinine in the following order of preference:
  1. Median value within 3 months of the hospital admission. If not available:
  2. Median value between 3 and 6 months prior to hospital admission. If not available:
  3. At hospital admission.

## 5.2 Exclusion criteria

Participants meeting any of the following criteria at screening assessment, unless otherwise specified at randomization (Day 1) , are not eligible for inclusion in this study.

1. Not expected to survive for 24 hours.

2. Not expected to survive for 30 days due to medical conditions other than SA-AKI.

3. History of CKD with a documented estimated GFR <45 ml/min prior to development of AKI.

4. Receiving RRT or a decision has been made to initiate RRT within 24 hours of admission.

5. Weight is less than 40 kg or more than 125 kg .

6. Has life support limitations (eg, do not resuscitate, do not dialyze, do not intubate).

7. AKI diagnosis according to the AKI inclusion criteria for a period longer than 48 hours prior to study drug administration.

8. Presence of AKI for a period longer than 48 hours prior to study drug administration as suggested by clinical manifestations, e.g., prolonged oliguria or severe renal dysfunction (eg, serum creatinine > 4 mg/dL) on admission without a history of CKD.

9. Evidence of recovery from AKI based on the investigator's clinical judgement prior to randomization.

10. AKI is most likely attributable to causes other than sepsis such as nephrotoxic drugs (Non-steroidal anti-inflammatory drugs (NSAIDs), contrast, aminoglycosides), other medical conditions (e.g. heart failure, liver failure, acute abdominal aortic aneurysm, dissection, renal artery stenosis) or urinary obstruction.

11. Documented (biopsy proven) or suspected history of acute or sub-acute kidney diseases such as rapidly progressive glomerular nephritis (RPGN) and acute interstitial nephritis (AIN).

12. Patients who are post-nephrectomy.

13. Patients who are on dual antiplatelet therapy.

14. Patients who are thrombocytopenic at screening (Platelet count <100,000 microliter) or other high risk for bleeding in the opinion of the investigator.

15. Immunosuppressed patients:

- History of immunodeficiency diseases or known HIV test positive.
- Is receiving immunosuppressant treatment or is on chronic high doses (high-dose therapy exceeding 2 weeks of treatment) of steroids equivalent to prednisone/prednisolone 0.5 mg/kg/day, including solid organ transplant patients. Patients with septic shock treated with hydrocortisone (e.g., 3 × 100 mg) can be included.

16. Active hepatitis (defined as (a) abnormal liver enzymes (Alanine aminotransferase (ALT), Gamma-glutamyl transferase (GGT), 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 or patients with advanced chronic liver disease, confirmed by a Child-Pugh score of 10–15 (Class C).

17. Acute pancreatitis with no established source of infection.

18. Active hematological malignancy (previous hematological malignancies that are not actively treated are allowable).

19. Burns requiring ICU treatment.

20. Sepsis attributed to confirmed COVID-19.

21. Use of other investigational drugs within 5 half-lives of enrollment within 30 days (e.g., small molecules) / or until the expected pharmacodynamic effect has returned to baseline (e.g., biologics), whichever is longer; or longer if required by local regulations.

22. History of hypersensitivity to the study treatment or its excipients or to drugs of similar chemical classes.

23. Any medical conditions that could significantly increase risk of participants' safety by participating in this study according to investigator's judgement.

24. Women with a positive pregnancy test, pregnancy or breast feeding.

25. 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 for 38 days of study treatment after stopping medication. 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, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks before taking investigational drug. 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.

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.

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

## 5.3 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 randomly assigned to study treatment. 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 SAE.

No rescreening is permitted in this study.

### 5.3.1 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 study. 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 will be manufactured by Novartis and supplied to the unblinded site 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). A blinded nurse/blinded qualified specialist will administer TIN816 (as described in the Pharmacy Manual). The placebo will be sourced locally by the study site as 0.9% saline solution. Saline sourced locally will also be

used a dilutant during the preparation of TIN816. Preparation and administration of the study treatment will be in a blinded fashion.

Details on the requirements for storage and management of study treatment, and instructions to be followed for participant numbering and administration of the study treatment are outlined in the Pharmacy Manual.

## 6.1 Study treatment(s)

The investigational drug, TIN816 (Table 6-1) will be supplied as open labeled medication in vials to an unblinded site pharmacist or an unblinded qualified site designee. Each vial contains 70mg TIN816.

TIN816 is provided as a lyophilisate which needs to be reconstituted with sterile water for injection (SWFI) and, diluted using sterile 0.9% saline solution before use.

An unblinded pharmacist or an unblinded qualified site designee will prepare the investigational and control drug to dispense to the blinded staff for study drug administration. Please refer to Pharmacy Manual for detailed instructions.

Study treatment will be administered as a 2 hour IV infusion (approximately) via a perfusor syringe at the clinical site by the study personnel in accordance with the specified study procedures and the Pharmacy Manual.

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

**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 70mg (lyophilisate in vial) | Powder for Solution for infusion | Intravenous use | Open label supply; vials | Sponsor (global) |
| Placebo (Saline) | 0.9% sodium chloride solution | Intravenous use | Open label infusion bags | Site (local) |

### 6.1.1 Additional study treatments

No other study treatment beyond investigational drug are included in this study.

### 6.1.2 Treatment arms/group

Approximately 20 participants will be assigned at Day 1 to one of the following two treatment arms/groups in a ratio of 3:1; TIN816:placebo

- TIN816: 2 mg/kg; intravenous infusion; one-time administration
- Placebo: intravenous infusion; one-time administration

### 6.1.3 Treatment duration

TIN816 is a one-time, single dose treatment for SA-AKI at the randomization (Day 1) visit (refer to Section 6.1).

Study treatment drug will be administered as an 2 hour IV infusion (approximately) via a perfusor syringe at the clinical site by the study personnel in accordance with the specified study procedures.

## 6.2 Preparation, handling, storage, and accountability

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section in Table 6-1. For details on drug preparation, please refer to the Pharmacy Manual.

A unique medication number is printed on the study medication label.

An unblinded pharmacist/qualified site designee will identify the study medication kits to prepare the TIN816 treatment for this one-time administration by contacting the interactive response technology (IRT) and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), the unblinded site personnel (pharmacist or 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 the unblinded pharmacist or a qualified site designee at the study site, handled and stored safely and properly and kept in a secured location to which only the unblinded pharmacist or qualified site designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels for TIN816 and as per packaging instructions for locally sourced saline (placebo). Clinical supplies are to be prepared and administered for IV administration only in accordance with the protocol and the Pharmacy Manual. 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 unblinded designated site staff 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 study. The unblinded pharmacist or unblinded designated site staff must provide accountability also for locally sourced materials used for administration (i.e., saline solution).

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

There should be a period of at least 1 hour after the infusion whereby 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 randomization visit (Day 1), all eligible participants will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. 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 unique medication numbers of study treatment TIN816 to be administered to the participant or placebo treatment administered as 0.9% saline solution, sourced locally.

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.

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, and persons performing the assessments will remain blind to the identity of the treatment from the time of randomization until database lock. All unblinded personnel will keep randomization lists and data or information that could unblind other study team members confidential and secure except as described below.

Novartis Clinical Trial Team (CTT), including sample analyst(s) (PK, PD [redacted]) will be unblinded to the identity of treatment and will have full access to trial data.

**Site staff**

With the exception of any unblinded site staff identified below, all site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

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

**Sponsor staff**

In addition to Novartis CTT, the following unblinded sponsor roles are required for this study.

- Unblinded field monitor(s)
- Unblinded clinical staff managing drug re-supply to site

The unblinded field monitors are required to review drug accountability and allocation at site. The unblinded monitors are not provided with a randomization list directly but will be unblinded through review of source documentation compiled by the unblinded pharmacist, which details treatment allocation to individual participants. The unblinded monitors will also be able to review the treatment allocation provided by IRT to the unblinded pharmacist.

If sponsor clinical staff are required to assist in the management and re-supply of investigational drug product, these individuals are not provided with randomization lists directly, but may be unblinded through communication of drug re-supply needs via the unblinded site pharmacists.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team.

The study statistician will be able to access the full randomization list from the start of the study and is allowed to share unblinded information with the rest of the clinical trial team as appropriate for internal decision purposes. For example, unblinded summaries and unblinded individual data can be shared with the team whenever necessary.

Study programmers and other personnel involved in study data analysis [redacted] are allowed to access treatment assignment information from the start of the study for the purpose of data analysis.

The clinical trial team is allowed to share unblinded results with other sponsor staff (e.g. decision boards) and to an external Steering Committee, as required for internal decision making on the study or the project at the time of interim analyses while the study is ongoing.

Following final database lock all roles may be considered unblinded.

**Table 6-2 Blinding and unblinding plan**

| **Role** | **Time or Event** | | |
|---|---|---|---|
| | Randomization list generated | Treatment allocation & dosing | Safety event (single subject unblinded) |
| Participants | B | B | B |
| Site Staff | B | B | UI |
| Unblinded site staff, e.g. pharmacy staff | B | UI | B |
| Sponsor CTT | B | UI | UI |
| All other Sponsor staff not identified above (i.e. project team, management & decision boards, support functions) | B | UI | UI |
| Independent committees used for assessing interim results, if required (e.g. DMC) | B | 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 in order to treat the participant safely.

Most often, 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 system 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

An one time intravenous infusion will be administered in the ICU/HDU. This information must be captured in the source document, the appropriate eCRF and in the Drug Accountability Log. The site personnel should reflect total volume administered as well as the date and time of administration in the eCRF page. Any reason for dose interruption of the IV infusion will also be captured in the source document and the eCRF.

PK parameters (measures of treatment exposure) will be determined in all participants treated with TIN816, as detailed in PK section (Section 8.7).

### 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 study drug. 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 eCRF.

## 6.5 Dose modification

Investigational or other study treatment dose adjustments are not permitted as this is an one-time IV dose administration.

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

Not applicable for this PK study of a single dose IV infusion investigational drug.

### 6.6.1 Post trial access

Not applicable for this PK study of a single dose IV infusion investigational drug.

## 6.7 Treatment of overdose

Study treatment overdose is the administration of a quantity of the investigational medicinal product which is above the maximum recommended dose according to study protocol.

In the event of an overdose, the treating physician, in collaboration with the investigator should:

- Contact the medical monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study drug can no longer be detected systemically (at least 38 days).
- Obtain a plasma sample for PK analysis (within 15 minutes after infusion interruption or infusion end, the latter marking the first PK time point post-dose).
- Document the quantity of the excess dose.

### 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 administration errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE. Study treatment errors 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 medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate eCRFs.

Each concomitant drug must be individually assessed against all exclusion criteria/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.

Prior medications related to the treatment of sepsis and AKI taken within 2 weeks prior to screening will be recorded on the eCRF.

Administered resuscitation fluids should only be recorded as total daily volume in the concomitant eCRFs. Blood products should be recorded separately.

#### 6.8.1.1 Permitted concomitant therapy requiring caution and/or action

Administration of nephrotoxic drugs such as contrast agents, NSAIDs, angiotensin-converting enzyme (ACE) inhibitors, amphotericin B, high doses of loop diuretics, anti-microbial drugs like acyclovir and aminoglycoside drugs should be avoided or used with caution, as recommended in the KDIGO Clinical Practice Guideline for AKI (KDIGO (2012)).

In addition, based on the mechanism of action of TIN816 (removal of ADP and inhibition of P2Y12 activation), there is a theoretical bleeding risk. Although no relevant bleeding complications were observed in the preclinical toxicology and FIH study at exposure resulting in a full inhibition of ADP/thrombin-induced platelet aggregation, an additive inhibitory effects of platelet aggregation caused by TIN816 was found in the presence of antiplatelet drugs (ticagrelor or acetylsalicylic acid) at a clinical therapeutic dose. Thus, careful monitoring of coagulation/clinical signs of bleeding should occur if antiplatelet agents or other anticoagulant drugs are used concomitantly during the study. Management of bleeding in patients treated with TIN816 may include temporary discontinuation of antiplatelet or anticoagulant drugs, resuscitation with intravenous fluid, packed red cell transfusion and platelet transfusions, as per local practice.

### 6.8.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed after the start of study treatment

**Table 6-3 Prohibited medication**

| Medication | Prohibition period | Action taken |
|---|---|---|
| Dual antiplatelet therapy | 30 days after randomization | Discontinue dual antiplatelet therapy |

# 7 Discontinuation of study treatment and participant discontinuation/withdrawal

## 7.1 Discontinuation of study treatment

Since this is a one time single dose intravenous infusion, a permanent interruption of the infusion will be considered as discontinuation from study treatment.

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
- Any situation in which continued study participation might result in a safety risk to the participant

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 agree to return for the end of treatment and 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 done according to the study visit schedule.

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 defined as when a participant permanently stops any 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.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

Study treatment must be discontinued and no further assessments will 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/opposition to use data/biological samples/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 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 Early study termination by the Sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination include (but are 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 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 in 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 Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) of the early termination of the study.

# 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.

Adherence to the study design requirements, including those specified in Section 1.3 Schedule of Activities, is essential and required for study conduct.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

## 8.1 Screening

Re-screening is not allowed if a participant fails screening and does not meet eligibility criteria.

### 8.1.1 Eligibility Screening

Patients admitted to ICU or intermediate/HDU care with AKI and a suspected or proven sepsis can be considered to be enrolled in the study.

The following key assessments and procedures will be performed at the screening visit:

- Signature of the ICF by the participant, or his/her legal representative, or other according to local regulatory requirements.
- Sepsis and AKI diagnosis
- SOFA score
- Hematology (local lab)
- Clinical Chemistry (local lab)
- Hepatitis screen (local lab)
- [redacted]
- Collection of demographics, vital signs, medical history/current medical conditions (including alcohol and smoking history), and concomitant medications
- Reference serum creatinine
- Pregnancy test (serum) performed by local laboratory.

### 8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate 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 SAE Section 8.6.2 for reporting details). 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.

Participants who are randomized and fail to start treatment, e.g. participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate 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 eCRF.

The following key assessments will be performed at the baseline (Day 1) visit, unless otherwise specified:

- Vital signs (temperature, heart rate, respiratory rate, and blood pressure)
- AKI diagnosis
- APACHE II score
- SOFA score
- [redacted]
- Clinical chemistry (local lab)
- Hematology (local lab)
- Urinalysis (local lab)
- PK/PD/ADA blood collection (central lab)
- Urine collection (central lab)
- Serum creatinine, creatinine clearance (central lab)

Demographics, relevant medical histories and current medical conditions collected at screening visit are considered as baseline.

### 8.2.1 Demographics and Medical History

Demographics to be collected include age, sex, race/predominant ethnicity (if permitted) and medical history (until date of signature of informed consent) should be recorded at screening. Medical history at screening should be recorded in the appropriate section of the eCRF with special emphasis on pre-existing renal disease and the use of immunosuppressant medication, steroids, and nephrotoxic drugs.

For determination of study drug dosage and calculation of fluid corrected creatinine, body weight (in kg/lb) should be estimated or measured.

Height and weight will be collected at screening for calculation of body mass index (BMI) (BMI= body weight (kg)/[height (m)]$^2$). Depending on availability, the order of preference for weight value to be used for dose calculation is:

1. Hospital admission measured weight

2. Patient reported weight

3. Ideal body weight (Devine formula)(Devine, 1974)
- Men = 50kg +2.3kg x (height - 60inches)
- Women = 45.5kg +2.3kg x (height - 60 inches)

4. Estimated body weight

## 8.3 Efficacy assessments

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

For additional information on PK, refer to Section 8.7.

### 8.3.1 Creatinine clearance (CrCl)

Creatinine clearance is the volume of blood plasma cleared of creatinine per unit time. It can be measured using the comparative values of creatinine in blood and urine. To calculate the time corrected endogenous creatinine clearance, paired urine and serum creatinine samples will be collected from participants at all visits from baseline to Day 90/EOS and shipped to the central laboratory.

For the 6 hour measurement, one serum creatinine sample will be collected at the midpoint of the 6 ±1 hour urine collections. When participants are discharged from the hospital, 6-hour urine collection at home is not considered feasible or reliable; thus, it will not be performed. As a result, 24-hour urine collection should be considered once patients have been discharged home. For the 24 hour creatinine clearance calculation, urine collection should take place one day prior to the study visit, and one serum sample will be taken at the approximately 24 hours later at the study visit. Calculations will be performed by the central laboratory. If reliable urine collection is not possible, one serum creatinine sample still needs to be taken for calculating eGFR (Delgado et al., 2021).

Urine must be collected for a period of 6 ± 1 hour for each study visit day the participant is admitted in hospital. Baseline creatinine clearance should be performed prior to administration of the study treatment. The collection period will take a minimum of 5 hours, and a maximum of 7 hours. The exact duration of urine collection period and of volume collected will be recorded in the eCRF. The volume should be corrected to account for the volume of samples previously taken from the total urine initially collected. Endogenous creatinine clearance will be calculated as follows: clearance = (urine volume × concentration in urine) / concentration in serum. When participants leave the ICU or intermediate/HDU care unit, but are still in the hospital, the 6-hour urine collection will continue. In case the Foley catheter is removed, a participant might urinate spontaneously. All efforts should be made to begin the 6 hour collection starting at any time after voiding and continue to include a voiding at the 6 hour point. A blood sample for serum creatinine will be drawn at approximately the mid-point of the urine collection. The urine volume produced over the last approximately 6 hours will be entered in the eCRF.

[redacted]

[redacted]

### 8.3.3 Kidney disease improving global outcomes (KDIGO) stage

Determination of severe AKI will be grounded in the staging system outlined in the KDIGO Guidelines for acute kidney injury. This classification system stages AKI into three levels based on the extent of sCr elevation in parallel with the degree and duration of oliguria; patients are classified based on the worst finding (either sCr or oliguria). Three stages of AKI are classified in the table below:

**Table 8-1 Staging of AKI**

| Stage | Serum creatinine | Urine output |
|---|---|---|
| 1 | 1.5-1.9 times baseline<br>OR<br>≥0.3 mg/dl (≥26.5 µmol/l) increase | <0.5 ml/kg/h for 6-12 hours |
| 2 | 2.0-2.9 times baseline | <0.5 ml/kg/h for ≥12 hours |
| 3 | 3.0 times baseline<br>OR<br>Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 µmol/l)<br>OR<br>Initiation of renal replacement therapy | <0.3 ml/kg/h for ≥24 hours<br>OR<br>Anuria for ≥12 hours |

### 8.3.4 Renal replacement therapy (RRT)

**Initiation of RRT**: RRT should be initiated as per local protocol but recommended based on the criteria described by Bellomo et al (2012). Meeting at least one criterion of the below makes the patient eligible for initiation of RRT:

1. Anuria (negligible urine output for 6 hours)

2. Severe oliguria (urine output < 200 mL over 12 hours)

3. Hyperkalemia (potassium concentrations > 6.5 mmol/L)

4. Severe metabolic acidosis (pH < 7.2 despite normal or low partial pressure of carbon dioxide in arterial blood)

5. Volume overload

6. Pronounced azotemia (urea concentrations > 30 mmol/L (> 84 mg/dL) or creatinine concentrations > 300 µmol/L (> 3.4 mg/dL))

7. Clinical complications of uremia (e.g., encephalopathy, pericarditis, neuropathy)

**Timing of termination of RRT:** RRT should be terminated as per local protocol but is recommended based on criteria as used in the Veterans Affairs/National Institutes of Health (VA/NIH) Acute Renal Failure Trial Network Study (Palevsky et al., 2008). If diuresis > 30

mL/hour and there are no other indications for RRT, then endogenous creatinine clearance should be calculated using a 6-hour urine collection period. If endogenous creatinine clearance ≥ 20 mL/min, RRT should be discontinued. If endogenous creatinine clearance ≤ 12 mL/min, RRT should be continued. However, although the criteria for starting and stopping mentioned above are strongly preferred within the protocol setting, based on clinical judgment investigators may deviate from these criteria.

### 8.3.5 Scoring Systems

#### 8.3.5.1 Sequential Organ Failure Assessment Score (SOFA)

The SOFA score was developed to assess the acute morbidity of critical illness at a population level and has been widely validated as a tool for this purpose across a range of healthcare settings and environments (Vincent et al., 1996, Vincent et al 1998). Following the development of new definitions, it is now used as a key criterion in the diagnosis of sepsis syndrome on an individual patient level. The score is routinely calculated on admission to ICU and at each 24-hour period that follows. It is composed of six criteria which reflect the function of a specific organ system (respiratory, cardiovascular, renal, neurological, hepatic and hematological) and allocates a score of 0-4.

Scores ranges from 0-24, with higher scores indicating greater dysfunction.

The SOFA score has been applied in a range of clinical and research applications.

In the context of randomized controlled trials, a meta-analysis identified 25 studies where the change in SOFA score from baseline or maximum to a defined time point was used and revealed a strong association between change in SOFA and mortality – with 32% of the observed mortality effects explained by the delta SOFA score (de Grooth et al., 2017). This association of SOFA score at admission and during ICU stay with longer term outcomes has led to the acceptance by the EMA that use of delta SOFA is a valid surrogate endpoint in exploratory clinical trials of patients with sepsis (CHMP 2006).

The SOFA score will be assessed based on local laboratory results due to time requirements.

**Table 8-2 Components of the SOFA score**

| | **Score** | | | | |
|---|---|---|---|---|---|
| | **0** | **1** | **2** | **3** | **4** |
| **Respiratory system** | | | | | |
| $PaO_2/FiO_2$ (mmHg) | ≥400 | <400 | <300 | <200 with respiratory support | <100 with respiratory support |
| **Hepatic system** | | | | | |
| Bilirubin (mg/dL) | <1.2 | 1.2-1.9 | 2.0-5.9 | 6.0-11.9 | >12.0 |
| **Cardiovascular system** | | | | | |

| | MAP ≥70 mmHg | MAP <70 mmHg | Dopamine <5 mcg/kg/min or dobutamine (any dose)[a] | Dopamine 5.1-15 mcg/kg/min or epinephrine ≤0.1 mcg/kg/min or norepinephrine ≤0.1 mcg/kg/min[a] | Dopamine >15 mcg/kg/min or epinephrine >0.1 mcg/kg/min or norepinephrine >0.1 mcg/kg/min[a] |
|---|---|---|---|---|---|
| **Coagulation** | | | | | |
| Platelets × $10^3$ µl | ≥150 | <150 | <100 | <50 | <20 |
| **Central nervous system** | | | | | |
| Glasgow coma scale | 15 | 13-14 | 10-12 | 6-9 | <6 |
| **Renal system** | | | | | |
| Creatinine (mg/dL) | <1.2 | 1.2-1.9 | 2.0-3.4 | 3.5-4.9 | >5.0 |
| Urine output (mL/d) | - | - | - | <500 | <200 |

Notes: [a]All catecholamine doses represent µg/kg/min. Organ dysfunction is identified as an increase in the SOFA score of ≥2 points. In patients with not known preexisting organ dysfunction, the baseline SOFA score is assumed to be zero. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. 22(7), 1996, 707-710.Vincent JL. Moreno R, Takala J, et al.
Abbreviations: $PaO_2$, partial pressure of oxygen; $FiO_2$, fraction of inspired oxygen; MAP, mean arterial pressure.
Source: Lopez et al., 2017

### 8.3.5.2 Acute Physiology and Chronic Health Evaluation Score (APACHE-II)

The APACHE-II (acute physiology and chronic health evaluation II) score is a severity-of-disease classification system for the assessment of critically unwell patients. It is applied within 24 hours of admission of a patient to an ICU or intermediate/HDU. An integer score from 0-71 is computed based on several measurements: higher scores correspond to more severe disease and a higher risk of death in ICU patients.

The APACHE-II score will be assessed at baseline and recorded in the eCRF.

**Table 8-3 Components of the APACHE-II score**

| **Physiologic variable[b]** | | **Point score** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **+4** | **+3** | **+2** | **+1** | **0** | **+1** | **+2** | **+3** | **+4** |
| 1 | Temperature | ≥41° | 39-40.9° | - | 38.5-38.9° | 36-38.4° | 34-35.9° | 32-33.9° | 30-31.9° | ≤29.9° |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 2 | Mean arterial pressure (mmHg) | ≥160 | 130-159 | 110-129 | - | 70-109 | - | 50-69 | - | ≤49 |
| 3 | Heart rate | ≥180 | 140-179 | 110-139 | - | 70-109 | - | 55-69 | 40-54 | ≤39 |
| 4 | Respiratory rate(non-ventilated or ventilated) | ≥50 | 35-49 | - | 25-34 | 12-24 | 10-11 | 6-9 | - | ≤5 |
| 5 | Oxygenation: | ≥500 | 350-499 | 200-349 | - | <200 | - | - | - | - |
| | a)$FiO_2$≥0.5: use A-a$DO_2$<br>b)$FiO_2$<0.5: use $PaO_2$ (mm Hg) | - | - | - | - | >70 | 61-70 | - | 55-60 | <55 |
| 6 | Arterial pH | ≥7.7 | 7.6-7.69 | - | 7.5-7.59 | 7.33 - 7.49 | - | 7.25 - 7.32 | 7.15 - 7.24 | <7.15 |
| 7 | Serum Na (mMol/L) | ≥180 | 160-179 | 155-159 | 150-154 | 130-149 | - | 120-129 | 111-119 | ≤110 |
| 8 | Serum K (mMol/L) | ≥7 | 6-6.9 | - | 5.5-5.9 | 3.5-5.4 | 3-3.4 | 2.5-2.9 | - | <2.5 |
| 9 | Serum creatinine (mg/dL):double point score for acute renal failure | ≥++++3.5 | 2-3.4 | 1.5-1.9 | - | 0.6-1.4 | - | <0.6 | - | -- |
| 10 | Hematocrit (%) | ≥60 | - | 50-59.9 | 46-49.9 | 30-45.9 | - | 20-29.9 | - | <20 |
| 11 | WBC (in 1000s) | ≥40 | - | 20-39.9 | 15-19.9 | 3-14.9 | - | 1-2.9 | - | <1 |
| 12 | Glasgow coma score | Score= 15 minus actual Glasgow coma score | | | | | | | | |
| Acute physiology score is the sum of the 12 individual variable points<br>Add 0 points for the age <44.2 points. 45-54 years: three points. 55-64 years: five points. 65-74 years: six points ≥ 75 years<br>APACHE II score = acute physiology score + age points + chronic health points. Minimum score = 0; maximum score = 71. Increasing score is associated with increasing risk of hospital death<br>Add chronic health status points: two points if elective postoperative patient with immunocompromise or history of severe organ insufficiency: five points for nonoperative patient or emergency postoperative patient with immunocompromise or severe organ insufficiency[c] | | | | | | | | | | |
| 13[d] | Serum HC | ≥52 | 41-51.9 | - | 32-40.9 | | 22-31.9 | - | 18-21.9 | 15-17.9 | <15 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $O_3$ ( Ven ous-mM ol/L) use only if no ABG s52 | | | | | | | | | |

Adapted from (Knaus et al., 1985) APACHE II: A severity of disease classification system. Critical care medicine 13: 818-829, 1985. Interpretation of APPACHE II scores (predicted mortality rate).
0-4=~4% death rate 10-14 =~15% death rate 20-24=~40% death rate 30-34=~75% death rate
5-9=~8% death rate 15-19=~25% death rate 25-29=~55% death rate Over 34=~85% death rate
[a]APACHE II score = acute physiology score + age points + chronic health points. Minimum score = 0; maximum score = 71. Increasing score is associated with increasing risk of hospital death
[b]Choose worst value in the past 24h.
[c]Chronic health status: Organ sufficiency (e.g. hepatic, cardiovascular, renal, pulmonary) or immuno-compromised state must have preceded current admission.
[d]Optional value: use only if no ABGs.
Source: (Sam et al., 2009)

### 8.3.6 Appropriateness of efficacy assessments

There are no efficacy assessments for the primary and secondary endpoints.

### 8.3.7 Serum Creatinine

Serum creatinine samples will be collected as part of the creatinine clearance assessments and shipped to the central laboratory. For the 6 ±1 hour urine collections whilst an inpatient on the ICU or intermediate/HDU, one sample will be taken at approximately the mid-point of the urine collection. If the participant is discharged from the ICU or intermediate care unit to general ward, the Foley catheter might be removed. In this case, a participant might urinate spontaneously and all efforts should be undertaken to start collecting urine produced from this time point onward for the next 6 hours. A blood sample for serum creatinine will be drawn at approximately the mid-point of the urine collection. The urine volume produced over approximately 6 hours will be entered in the eCRF. After participants are discharged from hospital, only one blood sample for serum creatinine will be drawn at the end of the 24 hour urine collection period.

## 8.4 Safety and tolerability assessments

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

The following assessments will be considered safety measurements:

- Vital signs, including blood pressure, respiratory rate and body temperature at baseline Day 1 and at all post-baseline visits.
- Physical examination at screening, baseline Day 1, Day 14 and Day 90 visits.
- Local ECG at baseline Day 1 visit.

- Local arterial/venous blood gas sampling for PaO2/carbon dioxide partial pressure (PaCO2)/pH/HCO3
- Local laboratory at screening, baseline Day1 visit and at post-baseline visits.
  - Hematology at screening and baseline Day 1, Day 5, Day 14, Day 30 and Day 90 visits.
  - Clinical chemistry, including liver function parameters at screening and baseline Day 1, Day 5, Day 14, Day 30 and Day 90 visits.
  - Urinalysis at screening, baseline Day 1, Day 3, Day 5, Day 14, Day 30 and Day 90.
  - Coagulation parameters at screening, baseline Day 1, Day 5, Day 14, Day 30 and Day 90.
- Central laboratory for anti-drug antibodies at baseline (Day 1/ pre-dose) and at visits on Days 14, 30 and 90.
- Concomitant medication at screening and all visits from Day 1 to Day 90.
- AEs/SAEs during the duration of the study.
- Mortality (monitored continuously throughout the study)

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 be performed as per local standard/guidelines at screening, baseline Day 1, Day 14 and Day 90 visits (Table 1-2). If indicated based on medical history and/or symptoms, further focused organ specific exams should be performed. The physical examination should be performed by a physician or another study team member with appropriate training to perform the examination.

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 eCRF 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.

#### 8.4.1.1 Height and weight

Height is obtained in centimeters (cm) and body weight is obtained in kilograms (kg) and rounded to the nearest 0.1 kg.

Depending on availability, the order of preference for weight value to be used for dose calculation is:

1. Hospital admission measured weight

2. Patient reported weight

3. Ideal body weight (Devine formula)(Devine, 1974)

- Men = 50kg +2.3kg x (height - 60inches)
- Women = 45.5kg +2.3kg x (height - 60 inches)

4. Estimated body weight

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. Body weight measurements will be taken at screening, baseline Day 1, Day 14, Day 30, Day 60 and Day 90.

### 8.4.2 Vital signs

Vital signs will include the collection of body temperature (recorded in °C), blood pressure (BP), and pulse measurements at all visits (Table 1-2).

In those participants who already have an arterial line placed as part of standard of care, readings from invasive blood pressure monitoring will be recorded preferentially. Otherwise, non-invasive blood pressure measurements should be used.

Additionally, vital signs will also be monitored during study drug infusion, and data will be collected at the following timepoints: a) immediately before the administration of the study drug, and b) immediately after the completion of the administration of the study drug, which includes post-dose saline flushing. Routine monitoring can continue based on local guidelines.

### 8.4.3 Electrocardiograms

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

During study drug infusion, participants should have continuous ECG monitoring as per local guidelines. A 12 lead ECG should be acquired 15 minutes after the end of study drug infusion and evaluated for new abnormalities. Interpretation of the tracing must be made by a qualified physician. 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 ECG abnormalities present at the screening or baseline visit should be reported on the appropriate eCRF. Clinically significant abnormalities must be recorded on the eCRF as either medical history/current medical conditions or adverse events as appropriate. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

The original ECGs 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. ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings at baseline before administration of study treatment and during the study.

### 8.4.4 Clinical safety laboratory tests

A local laboratory will be used for analysis of all specimens collected as part of routine clinical care and will be entered in the eCRF(Table 8-4).

A central laboratory and sponsor designated laboratories will be used for analysis of the following: PK, immunogenicity, serum creatinine, cystatin C, serum purine metabolites, [redacted]

Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Section 10.3.1.

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.

Local laboratory assessments may be performed on an as-needed basis to monitor safety tolerability to study drug (e.g. unscheduled visits).

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

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

In case of significant safety findings or a need to retest abnormal values, the local lab will be used to guide patient management. The results have to be made available to study investigators immediately, and the findings should be included in the eCRFs and the study database, properly identified as either local or central lab values.

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/or initial baseline, a decision regarding whether the result is of clinical significance or not shall be made by the investigator (in consultation with the sponsor) and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to randomization.

Sample(s) will be collected at the time point(s) defined in the Assessment Schedule (Table 1-2).

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.

**Urinalysis**

When available, urine samples will be obtained from urinary catheters. In those patients without a catheter, a mid-stream urine sample (approx. 30 mL) will be obtained in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

**Table 8-4 Local Laboratory evaluations**

| Test Category | Test Name |
|---|---|
| Hematology | Hematocrit, hemoglobin, platelets (platelets count, platelets clumps count, mean platelets volume), erythrocytes, leukocytes, differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils, bands, other (absolute value and percentage) |
| Chemistry | Albumin, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), bicarbonate, gamma-glutamyl-transferase (GGT), lactate dehydrogenase (LDH), C-reactive protein (CRP), calcium, magnesium, phosphate, chloride, sodium, potassium, creatinine, creatinine kinase (CK), direct bilirubin, indirect bilirubin, total bilirubin, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), total protein, triglycerides, blood urea nitrogen (BUN) or urea, uric acid, lipase, amylase, glucose, ferritin, cystatin C. |
| Urinalysis | Microscopic panel (erythrocytes, leukocytes, casts, crystals, bacteria, epithelial cells)<br>Macroscopic panel (dipstick) (color, bilirubin, blood, glucose, ketones, leukocytes esterase, nitrite, pH, protein, specific gravity, urobilinogen) |
| Coagulation | Prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), activated partial thromboplastin time (APTT) |
| Thyroid | T3 [free], T4 [free], Thyroid-stimulating hormone (TSH) |
| Hepatitis markers | Hepatitis B virus surface antigen (HBsAg), anti-HBs, anti-HBc, anti-HCV, HCV polymerase chain reaction if anti-HCV is positive (screening). |
| Pregnancy Test | Serum pregnancy test / urine pregnancy test (refer to Section 8.4.5) |

### 8.4.5 Pregnancy testing

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

At screening, a locally-analyzed serum pregnancy test with beta-human chorionic gonadotropin (β-hCG) must be performed for all females of childbearing potential. Any participant with a positive pregnancy test at screening will be excluded from enrolling in the study. The test result must be negative in order to proceed with the administration of the study treatment.

In general, the levels of a TIN816 in semen is expected to be low, the subsequent levels in female partner would be negligible. Based on this principle, the probability that TIN816 would cause teratogenicity is very low. Therefore, no restrictions will be placed on male participants with regard to sexual activity or condom use.

If participants cannot visit the site to have serum pregnancy tests 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, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. A communication process should be established with the participant so that the site is informed and can verify the pregnancy test results (e.g., following country specific measures).

#### 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 his medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy

2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, follicle stimulating hormone (FSH) testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

### 8.4.6 Appropriateness of safety measurements

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

## 8.5 Additional assessments

No additional tests will be performed on participants entered into this study.

### 8.5.1 Clinical Outcome Assessments (COAs)

Not applicable.

## 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 (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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 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 participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on study-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. The common terminology criteria for adverse events (CTCAE) grade (version 5 or higher).

If CTCAE grading does not exist for an adverse event, use 1=mild; 2=moderate, 3=severe; and 4=life threatening. CTCAE 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
- 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.

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. Alert ranges for laboratory and other test abnormalities are included in Section 10.3.

### 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 International Council for Harmonization 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 2004).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

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). Novartis 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 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:

Sepsis, Septic shock, Acute kidney injury, Multiple organ dysfunction syndrome, Acute respiratory distress syndrome, Disseminated intravascular coagulation, Pneumonia, Hypotension, Fever, Tachypnea, Leucocytosis, Leucopenia, Respiratory alkalosis, Metabolic acidosis.

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. INs 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.

SUSARs will be collected and reported to the competent authorities and relevant ethics committees in accordance with *European (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.

### 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 study participant becomes pregnant, the pregnancy consent form should be presented to the study 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 90 day 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

The following are adverse events of special interest:

Bleeding

TIN816 ability to decrease ADP levels can reduce ADP and thrombin-induced platelet aggregation and is linked to a potential risk of increased bleeding. In the FIH study cohorts 1-

4, inhibition of ADP-induced platelet aggregation was seen in ex vivo whole blood aggregometry assay and was not associated with bleeding AE. In one participant in cohort 3 at 1.0 mg/kg that suffered from trauma and had subsequent surgeries, no abnormal bleeding nor hemorrhage were seen during and after surgical interventions despite inhibition of ex vivo ADP-induced platelet aggregation. In cohort 4 at 2.0 mg/kg, compared to placebo and baseline, no increase in bleeding/clotting time was noted in 5 out of 6 participants receiving TIN816, although a slight increase in closure time was noted up to 2 weeks after TIN816 administration in the ex vivo platelet function assay using a P2Y cartridge. One participant had a slight increase in bleeding/clotting time from baseline to Day 8 (within normal range) and returned to normal values by Day 15.

Standard coagulation tests (including PT, PTT and INR) should be monitored. In the CTIN816B12201 study, TIN816 will not be used in participants who are receiving dual antiplatelet agents; therefore, these participants will be excluded from study participation. In addition, adequate monitoring of respective coagulation parameters will be done in study participants.

Perivascular/vascular mineralization

Perivascular/vascular mineralization of minimal to mild severity was observed in minipig. In the FIH study cohorts 1-4, there was no change in serum calcium nor serum phosphorus noted. No changes were observed in kidney function markers (e.g., eGFR) and no abnormalities were seen in urine dipstick parameters (protein, blood glucose, ketones, bilirubin, urobilinogen, pH, leukocyte esterase, specific gravity). There was no change in cardiovascular parameters (blood pressure, ECG) or joint AE pointing to mineralization.

In the CTIN816B12201 study, the risk is minimized by administration of single dose only and ensuring an appropriate safety margin and dose which was tested in healthy volunteers. In addition, serum calcium, phosphorus and free pyrophosphate levels should be monitored in study participants.

Infusion reactions and hypersensitivity

Injection of a foreign protein into humans may trigger immune response with or without inflammatory signs and symptoms. Such reactions, if they occur, may be immediate or delayed up to several weeks. Since TIN816 is a modified version of a naturally occurring human protein, immunogenicity may occur.

The CTIN816B12201 study will apply single dosing. A prolonged IV infusion time of 2 hours will reduce $C_{max}$ exposure, and a single dose administration of TIN816 will further reduce the exposure duration. Despite the very low risk of a theoretical infusion reaction due to Monocyte chemoattractant protein-1 (MCP-1) related histamine release, signs and symptoms of any allergic reaction should be closely monitored, and IV infusion could be stopped at any time.

Anti-drug antibody mediated reactions (immunogenicity)

As with other therapeutic recombinant proteins, there is a possibility of TIN inducing an immune response in human participants. Presence of host cell proteins in preclinical and clinical TIN816 batches, is also known to enhance the risk of immunogenicity (Vanderlaan et al., 2018). The primary consequence of immunogenicity may be altered PK and

PD properties of the drug, leading to a potential loss in efficacy. There is also a theoretical possibility of immune-mediated reactions.

Development of anti-TIN816 antibodies and their neutralization potential of TIN816 and/or endogenous CD39 will be assessed in dedicated plate and cell-based in-vitro assays and are interpreted in the context of PK, PD and safety. Potential reactions related to such antibodies, such as antibody-mediated arthropathy, should be monitored closely.

## 8.7 Pharmacokinetics

PK serum samples will be collected at the time points defined in the Assessment Schedule (Table 1-2). Two samples will be collected on Day 1: one sample pre-dose and one sample post-dose within 15 minutes at the end of the two hour study drug infusion. In addition, PK samples should be collected at additional days as indicated in Table 1-2, optimally always at that time point of the day when study drug administration started on Day 1 (e.g. Day 2 sample should be taken 24 h after starting TIN816/placebo infusion).

Instructions regarding sample collection, numbering, processing and shipment are outlined in the Laboratory Manual. The exact time of treatment administration, sample number and time of sample collection are recorded for each sample collected in the eCRF. Sampling problems are to be documented in the eCRF and may include but are not limited to hemolyzed or lipemic samples, insufficient sample volumes, and/or a lack of sample collections.

Pharmacokinetic (PK) samples will be evaluated in all participants treated with TIN816.

TIN816 concentrations will be determined in serum by a validated ligand binding assay with a lower limit of quantification (LLOQ) of approximately 10 ng/mL. The detailed method description of analysis will be given in the method validation report. Concentrations below the LLOQ will be reported as “zero” and missing data will be labeled as such in the Bioanalytical Data Report. Values below the LLOQ will be treated as zero for calculation of PK parameters as well as for summary statistics.

For standard pharmacokinetic abbreviations and definitions refer to Appendix 2 (Section 10.2) of this protocol. The following pharmacokinetic parameters will be determined from the serum concentration time data using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher): $C_{max}$, $T_{max}$, $AUC_{last}$, $AUC_{inf}$, $T_{1/2}$, Vz, Cl, and other relevant PK parameters (data permitting).

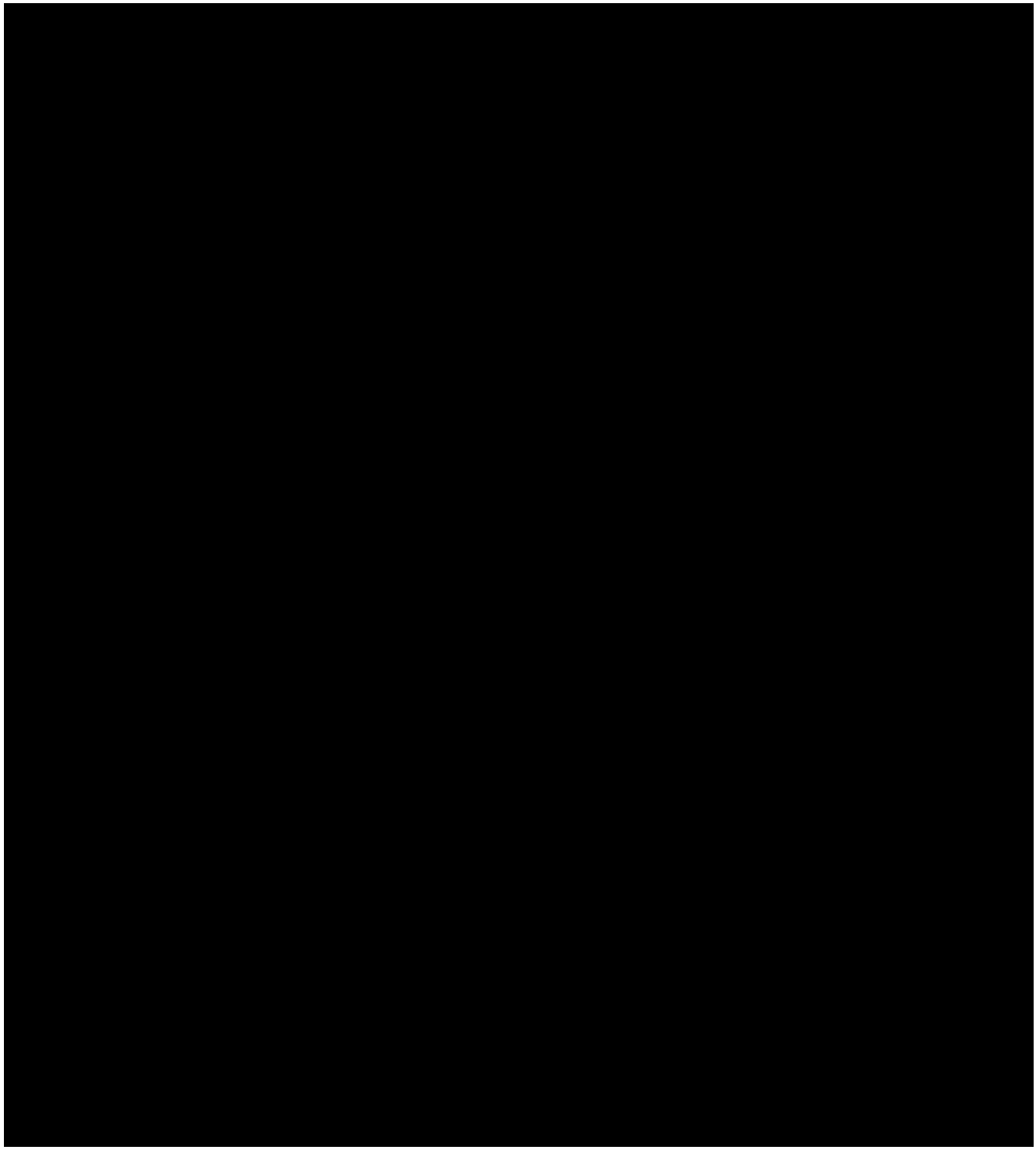
The linear trapezoidal rule will be used for AUC calculation, starting with the initiation of IV infusion. Regression analysis of the terminal elimination phase for the determination of the $T_{1/2}$ will include at least 3 data points after $C_{max}$. If the adjusted $R^2$ value of the regression analysis of the terminal phase is less than 0.75, no values will be reported for the corresponding $T_{1/2}$. If the $T_{1/2}$ is not calculable, $AUC_{inf}$, Vz and CL will not be reported and $AUC_{last}$ will be used.

Urine collected for creatinine clearance as defined in the Assessment Schedule (Table 1-2) will also be saved for potential urine PK analysis (refer to Creatinine Clearance Section 8.3.1 for additional sample collection details).

TIN816 urine concentrations will be determined by a qualified ligand binding assay. Concentrations below the LLOQ will be reported as “zero” and missing data will be labeled as

such in the Bioanalytical Data Report. Values below the LLOQ will be treated as zero for calculation of PK parameters as well as for summary statistics.

If data permit, renal clearance (CLr) will be determined using blood and urine TIN816 concentrations, the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher).



Sample(s) will be collected at the time point(s) defined in the Assessment Schedule (Table 1-2).

## 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 (Table 1-2). Unscheduled ADA samples may be collected in case of a safety event (Section 8.4) which is considered to be 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 assay approach. 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.

[redacted]

## 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

## 9.1 Analysis sets

The Randomized Analysis Set (RAS) consists of all randomized participants. This analysis set will not be used for any analyses and is solely intended for providing complete information on how participants were randomized.

The PK analysis set will include all participants who survive Day 7 with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received complete study drug regardless of infusion duration.

The PD analysis set will include all participants with available PD data. Participants will be analyzed according to actual study treatment received.

The full analysis set (FAS) comprises all participants to whom study treatment has been assigned by randomization. According to the intent to treat principle, participants will be analyzed according to the treatment they have been assigned to during the randomization procedure. Mis-randomized participants, that is, participants who were randomized incorrectly

and did not receive any study drug will be excluded from this set. This will be the analysis set used for all efficacy analyses.

The safety set (SAF) includes all participants who received one dose of study treatment. Participants will be analyzed according to the study treatment received, where treatment received is defined as the participant took at least one dose of that study treatment regardless treatment group randomized to. This will be the analysis set used for safety analysis except for PK/PD analysis.

## 9.2 Statistical analyses

### 9.2.1 General considerations

This study is to investigate PK, safety, tolerability and efficacy. There is no inferential analysis to be performed. The analyses will be mainly based on descriptive statistics.

Categorical data will be presented as frequencies and percentages, including quartiles. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For PK parameters, n, mean, median, minimum, maximum, coefficient of variation (CV (%)) to mean, geometric mean, and CV(%) to geometric mean will be presented.

The baseline visit is defined at Day 1 unless specified. Parameters that are not collected at Day 1, the screening visit will be used as baseline.

For hospital-acquired AKI, a stable serum creatinine obtained in the hospital prior to AKI will be used used as reference baseline: otherwise, a baseline serum creatinine is defined in the following order of preference:

1. Median value within 3 months of the hospital admission. If not available:
2. Median value between 3 and 6 months prior to hospital admission. If not available:
3. At hospital admission.

The study will exclude participants whose AKI diagnosis or AKI presence based on investigator's clinical judgement has a period longer than 48 hours prior to study drug administration because of the criticality of an early treatment for patients with SA-AKI.

### 9.2.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively for all participants and by treatment group.

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

### 9.2.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented. Descriptive statistics will be provided.

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

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

The primary endpoint is all TIN816 concentrations in serum PK parameters, including $C_{max}$, $T_{max}$, $T_{1/2}$, Cl, $V_z$, $AUC_{last}$ and $AUC_{inf}$. It will be summarized descriptively for participants with at least one dose of study treatment.

There is no inferential analysis to be performed.

### 9.3.1 Definition of primary endpoint(s)

The primary endpoint is all PK related parameters (Table 9-1). The analyses will be performed on PK population set.

TIN816 serum concentration data will be listed by treatment, participant and visit/sampling time point. Descriptive summary statistics of TIN816 serum concentration data will be provided by treatment, and visit/sampling time point, including the frequency of concentrations below the LLOQ and reported as zero.

Summary statistics will include mean (arithmetic and geometric), Standard Deviation (SD), CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented. PK data will also be represented graphically (including spaghetti plots, boxplots and mean plots with SD) by treatment arm, participant and visit.

Drug concentrations below LLOQ will be treated as missing for the calculation of the geometric means and geometric CV%, and as zero for all other calculations including calculation of PK parameters. Pharmacokinetic parameters will be calculated as described in Section 8.7 and will be listed by treatment and participant and summarized by treatment with descriptive statistics as listed below.

The pharmacokinetic parameters listed in the table below will be determined from the serum concentration time data using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher). Other relevant PK parameters may be added (data permitting).

**Table 9-1 Non-compartmental pharmacokinetic parameters**

| PK parameter | Definition |
|---|---|
| $AUC_{last}$ | The AUC from time zero to the last measurable concentration sampling time (tlast) (mass × time × volume$^{-1}$) |
| $AUC_{inf}$ | The AUC from time zero to infinity (mass × time × volume$^{-1}$) |
| $C_{max}$ | The maximum (peak) observed serum drug concentration after single dose administration (mass × volume$^{-1}$) |

| | |
|---|---|
| $T_{max}$ | The time to reach maximum (peak) serum drug concentration after single dose administration (time) |
| $T_{1/2}$ | The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives |
| Cl | The total body clearance of drug from the serum following intravenous administration (volume × $time^{-1}$) |
| $V_z$ | The apparent volume of distribution during terminal phase following intravenous administration (associated with λz) (volume) |

### 9.3.2 Statistical model, hypothesis, and method of analysis

The analysis will be mainly based on summary statistics, no inferential statistical analysis is planned. The graphical summaries on PK concentration will also be provided.

### 9.3.3 Handling of intercurrent events of primary estimand (if applicable)

All PK data will be presented as recorded in the descriptive statistics. For participants who discontinue from study or death where PK information is not available, the impact of this on the interpretation of the results will be considered. Additional summaries as needed to support this interpretation may be presented. It is not intended to impute missing data after discontinuation.

### 9.3.4 Handling of missing values not related to intercurrent event

Missing primary endpoint values due to protocol deviations or other issues related to a pandemic are not anticipated as measures have been put in place, where possible, to allow for the protocol assessments to be conducted. In case missing values do occur for such reasons, only data available will be used.

### 9.3.5 Sensitivity analyses

No sensitivity analyses are planned.

### 9.3.6 Supplementary analysis

No subgroup analyses or other supplementary analyses are planned.

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

The analysis for secondary endpoints will be based on descriptive statistics by treatment group.

### 9.4.1 Efficacy and/or pharmacodynamic endpoint(s)

The secondary endpoint is all safety. There is no efficacy analysis in secondary endpoint.

### 9.4.2 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).

#### 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 participant and investigator-blind 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.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

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

The number (and proportion) of participants with adverse events of special interest/related to identified and potential risks will be summarized by treatment.

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.

The following adverse events will be counted during 90-day study period:

- These events are those with an onset after the start of the treatment period, or which were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected of study treatment relationship, or developed into SAEs after the start of the treatment period.

#### Vital signs

Summary statistics will be provided for all vital signs data by treatment and visit/time. Where ranges are available, abnormalities (and relevant orthostatic changes) will be listed by treatment group, participant, and visit/time. If appropriate, summary statistics of the occurrence of abnormalities may be provided by treatment.

#### Clinical laboratory evaluations

Summary statistics for all laboratory data will be provided by treatment and visit/time. Shift tables using the low/normal/high/ (low and high) classification may be used, as appropriate, to compare baseline to the worst on-treatment value. Where normal ranges are available, abnormalities in laboratory data will be listed by treatment group, participant, and visit/time.

Graphical displays of selected safety parameters (e.g. hematological parameters, thyroid and reproductive hormone levels) over time will be provided by treatment group.

### Immunogenicity

All immunogenicity results will be listed by cohort, treatment group, subject and visit/time. The listing will contain ADA status (negative or positive) and for ADA-positive samples a titer and ADA neutralization potential of TIN816 and/or endogenous CD39. Subjects with one or more treatment emergent ADAs are counted as ADA-positive subjects and they will be summarized by treatment arm to derive an ADA incidence. Incidences for neutralizing ADAs will be assessed as well, if appropriate. Visualizations overlaying ADA status including characterizations, along with PK concentration and potentially efficacy read-outs, will be presented.

## 9.4.3 Pharmacokinetics

Please refer to Section 9.3.1 for details.

[redacted]

## 9.6 (Other) Safety analyses

Not applicable

## 9.7 Other analyses

No other analyses are planned.

## 9.8 Interim analysis

An interim analysis is planned when approximately 8 patients complete Day 14 visit. The study will continue to recruit participants while this interim analysis is being completed up to a cap of 12 participants. The study will continue without modification if a similar PK profile of TIN816 to that in the healthy volunteers (CTIN816A02101) is confirmed. Otherwise, the study may be amended with options of additional arms for testing a higher dose, multiple bolus doses, extended infusion dosing regimens or combination of bolus dose and extended infusion. The total sample size may increase to provide adequate PK data after dose level and/or dose regimens are changed. In the circumstance that the data from the first IA does not provide sufficient PK data to support the phase 2b, an additional IA will be added when all 20 patients complete Day 14 visit.

## 9.9 Sample size determination

The sample size was determined to achieve a target margin of error of the mean for PK parameters $C_{max}$ and $AUC_{inf}$. The assumption of geometric coefficient of variation (GCV) rate was referenced from FIH study (CTIN816A02101) interim safety report.

### 9.9.1 Primary endpoint(s)

The proposed sample size of 15 participants in TIN816 study treatment arm is sufficient to achieve a target margin of error not larger than 15% of the geometric mean (half-width of a 2-sided 95% confidence interval for the PK parameters) assuming geometric coefficient of variant (GCV) is 0.25 in AUCinf or $C_{max}$. It will also be able to exclude a 1.5-fold change in AUCinf or $C_{max}$ assuming GCV increased variability of 0.75.

Different GCV rates and corresponding precision of confidence interval are shown in below table.

**Table 9-2 Sensitivity of confidence interval precision to change in assumption for GCV rate**

| GCV rate * | Width of 95% confidence interval |
|---|---|
| 0.25 | [GCV mean/1.15, GCV mean x 1.15] |
| 0.50 | [GCV mean/1.31, GCV mean x 1.31] |
| 0.75 | [GCV mean/1.47, GCV mean x 1.47] |

*GCV mean of AUCinf and $C_{max}$ for 2 mg/kg are 8% and 22%, respectively in FIH study (CTIN816A02101) interim safety reports

# 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 Code of Federal Regulation (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 or their legally authorized representative (defined as individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the procedure(s) involved in the research) and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives 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 or their legally authorized representative.

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

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her level of understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

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 Global Informed Consent
- Legal Authorized Representative consent

Both consents will also include:

- 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

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

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 prevail 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.

Novartishas 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 Steering Committee

The Steering Committee (SC) may be comprised of investigators participating in the study. A Steering Committee member will not be a member of the data monitoring Committee (DMC) and Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

### 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.

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 eCRFs. 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 electronic data capture (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 contract research organization (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 and study completion, as well as randomization codes and data about the study treatment administered to the participant will be tracked using an IRT system. 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. Unblinded data will be available during the trial conducting period for programmer and statistician. 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 eCRF. Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF 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 Good Clinical Practice (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 /Computing Research Association (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 . 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 and EudraCT. 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 patient 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

| | |
|---|---|
| ACE | Angiotensin-converting enzyme |
| ADA | Anti-drug antibodies |
| ADP | Adenosine diphosphate |
| AE | Adverse event |
| AIN | Acute interstitial nephritis |
| AKI | Acute kidney injury |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| AMP | Adenosine monophosphate |
| APACHE II | Acute physiology and chronic health evaluation II |
| APTT | Activated partial thromboplastin time |
| AST | Aspartate transaminase |
| ATC | Anatomical therapeutic chemical |
| ATP | Adenosine triphosphate |
| AUC | Area under the curve |
| BMI | Body mass index |
| BP | Blood pressure |
| BUN | Blood urea nitrogen |
| CDER | Center for drug evaluation and research |
| CFR | Code of federal regulations |
| CHMP | Committee for medicinal products for human use |
| CIOMS | Council for international organizations of medical sciences |
| CK | Creatinine kinase |
| CKD | Chronic kidney disease |
| CLP | Cecal ligation and puncture |
| CLr | Renal clearance |
| Cmax | Maximum serum concentration |
| CMO&PS | Chief medical office and patient safety |
| CO2 | Carbon dioxide |
| COA | Clinical outcome assessment |
| CONSORT | Consolidated standards of reporting trials |
| COVID-19 | Coronavirus SARS-CoV-2 |
| CPAP | Continuous positive airway pressure |
| CPK | Creatine phosphokinase |
| CR | Creatinine |
| CRA | Computing Research Association |
| CrCl | Creatinine clearance |
| CRF | Case report/record form (paper or electronic) |
| CRO | Contract research organization |

| | |
|---|---|
| CRP | C-reactive protein |
| CSR | Clinical study report |
| CTCAE | Common terminology criteria for adverse events |
| CTT | Clinical trial team |
| CV | Coefficient of variation |
| DILI | Drug-induced liver injury |
| DIN | Drug inducted nephrotoxicity |
| DLT | Dose limiting toxicity |
| DMC | Data monitoring committee |
| ECG | Electrocardiogram |
| eCRF | Electronic case report/record form |
| EDC | Electronic data capture |
| eGFR | Estimated glomerular filtration rate |
| EMA | European medicines agency |
| EOS | End of Study |
| eSAE | Electronic serious adverse event |
| EU | European Union |
| FAS | Full analysis set |
| FDA | Food and drug administration |
| FIH | First in human |
| FiO2 | Fraction of inspired oxygen |
| FSH | Follicle stimulating hormone |
| GCP | Good clinical practice |
| GCS | Global clinical supply |
| GCV | Geometric coefficient of variation |
| GFR | Glomerular filtration rate |
| GGT | Gamma-glutamyl transferase |
| GLDH | Glutamate dehydrogenase |
| h | Hour |
| HBsAg | Hepatitis B virus surface antigen |
| HBV | Hepatitis B Virus |
| HCV | Hepatitis C Virus |
| HDL | High density lipoprotein |
| HDU | High dependency care unit |
| HIV | Human immunodeficiency virus |
| HRQoL | Health-related quality of life |
| HV | Healthy volunteer |
| IA | Interim analysis |
| 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 |
| IDFU | Investigational directions for use |
| IEC | Independent ethics committee |
| IG | Immunogenicity |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| 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 |
| IV | Intravenous |
| KDIGO | Kidney disease improving global outcomes |
| LDH | Lactate dehydrogenase |
| LDL | Low density lipoprotein |
| LFTs | Liver function tests |
| LLOQ | Lower limit of quantification |
| LOCF | Last observation carried forward |
| LPLV | Last patient last visit |
| LPS | Lipopolysaccharide |
| MAKE | Major adverse kidney event |
| MCP-1 | Monocyte chemoattractant protein-1 |
| MedDRA | Medical dictionary for regulatory activities |
| mg | Milligram(s) |
| mL | Milliliter(s) |
| MRI | Magnetic resonance imaging |
| Nab | Neutralizing antibody |
| NOAEL | No observed adverse effect level |
| NSAID | Non-Steroidal Anti-inflammatory Drug |
| PaCO2 | Carbon dioxide partial pressure |
| PaO2 | Partial pressure of oxygen |
| PCR | Protein-creatinine ratio |
| PD | Pharmacodynamic(s) |
| PEEP | Positive end-expiratory pressure |
| PK | Pharmacokinetic(s) |
| PPi | Inorganic pyrophosphate |
| PT | Prothrombin time |
| PTT | Partial thromboplastin time |
| QTcF | QT interval corrected by Fridericia's formula |
| RAS | Randomized analysis set |

| | |
|---|---|
| RPGN | Rapidly progressive glomerular nephritis |
| RRT | Renal replacement therapy |
| SA-AKI | Sepsis-associated acute kidney injury |
| SAE | Serious adverse event |
| SAF | Safety set |
| SC | Steering committee |
| SD | Standard deviation |
| SMQ | Standardized MedDRA Query |
| SoA | Schedule of activities |
| SOFA | Sequential organ failure assessment |
| SUSAR | Suspected unexpected serious adverse reaction |
| SWFI | Sterile water for injection |
| Tmax | Time to maximum concentration |
| TSH | Thyroid-stimulating hormone |
| ULN | Upper limit of normal |
| ULOQ | Upper limit of quantification |
| US | United States |
| UTI | Urinary tract infection |
| VA/NIH | Veterans affairs/National Institutes of Health |
| WB | Whole blood |
| WHO | World health organization |

### 10.2.2 Definitions

| | |
|---|---|
| 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) |
| Assessment | A procedure used to generate data required by the study |
| AUCinf | The AUC from time zero to infinity (mass × time × volume$^{-1}$) |
| AUClast | The AUC from time zero to the last measurable concentration sampling time (tlast) (mass × time × volume$^{-1}$) |
| Biologic Samples | A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant |
| Cl | The total body clearance of drug from the serum following intravenous administration (volume × time$^{-1}$) |
| Clinical Outcome Assessment (COA) | A measure that describes or reflects how a participant feels, functions, or survives |
| 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. |
| Cmax | The maximum (peak) observed serum drug concentration after single dose administration (mass × volume$^{-1}$) |
| 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 |

| | |
|---|---|
| Control drug | A study intervention (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 intervention 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. |
| 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 Novartis 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. |
| Healthy volunteer | A person with no known significant health problems who volunteers to be a study participant |
| 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 |
| 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, 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) |
| 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-Reported Outcome (PRO) | A measurement based on a report that comes directly from the participant about the status of a participant's health condition without amendment or interpretation of the participant'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 |
| Perpetrator drug | A drug which affects the pharmacokinetics of the other drug |
| 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. |
| 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 |
| Remote | Describes any trial activities performed at a location that is not the investigative site. |
| Rescreening | 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 |
| 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 |
| 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 |
| T1/2 | The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives |

| | |
|---|---|
| Tele-visit | Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the Investigator will conduct the trial. |
| Tmax | The time to reach maximum (peak) serum drug concentration after single dose administration (time) |
| Treatment arm/group | A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. |
| Treatment of interest | The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment. |
| 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. |
| Vz | The apparent volume of distribution during terminal phase following intravenous administration (associated with λz) (volume) |
| 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.<br>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. |

## 10.3 Appendix 3: Clinical laboratory tests

### 10.3.1 Clinically notable laboratory values and vital signs

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.

**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 | $\times 10^6/\mu L$ | >50% increase, >30% decrease | $\times 10^{12}/L$ |
| 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 | $\times 10^3/\mu L$ | >50% increase, >50% decrease | $\times 10^9/L$ |
| Platelet Count | >75% increase, >50% decrease | $\times 10^3/\mu L$ | >75% increase, >50% decrease | $\times 10^9/L$ |
| **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 |
| Creatine phosphokinase (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% | mEq/L | >20% increase, >20% | mmol/L |

| Parameter | Conventional Alert Value | Conventional Units | SI Alert Value | SI Units |
|---|---|---|---|---|
| | decrease, or any value >5.3 | | decrease, or any value >5.3 | |
| 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.

Thank You letter

Plain language trial summary - after Clinical study report (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.

If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate eCRF.

If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.

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.

Imaging such as abdominal US, CT or Magnetic Resonance Imaging (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 eCRF.

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

**Table 10-2 Liver event and laboratory trigger definitions**

| | **Definition/ threshold** |
|---|---|
| If ALT or AST normal at baseline: | |
| Liver laboratory triggers | 3 × ULN < ALT or AST ≤ 5 × ULN<br>TBL > ULN* |

| | |
|---|---|
| Liver events | ALT or AST > 5 × ULN<br>ALP > 2 × ULN (in the absence of known bone pathology)<br>Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome)<br>ALT or AST > 3 × ULN AND (TBL > 2 × ULN OR INR > 1.5)<br>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)<br>Any clinical event of jaundice (or equivalent term)<br>ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia<br>Any adverse event potentially indicative of a liver toxicity |
| If ALT or AST elevated at baseline: | |
| Liver laboratory triggers | ALT or AST > 2 × baseline or > 200 U/L (whichever occurs first)<br>TBL > ULN* |
| Liver events | ALT or AST > 3 × baseline or > 300 U/L (whichever occurs first)<br>(ALT or AST > 2 × baseline or > 200 U/L [whichever occurs first]) AND (TBL > 2 × ULN OR INR > 1.5)<br>ALT or AST > 5 × ULN<br>ALP > 2 × ULN (in the absence of known bone pathology)<br>Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome)<br>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)<br>Any clinical event of jaundice (or equivalent term)<br>(ALT or AST > 2 × baseline or > 200 U/L [whichever occurs first]) accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia<br>Any adverse event potentially indicative of a liver toxicity |

* Fractionate bilirubin, evaluate for cholestatic liver injury (ALP) or alternative causes of bilirubin elevation. Treat alternative causes according to local institutional guidelines

**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:**<br>ALT > 3 × ULN<br>**If elevated at baseline:**<br>ALT > 2 × baseline<br>or > 300 U/L (whichever occurs first) | Normal<br>For participants with Gilbert's syndrome: No change in baseline TBL | None | • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and Glutamate dehydrogenase (GLDH) in 48-72 hours.<br>• Follow-up for symptoms. |
| **If normal at baseline:**<br>ALT > 5 × ULN for more than two weeks<br>**If elevated at baseline:**<br>ALT > 3 × baseline<br>or > 300 U/L (whichever occurs first) for more than two weeks | Normal<br>For participants with Gilbert's syndrome: No change in baseline TBL | None | • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours.<br>• Follow-up for symptoms.<br>• Initiate close monitoring and workup for competing etiologies. |
| **If normal at baseline:**<br>ALT > 8 × ULN | Normal | None | |
| **ALT increase with bilirubin increase:** | | | |
| **If normal at baseline:**<br>ALT > 3 × ULN<br>**If elevated at baseline:**<br>ALT > 2 × baseline<br>or > 300 U/L (whichever occurs first) | TBL > 2 × ULN (or INR > 1.5)<br>For participants with Gilbert's syndrome: Doubling of direct bilirubin | None | |
| **If normal at baseline:**<br>ALT > 3 × ULN<br>**If elevated at baseline:**<br>ALT > 2 × baseline<br>or > 300 U/L (whichever occurs first) | Normal or elevated | Severe fatigue, nausea, vomiting, right upper quadrant pain | |

**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 | • Maintain treatment<br>• Repeat Liver Function Tests (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) | • Interrupt treatment<br>• Repeat LFTs within 48-72 hours<br>• Hospitalize if clinically appropriate<br>• Establish causality<br>• Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate eCRF | Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT)<br>Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin) |
| > 10 × ULN | • Discontinue the study treatment immediately<br>• Hospitalize the participant<br>• Establish causality<br>• Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate eCRF | ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution (frequency at investigator discretion) |
| Any AE potentially indicative of a liver toxicity | • Consider study treatment interruption or discontinuation<br>• Hospitalization if clinically appropriate<br>• Establish causality<br>• Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate eCRF | Investigator discretion |

Based on the Investigator's clinical judgement, investigation(s) of the 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, and/or exclusion of underlying liver disease.

## 10.6 Appendix 6: Renal safety monitoring

Once a participant is exposed to study treatment, the following two categories of abnormal renal laboratory alert values should be assessed during the study period:

Serum creatinine increase ≥ 25% compared to baseline during normal hydration status

Any one of the following:

Urine protein-creatinine ratio (PCR) ≥1g/g or ≥100 mg/mmol, OR

New onset dipstick proteinuria ≥ 3+, OR

New onset dipstick hematuria ≥ 3+ (after excluding menstruation, Urinary tract infection (UTI), extreme exercise, or trauma)

Abnormal renal event findings must be confirmed within 24-48 hours after the first assessment.

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events should be monitored and followed-up by the Investigator or designated trial staff as summarized in Table 10-5.

### 10.6.1 Specific Renal Alert Criteria and Actions and Event Follow-up

**Table 10-5 Specific renal alert criteria and actions**

| Renal event | Actions |
|---|---|
| Confirmed serum creatinine increase of 25-49% from baseline | • Consider causes and possible interventions<br>• Follow-up within 2-5 days |
| Confirmed serum creatinine increase ≥ 50% from baseline (corresponds to KDIGO criterion for acute kidney injury) | • Consider causes and possible interventions<br>• Repeat assessment within 24-48h if possible<br>• Consider patient hospitalization and specialized treatment |
| New onset dipstick proteinuria ≥ 3+<br>OR<br>Protein-creatinine ratio (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory) | • Consider causes and possible interventions<br>• Assess serum albumin and serum total protein<br>• Repeat assessment to confirm |
| New onset of hematuria ≥ 3+ on urine dipstick | Assess and document<br>• Repeat assessment to confirm<br>• Exclude infection, trauma, bleeding from the distal urinary tract or bladder, menstruation<br>• Distinguish hemoglobinuria from hematuria<br>• Urine sediment microscopy<br>• Assess serum creatinine<br>• Consider bleeding disorder |

#### 10.6.1.1 Follow-up of renal events

Assess and document:

Urine dipstick and sediment microscopy evidence of drug-induced nephrotoxicity (DIN): crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells.

Blood pressure and body weight.

Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium) and uric acid.

Urine output.

Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and any additional local diagnostic procedures performed in the CRF.

Monitor patient regularly (frequency at investigator's discretion) until:

Event resolution: serum creatinine within 10% of baseline or PCR < 1g/g creatinine, or albumin-creatinine ratio < 300 mg/g creatinine

Or

Event stabilization: serum creatinine level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.

Analysis of urine markers in samples collected over the course of the DIN event.

# 11 References

References are available upon request

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

Baumann TJ, Staddon JE, Horst HM, et al (1987) Minimum urine collection periods for accurate determination of creatinine clearance in critically ill patients. Clin Pharm; 6(5):393-8.

Bellomo R, Cass A, et al (2012) An observational study fluid balance and patient outcomes in the Randomized Evaluation of Normal vs. Augmented Level of Replacement Therapy trial. Crit Care Med; 40(6):1753-60.

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

Burnstock G, Verkhratsky A (2010) Long-term (trophic) purinergic signalling: purinoceptors control cell proliferation, differentiation and death. Cell Death Dis; (1):1.

Carlier M, Dumoulin A, Janssen A, et al (2015) Comparison of different equations to assess glomerular filtration in critically ill patients. Intensive Care Med; 41(3):427-35.

CDER (2005) Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. https://www.fda.gov/media/72309/download

CHMP (2006) Committee for human medicinal products, European Agency for the Evaluation of Medicinal Products. Guideline on clinical investigation of medicinal products for the treatment of sepsis. London, UK. CHMP/EWP/4713/03 20.

CHMP (2017) Committee for medicinal products for human use. EMA/829219/2017

Chua HR, Wong WK, Ong VH, et al (2020) Extended Mortality and Chronic Kidney Disease After Septic Acute Kidney Injury. J Intensive Care Med; 35(6):527-535.

Cohen J, Vincent JL, Adhikari NKJ, et al (2015) Sepsis: a roadmap for future research. Lancet Infect Dis; 15(5): 581-614.

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

de Grooth HJ, Geenen IL, Girbes AR, et al (2017) SOFA and mortality endpoints in randomized controlled trials: a systematic review and meta-regression analysis. Crit Care; 21(1):1-9.

Delgado C, Baweja M, Crews DC, et al (2021) A Unifying Approach for GFR Estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease. Am J Kidney Dis; 32:2994–3015.

Devine BJ (1974) Gentamicin Therapy. Drug Intell Clin Pharm; 8:650–5

Dwyer KM, Kishore BK, Robson SC (2020) Conversion of extracellular ATP into adenosine: a master switch in renal health and disease. Nat Rev Nephrol; 16(9):509-524.

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.

Fleischmann C, Scherag A, Adhikari NK, et al (2016) Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. Am J Respir Crit Care Med;193(3):259-72.

Fleischmann-Struzek C, Mikolajetz A, Schwarzkopf D, et al (2018) Challenges in assessing the burden of sepsis and understanding the inequalities of sepsis outcomes between National Health Systems: secular trends in sepsis and infection incidence and mortality in Germany. Intensive Care Med; (44)11:1826-1835.

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.

Guan Z, Inscho EW (2011) Role of adenosine 5'-triphosphate in regulating renal microvascular function and in hypertension. Hypertension; 58(3): 333-40.

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.

ICH E2D (2004) Clinical Safety Data Management: Definitions and Standards for expedited reporting (Internet) Available from: <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific guideline/2009/09/WC500002807.pdf> (Accessed 02-Dec-2016).

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.

Imaeda T, Nakada TA, Takahashi N, et al (2021) Trends in the incidence and outcome of sepsis using data from a Japanese nationwide medical claims database-the Japan Sepsis Alliance (JaSA) study group. Crit Care; 25(1): 338.

KDIGO (2012) Clinical Practice Guideline for Acute Kidney Injury (Internet) Available from: <http://https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf> (Accessed 28-Mar-2022).

Kellum JA, Artigas A, Gunnerson KJ, et al (2021) Use of Biomarkers to Identify Acute Kidney Injury to Help Detect Sepsis in Patients With Infection. Crit Care Med; 49(4):e360-e368.

Knaus WA, Draper EA, Wagner DP, et al (1985) APACHE II: a severity of disease classification system. Crit Care Med; 13(10):818-29.

Ledderose C, Bao Y, Kondo Y, et al (2016) Purinergic Signaling and the Immune Response in Sepsis: A Review. Clin Ther; 38(5):1054-65.

Li X, Kondo Y, Bao Y, et al (2017) Systemic Adenosine Triphosphate Impairs Neutrophil Chemotaxis and Host Defense in Sepsis. Crit Care Med; 45(1): e97-e104.

Liu J, Xie H, Ye Z, et al (2020) Rates, predictors, and mortality of sepsis-associated acute kidney injury: a systematic review and meta-analysis. BMC Nephrol; 21(1):318.

Lopez ON, Cambiaso-Daniel J, Branski LK, et al (2017) Predicting and managing sepsis in burn patients: current perspectives. Ther Clin Risk Manag; 13:1107-1117.

Mayr FB, Yende S, Angus DC (2014) Epidemiology of severe sepsis. Virulence; 5(1):4-11.

Menzies RI, Tam FW, Unwin RJ, et al (2017) Purinergic signaling in kidney disease. Kidney Int; 91(2):315-323.

Palevsky PM, Zhang JH, O'Connor TZ, et al (2008) Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med; 361(24):7-20.

Peerapornratana S, Manrique-Caballero CL, Gómez H, et al (2019) Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. Kidney Int; 96(5):1083-1099.

Peters E, Antonelli M, Wittebole X, et al (2018) A worldwide multicentre evaluation of the influence of deterioration or improvement of acute kidney injury on clinical outcome in critically ill patients with and without sepsis at ICU admission: results from The Intensive Care Over Nations audit. Crit Care; 22(1):1-11.

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):1227-1237.

Pickering JW, Endre ZH (2012) Challenges facing early detection of acute kidney injury in the critically ill. World J Crit Care Med; 1(3):61-6.

Pickkers P, Heemskerk S, Schouten J, et al (2012) Alkaline phosphatase for treatment of sepsis-induced acute kidney injury: a prospective randomized double-blind placebo-controlled trial. Crit Care; 16(1):R14.

Pickkers P, Mehta RL, Murray PT, et al (2018) Effect of Human Recombinant Alkaline Phosphatase on 7-Day Creatinine Clearance in Patients With Sepsis-Associated Acute Kidney Injury: A Randomized Clinical Trial. JAMA; 320(19):1998-2009.

Prowle JR, Kolic I, Purdell-Lewis J, et al (2014) Serum creatinine changes associated with critical illness and detection of persistent renal dysfunction after AKI. Clin J Am Soc Nephrol; 9(6):1015-23.

Rhee C, Dantes R, Epstein L, et al (2017) Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009-2014. JAMA; 318(13):1241-1249.

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.

Rudd KE, Johnson SC, Agesa KM, et al (2020) Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet;395(10219):200-211.

Sam KG, Kondabolu K, Pati D, et al (2009) Poisoning severity score, APACHE II and GCS: effective clinical indices for estimating severity and predicting outcome of acute organophosphorus and carbamate poisoning. J Forensic Leg Med; 16(5):239-47.

Scialli AR, Bailey G, Beyer BK, et al (2016) Potential seminal transport of pharmaceuticals to the conceptus. Reprod Toxicol; 59:22-30.

Sumi Y, Woehrle T, Chen Y, et al (2014) Plasma ATP is required for neutrophil activation in a mouse sepsis model. Shock; 42(2): 142-7.

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.

Tian H, Zhou J, Du B (2019) Epidemiology of Sepsis-3 in a sub-district of Beijing: secondary analysis of a population-based database. Chin Med J; 132(17):2039-45.

Vanderlaan M, Zhu-Shimoni J, Lin S, et al (2018) Experience with host cell protein impurities in biopharmaceuticals. Biotechnol Prog; 34(4):828-837.

Vincent JL, de Mendonça A, Cantraine F, et al (1998) Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med; 26(11):1793-800.

Vincent JL, Moreno R, Takala J, et al (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med; 707-10.

Yu WK, McNeil JB, Wickersham NE, et al (2021) Angiopoietin-2 outperforms other endothelial biomarkers associated with severe acute kidney injury in patients with severe sepsis and respiratory failure. Crit Care; 25(1):1-12.