STATISTICAL ANALYSIS PLAN

A Phase 1b study of RMC-035 in subjects undergoing Cardiac Surgery

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1.0	11-06-2021	Final Version	Not applicable

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ABBREVIATIONS

Abbreviation	Definition
8OH-dG	8 hydroxy 2 deoxyguanosine
A1M	Alpha-1-microglobulin
ADA	Anti-drug antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
AKI	Acute kidney injury
ALT	Alanine aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the plasma concentration time curve
AUCτ	Area under the curve from 0 to t, where t is the last measurable sample
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
C_{max}	Maximum (peak) concentration observed
CO	Cardiac output
C_{trough}	Lowest concentration reached by a drug before the next dose is administered
CrCl	Creatinine clearance
CRP	C-reactive protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CVP	Central venous pressure
ECG	Electrocardiogram
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
GFR	Glomerular filtration rate
h	hour(s)
ICU	Intensive care unit
IGFBP7	Insulin like growth factor binding protein 7
IL	Interleukin
IMP	Investigational Medicinal Product
IRR	Infusion related reaction
ISR	Infusion site reactions
IV	Intravenous

Abbreviation	Definition
KDIGO	Kidney Disease Improving Global Outcome
KIM-1	Kidney injury molecule-1
L-FAPB	Liver-type fatty acid-binding protein
LLOQ	Lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
NCA	Non-compartmental analysis
NGAL	Neutrophil gelatinase associated lipocalin
NT-proBNP	N-terminal pro b-type natriuretic peptide
PK	Pharmacokinetic
PT	Preferred term
PTR	Peak to trough ratio
$R_{ac\ (AUC)}$	Accumulation ratio calculated from AUCτ,ss and AUCτ after single dosing
ROS	Reactive oxygen species
SAE	Serious adverse event
SAP	Statistical analysis plan
SCr	Serum Creatinine
SD	Standard deviation
SOC	System organ class
SS	Steady state
SvO2	Mixed venous saturation
TEAE	Treatment emergent adverse event
TIMP2	Tissue inhibitor of metalloproteinases 2
$t_{½}$	Elimination half-life

1 GENERAL

This Statistical Analysis Plan (SAP) specifies the statistical methods to be applied in the analysis of this study. It was written by the responsible biostatistician prior to unblinding/closure of the database according to SOPs of KLIFO GmbH. This SAP is based upon the Study Protocol (version 2.0 of 22-Dec-2020) and contains a specification of the statistical methods described therein. The SAP was written without knowledge of the randomisation code.

The primary objective of this phase 1b study is to evaluate the safety and tolerability of RMC-035 in subjects undergoing non-emergent, on-pump Coronary Artery Bypass Graft (CABG) and/or valve surgery.

For this purpose, this trial has been designed as a phase 1b, randomised, double-blind, parallel treatment group clinical study.

The patients are randomised to receive RMC-035 or a matching placebo in a 2:1 ratio in a double-blind fashion.

A total of 7 visits are scheduled as follows:

- Screening: Visit 1 (Day -1)
- Treatment period: Visit 2 (Baseline, Day 1)
  Visit 3 (Day 2),
  Visit 4 (End of Treatment [EOT], Day 3)
- Safety follow-up period: Visit 5 (Day 4)
  Visit 6 (Day 7)
  Visit 7 (End of Study [EOS], Day 31)

2 EFFICACY AND SAFETY VARIABLES

2.1 General procedures

2.1.1 Time definitions and handling of visits

A total of 7 visits with investigations are planned including a screening visit.

In general, variables will be analysed according to the visit as documented in the eCRF. Details of the scheduled visits and time windows will be as follows:

Visit	**Visit No.**	**Scheduled for Visit Day**	**Time window [days]**	**Documented in eCRF as**	**Presented in the analysis as time point**
Screening	Visit 1	Day -1	-5	SCREENING	Screening
Treatment (Baseline)	Visit 2	Day 1	±0	Day 1 (TRT)	Baseline (Day 1)
Treatment	Visit 3	Day 2	±0	Day 2 (TRT)	Day 2
Treatment (EOT)	Visit 4	Day 3	±0	Day 3 (EOT)	Day 3 (EOT)
Follow-up	Visit 5	Day 4	±0	Day 4 (FU)	Day 4 (FU)
Follow-up	Visit 6	Day 7	±1	Day 7 (FU)	Day 7 (FU)
Follow-up (EOS)	Visit 7	Day 31	±3	Day 31 (FU; EOS)	Day 31 (FU, EOS)

Some measurements are performed at baseline at various time points. These time points will be presented in the analyses as follows.

- Baseline (pre-surgery)
- Day 1 (start first IMP infusion)
- Day 1 (15 min)
- Day 1 (30 min)
- Day 1 (1 h)
- Day 1 (2 h)
- Day 1 (3 h)
- Day 1 (4 h)
- Day 1 (5 h)
- Day 1 (6 h)
- Day 1 (12 h)

where time point in () is time since start of first IMP infusion.

2.1.2 Change from baseline

For continuous variables assessed at any time point after baseline, the absolute change from baseline will be calculated as [value at the time point] – [baseline value]. Relative change [%] will be calculated by dividing the absolute change by the baseline value and multiplication with 100 to obtain a percentage. Baseline value will be the last available value pre-surgery. If the pre-surgery baseline value is missing at Visit 2, the screening value will be used, if applicable. If any of the two values (i.e. baseline value or value at the respective time point) is missing, the absolute and relative change from baseline will be missing as well.

2.1.3 Safety laboratory parameters: Technical failure and values reported as '< x' or '> x'

In case a value is assessed as technical failure by the investigator, the value will be set to missing for summary tables and prior to the calculation of changes between visits.
Values reported as '< x' or '> x' will be set to 'x' for quantitative analyses (e.g. for the calculation of mean values in summary tables and for the calculation of changes between visits). This means that values below the lower limit of quantification will be set to the lower limit of quantification for quantitative analyses.

2.2 Primary Endpoint

The primary objective of this study is to evaluate the safety and tolerability of RMC-035 in subjects undergoing non-emergent, on-pump Coronary Artery Bypass Graft (CABG) and/or valve surgery. Therefore, the primary endpoint is the nature, frequency and severity of Adverse Events (AEs).

2.3 Secondary Endpoints

In addition to the primary endpoint described in Section 2.2 the following endpoints will be analysed:

- Clinically significant changes in safety laboratory tests (hematology, biochemistry,

urinalysis)

- Changes in vital signs (blood pressure, heart rate, respiratory rate)
- Changes in 12-lead ECG
- Pharmacokinetics of RMC-035 in plasma: C_{max}, C_{trough}, t_{max}
- Pharmacokinetics of RMC-035 in plasma after **fourth** dose: AUC_{τ}, C_{max}, C_{trough}, PTR, $R_{ac(AUC)}$, $t_{1/2}$
- Presence and titers of Anti-Drug-Antibodies (ADA) 30 days after surgery
- Characteristics of ADA developed 30 days after surgery with regards to isotype, neutralizing capacity and cross-reactivity with endogenous alpha-1-microglobulin

2.4 Exploratory Endpoints

- Post-baseline changes in specific categories of biomarkers:
    - Renal tubular damage and stress markers, e.g.
        - KIM-1, TIMP2, IGFBP7, IL-18, L-FAPB, NGAL (urine)
        - KIM-1, NGAL and A1M (plasma or serum)
    - Oxidative stress markers e.g.
        - 8OH-dG (serum and urine)
    - Inflammatory cytokines e.g.
        - IL-6 and IL-8 (plasma)
    - Cardiac biomarkers, e.g.
        - NT-proBNP and Troponin T
- Concentration of RMC-035 in urine

Evaluation of exploratory biomarkers and urine concentration of RMC-035 may be performed and reported separately. Cardiac biomarkers NT-proBNP and Troponin T will be reported as per this SAP.

- Post-baseline changes in hemodynamic assessments, including cardiac output (CO), mixed venous saturation (SvO2) and central venous pressure (CVP) (i.e., right ventricular pressure systolic/diastolic, pulmonary artery pressure systolic/diastolic),
- Presence of major adverse kidney event at 30 days (MAKE30), defined as a composite of either death, dialysis or ≥ 25% eGFR reduction.

  Presence of MAKE30 is 'Yes', if at least one of the following apply:

  - Death, which will be documented as an AE with seriousness 'Serious - results in death'

  - Dialysis, which is 'Yes', if at least at one visit the question 'Was dialysis started since last visit?' is 'Yes'.

  - ≥ 25% eGFR reduction from baseline to Visit 7, where eGFR criterion is considered fulfilled if eGFR reduction is ≥ 25% based on any of the following eGFR equations: CKD-EPI (SCr), CKD-EPI (Cys C), CKD-EPI (SCr and Cys C).

  Presence of MAKE30 will be No, if the following apply:

  - No AE with seriousness 'Serious - results in death' documented AND

- At each documented visit the question 'Was dialysis started since last visit?' is 'No' AND

- < 25% eGFR reduction from baseline to Visit 7, where eGFR criterion is considered fulfilled if eGFR reduction is < 25% based on any of the following eGFR equations: CKD-EPI (SCr), CKD-EPI (Cys C), CKD-EPI (SCr and Cys C).

Otherwise MAKE30 will be 'not evaluable'.

- Percent increase (from baseline to all subsequent time points) and maximum percent increase in SCr and Cystatin C (and corresponding estimated GFR values based on any of the following eGFR equations: CKD-EPI (SCr), CKD-EPI (Cys C), CKD-EPI (SCr and Cys C)) over the time points visit 3, 4, 5 and 6.

  At all time points of visit 1 to 7 when clinical chemistry blood samples are taken, eGFR will be calculated in mL/min/1.73 m² using any of the following eGFR equations: CKD-EPI (SCr), CKD-EPI (Cys C), CKD-EPI (SCr and Cys C). The eGFR value based on CKD-EPI equation for SCr will be calculated by the laboratory and entered in the eCRF. The eGFR value based on CKD-EPI equation for SCr and Cystatin C will be calculated in the eCRF directly and the third eGFR value, which is based on the CKD-EPI equation for Cystatin C only, will be calculated within the process of data derivation as follows:

$$CCC - EEE\ (CCCCCCCC\ C) = 133\ x\ \left(\frac{SSCC}{0.8}\right)^{A}\ x\ 0.995^{aaa}\ x\ B$$

  Where Scys is serum Cystatin C in mg/L, age is measured in years and A and B are as follow:

Female		**Male**	
Scys ≤ 0.8	A = -0.499	Scys ≤ 0.9	A = -0.499
	B = 0.932		B = 1
Scys > 0.8	A = -0.499	Scys > 0.9	A = -0.499
	B = 0.932		B = 1

- Post-baseline AUC of Serum Creatinine (SCr) and Cystatin C levels (and corresponding eGFR values) from baseline to 48 hours, 72 hours and Visit Day 7 post-surgery

  AUC of Serum Creatinine and Cystatin C levels (and corresponding eGFR values) will be calculated as follows:

  AUCs are calculated according to the linear trapezoidal rule. Actual times when the samples were taken are used for the calculation, except for the 0h and the last sample of the respective AUC (i.e., 48 hours sample, 72 hours sample, or 6 days post-surgery sample), where the following will apply: In order to calculate for example a 48h AUC (τ=48h), the start time of first IMP administration will be used for the 0h measurement, whereby the 0h measurement will be the respective parameter (Serum Creatinine, Cystatin C or the corresponding eGFR values) of the pre-surgery clinical chemistry sample. 48h after start of first IMP administration will be used for the 48h measurement. The other AUCs will be calculated analogously.

If the actual time is not given, the scheduled time is used.

Missing values will be interpolated.

AUCs are not calculated and a profile is considered as not evaluable, if either

- in case the baseline value is missing or
- in case the last value of the respective AUC (i.e., 48 hours value, 72 hours value, or Visit Day 7 post-surgery value) is missing or

- Severity of AKI defined as the following:
  - Stage 1: SCr 1.5 to 1.9 times baseline within 7 days, OR increase of ≥0.3 mg/dL (≥ 26.5 µmol/L) within 48 hours OR urine output <0.5 mL/kg/h for 6 to <12 consecutive hours
  - Stage 2: SCr 2.0-2.9 times baseline within 7 days OR urine output <0.5 mL/kg/h for ≥ 12 consecutive hours
  - Stage 3: SCr 3.0 times baseline within 7 days, OR increase in SCr 5.0 mg/dL (≥353.6 µmol/L), OR initiation of renal replacement therapy OR urine output <0.3 mL/kg/h for ≥24 consecutive hours OR anuria for ≥12 hours, where initiation of renal replacement therapy is 'Yes', if at least at one visit the question 'Was dialysis started since last visit?' is 'Yes' in the first 7 days. Anuria is defined as urine output <100 mL per day (over a 24h time period).

  For assessment for urine output values from the time urine collection is started, i.e. before surgery, will be used and only hourly recording of urine output until 48 hours after start of 1st IMP infusion will be included. For calculation of urine output in mL/kg/h weight at the respective visit will be used. If no valid value for weight is available at the respective visit, the last valid value of weight from a previous visit will be used.

  For AKI stage 1 the urine output criterion is assessable, if at least one time window of at least 6 consecutive hours with valid urine output values is available. Otherwise urine output criterion for stage 1 is not assessable.

  For AKI stage 2 the urine output criterion is assessable, if at least one time window of at least 12 consecutive hours with valid urine output values is available. Otherwise urine output criterion for stage 2 is not assessable.

  For AKI stage 3 the urine output criterion is assessable, if at least one time window of at least 24 consecutive hours with valid urine output values is available. Otherwise urine output criterion for AKI stage 3 is not assessable. The anuria criterion is assessable, if one time window of at least 36 hours with valid urine output values is available. Otherwise the anuria criterion is not assessable.

  If the urine output criterion is not assessable for the respective stage of AKI severity, the assessment of AKI severity will be based on the remaining criteria of the respective stage. In addition for AKI stage 3, if the anuria criterion is not assessable, the assessment of AKI severity will be based on the remaining criteria of AKI stage 3.

  The highest stage of AKI severity will be tabulated.

- Duration and persistence of AKI defined as either of the following

- The number of days from start of AKI (KDIGO definition) where either SCr increase ≥ 0.3 mg/dL above pre-AKI reference point (first comparison is versus pre-surgery baseline, or a reference value after baseline if AKI occurs after 48 hours post-surgery) or if SCr increase is ≥ 1.5 times baseline or dialysis in the first 7 days, or up to discharge if prior to 7 days. Number of days will be counted until SCr value will drop below the threshold of the AKI definition (stage 1 or higher) and other parts of the AKI definition are not fulfilled either (e.g. urinary output criteria). Possible end dates will be at any of the study visits. Duration of AKI [days] will be calculated as end date of AKI minus start date of AKI +1. If AKI will persist at last documented visit in the eCRF, the date of last documented visit will be used as end date of AKI for calculation of a continuous variable. For calculation of a categorical variable the duration will be set to 'ongoing'.

  The continuous variable of duration of AKI will be presented in a summary table for continuous variables. Additionally, the categorical variable of duration of AKI will be presented in a summary table for categorical variables using the following categories: 1-3, 4-7, 8-14, 15-21, 21+ and 'ongoing'.
- Persistent AKI defined as AKI (KDIGO definition) for >48 hours

- Length of index Intensive Care Unit (ICU) stay and index hospital stay
  - Index ICU stay (in Days) defined as the duration of stay in the ICU immediately following surgery or recovery room post-surgery until ICU discharge

    It will be calculated as date of discharge from ICU – date of admission to ICU after surgery/recovery room + 1.
  - Index hospital stay (in Days) is defined as the duration of stay in the hospital from admission to hospital discharge for the index surgery

    It will be calculated as date of discharge from hospital – date of admission to hospital + 1.
- Nature of patient discharge facility (e.g. home, skilled nursing facility, rehabilitation center)

3 STATISTICAL ANALYSIS SETS

The evaluation of the primary endpoint and the safety analysis of the secondary endpoints will be performed using the Safety Analysis Set (SAF). The Full Analysis Set (FAS) will be used for the evaluation of the exploratory endpoints and the evaluation of PK endpoints will be performed using the PK Analysis Set (PK). All analysis sets will be based on actual treatment as the primary objective of this phase I clinical trial is to evaluate the safety and tolerability of RMC-035 and the FAS, which is defined to allow for exploratory SCr-based efficacy evaluations, will be used for exploratory analysis only.

In addition to SAF, FAS and PK the all subjects screened (SCR) and all subjects randomised (RND) analysis sets are defined in Section 3.1 and 3.2 and will be used for listings and selected overview summary tables, for completeness of presentation of all data documented in the eCRF.

A subject classification document will be prepared which details subject inclusions into the analysis sets. The document will be completed before unblinding of study statistician, pharmacokineticist and other persons participating in the blind data review meeting. Subject

classification will be performed (if feasible) during this meeting.

In case subjects will be replaced according to protocol section 7.3.1, both, subjects to be replaced and replacing subjects will be analysed and allocated to the corresponding analysis sets.

3.1 All Subjects Screened (SCR)

The set of all subjects screened will include all patients with data documented at the screening visit. This set will be used to calculate the proportion of patients screened but not randomised and the frequencies of the reasons for non-randomisation.

3.2 Randomised Subjects (RND)

All subjects who have been randomised at Day -1, independent of whether they have received any IMP or not. This analysis set will be used for data listings.

3.3 Safety Analysis Set (SAF)

The Safety Analysis Set will consist of all randomised subjects who have received at least 1 dose of IMP. SAF will be used for safety endpoints.

3.4 Full Analysis Set (FAS)

The Full Analysis Set will consist of all randomised subjects who have received at least 1 dose of IMP and with at least one post-dose SCr (eGFR) assessment. FAS will be used for exploratory endpoints.

3.5 PK Analysis Set (PK)

PK Analysis Set will be used for the PK evaluation and will consist of all randomised subjects with no relevant protocol deviations affecting the evaluation of the PK parameters.

Protocol deviations affecting the evaluation of the PK parameters may include:

- AEs that may interfere with IMP use or effect and/or sampling:

  A list of patients with such AEs will be provided by medical expert of pharmacovigilance KLIFO A/S before blind data review meeting.

- Insufficient pharmacokinetic samples which do not enable calculation of reliable pharmacokinetic parameters:

  Information about insufficient PK samples will be provided by PK laboratory or PK expert before or during blind data review meeting.

- Other major protocol deviations which are assessed to significantly affect PK assessments (e.g. failure to properly use the IMP)

Further details of protocol deviations will be discussed in the blind data review meeting, where protocol deviations will be classified as minor and major. Patients with major protocol deviations will be excluded from the PK analysis set.

4 STATISTICAL EVALUATION

4.1 General

The statistical analysis will be performed using the software package SAS® version 9.4 or higher (SAS Institute Inc., Cary, NC 27513, USA).

Patient listings will be generated for all data items collected in the eCRF and paper-based forms. Relevant data of screening failures (i.e. of patients not eligible for treatment because of violations of in- or exclusion criteria) will also be listed.

All statistical analyses will be descriptive. Continuous data will be summarised using descriptive statistics including the arithmetic mean, the standard deviation, median, minimum, maximum, and the number of patients with non-missing values. Except for PK analysis where number of patients with non-missing values, arithmetic mean, SD, CV, median, minimum, maximum, geometric mean, geometric CV% will be used.

Categorical data will be summarised using absolute and relative frequencies.

Any changed in the planned statistical analysis will be documented in the study report.

4.2 Study Patients

4.2.1 Disposition of Patients

- Number of patients screened, randomised, number of patients included in each analysis set, and reasons for exclusion from analysis sets
- Completion of treatment period, reason for premature discontinuation of treatment
- Completion of follow-up period, reason for premature discontinuation
- Completion of full study, reason for premature discontinuation

  Completion of full study is reached, if the treatment period and the follow-up period are completed.

If multiple reasons of premature discontinuation are given, these will be presented by all observed combinations.

- Study duration: Last visit of the study will be the last visit where a visit date has been documented

4.2.2 Protocol Deviations

Protocol deviations affecting the evaluation of the PK parameters are defined in Section 3.5. All protocol deviations (documented in the protocol deviation log of the project management) will be listed and the following additional aspects will be tabulated:

- Violations of any eligibility criteria
- Compliance with scheduled time windows, assessed based on the
    - Difference between the dates of Screening visit and Baseline visit,
    - Difference between the dates of Baseline visit and of each subsequent visit of the complete study period

The following table will show the calculated differences categorised as 'Less than scheduled time window', 'Scheduled time window' and 'More than scheduled time window' per visit. The differences will be categorised as follows:

Visit	Less than scheduled time window	Scheduled time window	More than scheduled time window
Visit 1	<-7	[-7; -2]	>-2
Visit 2	-	-	-
Visit 3	<1	1	>1
Visit 4	<2	2	>2
Visit 5	<3	3	>3
Visit 6	<5	[5; 7]	>7
Visit 7	<27	[27; 33]	>33

- Differences between start time of first IMP administration at Baseline and start time of each subsequent IMP administration will be calculate in hours and presented in a listing.
- Compliance with the schedule of PK sampling will be analysed using a listing (CSP V1.0 Table 4 may serve as template for this listing). This will provide for each IMP administration differences between start time of first PK sampling (pre- dose) and time of corresponding IMP administration and differences between time of IMP administration and time of all corresponding subsequent PK samplings calculated in minutes (for PK samples planned to be taken pre-dose or up to 1 hour after corresponding IMP administration) or hours (for samples planned to be taken 2 hours after corresponding IMP administration or later). See CSP V1.0 Table 4.

- Compliance with scheduled IMP dose and overall compliance with scheduled IMP doses

  For the 1st IMP dose, compliance with scheduled dose will be 'yes', if the value of eGFR is ≥60 mL/min/1.73m^2 at baseline and the patient has received a dose of 1.3 mg/kg of IMP at the respective time point, or if the value of eGFR is 30 to <60 mL/min/1.73m^2 at baseline and the patient has received a dose of 0.65 mg/kg of IMP at the respective time point. For the 2nd IMP dose, compliance with scheduled IMP dose will be 'yes', if the dose is the same as the first IMP dose and compliance with scheduled IMP dose for the 1st IMP administration is 'yes'.

  For the 3rd, 4th and 5th IMP dose compliance with scheduled dose will be 'yes', if the value of CrCl(/eGFR) is ≥60 mL/min(/1.73m2) and the patient has received a dose of 1.3 mg/kg at the respective time point, or - if the previous received dose was lower than 1.3 mg/kg - the patient has received the previous received dose. Compliance with scheduled dose will also be 'yes', if the value of CrCl(/eGFR) is 30 to <60 mL/min(/1.73m2) and the patient has received 0.65 mg/kg at the respective time point, or - if the previous received dose was 0.43 mg/kg - the patient has received a dose of 0.43 mg/kg. Compliance with scheduled dose will also be 'yes', if the value of CrCl(/eGFR) is <30 mL/min(/1.73m2) and the patient has received a dose of 0.43 mg/kg at the respective time point.

  Compliance with the respective scheduled IMP dose will be 'no' otherwise.

Overall compliance with scheduled IMP doses will be 'yes', if compliance with scheduled dose is 'yes' for each IMP administration.

Overall compliance with scheduled IMP doses will be 'no', if compliance with scheduled dose is 'no' for at least one IMP administration.

4.2.3 Demographic and Other Baseline Characteristics

The following demography data, medical/surgical history, disease characteristics and baseline characteristics will be shown for SAF and PK:

- Demographic data at screening:
    - Gender
    - Age (years)
    - Age group (18-69 years of age and ≥70 years of age)
    - Age group (18-64 years of age, 65-84 years of age and ≥85 years of age)
    - Ethnicity (Hispanic or Latino, non-Hispanic or Latino)
    - Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White)
    - Height (cm)
    - Weight (kg with one decimal)
    - Body Mass Index (BMI)

  BMI will be calculated for every Visit as follows:

(body weight at Visit [kg]) / (body height at Screening [cm]/100)^2 and will be rounded to one decimal. In case of missing body height at Screening BMI will be not available.

- Medical/surgical history and disease characteristics

  Medical history, disease characteristics, relevant past and current diseases documented on the medical history form in the eCRF will be coded using MedDRA and will be classified by System Organ Class (SOC) and Preferred Term (PT).

  Frequency (number and percentage) of subjects with diseases / symptoms / findings per treatment group will be summarised by SOC and PT.

  Surgical history will be analysed analogously.

- Renal function at baseline

  To analyse renal function at baseline, eGFR (based on serum creatinine with CKD-EPI equation) will be presented in a summary table per treatment group. Additionally eGFR at baseline will the categorised follows:

    - eGFR<60mL/min/1.73m^2
    - eGFR≥60mL/min/1.73m^2

Number and percentage of patient in each category will be tabulated per treatment group.

- Physical examination at screening:

  This will be summarised by presenting absolute and relative frequencies of patients with any pathological findings (yes/no).

4.2.4 Treatment Compliance

Compliance will be analysed using descriptive statistics and will be analysed per IMP administration for the following:

- IMP dose
- Total infusion volume [mL]
- Infusion rate [mL/min]
- Duration of administration: Stop time of IMP administration – Start time of IMP administration. If any of the two values is missing, the duration of administration will be missing as well.
- Irregularities in IMP administration

In addition, the

- Overall number of infusions per subject
- Any dose reduction in subject due to creatinine clearance (CrCL) or eGFR <30 mL/min or 30 to <60 mL/min (yes/no)

  Any dose reduction is 'yes', if at least one of the 3rd, 4th or 5th IMP infusions was administered and the patient received a lower dose than the one received at 1st IMP administration on at least one of these administrations.

  Any dose reduction is 'no', if the dose received at 1st IMP administration was given throughout the treatment phase.

  Otherwise any dose reduction is 'not evaluable'.
- Any irregularities in any IMP administration (yes/no) per subject

will be summarised per treatment group.

4.2.5 Concomitant Treatment

Concomitant therapies will be coded and frequencies will be calculated by the first and the second level of the Anatomical Therapeutical Chemical (ATC) classification. The following summary tables will be provided, all summaries will be presented by treatment group and overall based on SAF:

- All documented therapies (prior or during the study)
- Concomitant therapies administered during the treatment period
- Concomitant therapies administered during the follow-up period

Medications are classified as prior if the stop date is before or on the day for obtaining informed consent.

A therapy will be included in the summary table of a study period, unless the therapy end date

is prior to the beginning of the study period and unless the therapy onset date is after the end date of the study period. A concomitant therapy can be included in more than one summary table.

The following start and end dates of the study period will be used for this purpose:

- Treatment period: date of Visit 2; date of Visit 4 (EOT)
- Safety follow-up period: date of Visit 4 (EOT) +1; date of Visit 7 (EOS)

Handling of incomplete therapy dates:

If month and year or only the year of the therapy end date is available and before the month and year or the year of the start date of the study period, the therapy will not be allocated to the study period.

If month and year or only the year of the therapy start date is available and after the month and year or the year of the end date of the study period, the therapy will not be allocated to the study period.

If a therapy start date is missing, the concomitant medication will be allocated to all study periods, in which the patient participated, prior the therapy end date. If a therapy end date is missing, the therapy will be allocated to all study periods, in which the patient participated, depending on the therapy start date. If both therapy start date and therapy end date is missing, the therapy will be allocated to all applicable study periods.

4.3 Safety, Tolerability and Pharmacokinetics Evaluation

The evaluation of safety and tolerability will be performed for the SAF and the evaluation of PK will be performed for the PK analysis set.

No statistical hypotheses are planned to be tested in this study.

4.3.1 Primary Evaluation

The primary endpoint of this study is described in section 2.2. The nature, frequency and severity of AEs will be analysed for the evaluation of safety and tolerability of RMC-035 in subjects undergoing non-emergent, on-pump CABG and/or valve surgery.

AEs will be coded using MedDRA and will be classified by System Organ Class (SOC) and Preferred Term (PT).

Additionally, AEs will be categorized as

- pre-treatment,
- treatment-emergent,
- post-treatment.

AEs are assigned to one of the above categories using the start date of the AE and the dates of first and last administration of IMP.

Treatment-emergent AEs (TEAEs) are defined as AEs occurring after the first IMP administration, with onset date on or after the day of first administration of IMP, and occurring up to four days after last IMP administration.

Pre-treatment AEs are defined with an onset date prior to the day of first IMP administration, for patients with a documented screening visit.

Post-treatment AEs are defined as AEs with onset day at least five days after last IMP administration.

In case of an incomplete AE start date, the AE will be categorized as treatment-emergent (worst case). In case an investigator comment on the AE page provides different information concerning the timing of AE onset, the AE onset will be categorized based on this comment.

Adverse Events of Special Interest (AESI) in this study are defined as Injection Site Reaction (ISR) or Infusion Related Reaction (IRR) adverse events.

The incidence of the following categories of AEs will be analysed for the SAF:

- Number (%) of subjects with at least one TEAE
- Number (%) of subjects with at least one treatment-emergent SAE
- Number (%) of patients with at least one non-serious TEAE
- Number (%) of patients with at least one treatment-emergent AESI
- Number (%) of subjects with at least one treatment-emergent AEs reported as related (possible/probable) to IMP
- Number (%) of patients with at least one treatment-emergent AEs leading to withdrawal of IMP

An overview summary table will present the number (%) of subjects for all of the above categories by treatment group.

In addition, separate summary tables will be generated for each of the above categories. These will present the number of events and number (%) of patients with an AE in the respective category classified in SOCs and PTs.

An overview summary table will present the number (%) of patients with at least one TEAE by seriousness, severity (Common Terminology Criteria for Adverse Events (CTCAE) grade), causality, measures (AE treatment and action taken to IMP) and outcome.

In addition, summary tables for TEAEs will present the number (%) of patients with each SOC and PT grouped by seriousness, severity, causality, measures and outcome.

Individual patient listings will be provided for AEs, SAEs, AESI, AEs reported as related (possible/probable) to IMP and for AEs leading to withdrawal of IMP. AEs will be flagged in these patient data listings as pre-treatment, treatment-emergent and post-treatment, according to the definitions provided at the beginning of this section.

Patient data listings will display the duration of each AE. In case of a complete AE start date and a complete AE end date the duration of an AE will be calculated as (AE end date) - (AE start date) + 1. Otherwise, the duration of an AE will not be determined.

4.3.2 Secondary Evaluation

4.3.2.1 Safety Evaluation

The safety evaluation will be based on SAF. Summary tables will be provided containing the following:

- Physical examination; the overall assessment of any changes to any body system compared to screening examination ("No", "Clinically non-significant changes and/or improvements only", "Clinically significant deteriorations or new findings") will be summarised at Day 3 (EOT) by treatment group. In addition, a shift table between the overall assessment at Day 3 (EOT) and the variable "Did the physical examination reveal any pathological findings" ("Yes", "No") assessed at screening will be presented.
- Vital signs; systolic/diastolic blood pressure, respiratory rate, heart rate and body temperature at each time point and changes from baseline to each time point will be summarised by descriptive statistics by treatment group. The overall assessment of vital signs categorized as "normal", "abnormal, not clinically significant" or "abnormal, clinically significant" (as judged by the investigator) will be summarised by time point using frequency tables and listings presented by treatment group. In addition, shift tables for the overall assessment of vital signs between baseline and each subsequent time point will be presented.
- 12-lead ECG; will be listed for each subject and summarized as the vital signs parameters.
- The overall assessment of continuous ECG monitoring will be summarised at Day 3 (EOT) by treatment group.
- Safety laboratory analyses data (hematology, clinical chemistry incl. liver function test, urinalysis);

  The following analyses will be performed for quantitative parameters (hematology, clinical chemistry incl. liver function test) and for qualitative parameters (results from urine dipstick test):
  - Standard descriptive summary statistics and for quantitative parameters additionally geometric mean and geometric standard deviation will be calculated.
  - Standard descriptive summary statistics, geometric mean and geometric standard deviation will be calculated for the absolute changes in quantitative parameters.
  - Frequencies of normal, above normal, and below normal values will be computed for quantitative parameters with normal ranges.
  - Shift tables displaying changes with respect to the normal range over time will be provided for quantitative parameters with normal ranges.
  - All laboratory data will be listed. These listings will include flags so that all normal and all abnormal values can be found.
  - Overall assessment will be summarised for hematology, clinical chemistry incl. liver function test, and urinalysis by treatment group. In addition, shift tables for the overall assessment between baseline and each subsequent time point will be presented.
- CrCl, calculated by site before IMP administrations 3-5 in mL/min will be summarised by time point. In addition, CrCl will be categorized as follows
  - CrCl $\geq$ 60 mL/min
  - 30 mL/min $\leq$ CrCl < 60 mL/min
  - CrCl <30 mL/min,

  and will be presented using absolute and relative frequencies.
- Overall assessment of urinary output at Day 3 (EOT) will be summarised by treatment group. Further details on urinary output will be listed.

- Hemoglobin A1c (HbA1c) in blood at screening and Day 31 (EOS) will be listed.

Quantitative longitudinal parameters will also be presented graphically as mean-by-visit plots and subject-profile-by-visit plots.

4.3.2.2 ADA Evaluation

Analysis of presence and titers of ADA will be performed on SAF. Summary tables will be provided, including a shift table for presence of ADA between Baseline and Visit 7 (EOS). ADA samples obtained beyond the protocol specified time window for Visit 7 will be accepted.

For this evaluation, presence of ADA at a visit will be defined as follows:

Presence of ADA at a visit is negative, if

- initial result is reported as negative or
- initial result is reported as positive and confirmatory result is reported as negative.

Presence of ADA at a visit is positive, if

- both, initial and confirmatory result is reported as positive.

If the confirmatory result is missing, presence of ADA will be identical to the initial reported result. Otherwise presence of ADA will be not evaluable.

The characteristics of ADA will be listed.

4.3.2.3 PK Evaluation

The PK analysis will be based on the PK set.

Descriptive statistics will be presented for plasma concentrations by scheduled sample time. For scheduled sample time see CSP V1.0 Table 4.

The PK parameters will be calculated by non-compartmental analysis (NCA) using software Phoenix WinNonlin® version 8.3 (Build 8.3.2.116) or higher.

The following PK parameters for RMC-035 in plasma will be assessed for each of the 5 IMP administrations:

- C_{max} (maximum observed concentration after each IMP administration)
- C_{trough} (lowest concentration reached before next dose is administered)
- t_{max} (time after each IMP administration when C_{max} is observed)

The following PK parameters for RMC-035 in plasma will be additionally assessed:

- $AUC_{0\text{-}24h\ ss}$ (area under the curve from 0 to 24 hours after fourth dose administration, where 0 is the pre-dose measurement of fourth dose and 24h is the pre-dose measurement of fifth dose)
- Peak to trough ratio (PTR) (after fourth dose)
- $R_{ac\ (AUC)}$ (Accumulation ratio calculated from $AUC_{0\text{-}5h,ss}$ and $AUC_{0\text{-}5h}$ after single dosing) with the following formula:

$$R_{aa\ (AAA)} = \frac{AAC_{0-5\text{h,ss}}}{AAC_{0-5\text{h,single dose}}}$$

where $AUC_{0\text{-}5h,single\ dose}$ is the AUC from 0 to 5 hours after first dose administration, where 0 is the pre-dosemeasurement before first dose and 5 is the 5 hour measurement after first dose. $AUC_{0\text{-}5h,ss}$ will be calculated as the AUC from 0 to 5 hours after fourth dose administration, where 0 is the pre-dose measurement before fourth dose administration and 5 is the 5 hour measurement after fourth dose.

- $t_{½}$ (terminal half-life after fourth dose) (Help parameters for calculation of $t_{½}$ will be given: λz (LAMZ), Lambda z upper (LAMZUL), Lambda z lower (LAMZLL), Number of points used for λz (LAMZNPT), R^2)
- PK parameters (AUC_{τ} and $t_{½}$) will also be calculated or extrapolated after all other dose administrations, if possible. Since τ varies between the different dose administrations and therefore the values of AUCs cannot be compared, τ will be replaced by the respective time window as follows:
    - $AUC_{0\text{-}6h,\ 1st\ dose}$: Using the pre-dose measurement of first dose to pre-dose measurement of second dose, which will be a time window of 6 hours.
    - $AUC_{0\text{-}6h,\ 2nd\ dose}$: Using the pre-dose measurement of second dose to pre-dose measurement of third dose, which will be a time window of 6 hours.
    - $AUC_{0\text{-}12h,\ 3rd\ dose}$: Using the pre-dose measurement of third dose to pre-dose measurement of fourth dose, which will be a time window of 12 hours.
    - $AUC_{0\text{-}2h,\ 5th\ dose}$: Using the pre-dose measurement of fifth dose to 2 hours after fifth dose administration, which will be a time window of 2 hours.

  Additionally $AUC_{0\text{-}2h}$ will be calculated for all doses, if possible.

An overview of the different time windows of the AUCs to be calculated will be presented in the following table:

Dose No.	**Calculated AUCs**				
	0-2h	**0-5h**	**0-6h**	**0-12h**	**0-24h**
1	x	x	x*		
2	x		x*		
3	x			x*	
4	x	x			x*
5	x*				

*AUC_{τ} for the different administration occasions

For the PK calculations the received concentration values will be used. Actual dose and actual blood sampling time point will be used in the NCA.

The infusion length is 60 min for the first dose administration and 30 min for second to fifth dose administration.

The AUC method used will be the 'lin up/log down', and the plasma model (200-202). The λz will be estimated for each profile after each dose based on visual inspection of the terminal part of the log-concentration time plot including at least three data points. If the terminal phase regression based on R^2 will be less than 0.85, then the following parameters could not be reported; t½, λz.

Pre-treatment values (before first dose) below LLOQ will be set to zero in the NCA calculation.

Concentration values below the lower limit of quantitation (LLOQ) that precede the first quantifiable concentration value will be set to zero for linear plots and for all calculations and summary statistics but will be excluded from semi-logarithmic plots. All other LLOQ values will be treated as missing for all analyses. Possible outlying concentration values excluded from the PK analysis will be reported and justified in the study report.

Listings for the PK parameters will be presented over time by treatment group and age group (18-69 years of age and ≥70 years of age) and additionally by treatment group and renal function at baseline. Listings will also include dosing of the respective IMP administration. The parameters will also be summarized with number of patients with non-missing values, arithmetic mean, SD, CV, median, minimum, maximum, geometric mean, geometric CV% for each of the 5 IMP administrations. In addition, the individual and mean concentration-time profiles will be illustrated graphically with line charts. Dose proportionality will be evaluated for C_{max} and AUC_{τ} using descriptive statistics and graphs (i.e. scatter plots). Different IMP doses will be indicated by color.

4.4 Evaluation of exploratory endpoints

The evaluation of exploratory variables, described in section 2.4, will be based on FAS.

Exploratory efficacy/pharmacodynamics/biomarkers measured before database lock will be summarised using frequency tables and descriptive statistics for absolute and/or relative change from baseline by time point.

For scheduled sample time points of biomarkers see CSP V1.0, Table 4.

Evaluation of exploratory biomarkers and urine concentration of RMC-035 may be performed and reported separately. Cardiac biomarkers NT-proBNP and Troponin T will be reported as per this SAP.

Presence of MAKE30 (yes/no) and combinations of categories met will be tabulated using absolute and relative frequencies.

4.5 Missing Values

Baseline value will be the last available value pre-surgery. If the pre-surgery baseline value is missing at Visit 2, the screening value will be used, if applicable.

Handling of technical failures and values reported as '< x' or '> x in context of the safety laboratory is described in Section 2.1.3.

Handling of missing start and/or end dates of concomitant therapies in described in Section 4.2.5.

Handling of concentration values below the LLOQ in context of the PK analysis is described in Section 4.3.2.3.

5 INTERIM ANALYSIS

No interim analysis is planned.

6 CHANGES FROM PROTOCOL

The analyses planned in this analysis plan are consistent with the provisions in the clinical study protocol, except with regard to the following:

- Analysis sets SCR and RAN were added. This will guarantee complete data listings of all data documented in the eCRF.
- Analysis set FAS was additionally defined to allow for exploratory SCr-based efficacy evaluations.
- AEs will not be presented classified in PTs and investigator terms, but only presented classified in SOCs and PTs, which both are coded. However, the investigator term is part of the AE data listings.
- The secondary endpoint 'Clinically significant changes in vital signs (blood pressure, heart rate, respiratory rate)' was changed to 'Changes in vital signs (blood pressure, heart rate, respiratory rate)' and the secondary endpoint 'Clinically significant changes in 12- lead ECG was changed to 'Changes in 12-lead ECG'.

  The reason for this is that the summary tables described in 4.3.2.1 will only make an overall statement about 'clinical significant changes' but not about clinical significant changes for a single parameter (e.g. heart rate). But as according to CSP Section 8.3 any abnormal laboratory test result (hematology, clinical chemistry or urinalysis) or other safety assessments (e.g. ECG, continuous ECG monitoring, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e. not related to progression of underlying disease or medical procedure, i.e. cardiac surgery) has to be documented as an AE, details on clinically significant assessments are part of the AE data listings and AE summary tables described in Section 4.3.1.
- Cardiac biomarker Troponin T will be evaluated instead of Troponin I, since this is the only value the safety laboratory can measure.

7 SUMMARY TABLES AND DATA LISTINGS

7.1 Summary Tables

The summary tables planned for this analysis are listed in Appendix A.

Treatment groups will be labelled as RMC-035 and Placebo, respectively.

In tables presenting baseline characteristics summary statistics will be provided for each treatment group and for the treatment groups pooled.

General format for categorical variables (SAS output):

	RMC-035 (N=XX)	Placebo (N=XX)	Total (N=XX)
X-variable			
Category 1	X (XX.X)	X (XX.X)	X (XX.X)
Category 2	X (XX.X)	X (XX.X)	X (XX.X)

Numbers showing number of subjects and percentage of subjects in brackets with N as denominator

More than one X-variable may be analysed within a table. Variables can have more than two categories. Percentages are displayed with 1 decimal.

General format for continuous variables (SAS output):

	RMC-035 (N=XX)	Placebo (N=XX)	Total (N=XX)
X-variable			
N			
Mean			
SD			
Min			
Median			
Max			

Abbreviations: n = number of subjects with non-missing value, SD = Standard Deviation

More than one x-variable may be analysed within a table.

In tables presenting PK parameters summary statistics will be provided for each treatment group and for the treatment groups pooled. The different dose levels for verum patients will be pooled. Additionally, tables with summary statistics for each dose level of RMC-035 (i.e. 1.3 mg/kg, 0.65 mg/kg, and 0.43 mg/kg) per time point will be provided. In these tables values for placebo and treatment groups pooled will not be repeated.

The general format for tables of PK Analysis will look analogous to the summary statistics for baseline characteristics described above.

The number of decimals used for minima and maxima depends on the scaling of the respective data. Mean (arithmetic and geometric), median, standard deviation, CV and geometric CV% will be displayed with one additional decimal. Frequencies will be displayed with no decimals.

7.2 Data Listings

The data listings planned are listed in Appendix B.

Data listings will include all randomised patients, the disposition listing will include all screened patients. Flags will be provided in the listings indicating which patients are included in the different analysis sets. RND analysis set will be used except of the disposition listing where SCR analysis set will be used.

In general, data listings will be presented by treatment group. Within each treatment group, patients will be sorted by the screening number.

Listings for the PK parameters will be presented over time by treatment group and age group (18-69 years of age and ≥70 years of age) and additionally by treatment group and renal function at baseline. These listings will also include dosing of the respective IMP administration.

7.3 Figures

Figures planned are listed in Appendix C.

8 SIGNATURE

Sponsor

[redacted], Statistician

(Signatures continue on next page)

Signatures (continued)

Biostatistician:

[redacted]

KLIFO GmbH, Germany

9 APPENDICES

A List of Summary Tables

B List of Data Listings

C List of Figures

List of Summary Tables

Analysis Sets:

SCR = All Patients Screened
RND = All Patients Randomised
FAS = Full Analysis Set
SAF = Safety Analysis Set
PK = PK Analysis Set

No.	Title/Content	Analysis Sets
1. Study Patients		
1 - 1.1	Number of patients screened, randomised and included in each analysis set, proportion of patients screened but not randomised, frequency of reasons for non-randomisation, reasons for exclusion from PK analysis set	SCR
1 - 1.2	Completion of full treatment period, follow-up period and full study, reasons for premature discontinuation Note: Reasons for premature discontinuation will be presented by all observed combinations.	SAF
1 - 1.3	Study duration: Last visit of the study	SAF
1 - 2.1	Inclusion and exclusion criteria	SAF
1 - 2.2	Protocol deviations affecting the evaluation of the PK parameters	SAF
1 - 2.3	Compliance with scheduled time windows - Difference between the dates of baseline and screening, and difference between the dates of basline visit and of each subsequent visit	SAF
1 - 2.4	Compliance with scheduled IMP dose and overall compliance with scheduled IMP doses	SAF
1 - 3.1	Demographic data Gender, age, age groups, ethnicity, race, height, weight, BMI	SAF/PK
1 - 3.2	Medical history and disease charcteristics	SAF/PK
1 - 3.3	Surgical history	SAF/PK
1 - 3.4	Renal function at baseline - eGFR (based on serum creatinine with CKD-EPI equation) Note: including categorisation of eGFR	SAF/PK
1 - 3.5	Physical examination at screening	SAF/PK
1 - 4.1	Treatment compliance - IMP dose per IMP administration	SAF
1 - 4.2	Treatment compliance - Total infusion volume [mL]	SAF
1 - 4.3	Treatment compliance - Infusion rate [mL/min] per IMP administration	SAF
1 - 4.4	Treatment compliance - Duration of administration per IMP administration	SAF
1 - 4.5	Treatment compliance - Irregularities in IMP administration per IMP administration	SAF
1 - 4.6	Treatment compliance - Number of infusions	SAF
1 - 4.7	Treatment compliance - Any dose reduction due to creatinine clearance or eGFR <30 mL/min or 30 to <60 mL/min (yes/no)	SAF
1 - 4.8	Treatment compliance - Any irregularities in any IMP administration	SAF

No.	Title/Content	Analysis Sets
1 - 5.1	All documented therapies (prior or during the study)	RND/SAF
1 - 5.2	Concomitant therapies administered during the treatment period	SAF
1 - 5.3	Concomitant therapies administered during the follow-up period	SAF

No.	Title/Content	Analysis Sets
2. Safety and Tolerability Evaluation - Primary Endpoint		
2 - 1	Number of subjects with different adverse event categories, overview	SAF
2 - 2	Treatment-emergent adverse events by System Organ Class (SOC) and Preferred Term (PT)	SAF
2 - 3	Treatment-emergent serious adverse events by System Organ Class (SOC) and Preferred Term (PT)	SAF
2 - 4	Treatment-emergent non-serious adverse events by System Organ Class (SOC) and Preferred Term (PT)	SAF
2 - 5	Treatment-emergent adverse events of Special Interest by System Organ Class (SOC) and Preferred Term (PT)	SAF
2 - 6	Treatment-emergent adverse events reported as related (possible/probable) to IMP by System Organ Class (SOC) and Preferred Term (PT)	SAF
2 - 7	Treatment-emergent adverse events leading to withdrawal of IMP by System Organ Class (SOC) and Preferred Term (PT)	SAF
2 - 8	Treatment-emergent adverse events by seriousness, severity, causality, measures (AE treatment and action taken to IMP) and outcome, overview	SAF
2 - 9	Treatment-emergent adverse events by seriousness, System Organ Class (SOC) and Preferred Term (PT)	SAF
2 - 10	Treatment-emergent adverse events by severity, System Organ Class (SOC) and Preferred Term (PT)	SAF
2 - 11	Treatment-emergent adverse events by causality, System Organ Class (SOC) and Preferred Term (PT)	SAF
2 - 12	Treatment-emergent adverse events by measures (AE treatment and action concerning IMP), System Organ Class (SOC) and Preferred Term (PT)	SAF
2 - 13	Treatment-emergent adverse events by outcome, System Organ Class (SOC) and Preferred Term (PT)	SAF

3. Safety and Pharmocokinetics Evaluation		
3 - 1	Physical examination at Day 3 (EOT) and changes from screening to EOT. Note: Change from screening to EOT will be presented by shift table	SAF
3 - 2.1	Vital signs by time point and absolute changes from baseline by time point - Systolic blood pressure - Diastolic blood pressure - Respiratory rate - Heart rate - Body temperature	SAF
3 - 2.2	Overall assessment of vital signs by time point	SAF
3 - 2.3	Overall assessment of vital signs: Change from baseline by time point Note: Shift tables	SAF

No.	Title/Content	Analysis Sets
3 - 3.1	12-lead ECG parameter and absolute changes from baseline by time point - Heart rate - PR interval - QRS interval - QT interval - QTc interval	SAF
3 - 3.2	Overall 12-lead ECG assessment by time point	SAF
3 - 3.3	Overall 12-lead ECG assessment: change from baseline by time point visit Note: Shift tables	SAF
3 - 3.4	Overall continuous ECG assessment at Day 3 (EOT)	SAF
3 - 4.1.1 - 3 - 4.1.13	Hematology: Laboratory parameters by time point - Leukocytes - Erythrocytes - Hemoglobin - Erythocyte Volume Fraction (EVF) - Mean corpuscular volume (MCV) - Mean corpuscular hemoglobin (MCH) - Mean corpuscular hemoglobin concentration (MCHC) - Thrombocytes - Neutrophils abs. - Monocytes abs. - Lymphocytes abs. - Eosinophils abs. - Basophils abs.	SAF
3 - 4.2.1 - 3 - 4.2.13	Hematology: Absolute changes in laboratory parameters from baseline by time point - Leukocytes - Erythrocytes - Hemoglobin - Erythocyte Volume Fraction (EVF) - Mean corpuscular volume (MCV) - Mean corpuscular hemoglobin (MCH) - Mean corpuscular hemoglobin concentration (MCHC) - Thrombocytes - Neutrophils abs. - Monocytes abs. - Lymphocytes abs. - Eosinophils abs. - Basophils abs.	SAF

No.	Title/Content	Analysis Sets
3 - 4.3.1 - 3 - 4.3.13	Hematology: Normality of laboratory parameters by time point - Leukocytes - Erythrocytes - Hemoglobin - Erythocyte Volume Fraction (EVF) - Mean corpuscular volume (MCV) - Mean corpuscular hemoglobin (MCH) - Mean corpuscular hemoglobin concentration (MCHC) - Thrombocytes - Neutrophils abs. - Monocytes abs. - Lymphocytes abs. - Eosinophils abs. - Basophils abs.	SAF
3 - 4.4	Hematology: Shift table for laboratory parameters from baseline to each subsequent time point Note: Changes from normal to abnormal and from abnormal to normal	SAF
3 - 4.5	Hematology: Overall assessment by timepoint	SAF
3 - 4.6	Hematology overall assessment: Change from baseline by time point visit Note: Shift tables	SAF
3 - 5.1.1 - 3 - 5.1.21	Clinical chemistry incl. liver function: Laboratory parameters by time point - Sodium - Potassium - Phosphate - Urea nitrogen - Serum Creatinine - eGFR (based on serum creatinine) - C-reactive protein (CRP) - Albumin - Calcium - Chloride - Cystatin C - Magnesium - Urid acid - eGFR (based on serum creatinine and cystatin C) - Total bilirubin - Conjugated bilirubin - AST - ALT - Gamma-glutanyltransferase (GGT) - ALP - eGFR (based on cystatin C)	SAF

No.	Title/Content	Analysis Sets
3 - 5.2.1 - 3 - 5.2.21	Clinical chemistry incl. liver function: Absolute changes in laboratory parameters from baseline by time point - Sodium - Potassium - Phosphate - Urea nitrogen - Serum Creatinine - eGFR (based on serum creatinine) - C-reactive protein (CRP) - Albumin - Calcium - Chloride - Cystatin C - Magnesium - Urid acid - eGFR (based on serum creatinine and cystatin C) - Total bilirubin - Conjugated bilirubin - AST - ALT - Gamma-glutanyltransferase (GGT) - ALP - eGFR (based on cystatin C)	SAF
3 - 5.3.1 - 3 - 5.3.21	Clinical chemistry incl. liver function: Normality of laboratory parameters by time point - Sodium - Potassium - Phosphate - Urea nitrogen - Serum Creatinine - eGFR (based on serum creatinine) - C-reactive protein (CRP) - Albumin - Calcium - Chloride - Cystatin C - Magnesium - Urid acid - eGFR (based on serum creatinine and cystatin C) - Total bilirubin - Conjugated bilirubin - AST - ALT - Gamma-glutanyltransferase (GGT) - ALP - eGFR (based on cystatin C)	SAF

No.	Title/Content	Analysis Sets
3 - 5.4	Clinical chemistry incl. liver function: Shift table for laboratory parameters from baseline to each subsequent time point Note: Changes from normal to abnormal and from abnormal to normal	SAF
3 - 5.5	Clinical chemistry: Overall assessment by timepoint	SAF
3 - 5.6	Clinical chemistry overall assessment: Change from baseline by time point visit Note: Shift tables	SAF
3 - 6.1.1 - 3 -6.1.10	Urinalysis: Laboratory parameters by time point - Specific gravity - pH - Leucocytes - Nitrite - Protein - Glucose - Ketones - Urobilinogen - Bilirubin - Erythrocytes	SAF
3 - 6.2	Urinalysis: Overall assessment by time point	SAF
3 - 6.3	Urinalysis overall assessment: Change from baseline by time point visit Note: Shift tables	SAF
3 - 7.1	Urinary output: Overall assessment at Day 3 (EOT)	SAF
3 - 7.2	Urinary output: Creatinine clearance (urine) by time point	SAF
3 - 7.3	Urinary output: Categorised creatinine clearence (urine) by time point	SAF
3 - 8.1	Plasma concentration of RMC-035 by scheduled sample time Note: Summary statistics are provided for each treatment group (RMC-035; Placebo) and for the treatment groups pooled. Additionally, tables with summary statistics for each dose level of RMC-035 by time point are provided.	PK
3 - 8.2.1 - 3 - 8.2.5	PK Parameters for RMC-035 in plasma after each of the 5 IMP infusions: - C_{max} - C_{trough} - t_{max} - AUCs* - $t_{1/2}$ Note: Summary statistics are provided for each treatment group (RMC-035; Placebo) and for the treatment groups pooled. Additionally, tables with summary statistics for each dose level of RMC-035 are provided. * For each IMP infusion all calculated AUCs will be tabulated separately (see AUC-table in SAP Section 4.3.2.3)	PK

No.	Title/Content	Analysis Sets
3 - 9.3.1 - 3 - 9.3.2	PK Parameters for RMC-035 in plasma after fourth dose: - PTR - $Rac_{(AUC)}$ Note: Summary statistics are provided for each treatment group (RMC-035; Placebo) and for the treatment groups pooled. Additionally, tables with summary statistics for each dose level of RMC-035 by time point are provided.	PK
3 - 10.1	Presence of ADA at Baseline and Visit 7 (EOS) Note: A shift table of presence of ADA between Baseline and Visit 7 (EOS) will also be presented.	SAF
3 - 10.2	Titers of ADA at Baseline and Visit 7 (EOS)	SAF

4. Exploratory Evaluation and Other Variables		
4 - 1.1.1 - 4 - 1.1.2	Biomarkers: Cardiac biomarkers by time point - NT-proBNP - Troponin-T	FAS
4 - 1.2.1 - 4 - 1.2.2	Biomarkers: Cardiac biomarkers - changes from baseline by time point - NT-proBNP - Troponin-T	FAS
4 - 1.3	Cardiac biomarkers: Overall assessment by timepoint	FAS
4 - 2.1.1 - 4 - 2.1.6	Hemodynamic assessments by time point: - Cardiac output (CO) - Mixed venous saturation (SvO2) - Central venous pressure (CVP): Right ventricular pressure systolic - Central venous pressure (CVP): Right ventricular pressure diastolic - Central venous pressure (CVP): Pulmonary artery pressure systolic - Central venous pressure (CVP): Pulmonary artery pressure diastolic	FAS
4 - 2.2.1 - 4 - 2.2.6	Hemodynamic assessments: Changes from baseline by time point: - Cardiac output (CO) - Mixed venous saturation (SvO2) - Central venous pressure (CVP): Right ventricular pressure systolic - Central venous pressure (CVP): Right ventricular pressure diastolic - Central venous pressure (CVP): Pulmonary artery pressure systolic - Central venous pressure (CVP): Pulmonary artery pressure diastolic	FAS
4 - 3	Presence of major adverse kidney event until Day 31 (FU, EOS) (MAKE) and combination of MAKE criteria met	FAS

No.	Title/Content	Analysis Sets
4 - 4.1.1 - 4 - 4.1.2	Percent increase from baseline by time point in - Serum creatinine - Cystatin C	FAS
4 - 4.2.1 - 4 - 4.2.2	Maximum increase from baseline during the study until Visit 6 in - Serum creatinine - Cystatin C	FAS
4 - 4.3.1 - 4 - 4.3.3	Percent increase from baseline by time point in - eGFR (SCr) - eGFR (Cystatin C) - eCRF (SCr and Cystatin C)	FAS
4 - 4.4.1 - 4 - 4.4.3	Maximum increase from baseline during the study until Visit 6 in - eGFR (SCr) - eGFR (Cystatin C) - eCRF (SCr and Cystatin C)	FAS
4 - 4.5	Post-baseline AUC of Serum creatinine levels from baseline to 48 hours, 72 hours and Visit Day 7 post-surgery	FAS
4 - 4.6	Post-baseline AUC of Cystatin C levels from baseline to 48 hours, 72 hours and Visit Day 7 post-surgery	FAS
4 - 4.7	Post-baseline AUC of eGFR(SCr) levels from baseline to 48 hours, 72 hours and Visit Day 7 post-surgery	FAS
4 - 4.8	Post-baseline AUC of eGFR(Cystatin C) levels from baseline to 48 hours, 72 hours and Visit Day 7 post-surgery	FAS
4 - 4.9	Post-baseline AUC of eGFR(SCr and Cystatin C) levels from baseline to 48 hours, 72 hours and Visit Day 7 post-surgery	FAS
4 - 5.1	Severity of AKI	FAS
4 - 5.2	Duration (days) and persistence of AKI	FAS
4 - 6.1	Length of index Intensive Care Unit (ICU) stay and index hospital stay	FAS
4 - 6.2	Nature of patient discharge facility	FAS

List of Data Listings

Analysis Sets:
SCR = All Patients Screened
RND = Randomized patients

No.	Title	Set	Variables to be included/Variables of the following form in the eCRF and corresponding derived variables
Patient Disposition and Baseline Characteristics			
1 – 1.1	Patient disposition - Allocation to analysis sets, reasons for exclusion from analysis sets, and treatment group in treatment period	SCR	Randomised; FAS; PK set; exclusion from PK set; treatment group
1 – 1.2.1	Randomisation - Not randomised patients	SCR	Month/year of birth; Screening date; Reason and specification for non-randomisation
1 – 1.2.2	Randomisation - Randomised patients	RND	Randomisation (incl. Date, Time, Randomisation Number); Reason and specification for non-randomisation
1 – 1.3.1	Completion of treatment period	RND	Completion of full treatment period; Reasons for premature discontinuation (EOT form)
1 – 1.3.2	Completion of follow-up period	RND	Completion of follow-up period; Reasons for subject withdrawal from study (EOS form)
1 – 1.3.3	Completion of full study	RND	Completion of full study; Reason for non-completion (combination of EOT and EOS form)
1 – 1.4	Study duration	RND	Last Visit during study; First dose of IMP; Last dose of IMP; Number of IMP administration; Withdrawal Date
1 – 1.5.1	Visit dates and differences between visit dates	RND	Visit; Visit Date; Date Difference;
1 – 1.5.2	Differences between visit dates (categorized)	RND	Visit; Visit Date; Date Difference (categorized)
1 – 1.5.3	Differences between start time of first IMP administration at baseline and start time of each subsequent IMP administration	RND	All related variables
1 – 1.5.4	PK sample times and differences between IMP infusion and corresponding PK samples	RND	Start date and time of IMP infusion, date of pre-dose PK sample, PK sample times, Difference between start IMP infusion and PK sample time; Irregularities in plasma PK sampling Note: Per IMP administration

No.	Title	Set	Variables to be included/Variables of the following form in the eCRF and corresponding derived variables
1 – 1.5.5	Differences between IMP infusion and corresponding PK samples	RND	Difference between start IMP infusion and PK sample time Note: Per IMP administration Note: CSP V1.0 Table 4 serves as template for this listing
1 – 2.1	Protocol deviations affecting evaluation of PK parameters	RND	Type of deviation with specification and details; minor or major; reason if minor
1 – 2.2	Protocol deviations - overall	RND	Data from protocol deviations log
1 - 2.2	Inclusion and exclusion criteria	SCR	ELIG/RAND Form: Eligibility check variables
1 – 2.3	Compliance with scheduled IMP dose and overall compliance with scheduled IMP doses	RND	All related variables
1 – 3.1	Demographic data I	RND	Gender, age, age groups, ethnicity, race, height, weight, BMI
1 – 3.2	Demographic data II: Women related information	RND	Child-bearing potential; Pregnancy Test
1 – 3.3	Medical history and disease characteristics	RND	Any disease/symptom/findings; Disease/symptom/finding; Onset of disease; Ongoing at screening; Date of resolution; Relevant details; MedDRA coding
1 – 3.4	Surgical history	RND	Any surgeries; Surgery; Date; Relevant details on surgery; MedDRA coding
1 – 3.5	Renal function at baseline	RND	eGFR at baseline; eGFR categorized at baseline Note: eGFR at baseline based on serum creatinine
1 – 3.6	Physical examination at screening	RND	Performed; Systems assessed; Pathological findings
1 – 4	Treatment compliance	RND	Variables stated in section 4.2.4 of the SAP
1 – 5	IMP administration	RND	All variables from IMP ADMIN, PK SAMPL form if not listed above and except for variables regarding plasma sampling for pharmacokinetics
1 – 6.1	Concomitant medication (Part 1)	RND	ATC Levels
1 – 6.2	Concomitant medication (Part 2)	RND	Pharmaceutical formulation; Indication; Dose
1 – 6.3	Concomitant medication (Part 3)	RND	Frequency; CM Number; Generic Name; Frequency; Specification other frequency; Route of Administration; Specification other route of administration; Start and End of drug therapy; Therapy ongoing; Used pre-study; Used during treatment period; Used during FU period

No.	Title	Set	Variables to be included/Variables of the following form in the eCRF and corresponding derived variables
1 – 7	Surgery	RND	All variables from SURGERY from
1 – 8	Pregnancy of female partner	RND	All related variables
1 – 9	Formal fields (several parts)	SCR	
1 – 10	Investigator's comments (optional)	SCR	

No.	Title	Set	Variables
Safety and Tolerability			
2 – 1	Adverse events	RND	Variables from AE form and corresponding derived variables
2 – 2	Serious adverse events and deaths	RND	see Listing 2 - 1
2 – 3	Adverse events of special interest (AESI)	RND	see Listing 2 - 1
2 – 4	AEs reported as related (possible/probable) to IMP	RND	see Listing 2 - 1
2 - 5	Adverse events leading to withdrawal of IMP	RND	see Listing 2 - 1
2 - 6	Pre-treatment adverse events of all patients included into the study	SCR	see Listing 2 - 1

No.	Title	Set	Variables
Safety and Pharmocokinetics			
3 – 1	Physical examination at EOT	RND	Performed; Systems assessed; Any changes compared to the screening examination
3 – 2.1	Vital signs - Systolic and diastolic blood pressure and absolute changes	RND	Visit; Time point; Date; Time; Values; Absolute changes from Baseline
3 – 2.2	Vital signs - Respiratory rate, heart rate and body temperature and absolute changes	RND	see above; Temperature measurement method
3 – 2.3	Vital signs - Overall assessment	RND	Visit; Time point; Value
3 – 3.1	12-lead ECG - Heart rate, PR interval, QRS interval, QT interval, QTc interval and absolute changes	RND	Visit; Time point; Date; Time; Absolute changes from baseline
3 – 3.2	12-lead ECG - Overall assessment	RND	Visit; Time point; Overall ECG assessment; Reason for no assessment
3 – 3.3	Overall continuous ECG monitoring	RND	ECG monitoring initiated; Start date and time; Stop date and time; Reason for not done; Overall assessment at EOT
3 – 4.1.1	Safety laboratory: Formal fields, sampling dates and times	RND	For Hematology, Clinical chemistry, and Hba1c analysis
3 – 4.1.2	Safety laboratory: Irregularities	RND	For Hematology, Clinical chemistry, Urinalysis
3 – 4.1.3	Safety laboratory: Overall assessments	RND	For Hematology, Clinical chemistry, Urinalysis
3 – 4.2.1 - 3 – 4.2.13	Hematology: Laboratory parameters and absolute changes - Leukocytes - Erythrocytes - Hemoglobin - Erythocyte Volume Fraction (EVF) - Mean corpuscular volume (MCV) - Mean corpuscular haemoglobin (MCH) - Mean corpuscular hemoglobin concentration (MCHC) - Thrombocytes - Neutrophils abs. - Monocytes abs. - Lymphocytes abs. - Eosinophils abs. - Basophils abs.	RND	Visit; Time point; Value; Unit; Lower and upper limit NR; NR Flag; Technical failure; Clinical assessment; Absolute change from baseline

3 – 4.3.1 - 3 – 4.3.21	Clinical chemistry incl. liver function: Laboratory parameters and absolute changes - Sodium - Potassium - Phosphate - Urea nitrogen - Serum Creatinine - eGFR (based on serum creatinine) - C-reactive protein (CRP) - Albumin - Calcium - Chloride - Cystatin C - Magnesium - Urid acid - eGFR (based on serum creatinine and cystatin C) - Total bilirubin - Conjugated bilirubin - AST - ALT - Gamma-glutanyltransferase (GGT) - ALP - eGFR (based on cystatin C)	RND	Visit; Time point; Value; Unit; Lower and upper limit NR; NR Flag; Technical failure; Clinical assessment; Absolute change from baseline
3 – 4.4	HbA1c analysis		Visit; Value; Unit; Lower and upper limit NR; NR Flag; Technical failure; Clinical assessment; Irregularities
3 – 5.1 - 3 – 5.10	Urinalysis: Laboratory parameters - Specific gravity - pH - Leucocytes - Nitrite - Protein - Glucose - Ketones - Urobilinogen - Bilirubin - Erythrocytes	RND	Visit; Value; if applicable: Lower and upper limit NR and NR Flag
3 – 6.1	Urinary output: Hourly recording	RND	All related variables
3 – 6.2	Urinary output: Overall assessment at EOT	RND	Visit; Value
3 – 6.3	Urinary output: Creatinine Clearance	RND	All related variables
3 – 7.1	Plasma concentration of RMC-035: Date and time of samples taken	RND	Visit; Time point; Date and time of pre-dose sample; Time of corresponding subsequent samples

3 – 7.2.1	Plasma concentration of RMC-035 by treatment group and age group	RND	Visit; Time point; Dosing of the respective IMP administration; Value Note: Age group: 18-69 years or ≥70 years of age at baseline Note: Time point should also reflect the number of the planned IMP administration
3 – 7.2.2	Plasma concentration of RMC-035 by treatment group and renal function at baseline	RND	Visit; Time point; Dosing of the respective IMP administration; Value Note: Renal function at baseline: Categorisation of eGFR Note: Time point should also reflect the number of the planned IMP administration
3 – 7.3.1	PK Parameters for RMC-035 in plasma after each of the 5 IMP infusions by treatment group and age group: - C_{max} - C_{trough} - t_{max} - AUCs* - $t_{1/2}$	RND	Visit; Time point; Dosing of the respective IMP administration; PK values Note: Age group: 18-69 years or ≥70 years of age at baseline Note: Time point should also reflect the number of the planned IMP administration * For each IMP infusion all calculated AUCs will be listed (see AUC-table in SAP Section 4.3.2.3)
3 – 7.3.2	PK Parameters for RMC-035 in plasma after each of the 5 IMP infusions by treatment group and renal function at baseline: - C_{max} - C_{trough} - t_{max} - AUCs* - $t_{1/2}$	RND	Visit; Time point; Dosing of the respective IMP administration; PK values Note: Renal function at baseline: Categorisation of eGFR Note: Time point should also reflect the number of the planned IMP administration * For each IMP infusion all calculated AUCs will be listed (see AUC-table in SAP Section 4.3.2.3)
3 – 7.4.1	PK Parameters for RMC-035 in plasma after fourth dose by treatment group and age group: - PTR - $Rac_{(AUC)}$	RND	Visit; Time point; Dosing of the respective IMP administration; PK values Note: Age group: 18-69 years or ≥70 years of age at baseline Note: Time point should also reflect the number of the planned IMP administration
3 – 7.4.2	PK Parameters for RMC-035 in plasma after fourth dose by treatment group and renal function at baseline: - PTR - $Rac_{(AUC)}$	RND	Visit; Time point; Dosing of the respective IMP administration; PK values Note: Renal function at baseline: Categorisation of eGFR Note: Time point should also reflect the number of the planned IMP administration
3 – 8	Presence and titers of ADA and characteristics of ADA	RND	All related variables

No.	Title	Set	Variables
Exploratory Evaluation and Other Variables			
4 – 1	Biomarkers: Formal fields, sampling dates and times	RND	All related variables for plasma, serum, and urine
4 – 2.1	Cardiac biomarkers: Formal fields, sampling dates and times	RND	All related variables
4 – 2.2.1 - 4 – 2.2.2	Cardiac biomarkers: Laboratory parameters and absolute changes - NT-proBNP - Troponin-T	RND	Visit; Time point; Value; Absolute change from baseline; Irregularities in cardiac biomarker analysis
4 – 2.3	Cardiac biomarkers: Overall assessment	RND	Visit; Time point; Value
4 – 3	Concentration of RMC-035 in urine: Formal fields, sampling dates and times	RND	All related variables
4 – 4.1	Hemodynamic assessments: Formal fields, sampling dates and times	RND	All related variables
4 – 4.2.1 - 4 – 4.2.6	Hemodynamic assessments and changes from baseline - Cardiac output (CO) - Mixed venous saturation (SvO2) - Central venous pressure (CVP):Right ventricular pressure systolic - Central venous pressure (CVP): Right ventricular pressure diastolic - Central venous pressure (CVP): Pulmonary artery pressure systolic - Central venous pressure (CVP): Pulmonary artery pressure diastolic	RND	Visit; Time point; Value; Absolute change from baseline
4 – 5.1	Major adverse kidney event (MAKE30) during the trial	RND	MAKE during the trial (yes/no)
4 – 5.2	Major adverse kidney event (MAKE30) and components of MAKE30 by visit	RND	Visit; MAKE30 (yes/no); MAKE criteria
4 – 5.3	Dialysis information	RND	Visit; Variables regarding dialysis from the V-Start form
4 – 6.1.1 - 4 – 6.1.5	Percent increase from baseline in - Serum creatinine - Cystatin C - eGFR(SCr) - eGFR(Cystatin C) - eGFR(SCr and Cystatin C)	RND	Visit; Time point; Value; Absolute change from baseline; Relative change from baseline
4 – 6.2	Maximum percent increase from baseline until Visit 6 in Serum creatinine, Cystatin C, and in the corresponding eGRF values	RND	Maximum percent increase from baseline until Visit 6 for - Serum creatinine - Cystatin C - eGFR(SCr) - eGFR(Cystatin C) - eGFR(SCr and Cystatin C)

4 – 6.3.1 - 4 – 6.3.5	Post-baseline AUC 48 hours, 72 hours and at Visit Day 7 post-surgery for - Serum Creatinine (SCr) - Cystatin C levels - eGFR(SCr) - eGFR(Cystatin C) - eGFR(SCr and Cystatin C)	RND	All related variables
4 – 7.1	Severity, duration and persistence of AKI	RND	Maximum AKI stage until Visit 6; Duration of AKI, persistence of AKI (yes/no) Note: Maximum AKI stage: The highest stage per patient will be used
4 – 7.2	AKI Stage and its components by visit	RND	AKI stage by visit (until Visit 6); SCr 1.5 to 1.9 times baseline value (yes/no), Increase in SCr ≥0.3 mg/dL (≥ 26.5 µmol/L) within 48 hours (yes/no); Urine output <0.5 mL/min/h for 6 to <12 hours (yes/no); SCr 2.0-2.9 times baseline value (yes/no); urine output <0.5 mL/min/h for ≥ 12 hours (yes/no); SCr 3.0 times baseline value (yes/no); Increase in SCr 5.0 mg/dL (≥353.6 µmol/L) (yes/no); initiation of renal replacement therapy (yes/no); Urine output <0.3 mL/min/h for ≥24 hours (yes/no); Anuria for ≥12 hours (yes/no)
4 – 8.1	Length of index Intensive Care Unit (ICU) stay	RND	Variables from ICU form and corresponding derived variables
4 – 8.2	Length of index hospital stay and discharge facility	RND	Variables from HOSP form and corresponding derived variables

NOTE: The wording may be adapted in the final output, also some listings may be split into two or more parts if they do not fit on the page, and several listings may be combined where reasonable depending on size.

List of Figures

Analysis Sets:
SAF = Safety Analysis Set
PK = PK Analysis Set

No.	Title	Type	Set
Safety and Pharmocokinetics Evaluation			
3 – 1.1.1 - 3 – 1.1.5	Vital signs – Mean-by-visit: - Systolic blood pressure - Diastolic blood pressure - Respiratory rate - Heart rate - Body temperature	Box plots	SAF
3 – 1.2.1 - 3 – 1.2.5	Vital signs – Subject-profile-by-visit: - Systolic blood pressure - Diastolic blood pressure - Respiratory rate - Heart rate - Body temperature	Line charts	SAF
3 – 2.1.1 - 3 – 2.1.5	12-lead ECG – Mean-by-visit: - Heart rate - PR interval - QRS interval - QT interval - QTc interval	Box plots	SAF
3 – 2.2.1 - 3 – 2.2.5	12-lead ECG - Subject-profile-by-visit: - Heart rate - PR interval - QRS interval - QT interval - QTc interval	Line charts	SAF
3 – 3.1.1 - 3 – 3.1.13	Hematology laboratory parameters - Mean-by-visit: - Leukocytes - Erythrocytes - Hemoglobin - Erythocyte Volume Fraction (EVF) - Mean corpuscular volume (MCV) - Mean corpuscular hemoglobin (MCH) - Mean corpuscular hemoglobin concentration (MCHC) - Thrombocytes - Neutrophils abs. - Monocytes abs. - Lymphocytes abs. - Eosinophils abs. - Basophils abs.	Box plots	SAF

No.	Title	Type	Set
Safety and Pharmocokinetics Evaluation			
3 – 3.2.1 - 3 – 3.2.13	Hematology laboratory parameters - Subject-profile-by-visit: - Leukocytes - Erythrocytes - Hemoglobin - Erythocyte Volume Fraction (EVF) - Mean corpuscular volume (MCV) - Mean corpuscular hemoglobin (MCH) - Mean corpuscular hemoglobin concentration (MCHC) - Thrombocytes - Neutrophils abs. - Monocytes abs. - Lymphocytes abs. - Eosinophils abs. - Basophils abs.	Line charts	SAF
3 – 4.1.1 - 3 – 4.1.21	Clinical chemistry incl. liver function laboratory parameters – Mean-by-visit: - Sodium - Potassium - Phosphate - Urea nitrogen - Serum Creatinine - eGFR (based on serum creatinine) - C-reactive protein (CRP) - Albumin - Calcium - Chloride - Cystatin C - Magnesium - Urid acid - eGFR (based on serum creatinine and cystatin C) - Total bilirubin - Conjugated bilirubin - AST - ALT - Gamma-glutanyltransferase (GGT) - ALP - eGFR (based on cystatin C)	Box plots	SAF

No.	Title	Type	Set
Safety and Pharmocokinetics Evaluation			
3 – 4.2.1 - 3 – 4.2.21	Clinical chemistry incl. liver function laboratory parameters – Subject-profile-by-visit: - Sodium - Potassium - Phosphate - Urea nitrogen - Serum Creatinine - eGFR (based on serum creatinine) - C-reactive protein (CRP) - Albumin - Calcium - Chloride - Cystatin C - Magnesium - Urid acid - eGFR (based on serum creatinine and cystatin C) - Total bilirubin - Conjugated bilirubin - AST - ALT - Gamma-glutanyltransferase (GGT) - ALP - eGFR (based on cystatin C)	Line charts	SAF
3 – 5.1	PK Analysis - Individual concentration-time profiles	Line chart	PK
3 – 5.2	PK Analysis - Mean concentration-time profile	Line chart	PK
3 – 6.1	PK Analysis - Dose proportionality for C_{max}	Scatter plots	PK
3 – 6.2	PK Analysis - Dose proportionality for AUC_{τ} Note: Since τ varies between the different dose administrations, the following AUCs will be used: $AUC_{0\text{-}6h,\ 1st\ dose}$, $AUC_{0\text{-}6h,\ 2nd\ dose}$, $AUC_{0\text{-}12h,\ 3rd\ dose}$, $AUC_{0\text{-}24h,\ 4^{th}\ dose}$, $AUC_{0\text{-}2h,\ 5th\ dose}$ (see SAP Section 4.3.2.3)	Scatter plots	PK

NOTE: Some figures may be combined in one output file where reasonable.