NOVARTIS

Clinical Development

TIN816

CTIN816A12201 / NCT05524051

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

Statistical Analysis Plan (SAP)

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List of abbreviations

ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse events of special interest
AKIN	Acute Kidney Injury Network
ATC	Anatomical Therapeutic Classification
CCI	
CPB	Cardio-pulmonary bypass
CSR	Clinical Study report
CV	Coefficient of variation
DMC	Data monitoring committee
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
FFP	Fresh frozen plasma
IA	Interim Analysis
IG	Immunogenicity
KDIGO	Kidney disease improving global outcome criteria
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
MAKE	Major adverse kidney event
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mg	Milligram(s)
PD	Pharmacodynamics
CCI	
PoC	Proof of concept
PPoS	Predictive probability of success
PRO	Participant-reported Outcomes
PT	Preferred Term
QoL	Quality of Life questionnaire
RAP	Report and Analysis Plan
RIFLE	Risk, Injury, Failure, Loss of kidney function, and Ens-stage kidney disease
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCr	Serum creatinine
SD	Standard deviation
SOC	System Organ Class
TFLs	Tables, Figures, Listings
ULN	Upper limit of normal
ULOQ	Upper limit of quantification

1 Introduction

The Statistical analysis plan (SAP) describes implementation of the statistical analysis planned in the protocol for the Clinical Study Report (CSR) for trial "CTIN816A12201", A randomized, multi-centric, placebo-controlled, participant and investigator-blinded study to evaluate the safety, tolerability and efficacy of TIN816 in adult participants at risk for acute kidney injury following cardiac surgery. The SAP also includes some of the analyses that were prepared for Data Monitoring Committee (DMC) meetings conducted while the study was ongoing.

The content of this SAP is based on the

- Protocol CTIN816A12201 version v02, dated 25-Jan-2024.

1.1 Study design

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

There will be 3 groups in the study:

- Placebo
- TIN816 [redacted] mg/kg; participants enrolling under original protocol and amendment 1
- TIN816 [redacted] mg/kg from protocol amendment 2 onwards

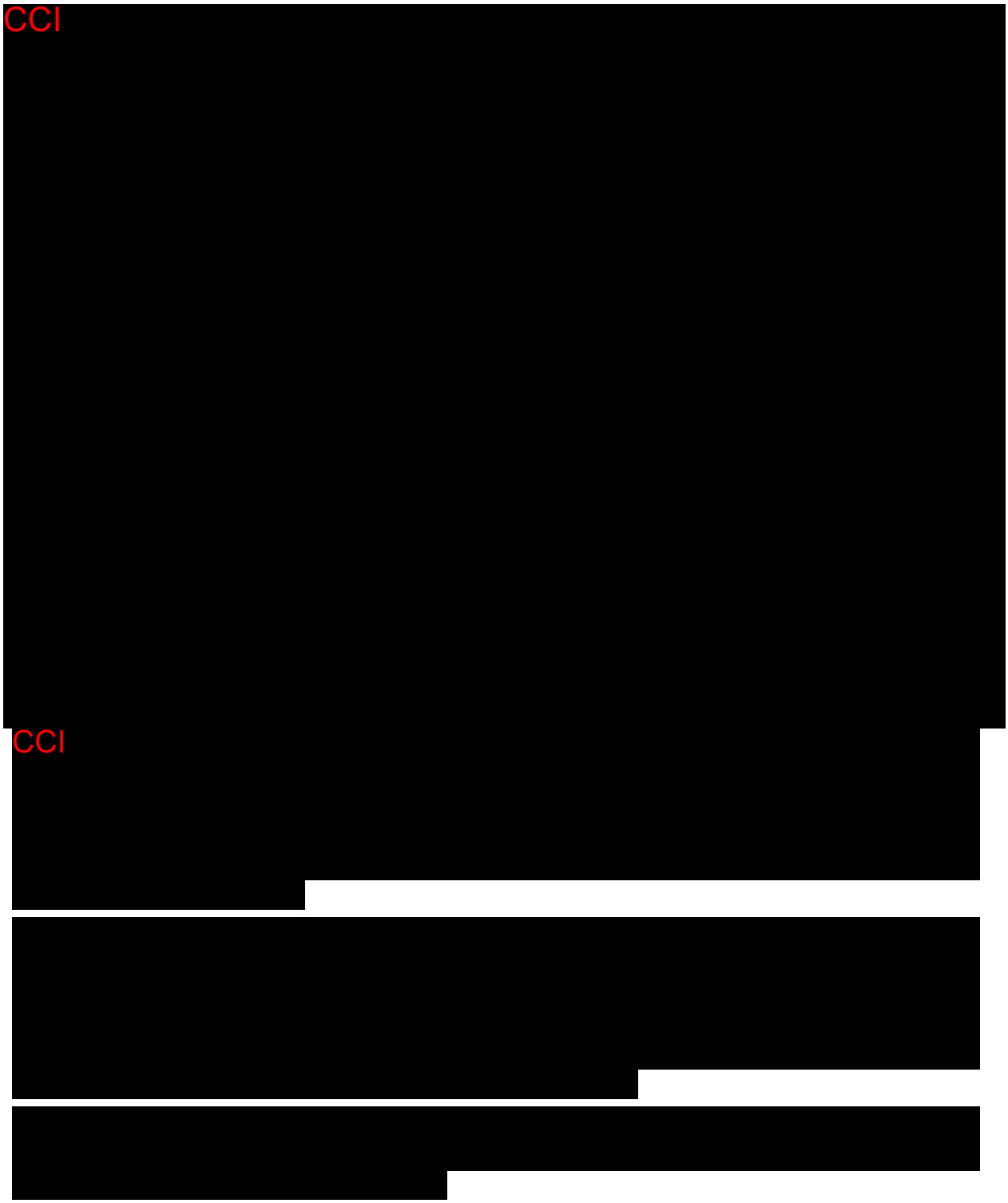
The study consists of a pre-operative period (screening visit), a treatment day period (Day 1, including data pre-surgery, intra-surgery and post-surgery, and distinguished wherever possible) and a post-treatment follow-up period (Day 2 to Day 90 (EOS)). Participants will be followed daily in the hospital from Day 2 to Day 8 (or at home/nearby accommodation (e.g., hotel) or rehabilitation unit if discharged earlier than Day 8), and then as an out-participant until the end of study (Day 30 and Day 90 (EOS) visits).

On Day 1, the participants will undergo cardiac surgery. Randomization will be performed at the start of surgery based on the leading surgeon or delegate's expectation of a CPB time of at least 60 min. No study treatment will be administered in cases where CPB time remains below 60 min.

[redacted] TIN816 or placebo will only be administered once the main surgery has been completed and preparations are ongoing to close the wound, and the leading surgeon has confirmed that there is no ongoing or active bleeding, and it is safe to proceed with wound closure.

Participants will receive [redacted] i.v. infusion of TIN816 or placebo on Day 1, after surgery. [redacted]

Figure 1-1 Study design



1.2 Study objectives, endpoints and estimand(s)

Study objectives and endpoints are described in Table 1-1

Table 1-1 Objectives and related endpoints

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

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

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

1.2.1 Primary estimand(s)

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

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

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

The primary estimand is described by the following attributes:

1. Population: adult participants undergoing non-emergent CPB surgery and at high risk of developing AKI.
2. Endpoint: ratio of the highest serum creatinine value within 5 days post dose (up to and including Study Day 6) vs. Baseline serum creatinine.
3. Treatment of interest: the randomized treatment (the investigational treatment TIN816 or the placebo treatment) with or without the allowed concomitant medications.
4. Handling of intercurrent events:
    a. In the presence of prohibited concomitant medications, and/or factors that may have caused changes in serum creatinine (Iodinated contrast agents and Extracorporeal filtration techniques), a While-on-treatment policy strategy will be applied. Please refer to Section 2.5.4 for more details.
    b. In the event of death (up to and including Day 6), While-on-treatment strategy will be applied. Please refer to Section 2.5.4 for more details.
5. Summary of measure: the ratio of the geometric mean ratio to baseline in serum creatinine (in terms of ratio of the highest serum creatinine value up to and including Study Day 6vs Baseline) between TIN816 and placebo.

1.2.2 Secondary estimand(s)

Not applicable.

2 Statistical methods

This section contains information that will be used to draft CSR Section 9.7 on statistical analysis.

2.1 Data analysis general information

The final CSR analysis will be performed by Novartis.

SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings.

CCI [redacted]

Data from TIN816 treatment groups (CCI [redacted]) will not be pooled for the analyses and will be reported separately. All the placebo participants will be pooled for the analyses.

All inferential analyses will use 1-sided tests, 0.1 significance level and 90% confidence CCI [redacted]

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

CCI [redacted]

2.1.1 General definitions

Study treatment

TIN816 CCI [redacted] mg/kg, TIN816 CCI [redacted] mg/kg and placebo

Study Day

Day 1 is defined as the date of first dose of study drug (TIN816 or placebo).

Study day is defined as the number of days since the date of first dose of study treatment (Day 1).

Therefore, for a particular date, the study day will be calculated as follows:

- for dates on or after the first administration of study treatment,

Study day = Assessment date – Date of first dose of study treatment +1

- for dates prior to the date of first administration of study treatment,

Study day = Assessment date – Date of first dose of study treatment.

Thus, the analysis reference date (date of first administration of study treatment) will be study day 1 and the date directly prior the analysis reference date will be study day -1 (there is no study day 0).

The term “unscheduled visit” refers to visits that occurred not as part of the Clinical Trial Protocol assessment schedule. Data collected at unscheduled visits will, in general, not be used in ‘by-visit’ tabulations or graphs. For efficacy evaluations, measurements from unscheduled

visits will generally not be used, unless where otherwise specified. All data collected at both scheduled and unscheduled visits will be included in the data listings.

Baseline:

Baseline for the various analyses is provided below:

Analyses	Baseline definition
Primary endpoint	The last available non missing SCr assessment before start of surgery. No imputation will be done for participants with missing baseline.
Safety analysis	The last available non missing assessment before start of surgery, unless specified otherwise.
Incidence and severity of AKI	The last available non missing SCr assessment before start of surgery.
Incidence of AKD	The last available non missing SCr assessment before start of surgery.
CCI	
Immunogenicity	Pre-surgery assessment
CCI	

2.2 Analysis sets

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

The safety analysis set will include all participants that received any study treatment (TIN816 or Placebo).

CCI

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

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

Additional details on the analysis set definitions are provided in Table 5-3.

Participants with protocol deviations will be presented and listed for all participants in safety analysis set. The number of participants with protocol deviations will be tabulated by deviation category by treatment.

2.3 Participant disposition, demographics and other baseline characteristics

2.3.1 Participant disposition

The participant disposition will be summarized by treatment group and overall, for all participants.

The number and percentage of participants screened, randomized, treated, completed and discontinued from the study will be summarized with reasons for discontinuation for all participants.

2.3.2 Demographics and other baseline characteristics

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

Demographic table will include but not limited to the following information:

- Age
- Age group (45-64, 65-74, and ≥75)
- For EU-CT requirement, Age group (18-64, 65-84, and ≥85)
- CCI
- Sex
- Ethnicity
- Race
- Weight [kg]
- Height [cm]
- Body mass index (BMI) [kg/m2]

The baseline characteristics table will include the following information:

- CCI
- Type of surgery (on Treatment Day 1)
- Duration of surgery (on Treatment Day 1) (Hours)
- Duration of Cardiopulmonary bypass (CPB) (Hours)

- Medical history with relevance to AKI (CKD, metabolic diseases, etc.)

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

Complete medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term by treatment group using safety analysis set. A listing will be generated for medical histories and conditions.

A summary table for countries and sites by treatment group and overall will be created using the safety analysis set.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Analyses of study treatment data will be based on the safety analysis set.

Data on administration of study drug will be listed by treatment group and participant.

2.4.2 Prior, concomitant and post therapies

The safety analysis set will be used for the analyses below.

Data for concomitant medications and non-drug therapies will be listed by treatment group and participant.

Concomitant medications and non-drug therapies will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group and following period.

- Pre-operative period: The screening period i.e., from the date of ICF to immediately before surgery.
- Post-operative period: The period starts from study drug infusion to end of study.

The concomitant medications or therapies administered will also be summarized for the overall period by ATC class and treatment group.

A separate summary will be created for vasoactive agents which is getting administered during peri-operative period i.e., period during the surgical procedure itself, and immediately post-surgery until start of study drug infusion. A separate listing will be created for vasoactive agents.

CCI [redacted]

2.5 Analysis supporting primary objective(s)

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

2.5.1 Primary endpoint(s)

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

2.5.2 Statistical hypothesis, model, and method of analysis

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

[redacted]

2.5.3 Sensitivity analyses

Not Applicable.

2.5.4 Handling of intercurrent events

[redacted]

CCI [redacted]

2.5.5 Handling of missing values not related to intercurrent event

CCI [redacted]

2.5.6 Supportive analyses

CCI [redacted]

2.5.7 Supplementary analyses

CCI [redacted]

2.6 Analysis supporting secondary objectives

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

2.6.1 Secondary endpoint(s)

The secondary endpoints are:

- Assessment of safety based on vital signs, physical examination, ECGs, laboratory assessments, and collection of AEs assessed from baseline until the end of the study visit
- AKI stages 1, 2 and 3 as defined by modified AKI Network (AKIN) criteria
- Anti-drug antibodies (ADA) against TIN816
- Occurrence of major adverse kidney event at Day 90 (MAKE90) as a composite of individual components
- Occurrence of MAKE30 as a composite of individual components

- Occurrence of individual components of the MAKE criteria at Days 30 or 90

2.6.2 Statistical hypothesis, model, and method of analysis

The statistical evaluation of all secondary efficacy data will be descriptive. Hypothesis testing will not be performed.

Assessment of safety is defined in Section 2.7 and ADA analysis is defined in Section 2.9.

2.6.2.1 Acute Kidney Injury based on AKIN criteria

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2.6.2.2 Major Adverse Kidney Events

All MAKE30 and MAKE90 related analyses will be performed based on the safety set.

MAKE30 and MAKE90 are defined as a composite of:

1. death through day 30/90,
2. initiation of renal replacement therapy through day 30/90, or
3. ≥25% reduction in calculated eGFRcre from baseline to 30/90 days after surgery.

The proportion of participants per MAKE30 outcome (Yes, No, Not Available) and MAKE90 outcome (Yes, No, Not Available) will be summarized by treatment. MAKE30 and MAKE90 outcome will also be listed by participant and treatment.

There will be three categories: Yes for the participants meeting at least one of the above-mentioned criteria, No for the participants not meeting any of the criteria, and Not Available for the participants who do not have sufficient data to conclude MAKE30 or MAKE90.

Similarly, the proportion of participants by each of the individual components of MAKE90 and MAKE30 mentioned above will be summarized by treatment. The individual components will also be listed by participant and treatment.

2.6.3 Handling of intercurrent events

Not applicable.

2.6.4 Handling of missing values not related to intercurrent event

Refer Appendix 5.1 for imputation rules, and Appendix 5.3 for laboratory parameters derivation. No other imputation will be done.

2.6.5 Sensitivity analyses

Not Applicable.

2.6.6 Supplementary analyses

Not Applicable.

2.7 Safety analyses

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

Safety summaries (tables, figures) will show events that started on Study Day 1 (including data collected for events prior to start of treatment, i.e. intra-surgery, as well as post start of treatment, i.e., post-surgery), and events that started on Study Day 2 and later. Baseline data, which may have been reported on Study Day 1 prior to surgery or on Day of Screening, will also be summarized where appropriate (e.g., change from baseline summaries), utilizing Day 1 data whenever available for both days. In addition, a separate summary for deaths including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period i.e., from Day 1 (treatment-emergent AEs).

The on-treatment period lasts from the date of first administration of study treatment until EOS (i.e., D90 or date of last study visit in the event of early study discontinuation).

2.7.1 Adverse events (AEs)

All information obtained on adverse events will be listed by treatment group and participants.

All AE summary tables will be created for two periods: AEs which occurred only on Day 1, vs. AEs that occurred on and after Day 2 and end by Day 90 (EOS).

The treatment emergent adverse events (TEAEs) are defined as the events started from Day 1 or events present prior to start of Day 1 but increased in severity based on preferred term. The number and percentage of participants with TEAEs will be summarized in the following ways for both periods (defined above) and overall (from Day 1 to EOS):

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

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, and other significant adverse events leading to discontinuation, dose interrupted/withdrawn, and adverse events by severity class by period, treatment, primary system organ class and preferred term.

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.

A ‘Total’ column will be shown for all AEs related summaries.

A similar separate summary will be created for non-serious adverse events accounting for >5% of all recorded adverse events by system organ class and preferred term.

All adverse events and serious adverse events will be listed by study day, treatment group and participant.

2.7.1.1 Adverse events of special interest / grouping of AEs

CCI [redacted]

2.7.2 Deaths

Incidence of death will be summarized by treatment groups and will be listed by treatment groups and participant.

2.7.3 Laboratory data

Some laboratory parameters were collected from both, local and central labs. In case of duplicate information, local lab results will be preferred over central labs.

All laboratory data (absolute, change from baseline and ratio to baseline) will be summarized by treatment group, and visit/time.

All laboratory data parameters (hematology, clinical chemistry, lipid panel, renal chemistry, urine chemistry, urine microscopy/sediment, urine dipstick, CCI [redacted] hepatitis testing, and liver event/follow-up testing) will additionally be listed by treatment group, participant and visit/time, and if local normal ranges are available, then abnormalities will be flagged in the listing.

Below notable severe drug induced liver injury (including Hy's law) will be summarized using count and percentage by treatment group:

- ALT or AST > 5x ULN
- ALT or AST >3xULN
- ALT or AST >3x ULN and TBL >2x ULN
- ALT or AST >3xULN and INR >1.5xULN)

- ALP >2xULNALT or AST >3x ULN and TBL >2x ULN and ALP <2xULN (Hy's law cases).

A spaghetti plot and box plot will be created for all laboratory parameters over time by treatment group, with a line indicating the treatment group mean.

CCI

Another spaghetti plot will be generated for the liver monitoring parameters from liver monitoring visits and local/central lab, over study day, by treatment. In case of more than one record is available at a particular day, the highest value will be considered. The AKI stage 2 and stage 3 participants will be highlighted in the plot.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

PR, QRS, QT, QTcF, RR intervals and Mean heart rate (HR) will be obtained from 12-lead ECGs for each participant during the study. CCI

Categorical analysis of QT and QTcF interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTcF intervals or changes from baseline will be presented. This categorical analysis will be based on post-baseline visits. In addition, a listing of these participants will be produced by treatment groups.

- QT, QTcF
  - Absolute value of > 450 and ≤ 480 ms
  - Absolute value of > 480 and ≤ 500 ms
  - Absolute value of > 500 ms
  - Increase from baseline by > 30 ms to ≤ 60 ms
  - Increase from baseline by> 60 ms
- PR
  - Increase from baseline by >25% and to a value > 200 ms
  - Absolute value of > 200 ms and <=220ms
  - Absolute value of > 220 ms
- QRS
  - Increase from baseline by >25% and to a value > 110 ms
  - Absolute values of QRS > 110 ms and <=120ms
  - Absolute values of QRS > 120

- HR
  - Increase from baseline by >25% and to a value > 100 bpm
  - Decrease from baseline by >25% and to a value < 50 bpm

All ECG data will be listed by treatment group, participant, and visit/time; abnormalities will be summarized and flagged based on the criteria above. All ECG data will be summarized by treatment group and visit/time. A box plot will also be created for ECG parameters over time by treatment groups. For each treatment group, individual participant spaghetti plots will also be created for ECG parameters.

2.7.4.2 Vital signs

All vital signs data (including Oxygen Saturation) will be listed and summarized by treatment group and visit/time and if ranges are available, abnormalities (defined below) and relevant orthostatic changes (if collected) and notable criteria (defined below) will be flagged in listing. Summary statistics will be provided by treatment group and visit/time for raw and change from baseline. Spaghetti plot will be created for all vital signs parameters except body weight.

Notable criteria (High/Low):

- Systolic blood pressure [mmHg]: >140/<90 mmHg
- Diastolic blood pressure [mmHg]: >90/<50 mmHg
- Pulse rate [bpm]: >90/<45 bpm
- Weight [kg]: >120/<50 kg
- Temperature [°C]: >37.5/<35 °C

2.7.4.3 CCI

CCI

CCI

[redacted]

2.7.4.4 CCI

CCI

[redacted]

2.7.4.5 Surgery related information

All surgery related details will be listed by treatment group using the safety analysis set.

Descriptive statistics will be provided for the duration of cardiopulmonary bypass (hours), duration of surgery (hours), duration of total mechanical ventilation (hours), duration of pre-surgery mechanical ventilation (hours) and duration of post-surgery mechanical ventilation (hours).

Counts and percentages of the below combination of surgeries will also be summarized by treatment group:

CCI

[redacted]

CCI [redacted]

2.7.4.6 CCI [redacted]

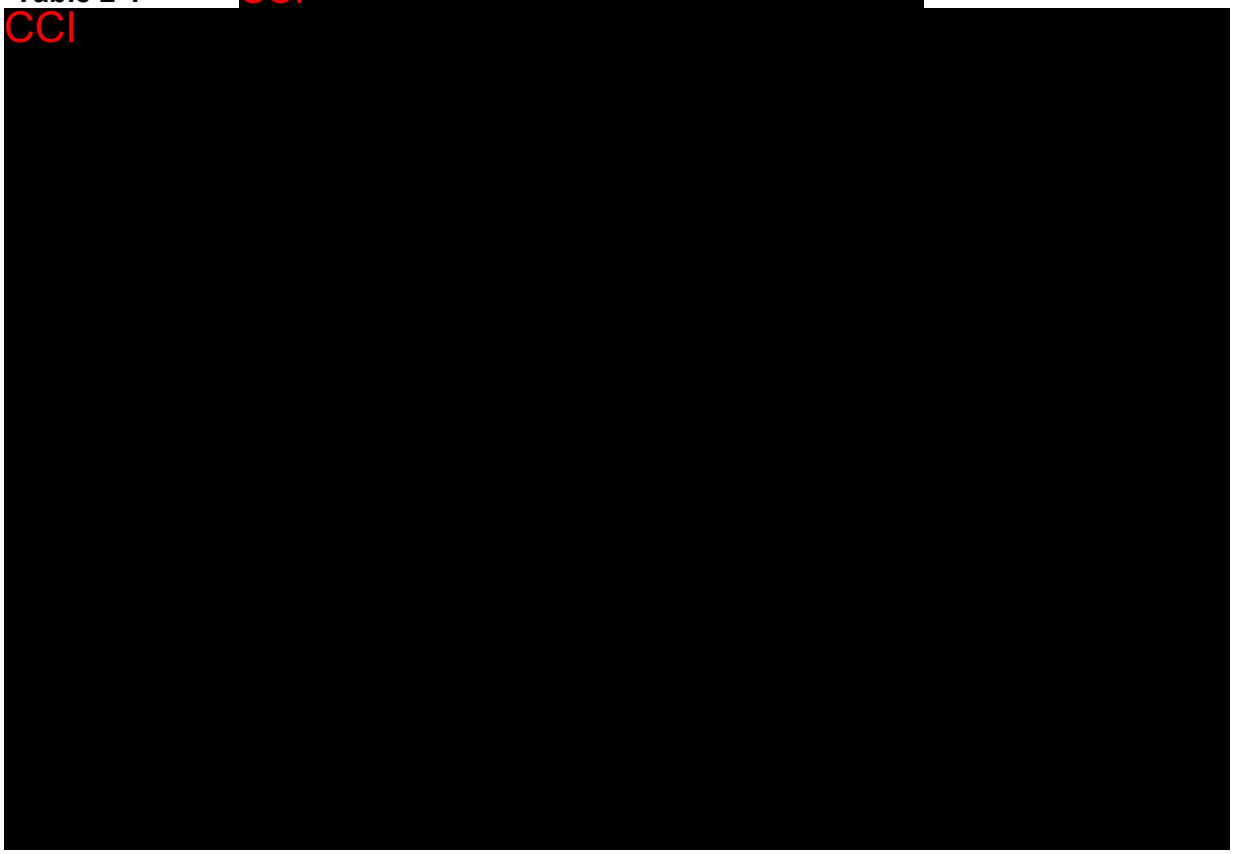
[redacted]

2.8 CCI [redacted]

CCI [redacted]

Table 2-1 CCI

CCI



2.8.1 CCI

CCI

2.9 Immunogenicity

The analysis will be performed based on the IG analysis set.

Immunogenicity results will be listed by treatment group, participant and visit/time. The listing will contain ADA status (negative or positive) and for ADA-positive samples a titer CCI [redacted]. Participants with one or more treatment emergent ADAs are counted as ADA-positive participants and they will be summarized by treatment group to derive an ADA incidence. Treatment emergent ADAs are defined as induced or boosted ADAs developed after the treatment with TIN816. The ADA incidence will be provided by overall population, indicating the number and percentage of participants with treatment emergent ADAs at any time post-dose, compared with the total number of participants in the analysis set who received TIN816. CCI [redacted]

The proportion of participants with presence or absence of CCI [redacted] will be summarized by treatment and visit and listed by treatment, participant and visit.

A proper determination of ADA status of a participant is not possible if there are no post-dose ADA samples accessible for analysis. In that case, the pre-dose sample is analyzed in a three-tiered approach, but neutralizing ADA characterization assays are not performed.

CCI [redacted]

2.10 CCI [redacted]

CCI [redacted]

Table 2-2 CCI [redacted]

CCI [redacted]

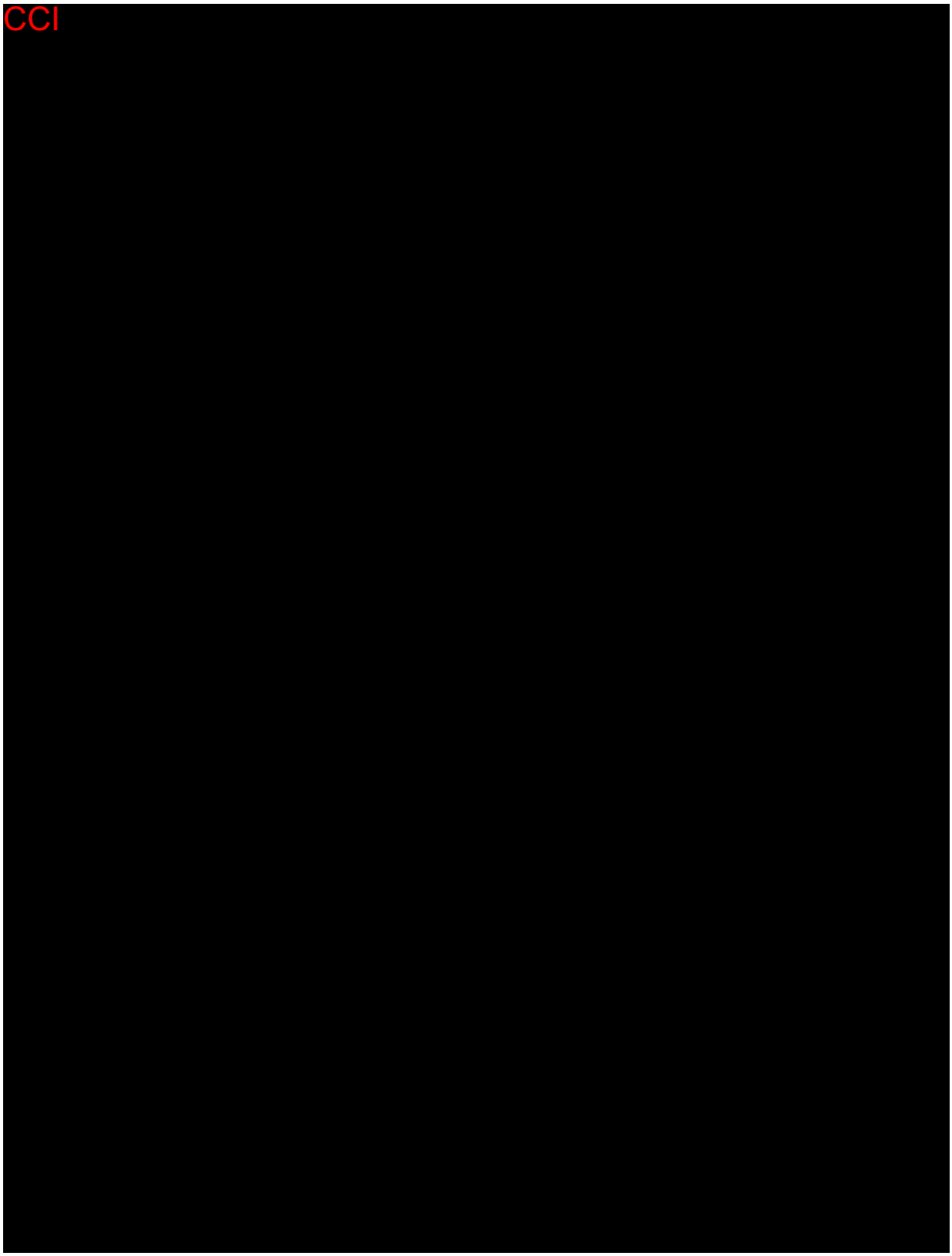

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Table 2-3 CCI

CCI

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2.11 CCI

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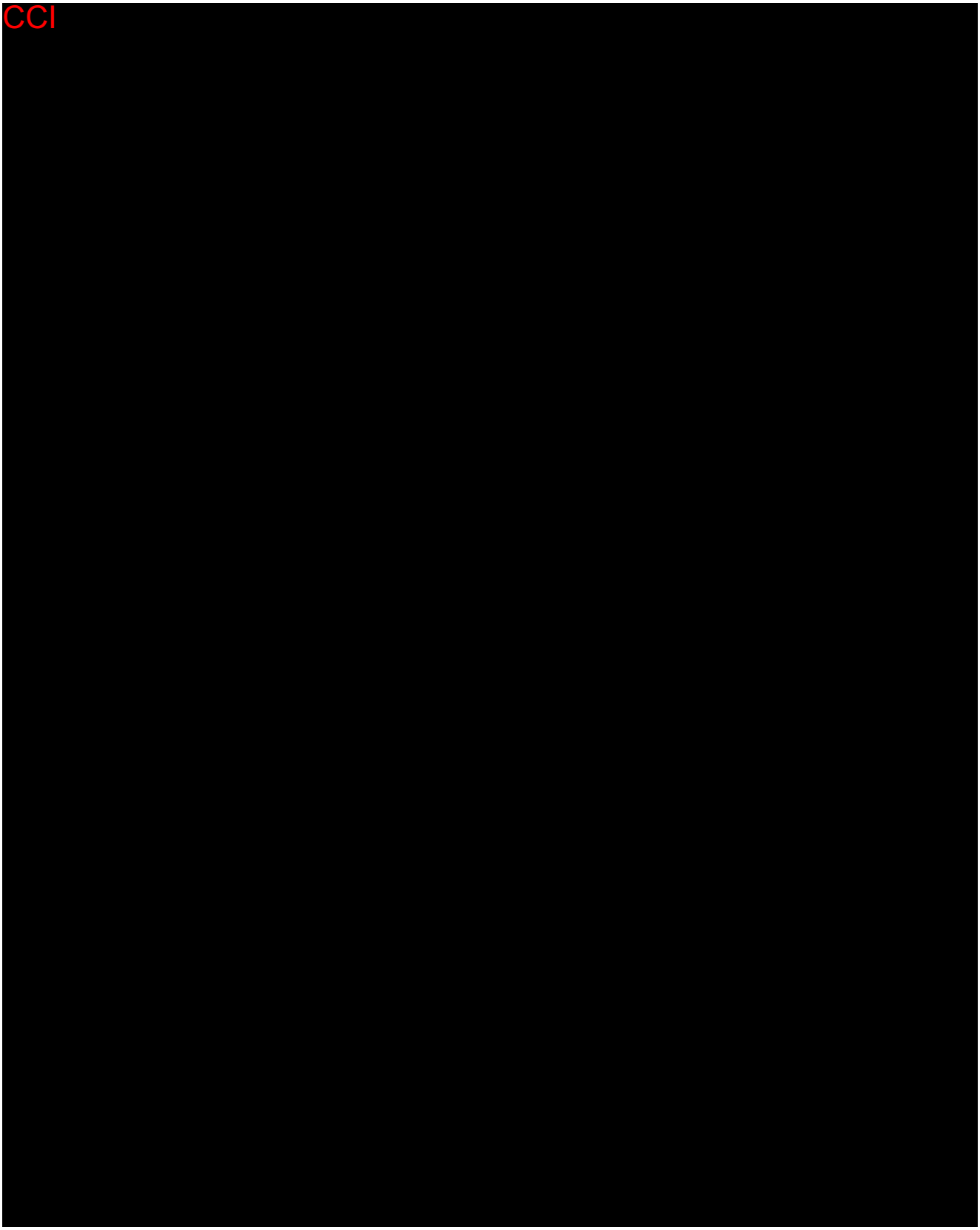
CCI

2.12 Interim analysis

CCI

[redacted]

3 Sample size calculation

CCI

[redacted]

4 Change to protocol specified analyses

CCI

[redacted]

5 Appendix

5.1 Imputation rules

The below imputation rules will be used for the analyses.

5.1.1 Study drug

No imputation will be made to the start date and end date of study treatment.

5.1.2 AE date imputation

The below tables (Table 5-1 and Table 5-2) are for the imputation techniques for the dates of adverse events, concomitant medications and other safety assessment dates.

Table 5-1 Imputation of start dates and time for AE, CM

Missing Element	Rule
Day, month, and year	No imputation will be done for completely missing dates
Day, month	If available year = year of study treatment start date, then start date = 01JanYYYY if stop date contains a full date, and stop date is earlier than study treatment start date, else set start date = study treatment start date. If available year > year of study treatment start date, then 01JanYYYY. If available year < year of study treatment start date, then 01JulYYYY.
Month	If start date year is equal to treatment start year and the stop date is earlier than treatment start, then MONTH =01, else MONTH = TREATMENT MONTH.
Day	If available month and year = month and year of study treatment start date, then set start date= 01MONYYYYif stop date contains a full date and stop date is earlier than study treatment start date, . else set start date = study treatment start date. If available month and year > month and year of study treatment start date, then 01MONYYYY. If available month and year < month year of study treatment start date, then 15MONYYYY.
Time	If time is missing, then start time will be imputed by 23:59

Table 5-2 Imputation of end dates and time for Adverse Events and Concomitant Medications

Missing Element	Rule
Day, month, and year	Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period* or EOS date, whichever is earlier
day, month	If partial end date contains year only, set end date = 31DecYYYY or end date of the on-treatment period *, whichever is earlier
Day	If partial end date contains month and year, set end date = last day of the month or end date of the on-treatment period*, whichever is earlier
Time	If time is missing, then end time will be imputed by 00:00 (24hr clock)

* last treatment group date plus 30 days not > (death date, cut-off date, withdrawal of consent date

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

5.1.3 Concomitant medication date imputation

Refer to Section 5.1.2

5.1.3.1 Prior therapies date imputation

Not applicable

5.1.3.2 Post therapies date imputation

Not applicable.

5.1.3.3 Other imputations

CCI

5.2 AEs coding/grading

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

5.3 Laboratory parameters derivations

Any quantitative clinical laboratory values given as "<X.X> or <X.X or >X.X" in the database will be imputed with the value of the number without the sign for the descriptive statistics and the calculation of changes from baseline, e.g., a value of "<2.2" will be imputed as 2.2 for the calculations. If the collected value is given as "X.X-Y.Y", then it will get imputed as average of the range. For example, if the value is 3-10 in database, then it will get imputed as 6.5.

There will be no imputation in the data listings; all values will be displayed as recorded in the database. This is not applicable for lab parameters that fall under qualitative category.

5.4 Statistical models

5.4.1 Analysis supporting primary objective(s)

Not applicable.

5.4.2 Analysis supporting secondary objective(s)

Not applicable.

5.5 Additional details on the analysis sets definitions

All Protocol Deviations were reviewed before database lock to determine whether these deviations warrant the exclusion of a participant from the statistical analyses or summary statistics. PDs considered relevant, together with the resulting rules for exclusion from analysis sets are listed in Table 5-3.

Table 5-3 Criteria leading to exclusion

Analysis Set	Criteria that cause participants to be excluded
CCI	
PD	1. Deviation from INCL01 (inclusion criterion #1): Signed informed consent must be obtained prior to participation in the study
	CCI
	3. Meeting EXCL16 (exclusion criterion #16): Exclude participants with a medical history of nephrectomy
IG	1. Deviation from INCL01 (inclusion criterion #1): Signed informed consent must be obtained prior to participation in the study)

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL. CCI PD (Pharmacodynamics), IG (Immunogenicity).

5.6 AKI incidence and severity

AKI incidence over the first week after surgery will be measured using the modified AKIN classification system, based on changes in serum creatinine compared to baseline defined in Section 2.1.1. Severity of AKI will be assessed using three stages, with stage 1 being the less severe and stage 3 the most severe (see Table 5-4).

CCI

CCI [redacted]

Table 5-4 The modified AKIN classification system of acute kidney injury

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

↑ Increase from baseline [a]Stage 3 also includes participants requiring RRT independent of the stage (defined by SCr) they are in at the moment they initiate RRT

* Within 7 days post-surgery includes the data until Follow-up Day 8; within 2 days post-surgery includes the data until Follow-up Day 3.

Adapted from (Barry, James 2015)

Table 5-5 The kidney disease improving global outcomes (KDIGO) classification

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

↑ Increase from baseline

Table 5-6 The RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) classification

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

SCr = serum creatinine, eGFR = estimated glomerular filtration rate
↑ Increase from baseline, ↓ decrease from baseline

5.7 CCI

CCI [redacted].

Table 5-7 CCI [redacted]

6 Reference

- ICH E9(R1) Harmonized Guideline: addendum on estimand and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Final version on 20 November 2019.
- Barry R, James MT (2015) Guidelines for Classification of Acute Kidney Diseases and Disorders. Nephron; 131(4):221-6.
- CCI [redacted]