Statistical Analysis Plan
for
Final Analysis

Version 2.0

Study:	Double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of ilofotase alfa in patients at risk for renal damage following open heart surgery
Study-ID:	AP-recAP-CSA-RD-02-01
Sponsor /Contact:	AM-Pharma B.V. Stadsplateau 7 3521 AZ Utrecht, The Netherlands
Version:	Version 2.0 of 05Dec2025
Previous versions:	Version 1.0 of 09Aug2024

Revision History

Version	Author	Date	Change description
1.0	*X*[1]	09Aug2024	1st final version
2.0	*X*[1]	05Dec2025	Section 3: Subgroup analyses (Baseline eGFR ≤ 45 / > 45) are introduced for selected efficacy endpoints, marked in TFL shells (Appendix A) Section 4.2: 1) MAKE60 endpoint has been shifted from exploratory endpoint to secondary efficacy endpoint 2) AEs/SAEs through Day 28 (secondary objectives) have been shifted from 4.2. to section 4.4 (safety endpoints) Section 4.3: 1) Additional exploratory endpoints have been added (sCreatRatio threshold, MAKE60a, MAKE60-WinRatio, AKI incidence) 2) Endpoint 'MAKE60' shifted to section 4.2 3) Endpoint 'Postoperative surgery related complications' shifted to section 4.4 Section 5.4.2: Section on baseline CKD stage has been added Section 5.4.9: Specifications for the identification of nephrotoxic drugs have been added Section 5.6.1: Section revised to also include estimands for secondary endpoint MAKE60 Section 5.6.2: Further sensitivity analyses and potential post-hoc analyses have been added. Normality checks have been adapted Section 5.6.3: Section has changed to contain the analysis strategy for the secondary efficacy endpoint (MAKE60) including handling of missing values. Sensitivity analyses and potential post-hoc analyses have been specified Section 5.6.4: Section has been updated to contain

Version	Author	Date	Change description
			analysis strategies for all endpoint defined in section 4.3. Details of analysis of AUC of AKI has been updated Section 5.7.1: section was added to contain the analysis strategy for the safety endpoint 'Adverse events through Day 28' Section 5.8: Descriptive analysis and graphical presentation of PK concentration data has been added Section 5.9: Handling of PD classification during BDRM added Section 5.11: Imputation strategies for the endpoints MAKE60, MAKE60a and AUC-KDIGO-AKI have been added. Handling of early terminations after Day 61 added. Appendix A: New tables have been added for displaying the results of the additional analyses described above Appendix B: 'Identification of nephrotoxic drugs' added Appendix C: 'Laboratory values – conversion factors' added Minor editorial changes

1. Taken out to comply with GDPR

Table of Contents

LIST OF ABBREVIATIONS

In the following abbreviations are listed as used within this statistical analysis plan or which might occur within the tables, figures, and listings (TFL) outputs:

AE	Adverse event
ADA	Anti-drug antibodies
ADaM	Analysis data model
AKI	Acute kidney injury
ANCOVA	Analysis of covariance
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
BDRM	Blind data review meeting
BMI	Body mass index
CABG	Coronary artery bypass grafting
(e)CRF	(electronic) case report form
CPB	Cardiopulmonary bypass
EC	Exclusion criteria
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EoT	End of trial
EuroScore	European System for Cardiac Operative Risk Evaluation
FAS	Full analysis set
H_0	Null hypothesis
H_1	Alternative hypothesis
IC	Inclusion criteria
ICE	Intercurrent event
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
IP	Investigational product
ITT	Intention-to-treat
KDIGO	Kidney disease improving global outcomes
MAKE	Major adverse kidney events
MedDRA	Medical dictionary for regulatory activities
N	Number of patients
PD	Protocol deviation
PK	Pharmacokinetic
PPS	Per-protocol set
PT	Preferred term
RD	Renal damage
RRT	Renal replacement therapy
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
sCreat	Serum creatinine
SD	Standard deviation
SDTM	Study data tabulation model
SOC	System organ class
STS	Society of Thoracic Surgeons
TEAE	Treatment-emergent adverse event
TESAE	Treatment emergent serious adverse event
TFLs	Tables, figures, listings,
WHO-DD	World health organization - Drug dictionary

1 Introduction

This Statistical Analysis Plan (SAP) was defined by the Sponsor and the responsible Statistician without knowledge of the randomization code. It is based upon the Study Protocol (version 4.0 of 31Jul2025) and the current (electronic) case report forms ((e)CRF) version 2.0 and contains detailed description of the statistical methods described therein.

The SAP was finalized before database lock and unblinding.

This SAP does not include analyses of anti-drug antibodies (ADAs), pharmacokinetic (PK) data (except for PK concentration (graph and descriptive statistics)) and biomarkers (only optional after the end of the trial).

1.1 Study Objectives

Primary Objective

The primary objective is to assess the effect of ilofotase alfa on renal function. For details on the related endpoints see section 4.1.

Secondary Objective

The secondary objective is to assess the efficacy and safety of ilofotase alfa in patients undergoing open chest heart surgery. For details on the related endpoints see section 4.4.

Exploratory Objectives

Exploratory objectives are:

- To investigate incidence, duration, and severity of acute kidney injury (AKI)
- To assess the effect on surgery related complications
- To assess the duration of critical care after the scheduled surgery
- To investigate biomarkers of AKI (optional)

For details on the related endpoints see section 4.2 and 4.3.

The pharmacokinetic objective is not part of this SAP.

1.2 Study Design

This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled, 2-arm parallel group design trial in patients at risk for renal damage (RD) following open heart surgery. The clinical trial consists of a pre-treatment period of up to 30 days, a treatment period of 1 day and a follow-up period of 60 days. The total duration of trial participation for a patient will be about 3 months.

1.3 Sample Size Justification

The effect size of 20% has been estimated based on the evaluation of data from patients with complex cardiac surgery and pre-operative impaired renal function from the CERNER database (AM-Pharma report RAP-CLIN-0159). Assuming a mean of 1.28 sCreat ratio for the placebo arm, a pooled standard deviation of 0.465 and a one sided alpha of 2.5%, a 20% difference in sCreat ratio between treated and control patients can be detected with a power of 91.7% and a sample size of 150. To detect a 15% difference in sCreat ratio between treated and control patients up to 250 patients are needed with a similar power (90.1%) and equal assumption on mean, SD and alpha. Drop-outs are not considered within the 250 patients.

1.4 Randomization and Blinding

Randomization

After screening and baseline assessments, eligible patients will be randomized 1:1 to either 2 doses of 128 mg ilofotase alfa, or 2 doses of placebo control. Randomization will be stratified by baseline estimated glomerular filtration rate (eGFR) (≤45 mL/min/1.73m^2 or >45 mL/min/1.73m^2) and type of surgery (coronary artery bypass grafting (CABG) with 3 or more distal anastomoses or CABG combined with valve surgery or aortic valve plus root and/or ascending aorta [excluding aortic arch]).

The planned type of surgery as described in the randomization list includes only "CABG with 3 or more distal anastomoses" and "CABG combined with valve surgery". In protocol V3.0 an additional surgery type ("Aortic valve plus root and/or ascending aorta [excluding aortic arch]") has been introduced. This additional surgery type was randomized into the "CABG combined with valve surgery" stratum. Within this SAP and in all TLGs only the original stratum wording is displayed.

Blinding

During the entire trial, patients, investigators, the sponsor, and all other persons involved in the conduct of the trial will be blinded to treatment. To maintain the blind, the ilofotase alfa 128 mg and the placebo concentrate for preparing a solution for infusion will have identical appearance, shape, and color, and will have identical labeling and packaging.

2 Statistical Analysis Sets

Set	Definition	Treatment used for analysis
All enrolled set	All patients who provided informed consent.	Planned treatment
Safety analysis set (SAF)	All patients who received at least one dose of investigational product (IP). If it is uncertain if the patient has received IP, the patient will be included in the SAF.	Actual treatment
Full analysis set (FAS)	All patients who were randomized and received both planned doses of IP.	Planned treatment
Per-protocol set (PPS)	All patients included in the FAS without any relevant protocol deviation (PD) with impact on the individual primary efficacy endpoint. PDs will be identified and classified for each patient during a blind data review meeting (BDRM) (see section 5.12).	Planned treatment

Actual treatment means that all patients will be analyzed by the treatment they received.
Planned treatment means that all patients will be analyzed by the treatment group to which they were randomized ("intention-to-treat" (ITT)).

The FAS will be the analysis set applied to the evaluation of all efficacy endpoints. The PPS will be used for supplementary analysis of the primary efficacy endpoint. The SAF will be the analysis set for all safety analyses (including secondary endpoint related to safety).

Patients will be allocated to analysis sets (SAF, FAS and PPS) during a BDRM before database lock and unblinding.

3 Subgroup Analysis

The following subgroups will be analyzed for selected tables:

Baseline eGFR ≤ 45 mL/min/1.73m² vs. Baseline eGFR > 45 mL/min/1.73m²

The primary and secondary efficacy endpoint will be analyzed within these subgroups. Additionally, certain exploratory endpoints will be evaluated for these subgroups. In Appendix A, selected tables are marked with an asterisk (*) to indicate the subgroup analysis.

4 Efficacy and Safety Endpoints

4.1 Primary Efficacy Endpoint

- Ratio between the highest sCreat value post-surgery (post-surgery Day 1 and Days 2, 3, 4, and 5) and baseline sCreat (pre-surgery, Day -1/Day1).

4.2 Secondary Efficacy Endpoint

- Major adverse kidney events (MAKE60)

  A MAKE60 event is defined by fulfilling one of the following three criteria (MAKE60 = yes):

  - death up to and including Day 61
  - received or are receiving new RRT up to and including Day 61, or
  - a decrease in eGFR ≥25% on Day 61 compared to the pre-surgery baseline eGFR reference value.

  If none of the criteria is fulfilled and if eGFR at date of visit Day 61 is available, MAKE60='no'.

  If no criterion is fulfilled and the sCreat value for visit Day 61 is not available, MAKE60='missing' and will be imputed (see section 5.11).

4.3 Exploratory Efficacy Endpoints

- sCreat ratio </≥ 1.25

  Endpoint is set to 'Yes', if the sCreat ratio (as defined in 4.1) is ≥1.25. It is set to 'No' if the sCreat ratio is < 1.25.

- Major adverse kidney events (MAKE60a)

  As defined in section 4.2, without the death component.

- Major adverse kidney events (MAKE60) – WinRatio

  An unmatched pair approach will be used, based on the comparison of each placebo patient with each ilofotase alfa patient with respect to the different components in a hierarchy of medical importance.

Comparison of each potential patient pair (i.e. one from treatment group and one from placebo group)	**How event is assessed**
Step 1: Death	
- Placebo patient died, treatment patient survived - Placebo patient died, treatment patient premature discontinued study (later than death of placebo patient) - Placebo and treatment patient died: Placebo patient died prior to treatment patient	Treatment wins
- Treatment patient died, placebo patient survived - Treatment patient died, placebo patient premature discontinued study (later than death of treatment patient) - Placebo and treatment patient died: Treatment patient died prior to placebo patient	Placebo wins
- Placebo patient premature discontinued study prior to death of treatment patient - Treatment patient premature discontinued study prior to death of placebo patient - Neither of the patients died	**Tie → go to step 2**
Step 2: RRT (all patient pairs with tie in step 1)	
- Duration* on RRT in treatment patient < Duration* on RRT in placebo patient - Treatment patient premature discontinued study (without RRT event) later than start of 1st RRT event in placebo patient - Treatment patient completed study (without RRT event) when Placebo patient has RRT event	Treatment wins
- Duration* on RRT in treatment patient > Duration* on RRT in placebo patient - Placebo patient premature discontinued study (without RRT event) later than start of 1st RRT event in treatment patient - Placebo patient completed study (without RRT event) when Treatment patient has RRT event	Placebo wins
- Duration* on RRT in treatment patient = Duration* on RRT in placebo patient - Neither of the patients on RRT (irrespectively of premature discontinuation)	**Tie → go to step 3**

Comparison of each potential patient pair (i.e. one from treatment group and one from placebo group)	**How event is assessed**
- Treatment patient premature discontinued study (without RRT event) prior to start of 1st RRT event in placebo patient - Placebo patient prematurely discontinued study (without RRT event) prior to start of 1st RRT event in treatment patient	
Step 3: eGFR (all patient pairs with tie in step 2)	
Placebo patient meets criterion**, treatment patient does not meet criterion**	Treatment wins
Treatment patient meets criterion**, placebo patient does not meet criterion**	Placebo wins
- Both meet criterion** - Neither meets criterion** - Placebo and/or treatment patient premature discontinued or sCreat at Day 61 is not available	**Tie**

* Duration = stop date of RRT event - start date of RRT event +1; for patients with more events, the sum of durations from the individual events is taken; for patients without an RRT event, duration is set to 0.
** Criterion is defined as ≥25% reduction of eGFR on Day 61 compared to Baseline.

- KDIGO AKI stage

The area under the curve (AUC) of AKI (kidney disease improving global outcomes (KDIGO) using sCreat), defined as duration (in days) and severity of AKI; measured over the first 5 days after surgery.

The KDIGO AKI stage will be assessed after surgery daily through Day 5 using sCreat values:

Stage	**sCreat**
0	<1.5 times the baseline value
1	1.5 to 1.9 times baseline value OR ≥0.3 mg/dL (≥26.5 µmol/L) increase
2	2.0 to 2.9 times baseline value
3	3.0 times baseline value OR increase to ≥4.0 mg/dL (≥353.6 µmol/L) OR initiation of RRT

sCreat ratio will be rounded to one decimal place for this.

The change in severity of KDIGO AKI stage over time (Baseline through Day 5), expressed as $AUC_{1(post)\text{-}5days}$, will be summarized by treatment. The $AUC_{1(post)\text{-}5days}$ will be calculated using linear trapezoidal rule as follows:

Visit	Day 1 - post-surgery	Day 2	Day 3	Day 4	Day 5
Visit Value	1	2	3	4	5
KDIGO stage value	X_1	X_2	X_3	X_4	X_5

$$AUC_{(t_{i+1}-t_i)} = (t_{i+1} - t_i) * (Value(t_{i+1}) + Value(t_i))/2$$

$AUC_{1(post)\text{-}5days}$ = Sum of all $AUC_{(t_{i+1}-t_i)}$

For this specific endpoint it is:

$AUC_{1(post)-5days} = (2-1)*(X_2+X_1)/2 + (3-2)*(X_3+X_2)/2 + (4-3)*(X_4+X_3)/2 + (5-4)*(X_5+X_4)/2$

For handling of missing values please refer to section 5.11.

- KDIGO AKI

  The KDIGO AKI endpoint on patient level is defined 'Yes' if the individual AKI stage is > 0 for at least one day during Day 1-5, otherwise its 'No'.

- Length of stay in the intensive care unit (ICU) in days after the initial surgery

  Defined as Length of stay = Discharge date - Admission date + 1.

- Changes in biomarkers of AKI compared to Baseline

  Biomarker samples are collected for potential future analyses. Statistical analyses of biomarker data are not in scope of this SAP. A separate report will be generated by a third party when applicable.

4.4 Safety Endpoints

- AEs
  - Number of adverse events (AEs) and serious AEs (SAEs) through Day 28.
  - Number of treatment emergent AEs/SAEs (TEAEs/TESAEs).
- Number of Postoperative surgery related complications within 28 days of surgery, assessed according to the Society of Thoracic Surgeons (STS) definition.
- Safety laboratory
- Mortality
- Anti-drug antibodies (ADAs): ADA data analyses are not in scope of this SAP. A separate report will be generated by a third party.

4.5 Pharmacokinetics

- Population (Pop) PK: Analyses of PK data are not in scope of this SAP (except for PK concentration (graph and descriptive statistics)). A separate report will be generated by a third party.

5 Statistical Evaluation

5.1 General Analysis Considerations

Data will be summarized by treatment group and overall.

For qualitative variables the number and percentage in each category will be calculated. Percentages will be presented to one decimal place. The calculation of percentages will be based on the number of non-missing values, if not stated otherwise. Missing values (including user-defined missing values as "not done", "unknown", "not applicable", "not documented") will not be presented and not be included in the calculation of percentages.

For quantitative variables, unless otherwise stated, the number of patients (N), the mean, standard deviation (SD), minimum, first quartile, median, third quartile, and maximum will be provided. In the description of the tables this will be denoted by „summary statistics". CRF records will be displayed with the same precision as they were recorded, derived or standardized values will be rounded to a reasonable number of digits. Mean, median, SD, and quartiles will be presented with one decimal place more than the precision of the data. Minimum and maximum will be presented with the same precision as the raw data. P-values will be reported with four decimal places (i.e., 0.xxxx). In summary statistics tables the overall number of missing values will not be given.

As randomization was done using baseline eGFR and type of surgery as stratification factors, the following procedure will be followed in case of randomization in an incorrect stratum:

Use of the planned stratum information ("as randomized") for stratified analyses, where also the planned treatment group is used, which is in line with the spirit of the ITT principle and keeps balance of the strata. If the actual stratification information deviates for a considerable number of cases, the actual stratum could be used in an additional sensitivity analysis. This should be discussed during the BDRM and decided before database lock and unblinding.

If randomization in an incorrect stratum occurred, i.e., the (planned) stratum information used for randomization deviates from the (actual) stratum information collected after randomization, the planned stratum information is used for stratified analyses. Deviations will be discussed during the BDRM and decided before database lock and unblinding.

5.2 Specifications and Definitions

- Baseline assessments will take place at the Baseline on Day -1 / Day 1. For sCreatinine Screening value is used if no Baseline value is available.
- Study days are calculated as follows:

  if study date < treatment start date then study day = study date – treatment start date;
  if study date >= treatment start date then study day = study date – treatment start date + 1 [day]
- Unscheduled visits will only be listed and not included in any tables except table "Patients per visit".
- Visit terminology:

Notation used in the protocol	Notation used for TFLs
Screening (Day -30 to Day -1)	Screening
Baseline (Day -1/ Day1)	Baseline
Treatment (Day 1) - pre-surgery	Day 1 - Pre-surgery
Treatment (Day 1) - post-surgery	Day 1 - Post-surgery
Follow-up (Day 2)	Day 2
Follow-up (Day 3)	Day 3
Follow-up (Day 4)	Day 4
Follow-up (Day 5)	Day 5
Follow-up (Day 28 ± 4 d)	Day 28
Follow-up (Day 61 + 10 d)	Day 61
Follow-up (EoT + 10 d)	EoT

EoT = End of trial

5.3 Disposition of Patients and Analysis Sets

The disposition of patients and analysis sets, patients per visit, per country and per center, inclusion and exclusion criteria and the status at EoT (including number of early terminations and reason for early terminations) will be shown for all patients of the all enrolled set. Patients excluded from analysis sets will be listed with the reason for exclusion.

All variables will be analyzed for the all enrolled set, unless otherwise specified. No inferential assessments will be performed on disposition data.

5.4 Demographics and Other Covariates

No inferential assessments will be performed on demographics and other covariates. All variables will be analyzed for the FAS, unless otherwise specified.

Demographic and other covariates will be summarized descriptively by treatment group to describe the trial population.

5.4.1 Demographic Data

Demographic data (sex, age at time of consent, race, body height, body weight and auto-calculated body mass index (BMI)) will be summarized descriptively at pre-operative Baseline for the FAS. Additionally, age will be categorized as follows:

< 18 years
18-64 years
65-84 years
≥ 85 years

5.4.2 CKD stage at baseline

CKD stages at baseline are defined according to the following table:

CKD stage	Description	Baseline eGFR (ml/min/1.73m^2)
G1	Normal or high	≥ 90
G2	Mildly decreased	60-<90
G3a	Mild to moderate decreased	45-<60
G3b	Moderate to severe decreased	30-<45
G4	Severe decreased	15-<30
G5	Kidney failure	< 15

Number and frequencies of patients for different CKD stages will be summarized by treatment group.

5.4.3 Pregnancy Test

The information on reproductive system and results of the pregnancy test (for women of childbearing potential) will be listed.

5.4.4 Electrocardiogram (ECG)

Frequencies of the ECG interpretation (Normal/ Abnormal/ Unevaluable) will be presented.

A listing including only abnormal values will be presented.

5.4.5 EuroScore II

The results of EuroScore II (%) will be analyzed descriptively using summary statistics.

5.4.6 Physical Examination

The physical examination including examination of the head, neck, eyes, ears, nose, and throat, cardiovascular system, pulmonary system, lymphatic system, thyroid gland, muscular and skeletal system, general appearance, extremities, abdomen, skin (whole body), and neurological system will be performed at Screening only.

Frequencies of the overall PE outcome (Normal/ Abnormal/ Unevaluable) as well as clinical significance for abnormal findings will be presented.

5.4.7 Medical History

Medical history will be summarized using the Charlson co-morbidity index. The index will be calculated by adding the following points as follows:

Question	Value	Points
Age	< 50 years	0
	50-59 years	1
	60-69 years	2
	70-79 years	3
	≥ 80 years	4
Myocardial Infarction	no	0
	yes	1
Congestive Heart Failure	no	0
	yes	1
Peripheral Vascular Disease	no	0
	yes	1
Cerebrovascular Accident or Transient Ischemic Attack	no	0
	yes	1
Dementia	no	0
	yes	1
Chronic Obstructive Pulmonary Disease	no	0
	yes	1
Connective Tissue Disease	no	0
	yes	1
Peptic Ulcer Disease	no	0
	yes	1
Liver Disease	none	0
	mild	1
	moderate to severe	3
Diabetes Mellitus	none or diet-controlled	0
	uncomplicated	1
	end-organ damage	2
Hemiplegia	no	0
	yes	2
Moderate to Severe Chronic Kidney Disease	no	0
	yes	2
Solid Tumor	none	0
	localized	2
	metastatic	6
Leukemia	no	0
	yes	2
Lymphoma	no	0
	yes	2
AIDS	no	0
	yes	6

Thus, this Charlson co-morbidity index ranges from 0 to 37 points. The Charlson co-morbidity index will be presented using summary statistics.

Additionally, medical history will be coded according to MedDRA and tabulated by system organ class (SOC) and preferred term (PT) (MedDRA).

5.4.8 Surgical parameters

The following parameters are captured on the eCRF page “Surgical parameters”:

- Type of surgery actually performed
- Surgical approach
- Number of valves
- Types of valves
- Number of bypasses (i.e. “Number of distal anastomoses”)
- Duration of surgery
- Type of cardioplegia
- Volume of cardioplegia
- Priming volume cardiopulmonary bypass (CPB) pump
- Time on CPB pump
- Cross-clamp time
- Lowest hematocrit recorded in the operating room
- Estimated blood loss
- Packed cells needed
- Number of packed cells used
- Time of episodes with mean blood pressure <50 mmHg during surgery
- Number of episodes with mean blood pressure <50 mmHg during surgery

Number and frequencies of patients for the categorical surgical parameters will be summarized by treatment group, except for ‘Volume of cardioplegia’ and ‘Priming volume cardiopulmonary bypass (CPB) pump’.
Descriptive statistics will be used to summarize non-categorial surgical parameters by treatment group.

5.4.9 Prior and Concomitant Medication

Number and frequency of patients with prior or concomitant medication will be summarized by treatment group.

Prior and Concomitant medications as well as vasopressors and inotropes will be coded by WHO-DD and analyzed descriptively by anatomical therapeutic chemical (ATC) level 2, ATC level 3, and preferred name.

Use of vasopressors and/or inotropic drugs is entered on eCRF page “Vasopressor and Inotropic Agents” yes/no).

In addition, frequencies of patients using medications which are known to cause kidney problems (i.e. nephrotoxic drugs) will be tabulated separately according to classification described in Appendix B.

If no preferred name can be found in the WHO-DD for a documented medication, an umbrella term from the WHO-DD will be used instead. A corresponding footnote will be added to the tables and listings concerned.

Concomitant medications are defined as all medications with start date/time or end date $\geq$ first administration of the IP or ticked as continuing/ongoing. Prior medications include all medications that were stopped before first administration of the IP.

Handling of incomplete dates

To assign a medication to be prior or concomitant, the following rules will be applied to impute incomplete start dates (imputed dates will not be displayed in listings):

yyyy	mm	dd	Imputation
available	available	missing	yyyy-mm-01
available	missing	missing	yyyy-01-01
missing	missing	missing	no imputation

The following rules will be applied to impute incomplete end dates:

yyyy	mm	dd	Imputation
available	available	missing	Last day of yyyy-mm
available	missing	missing	yyyy-12-31
missing	missing	missing	no imputation

If the start or end date is completely missing and the allocation to prior/previous or concomitant is not clear the medication will be considered concomitant.

In listings the generic name and all coding levels used for tabulation will be displayed.

- Prior medication will be tabulated by ATC level2/ATC level 3/ Preferred Name
- Concomitant medication will be tabulated by ATC level2/ATC level 3/ Preferred Name
- Inotropes and vasopressors will be tabulated by ATC level2/ATC level 3/ Preferred Name
- Perioperative and standard of care medications will be tabulated by categories as collected in the eCRF

5.5 Exposure and Compliance

Number and percentage with respect to IP administration (pre- and post-surgery) will be tabulated (CRF questions 'Was IP administered', 'Was IP solution prepared correctly?', 'Was the correct volume administered?', 'Was IP administration interrupted'). Details on IP administrations will be listed.

5.6 Efficacy Analysis

5.6.1 Estimands

Treatment: The patients will be treated with the IP (ilofotase alfa or placebo) on the day of surgery (1st infusion pre-surgery , 2nd infusion post surgery). The ilofotase alfa dose is a fixed dose of 128 mg per infusion. The matching placebo contains aqueous buffer supplied in glass vials that are identical to the ilofotase alfa vials in order to maintain the blind.

Population: The target population consists of male and female adult patients scheduled for CABG with 3 or more distal anastomoses or CABG combined with valve surgery that are at risk of developing renal damage based upon pre-operative impaired kidney function (eGFR ≥ 25 and ≤ 65 mL/min/1.73m²).

5.6.1.1 Primary Estimand (sCreat Ratio)

Variable: sCreat ratio.

Intercurrent events (ICE): The following ICEs are considered:

1. Use of concomitant medications during surgery or until Day 5 which might influence the efficacy assessment (i.e. nephrotoxic drugs),
2. Any deviation of the evaluation of sCreat (incorrect storage of sample, etc.),
3. Death after second IP administration.

The occurrence of ICEs 1 and 2 will be handled using the treatment policy strategy defined according to ICH guideline E9 (R1). All values will be used regardless of occurrence of the above mentioned ICEs during the study period. The occurrence of ICE number 3 will be handled using a composite strategy. If a patient dies after the second IP administration and before sCreat measurement on Day 5, the sCreat ratio will be set to 1.25, irrespectively of any measured sCreat values.

Population-level summary: The sCreat ratio will be compared between ilofotase alfa and placebo by means of LS means and LS means differences of an analysis of covariance (ANCOVA) with pre-operative sCreat baseline value, eGFR stratification category, and type of surgery stratification category as covariates.

5.6.1.2 Secondary Estimand (MAKE60)

Variable: MAKE60.

Intercurrent events (ICE): The following ICEs are considered:

1. Use of concomitant medications during surgery or until Day 61 which might influence the efficacy assessment (i.e. nephrotoxic drugs),
2. Any deviation of the evaluation of sCreat (incorrect storage of sample, etc.),

The occurrence of ICEs 1 and 2 will be handled using the treatment policy strategy defined according to ICH guideline E9 (R1). All values will be used regardless of occurrence of the above mentioned ICEs during the study period.

Population-level summary: The proportion of patients with MAKE60 (yes/no) will be compared between ilofotase alfa and placebo by means of a logistic regression approach with pre-operative sCreat baseline value, eGFR stratification category, and type of surgery stratification category as covariates.

5.6.2 Analysis of Primary Efficacy Endpoint

The primary objective is to assess the effect of ilofotase alfa on renal function. Therefore, the ratio between the highest sCreat value post-surgery (post-surgery Day 1 and Days 2, 3, 4, and 5) and sCreat at Baseline (pre-surgery, Day -1/Day1) for sCreat will be analyzed by means of an ANCOVA. The ratio will be derived as maximum post-surgery value/baseline value.

The ANCOVA methodology will test the null hypothesis that the mean sCreat ratio is equal between the two treatment groups:

H_0: $\mu_{\text{Ilofotase alfa}} = \mu_{\text{Placebo}}$

vs.

H_1: $\mu_{\text{Ilofotase alfa}} \neq \mu_{\text{Placebo}}$

where $\mu_{\text{Ilofotase alfa}}$ is the mean of sCreat of patients in the ilofotase alfa group and μ_{Placebo} is the mean of sCreat of patients in the placebo group. The respective p-value is used for the hierarchical test procedure described in section 5.13

The pre-operative baseline sCreat value will be included as covariate. To account for the stratification factors, baseline eGFR ≤45 mL/min/1.73m² (≤45 mL/min/1.73m2 vs. >45 mL/min/1.73m2) and type of surgery (CABG with 3 or more distal anastomoses vs. CABG combined with valve surgery) will additionally be included as covariates. In case of violation of the assumption of normality, a sensitivity analysis will be undertaken based on the log- or square-root transformation.

The assumptions for normality will be checked using a visual check of the QQ-plot (quantile-quantile plot). Normality of data cannot be assumed if the plotted points do not approximately lie on the diagonal line y = x.

Results of this will be filed in appendix 16.1.9 of the Clinical Trial Report.

The primary analysis will be based on the FAS.

- Sensitivity analyses
  - The analysis will be repeated on the PPS as supplementary analysis.
  - An additional sensitivity analysis will further include pump time and cross-clamp time as covariates into the model. Pump time will be set to '0' in case of missing start time of CPB pump, stop time of CPB pump, duration time of CPB pump, and priming volume of CPB pump. Cross-clamp time will be set to '0' in case of missing start time of cross-clamp, stop time of cross-clamp, and duration of cross-clamp.
  - A sensitivity analysis will be done, excluding patients 'off-pump' (no start and stop time of CPB pump) from the analysis
  - A sensitivity analysis will be done with sCreat ratio </≥ 1.25 as threshold.
    The number and percentage of patients with sCreat ratio </≥ 1.25 will be summarized by treatment group.
    A comparison between treatments will be done by means of a logistic regression using the stratification factors baseline eGFR ≤45 mL/min/1.73m² (≤45 mL/min/1.73m2 vs. >45 mL/min/1.73m2) and planned type of surgery (CABG with 3 or more distal anastomoses vs. CABG combined with valve surgery) as covariates.
  - Post hoc analyses (to be decided on based on the final results)
    - Model with imputation of sCreat ratio of 1.2 and 1.3 for patients who died prior to Day 5.
    - Model including a covariate for patients received nephrotoxic drugs (yes/no or number of nephrotoxic drugs taken), in case a difference between treatments with respect to exposure of nephrotoxic drugs is observed.

sCreat and estimated glomerular filtration rate (eGFR) will be summarized using summary statistics and plots.

sCreat values will be converted to umol/L, if measured in a different unit (see Appendix C)

5.6.3 Analysis of secondary efficacy endpoint

The number and percentage of patients with MAKE60 events (definition see section 4.2) will be summarized by treatment group.

MAKE60 endpoint will be analyzed by means of a logistic regression using the pre-operative baseline sCreat value and the stratification factors baseline eGFR ≤45 mL/min/1.73m² (≤45 mL/min/1.73m2 vs. >45 mL/min/1.73m2) and type of surgery (CABG with 3 or more distal anastomoses vs. CABG combined with valve surgery) as covariates.

Imputation of missing data for mortality, RRT and sCreat at Day 61 is described in section 5.11 in case patients premature discontinued or complete without sCreat value at Day 61.

The respective p-value is used for the hierarchical test procedure described in section 5.13.

The analysis of the secondary efficacy endpoint will be based on the FAS.

- Sensitivity analyses
  - A sensitivity analysis will be done, excluding patients 'off-pump' (no start and stop time of CPB pump) from the analysis.
  - Major adverse kidney events (MAKE60a)
    The number and percentage of patients with MAKE60a events (as defined in section 4.3) will be summarized by treatment group.
    A comparison between treatments will be done by means of a logistic regression using the pre-operative baseline sCreat value and the stratification factors baseline eGFR ≤45 mL/min/1.73m² (≤45 mL/min/1.73m2 vs. >45 mL/min/1.73m2) and

planned type of surgery (CABG with 3 or more distal anastomoses vs. CABG combined with valve surgery) as covariates.
Imputation of missing data for RRT and sCreat at Day 61 is described in section 5.11 in case patients premature discontinued or completed without sCreat value at Day 61.

- Major adverse kidney events (MAKE60) – WinRatio
  The win ratio is defined as (total # of treatment wins / total # of placebo wins) based on the definition of wins and losses described in section 4.3.
  The statistical comparison is based on the procedures described in Pocock (Pocock et al. (2012): The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities, European Heart Journal, 33, 176–182).
- Post hoc analyses (to be decided based on the results of the planned analyses described in this document):
  - As a sensitivity analysis, a jump-to-reference imputation will be done for missing sCreat values at Day 61 (see section 5.11).

5.6.4 Analysis of exploratory efficacy endpoints

All endpoints as described within this section will be analyzed for the FAS, unless otherwise specified.

- KDIGO AKI stage

  The area under the curve (AUC) of AKI (kidney disease improving global outcomes (KDIGO) using sCreat) (as defined in section 4.3) will be summarized using descriptive statistics. A comparison between treatments will be done using the van-Elteren-Test adjusted for the stratification factors baseline eGFR ≤45 mL/min/1.73m² (yes/no) and type of surgery (CABG with 3 or more distal anastomoses vs. CABG combined with valve surgery). The difference in median between treatment groups and the stratified sum of scores will be displayed as well as the test statistic (z-value) together with the 2-sided p-value.

  Additionally, severity stages of KDIGO AKI (as defined in section 4.3) as well as maximum AKI-stages and RRT events will be summarized.

- KDIGO AKI (overall incidence)

  Overall incidence of AKI (as defined in section 4.3) will be summarized using descriptive statistics.

  A comparison between treatments for the AKI rate (yes/no) will be done by means of a logistic regression using the stratification factors baseline eGFR ≤45 mL/min/1.73m² (≤45 mL/min/1.73m2 vs. >45 mL/min/1.73m2) and type of surgery (CABG with 3 or more distal anastomoses vs. CABG combined with valve surgery) as covariates.

- Sensitivity analyses:
  - A sensitivity analysis will be done, excluding patients ‘off-pump’ (no start and stop time of CPB pump) from the analysis

- Length of stay in the intensive care unit (ICU) in days after the initial surgery

  Length of stay in the ICU after the initial surgery will be assessed by using descriptive summary statistics. Other all-cause ICU stays will be listed only.

5.7 Safety Analysis

All safety analyses will be performed for the SAF, if not stated otherwise.

5.7.1 Adverse Events through Day 28

All adverse events will be coded according to the MedDRA (version 26.1).

(S)AEs through Day 28 are define as all (S)AEs with a start day prior or equal to Day 28 (Day 28 as reported in EDC).

(S)AEs through Day 28 will be presented stratified by SOC, PT, and severity.

The number of events, as well as the number and percentage of affected patients will be reported by treatment group

5.7.2 Adverse Events

All adverse events will be coded according to the MedDRA (version 26.1).

An AE overview table will be created displaying the number of events as well as the number and percentage of patients with:

- AEs
- Serious AEs
- Non-serious AEs
- Treatment-emergent AEs (TEAEs)
- Treatment emergent serious AEs (TESAEs)
- Non-serious TEAEs
- TEAEs related to the IMP
- TEAEs leading to discontinuation of the study
- TEAEs leading to death

All other above specified AE groups will be provided by SOC and PT.

Furthermore, AEs/SAEs, non-serious AEs as well as TESAEs and non-serious TEAEs will be presented stratified by SOC, PT, and severity.

The number of events, as well as the number and percentage of affected patients will be reported by treatment group.

Tables by SOC and PT will be presented if at least one event is available.

TEAEs related to the IP are defined as definitely, probably or possibly related or having missing relationship to IP.

All AEs / SAEs which occur after start of the first administration of the IP up to 14 days after last IP exposure are defined as TEAEs.

Handling of incomplete dates

To assign an adverse event to be treatment-emergent, the following rules will be applied to impute incomplete start dates:

yyyy	**mm**	**dd**	**Imputation**
available and = year of treatment start	available and = month of treatment start	missing	Treatment start date
available and = year of treatment start	available and ≠ month of treatment start	missing	yyyy-mm-01
available and ≠ year of treatment start	available	missing	yyyy-mm-01

yyyy	mm	dd	Imputation
available and = year of treatment start	missing	missing	Treatment start date
available and ≠ year of treatment start	missing	missing	yyyy-01-01
missing	missing	missing	no imputation

Imputed start date will be compared to recorded end date. If imputed start date is after end date, imputed start date will be replaced by end date.

The following rules will be applied to impute incomplete end dates:

yyyy	mm	dd	Imputation
available	available	missing	Last day of yyyy-mm
available	missing	missing	yyyy-12-31
missing	missing	missing	no imputation

All AEs noted during the trial will be listed. In listings, the start day of the AE relative to start of treatment will be displayed for complete start dates only.

5.7.3 Surgical complications

The following complications are captured on the eCRF page “Adverse events” (“Category for adverse event” and “Subcategory for adverse event”):

- Operative mortality
- Surgical re-exploration
- Postoperative renal failure
- Deep sternal wound infection
- Postoperative prolonged intubation (ventilation)
- Stroke/cerebrovascular accident
- Myocardial infarction

An overview of these surgical complications documented in the respective category and subcategory of AEs will be created displaying the number of events as well as the number and percentage of patients for each surgical complication category.

Furthermore, the following surgical complications will be captured until Day 28:

- Mild Acute Respiratory Distress Syndrome (ARDS)
- Mild to moderate Arrhythmia
- Mild Cardiogenic Pulmonary Oedema
- Mild Deep Vein Thrombosis
- Mild Delirium
- Mild Gastrointestinal Bleed
- Mild Myocardial Infarction
- Mild Paralytic Ileus
- Mild Surgical Site Infection
- Mild Urinary Tract Infection
- Mild Hypovolemia

- Need for Prolonged Hemodynamic Support
- Need for Prolonged Mechanical Ventilation
- Mild Blood Loss

An overview of additional surgical complications as documented on the CRF forms surgical complications / additional surgical complications will be created displaying the number of events as well as the number and percentage of patients for each of the categories.

5.7.4 Laboratory Parameters

The results of the safety laboratory assessments, i.e., hematology and blood chemistry, will be tabulated (by timepoint and treatment group) and listed for each patient. All laboratory variables will be assessed by the investigator with relationship to the normal range as: ‘normal’, ‘abnormal, but without clinical relevance’, or ‘abnormal with clinical relevance’. Out-of-range laboratory values that are considered ‘abnormal with clinical relevance’ and that were not present at Screening will be documented as AEs and additionally listed as such.

If the original results contain a '<' or '>' sign, these signs are shown only for the original results. For standardized results and summary tables, the signs have been omitted. If different units are used for a specific laboratory parameter, the conversions are given in the conversion document (see Appendix C).

5.7.5 Mortality

The number and percentage of patients died during the course of the trial will be tabulated. A listing with all information (death – no/yes; date of death, cause of death) will be provided.

5.8 Pharmacokinetic (PK)

The PK concentrations will be summarized in a descriptive way including a graphical presentation for the SAF.

5.9 Protocol Deviations

All PDs will be listed.

The evaluability of concerned patients for final data analysis (i.e. identification of PD with impact on the individual primary efficacy endpoint) will be discussed in a BDRM held prior to statistical analyses. During BDRM all PDs with a ‘major’ classification according to PD handling plan will be discussed. Discussed PDs including the result regarding allocation to PPS or potential exclusion from certain analysis will be listed separately.

5.10 Interim Analysis

No interim analysis is planned for this trial.

5.11 Missing Values

(1) For the primary analysis, the ratio between the highest sCreat value post-surgery (post-surgery Day 1 and Days 2, 3, 4, and 5) and the sCreat value at Baseline (pre-operative, Day -1) will be derived (post-surgery/Baseline). If the pre-operative baseline measurement and at least one post-surgery measurement are available and the patient is still alive after Day 5, these values will be used to calculate the ratio. If there is no sCreat value available beyond Day 1, set the value to 1.25. If the sCreat value at pre-operative Baseline is not available, the sCreat value at Screening can be used instead. If the patient dies after the second IP application and before Day 5, the ratio will be set to 1.25 irrespectively of any measured sCreat value.

(2) For the secondary efficacy endpoint MAKE60, the three components death, RRT event and sCreat value at Day 61 will be imputed in case of missing values.

The main analysis of MAKE60 (see section 5.6.3) is based on imputed values based on all patients included in the FAS.

In a first step, the probability of death and RRT event will be calculated using Kaplan-Meier curves with death or RRT event as an event and withdrawals to be censored.
The following formula will be used to calculate the conditional probability of an event by Day 61 conditional on being event-free at the day of withdrawal:

$$1 - \frac{Prob_{Day61}}{Prob_{DayWithdrawal}}$$

$Prob_{Day61}$ is the probability for not having an event (i.e. death or RRT) until Day 61.
$Prob_{DayWithdrawal}$ is the probability for not having an event (i.e. death or RRT) until individual day of withdrawal. For patients that are lost-to-follow up, the last available visit will be used. Other early terminations with a end of study date after Day 61 will be checked during BDRM. This overall probability is an individual value for each patient who prematurely discontinues from the study.

The MAKE60 event death/RRT will then be imputed by tossing a biased coin based on the conditional probability for the event as defined above. This will be done for each patient with missing death/RRT status to provide a collection of imputed outcomes.

In a second step, missing sCreat values at Day 61 will be imputed using an imputation model for predictive mean matching with the treatment group and the stratification factors baseline eGFR ≤45 mL/min/1.73m² (≤45 mL/min/1.73m2 vs. >45 mL/min/1.73m2) and type of surgery (CABG with 3 or more distal anastomoses vs. CABG combined with valve surgery) as covariates. The amount of imputations will be set to 100. All individual missing sCreat values at Day 61 will be imputed using the seed 36281.

These steps provide outcomes for those patients with missing death/RRT status and Day 61 sCreat value and enable the MAKE60 endpoint to be determined based on it's 3 components as in Section 4.2. This will be repeated 100 times.

Finally, the statistical analysis described in section 5.6.3 will be performed for each imputed dataset (this means 100 times). For the logistic regression model, the resulting β-estimates will be combined applying Rubin's rules (Rubin 1976; Rubin 1987) using SAS procedure PROC MIANALYZE. Resulting odds ratio and p-value will finally be displayed.

Summary statistics and frequency tables will be created for imputed data and for observed data. For the display of imputed data, the 100 imputations will be averaged.

For subgroup analyses, the same imputation based on all patients will be used.

(3) For the exploratory endpoint MAKE60a (i.e. MAKE60 without 'death' component), the two components RRT event and sCreat value at Day 61 will be imputed in case of missing values.

The main analysis of MAKE60a (see section 5.6.3) is based on imputed values based on all patients included in the FAS.

In a first step, the probability of RRT event will be calculated using Kaplan-Meier curves with RRT event as an event and withdrawals and deaths to be censored. For patients that are lost-to-follow up, the last available visit will be used.
The following formula will be used to calculate the conditional probability of an event by Day 61 conditional on being event-free at the day of withdrawal:

$$1 - \frac{Prob_{Day61}}{Prob_{DayWithdrawal}}$$

$Prob_{Day61}$ is the probability for not having an event (i.e. RRT) until Day 61.
$Prob_{DayWithdrawal}$ is the probability for not having an event (i.e. RRT) until individual day of withdrawal. For patients that are lost-to-follow up, the last available visit will be used. Other early terminations with a end of study date after Day 61 will be checked during BDRM. This overall probability is an individual value for each patient who prematurely discontinues from the study.

The MAKE60 event RRT will then be imputed by tossing a biased coin based on the conditional probability for the event as defined above. This will be done for each patient with missing RRT status to provide a collection of imputed outcomes.

In a second step, missing sCreat values at Day 61 will be imputed using an imputation model for predictive mean matching with the treatment group and the stratification factors baseline eGFR ≤45 mL/min/1.73m² (≤45 mL/min/1.73m2 vs. >45 mL/min/1.73m2) and type of surgery (CABG with 3 or more distal anastomoses vs. CABG combined with valve surgery) as covariates. The amount of imputations M will be set to 100. All individual missing sCreat values at Day 61 will be imputed using the seed 36281.

These steps provide outcomes for those patients with missing RRT event and Day 61 sCreat value and enable the MAKE60 endpoint to be determined based on it's 2 components as in Section 4.2. This will be repeated 100 times.

Finally, the statistical analysis described in section 5.6.3 will be performed for each imputed dataset (this means 100 times). For the logistic regression model, the resulting β-estimates will be combined applying Rubin's rules (Rubin 1976; Rubin 1987) using SAS procedure PROC MIANALYZE. Resulting odds ratio and p-value will finally be displayed.

Summary statistics and frequency tables will be created for imputed data and for observed data. For the display of imputed data, the M imputations will be averaged.

(4) For the calculation of AUC for KDIGO AKI stage (exploratory endpoint, see section 4.3), the following rules will be followed for missing values: In case of missing intermediate sCreat value an interpolation will be used before derivation of stages. In case of missing Day 1 post-surgery value, an interpolation from Baseline to Day 2 will be used. In case of a missing values at the end of the 5 day observational period, a last observation carried forward (LOCF) approach will be used.
(5) KDIGO AKI (yes/no) will be set to 'missing' in case only the sCreat value for Day1 (post-surgery) is available (but no data from Day 2 to Day 5).

For all other endpoints missing data will not be replaced.

5.12 Data Base Closure and Blind Data Review Meeting

The database will be closed before the analysis. All parameters will be checked, as specified in the data validation plan, and all queries resolved before database closure and analysis.

A blind data review will be conducted before unblinding based on all data to check for protocol deviations and to allocate the patients to the analysis sets. At least the following items will be discussed:

- Any violation of inclusion/exclusion criteria
- Any incorrect IP infusions (incomplete, incorrect dose etc.)
- Incorrect allocation to treatment group
- Randomization in wrong stratum
- Unblinding within the conduct of the study
- Premature discontinuation during the study

- Missing values for primary efficacy endpoint
- Medications which are known to cause kidney problems

Possible additional ICEsThese evaluations and assessments will be done together and in agreement with the Sponsor, CRO will provide the Sponsor with the appropriate patient listings prior to the BDRM (as defined in Appendix A).

The assignment of patients to the SAF, FAS, and PPS will be done before unblinding.

Data unblinding on the basis of the randomization listing and the analysis will be done after blind data review has been conducted and blind data review minutes have been signed by both the Sponsor and CRO.

5.13 Multiplicity

Hierarchical testing

The primary efficacy endpoint and the secondary efficacy endpoint MAKE60 will be tested in a hierarchical way. The first test will be done based on the ANCOVA analysis of the primary endpoint. In case this first test is statistically significant ($p < 0.05$), the second test will be based on the logistic regression analysis of the MAKE60 endpoint (p-value for corresponding Odds Ratio, resulting from β-estimates from multiple imputation, for treatment group). In case the first test is not statistical significant, the p-value of the second test will be regarded as nominal.

5.14 Miscellaneous

Study Data Tabulation Model (SDTM) datasets will be used to create Analysis Data Model (ADaM) datasets using ADaM Implementation Guide (version 1.3) and Analysis Data Model (version 2.1). An ADaM specification document will be set-up as a Microsoft Excel spreadsheet, describing the ADaM datasets. The define.xml (version 2.1) will be created when the ADaM datasets and the specification documents are final.

A detailed description of the planned TFLs is given in Appendix A.

TFLs might differ from the ones illustrated in Appendix A in terms of their layout (e.g., labels and order of variables or footnotes). The real design will be determined by the technical possibilities within SAS and may not look identical to the examples provided. All information as displayed will be included.

Listings will always be sorted by treatment group and patient. If a different sorting order should be used for some listings, this will be noted separately. The treatment group will be displayed as “by-variable” within a subtitle. In all listings the variable SUBJID will be displayed as patient number.

Indicator variables for further analysis sets, e.g. FAS, will be added for the patient disposition listing and selected listings only, where informative.

Dates and times will be displayed in data listings using the format YYYY-MM-DD and hh:mm:ss or hh:mm, respectively.

Screened but not treated patients (e.g., withdrawal before first IP infusion) will be considered in tables or listings describing disposition of patients (including treatment and study termination), analysis sets, in-/exclusion criteria (including date informed consent signed), as well as patient demographics.

The following title will be used for all generated TFLs:

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Final analysis Table/Figure/Listing <x.x>

<Title of TFL>

<Analysis set>

The numbering of the TFLs will be stated in the detailed description (Appendix A).

The following footnote will be used for all generated TFLs:

Program: <Name of program> Run Date/Time: <Actual date(yyyy-mm-ddThh:mm)>

All TFLs will be generated in DIN A4 paper format.

The statistical evaluation will be performed using SAS version 9.4 or higher.

6 Changes to the Analyses Planned in the Protocol

In the following any changes on statistical aspects as described in the protocol (version 4.0) are given:

- Protocol: Subgroup analyses have not been specified in the protocol.

  SAP: As additional analyses, the subgroups Baseline eGFR ≤ 45 mL/min/1.73m² vs. Baseline eGFR > 45 mL/min/1.73m² have been added to the analysis (selected tables).

- ICE 1 for secondary estimand was changed from “Use of concomitant medications during surgery or until Day 5 which might influence the efficacy assessment” to “Use of concomitant medications during surgery or until Day 61 which might influence the efficacy assessment”. “Nephrotoxic drugs” was added for ICE 1 of both estimands for specification of concomitant medications which might influence the efficacy assessment.

- “Incidence rate” of adverse events in section 4.4 has been changed to “Number of” adverse events as this is what was originally meant by this endpoint. Thus, only wording changed, but not intent of analysis.

7 Signatures

Statistician:	
X[1]	
05-Dec-2025	*X*[1]
Date (ddmmmyyyy)	Signature

Sponsor:	
X[1] Stadsplateau 7 3521 AZ Utrecht, The Netherlands	
08-Dec-2025	*X*[1]
Date (ddmmmyyyy)	Signature

1. Taken out to comply with GDPR