STATISTICAL ANALYSIS PLAN

(Short) study title:	An Open-Label Single-Arm Treatment Extension Study to Evaluate the Long-Term Efficacy and Safety of Oxabact for Patients with Primary Hyperoxaluria who Completed Study OC5-DB-02.
Name of the sponsor:	OxThera Intellectual Property AB
Protocol identification:	OC-OL-02 (EudraCT Number 2018-003576-12, IND number 15881, NCT Number NCT03938272).
Protocol name	ePHex-OLE
Version and date of SAP:	Final version 1.0, 25 May 2021

VERSION HISTORY

Version	Date	History list
1.0	25 May 2021	Final version

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.

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LIST OF ABBREVIATIONS

ADaM	Analysis Data Model
AE	Adverse Event
AKI	Acute kidney injury
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
AR(1)	First order regressive
ASP	Apical Sparing Patterns
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BDRM	Blind Data Review Meeting
BMI	Body Mass Index
BUN	Blood urea nitrogen
C	Celsius
CA++	Calcium
CDISC	Clinical Data Interchange Standards Consortium
CKD	Chronic kidney disease
CI	Confidence Interval
Cl	Chloride
cm	centimetre
CO2	Carbon dioxide
CRP	C-reactive protein
CFB	Change from baseline
CHQ/PF50	Child Health Questionnaire - Parent Form 50
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMO	Chief Medical Officer
CMYK	A subtractive colour model used in colour printing
CRF	Case report form
CS	Compound Symmetry
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DM	Data Manager
DSMB	Data and Safety Monitoring Board

eGFR	Estimated Glomerular Filtration Rate
ESRD	End stage renal disease
F	Fahrenheit
FAS	Full Analysis Set
FU	Follow-up
GCP	Good Clinical Practice
GLS	Global Longitudinal Strain
HCO3-	Bicarbonate
ICH	International Conference on Harmonisation
K+	Kalium
kg	kilogram
lb	pounds
LOQ	Limit of Quantification
LS	Least Squares
LS	Longitudinal Strain
LVEF	Left Ventricular Ejection Fraction
m	meter
MAR	Missing at random
MCAR	Missing completely at random
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MEdDRA	Medical Dictionary for Regulatory Activities
Mg++	Magnesium
MI	Multiple Imputation
MNAR	Missing not at random
MRMM	Mixed-effect Repeated Measures Model
NA+	Natrium
OC5	Oxabact
PDF	Portable Document Format
pH	Potential hydrogen, representing the relative acidity
PH	Primary Hyperoxaluria
PM	Project Manager
PMM	Pattern-Mixture Model
PNG	Portable Network Graphics
PP	Per protocol

PT	Preferred Term
Q1	The first quartile, being the 25th percentile of the data
Q3	The third quartile, being the 75th percentile of the data
QoL	Quality of Life
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard Deviation
SE	Standard Error
SF36V2	36-Item Short Form Health Survey, version 2
SOC	System Organ Class
SDTM	Study Data Tabulation Model
STE	Speckle Tracking Echocardiography
TE	Traditional Echocardiography
TEAE	Treatment Emergent Adverse Event
UN	Unstructured
US	United States of America
VS	Vital signs
WBC	White Blood Cell
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. / Certara for study OC5-OL-02. This plan is written in agreement with protocol version 2, dated 06 July 2020, annotated CRF version 6.0, dated 28 August 2020, the relevant GCP-ICH guidelines and sponsor requirements. Additional changes or updates of those documents or requirements may result in a new version of the statistical analysis plan.

A signed version of the SAP for study OC5-OL-02 is preferably to be finalized before database lock and unblinding of study OC5-DB-02.

2 STUDY INFORMATION

2.1 Study Objective(s)

The primary objective of this study is to evaluate the efficacy of Oxabact following two years continued treatment in subjects who have completed the Oxabact OC5-DB-02 study.

The secondary objective of this study is to obtain additional safety data from two years continued treatment with Oxabact.

2.2 Design of the Study

This study is a single arm, open label international multi-center study (OC5-OL-02, ePHex-OLE) to evaluate the efficacy and safety of Oxabact (OC5) treatment for an additional two years in subjects with Primary Hyperoxaluria (PH) who have previously been treated with Oxabact or placebo in the OC5-DB-02 (ePHex) study.

Henceforth in the document the OC5-DB-02 will be referred to as the ePHex study and the OC5-OL-02 will be referred to as the ePHex-OLE study.

2.3 Study medication

Subjects will receive open label OC5 (Oxabact) twice daily for 24 months.

2.4 Sample size

Approximately 16 subjects were anticipated to be included in the study, dependent on the number of subjects who complete ePHex and chose to participate in ePHex-OLE. It is anticipated, based on a drop-out rate of 25% per year, that there will be approximately 12 subjects completing the 12-month visit, and 9 subjects completing the 24-month visit.

Assuming a difference between treatment groups in eGFR change at month 24 from baseline of 5 mL/min/1.73 m^2 with an SD of 3, the power will be greater than 90% with a sample size of 16 subjects. This power calculation is done using a repeated measures model in a two-sided approach with α=5%, a 1:1 allocation ratio for a total of 16 subjects, and assuming a within subject correlation of 0,70.

At the time of signing off the Statistical Analysis Plan it is known that 18 subjects were included.

2.5 Study flow chart

	Treatment (24 Months)											Post-treatment follow-up (4 weeks)[8, 9]
Month	0[1]	2	4	6	8	10	12	15	18	21	24	
Day (+/- 7 days)	0	61	122	183	243	304	365	456	547	638	730	
Visit Number[2]	0	1	2	3	4	5	6	7	8	9	10	NA
Clinic Visit	X	X	X	X	X	X	X	X	X	X	X	
Incl/Excl criteria	X											
Vital signs	X	X	X	X	X	X	X	X	X	X	X	
Physical exam.	X	X	X	X	X	X	X	X	X	X	X	
Conc. Med.	X	X	X	X	X	X	X	X	X	X	X	X
eGFR[3]	X	X	X	X	X	X	X	X	X	X	X	
Plasma Oxalate	X	X	X	X	X	X	X	X	X	X	X	
Stone events[4,]	X	X	X	X	X	X	X	X	X	X	X	X
Echocard.[5]	X			X			X		X		X	
Ultrasound	X						X				X	
Safety Labs[6]	X	X	X	X	X	X	X	X	X	X	X	
Stool	X			X			X		X		X	X
24-hour urine	X		X		X		X		X		X	
Quality of Life	X			X			X		X		X	
Pregancy test[7]	X										X	
Review Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Drug dispense/ Accountability	X	X	X	X	X	X	X	X	X	X	X	

[1] Month 0 (Visit 0; refererence time point) will be the same as the last visit (Week 52) in ePHex. For echocardiography of the heart and ultrasound of the kidneys, week 48 measurements in ePHex are considered Month 0. If there is no seamless transition (delay >1 month) from ePHex, a new clinic visit 0 (Month 0) will take place with applicable measurements prior to first dose of open label Oxabact® and further assessments should follow according to schedule.

[2] Visit window during treatment period +/- 7 days. In the case of an acute kidney injury occurring close to a scheduled visit, the visit will be rescheduled to ensure that the AKI does not adversely affect values (especially for eGFR). The days on which each visit should occur are detailed in Table 6 of the protocol.

[3] As determined by the Schwartz equation for children (age below 18), and CKD-EPI equation for adults (age 18 or above) based on serum creatinine.

[4] Kidney stone events and related symptoms will be captured at every visit, including events in between visits.

[5] Echocardiography to be done within +/- 2 weeks of the clinic visit at months 6, 12 and 18. If the images fail quality criteria, the examination will be repeated within 4 weeks.

[6] Safety Labs will include blood and urine sampling.

[7] If applicable.

[8] A post-treatment safety follow-up will be performed as a telephone call (the safety follow-up period will cover a duration of four weeks and the telephone call will be made maximum 3 working days after the safety follow-up period).

[9] Subjects will provide a post-treatment follow-up stool sample 4 weeks (plus maximum 3 working days) after intake of last dose of study drug.

3 PATIENTS FOR ANALYSIS

3.1 Analysis populations

3.1.1 Full-Analysis-Set (FAS)

The FAS includes all subjects who have received at least one dose of the investigational drug during the ePHex-OLE study and have at least one efficacy assessment during the ePHex-OLE study. This population will be used for the analysis of efficacy.

3.1.2 Safety-Analysis-Set (SAF)

The SAF includes all subjects who have received at least one dose of the investigational drug during the ePHex-OLE study. Safety summaries will be based on the SAF.

4 DATA REVIEW MEETING

Prior to database lock, data issues and protocol deviations and their impact on the statistical analyses will be discussed during the Data Review Meeting (DRM). For efficiency reasons, a pre-DRM may be held when data from a selection of subjects is cleaned, mainly to assess data quality. Invitees to these meetings are the OxThera Chief Medical Officer (CMO), the OxThera statistician, the OxThera and PSR/Ergomed Project Manager (PM), the PSR/Ergomed Lead Data Manager (DM) and the Author! /Certara Lead Statistician, but more roles can be invited if considered necessary. Input to the DRM will be supplied by PSR/Ergomed PM/Data Management at least one week in advance of the meeting: a list of all protocol deviations (including missing and outlier data), with specific detailing and description regarding the deviation. Other relevant data may also be shared by PSR/Ergomed for discussion. Furthermore, programmed data output as agreed will be shared by the Author!/Certara Lead Statistician.

The goal of this meeting is to reach consensus on data quality, meaning that we are confident that the database can be considered clean, no outstanding issues remain, and assess (important) protocol deviations to interpret a possible impact on the proposed statistical analyses.

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. Once all parties involved agree with the documented decisions, the document is finalized and signed by all attendees before database lock, and stored by the PM.

Furthermore, the COVID-19 impact will be evaluated. Possible decisions regarding additional analyses may be applicable, following the COVID-19 addendum.

5 PROTOCOL DEVIATIONS

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, deviations will be classified as important or not important and any data values excluded from analysis will be identified, along with their reason for exclusion. This includes PDs classified for their relation to COVID-19.

6 STUDY ENDPOINTS

6.1 Primary endpoint

The primary endpoint is change from baseline in kidney function (eGFR) after 12 and 24 months of open-label Oxabact treatment.

6.2 Key secondary endpoint(s)

The secondary endpoints are the following:

- Change from baseline in total plasma oxalate concentration after 12 and 24 months of open-label Oxabact treatment.
- Frequency of kidney stone events after 12 and 24 months of open-label Oxabact treatment. Stone events are defined as:
    - Patient- or investigator reported symptoms, or
    - Stone passages or removals, or
    - Increase in number of stones assessed by ultrasound.

6.3 Other endpoint(s)

In addition, a set of other endpoints are specified, which are considered supportive to the primary and key secondary endpoints:

- Change from baseline in in myocardial function as measured by Speckle Tracking and traditional echocardiography.
- Change from baseline in free plasma oxalate concentration.
- Change from baseline in urinary oxalate excretion.
- Grade of nephrocalcinosis as assessed by Ultrasound.
- Change in number of *O. formigenes* in stool.
- Association between change in number of *O. formigenes* in stool and change in total plasma oxalate concentration.
- Change from baseline in score of Quality of Life questionnaire.
- Change from baseline after 12 and 24 months of open-label treatment in markers for renal function, renal tubular capacity and inflammation
    - Urine: magnesium, phosphorus, citrate, calcium, glycolate, creatinine, urea, calcium oxalate crystals, pH, osmolality and urinary volume.
    - Blood: magnesium, phosphorus, citrate, calcium, BUN, ALP, bicarbonate, CRP, WBC, creatinine and Cystatin-C.

6.4 Safety endpoint(s)

The safety parameters to be evaluated are:

- Adverse events.
- Vital signs.
- Physical examination.
- Laboratory safety measurements: haematology, clinical chemistry and urinalysis.

7 STATISTICAL ANALYSIS

7.1 General considerations

Depending on the results from the ePHex study, three options for data analyses for ePHex-OLE are proposed:
1) If ePHex is positive, the SAP is followed completely as described, integration with ePHex data will be performed and all outputs will be based on CDISC data.
2) If ePHex is negative and the ePHex-OLE study is prematurely closed, the analysis for ePHex-OLE will be limited to simple listings and descriptive summaries for demographics, disposition, primary and key secondary efficacy, and exposure and safety, programmed on raw data following the FDA guideline on Abbreviated Reports[1]. No statistical analysis will be performed, and no integration with ePHex (CDISC) data will be done, except for the use of randomisation information from ePHex.
3) If ePHex is ambiguous, an additional data evaluation will be done using an agreed selection of outputs, programmed on raw data and without integration with ePHex (CDISC) data, except for the use of randomisation information from ePHex. Following the results, option (1) or (2) will be further pursued.

For a number of analyses in this study, data from study ePHex will need to be integrated (see appendix referred in section 11.1). Efficacy analyses, summaries and graphical presentations will include pooled data from both the ePHex and ePHex-OLE studies based on the FAS, and will be presented both for the overall population and according to the randomisation ('as randomised)' as applied in the ePHex study. Safety summaries will include the safety data reported in the ePHex-OLE study only and will be based on the SAF. Where applicable, presentations will be done per visit. Baseline data such as demographics, eligibility and prior medication has been collected for ePHex-OLE and will be presented without inclusion of ePHex data. Where presentations are done per treatment group, this will be as randomised during the ePHex study and these will be presented as (O - O) and (P – O), respectively, where O=Oxabact and P=Placebo. Historical data as collected during ePHex study will not be included and presented again. Lastly, change from baseline values will be calculated two different baselines: the baseline as per study ePHex, and as collected for study ePHex-OLE as supportive (only for the subjects that received placebo during ePHex).

Raw data (in listings) will be presented in the same precision as received. Appropriate rounding will be performed for the following summary statistics: arithmetic mean, LS mean, median, Q1 and Q3, SD (standard deviation), SE (standard error) and two-sided 95% confidence limits will be presented with at least 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 (except for 100%, if that is the maximum value), 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 general summary tables will be the number of non-missing observations (n), arithmetic mean, SD, SE, median, Q1, Q3, minimum and maximum for quantitative data. For qualitative data, frequency counts and percentages will be determined. The

[1] https://www.fda.gov/files/drugs/published/Submission-of-Abbreviated-Reports-and-Synopses-in-Support-of-Marketing-Applications..pdf

denominator used when calculating percentages will be the number of subjects in the applicable analysis population. Statistical output will present LS means, SE and two-sided 95% confidence limits, where applicable. All plots will be created using scheduled protocol time or visit on the x-axis. Mean plots will be presenting mean +/- SE.

Baseline is generally defined as the last non-missing planned and valid measurement/assessment before first dose of study drug, unless otherwise specified. 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:

- The first baseline is defined as the baseline of the ePHex study, which is specified per ePHex SAP for each of the assessments.
- A second baseline is defined as the last planned measurement prior to open-label treatment in the ePHex-OLE stdy. This may be the last visit of the ePHex study or Visit 0 of the ePHex-OLE study, depending on whether the subject has a seamless transfer from one study to the other. If a Visit 0 result is available for a subject, it will be assumed the subject did not have a seamless transfer and that value will be used as the second baseline. This second baseline is only applicable for subjects that received Placebo treatment during ePHex.

For safety parameters, only the second baseline is used to calculate change from baseline. For efficacy parameters (eGFR, plasma oxalate, urine oxalate excretion, faeces, echocardiography, ultrasound, Quality of Life, renal markers), both baselines will be applied as applicable.

For all efficacy analyses, the observed values and the change from baseline will be presented in summary tables and plots.

A treatment emergent adverse event (TEAE) is defined as an adverse event reported on or after first dose date of study drug in the ePHex-OLE study and up to 4 weeks after last dose of open label medication in the study.

Collected data will be presented in individual data listings, and derived data will be added when needed. For all relevant listings, study day will be added. The calculation for this day is as described in the addendum as referred in section 11.1. All listings will include information on subject number, treatment ((O - O) and (P – O)), and age, race and sex information as collected during baseline of ePHex-OLE.

Considering the limited sample size, the statistical analyses proposed, beyond summaries and graphical presentations of the data collected, will only be performed as supportive and depending on the sample size. No formal statistical testing will be done and statistical significance will be viewed with caution, considering the very small and heterogeneous patient population. Any determined p-value can only be indicative. No correction for multiple comparisons will be applied for any of the endpoints.

7.2 Missing data

For handling missing data of the statistical analyses applied to the primary and key secondary endpoints, refer to the respective analysis sections. Other data will not be imputed unless 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. Date imputations are listed below.

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.
    - If any of the above imputations would lead to a date after end of study, then the date of end of study will be used.
  - 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.
- If 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 (CTCAE grade 3).
- In case causality is missing for a certain TEAE, this will be regarded as related.
- In case seriousness is missing for a certain TEAE, it will be queried by DM. If the query is not resolved, an imputation of serious will be done, leading to a mismatch with the PV documentation.

In case other date imputations are performed (e.g. for the purpose of calculation of durations) a simple approach will be used:

- if the day is missing, the first of the month will be used
- if the month is missing, the first month of the year will be used
- if year is missing no imputation will be performed and the resulting calculation based on the date will be missing

7.3 Interim analysis

An interim analysis summarising both efficacy and safety will be performed when all subjects enrolled in the ePHex-OLE study have 12 months data.

7.4 Subject and study disposition

Unless stated otherwise, all data will be listed.

7.4.1 Inclusion/exclusion criteria

A summary table (percent and frequency) of subjects violating inclusion/exclusion criteria will be presented.

7.4.2 Disposition

An overview table will be created, stating the number and percentage of subjects per site, including country and site number and investigator name.

Subject disposition will be presented with a summary of the number/percentage of subjects treated, completed, and reasons for non-completion, per treatment group and overall. Additionally, in the same summary, the number/percentage of subjects in the FAS and the SAF will be presented. Number and percentage of subjects included in the applicable subgroups will be presented, plus descriptive statistics on follow-up time, calculated from first treatment dose in the ePHex-OLE study.

The listing to be created will include on a per-subject level the reasons for withdrawal of both study and/or treatment, as well as information on WIC date and center/site. Follow-up time for each subject calculated from first treatment dose in the ePHex-OLE study will also be presented.

7.4.3 Protocol Deviations

Important protocol deviations, as agreed prior to database lock, will be summarized according to their classification. All protocol deviations will be listed.

7.5 Baseline characteristics

Both baseline characteristics in the ePHex study and in the ePHex-OLE study will be described for the subjects enrolled in the ePHex-OLE study.

Baseline characteristics will also be described for subjects included in the FAS of the ePHex study, but not participating in the ePHex-OLE study.

7.5.1 Demographics

Data (including weight, height and BMI measurements at screening) for FAS and SAF per treatment group and overall will be summarized, using metric units where applicable (see section 11.1 for reference to addendum). Appropriate descriptive statistics for age, height, weight, BMI, race and sex will be given.

Demographics in the ePHex study and in the ePHex-OLE study will be described for the subjects enrolled in the ePHex-OLE study. Demographics will also be described for subjects included in the FAS of the ePHex study, but not participating in the ePHex-OLE study.

The listing of demographic data will include information on childbearing potential (for females only).

7.5.2 Medical history

Medical history will be coded by SOC and PT using MedDRA and presented as number/percentage of subjects in each SOC and PT per treatment group and overall for the FAS population. 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 subject level. Note that medical history as collected for this study are medical events occurring before first dosing for ePHex-OLE but after the safety follow-up period in the ePHex study, as well as medical history from the ePHex that is still ongoing in the ePHex-OLE study.

For handling missing dates, see section 7.2.

7.5.3 Other (screening) data

Pregnancy tests will be listed for females of child-bearing potential only.

7.6 Statistical analysis primary and secondary endpoints

7.6.1 Primary endpoint

The primary efficacy endpoint is the change from baseline in kidney function (eGFR) after 12 and 24 months of open-label Oxabact treatment. The primary endpoint will be presented using the FAS population.

The primary analysis will be based on the 24-month data and using the baseline of the ePHex as primary baseline, while other time-points presented will be considered as supportive. A second analysis is done using the baseline of ePHex-OLE for the ePHex placebo subjects as baseline.

Change from baseline in kidney function (eGFR) will be calculated at each visit, using the two different baselines. Summary statistics of the measurements will be presented on a per-visit basis. Presentations will be per treatment group and overall.

To visualize the effects through time graphically, the following plots will be created:

- Individual plots will be created to visualize the course of eGFR values through time (including the ePHex values, as applicable). Both the actual values as well as change from baseline values will be presented.
- Mean +/- SE will be created to visualize the course of eGFR values through time (including the ePHex values, as applicable). Both the actual values as well as change from baseline values will be presented for the overall group and for both treatment groups, preferably in the same plot.
- Spaghetti plots per treatment group of the actual values will be created to visualize the group course of eGFR through time, using the same y-axis for visual comparison between groups. No spaghetti plots will be created for change from baseline. One plot will be created, using colors to discriminate both treatment groups (which combined will show the overall group).
- A plot presenting LS estimates +/- SE will be created, based on the mixed-effect repeated measures model stated below.

A statistical analysis will be performed using a mixed-effect repeated measures model (MRMM) on the change from baseline value at 12 and 24 months, with the following independent variables: treatment group, baseline eGFR value, time and time*treatment group interaction. 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 <time>;
  model change=treatment time treatment*time baseline;
  repeated time / subject=usubjid(treatment) type=…;
run;
```

The time variable will preferably be the same as used for ePHex, to be able to make comparisons.

Considering the variability of eGFR, an AR(1) covariance matrix will be used in the model, which assumes that a correlation between two consecutive measurements is higher than between two measurements further apart in time. If the model does not converge, an unstructured (UN) covariance matrix will be applied, to allow variances and covariance 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), the model is likely not converge if AR(1) already did not converge. If that occurs, the structure will be adapted to respectively Toeplitz or Compound Symmetry (CS).

From this model, the comparison at 12 and 24 months will be extracted (both overall as well as per treatment group). Comparisons of other visits will be extracted as well and presented as secondary. The tables will display the LS means, SE, 95% CI for each visit and the p-values for the differences at 12 and 24 months.

In addition, since the model provides a test of difference in slopes using the proposed time-by-treatment interaction, treatment slopes and slope differences on change will be presented as well. Only the values after first open label treatment will be used for determination of the slopes.

As a sensitivity analysis for the primary endpoint, the same model will be used after applying a multiple imputation (MI) method for missing data under the missing at random assumption (MAR). Missing data patterns and covariates related to the missing data patterns will be examined and described. A total of 10 multiple imputations will be generated using predicted mean matching based on a monotone regression (in case the missing data pattern is monotone) or on a fully conditional specification regression (in case the missing data pattern in arbitrary and non-monotone). The predicted mean matching method imputes an observed value which is closest to the predicted value from the simulated regression model for each missing value. It ensures that imputed values are plausible and might be more appropriate than the regression method if the normality assumption is violated. The regression model will condition on observed values of the primary outcome measured at other time points (including baseline measurements) and possible other covariates that are related to the missing data pattern and/or primary endpoint.

The mixed-effect repeated measures model described above will be applied to each imputed dataset separately. The estimated parameters will be pooled using Rubin's combining rules. Only the primary comparisons at 12 and 24 months will be analysed using this approach.

The analysis above will be done under the assumption of missing at random (MAR). Since it concerns a supportive analysis of the descriptive statistics, no further analysis will be done to assess the robustness of the primary analysis to possible deviations from the missing at random (MAR) assumption.

As a secondary method of analyses corresponding to the MMRM above will be done using an ANCOVA model with treatment group, baseline/second baseline as covariates and change from baseline/second baseline in eGFR at 12 and 24 months as a dependent variable.

An additional statistical analysis using MRMM will be employed to evaluate the change in eGFR when on Oxabact treatment for a period of 12 months or 24 months, depending on when the subject actually received Oxabact for the first time (for O – O this is the start of treatment during the ePHex study, for P – O this is the start of treatment during the current study).

If the models cannot be run because of the small sample size of the study, either or not in combination with too many missing data, then analysis will be limited to descriptive statistics and graphical displays as described.

All the analyses described above for eGFR are based primarily on the Creatinine-based "Bedside Schwartz" for children and CKD-EPI 2009 equations[2] for adults. For subjects aged between 18 and 23 years (both inclusive) of age, the mean of the children and adult equation results will be calculated as described in the appendix referred in section 11.1).

In addition, supportive analyses based on the Cystatin-C based CKiD for children and CKD-EPI 2012 equations[3] for adults (see section 11.1) will be carried out, and similar analyses and presentations as for the Creatinine-based "Bedside Schwartz"/ CKD-EPI 2009 equation will be done. For Cystatin-C based equations, no modification for subjects between 18 and 23 years will be performed.

For children, height values are collected at each visit, and therefore the additional supportive eGFR values will need to be adjusted on a per-visit basis accordingly.
Adults only have one height collected at baseline, and this will be used throughout. Age will need to be determined at each visit, if not collected. Given that for most subjects no full birth date will be available, an estimation of age will be used following section 7.2.

[2] Children: $eGFR=41{,}3 \times (height / S_{Cr})$, Adults: $eGFR=141 \times \min(S_{Cr}/\kappa,1)^{\alpha} \times \max(S_{Cr}/\kappa,1)^{-1{,}209} \times 0{,}993^{age} \times \gamma$, with S_{Cr} = serum creatinine (mg/dL), $\kappa = 0{,}7$ (females) or 0,9 (males), $\alpha = -0{,}329$ (females) or -0,411 (males), $\gamma = 1{,}018$ (female) or 1,159 (black) or 1 (otherwise), age in years and height in m.

[3] Children: $eGFR=39{,}8 \times (height / S_{Cr})^{0{,}456} \times (1{,}8/S_{cys})^{0{,}418} \times (30/BUN)^{0{,}079} \times 1{,}076^{male} \times (height/1{,}4)^{0{,}179}$, Adults: $eGFR=135 \times \min(S_{Cr}/\kappa,1)^{\alpha} \times \max(S_{Cr}/\kappa,1)^{-0{,}601} \times \min(S_{cys}/0{,}8,1)^{-0{,}375} \times \max(S_{cys}/0{,}8,1)^{-0{,}711} \times 0{,}993^{age} \times 0{,}969^{female} \times 1{,}08^{black}$, with S_{Cr} = serum creatinine (mg/dL), S_{cys} = serum cystatine-C (mg/L), $\kappa = 0.7$ (females) or 0.9 (males), $\alpha = -0.248$ (females) or -0.207 (males), BUN = Blood Urea Nitrogen (mg/dL), age in years and height in m.

7.6.2 Key secondary endpoints

The key secondary endpoints will be presented using the FAS population, and all individual data will be listed as well.

Total plasma oxalate

The key secondary endpoint change from baseline in total plasma oxalate concentration, will be analysed using a similar analysis (descriptive plus supportive MRMM including the slopes) as proposed for the primary endpoint (see section 7.6.1), and no additional sensitivity analyses will be performed. Similar descriptive statistics per visit (absolute and change from baseline) and plots will be created.

Additionally, a combined plot for total plasma oxalate concentration and eGFR over time will be created using a double-axis display – this plot will be created for each subject, and a summary plot presenting mean +/- SE values per treatment group and overall will be made.

Summary statistics will also be created for the observed minimum and maximum total plasma oxalate concentration values during ePHex-OLE, as well as its changes from baseline using both baselines. Also, plots will be created to present the shift from baseline to the minimum or maximum value, combined for all subjects per treatment group and overall.

In addition, a frequency tabulation will be created based on the number of subjects achieving 'near-normalization' of total plasma oxalate concentration (<10 µmol/L) at least twice during 12 months and during 24 months of open-label treatment. This table will also include the response assessments for < 10 µmol/L during 12 months and during 24 months of open-label treatment.

Furthermore, percent change from baseline in total plasma oxalate concentration after 12 and 24 months of treatment will be displayed descriptively per treatment and overall, using both baselines.

Kidney stone events

Kidney stone events are defined as subject- or investigator reported symptoms (as in the CRF AE or PH medical history pages), or number of stones assessed by Ultrasound (US). As a consequence, three summary tables on stone events will be presented, as follows:

- Stone events during treatment, based on AE
- Stone events during treatment, based on US

Here, during treatment is defined as first to last dose date of ePHex-OLE. Where applicable, stones left and right will be combined into one overall kidney stone number for summary tables and analysis.

Descriptive statistics of the occurrence of kidney stones and the number of subjects with a stone event after 12 and 24 months of open label treatment will be presented per treatment group and overall, separately as based on AE and based on US datasets.

Descriptive statistics on stone events using the AE dataset will include a summary of days missed at school/work due to a stone event and other relevant data related to stone events.

Incidence rate of kidney stones is the rate at which kidney stone events occur in the population, and defined as the number of kidney stone cases per subject-year(s). The calculation of the incidence rate is the number of kidney stone occurrences during the study time period divided by the group of subjects susceptible to a stone event (i.e. the FAS), expressed as person-time and

calculated as sum of the treatment duration time of all subjects in the FAS. This calculation is accomplished as follows:

- Denominator: $\sum t_i$, where t_i= treatment duration of subject i in years (total # days divided by 365.25), where treatment duration is determined based on first and last dose date.
- Numerator: the total number of kidney stone occurrences during treatment (first to last dose date)
- Incidence rate=numerator/denominator

Since this analysis is done both after 12 months and after 24 months of treatment, in case of 12 months the date of visit 6 is used instead of last dose date.

The use of this measure implies the assumption that the incidence rate is constant of different periods of time. The incidence rates will be presented per treatment group. As these incidence rates are determined per treatment group, comparisons can be done using descriptive statistics of incidence rate difference (IRD) and incidence rate ratios (IRR). IRD and IRR are defined as follows, assuming the following exposure table:

			Treatment exposure	
			O - O	**P - O**
Outcome	12 months	Occurrences	a	B
		Person-time	PT1	PT2
	24 months	Occurrences	a	b
		Person-time	PT1	PT2

Then IRD=(a/PT1) - (b/PT2) and IRR=(a/PT1)/(b/PT2) is calculated for 12 months and 24 months. These will be presented in combination with a 95% CI.

If sample size allows it, for comparison between treatments on the total number of kidney stone events, an appropriate model fitting the specific count data will be used, if feasible considering the small sample size. This can be either a Poisson model or a Negative Binomial model, depending on the overdispersion. First a Pearson Chi-squared dispersion statistic is determined. When the dispersion statistic is close to one (i.e. mean is approximately the same as the variance), the Poisson model will be used. If the dispersion statistics however is larger than one (variance >> mean), it is more appropriate to use the Negative Binomial instead. If necessary, depending upon the number of zeros in the underlying data, a zero-inflated model will be used. This analysis is considered the last analysis in the hierarchical approach.

All other US data will be presented in a descriptive summary.

7.6.3 Other endpoints

All endpoints mentioned below will be presented using the FAS population.

Myocardial function

The change from baseline after 12 and 24 months in myocardial function markers as measured by Speckle Tracking (STE) and traditional echocardiography (TE) will be evaluated, comparing between treatments.

STE and TE parameters will be provided by Bioclinica according to an agreed data transfer agreement (DTA).

Summary statistics of the parameters will be presented on a per-visit basis. For all parameters (except for the categorical parameters), both the actual value as well as the change from baseline value will be presented for each treatment group and overall. For the categorical parameters, the number/percentage of observations in the different categories will be presented per visit and treatment/overall.

To visualize the effects through time graphically, the following plots will be created:

- Mean +/- SE per treatment group and overall, and individual plots will be created for GLS/LVEF values through time. Presentations are made for the actual values and the CFB values.
- Combined spaghetti plots will be created using the actual values for GLS/LVEF values through time. No spaghetti plots will be created for change from baseline. One plot will be created, using colors to discriminate both treatment groups (which combined will show the overall group).

Free plasma oxalate

Free plasma oxalate values will be analysed using the same descriptive statistics as proposed for primary endpoint, and no statistical analysis will be applied. Similar descriptive statistics per visit (absolute and change from baseline) and plots will be created.

Urinary oxalate excretion

Urinary oxalate excretion values will be analysed using the same descriptive statistics as proposed for the primary endpoint, and no statistical analysis will be applied. Similar descriptive statistics per visit (absolute and change from baseline) and plots will be created.

Urinary oxalate excretion is collected both as centrifuged and non-centrifuged. Both will be presented.

Grade of nephrocalcinosis

Descriptive statistics (frequency and percentages), including shifts from baseline (using both baselines) after 12 and 24 months of open label treatment, will be presented for the grade of nephrocalcinosis per treatment group and overall using a tabular display. Grade of nephrocalcinosis will be assessed by ultrasound images using grade values 0-3, with the following meaning:

grade 0: no echogenicity
grade 1: mild echogenicity around medullary pyramid borders
grade 2: moderate echogenicity around and inside pyramids
grade 3: severe echogenicity of entire pyramids

Grades and shifts will be summarized for left and right kidney separately. In addition, shifts will be classified (and presented) following the addendum referred to in section 11.1. Shift tables will be presented as a crosstabulation comparing baseline and 12/24 months values.

Stool

Data collected for *O.formigenes* in stool (as genotype 1 and genotype 2) will only have measurable values if above the Limit of Detection (LOD). Values below the LOD will be replaced for calculation purposes in descriptive statistics, plots and statistical analyses (see section 11.1). The proposed analyses will only be performed if there is a limited amount (<15%) of data below LOD present on-treatment. The values will be presented as '< LOD' in the listings.

Note that in case of a provided actual value lower than the LOD, it will be presented and used as is and not imputed.

Based on previous studies, it is expected that the number of subjects positive for genotype 2 at screening/baseline and throughout the study will be very low. Therefore, in case genotype 1 or 2 is not detectable in the majority of data (see above), the analysis for that genotype will not be performed and data for that genotype will then be limited to a listing. All descriptive statistics and plots will be done separately on number of *O. formigenes* genotype 1 and 2 respectively, if applicable.

Descriptive statistics will be used to present the observed and change from baseline values per treatment group and overall over time, using two baselines. Change in number of *O. formigenes* stool will be based on number of *O. formigenes* at month 24 compared to baseline in the O - O group versus the P - O group. The measurement at month 12 will be used as supportive data.

Analyses on the total number of *O.formigenes* (i.e. the sum of genotype 1 and genotype 2) may be done as post-hoc analyses, and this depends upon the number of values <LOD.

Quality of Life questionnaires

Quality of life scoring is assessed with the questionnaires SF36V2 (for adults ≥ 18 years) or CHQ/PF50 (for children ≥ 5 years). For children younger than 5 years of age, it is likely that no information from the questionnaire is available, and data will remain missing.

SF-36V2 scores are established using 8 scales (PF=Physical Functioning, RP=Role - Physical, BP=Bodily Pain, GH=General Health, VT=Vitality, SF=Social Functioning, RE=Role - Emotional, MH=Mental Health) and 2 summary measures (PCS=Physical Component Summary, and MCS=Mental Component Summary). In addition, a separate scale is available for HT=Reported Health Transition.

CHQ/PF50 are established using 13 scales (PF=Physical Functioning, RP=Role-Physical, GH=General Health perceptions, BP=Bodily Pain, FA=Family Activities, REB=Role/Social Emotional/Behavior, PT=Parental impact - Time, PE=Parental impact - Emotional, SE=Self Esteem, MH=Mental Health, BE=Behavior, FC=Family Cohesion, CH=Change in Health) and 2 summary measures (PhS=Physical Summary, and PsS=Psychosocial Summary).

Quality of life will be presented descriptively per questionnaire type, for the two treatment groups and overall, using the selection of subjects taking the specific QoL questionnaire (i.e. adults or children). Descriptive statistics of domain scales and summary scores as well as the change from baseline for both will be presented on a per-visit basis by treatment group and overall, using the calculated T-scores and the two baselines. It should be noted that results may not be comparable or combinable, if subjects in the ePHex-OLE study fall into a different age category as compared to the ePHex study and change from baseline cannot be calculated then using the ePHex baseline values.

Individual domain scales and individual summary scores will be listed additionally, raw individual question scores and intermediate calculated scores will only be kept in the associated CDISC domains. Note that for SF-36V2 the HT scale is not used in any of the domains or summary scores, and will thus will be presented separately in the descriptive table and will be listed. For CHQ/PF50, 3 subscores were not used for the calculation of the T-scores (CH, FA and FC), and will be handled similarly as the HT scale for SF36.

Missing data (missing raw score/question, missing domain scale or missing summary measures) will be handled as described in the specific quality of life questionnaire documentation, or otherwise remain missing.

Refer to the addendum mentioned in section 11.1 for the calculations.

Renal

Markers for renal function, renal tubular capacity and inflammation are the following:

- *Urine*: magnesium, phosphorus, citrate, calcium, glycolate, creatinine, urea, calcium oxalate crystals, pH, osmolality and urinary volume.
- *Blood*: magnesium, phosphorus, citrate, calcium, glycolate, BUN, ALP, bicarbonate, CRP, WBC, creatinine and cystatine C.

These markers will be presented with descriptive statistics in tabular format using the actual values and change from baseline, per visit and treatment group/overall.

These markers will be presented as endpoint for the FAS population, and will therefore not be presented in the safety laboratory summaries. They will however be combined into the same listings section.

Note that for the 24h urine concentration parameters, an additional conversion may be necessary to obtain excretion values: see the addendum as referred in section 11.1.

7.6.4 Subgroup analyses

Subgroup analyses using descriptive statistics of the following endpoints may be presented if considered feasible: change from baseline for eGFR, change from baseline for total and free plasma oxalate concentration, change from baseline for 24h urine oxalate excretion (non-centrifuged only), stone events incidence rate (as per adjudicated data) and change from baseline for speckle tracking and traditional echocardiography (limited to LVEF/GLS). Presentations will be done for each visit. Both baselines will be used. The analyses will be based on the following subgroups, provided the subgroups are sufficiently large (>2):

- Subjects with a baseline urinary oxalate excretion (non-centrifuged) above and equal to or below 1.87 mmol/L/24h/1.73 m^2 respectively (mean of the two values during screening/baseline of the ePHex study).
- Subjects above or equal to and below 18 years of age at baseline of the ePHex study.
- Subjects with a baseline eGFR above or equal to (≥) and below (<) 60 ml/min/1.73m^2 respectively (mean of the obtained values during screening/baseline of the ePHex study calculated by the Schwartz/CKiD equation[4]), with correction for 18-23 years.
- Race.
- Gender.
- Progressors and non-progressors (see section 11.1) based on historical eGFR (i.e. eGFR prior to treatment start including the baseline/screening values of the ePHex study), using the Schwartz/CKiD equation.

[4] The Schwartz CKiD 2009 creatinine-based "bedside Schwartz" equation for children (below 18 years of age) and 2009 creatinine-based CKD-EPI equation for adults.

For the subgroup analyses only the FAS population will be used. No formal testing of subgroups will be performed due to small sample sizes. No plots will be created.

7.7 Safety and tolerability evaluation

The safety population is used for all safety presentations. All summaries will be presented for the overall group and per treatment as randomised during the ePHex study. Where change from baseline is mentioned, this refers to the baseline of the ePHex study.

Note that all data collected are presented in listings as well, and safety listings will be presented including subject number, treatment ((O - O) and (P – O)), and age, race and sex as collected during baseline of ePHex-OLE.

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.

Study phase will be added to the AE and prior/concomitant medication presentations. Study phase will be defined for ePHex-OLE as: baseline (meaning pre-treatment of ePHex-OLE), treatment, safety follow-up and post safety follow-up, using the applicable ADaM domain with manipulation to obtain the post follow-up phase from STDM domain EPOCH. The post follow-up phase is the phase following the four-week safety follow-up after the last dose of study treatment. Post follow-up data will only be presented in listings and not taken into consideration in any descriptive statistics.

7.7.1 Adverse events

Treatment emergent adverse events (TEAE) are defined as adverse events reported on or after first dose of study treatment during ePHex-OLE study and up to the end of the safety follow up phase, being 4 weeks after last dose of open label medication in the study. All AEs reported in the study will be listed.

Kidney stone events are also collected as part of the CRF AE pages and, although included as a key secondary efficacy assessment, will also be included in the AE safety analyses as described in this section.

A TEAE overview table will be created displaying the number of subjects (and percentage) experiencing a treatment-emergent adverse event (TEAE) and the number of TEAEs for: any TEAE, any TEAE per severity grade (1-5, per CTCAE version 4.0), any related/unrelated TEAE, any SAE, any Fatal AEs/Deaths during study and any TEAE leading to study discontinuation. Tabulation will be done by treatment group and overall.

All TEAEs are tabulated by System Organ Class (SOC) and Preferred Terms (PTs) within each SOC according to the MedDRA terminology list. TEAEs will also be tabulated by severity grade (1-5, per CTCAE version 4.0) and by relationship to study medication (related/unrelated), using frequency counts (number of subjects with at least one event, and number of events) and percentage of subjects with the event. Similar tables will be created for TEAEs leading to premature discontinuation, SAEs and fatal AEs/deaths, if applicable. 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 on or after first dose), PT (MedDRA), SOC

(MedDRA), severity grade, 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 included in the AE listing. In this listing, a clear distinction will be made between prior and treatment emergent events. Day and phase will be added as well.

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 'Certain', 'Probably/likely', 'Possible', 'Unclassifiable' or missing. In other instances, the AE will be considered unrelated for summary tables. The original causality description will be used in listings, and a footnote will be added to the summary tables to explain the classification.

7.7.2 Clinical laboratory

The following laboratory safety data are collected for this study:

Haematology	Chemistry	Urinalysis
RBC (Erythrocytes)	Blood Urea Nitrogen	Protein
WBC (Leucocytes)	Electrolytes (Na+, K+, Mg++, Ca++, HCO3-, Cl-)	Glucose
Lymphocytes	Glucose	pH
Monocytes	Albumin	
Neutrophils	Alkaline phosphatase	
Basophils	ALT	
Eosinophils	AST	
Platelets	Total bilirubin	
Haemoglobin		
Haematocrit		
MCV		
MCHC		

Urine 24h measurements are already presented as 'Other endpoints' markers for renal function, renal tubular capacity and inflammation (see section 7.6.3).

Laboratory safety data for haematology, biochemistry and urinalysis will be summarized using descriptive statistics for values over time, change from baseline and percent change from baseline per visit and treatment group/overall, using protocol visits. Listings will include the change from baseline values.

Safety laboratory parameters are collected both in conventional units and SI units: SI units will be used in the tabular presentations.

Lastly, for clinical laboratory parameters, a listing will be created presenting all data that are out of reference range on a per-subject level, including any available unscheduled measurements. The investigator has judged the out-of-range values on their clinical significance, and this information will be added as well. Information regarding age at screening and gender will be added to this listing.

7.7.3 Vital Signs

Vital sign data consist of measurements for pulse rate, systolic and diastolic blood pressure, body temperature and respiration rate. Vital signs will be summarized and listed per visit and per treatment group, using protocol visits and metric units (see section 11.1). 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.

7.7.4 Prior and concomitant medication

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

In addition, frequency tables for prior and concomitant medications will be created, presenting the number of subjects with any prior/concomitant medication, and the number of subjects for each ATC System Pharmacological/Therapeutic group (2^{nd} level of WHO classification) and the Chemical Substance (5^{th} level of WHO classification), irrespective of duration of receipt, frequency or dose. The presentation will be done per treatment group and overall.

A separate summary will present concomitant medications starting or ongoing at Day 1 (first dose date of investigational medicinal product).

If a medication is started prior to first dose of open-label treatment in the ePHex-OLE study, this is considered prior medication. Concomitant medication is defined as started before first open-label treatment in the ePHex-OLE study and continuing thereafter or starting on/after first dose date of open-label treatment in the ePHex-OLE study. 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 start dates is determined using the rules for missing data detailed in Section 7.2. Furthermore, considering the data integration necessary to include the ePHex data, further details on prior medication are provided in the document referred in section 11.1.

7.7.5 Physical examination

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

7.8 Scheduled visits, Dosing and Treatment Compliance

7.8.1 Visit dates

A listing with actual visit dates (and times, if applicable) per subject will be presented. This listing will include study day information as well.

7.8.2 Dosing and drug accountability

Relevant dosing information (first dosing date, last dosing date, missed doses), scheduled and actual dosing dates/times and drug accountability (total dispensed and returned medication) will be listed for each subject.

8 CHANGES FROM PROTOCOL AND OTHER RELEVANT REMARKS

The descriptive statistics on percent change from baseline in total plasma oxalate concentration, on subjects subjects achieving 'near-normalization' of total plasma oxalate concentration (<10 μmol/L), and on the shifts to minimum and maximum values for total plasma oxalate concentration were not mentioned in the protocol, but added as these were considered relevant in the ePHex study.

Subgroup analysis based on type of PH (as per randomization for ePHex) will not be conducted due to the expected insufficient number of subjects in the subgroups.

The sensitivity analysis for the MRMM for eGFR will be done under the assumption of missing at random (MAR). Since it concerns a supportive analysis of the descriptive statistics with a small sample size, no further analysis will be done to assess the robustness of the primary analysis to possible deviations from the missing at random (MAR) assumption, and therefore the pattern-mixture analysis is removed from the SAP.

Furthermore, the regression analysis to determine slopes for eGFR, and the summary table and statistical thereof is excluded from the SAP, considering slopes are already determined based on a MRMM. Any apparent differences in slopes can best be assessed based on the individual slope results of the MRMM analyses and viewing the spaghetti and mean plots.

Any post-hoc analyses or changes in regards to the statistical analysis plan when performing the final analyses after data base lock, will be captured in a Note to File and used for the relevant sections in the clinical study report.

9 COVID-19 DETAILS

This study is conducted during the Covid-19 outbreak. A number of data capture decisions are taken due to national, local, or site-specific restrictions imposed due to Covid-19, with the primary need to prioritize the safety of clinical study teams and subjects, and to maintain the integrity of the study/data collection.

The impact of the Covid-19 outbreak on the data and the proposed statistical analyses is detailed in a separate document (Addendum 2), which will be maintained as a living document throughout the study continuation and is dependent on the duration and impact of the Covid-19 situation. The document will be finalized during DRM, prior to database lock and unblinding.

10 DATA RECEIPT

Clinical CRF 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 datafiles to be received from Bioclinica (echocardiography and renal ultrasound parameters) will be provided by Bioclinica according to an agreed DTA as SAS and .txt files. Only the SAS files will be used and transferred to SDTM as well.

In addition, a number of excel files are received complementary to the data from the database:

- The information regarding protocol deviations (a so-called “protocol deviations log”)
- Information regarding missing data

The protocol deviation excel file will be imported into SAS and transferred to SDTM.

Compliance can be estimated using the drug accountability data. If the evaluation is done manually an excel file may be created. This excel will not be imported or used in the CDISC domains or TLFs.

Relevant SDTM files will be recoded to ADaM format as applicable, and several adjustments are made following the programming addendum as referred in section 11.1 of this SAP. Listings will be programmed on the SDTM and, if necessary, ADaM datasets. Statistical analyses, tables and figures will be programmed on ADaM datasets. Only necessary adaptations, not being able to be handled on database level, will be described either in this SAP or in NTFs and used for adaptations in the ADaM datasets and a clarification is included in the applicable ADaM documentation.

11 TECHNICAL DETAILS

11.1 Programming conventions

A separate living document is available regarding detailed programming conventions (Addendum 1) and data integration of study ePHex and study ePHex-OLE.

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

11.2 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.

11.3 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 and PDF format. SAS graphs will be saved in PNG format. The tables and listings will be imported into PDF. The PDF package will be supplied to OxThera and the Medical Writer for use in the clinical study report, and RTF/PNG output may be shared as separate documents with OxThera as necessary. The graphs may be added to this document or supplied separately.

11.4 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, also font Times New Roman will be used, and output will be created as PNG plot. Graphs for a clinical study report are preferably created using black, grey and white colour only, to facilitate black-and-white printing. Different line patterns and symbols may be used to

differentiate between classification or treatment levels. If a certain plot can only be visually improved by using colours, then a SAS colour scheme will be used. 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.

12 TABLES, LISTINGS, GRAPHS

12.1 General

A detailed list of tables, graphs and listings is presented, if applicable, per report section in sections 12.2, 12.3 and 12.4.

Template tables and listings as well as *example* plots will be used as a reference for creation of all output, and a separate document will be created for this. Table numbering will be followed where possible, however, if the data give cause for combining or splitting tables or listings, table numbering may be adapted as necessary.

12.2 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, and will not need to be programmed unless this is requested by the Medical Writer. These in-text tables will also use font Times New Roman. Complex in-text tables can be requested to be created using SAS programming.

12.3 Tables and graphs

Following ICH E3 guidelines, tables and graphs mentioned will be presented in Section 14 of the CSR, and output will be prepared in the order and with section number as stated. Final table/graph/listing numbering can be different from what is presented here.

Table or graph number	Contents of table/graph
14.1 Demographic Data Summary figures and tables	
14.1.1	Summary of subject enrolment by country and site
14.1.2	Summary of inclusion/exclusion criteria
14.1.3	Disposition
14.1.4	Important protocol deviations
14.1.5	Demographics
14.1.6	Medical history
14.1.7	Prior medication
14.2 Efficacy Data Summary figures and Tables	

14.2.1	Descriptive statistics eGFR and change in eGFR during treatment compared to start of ePHex as baseline, per visit and treatment. (FAS.) - Two calculation methods (2009 and 2012 formulae), and two baselines.
14.2.2	Descriptive statistics eGFR (raw and cfb) by subgroup, per visit and treatment (FAS). - Two calculation methods (2009 and 2012 formulae), and two baselines.
14.2.3	Mixed Repeated Measures Model result eGFR. (FAS) - Two calculation methods (2009 and 2012 formulae).
14.2.4	LS estimates eGFR. (FAS) - Two calculation methods (2009 and 2012 formulae).
14.2.5	Slope results eGFR. (FAS) - Two calculation methods (2009 and 2012 formulae).
14.2.6	Multiple imputation result eGFR. (FAS) - Two calculation methods (2009 and 2012 formulae).
14.2.7	ANCOVA result eGFR. (FAS) - Two calculation methods (2009 and 2012 formulae).
14.2.8	Additional MRMM result eGFR on being treated 12 or 24 months. (FAS) - Two calculation methods (2009 and 2012 formulae).
14.2.9	Mean (+/-SE) eGFR versus time plot, per treatment (FAS). Similar plot for change from baseline. - Two calculation methods (2009 and 2012 formulae), and two baselines.
14.2.10	Individual eGFR versus time plot (FAS). Similar plot for change from baseline - Two calculation methods (2009 and 2012 formulae), and two baselines.
14.2.11	Spaghetti plots per treatment group of eGFR values (FAS) - Two calculation methods (2009 and 2012 formulae)
14.2.12	LS mean +/- SE plot eGFR (FAS) - Two calculation methods (2009 and 2012 formulae)
14.2.13	Descriptive statistics total plasma oxalate levels and change in total plasma oxalate levels during treatment compared to baseline, per treatment. (FAS) - Two baselines.
14.2.15	Descriptive statistics total plasma oxalate (raw and cfb) by subgroup, per visit and treatment (FAS). Two baselines.
14.2.16	Summary statistics for minimum and maximum total plasma oxalate values, including change from baseline. (FAS). Two baselines.
14.2.17	Total plasma oxalate concentration (unit) percent change from baseline over time (FAS). Two baselines.

14.2.18	Frequency tabulation on subjects with 'near-normal' total plasma oxalate levels (FAS). Two baselines.
14.2.19	Mixed Repeated Measures Model result total plasma oxalate. (FAS)
14.2.20	LS estimates total plasma oxalate. (FAS)
14.2.21	Slope results total plasma oxalate. (FAS).
14.2.22	Mean (+/-SE) total plasma oxalate versus time plot, per treatment (FAS). Similar plot for change from baseline.
14.2.23	Individual total plasma oxalate versus time plot (FAS). Similar plot for change from baseline.
14.2.24	Shift plots from baseline to minimum/maximum value for total plasma oxalate. (FAS).
14.2.25	Spaghetti plots per treatment group of the actual total plasma oxalate concentration values (FAS).
14.2.26	LS mean +/- SE plot total plasma oxalate (FAS)
14.2.27	Mean (+/- SE) plots eGFR/total plasma oxalate versus time using double axes (FAS) - Two calculation methods (2009 and 2012 formulae).
14.2.28	Mean (+/- SE) plots eGFR/total plasma oxalate versus time using double axes (FAS) - Two calculation methods (2009 and 2012 formulae).
14.2.29	Descriptive statistics kidney stone events (FAS), based on AE and US, respectively
14.2.30	Incidence rate of kidney stone events (FAS), based on AE and US, respectively
14.2.31	Descriptive statistics stone frequency by subgroup (FAS)
14.2.32	Descriptive statistics US data (FAS)
14.2.33	Statistical analysis stone frequency, based on AE and US, respectively
14.2.34	Descriptive statistics STE parameters (FAS) – raw and cfb
14.2.35	Descriptive statistics traditional echocardiography parameters (FAS) – raw and cfb
14.2.36	Descriptive statistics main STE/TE parameters (LVEF/GLS) by subgroup (FAS) – raw and cfb
14.2.37	Mean (+/-SE) main STE/TE parameters (LVEF/GLS) versus time plot, per treatment (FAS)
14.2.38	Individual main STE/TE parameters (LVEF/GLS) versus time plot, per treatment (FAS)

14.2.39	Descriptive statistics free plasma oxalate (FAS) – raw and cfb
14.2.40	Descriptive statistics free plasma oxalate by subgroup (FAS) – raw and cfb
14.2.41	Mean (+/-SE) free plasma oxalate versus time plot, per treatment (FAS). Similar plot for change from baseline.
14.2.42	Individual free plasma oxalate versus time plot (FAS). Similar plot for change from baseline.
14.2.43	Spaghetti plots per treatment group of the actual free plasma oxalate values (FAS)
14.2.44	Descriptive statistics urinary oxalate excretion (FAS) – raw and cfb - both centrifuged and non-centrifuged urinary oxalate
14.2.45	Descriptive statistics urinary oxalate excretion by subgroup (FAS) – raw and cfb - only non-centrifuged urinary oxalate
14.2.46	Descriptive statistics grade of nephrocalcinosis (FAS), left and right kidney separately. Including shifts classifications, unilateral and bilateral
14.2.47	Descriptive statistics O.formigenes - (FAS) – raw and cfb
14.2.48	Descriptive statistics O.formigenes by subgroup (FAS)
14.2.49	Descriptive statistics QoL SF36V2 (FAS) – raw and cfb
14.2.50	Descriptive statistics QoL CHQ/PF50 (FAS) – raw and cfb
14.2.51	Renal markers urine including excretion values (FAS) – raw and cfb
14.2.52	Renal markers blood (FAS) – raw and cfb
14.3 Safety Data Summary figures and tables – 14.3.1 Displays of Adverse Events	
14.3.1.1	Overview of treatment emergent events
14.3.1.2	Treatment emergent adverse events, by SOC and PT
14.3.1.3	Treatment emergent adverse events by SOC, PT and grade
14.3.1.4	Related treatment emergent adverse events by SOC and PT
14.3.1.5	Related treatment emergent adverse events by SOC, PT and grade
14.3.1.6	Treatment emergent adverse events leading to premature treatment/study discontinuation, by SOC and PT
14.3.1.7	Serious treatment emergent AEs, by SOC and PT
14.3.1.8	Serious and related treatment emergent AEs, by SOC and PT

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 subject)	
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

12.4 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 (16.2.5.2 and 16.2.5.3), study day will be calculated and added, following the calculation rule as stated in the addendum mentioned in section 11.1.

Listing number	**Contents of listing**
16.2.1 Discontinued subjects	
16.2.1.1	Inclusion/exclusion criteria – deviations
16.2.1.2	Subject disposition and study completion
16.2.2 Protocol deviations	
16.2.2	Protocol deviations
16.2.3 Subjects excluded from the efficacy analysis	
16.2.3	Subjects excluded from the efficacy analysis

16.2.4 Demographic data	
16.2.4.1	Demographics
16.2.4.2	Medical history
16.2.5 Compliance and/or drug concentration data	
16.2.5.1	Randomization information, based on ePHex
16.2.5.2	Dosing information and drug accountability
16.2.5.3	Study visits
16.2.6 Individual efficacy response data	
16.2.6.1	Individual eGFR values, presenting the raw data and the adjusted formulae values.
16.2.6.2	Individual plasma oxalate values (total plasma oxalate, free plasma oxalate)
16.2.6.3	Individual ultrasound data (US)
16.2.6.4	Individual myocardial function (ECHO) – Speckle tracking/ Traditional echocardiography
16.2.6.5	Individual number of *O.formigenes* in stool
16.2.6.6	Individual Quality of Life - SF36V2
16.2.6.7	Individual Quality of Life - CHQ/PF50
16.2.6.8	Individual renal markers - Urine, including calculated excretion values for 24h urine assessments
16.2.6.9	Individual renal markers – Blood.
16.2.7 Adverse event listings	
16.2.7.1	Adverse events
16.2.7.2	SAEs/deaths
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 subject	
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	General comments from all datasets