STATISTICAL ANALYSIS PLAN

(Short) study title: A phase 2 open-label, multi-centre study to evaluate the efficacy and safety of Oxabact® to reduce plasma oxalate in patients with primary hyperoxaluria who are on dialysis

Name of the sponsor: OxThera Intellectual Property AB

Protocol identification: OC-OL-01 (EudraCT Number 2013-004368-74)

Version and date of SAP: Final version 12.0, 20 January 2020

VERSION HISTORY

Version	Modified By	Date	Description of Changes
1	Johanna Tilly	2014-01-30	Initial draft for internal review
2	Johanna Tilly	2014-01-31	Incorporated comments from internal review. Draft version to be sent to sponsor for review
3	Johanna Tilly	2014-02-21	Incorporated comments from sponsor. Draft 2 version to be sent to sponsor for review
4	Johanna Tilly	2014-03-09	Incorporated comments from sponsor. Final version
5	Johanna Tilly	2014-03-25	Minor updates due to new version of the protocol (protocol version 1, including amendment 1, dated 14 February 2014)
6	Johanna Tilly	2014-06-03	Minor updates due to protocol amendment II and III
7	Nils Eckerdal	2016-02-19	Minor updates according to protocol amendment four, five and six.
8	Just van Es	2017-04-10	Ownership of the document was transferred to AUTHOR! et al B.V. from PCG. Minor revisions according to pending comments and protocol amendments 7 and 8.
9	Just van Es	2018-02-15	Revisions due to protocol amendments 9, 10, and 11, and sponsor comments thereof. Final version including signature.
10	Rob Kessels	2018-11-26	Use of different template SAP, inclusion of several programming items and the inclusion of an additional interim analyses.
11	Corine Baljé-Volkers	2019-10-23	Removal of the wording pre-dialysis, addition of analysis population for the extension data, addition of baseline for the

			CT phase, removal of analysis for baseline treatment data, addition of interim analysis, removal of ratio total:free pox, adapted definition TEAE, adaptations to handling missing data section, adapted calculation of compliance, adding abbreviations, restructuring of certain sections, addition of descriptive statistics, adding graphical presentations, addition of post-hoc analyses, addition of assessment day in listings, adapting changes from protocol section and other sections to latest protocol amendment version 12. Final version including signature.
12	Corine Baljé-Volkers	2020-01-20	Adaptation on handling stool values below LOQ. Final version including signature.

APPROVAL PAGE

I hereby declare that I have read and reviewed this document. To the best of my knowledge, the content accurately states the intended analyses and output to be provided. This document is intended for an agreement on analysis and reporting details between the sponsor and AUTHOR! et al B.V.

(Lead) Statistician:

Name, title, company: C. Baljé-Volkers, Head Biostatistics and Programming, AUTHOR! et al. B.V.

_____	_____
Signature	Date

Sponsor contact:

Name, title, company: A. Banos, Director of Biostatistics & Data Management, OxThera Intellectual Property AB

Ana Banos	23 Jan 2020
_____	_____
Signature	Date

Name, title, company: B. Dehmel, Chief Medical Officer, OxThera Intellectual Property AB

_____	_____
Signature	Date

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LIST OF ABBREVIATIONS

AE	Adverse Event
AR(1)	First-order Autoregressive
ATC	Anatomical Therapeutic Chemicals
BMI	Body Mass Index
CFB	Change from Baseline
CFU	Colony Forming Units
CRF	Case Report Form
CS	Clinically Significant
CS	Compound Symmetry
CT	Continued Treatment period
DDP	Data Display Plan
ESRD	End Stage Renal Disease
FAS	Full Analysis Set
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
LOCF	Last observation carried forward
LOD	Limit of Detection
LS	Longitudinal Strain
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MH	Medical History
Min	Minimum
MRMM	Mixed Repeated Measurement Model
n	Number of non-missing observations
N	Number of subjects/patients
NCS	Not Clinically Significant
OC5	Investigational Drug
PH	Primary Hyperoxaluria
PT	Preferred Term
RALS	Relative Apical Longitudinal Strain
REML	Restricted Maximum Likelihood
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SI	Système International d'unités (International System of units)
SOC	System Organ Class
STE	Speckle Tracking Echocardiography
SQRT	Square root
TE	Traditional Echocardiography
TEAE	Treatment-emergent Adverse event
TRT	Overall Treatment period
UN	Unstructured
WHO	World Health Organization

1   GENERAL

This Statistical Analysis Plan (SAP) describes in detail the methods and presentation of the data analyses which will be conducted by AUTHOR! et al. B.V. for study OC5-OL-01. This plan is written in agreement with protocol version 12, dated 14 October 2019, blank CRF version, dated 16 October 2019, and the relevant GCP-ICH guidelines. Furthermore, sponsor requirements for reporting are considered. Additional changes or updates of those documents or requirements may result in a new version of the reporting/statistical analysis plan.

A signed version of the SAP is to be finalized before first interim analysis.

2   STUDY INFORMATION

2.1   Study Objective(s)

The primary objective of this study is to evaluate the efficacy of OC5 to reduce total plasma oxalate levels during OC5 treatment in patients with Primary Hyperoxaluria (PH) who are on dialysis.

The secondary objectives of this study are:

- To evaluate the efficacy of OC5 to reduce free plasma oxalate levels during OC5 treatment in patients with Primary Hyperoxaluria (PH) who are on dialysis.
- To evaluate the safety of OC5 in patients with PH who are on dialysis.
- To evaluate changes in number of *O. formigenes* in faeces following administration of OC5.
- To evaluate effect of stopping OC5 treatment for 4 weeks after the first 6 weeks of treatment.
- To evaluate results from Speckle Tracking Echocardiography and traditional echocardiography.

2.2   Design of the Study

This study is an open label multi-centre study to evaluate the efficacy and safety of OC5 (Oxabact®) to reduce plasma oxalate in PH patients on dialysis.

The study is set up in two different treatment phases: the initial 14-week treatment phase (TRT) and the continued treatment phase (CT) for 36 months after week 14. Not all patients included in the TRT phase will continue into the CT phase.

2.3   Study medication

Patients will receive OC5 twice daily during the treatment phase and, if applicable, during the continued treatment phase.

2.4   Sample size

Approximately 6 to 12 patients will be enrolled in the study, to have a minimum of 6 patients completing the first year of continued treatment (i.e. week 52). It is estimated that 2 of the enrolled patients will be children.

The sample size is not based on assumptions of efficacy outcome and statistical power. Any inferences from the data will be based on clinical relevance rather than statistical significance.

2.5 Study flow chart

Table 1 Schedule of assessments – the first 14 weeks of the study

Study period:	Screening	Baseline				Treatment						Post-treatment			
Week:	-4 – 0 "0"	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Clinic visit	1		2		3		4		5		6		7		8
Incl/Excl criteria[1]	X				X										
Demographics	X														
Vital signs	X														X
Physical exam	X				X						X				X
PH Med History	X														
Medical history	X														
Concomitant med	X		X		X		X		X		X		X		X
Pregnancy test	X														
Plasma oxalate			X		X		X		X		X		X		X
Faeces					X						X				X
Safety Labs[2]	X				X						X				X
Treatment						X	X	X	X	X	X				
Adverse events							X		X		X		X		X
Speckle Tracking Echocardiography	X[3]														

1. Eligibility criteria will be evaluated at Screening and after Baseline. A stable dialysis regimen should be maintained for 2 weeks before start of baseline (2 weeks before visit week 2) and during the whole study.

2. Safety labs include: haematology analysis, clinical chemistry analysis and urinalysis and will be analysed at the local lab. Safety labs will be analysed at screening visit and at week 4, 10 and 14 +/- 1 week.

3. Speckle Tracking Echocardiography and traditional echocardiography should be done at screening visit +/- 1 month.

Table 2 Schedule of assessments – continued treatment Year 1 and 2

Study period	Continued treatment Year 1 and 2								
Week	0	4	8	12	16	20	24	28	32[1]
Clinic visit	9[2]	10[3]	11	12	13	14	15	16	17
Vital signs			X		X		X		X
Physical exam			X		X		X		X
Concomitant med	X	X	X	X	X	X	X	X	X
Plasma oxalate	X	X	X	X	X	X	X	X	X
Faeces			X		X		X		X
Safety Labs[4]	X	X	X	X	X	X	X	X	X
Pregnancy test[5]	X						X		
Treatment	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X
Speckle Tracking Echocardiography	(X)[6]						X[7]		

[1]. Treatment will continue until the patient is transplanted. The maximal length of the continued treatment period will be 36 months. Visit intervals and examinations/samplings will be kept the same throughout the year 1 and 2 of the continued treatment period.

[2] Visit 9 may coincide with visit 8 for patients continuing on treatment immediately after week 14 visit.

3. Visit 10 will be scheduled 28 days (+/- 3 days) after first day of continued treatment after study week 14.

4. Safety labs include: haematology analysis, clinical chemistry analysis and urinalysis and will be analysed at the local lab.

5. Pregnancy test will be repeated every 6 months during the continued treatment period.

6. For patients who did not have a Speckle Tracking/Traditional Echocardiography performed at screening, an effort will be made to perform this examination before start of continued treatment.

7. Speckle Tracking/Traditional Echocardiography will be repeated every 6th month during the continued treatment period in weeks 0, 24, 48, 72 and 104.

Table 3 Schedule of assessments – continued treatment Year 3

Study period	Continued treatment Year 3			
Week	116	128	140	156
Clinic visit	28	29	30	31
Vital signs	X	X	X	X
Physical exam	X	X	X	X
Concomitant med	X	X	X	X
Plasma oxalate	X	X	X	X
Faeces	X	X	X	X
Safety Labs[1]	X	X	X	X
Pregnancy test		X		X
Treatment	X	X	X	X
Adverse events	X	X	X	X
Speckle Tracking Echocardiogr aphy		X		X

1. Safety labs include: haematology analysis, clinical chemistry analysis and urinalysis and will be analysed at the local lab.

3   PATIENTS FOR ANALYSIS

3.1   Analysis populations

3.1.1   Full-Analysis-Set (FAS)

The FAS includes all patients who have received at least one dose of the investigational drug. This population will be used as primary analysis population for the analysis of efficacy.

3.1.2   Modified Full-Analysis-Set (mFAS)

The mFAS includes all patients who have received at least one dose of the investigational drug and have received at least one dose of the continued treatment phase. This population is used as additional analysis population for several post-hoc efficacy analyses during the CT phase.

3.1.3   Safety population

The safety population includes all patients who have received at least one dose of the investigational drug. The safety population is the same as the FAS for this study, and thus the FAS set wording will be used in all safety presentations.

4   BLIND DATA REVIEW MEETING

Protocol deviations will be identified to the extent possible by individuals responsible for data collection/compliance, and its analysis and interpretation.

Prior to database lock, the protocol deviations will be discussed during the (Blind) Data Review Meeting (BDRM). Invitees to this meeting are the OxThera Chief Medical Officer (CMO), the OxThera Statistician, the OxThera Project Manager (PM), the PSR Lead Data Manager (DM) and the AUTHOR! (Lead) Statistician, but more roles can be invited if considered necessary. Input to this meeting will be supplied by PSR PM/Data Management at least one week in advance of the meeting along with all protocol deviations identified during the study to the extent possible by individuals responsible for data collection/compliance, and its analysis and interpretation. The meeting is intended to resolve any outstanding data cleaning issues and consider the impact of certain protocol deviations on statistical analyses. Protocol deviations will be classified as important or not important.

The decisions taken during the meeting will be documented by the PM (or a delegate as agreed) and sent for review to all parties involved as soon as possible after the meeting, but before database lock. If all parties involved agree, then the document is finalized, signed by all attendees, and stored before database lock by the PM.

5   STUDY ENDPOINTS

5.1   Primary endpoint

The primary endpoint is change from baseline over time in total plasma oxalate level during OC5 treatment.

5.2 Secondary endpoint(s)

The secondary endpoints are the following:

- Change from baseline in free plasma oxalate level during OC5 treatment.
- Change in total plasma oxalate levels from week 10 to week 14, following the 4 week off-treatment period.
- Change from baseline in number of *O. formigenes* in faeces during OC5 treatment.
- Change from baseline in echocardiography parameters during OC5 treatment as measured by Speckle Tracking Echocardiography and traditional echocardiography.

5.3 Safety endpoint(s)

The safety parameters to be evaluated are:

- Adverse events.
- Laboratory safety measurements: haematology, clinical chemistry and urinalysis.

6 STATISTICAL ANALYSIS

6.1 General considerations

All evaluations will be explorative in nature, unless stated otherwise. There will be no formal statistical significance testing.

Raw data (in listings) will be presented in the same precision as received. Appropriate rounding will be performed for the summary statistics: arithmetic mean, median, SD (standard deviation) and two-sided 95% confidence limits will be presented with one more decimal than the original data; minimum and maximum values will be presented with the same precision as the original data. In special cases, e.g. after conversion of data, the number of decimals will be determined based on relevance. In frequency tables, percentages will be presented with 1 decimal unless otherwise stated. P-values will be presented with 3 decimals, and those smaller than 0.001 will be replaced by <0.001.

Descriptive statistics presented in summary tables for continuous variables will be the number of non-missing observations (n), arithmetic mean, SD, SE, median, Q1 and Q3, minimum and maximum. All plots will be created using scheduled protocol time or visit on the x-axis. Mean plots will be presenting mean +/- SE. For qualitative data, frequency counts and percentages will be determined. The denominator used when calculating percentages will be the number of subjects in the applicable analysis population.

Baseline is generally defined as the last non-missing and valid measurement/assessment before first dose of study drug. Unscheduled measurements are excluded as baseline value, unless otherwise specified. Change from baseline is calculated as the value at a specific time point minus the value at baseline. For this study, the following definitions are used to define the baseline measurement:

Vital signs: The screening value is used as baseline.

Plasma oxalate: The primary baseline is defined as an average of the available baseline measurements at weeks 2 and 4 (i.e. Visits 2 and 3 respectively). If one baseline measurement is missing for plasma oxalate, the remaining value will be used as baseline value. An additional baseline is the week 10 (Visit 6) assessment of plasma oxalate levels which will serve (only) as a baseline for the assessment of the change in plasma oxalate levels following the 4 week off-treatment period (secondary endpoint). For analyses in the CT phase of the study, a third baseline is defined, being the week 14 value at week 14 of the initial TRT phase.

Faeces: The measurement at week 4 is considered the baseline value.

Echography: The screening value is used as baseline. If this value is missing, the CT week 0 value is used as baseline value instead.

Safety lab: Safety lab is determined at screening and at week 4. The week 4 measurement is considered the baseline value. If this value is missing, the screening value will be used instead.

Data for screening failures will not be presented in summary tables, except for disposition and end-of-study displays, provided end-of-study data includes screen failures. Data for screening failures will be listed as available.

For this study, a treatment emergent adverse event (TEAE) is defined as an adverse event reported on or after first dose of study treatment. AEs after last dose date, and thus also after study drop-out, are not collected.

All descriptive statistics tables will be presenting data per visit, if applicable.

Any statistical significance determined in the analyses will be viewed with caution, considering the very small and heterogeneous patient population. Any determined p-values can only be indicative. No correction for multiple comparisons will be applied for any of the endpoints.

All collected data will be presented as is in individual data listings, and no other (calculated) data will be added unless specifically specified in the respective section. In case derived variables are to be added to the listings, both the original variable as well as the derived will be presented. For all relevant listings, study day will be added. The calculation for this day is as described in section 9.1.

6.2   Missing data

No imputation will be performed on missing data, except for those listed below. All analysis will be performed on data available at the visit considered. In summary tables, the number of patients without missing data will be presented (per visit, if applicable), unless otherwise specified. When dates are imputed, a flag will be provided to the CDISC datasets to show this is an imputed rather than an actual date. Listings will only present the actual date, but any calculations can be done on imputed dates.

AE and prior/concomitant medication
Missing/incomplete information related to AEs and concomitant medications will be handled as listed below, when applicable. Following these steps using temporary programming will ensure that missing dates imputations uses the most conservative approach.

- In case of a missing stop date, the stop date will be imputed as follows:
  - In case stop date is partially missing:
    - If the day part is missing, and the month and year present then day will be set to the last day of the month.
    - If both day part and month part are missing, then day and month will be set to 31 December of that year.
  - In case the stop date is completely missing and ongoing is not marked:
    - The event will be assumed to be 'ongoing'.

- In case of a partially missing onset/start date, and stop date is determined to be after first dose date (possibly after imputation), the start date will be imputed as follows:
  - In case start date is partially missing:
    - If the day part is missing, and the month is equal to the month of first dosing date, then day will be set to the date of first dose.
    - If the day part is missing, and the month is not equal to the month of first dosing date, then day will be set to the first day of the available month.
    - If both day part and month part are missing, then day and month will be set to January 1st of the year, unless if year is the same as first dose date year: then the date will be imputed with the first dose date.
  - In case the start date is completely missing:
    - If the stop date is earlier than the first dose date, then the start date will be set to Jan 1st of the stop year. If the stop date is on or after first dose date, then the start date will be set to first dose date.
- In stop date is before first dose date, then start date does not need an imputation, and the event or medication is considered to be prior.
- In case full start date and full stop date are missing, the start date will be imputed to first dose date.

- Missing severity will be imputed as severe.
- In case causality is missing for a certain TEAE, this will be regarded as related.
- In case seriousness is missing for a certain TEAE, this will be discussed and addressed prior to database lock and unblinding in agreement with CMO, PM and DM.

Medical History

For PH medical history, time since PH diagnosis and time on dialysis are calculated. If the date of diagnosis or earliest date of dialysis is partially missing, then the following will be applied:
- If only day is missing, the first day of the month will be used.
- If day and month are both missing, 1 January of the same year will be used.
- If full date is missing, no imputation will be done.

For MH in the year prior to enrollment, the following imputation method will be used for treated patients if medical history terms have a partially missing date, based on the principle that the most conservative approach would be to appoint the MH to the year before enrolment.
- If full start date is missing, the date will be imputed as 1 year prior to first dose date, and thus the MH will be included as part of the 1 year prior to enrolment.
- If start day and start month are both missing, and the difference between the year of first treatment and the start year of MH is larger than 1 year, then day and month are imputed with the first month and the first day of that month of the available year.

- If the difference between the year of first treatment and the start year of MH is 1 year, then the following applies:
    o If start day and start month are both missing, then:
        ▪ If end month is available, then start months will be imputed with that month, and start day will be set to the first day of that month.
        ▪ If no end month is available, then the month of reference date (i.e. the first dose date) is used combined with day+1 of that month.
    o If only start day is missing and start month is available, then:
        ▪ If start month is the same as the month of the reference date (i.e. the first dose date), then start day is set to day+1 of that month.
        ▪ If start month is not the same as the month of the reference date (i.e. the first dose date), then start day is set to the first day of the start month.
- If the difference between the year of first treatment and the start year of MH is 0, then the following applies:
    o If start day is missing, it will be set to the first day of the start month.
    o If both start day and month are missing, then day and month are imputed with the first month and the first day of that month of the available year.
- If end date is completely missing and ongoing is not applicable, then end year is study treatment year–1, end month is the same as the month of the reference date (i.e. the first dose date), and end day is day+1 of that month.
- If the end year is available and the difference between the year of first treatment and the end year of MH is larger than 1 year, then the following applies:
    o If both end month and end day are missing, then the end date will be imputed as 31 December of the available year.
    o If only end day is missing, then the end date will be imputed as the last day of the available month.
- If the end year is available and the difference between the year of first treatment and the end year of MH is 1 year, then the following applies:
    o If month and day are both missing, then month is set to the month of the reference date (i.e. the first dose date), and end day is set to the day of the reference date+1.
    o If only day is missing and month is the same as the month of the reference date, (i.e. the first dose date), then end day is set to day+1 of that month.
    o If only day is missing and month is different from the month of the reference date, (i.e. the first dose date), then end day is set to the last day of the available month.
- If the difference between the year of first treatment and the end year of MH is 0, then the following applies:
    o If both end day and month are missing, then month is imputed with the month of the reference date (i.e. first dosing date) and the end day is set to day-1 of that month, unless the day of the reference is the first day of the month, in which case end day will be set to the same day.
    o If only end day is missing, then the day will be set to the last day of the available month.

For untreated patients, it is not possible to determine MH in the year prior, as there is no reference date (i.e. first dosing date) available.

Plasma Oxalate during 4 -week treatment-off period
In case of missing values for week 10, 12 or 14, the method of LOCF will be applied to calculate CFB values.

Other

Other missing data occur for example during the CT phase, considering not all patients of the FAS will continue treatment. There will be no imputation for these missing values in the FAS population, and this may impact the results of the primary and secondary statistical analyses. Statistical results should therefore be viewed with caution.

6.3 Interim analysis

A first interim analysis is planned when 6 of the enrolled patients have been followed for at least the first year of continued treatment (i.e. until week 52). Hence the statistical presentations and interim report of the first interim analysis will be created using the data from the first 6 patients who completed 12 months of continued treatment.

A second interim analysis is planned when all enrolled patients completed 24 months of continued treatment (i.e. until week 104) in the CT study phase, and no report is planned but the data will be used for the ASN (American Society of Nephrology) congress.

Both interim analyses are primarily intended to help understand if OC5 treatment in dialysis patients with PH:
- Stabilizes or reduces plasma oxalate
- Stabilizes or improves cardiac function parameters (assessed through Speckle tracking and traditional echocardiography)

6.4 Subject and study disposition

6.4.1 Inclusion/exclusion criteria

An individual patient listing of the deviations from inclusion and exclusion criteria will be presented. Eligibility information is collected at screening and at week 4 and will therefore be presented per visit in the listings.

It should be noted that the CRF and thus the database for inclusion/exclusion criteria differs between centers. This may lead to separate listings per center.

6.4.2 Screen failures

Data for screening failures including the reasons will be listed as available.

6.4.3 Disposition

An overview summary table will be created, stating the number of patients per site, including site number, location/country and investigator.

In addition, to present disposition, a summary of the number/percentage of patients screened (if available), enrolled, treated/exposed to treatment, completed and withdrawn will be created. In the same summary, the number/percentage of patients in the FAS, the mFAS, enrolled/ completed/withdrawn per treatment period (TRT and CT) will be presented. Frequency and percentage for withdrawal reasons as collected in the database will be added as well.

6.4.4 Protocol Deviations

All protocol deviations will be listed including classification of importance as agreed prior to database lock.

6.5 Baseline characteristics

6.5.1 Demographics

Descriptive tabulations of demographics at screening will be made. Demographic data (including weight, height and BMI measurements at screening/baseline) will be presented for the FAS and mFAS. Appropriate descriptive statistics for age, height, weight, BMI, race and sex will be given. The listing of demographic data will include information on childbearing potential (for females only).

6.5.2 PH medical history

A descriptive statistics table for PH medical history will be created for the FAS and mFAS, stating the following items: PH type, diagnosis confirmation, time since PH diagnosis (in months) and time on dialysis before screening (in months).

Time since PH diagnosis (in months) will be calculated as the difference in days between first dose date and the date of diagnosis + 1, divided by (365.25/12). Time on dialysis (in months) will be calculated as the difference in days between between first dose date and earliest occurrence of dialysis in the dialysis regimen page + 1, divided by (365.25/12). For handling missing dates, see section 6.2.

6.5.3 Other medical history

Other medical history (including concurrent illnesses and symptoms) will be coded by SOC and PT using MedDRA and presented as number/percentage of patients in each SOC and PT for the FAS and mFAS. SOC and PT will be presented in descending order of frequency. If several SOCs/PTs have the same number of frequencies, the SOCs/PTs will be presented in alphabetical order. These data will also be listed on a per patient level.

In addition, a medical history table will be created containing MH corresponding to the year prior to initial treatment. Identification of relevant medical history terms will be done based on the start date of first exposure to the IMP and the start dates of the medical history events. A cut-off of 365 days prior to the first exposure to the IMP will be used. For handling missing dates, see section 6.2.

6.5.4 Other screening data

Pregnancy tests will be listed per visit for females of childbearing potential only and will be combined with the laboratory listings.

6.6 Statistical analysis primary and secondary endpoints

6.6.1 Primary endpoint

The primary endpoint is change in total plasma oxalate level during OC5 treatment, compared to the baseline value. All primary endpoint analyses will be performed for the FAS as primary

analysis, and for the mFAS as post-hoc analysis. All primary endpoint analyses will be done on the overall treatment period, unless otherwise specified.

Summary statistics of the measurements will be presented on a per-visit basis. Both the actual value as well as the change from baseline value will be presented.

Summary statistics tables will also be presented for patients on hemodialysis only and for patients on peritoneal dialysis only separately, if there are more than 3 subjects in any of the groups. In case of less than 3 patients for one of the groups, the separation will not be made, and the summary statistics not presented.

To visualize the effects through time graphically, the following plots will be created:
- Mean +/- SE and individual plots will be created to visualize the course of total plasma oxalate values through time. Both the actual values as well as change from baseline values will be presented. These plots will be created for the overall treatment period as well as the continued treatment period (including the baseline value).
- Combined spaghetti plots will be created using the actual values, for the overall treatment period and the continued treatment period. No spaghetti plots will be created for change from baseline.

Taking into consideration the limited sample size, in addition, a mixed-effect repeated measures model (MRMM) may be performed on the change from baseline values using baseline total plasma oxalate and week as the independent variables. If the assumption of normality is violated, a log transformation will be applied first (and a back transformation will be done on the results). SAS PROC MIXED (with the REML default) will be used for the analysis. The basic SAS code will be as follows.

```
proc mixed data=…;
  class usubjid;
  model change= time baseline;
  repeated time / subject=usubjid type=…;
run;
```

Considering the variability of plasma oxalate, an unstructured covariance matrix will be used in the model: variances and covariance are allowed to differ at and between measurements. As the use of an unstructured (UN) covariance matrix requires estimation of a larger number of variance and covariance parameters (and is thus computationally more intense and results in a lower power), the model may not converge. If that occurs, the structure will be adapted to respectively AR(1), which assumes that a correlation between two consecutive measurements is higher than between two measurements further apart in time. If convergence is still an issue, then (in order) Toeplitz or Compound Symmetry (CS) will be applied.

The results of this MRMM will be presented in a table including parameter estimates of the regression coefficients, 95% confidence limits and p-values. Although it is understood that multiple patients may drop out and hence a large number of missing data will occur, no sensitivity analysis will be performed, as the sample size is too small to obtain trustworthy results by using a multiple imputation technique. As a consequence, results of the MRMM analysis will be considered only indicative. If too many missing data are causing the model to abort, only descriptive statistics will be displayed.

Furthermore, ordinary least square regressions will be performed for every patient separately using time as independent variable. The individual regression slopes will be averaged and presented in a table using descriptive statistics. Again, because of the number of missing data, results are only to be considered indicative.

6.6.2   Secondary endpoint

All secondary endpoint analyses will be performed for the FAS only, unless specifically stated that mFAS will also be used. All secondary endpoint analyses will be done on the overall treatment period, unless otherwise specified.

Free plasma oxalate
Change in free plasma oxalate level during OC5 treatment will be analyzed descriptively (tables and plots) as described for the primary endpoint.

Total and free plasma oxalate levels from week 10 to week 14
After 6 weeks of treatment, there is a 4 week off-treatment period scheduled. Change in total and free plasma oxalate levels following the 4 week off-treatment at week 12 and 14 will be calculated as the value at visit 12 or 14 minus the visit value at week 10. Summary statistics of the measurements will be presented on a per-visit basis. Both the actual value as well as the change from baseline value will be presented for the FAS. For handling missing data in summary statistics for CFB values, see section 6.2.

***O.formigenes* in faeces**
Data collected for *O.formigenes* in faeces will only have measurable values if above the Limit of Quantification (LOD). Values below the LOD will be replaced for calculation purposes in descriptive statistics, plots and statistical analyses (see section 9.1). The proposed analyses will only be performed if there is a limited amount (<15%) of data below LOD present. The values will be presented as '< LOD' in the listings. Note that in case of a provided value lower than the LOD, it will be presented and used as is and not imputed.

Change in the number of *O.formigenes* in faeces during OC5 treatment will be calculated at each visit as the visit value minus the baseline value. Summary statistics of the measurements will be presented on a per-visit basis. Both the actual value as well as the change from baseline value will be presented. Statistics will be presented for genotype 1, genotype 2 and the sum of both genotypes, only if there are enough data > LOD (to be checked separately for the treatment phase and the continued phase). If only for one of the genotypes this is the case, statistical presentations will just be performed on the data belonging to that specific genotype. Data for the other genotype will then be limited to a listing, and the sum for both genotypes will not be calculated.

To visualize the effects through time graphically, the following plots will be created. All faeces plots will be created for the overall treatment period as well as the continued treatment period (including baseline value) alone:
- Mean +/- SE and individual plots will be created for *O.formigenes* (genotype 1, genotype 2 and sum of both genotypes, when feasible) values through time. Only the actual values will be presented.
- Furthermore, the relationship between *O.formigenes* and total plasma oxalate over time will be evaluated graphically. These comprise of:

- o Mean +/- SE and individual plots plotting the time course of genotype 1, genotype 2 and total plasma oxalate (when feasible) in one graph using double axes.
- o Individual scatterplots and a combined scatterplot of faeces versus total plasma oxalate. Scatterplots will be created separately for the sum of both genotypes, genotype 1 and genotype 2 (when feasible). For these plots, only time points can be used when both assessments were made, where 'baseline' is considered the same time point even if assessed at different weeks.

If possible, a correlation analysis between *O.formigenes* and total plasma oxalate will be done as well. A repeated measures model can be used to determine the "repeated measures correlation" between total number of *O.formigenes*, or one of the genotypes with sufficient data, and total plasma oxalate. Note that the limiting factor here is the count data for *O.formigenes*: this type of data generally deviates from normality. Therefore, for this correlation analysis, the total number of *O.formigenes* may be log transformed by executing ln(*O.formigenes*) where ln is the natural logarithm. If this transformation does not suffice, another transformation may be used, however it should be noted that it is possible that no transformation will suffice with the desired effect of reaching normality, therefore results should be considered with caution. The correlation coefficient will be presented in a table.

Speckle Tracking/Traditional Echocardiography

Change in Speckle Tracking/Traditional Echocardiography parameters, collected at screening and during continued treatment, will be calculated at each visit as the visit minus the baseline value.

Speckle Tracking Echocardiography (STE) parameters are Image Quality, Global Longitudinal Strain (GLS), Global Circumferential Strain (GCS), Rotational Displacement, Average Apical Longitudinal Strain, Average Mid Longitudinal Strain, Average Basal Longitudinal Strain and Relative Apical Longitudinal Strain (RALS; defined as Average Apical Longitudinal Strain /(Average Basal Longitudinal Strain + Average Mid Longitudinal Strain).

Traditional Echocardiography (TE) parameters are Left Ventricular Ejection Fraction (LVEF), Left Ventricular Mass Index (LVMI), Left Ventricular End Diastolic (LVED) Dimension, Interventricular Septal (IS) Thickness at End-diastole, Pulse Wave doppler (PW) Thickness at End-diastole, e/é, e/a, Tricuspid Regurgitation and Continuous Wave Doppler.

Summary statistics of the parameters will be presented on a per-visit basis. For all parameters (except for Image Quality and Tricuspid Regurgitation), both the actual value as well as the change from baseline value will be presented. For Image Quality and Tricuspid Regurgitation, the number/percentage of observations in the different categories will be presented per visit. STE parameters and TE parameters will be presented in separate tables for the FAS and mFAS.

To visualize the effects through time graphically, the following plots will be created for FAS and mFAS, using the overall treatment period:
- Mean +/- SE and individual plots will be created for GLS/LVEF/RALS values through time. Presentations are made for the actual values and the CFB values.
- Combined spaghetti plots will be created using the actual values. No spaghetti plots will be created for change from baseline.
- Furthermore, the relationship between GLS/LVEF/RALS and total plasma oxalate/free plasma oxalate over time will be evaluated graphically. These comprise of:
  - o Mean +/- SE and individual plots plotting the time course of GLS/LVEF/RALS and total plasma oxalate/free plasma oxalate in one graph using double axes.

     o Individual scatterplots and a combined scatterplot of GLS/LVEF/RALS versus total plasma oxalate/free plasma oxalate. For these plots, only time points can be used when both assessments were made, where 'baseline' is considered the same time point even if assessed at different weeks.

6.7 Safety and tolerability evaluation

The FAS population is used for all safety presentations.

6.7.1 Adverse events

Treatment emergent adverse events (TEAE) are defined as adverse events reported on or after first dose of study treatment. AEs after last dose date, and thus also after study drop-out, are not collected. All AEs reported in the study will be listed.

An AE overview table will be created displaying the number of patients (and percentage) experiencing a treatment-emergent adverse event (TEAE) and the number of TEAEs for: any TEAE, any mild/moderate/severe TEAE, any related/unrelated TEAE, any SAE, any Fatal AEs/Deaths during study and any TEAE leading to study discontinuation. Unique adverse events are determined based on System Organ Class (SOC) and Preferred Term (PT).

All TEAEs are tabulated by SOC and PT within each SOC according to the MedDRA terminology list. TEAEs will also be tabulated by intensity (mild/moderate/severe) and by relationship to study medication (related/unrelated), using frequency counts (number of patients with at least one event, and number of events) and percentage of patients with the event. Similar tables will be created for TEAEs leading to premature discontinuation, SAEs and fatal AEs/deaths, if applicable. In addition, a summary table will be created for TEAEs by intensity and relationship with the IMP including patient identification. All summary tables will be presented by decreasing frequency of occurrence based on SOC and PT.

The summary tables will be accompanied by individual subject listings of *all* reported AEs including information on AE number, actual AE description, date/time of start and end of AE (or ongoing), treatment-emergent (as in: present to first dose), PT (MedDRA), SOC (MedDRA), intensity, relationship, seriousness, action taken and outcome. Pre-existing AEs are not considered to be treatment-emergent, except in case of worsening during/after study treatment (to be collected as separate AE in the database). AEs starting prior to administration of the study drug will only be listed. In this listing, a clear distinction will be made between prior and treatment emergent events.

Separate listings will be created for SAEs and deaths, if applicable.

For summary tables, an AE is considered related if the causality to the study medication is classified as either 'Definitely Related', 'Probably Related' of 'Possibly Related'. Note that missing is imputed as being related according to section 6.2. In other instances, causality will be considered unrelated for summary tables. The original description will be used in listings.

6.7.2 Clinical laboratory

The following laboratory safety data are collected for this study:

Hematology	Chemistry	Urinalysis
RBC (Erythrocytes)	Blood Urea Nitrogen	Protein

WBC (Leucocytes)	Electrolytes (Na+, K+, Mg++, Ca++, HCO3-, Cl)	Glucose
Lymphocytes	Glucose	pH
Monocytes	pH/CO2	
Neutrophils	Albumin	
Basophils	Alkaline phosphatase	
Eosinophils	ALT	
Platelets	AST	
Haemoglobin	Total bilirubin	
Haematocrit	Total protein	
MCV	Creatinine	
MCHC		

Hematology, biochemistry and urinalysis data will be summarized using descriptive statistics and listed per visit, using protocol visits. Change from baseline will be calculated and presented as well for quantitative data, using the same summary statistics. Screening and week 4 values are omitted from the CFB presentations. If applicable, laboratory safety data collected as additional/unscheduled assessments (i.e. apart from those per protocol) will only be listed and will not be used in summary statistics.

For laboratory safety data, all recorded and determined laboratory safety data will be listed, including information on the reference ranges, if available. In addition, information regarding age at screening and gender will be added to the listing.

Safety laboratory parameters will be presented in the tables and listings in the same units as supplied. In case a parameter is supplied in several different units, it will be investigated if it is possible to convert and present this parameter in standardized units or SI units for the presentation of descriptive statistics. Conversion factors and number of decimals for standardized values used will be supplied or approved by sponsor. If conversion is applicable, then the summaries will be provided in the standardized unit, and listings will contain both the raw data as well as the standardized values.

Lastly, for clinical laboratory parameters, a listing will be created presenting all data that are out of reference range on a per-patient level. The investigator judges the out-of-range values on their clinical significance, and this information will be added as well. In addition, information regarding age at screening and gender will be added to this listing.

6.7.3   Vital Signs

Vital sign data consist of measurements for body weight, pulse rate, systolic and diastolic blood pressure, temperature and respiration rate. Vital signs will be summarized (limited to: n, mean, SD, median, minimum and maximum) and listed per visit, using protocol visits. Change from baseline will be calculated and presented as well, using the same summary statistics. If applicable, vital sign measurements collected as additional/unscheduled assessments (i.e. apart from those per protocol) will only be listed and will not be used in summary statistics.

6.7.4   Prior and concomitant medication

The use of prior and concomitant medication will be listed for all patients: included will be the medication generic name, WHO coding information, dose, route of administration, start and stop date, frequency and reason for administration, as well as information if given for an AE. A differentiation (flag) will be made between prior and concomitant medication.

In addition, summaries for prior and concomitant medications will be created, presenting the number of patients with any prior/concomitant medication, and the number of patients for each ATC System Main Therapeutic Group (2nd level of WHO classification), irrespective of duration of receipt, frequency or dose.

If a comedication is started prior to first dose of study treatment, this is considered prior medication. Concomitant medication is defined as started before first study treatment and continuing thereafter or starting on/after first dose date of study medication. As a consequence, several medications may be defined both as prior as well as concomitant. Whether a medication is considered prior/concomitant/both in case of partially missing dates is determined using the rules for missing data detailed in Section 6.2.

6.7.5 Physical examination

General physical examination data will be tabulated and listed. The summary table will include number/percentage of patients with normal or abnormal observations and NCS/CS frequencies/percentages for abnormal observations.

6.7.6 Dialysis regimen

Dialysis regimen data will be listed.

6.8 Scheduled visits, Dosing and Treatment Compliance

6.8.1 Visit dates

A listing with actual visit dates (and times, if applicable) per patient will be presented.

6.8.2 Dosing and Treatment compliance

Relevant dosing information, scheduled and actual dosing dates/times (if available) and treatment compliance information will be listed for each patient. Compliance will be determined using the drug accountability information collected in the database. The total number of capsules dispensed minus the total number of capsules returned is considered the actual amount of trial medication taken. This should automatically include the number of missed doses and possible fluctuations in the number of capsules per vial. The duration between the date of treatment start and the stop date of study medicine is considered the period over which the study medication has been taken. The theoretical amount of trial medication would then be the duration times 2, considering there is a morning and evening dose. Percentage compliance is then calculated as (actual/theoretical) *100% and will be added to the listing.

7 CHANGES TO PROTOCOL OR OTHER RELEVANT REMARKS

The change from baseline in total:free plasma oxalate level during OC5 treatment was previously added as additional secondary endpoint (being considered a post-hoc analysis as the endpoint was not mentioned in the protocol) and was evaluated during the first interim analysis. It has been removed for the final analysis.

The wording "pre-dialysis" has been removed from all endpoints upon request of Sponsor, to avoid confusion with the terminology.

An additional STE parameter was added, to be calculated based on other parameters. This additional parameter was first called Apical Sparing Patterns (and was presented as such in the first interim) and was later renamed to Relative Apical Longitudinal Strain (abbreviated as RALS).

For the first interim analysis, STE parameters Global Radial Peak Systolic Strain and Global Circumferential Peak Systolic Strain have also been presented until 52 weeks, however following a previous protocol update, these parameters are removed from CRF and database.

AEs after last dose date, and thus also after study drop-out, are not collected. As a consequence, TEAE after last dose date will not be present.

The in-/exclusion criteria for the centers in Germany and France are different, as expressed by the latest blank CRF. Furthermore, there are some slight differences in criteria descriptions depending upon the protocol version used. For the listings, the results as presented in the database will be used.

8   DATA RECEIPT

All clinical data will be received as SAS files from the Data Management provider as agreed and will be transferred to SDTM format for the final analysis. The information regarding protocol deviations will be received as excel file (a so-called "protocol deviations log") and will be transferred to SDTM. The SDTM files will be recoded to ADaM format. Listings will be programmed on the SDTM and, if necessary, ADaM datasets. Tables and figures will be programmed on ADaM datasets. Only necessary adaptations, not being able to be handled on database level, will be described in NTFs and used for adaptations in the ADaM datasets and included in the applicable ADaM documentation.

Interim analyses will be programmed using raw SAS data or derived datasets instead of SDTM/ADaM datasets, considering that unclean data will cause errors in the CDISC formats.

9   TECHNICAL DETAILS

9.1   Programming conventions

In the database, the variable ETHNIC is collected. However, following SDTM, its contents are more in line with what should have been collected as RACE. Therefore, we convert this variable to race, and program ethnicity as UNKNOWN.

Due to a systematic error in molarity values reported, the values for total plasma oxalate need to be converted by multiplying the received values by a factor of 0.71. This will be done for all listings, tables and graphs displayed for the study.

O.formigenes (genotype 1, genotype 2 and sum of genotypes) counts will be reported in $x10^6$. Data collected for *O.formigenes* in faeces will only have measurable values if above the LOD. Values below the LOD will be reported as 0 in the dataset. These values will be replaced with LOD/$\sqrt{2}$ for calculation purposes in descriptive statistics, plots and statistical analyses, only when there is a limited amount of data < LOD present. The LOD values used are 118.000 $(0,118x10^6)$ for genotype1 and 37.900 $(0,0379x10^6)$ for genotype2. Note that in case of a

provided value lower than the LOD, it will be presented and used as is and not replaced with the LOD value.

BMI will be calculated in SAS as follows: weight/height^2, with weight in kg and height in meter (unit kg/m^2).

For STE and TE parameters, a value of -99 in the database indicates that the value is missing, and these values will be treated accordingly.

Relative Apical Longitudinal Strain (in STE data) will be added to the analysis. Relative Apical Longitudinal Strain (LS) is calculated as: RALS = Avg. apical LS / (Avg. basal LS + Avg. mid LS).

Durations, determination of baseline values and handling of missing data will be programmed as stated in the respective analysis sections.

Study day will be added to some of the listings and calculated as follows: if the study date is before the date of first study dosing, then study day = first dose date – collection date. If the study date is after first dosing, then study day = collection date – first dose date +1. Time will be no factor in the calculation. If the study date if (partly) missing, and study date is before first dose date, then the first day of the month, and/or the first month of the year will be used. If collection date is completely missing, then study day cannot be determined.

It may be necessary to convert safety laboratory parameters to standardized units when lab measurements are provided in different units. Conversion factors and number of decimals for standardized values used will be supplied or approved by sponsor.

Any other programming conventions that are not foreseen in preparation of this SAP, will be handled when encountered and documented separately.

9.2   Coding

Coding of adverse events, concomitant medication and medical history will be performed by the Data Management provider. Adverse events and medical history are coded with the MedDRA coding system. Concomitant medication is coded according to the WHO drug code and the ATC class code. Coding will be supplied as part of the data transfer, and the coding version used will be mentioned as a footnote to the relevant summaries and listings.

9.3   Analysis software

The statistical analysis and reporting will be done using SAS® for Windows™ version 9.4 or later. SAS tabular output (tables and listings) will be saved in RTF format. SAS graphs will be saved in PNG format. The tables will also be imported into Word® and supplied to OxThera and the Medical Writer for use in the interim and clinical study report. The plots will be supplied separately.

9.4   Presentation of tables, listings, graphs

All output will be generated as SAS tables, graphs and listings.

All tables and listings will be created such that they fit landscape pages. The tables for the end-of-text and listings for the appendix will be created using SAS with an RTF output, and font Times New Roman size 10 will be used.

For graphs, output will be as created as PNG plot. Preferably, graphs will be created using black, grey and white color only, to facilitate black-and-white printing. Different line patterns and symbols may be used to differentiate between classification or treatment levels. If certain plots can only be visually improved by using colours, then the CMYK colour model will be preferred for use instead. Graphs will be created such (i.e. taking into account line thickness and font size) that they can be presented as two (2) per page in the clinical study report.

10   TABLES, LISTINGS, GRAPHS

10.1   General

A detailed list of tables, graphs and listings is presented, if applicable, per report section in sections 10.2, 10.3 and 10.4.

Template tables and listings as well as *example* plots (as received from client or extracted from a relevant paper) will be used as a reference for creation of all output, and a separate document (DDP) will be created for this. Table/listing numbering will be followed, however, if the data give cause for combining or splitting tables or listings, table/listing numbering may be adapted as necessary.

10.2   In-text tables and graphs

In-text tables or graphs will be designed or extracted by the Medical Writer during creation of the Clinical Study Report, based on the tables and graphs created for section 14 of the CSR. These in-text tables will also use font Times New Roman. Complex in-text tables can be requested to be created using SAS programming.

10.3   End-of-text tables and graphs

Following ICH E3 guidelines, all tables and graphs mentioned here will be presented in Section 14 of the CSR, and tables will be prepared in the order and with section number as stated.

Table or graph number	Contents of table/graph
14.1 Demographic Data Summary figures and tables	
14.1.1	Number of patients per site
14.1.2	Disposition
14.1.3	Demographics
14.1.4	PH medical history
14.1.5	Medical history
14.1.6	Medical history 1 year prior initial treatment
14.1.6	Prior medication
14.2 Efficacy Data Summary figures and Tables	

14.2.1	Total plasma oxalate levels and change in total plasma oxalate levels during OC5 treatment compared to baseline
14.2.2	Mixed Repeated Measures Model result Total plasma oxalate
14.2.3	Regression result Total plasma oxalate
14.2.4	Mean +/- SE total plasma oxalate versus time plots. FAS/mFAS, TRT/CT.
14.2.5	Individual total plasma oxalate versus time plots. FAS/mFAS, TRT/CT.
14.2.6	Mean +/- SE total plasma oxalate CFB versus time plots. FAS/mFAS, TRT/CT.
14.2.7	Individual total plasma oxalate CFB versus time plots. FAS/mFAS, TRT/CT.
14.2.8	Spaghetti plots total plasma oxalate versus time. FAS/mFAS, TRT/CT.
14.2.9	Change in total plasma oxalate following 4 week off-treatment period
14.2.10	Total plasma oxalate (µmol/L), observed value and change from baseline in patients on hemodialysis only
14.2.11	Total plasma oxalate (µmol/L), observed value and change from baseline in patients on peritoneal dialysis only
14.2.12	Free plasma oxalate levels and change in free plasma oxalate levels during OC5 treatment compared to baseline
14.2.13	Mean +/- SE free plasma oxalate versus time plots. FAS/mFAS, TRT/CT.
14.2.14	Individual free plasma oxalate versus time plots. FAS/mFAS, TRT/CT.
14.2.15	Mean +/- SE free plasma oxalate CFB versus time plots. FAS/mFAS, TRT/CT.
14.2.16	Individual free plasma oxalate CFB versus time plots. FAS/mFAS, TRT/CT.
14.2.17	Spaghetti plots free plasma oxalate versus time. FAS/mFAS, TRT/CT.
14.2.18	Change in free plasma oxalate following 4 week off-treatment period
14.2.19	Free plasma oxalate (µmol/L), observed value and change from baseline in patients on hemodialysis only. If feasible.
14.2.20	Free plasma oxalate (µmol/L), observed value and change from baseline in patients on peritoneal dialysis only. If feasible.
14.2.21	O.formigenes in faeces, observed value and change from baseline
14.2.22	Mean +/- SE O.formigenes versus time plot. For Genotype 1, Genotype 2 and sum of genotypes, if feasible. FAS, TRT/CT.
14.2.23	Individual O.formigenes versus time plot. For Genotype 1, Genotype 2 and sum of genotypes, if feasible. FAS, TRT/CT.

14.2.24	Mean +/- SE O.formigenes (Genotype 1 and Genotype 2, if feasible) versus total plasma oxalate versus time plot using double axes. FAS, TRT/CT.
14.2.25	Individual O.formigenes (Genotype 1 and Genotype 2, if feasible) versus total plasma oxalate versus time plot using double axes. FAS, TRT/CT.
14.2.26	Combined scatter plot individual values O.formigenes vs. total plasma oxalate. For Genotype 1, Genotype 2 and sum of genotypes, if feasible. FAS, TRT/CT.
14.2.27	Individual scatter plots values O.formigenes vs. total plasma oxalate. For Genotype 1, Genotype 2 and sum of genotypes, if feasible. FAS, TRT/CT.
14.2.28	Repeated measures correlation O.formigenes – Total plasma oxalate
14.2.29	Speckle Tracking Echocardiography, observed value and change from baseline. FAS and mFAS.
14.2.30	Traditional Echocardiography, observed value and change from baseline. FAS and mFAS.
14.2.31	Mean +/- SE plots for GLS/LVEF/RALS values through time. FAS/mFAS, CT.
14.2.32	Individual plots for GLS/LVEF/RALS values through time. FAS/mFAS, CT.
14.2.33	Mean +/- SE for GLS/LVEF/RALS CFB values through time. FAS/mFAS, CT.
14.2.34	Individual plots GLS/LVEF/RALS CFB values through time. FAS/mFAS, CT.
14.2.35	Combined spaghetti plots for GLS/LVEF/RALS. FAS/mFAS, CT.
14.2.36	Mean +/- SE plots plotting the time course of GLS/LVEF/RALS and total plasma oxalate in one graph using double axes. FAS/mFAS, CT.
14.2.37	Mean +/- SE plots plotting the time course of GLS/LVEF/RALS and free plasma oxalate in one graph using double axes. FAS/mFAS, CT.
14.2.38	Individual plots plotting the time course of GLS/LVEF/RALS and total plasma oxalate in one graph using double axes. FAS/mFAS, CT.
14.2.39	Individual plots plotting the time course of GLS/LVEF/RALS and free plasma oxalate in one graph using double axes. FAS/mFAS, CT.
14.2.40	Combined scatter plot GLS/LVEF/RALS vs. total plasma oxalate. FAS/mFAS, CT.
14.2.41	Combined scatter plot GLS/LVEF/RALS vs. free plasma oxalate. FAS/mFAS, CT.
14.2.42	Individual scatter plot GLS/LVEF/RALS vs. total plasma oxalate. FAS/mFAS, CT.
14.2.43	Individual scatter plot GLS/LVEF/RALS vs. free plasma oxalate. FAS/mFAS, CT.

14.3 Safety Data Summary figures and tables – 14.3.1 Displays of Adverse Events	
14.3.1.1	Overview adverse events
14.3.1.2	Treatment emergent adverse events
14.3.1.3	Treatment emergent adverse events by intensity
14.3.1.4	Treatment emergent adverse events by relationship
14.3.1.5	Treatment emergent adverse events by intensity and relationship including subject identifications
14.3.1.6	Treatment emergent adverse events leading to premature discontinuation
14.3 Safety Data Summary figures and tables – 14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events	
14.3.2.1	Serious Adverse events
14.3.2.2	Deaths
14.3 Safety Data Summary figures and tables – 14.3.4 Abnormal Laboratory Value Listing (each patient)	
14.3.4.1	Out of range clinical laboratory
14.3.4.2-14.3.4.4	Clinical laboratory (raw and change from baseline) – haematology, clinical chemistry, urinalysis
14.3.5	Vital signs - raw and change from baseline
14.3.6	Physical Examination
14.3.7	Concomitant medication

10.4   Listings

Following ICH E3 guidelines, all listings mentioned here will be presented in Section 16.2 of the CSR, and listings will be prepared in the order and with section number as stated.

Individual listings will be prepared of the data collected in the database, following SDTM and ADaM data format. No combining of data other than mentioned in this paragraph will be performed. The key variables in the listings (except a few displaying screening data) will be subject number and treatment group. If applicable, visit number and visit date will be listed additionally. Furthermore, a listing containing study visit dates will be presented. For listings relating to exposure (16.2.5.1 and 16.2.5.2) and dialysis regimen (16.2.8.5), study day will be calculated and added, following the calculation rule stated in section 9.1.

Listing number	Contents of listing
16.2.1 Discontinued patients	
16.2.1.1	Inclusion/exclusion criteria – deviations (per center or country, if necessary)
16.2.1.2	Screen failures
16.2.1.3	Patient disposition
16.2.1.4	Study completion, including WIC date
16.2.2 Protocol deviations	
16.2.2	Protocol deviations
16.2.3 Patients excluded from the efficacy analysis	
16.2.3	Patients excluded from the efficacy analysis
16.2.4 Demographic data	
16.2.4.1	Demographics
16.2.4.2	PH medical history
16.2.4.3	Other medical history
16.2.5 Compliance and/or drug concentration data	
16.2.5.1	Dosing information and treatment compliance
16.2.5.2	Drug accountability
16.2.5.3	Study visits
16.2.6 Individual efficacy response data	
16.2.6.1	Plasma oxalate measurements
16.2.6.2	O.formigenes in faeces, per genotype
16.2.6.3	Speckle tracking echocardiography
16.2.6.4	Traditional echocardiography
16.2.7 Adverse event listings	
16.2.7.1	Adverse events
16.2.7.2	SAEs

16.2.7.3	Vital signs
16.2.7.4	Physical Examination
16.2.7.5	Prior and concomitant medication
16.2.8 Listing of individual laboratory measurements by patient	
16.2.8.1	Laboratory safety data – haematology
16.2.8.2	Laboratory safety data – clinical chemistry
16.2.8.3	Laboratory safety data – urinalysis
16.2.8.4	Pregnancy test
16.2.8.5	Dialysis regimen
16.2.8.6	General comments from all datasets