FINAL ABBREVIATED CLINICAL STUDY REPORT

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 test drug/investigational product:	*Oxalobacter formigenes* (Oxabact® [OC5])
Indication(s) studied:	Primary hyperoxaluria
Study design:	Open-label, multicentre
Name of Sponsor:	OxThera Intellectual Property AB
Protocol identification:	OC5-OL-02
Development phase of study:	3 – Follow-up
Study initiation date:	14 March 2019
Date of early study termination:	14 July 2021
Study completion date:	Not applicable
Sponsor reference of the report:	OC5-OL-02
Principal investigator:	Name: Dr. Gesa Schalk Affiliation: Kindernierenzentrum, Bonn, Germany
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Date of the report:	17 September 2021

This study was performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.

SYNOPSIS

Name of sponsor/company: OxThera Intellectual Property AB		**(*For National Authority use only*)**
Name of finished product: Oxabact® (OC5)		
Name of active ingredient: *Oxalobacter formigenes* strain HC-1		

Title of study:

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

Investigators:

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Publication (reference):

Not applicable

Studied period (years):	**Phase of development:**
2019-2021	3 – Follow-up

Objectives:

Primary:

To evaluate the efficacy of Oxabact following 2 years continued open-label treatment in subjects who have previously participated in and completed the (randomised, placebo-controlled, double-blind) OC5-DB-02 study.

Secondary:

To obtain additional safety data from 2 years continued open-label treatment with Oxabact.

Methodology:

This was an open-label, single-arm, multicentre study to evaluate the efficacy and safety of the long-term use (2 years of open-label Oxabact treatment) of Oxabact (*Oxalobacter formigenes* [*O. formigenes*]) to stabilise/improve kidney function, stabilise/reduce plasma oxalate (Pox) concentration, and to reduce oxalate deposits in primary hyperoxaluria (PH) patients. Included subjects were the subjects who underwent treatment (administered either Oxabact or placebo) in the OC5-DB-02 study and consented to participate in the OC5-OL-02 study. At the start of the OC5-DB-02 study, subjects had maintained renal function but with an estimated glomerular filtration rate (eGFR) below the lower limit of the normal ranges (< 90 ml/min/1.73 m^2) and a total Pox

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concentration ≥ 10 µmol/L at baseline. These criteria were not retested for inclusion into the OC5-OL-02 study protocol. Following the OC5-DB-02 study, all subjects (including those on placebo in the OC5-DB-02 study) were to be treated with Oxabact for 2 years (24 months) in the OC5-OL-02 study.

Number of subjects (planned and analysed):

Approximately 16 subjects were planned, and 22 subjects were enrolled (group receiving Oxabact in study OC5-DB-02 and study OC5-OL-02 [O-O group]: 11 subjects, group receiving placebo in study OC5-DB-02 and Oxabact in study OC5-OL-02 [P-O group]: 11 subjects). One subject completed the study, for 18 subjects the study was terminated early.

Diagnosis and main criteria for inclusion:

Patients were eligible for participation in this study if they had signed informed consent (as applicable for the age of the subject) and had participated in and completed the OC5-DB-02 study.

Test product, dose and mode of administration, batch number:

Oxabact, in gastro-resistant (enteric-coated) size 4 gelatine capsules, each containing ≥ 10^9 to < 5^{10} colony-forming units (CFU) of lyophilised *O. formigenes* (strain HC-1) for oral administration.

Batch numbers: 94806-1709-63, 94806-1711-59, 94806-1805-21, 94806-1805-22, 94806-1806-26, 94806-1806-27, 94806-1901-28, 94806-1901-29, 94806-1905-09, 94806-1905-10, 94806-1911-55, 94806-1911-57, 94806-2004-36, 94806-2004-37, 94806-2008-02 and 94806-2008-03.

Duration of treatment:

Subjects were treated with Oxabact for 24 months.

Criteria for evaluation:

As this is an abbreviated report, not all planned endpoints were analysed. Below, the endpoints that were analysed are presented. Raw data on endpoints not reported here are available upon request.

Primary efficacy endpoint:

- Change from baseline (CfB) in kidney function (eGFR) after 12 and 24 months of open-label Oxabact treatment.

Key Secondary endpoints:

- CfB in total Pox after 12 and 24 months of open-label Oxabact treatment.
- Frequency of kidney stones events after 12 and 24 months of open-label Oxabact treatment. Kidney stone events were defined as:
  - Subject- or investigator-reported symptoms, or
  - Kidney stone passage or removals, or
  - Increase in number of kidney stones assessed by ultrasound.

Other efficacy endpoints:

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- CfB in urinary oxalate (Uox) excretion.

Safety:

- Adverse events (AEs).
- Laboratory safety measurements (haematology, clinical chemistry and urinalysis).
- Vital Signs.

Statistical methods:

General:

The efficacy population (Full Analysis Set [FAS]) included all subjects enrolled into the OC5-OL-02 study who received at least one dose of open-label Oxabact treatment and had at least one efficacy assessment during the OC5-OL-02 study. The safety population (Safety Analysis Set [SAF]) included all subjects enrolled into the OC5-OL-02 study who received at least one dose of open-label Oxabact treatment.

Efficacy summaries included data from both the OC5-DB-02 and OC5-OL-02 studies based on the FAS, and were presented both for the overall population and according to the randomisation in the OC5-DB-02 study. Safety summaries included the safety data reported in the OC5-OL-02 study and were based on the SAF.

Baseline was defined as the baseline of the OC5-DB-02 study. A second baseline was calculated for the subjects randomised to placebo during the OC5-DB-02 study as the last measurement prior to open-label Oxabact treatment. All data evaluations were descriptive in nature due to the limited sample size. The primary analysis in the OC5-OL-02 was done using all available data and was limited to summaries and listings.

Efficacy:

Descriptive statistics were provided for:

- eGFR and CfB in eGFR using the OC5-DB-02 baseline (FAS)
- eGFR and CfB in eGFR using the OC5-OL-02 baseline for the P-O group (FAS)
- Total Pox and CfB in total Pox concentrations using the OC5-DB-02 baseline (FAS)
- Total Pox and CfB in total Pox concentrations using the OC5-OL-02 baseline for the P-O group (FAS)
- Kidney stone events based on AE and ultrasound (FAS)
- Non-centrifuged Uox excretion and CfB in Uox excretion using the OC5-DB-02 baseline (FAS)
- Non-centrifuged Uox excretion and CfB in Uox excretion using the OC5-OL-02 baseline for the P-O group (FAS)
- Centrifuged Uox excretion and CfB in Uox excretion using the OC5-DB-02 baseline (FAS)
- Centrifuged Uox excretion and CfB in Uox excretion using the OC5-OL-02 baseline for the P-O group (FAS)

Safety:

AEs were categorised by System Organ Class (SOC) and Preferred Term (PT) from Medical Dictionary for Regulatory Activities (MedDRA). Safety data were summarised for the overall study population SAF and according to the actual treatment received in the OC5-DB-02 study, O–O and P–O. AEs were considered to be treatment-emergent if the event occured on or after the first administration of open-label Oxabact treatment and up to 4 weeks after the last dose date of open-label Oxabact treatment of the OC5-OL-02 study. The incidence of AEs was summarised using descriptive statistics, by SOC, PT and severity grade (Common Terminology Criteria for

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Adverse Events [CTCAE]) for all treatment-emergent, serious, treatment-related, and serious treatment-related AEs. A listing of AEs was provided. Furthermore, listings of laboratory safety (haematology, clinical chemistry and urinalysis) and vital signs were presented.

Summary – conclusions:

Study subjects:

A total of 22 subjects from study OC5-DB-02 were enrolled in study OC5-OL-02 (O-O group: 11 subjects, P-O group: 11 subjects). Eighteen subjects (81.8%) discontinued due to study termination by sponsor, 1 subject completed the study.

Efficacy results:

The study was terminated early, and thus only a portion of subjects are included in the analysis below.

At Month 12, the mean CfB in eGFR in the O-O group was -5.840 mL/min/1.73 m^2, while it was -1.715 mL/min/1.73 m^2 in the P-O group using the OC5-DB-02 baseline and -0.994 mL/min/1.73 m^2 in the P-O group using the OC5-OL-02 baseline. Mean CfB in eGFR for the 2 groups combined was, -3.777 mL/min/1.73 m^2 using the OC5-DB-02 baseline and -3.417 mL/min/1.73 m^2 using the OC5-OL-02 baseline. At Month 24, only one subject remained in the study.

At Month 12, mean CfB in total Pox in the O-O group was 14.0 µmol/L, while it was 2.7 µmol/L in the P-O group using the OC5-DB-02 baseline and 0.4 µmol/L using the OC5-OL-02 baseline. Mean CfB in Pox for all subjects at Month 12 was, 8.3 µmol/L using the OC5-DB-02 baseline and 7.2 µmol/L using the OC5-OL-02 baseline. Several subjects in the O-O group (e.g., subjects 3401-04, 3401-05 and 3401-06) showed substantial increases in total Pox during the OC5-OL-02 study. Upon detailed review of these subjects, antibiotic use as treatment for AEs/SAEs of suspected kidney stone events may represent a possible explanation for the observed rise in Pox.

At Month 12, 2 subjects (10.5%) reported 1 kidney stone each (1 in the O-O group and 1 in the P-O group), as measured by ultrasound, while 1 further subject (5.3%) reported 2 kidney stones (in the P-O group). Four subjects (21.1%, 2 per treatment group) experienced 1 (suspected) stone event over the period between baseline and Month 12, as based on AEs. In the period between baseline and Month 12 two (suspected) stone events were experienced by 1 subject (5.3%) in the O-O group, 4 (suspected) stone events were experienced by 1 subject (5.3%) in the O-O group, and 7 (suspected) stone events were experienced by 1 subject (5.3%) in the P-O group, as based on AEs. At Month 24, no kidney stones, as measured by ultrasound, were reported for the 2 remaining subjects. Three subjects (15.8%) experienced 1 (suspected) stone event over the course of the study (1 in the O-O group and 2 in the P-O group), as based on AEs, while 1 further subject (5.3%, in the P-O group) experienced 2 (suspected) stone events over the course of the study.

At Month 12, mean CfB in Uox in the O-O group was -0.634 mmol/24hr/1.73 m^2, while it was -0.331 mmol/24hr/1.73 m^2 in the P-O group using the OC5-DB-02 baseline and -0.037 mmol/24hr/1.73 m^2 using the OC5-OL-02 baseline. Mean CfB in Uox for the 2 groups combined at Month 12 was -0.452 mmol/24hr/1.73 m^2 using OC5-DB-02 baseline and -0.276 mmol/24hr/1.73 m^2 using the OC5-OL-02 baseline.

Safety results:

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A total of 78 TEAEs were reported in 15 subjects. Most TEAEs were considered to be unrelated to the study treatment and mild to moderate in intensity. Of these TEAEs, 12 were considered to be at least possibly related to study treatment. Seven TEAEs, reported in 4 subjects, were serious. No related treatment-emergent SAEs nor fatal AEs were observed during the study. There were no AEs that lead to study or treatment discontinuation.

The most frequently reported AEs were in the SOCs infections and infestations (45.5%), gastrointestinal disorders (31.8%), renal and urinary disorders (27.3%), general disorders and administration site conditions (18.2%), musculoskeletal and connective tissue disorders (18.2%), nervous system disorders (18.2%), investigations (13.6%) and skin and subcutaneous tissue disorders (13.6%). AEs in the SOC renal and urinary disorders were reported in 6 subjects (18.2%, 4 events) Most AEs were considered to be Grade 1 (mild, 63.6%) to Grade 2 (moderate, 36.4%) in intensity.

No notable findings, except for a low eosinophil count in 4 subjects, were seen in laboratory measurements (including haematology, clinical chemistry and urinalysis), nor in vital signs measurements.

Overall, treatment with Oxabact was considered safe and well tolerated.

Conclusion:

The current study is an open-label single-arm treatment extension study to evaluate the long-term efficacy and safety of Oxabact for patients with PH who completed study OC5-DB-02.

Twenty-two subjects from study OC5-DB-02 were enrolled into the OC5-OL-02 study. Eighteen subjects (81.8%) discontinued due to study termination by sponsor. Two subjects (9.1%) discontinued due to physician decision and one subject (4.5%) discontinued due to another reason. One subject (4.5%) completed the study.

PH is an extremely rare orphan disease with very small patient numbers available for clinical studies. Therefore, this study included a small population, with 5 centres recruiting only 1 subject. In addition, the clinical, biochemical, and genetic heterogeneity of PH I is large, with some patients presenting in infancy with renal failure and others experiencing only occasional passage of stones in adult life with maintained renal function. This further complicates interpretation of the data. Moreover, given the early termination of the study, subjects only reached a mean of 10.5 months of observation instead of the planned 24 months, which limits interpretability of the data. It is worth noting that several subjects in the O-O group (e.g., subjects 3401-04, 3401-05 and 3401-06) showed substantial increases in total Pox during the OC5-OL-02 study. Upon detailed review of these subjects, antibiotic use as treatment for AEs/SAEs of suspected stone events may represent a possible explanation for the observed rise in Pox.

Overall Oxabact was safe and well tolerated. Most TEAEs were considered to be unrelated to the study treatment and Grade 1 (mild) to Grade 2 (moderate) in intensity. No related treatment-emergent SAEs nor fatal AEs were observed during the study. No subjects were withdrawn due to AEs.

Date of the report: 17 Sep 2021

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LIST OF ABBREVIATIONS

ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMC	Academic Medical Center, Amsterdam, the Netherlands
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CaOx	Calcium oxalate
CfB	Change from baseline
CFU	Colony-forming units
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	Coronavirus disease
CRP	C-reactive protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
(e)CRF	(Electronic) Case report form
eGFR	Estimated glomerular filtration rate
EU	European Union
FAS	Full analysis set
GC-MSD	Gas chromatography with mass selective detection
GCP	Good Clinical Practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
n	Number of subjects
N	Number of subjects included in the analysis population
O. formigenes	*Oxalobacter formigenes*

O-O group	Group receiving Oxabact in study OC5-DB-02 and study OC5-OL-02
P-O group	Group receiving placebo in study OC5-DB-02 and Oxabact in study OC5-OL-02
PH	Primary hyperoxaluria
Pox	Plasma oxalate
PT	Preferred term
QoL	Quality of life
SAE	Serious adverse event
SAF	Safety population
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
STE	Speckle tracking echocardiography
SUSAR	Suspected unexpected serious adverse reaction
TE	Traditional echocardiography
TEAE	Treatment-emergent adverse event
UK	United Kingdom
Uox	Urinary oxalate
USA	United States of America
WHO-UMC	World Health Organization – Uppsala Monitoring Centre

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan: Description

This study was terminated early. Therefore, an abbreviated Clinical Study Report (CSR) was produced. Raw data on all endpoints (efficacy and safety) detailed in the OC5-OL-02 Protocol are available upon request.

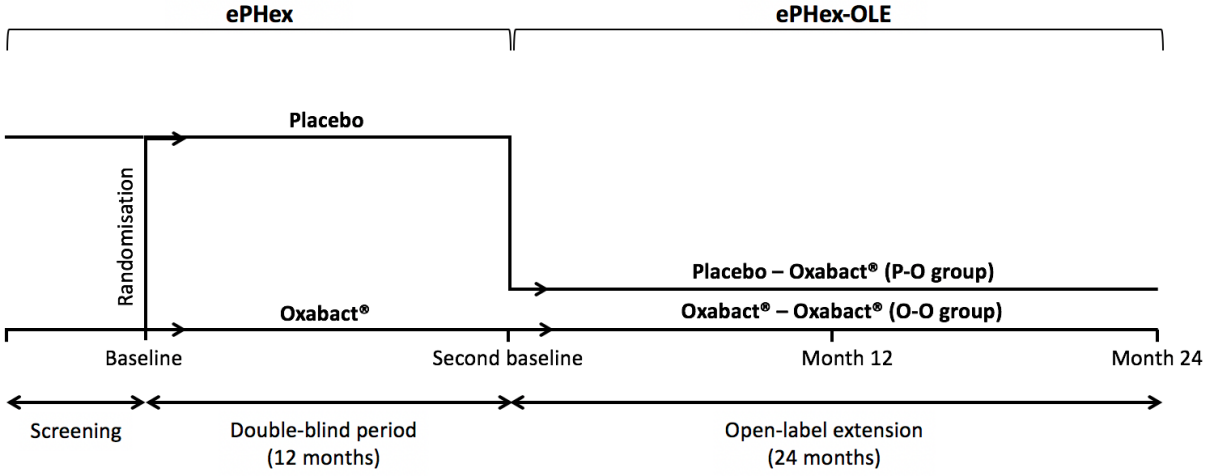
This study was an open-label, single-arm, multicentre study to evaluate the efficacy and safety of the long-term use (2 years of open-label treatment) of Oxabact (*Oxalobacter formigenes* [*O. formigenes*)] to stabilise/improve kidney function, stabilise/reduce plasma oxalate (Pox) concentration, and to reduce oxalate deposits in primary hyperoxaluria (PH) patients.

Included subjects were the subjects who underwent treatment (administered either Oxabact or placebo) in study OC5-DB-02 and consented to participate in the OC5-OL-02 study. At the start of the OC5-DB-02 study, subjects had maintained renal function but with an estimated glomerular filtration rate (eGFR) below the lower limit of the normal ranges (< 90 ml/min/1.73 m^2) and a total Pox concentration ≥ 10 µmol/L at baseline. These criteria were not retested for inclusion into the OC5-OL-02 study protocol.

Following the OC5-DB-02 study, subjects were to be treated with Oxabact for 2 years (24 months) in the OC5-OL-02 study. The study consisted of 2 groups: those randomised to placebo in study OC5-DB-02 and treated with Oxabact in the current study (P-O group), and those randomised to Oxabact in study OC5-DB-02 and continuing this treatment in the current study (O-O group).

Baseline, unless otherwise stated, was defined as the baseline of the OC5-DB-02 study. An additional baseline, specific to the OC5-OL-02 study (Figure 1), was calculated at the start of the OC5-OL-02 study prior to open-label Oxabact treatment for subjects who were randomised to placebo in the OC5-DB-02 (P-O group). This additional baseline is considered the second baseline.

Figure 1: Study Design of the OC5-DB-02 Study and the OC5-OL-02 Study



Abbreviations: ePHex=OC5-DB-02 study; ePHex-OLE=OC5-OL-02 study; P-O group=group receiving placebo in study OC5-DB-02 and Oxabact in study OC5-OL-02; O-O group: group receiving Oxabact in study OC5-DB-02 and study OC5-OL-02.

Visit 0 (Month 0; start of the OC5-OL-02 study) was the same as the last visit (Week 52) in the OC5-DB-02 study. A second baseline value for all parameters was recorded. Provided there was a seamless transition from the OC5-DB-02 study to the OC5-OL-02 study, second baseline values (Visit 0 for the OC5-OL-02 study) corresponded to the respective value taken from the last visit in the OC5-DB-02 study (Week 52). For operational reasons, baseline values for echocardiography and renal ultrasound data were derived from the assessment at Week 48 in the OC5-DB-02 study. If there was no seamless transition (delay > 1 month) from the last dose of study treatment in the OC5-DB-02 study, a new clinic Visit 0 (Month 0) took place with applicable second baseline measurements for all parameters prior to first dose of open-label Oxabact and further assessments followed according to schedule of assessments.

During the study period, subjects had visits every 2 to 3 months, i.e., at Months 2, 4, 6, 8, 10, 12, 15, 18, 21 and 24. During these visits, Pox and safety labs were taken. Subjects were asked to provide stool samples 4 times (Months 6, 12, 18 and 24) and 24-hour urine 5 times (Months 4, 8, 12, 18 and 24). In addition, subjects provided a post-treatment follow-up stool sample 4 weeks after intake of last dose of study treatment. Echocardiography (speckle tracking echocardiography [STE] and traditional echocardiography [TE]) was assessed 4 times (Months 6, 12, 18 and 24). Ultrasound of the kidney was done 2 times (Months 12 and 24). Quality of Life (QoL) was evaluated by a questionnaire during Months 6, 12, 18 and 24 (Table 1). Information on kidney stone events and related symptoms was captured throughout the study.

Adverse events (AEs) and concomitant medication were monitored throughout the study.

Safety evaluation included physical examination, vital signs and safety labs. Monitoring of AEs, concomitant medication and compliance with the administration of study treatment was performed

at each visit. In addition, there was a 4-week safety follow-up after intake of the last dose of study treatment. Furthermore, questions on kidney stone events and related symptoms were asked throughout the study.

The clinical study protocol and its amendments, and a sample case report form (CRF), are provided in, respectively Appendix 16.1.1 and Appendix 16.1.2.

9.2 Selection of Study Population

Patients were eligible for participation in this study if they had signed informed consent (as applicable for the age of the subject) and had participated in and completed the OC5-DB-02 study.

9.3 Efficacy and Safety Variables

9.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

The assessments and their timings are summarised in Table 1.

Table 1: Schedule of Assessments

Study period	Treatment (24 months)											Post-treatment follow-up (4 weeks)[h,i]
Month	0[a]	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[b]	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	
Inc/excl criteria	X											
Vital signs	X	X	X	X	X	X	X	X	X	X	X	
Physical examination	X	X	X	X	X	X	X	X	X	X	X	
Co-medication	X	X	X	X	X	X	X	X	X	X	X	X
eGFR[c]	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[d]	X	X	X	X	X	X	X	X	X	X	X	X
Echocardiography[e]	X			X			X		X		X	
Ultrasound	X						X				X	
Safety laboratory tests[f]	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	
QoL	X			X			X		X		X	
Pregnancy test[g]	X										X	
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	

Abbreviations: AKI=acute kidney injury; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; excl=exclusion; inc=inclusion; NA=not applicable; PH=primary hyperoxaluria; QoL=quality of life; STE=speckle tracking echocardiography; TE=Traditional echocardiography.

a. Month 0 (Visit 0; reference time point) was the same as the last visit (Week 52) in study OC5-DB-02. For STE/TE and ultrasound measurements, Week 48 measurements in OC5-DB-02 were considered Month 0. If there was no seamless transition (delay > 1 month) from study OC5-DB-02, a new clinic Visit 0 (Month 0) took

place with applicable measurements prior to first dose of open-label Oxabact and further assessments followed according to schedule.

b. Visit window during treatment period ±7 days. In the case of an AKI occurring close to a scheduled visit, the visit was rescheduled to ensure that the AKI did not adversely affect values (especially for eGFR).

c. As determined by the Schwartz equation for children (age < 18 years), and CKD-EPI equation for adults (age ≥ 18 years) based on serum creatinine.

d. Kidney stone events and related symptoms were captured at every visit, including events in between visits.

e. Echocardiography was to be done within ± 2 weeks of the clinic visit at Months 6, 12 and 18. If the images failed quality criteria, the examination was repeated within 4 weeks.

f. Safety laboratory measured included blood and urine sampling.

g. If applicable.

h. A post-treatment safety follow-up was performed as a telephone call (the safety follow-up period covered a duration of 4 weeks and the telephone call was made maximum 3 working days after the safety follow-up period).

i. Subjects provided a post-treatment follow-up stool sample 4 weeks (plus maximum 3 working days) after intake of last dose of study treatment.

9.3.1.1 Efficacy Measurements

As this is an abbreviated report, not all planned endpoints were analysed. Below, more details are presented on the endpoints that were analysed. For details on other planned efficacy measurements, please see the OC5-OL-02 Protocol Section 10. Raw data on endpoints not reported here are available upon request.

The **primary efficacy endpoint** of the study was change from baseline (CfB) in kidney function (eGFR) after 12 and 24 months of open-label Oxabact treatment.

The **key secondary efficacy endpoints** of the study were:

- CfB in total Pox concentration after 12 and 24 months of open-label Oxabact treatment.
- Frequency of kidney stones events after 12 and 24 months of open-label Oxabact treatment. Kidney stone events are defined as:
  - Subject- or investigator-reported symptoms, or
  - Kidney stone passages or removals, or
  - Increase in the number of kidney stones as assessed by ultrasound.

Other efficacy endpoints included:

- CfB in urinary oxalate (Uox) excretion.

For several analyses in this study, data from study OC5-DB-02 was integrated. Efficacy summaries included pooled data from both the OC5-DB-02 and OC5-OL-02 studies, based on the full analysis set (FAS), and were presented both for the overall population and according to the randomisation ('as randomised') as applied in the OC5-DB-02 study. Safety summaries included the safety data reported in the OC5-OL-02 study only and were based on the safety population (SAF). Where applicable, presentations were done per visit. Baseline data such as demographics, eligibility and

prior medication was collected for OC5-OL-02 and was presented without inclusion of OC5-DB-02 data. Where presentations were done per treatment group, this was as randomised during the OC5-DB-02 study and these were presented as (O-O) and (P–O), respectively, where O=Oxabact and P=Placebo. Historical data as collected during OC5-DB-02 study was not included and presented again. Lastly, CfB values were calculated with 2 different baselines: the baseline as per study OC5-DB-02, and as collected for study OC5-OL-02 as supportive (only for the subjects that received placebo during OC5-DB-02).

Baseline was generally defined as the last non-missing planned and valid measurement/assessment before first dose of study treatment, unless otherwise specified. Unscheduled measurements were excluded as baseline value, unless otherwise specified. CfB was calculated as the value at a specific time point minus the value at baseline. The following definitions were used to define the baseline measurement:

- The first baseline was defined as the baseline of the OC5-DB-02 study, which was specified per the OC5-DB-02 statistical analysis plan (SAP) for each of the assessments.

- A second baseline was defined as the last planned measurement prior to open-label treatment in the OC5-OL-02 study. This may be the last visit of the OC5-DB-02 study or Visit 0 of the OC5-OL-02 study, depending on whether the subject had a seamless transfer from one study to the other. If a Visit 0 result was available for a subject, it was assumed the subject did not have a seamless transfer and that value was used as the second baseline. This second baseline was only applicable for subjects that received placebo treatment during the OC5-DB-02 study.

9.3.1.1.1 Kidney Function Parameters

The primary efficacy endpoint was the CfB in kidney function (eGFR) after 12 and 24 months of open-label Oxabact treatment. The primary endpoint was presented using the FAS population.

The primary analysis used the baseline of the OC5-DB-02 study as primary baseline, while other time points presented were considered as supportive. A second analysis was done using the baseline of OC5-OL-02 study as baseline for the OC5-DB-02 placebo subjects. CfB in kidney function (eGFR) was calculated at each visit, using the 2 different baselines. Summary statistics of the measurements were presented on a per-visit basis. Presentations were per treatment group and overall.

Change in kidney function was evaluated based on eGFR calculation using the creatinine-based "Bedside Schwartz" 2009 equation for children (< 18 years of age) and the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) for adults (≥ 18 years of age). Subjects who turned 18 years of age during the study period were continuously evaluated using the Schwartz equation, i.e., the equation used at baseline was kept throughout the study.

Samples for eGFR calculations were processed at the clinical site and analysed at a central laboratory (Cerba Research). Each site was provided with kits and supplies for collection, processing and shipping of blood samples for determination of serum creatinine and cystatin C. Complete instructions for the collection, processing, storage and shipping of sample were provided in the site manual.

9.3.1.1.2 Plasma Oxalate

Samples for Pox were collected during each clinical visit, as specified in Table 1.

Samples for total Pox were processed at the clinical site and analysed at the Academic Medical Center, Amsterdam, the Netherlands (AMC). Each site was provided with kits and supplies for collection, processing and shipping of blood samples for determination of total Pox. Complete instructions for the collection, processing, storage and shipping of sample were provided in the site manual. Total Pox was measured using isotope dilution gas chromatography with mass selective detection (GC-MSD).

9.3.1.1.3 Kidney Stone Events

Kidney stones are hard deposits made of minerals and salts that form inside the kidneys. Most kidney stones (approximately 80%) are calcium stones, usually in the form of calcium oxalate (CaOx). Stones can also be composed of struvite, uric acid or cystine. Stones vary in size and shape, ranging from a few mms up to 40 mms. Subjects can typically pass the smaller stones in the urine. However, larger stones (e.g., > 10 mm) may require lithotripsy and surgical or endoscopic removal. A kidney stone may not cause symptoms until it moves around within the kidney, passes into the ureter, bladder, or urethra.

Stone events

In this study, kidney stone events were defined as follows:

- A kidney stone event was defined as the occurrence of one or more of the following symptoms due to a kidney stone that may or may not require medical intervention:
  - Abdominal, flank or groin pain, sometimes associated with nausea and vomiting.
  - Macroscopic haematuria (visible blood in the urine).
  - Urinary tract infection (cloudy or foul-smelling urine, more frequent and/or painful urination than normal, persistent need to urinate and/or urinating small amounts).
- Kidney stone events could also be defined by subject-reported stone passage or by medical procedures to remove identified kidney stones (e.g., lithotripsy, endoscopy, surgery).
  - An increase in the number of kidney stones as seen in a kidney ultrasound were also be defined as a stone event.

Duration between stone events: if symptoms of a stone event occurred simultaneously or close in time to another kidney stone event symptom, the investigator decided whether or not this was reported as the same stone event or as a new, separate stone event.

Assessments of stone events were collected by ultrasound (renal imaging) as well as subject-reported stone events or symptoms of events (see definition above). Ultrasound of the kidneys was done at the site hospital. Images were sent for central reading in a blinded manner. The examination was standardised and described in detail in the imaging manual. Ultrasound images were evaluated to determine the number of kidney stones. Historical kidney stone events

and related symptoms for the past 3 years preceding entry into study OC5-DB-02 were recorded at screening for OC5-DB-02. During the baseline and treatment period, information was collected concerning occurrence of self-reported kidney stone events and related symptoms. This information was captured by recording it in the Adverse Event eCRF at each visit throughout the study.

Frequency of kidney stone events was evaluated after 12 and 24 months of treatment.

9.3.1.1.4 Twenty-four Hour Urine Samples

Twenty-four-hour urine samples for analysis of Uox were taken at the subject´s home and sent to central laboratory TDL, London, United Kingdom (UK). Uox was analysed with a colorimetric enzymatic assay using oxalate oxidase, which oxidises oxalate to carbon dioxide and hydrogen peroxide. The analyses were described in more detail in the lab manual.

9.3.1.2 Safety Measurements

The following safety parameters were evaluated:

- AEs.
- Safety laboratory measurements (haematology, clinical chemistry and urinalysis).
- Vital signs.

Definitions

An adverse event (AE) was defined as any untoward medical occurrence in a patient or clinical study subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE could thus be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. AEs therefore included, e.g., worsening of a pre-existing illness and any injury or accident. This refers also to symptoms due to a pre-existing allergy, e.g., if seasonal allergy symptoms were within what was normally experienced, they were not be recorded as AEs. If the symptoms were worse than what was normally experienced, then they were to be recorded as AEs.

An AE does not include:

- Symptoms of the underlying disease (with the exception of kidney stone events) that might be reasonably anticipated to come and go, or progress, given the nature and severity of the condition. However, if the progression of the disease escalates and results in hospitalisation, is life-threatening, or is fatal, then progression of the disease should be reported as an AE of serious nature;
- Expected variations in severity of disease signs and symptoms that have previously been reported in the subject's medical history;
- Pre-planned medical or surgical procedures (e.g., surgery, tooth extraction, or transfusion) (Note: The condition that leads to the procedure may be an AE);

- Overdose of study treatment without any clinical signs or symptoms; or
- Clinically significant laboratory values. If abnormal laboratory values are accompanied by abnormal signs or symptoms, the signs or symptoms are considered an AE and should be recorded as such. Abnormal laboratory values associated with the underlying disease are not an AE, unless the values unexpectedly worsen.

An AE was classified as an adverse drug reaction (ADR) if further analyses prove that the event was caused, or partially caused, by the investigational product. This includes interaction, overdosing, abuse and development of addiction. Expected ADRs are also possible events due to the substance class of the investigational product, expected from analogue conclusions or theoretical considerations related to toxicological, pharmacological or kinetic characteristics.

An unexpected adverse reaction is any adverse reaction, the specificity or severity of which is not specified in the current the Investigator's Brochure. [1]

A serious adverse event (SAE) is one that suggests a significant hazard, contraindication, side effect or precaution that results in:

- the subject's death
- is life-threatening*
- requires inpatient hospitalisation or prolongation of existing hospitalisation†
- persistent or significant disability/incapacity; or
- congenital anomaly/birth defect
- corresponds to another important medical event as determined by the investigator.

A suspected unexpected serious adverse reaction (SUSAR) is an adverse drug reaction, the nature or severity of which is not consistent with the Investigator's Brochure. [1]

Relationship to Study Treatment

The following relationships to study treatment were used in the study (in accordance with the World Health Organization – Uppsala Monitoring Centre (WHO-UMC) Causality Categories, Table 2). Events classified as certain, probable/likely or possible were considered related to study treatment.

* Life threatening means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that the use or continued use of the investigational product would result in the patient's death. Life threatening does not mean that, had an AE occurred in a more severe form, it might have caused death.

† Hospitalization requires overnight stay at the hospital. Outpatient treatment in an emergency room is not itself a SAE. Hospital admission and/or operations planned before or during a study are not considered SAEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Table 2: WHO-UMC Causality Categories

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable / Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal is clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional / Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable / Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

Intensity Criteria

The intensity of AEs was recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)‡.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self care ADL§.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

If the intensity/grade changed within 24 hours, the maximum intensity was to be recorded. If the intensity changed over a longer period of time, the changes were to be recorded in the eCRF.

Recording of Adverse Events

Each subject was questioned about AEs at each visit and following the initiation of study treatment. The question asked was "Since your last clinic visit have you had any health problems?" The information could also be obtained from signs and symptoms observed during examinations, observed by the study personnel, or spontaneous reports from the subjects or by laboratory results.

The investigator recorded in the eCRF all directly observed AEs, all AEs per responses to the above open question, and all AEs spontaneously reported by the subject during the study.

The investigator recorded all AEs by:

- Description of event (recorded in standard medical terminology and avoiding abbreviations).
- Start and end date.
- Intensity (Grade 1 - 5).
- Seriousness (serious or not serious, according to definition).
- Causal relationship (certain, probable/likely, possible, unlikely, conditional/unclassified, unassessable/unclassifiable).
- Action taken (none, treatment required, study treatment interrupted, subject withdrawn, other).
- Outcome of the AE (recovered, recovered with sequelae, death, not recovered).

‡ Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

§ Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Reporting of Adverse Events

AE reporting started at the initiation of study treatment and continued during the course of the study. Thus, reported AEs included all AEs that occurred during the treatment phase and all AEs that occurred during the safety follow-up period. Spontaneously reported events by study subjects in between planned visits were also reported. ADRs that were unresolved at the time of the last follow-up visit were followed until resolution or, if persistent, were assessed as either "chronic" or "stable". AEs were reported for all subjects.

Unresolved AEs that occurred and were recorded during the OC5-DB-02 study were not recorded separately in the OC5-OL-02 study unless they changed in severity grade, seriousness or relatedness. Furthermore, any medical events (including stone events) that occurred in the time interval after the safety follow-up in the OC5-DB-02 study but before the first intake of study treatment in the OC5-OL-02 study, were reported in the Medical History page for the OC5-OL-02 study.

All AEs were reported in the eCRF. SAEs were reported by the investigator to the ProductLife Pharmacovigilance Department via the form in the eCRF or via fax or email. The initial SAE form (provided in the eCRF and in the Investigational Site File) was to be completed within 24 hours of awareness of the event. All SAEs were to be reported, regardless of their causality. After receipt of the initial report, the ProductLife Pharmacovigilance Department forwarded all information to the sponsor within 24 hours. The ProductLife Pharmacovigilance Department worked with the sponsor to review the information received and contacted the site to request any missing information/amendments needed. Follow-up information obtained by the investigator was also forwarded to the medical monitor within 24 hours.

The investigator submitted copies of SAE reports to the independent ethics committee (IEC) as required by local regulations. All serious and unexpected AEs were reported to the European authorities as per regulations.

ADRs, which were unresolved at the end of the safety follow-up period were followed by the investigator until the event has resolved or, if persistent, had been assessed as chronic or stable. This data was not recorded in the eCRF.

All SUSARs that were possibly, probably/likely or certainly related were subject to expedited reporting to regulatory authorities, ethic committees and participating Investigators in accordance with local requirements in force and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice (GCP) and the European Union (EU) Directive 2001/20/EC. The ProductLife Group Pharmacovigilance Department was responsible for ensuring expedited reporting of SUSARs.

Laboratory Safety Measurements

The laboratory safety tests at the timepoints indicated in Table 1 included:

- Haematology: erythrocytes, leucocytes, lymphocytes, monocytes, neutrophils, basophils, eosinophils, platelets, haemoglobin, haematocrit, mean corpuscular volume (MCV), and mean corpuscular haemoglobin concentration (MCHC).

- Chemistry: blood urea nitrogen (BUN), electrolytes (Na^+, K^+, Mg^{++}, Ca^{++}, $HCO3^-$, Cl^-), glucose, albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and total protein.
- Pregnancy test for women of childbearing potential at baseline and Month 24.
- Random urine (urinalysis): protein, glucose, pH.

Laboratory parameters for safety assessment from haematology and chemistry were assessed at the central laboratory. Urinalysis was done at the local laboratory at each clinic. Laboratory safety tests were performed at every clinic visit.

9.3.1.3 Vital Sign Measurements

Vital sign measurements included temperature and blood pressure (systolic and diastolic in a supine position), heart rate, respiratory rate (assessed after 5 minutes resting in a supine position) weight and height. Weight was measured using a calibrated scale with the subject lightly clothed and shoes off. Height was measured using a calibrated wall mounted stadiometer. Height was measured at each visit for all subjects where the Schwartz formula was used to determine eGFR. This applied to children (subjects < 18 years of age at the screening visit of the OC5-DB-02 study) and to any subject who turned 18 years of age during either the OC5-DB-02 study period or the OC5-OL-02 study period. For subjects who were adults at the screening visit of the OC5-DB-02 study, height for the OC5-OL-02 study was retrieved from the OC5-DB-02 database using the subject ID.

9.4 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.4.1 Statistical and Analytical Plans

The statistical analysis was done under the authority of the sponsor. For details, please refer to the SAP located in Appendix 16.1.9.

9.5 Changes in the Conduct of the Study or Planned Analyses

9.5.1 Changes in the Conduct of the Study

There has been 1 amendment to the protocol. The Revision History on page 2 in the final protocol (version 2, dated 27 April 2020), located in Appendix 16.1.1, provides a detailed description of the protocol amendment.

9.5.2 Changes in the Planned Analyses

Analyses for an abbreviated report were performed as described in the SAP in Appendix 16.1.9, with addition of the following:

- Instead of only using the randomisation information from OC5-DB-02, also the baseline data of OC5-DB-02 was used for certain assessments.
- No coronavirus disease (COVID-19) risk check was performed, due to the limited amount of data available for this analysis.
- Data for 3 subjects was mapped from an early withdrawal visit to a study visit as per Table 3:

Table 3: Withdrawal Data Mapping

Subject	Assessment Date of Withdrawal Visit	Timing in Study	Assessment	Closest Planned Visit	Mapping Decision
3201-04	09-Jul-2020	Approximately Month 6	eGFR, POX	Month 6	Month 6
3201-04	09-Jul-2020	Approximately Month 6	U24H	Month 6	Month 8
3201-03	14-Jun-2020	Approximately Month 6	U24H	Month 8	Month 8
3201-04	03-Jul-2020	Approximately Month 6	Ultrasound	Month 12	Month 12
3201-03	19-Jun-2021	Approximately Month 6	Ultrasound	Month 12	Month 12
4901-02	16-Feb-2021	Approximately Month 20	Ultrasound	Month 24	Month 24

10 STUDY PATIENTS

10.1 Disposition of Patients

For details on subject disposition, please refer to Table 14.1.1.1 and Listing 16.2.1.1. For details on demographics and other baseline characteristics, please refer to Table 14.1.2.1 (FAS), Table 14.1.2.2 (SAF) and Listing 16.2.4.1. For measurements of treatment compliance/drug accountability, please refer to Listing 16.2.5.1.

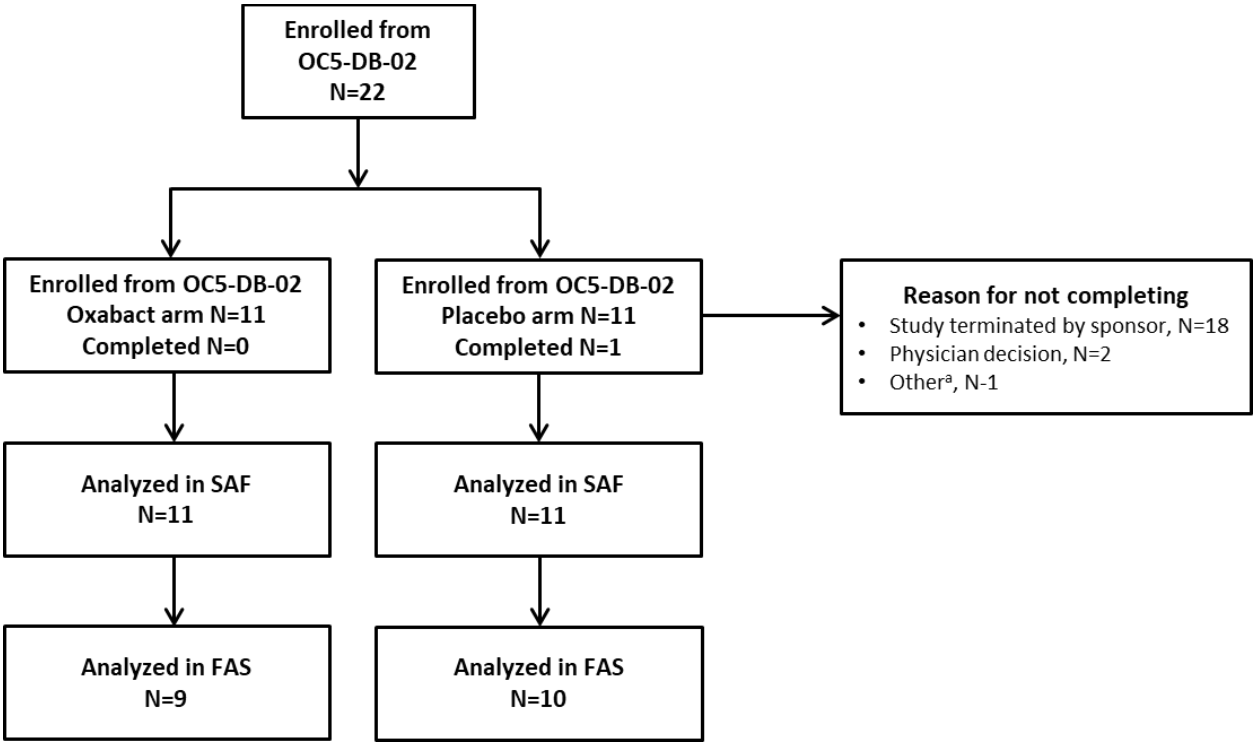
The study was initiated at 5 European sites (Liège, Belgium; Bonn, Germany; Barcelona, Spain; Nottingham, UK; London, UK), 1 USA site (Nashville, TN, United States of America [USA]) and 3 African sites (Sfax, Tunisia; Tunis, Tunisia; Sousse, Tunisia). All sites enrolled subjects (2 subjects at the CHU de Liège, Liège, Belgium; 6 subjects at the Kindernierenzentrum, Bonn, Germany; 7 subjects at the Vall d'Hebron Hospital, Barcelona, Spain; 1 subject at Hôpital Hédi Chaker, Sfax, Tunisia; 1 subject at the Hôpital Charles Nicolle, Tunis, Tunisia; 2 subjects at the Hôpital Universitaire Sahloul, Sousse, Tunisia; 1 subject at the Vanderbilt University Medical Center, Nashville, TN, USA; 1 subject at the Nottingham Children's Hospital, Nottingham, UK; and 1 subject at the Royal Free Hospital, London, UK). The disposition of subjects is summarised in Table 4. A graphical display is provided in Figure 2.

A total of 22 subjects from study OC5-DB-02 were enrolled in study OC5-OL-02 (O-O group: 11subjects, P-O group: 11 subjects). Eighteen subjects (81.8%) discontinued due to study termination by sponsor. Two subjects (9.1%) discontinued due to physician decision and 1 subject (4.5%) discontinued due to another reason ("subject wanted to be treated with Lumarisan"[**]). One subject (4.5%) completed the study. Subjects were followed-up from their first dose of study medication in OC5-OL-02 for a mean of 10.5 months (standard deviation [SD]: 7.35 months). Two subjects (9.1%) had their last study visit at Month 0, 4 subjects (18.2%) had their last study visit at Month 2, 2 subjects (9.1%) had their last study visit at Month 4, 1 subject (4.5%) had their last study visit at Month 6, 5 subjects (22.7%) had their last study visit at Month 12, 2 subjects (9.1%) had their last study visit at Month 15, 2 (9.1%) subjects had their last study visit at Month 18, and 1 subject (4.5%) had their last study visit at Month 24 (Table 14.1.1.1). Last study visits for the 3 subjects who withdrew early were mapped to, respectively, Month 6, Month 12 and Month 24.

Disposition data are listed by subject in Appendix 16.2.1.1.

[**] The term "Lumarisan" is per the database, most likely referring to the generic medication 'Lumasiran'.

Figure 2: Disposition of Subjects



N indicates the number of subjects included in the analysis population.
Abbreviations: FAS=full analysis set; SAF=safety population.

[a] The reason stated was: "subject wanted to be treated with Lumarisan". Source: Table 14.1.1.1 and Appendix 16.2.1.1.

Table 4: Disposition of Subjects

	O-O group (N=11)	P-O group (N=11)	Total (N=22)
Number of subjects			
Treated	11	11	22
Completed (n [%])	-	1 (9.1%)	1 (4.5%)
Reason for not completing			
Study terminated by sponsor, (n [%])	10 (90.9%)	8 (72.7%)	18 (81.8%)
Physician decision, (n [%])	-	2 (18.2%)	2 (9.1%)
Other[a], (n [%])	1 (9.1%)	-	1 (4.5%)
SAF	11	11	22
FAS	9	10	19

Abbreviations: O-O=group receiving Oxabact in study OC5-DB-02 and study OC5-OL-02; P-O=group receiving placebo in study OC5-DB-02 and Oxabact in study OC5-OL-02; FAS=full analysis set; NA=not applicable; SAF=safety population.
[a] The reason stated was: "subject wanted to be treated with Lumarisan"
Source: Table 14.1.1.1.
N indicates the number of subjects included in the analysis population.

11 EFFICACY EVALUATION

11.1 Efficacy Results

For descriptive statistics of eGFR and CfB in eGFR using the OC5-DB-02 baseline (FAS), please see Table 5 and Table 14.2.1.1. For descriptive statistics of eGFR and CfB in eGFR using the OC5-OL-02 baseline for the P-O arm (FAS), please see Table 5 and Table 14.2.1.2. For individual results, please see Listing 16.2.6.1.

For descriptive statistics of total Pox and CfB in total Pox concentrations using the OC5-DB-02 baseline (FAS), please see Table 6 and Table 14.2.2.1. For descriptive statistics of total Pox and CfB in total Pox concentrations using the OC5-OL-02 baseline for the P-O group (FAS), please see Table 6 and Table 14.2.2.2. For individual results, please see Listing 16.2.6.2.

For descriptive statistics of kidney stone events based on AE and ultrasound (FAS), please see Table 7 and Table 14.2.3.1. For individual results, please see Listing 16.2.6.3 and Listing 16.2.7.1.

For descriptive statistics of non-centrifuged Uox excretion and CfB in Uox excretion using the OC5-DB-02 baseline (FAS), please see Table 14.2.4.1.1. For descriptive statistics of non-centrifuged Uox excretion and CfB in Uox excretion using the OC5-OL-02 baseline for the P-O group (FAS), please see Table 14.2.4.1.2. For descriptive statistics of centrifuged Uox excretion and CfB in Uox excretion using the OC5-DB-02 baseline (FAS), please see Table 14.2.4.2.1. For descriptive statistics of centrifuged Uox excretion and CfB in Uox excretion using the OC5-OL-02 baseline for the P-O group (FAS), please see Table 14.2.4.2.2. For individual results, please see Listing 16.2.6.4.

11.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint of the study was CfB in kidney function (eGFR) after 12 and 24 months of open-label Oxabact treatment. The primary analysis on eGFR was based on the 2009 creatinine-based “Bedside Schwartz” equation (for children below 18 years of age) and 2009 creatinine-based CKD-EPI equation for adults. Summary statistics for eGFR and CfB over time are provided in Table 5.

At Month 12, mean CfB in eGFR in the O-O group was -5.840 mL/min/1.73 m^2, while it was -1.715 mL/min/1.73 m^2 in the P-O group using the OC5-DB-02 baseline and -0.994 mL/min/1.73 m^2 using the OC5-OL-02 baseline. Mean CfB in eGFR for the 2 groups combined was-3.777 mL/min/1.73 m^2 using the OC5-DB-02 baseline and -3.417 mL/min/1.73 m^2 using the OC5-OL-02 baseline. At Month 24, only one subject remained in the study. The O-O group generally shows a negative CfB over time, while this is not apparent for the P-O group, using either the OC5-DB-02 or the OC5-OL-02 baseline for this group. When the groups are examined together, no pattern is discernible, using either the OC5-DB-02 or the OC5-OL-02 baseline for the P-O group.

Table 5: Change from Baseline in eGFR (mL/min/1.73 m^2) using the OC5-DB-02 and the OC5-OL-02 Baseline - FAS

Month	OC5-DB-02 Baseline[a]			OC5-OL-02 Baseline[b]	
	O-O group N=9	P-O group N=10	Total N=19	P-O group N=10	Total N=19
n	7	9	16	9	16
Month 2 (mean [SD])	-1.568 (3.129)	-2.200 (9.001)	-1.923 (6.873)	-1.218 (5.255)	-1.371 (4.321)
n	7	6	13	6	13
Month 4 (mean [SD])	-3.246 (8.158)	-1.623 (8.916)	-2.497 (8.192)	-2.932 (9.889)	-3.101 (8.605)
n	6	7	13	7	13
Month 6 (mean [SD])	-9.547 (14.017)	5.573 (11.432)	-1.405 (14.449)	3.083 (8.614)	-2.746 (12.724)
n	4	2	6	2	6
Month 8 (mean [SD])	-9.293 (13.633)	9.187 (25.824)	-3.133 (18.329)	7.825 (4.264)	-3.587 (13.903)
n	2	2	4	2	4
Month 10 (mean [SD])	1.798 (3.312)	5.892 (20.895)	3.845 (12.441)	4.530 (0.665)	3.164 (2.508)
n	5	5	10	5	10
Month 12 (mean [SD])	-5.840 (11.672)	-1.715 (13.046)	-3.777 (11.871)	-0.994 (6.778)	-3.417 (9.354)
n	3	2	5	2	5
Month 15 (mean [SD])	-5.862 (8.954)	3.552 (22.323)	-2.097 (13.829)	2.190 (0.764)	-2.641 (7.725)
n	-	2	2	2	2
Month 18 (mean [SD])	-	4.147 (22.076)	4.147 (22.076)	2.785 (0.516)	2.785 (0.516)
n	1	1	2	1	2
Month 21 (mean [SD])	-12.193 (-)	13.267 (-)	0.537 (18.003)	-3.340 (-)	-7.767 (6.260)
n	-	1	1	1	1
Month 24 (mean [SD])	-	9.497 (-)	9.497 (-)	-7.110 (-)	-7.110 (-)

Abbreviations: CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; CRF=case report form; eGFR=estimated glomerular filtration rate; FAS=full analysis set; n=number of subjects; O-O=group receiving Oxabact in study OC5-DB-02 and study OC5-OL-02; P-O=group receiving placebo in study OC5-DB-02 and Oxabact in study OC5-OL-02; SD=standard deviation.

[a] Baseline is the average of the available measurements at Visits 1, 2 and 3 of the OC5-DB-02 study.

[b] For subjects in the O-O group, baseline is the average of the available measurements at Visits 1, 2 and 3 of the OC5-DB-02 study. For subjects in the P-O group, baseline is the last result before the start of treatment in the OC5-OL-02 study.

Source: Table 14.2.1.1 and Table 14.2.1.2.

eGFR (mL/min/1.73 m^2) is as collected on the CRF, i.e., calculated using Creatinine-based "Bedside Schwartz" for children and the CKD-EPI 2009 Equations for adults. No correction was done for emerging adults (subjects aged between 18 and 23 years).

N indicates the number of subjects included in the analysis population.

11.1.2 Key Secondary Efficacy Endpoints

11.1.2.1 Change from Baseline in Total Pox

The first key secondary efficacy endpoint of the study was CfB in total Pox concentration after 12 and 24 months of open-label Oxabact treatment. Summary statistics for CfB in total Pox are provided in Table 6. At Month 12, mean CfB in total Pox in the O-O group was 14.0 µmol/L, while it was 2.7 µmol/L in the P-O group using the OC5-DB-02 baseline and 0.4 µmol/L using the OC5-OL-02 baseline. Mean CfB in Pox for the 2 groups combined at Month 12 was 8.3 µmol/L using the OC5-DB-02 baseline and 7.2 µmol/L using the OC5-OL-02 baseline. At Month 24, only one subject remained in the study. The O-O group shows a CfB that is positive over time, as does the P-O group when using the OC5-DB-02 baseline. When using the OC5-OL-02 baseline, no pattern is discernible for the P-O group. In total, subjects show a positive CfB over time, using either the OC5-DB-02 or the OC5-OL-02 baseline for the P-O subjects.

Several subjects in the O-O group (e.g., subjects 3401-04, 3401-05 and 3401-06) showed substantial increases in total Pox during the OC5-OL-02 study. Upon detailed review of these subjects, antibiotic use as treatment for AEs/SAEs of suspected stone events may represent a possible explanation for the observed rise in Pox (see Section 12.3.2).

Table 6: Change from Baseline in Total Pox (µmol/L) using the OC5-DB-02 and the OC5-OL-02 Baseline - FAS

Month	OC5-DB-02 Baseline[a]			OC5-OL-02 Baseline[b]	
	O-O group N=9	P-O group N=10	Total N=19	P-O group N=10	Total N=19
n	7	9	16	9	16
Month 2 (mean [SD])	2.1 (7.2)	4.0 (5.8)	3.2 (6.3)	1.1 (7.0)	1.6 (6.8)
n	7	6	13	6	13
Month 4 (mean [SD])	4.0 (8.5)	3.8 (3.9)	3.9 (6.5)	1.3 (6.1)	2.8 (7.3)
n	6	7	13	7	13
Month 6 (mean [SD])	6.1 (10.0)	3.7 (6.1)	4.8 (7.9)	2.3 (4.8)	4.1 (7.6)
n	4	2	6	2	6
Month 8 (mean [SD])	13.8 (14.6)	0.0 (3.3)	9.2 (13.5)	-5.5 (0.7)	7.4 (15.1)
n	5	2	7	2	7
Month 10 (mean [SD])	5.4 (6.0)	-3.0 (4.7)	3.0 (6.7)	-8.5 (2.1)	1.4 (8.4)
n	5	5	10	5	10
Month 12 (mean [SD])	14.0 (15.7)	2.7 (7.0)	8.3 (12.9)	0.4 (5.7)	7.2 (13.2)
n	3	2	5	2	5
Month 15 (mean [SD])	12.3 (9.6)	9.5 (11.1)	11.2 (8.9)	4.0 (8.5)	9.0 (9.2)
n	-	2	2	2	2
Month 18 (mean [SD])	-	26.0 (27.3)	26.0 (27.3)	20.5 (24.7)	20.5 (24.7)
n	1	1	2	1	2
Month 21 (mean [SD])	-2.3 (-)	7.7 (-)	2.7 (7.1)	4.0 (-)	0.8 (4.5)
n	-	1	1	1	1
Month 24 (mean [SD])	-	-3.3 (-)	-3.3 (-)	-7.0 (-)	-7.0 (-)

Abbreviations: FAS=full analysis set; n=number of subjects; O-O=group receiving Oxabact in study OC5-DB-02 and study OC5-OL-02; P-O=group receiving placebo in study OC5-DB-02 and Oxabact in study OC5-OL-02; Pox=plasma oxalate; SD=standard deviation.
[a] Baseline is the average of the available measurements at Visits 1, 2 and 3 of the OC5-DB-02 study.
[b] For subjects in the O-O group, baseline is the average of the available measurements at Visits 1, 2 and 3 of the OC5-DB-02 study. For subjects in the P-O group, baseline is the last result before the start of treatment in the OC5-OL-02 study.
Source: Table 14.2.2.1 and Table 14.2.2.2.
N indicates the number of subjects included in the analysis population.

11.1.2.2 Frequency of Kidney Stone Events

The second key secondary efficacy endpoint of the study was the frequency of kidney stones events after 12 and 24 months of open-label Oxabact treatment. Summary statistics for on-treatment kidney stone events over time are provided in Table 7. At baseline, as measured by ultrasound, 2 subjects (10.5%, both in the P-O group) reported 1 kidney stone, 4 subjects (21.1%) reported 2 kidney stones (1 in the O-O group and 3 in the P-O group), and 1 subject (5.3%) reported 4 kidney stones (in the P-O group). At Month 12, 2 subjects (10.5%) reported 1 kidney stone each (1 in the O-O group and 1 in the P-O group), as measured by ultrasound, while 1 further subject (5.3%) reported 2 kidney stones (in the P-O group). Four subjects (21.1%, 2 per treatment group) experienced 1 (suspected) stone event over the period between baseline and Month 12, as based on AEs. In the period between baseline and Month 12 two (suspected) stone events were experienced by 1 subject (5.3%) in the O-O group, 4 (suspected) stone events were experienced by 1 subject (5.3%) in the O-O group, and 7 (suspected) stone events were experienced by 1 subject (5.3%) in the P-O group, as based on AEs. At Month 24, no kidney stones, as measured by ultrasound, were reported for the 2 remaining subjects. Three subjects (15.8%) experienced

1 (suspected) stone event over the course of the study (1 in the O-O group and 2 in the P-O group), as based on AEs, while 1 further subject (5.3%, in the P-O group) experienced 2 (suspected) stone events over the course of the study.

Table 7: On-Treatment Kidney Stone Events - FAS

Month/Variable		O-O group N=9	P-O group N=10	Total N=19
Baseline				
Total number of stones (ultrasound)[a]	0	8 (88.9%)	4 (40.0%)	12 (63.2%)
	1	-	2 (20.0%)	2 (10.5%)
	2	1 (11.1%)	3 (30.0%)	4 (21.1%)
	4	-	1 (10.0%)	1 (5.3%)
Month 12				
Total number of stones (ultrasound)[b]	0	5 (55.6%)	3 (30.0%)	8 (42.1%)
	1	1 (11.1%)	1 (10.0%)	2 (10.5%)
	2	-	1 (10.0%)	1 (5.3%)
Total number of (suspected) stone events (AE)[c]				
	0	5 (55.6%)	7 (70.0%)	12 (63.2%)
	1	2 (22.2%)	2 (20.0%)	4 (21.1%)
	2	1 (11.1%)	-	1 (5.3%)
	4	1 (11.1%)	-	1 (5.3%)
	7	-	1 (10.0%)	1 (5.3%)
Month 24				
Total number of stones (ultrasound)[d]	0	1 (11.1%)	1 (10.0%)	2 (10.5%)
Total number of (suspected) stone events (AE)[e]	0	5 (55.6%)	2 (20.0%)	7 (36.8%)
	1	1 (11.1%)	2 (20.0%)	3 (15.8%)
	2	-	1 (10.0%)	1 (5.3%)

Abbreviations: AE=adverse event; FAS=full analysis set; O-O=group receiving Oxabact in study OC5-DB-02 and study OC5-OL-02; P-O=group receiving placebo in study OC5-DB-02 and Oxabact in study OC5-OL-02.
[a] Assessed at Month 0. This was the same visit as the last visit (Week 52) in study OC5-DB-02. If there was no seamless transition (delay > 1 month) from study OC5-DB-02, a new clinic Visit 0 (Month 0) took place.
[b] Assessed at Month 12.
[c] Assessing the period from baseline up to and including Month 12.
[d] Assessed at Month 24.
[e] Assessing the period from > Month 12 to ≤ Month 24.
Source: Table 14.2.3.1.
N indicates the number of subjects included in the analysis population.
The denominator used to calculate the percentages is based on the FAS and not the number of subjects with results recorded.
Because the study was prematurely closed, the ultrasound data are very incomplete. Post-baseline results were only collected for 13 subjects and only 2 subjects had results recorded after Month 12.
For 2 subjects the number of stones in the left kidney could not be determined at the Month 12 visit and the total number of stones is regarded as missing, meaning that we have Month 12 results for only 11 subjects. One of these subjects, 3201-03, did not have any stones in the right kidney, the other subject, 4401-01, had 2 stones in the right kidney.

11.1.3 Other Efficacy Endpoints

11.1.3.1 Change from Baseline in Uox Excretion

CfB in Uox excretion was measured as an 'other efficacy endpoint'. Summary statistics for CfB in Uox excretion are provided in Table 8, Table 14.2.4.1.1 and Table 14.2.4.1.2. At Month 12, mean CfB in Uox in the O-O group was -0.634 mmol/24hr/1.73 m^2, while it was -0.331 mmol/24hr/1.73 m^2 in the P-O group using the OC5-DB-02 baseline and -0.037 mmol/24hr/1.73 m^2 using the OC5-OL-02 baseline. Mean CfB in Uox for the 2 groups combined at Month 12 was -0.452 mmol/24hr/1.73 m^2 using OC5-DB-02 baseline and -0.276 mmol/24hr/1.73 m^2 using the OC5-OL-02 baseline. At Month 24, only 1 subject remained in the study. The O-O group shows a CfB that is negative over time, as does the P-O group when using the OC5-DB-02 baseline, meaning that Uox excretion values tended to decrease over time. When using the OC5-OL-02 baseline, no pattern is discernible for the P-O group. In total, subjects show a negative CfB over time, using either the OC5-DB-02 or the OC5-OL-02 baseline for the P-O subjects.

Table 8: Change from Baseline in Non-Centrifuged Uox Excretion (mmol/24hr/1.73 m^2) using the OC5-DB-02 and the OC5-OL-02 Baseline - FAS

Month	OC5-DB-02 Baseline[a]			OC5-OL-02 Baseline[b]	
	O-O group N=9	P-O group N=10	Total N=19	P-O group N=10	Total N=19
n	6	6	12	6	12
Month 4 (mean [SD])	0.767 (1.415)	0.594 (1.448)	0.680 (1.368)	0.607 (1.132)	0.687 (1.224)
n	3	5	8	5	8
Month 8 (mean [SD])	-0.593 (0.191)	0.437 (1.349)	0.050 (1.155)	0.355 (0.742)	-0.001 (0.753)
n	2	3	5	3	5
Month 12 (mean [SD])	-0.634 (0.423)	-0.331 (0.938)	-0.452 (0.716)	-0.037 (0.463)	-0.276 (0.509)
n	1	2	3	2	3
Month 18 (mean [SD])	-0.753 (-)	-0.453 (0.735)	-0.553 (0.548)	0.067 (0.346)	-0.207 (0.533)
n	1	1	2	1	2
Month 24 (mean [SD])	-0.233 (-)	-0.212 (-)	-0.223 (0.015)	0.582 (-)	0.174 (0.576)

Abbreviations: FAS=full analysis set; n=number of subjects; O-O=group receiving Oxabact in study OC5-DB-02 and study OC5-OL-02; P-O=group receiving placebo in study OC5-DB-02 and Oxabact in study OC5-OL-02; SD=standard deviation; Uox=urinary oxalate.
[a] Baseline is the average of the available measurements at Visits 1, 2 and 3 of the OC5-DB-02 study.
[b] For subjects in the O-O group, baseline is the average of the available measurements at Visits 1, 2 and 3 of the OC5-DB-02 study. For subjects in the P-O group, baseline is the last result before the start of treatment in the OC5-OL-02 study.
Source: Table 14.2.4.1.1 and Table 14.2.4.1.2.
N indicates the number of subjects included in the analysis population.

11.2 Efficacy Conclusions

Due to the limited study data as a consequence of early study termination by the sponsor, conclusions on efficacy cannot be drawn.

12 SAFETY EVALUATION

12.1 Extent of Exposure

In total, 22 subjects were included in this study, all subjects received at least one dose of the study treatment. Subjects were to take 1 dose twice daily. The median treatment duration, calculated using the OC5-OL-02 baseline, was 12.8 months in the O-O group and 6.3 months in the P-O group (Table 14.1.1.1).

12.2 Adverse Events

12.2.1 Brief Summary of Adverse Events

An overview of AEs is presented in Table 9.

A total of 78 treatment-emergent adverse events (TEAEs) were reported in 15 subjects. Most TEAEs were considered to be unrelated to the study treatment and Grade 1 (mild) to Grade 2 (moderate) in intensity. Of these TEAEs, 12 were considered to be at least possibly related to study treatment. Seven TEAEs, reported in 4 subjects, were serious. None of the serious TEAEs were considered at least possibly related to study treatment. No subject discontinued the study or the treatment due to an AE. No deaths were reported during the study. No SUSARs were reported during this study.

Table 9: Overview of Treatment-Emergent Adverse Events - SAF

	O-O group (N=11)		P-O group (N=11)		Total (N=22)	
	n (%)	m	n (%)	m	n (%)	m
Any AE	7 (63.6%)	37	8 (72.7%)	41	15 (68.2%)	78
Any related AE	2 (18.2%)	6	3 (27.3%)	6	5 (22.7%)	12
AEs by severity[a]						
Grade 1	7 (63.6%)	19	7 (63.6%)	20	14 (63.6%)	39
Grade 2	4 (36.4%)	13	4 (36.4%)	19	8 (36.4%)	32
Grade 3	2 (18.2%)	5	1 (9.1%)	2	3 (13.6%)	7
Any SAE	3 (27.3%)	5	1 (9.1%)	2	4 (18.2%)	7
Any related SAE	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
AEs leading to treatment discontinuation	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
AEs leading to study discontinuation	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
AEs leading to death	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0

Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; m=number of events; n=number of subjects; O-O=group receiving Oxabact in study OC5-DB-02 and study OC5-OL-02; P-O=group receiving placebo in study OC5-DB-02 and Oxabact in study OC5-OL-02; SAE=serious adverse event; SAF=safety population.
[a] Refer to Section 9.3.1.2 for grade definitions. CTCAE grading version 4.0 was used.
Source: Table 14.3.1.1.1.
N indicates the number of subjects included in the analysis population.
In case relationship to treatment was missing, the AE was considered to be related to study treatment.
An AE is classified as possibly, probably/likely or certainly related is considered to be related to study treatment.
In case intensity is missing, the AE was considered to be severe.

12.2.2 Display of Adverse Events

Summary tables of all AEs and AEs by relationship are provided in Section 14 (Table 14.3.1.2.1 and Table 14.3.1.3.1, respectively). A descriptive summary of the data is provided in Section 12.2.3.

12.2.3 Analysis of Adverse Events

In total, 15 subjects (68.2%) experienced a total of 78 TEAEs.

Details of the AEs per system organ class (SOC), preferred term (PT) and study group are provided in Table 14.3.1.2.1. The most common AEs per SOC (occurring in 10% or more of subjects in the study) were as follows:

- Infections and infestations (19 events in 10 subjects [45.5%])
- Gastrointestinal disorders (13 events in 7 subjects [31.8%])
- Renal and urinary disorders (15 events in 6 subjects [27.3%])
- General disorders and administration site conditions (4 events in 4 subjects [18.2%])
- Musculoskeletal and connective tissue disorders (7 events in 4 subjects [18.2%])
- Nervous system disorders (4 events in 4 subjects [18.2%])
- Investigations (4 events in 3 subjects [13.6%])
- Skin and subcutaneous tissue disorders (4 events in 3 subjects [13.6%])

AEs that occurred in more than 2 subjects (> 10%) were COVID-19 (3 subjects [13.6%]), urinary tract infection (3 subjects [13.6%]), nephrolithiasis (4 subjects [18.2%]), pyrexia (4 subjects [18.2%]), flank pain (3 subjects [13.6%]), and headache (4 subjects [18.2%], Table 14.3.1.2.1). The number of events was too small for analysis. An impact of COVID-19 infection on study endpoints is not ruled out, as subject 3401-01 showed an increase in Pox which coincided with a COVID-19 infection (Appendix 16.2.6.2) and subject 4901-05 showed an increase in eGFR which coincided with a COVID-19 infection (Appendix 16.2.6.1).

Related TEAEs are presented in Table 10 by SOC, PT and treatment group.

Most AEs were considered to be unrelated to the study treatment. In total, 12 related AEs (as determined by the investigator) occurred in 5 subjects (22.7%). Seven related AEs in 4 subjects occurred in the SOC gastrointestinal disorders (1 event of abdominal pain, 3 events of abdominal pain upper and 3 events of diarrhoea). Two related AEs in 2 subjects occurred in the SOC renal and urinary disorders (1 event of haematuria and 1 event of renal pain). Additionally, 1 subject experienced 2 related AEs of flank pain (SOC: musculoskeletal and connective tissue disorders) and 2 subjects experienced a related AE of, respectively, alopecia and onychoclasis (SOC: skin and subcutaneous tissue disorders; Table 10).

Table 10: Related Treatment-Emergent Adverse Events - SAF

	O-O group (N=11)		P-O group (N=11)		Total (N=22)	
System Organ Class Preferred Term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Any AE	2 (18.2%)	6	3 (27.3%)	6	5 (22.7%)	12
Gastrointestinal disorders	2 (18.2%)	5	2 (18.2%)	2	4 (18.2%)	7
Abdominal pain	-	-	1 (9.1%)	1	1 (4.5%)	1
Abdominal pain upper	2 (18.2%)	3	-	-	2 (9.1%)	3
Diarrhoea	1 (9.1%)	2	1 (9.1%)	1	2 (9.1%)	3
Renal and urinary disorders	-	-	2 (18.2%)	2	2 (9.1%)	2
Haematuria	-	-	1 (9.1%)	1	1 (4.5%)	1
Renal pain	-	-	1 (9.1%)	1	1 (4.5%)	1
Musculoskeletal and connective tissue disorders	1 (9.1%)	1	-	-	1 (4.5%)	1
Flank pain	1 (9.1%)	1	-	-	1 (4.5%)	1
Skin and subcutaneous tissue disorders	-	-	1 (9.1%)	2	1 (4.5%)	2
Alopecia	-	-	1 (9.1%)	1	1 (4.5%)	1
Onychoclasis	-	-	1 (9.1%)	1	1 (4.5%)	1

Abbreviations: AE=adverse event; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of subjects; O-O=group receiving Oxabact in study OC5-DB-02 and study OC5-OL-02; P-O=group receiving placebo in study OC5-DB-02 and Oxabact in study OC5-OL-02; SAF=safety population.
Source: Table 14.3.1.3.1.
N indicates the number of subjects included in the analysis population.
In case relationship to treatment was missing, the AE was considered to be related to study treatment.
An AE classified as possibly, probably/likely or certainly related was considered to be related to study treatment.
In case intensity was missing, the AE is considered to be severe.
AEs were coded according to MedDRA version 24.0.

Most AEs were considered to be Grade 1 (mild, 63.6%) to Grade 2 (moderate, 36.4%) in intensity. Grade 1 and Grade 2 TEAEs occurrence in the same number of subjects in both treatment groups (Grade 1: 7 subjects [63.6%], Grade 2: 4 subjects [36.4%]). In total, 3 subjects (13.6%) experienced an AE of Grade 3 (severe) severity. None of the subjects experienced Grade 4 (life-threatening) or Grade 5 (death) TEAEs (Table 9).

12.2.4 Listing of Adverse Events by Patient

AEs are listed by subject in Appendix 16.2.7.1.

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

5.1.1.1 Deaths

No subjects died during the study (Table 14.3.1.1.1).

5.1.1.2 Other Serious Adverse Events

Table 11 details the serious TEAEs, by SOC, PT and treatment group. SAEs are listed by subject in Table 12. None of these serious events were considered to be related to study treatment.

In total, 7 treatment-emergent SAEs were reported in 4 subjects [18.2%] (all not Black or African American), with most SAEs belonging to the SOC renal and urinary disorders (3 SAEs in 2 subjects). An SAE of nephrolithiasis and an SAE of renal colic were reported in the same subject and 1 further SAE of nephrolithiasis was reported for another subject. Additionally, in the SOC infections and infestations, 1 SAE of pyelonephritis and 1 SAE of pyelonephritis acute was reported in the same subject. The SAE pyrexia was reported in 1 subject (SOC: general disorders and administration site conditions) and the SAE burns second degree was reported in 1 subject (SOC: injury, poisoning and procedural complications). None of the SAEs were considered related to the study treatment.

SAEs are listed by subject in Appendix 16.2.7.1.

Table 11: Serious Adverse Events by SOC and PT - SAF

	O-O group (N=11)		P-O group (N=11)		Total (N=22)	
System Organ Class Preferred Term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Any SAE	3 (27.3%)	5	1 (9.1%)	2	4 (18.2%)	7
Renal and urinary disorders	1 (9.1%)	1	1 (9.1%)	2	2 (9.1%)	3
Nephrolithiasis	1 (9.1%)	1	1 (9.1%)	1	2 (9.1%)	2
Renal colic	-	-	1 (9.1%)	1	1 (4.5%)	1
General disorders and administration site conditions	1 (9.1%)	1	-	-	1 (4.5%)	1
Pyrexia	1 (9.1%)	1	-	-	1 (4.5%)	1
Infections and infestations	1 (9.1%)	2	-	-	1 (4.5%)	2
Pyelonephritis	1 (9.1%)	1	-	-	1 (4.5%)	1
Pyelonephritis acute	1 (9.1%)	1	-	-	1 (4.5%)	1
Injury, poisoning and procedural complications	1 (9.1%)	1	-	-	1 (4.5%)	1
Burns second degree	1 (9.1%)	1	-	-	1 (4.5%)	1

Abbreviations: SAE=serious adverse event; SAF=safety population; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of subjects; O-O=group receiving Oxabact in study OC5-DB-02 and study OC5-OL-02; PT=preferred term; P-O=group receiving placebo in study OC5-DB-02 and Oxabact in study OC5-OL-02; SOC=system organ class.
Source: Table 14.3.1.4.1.
N indicates the number of subjects included in the analysis population.
AEs were coded according to MedDRA version 24.0.

Table 12: Serious Treatment-Emergent Adverse Events by Subject - SAF

Subject ID	Age[a]/Sex	Reported Term	Preferred Term	SOC	Start Date (Y/M/D)	Stop Date (Y/M/D)	Intensity	Related	Action Study Treatment	Outcome
O-O group										
3401-04	9/Male	superficial 2nd degree burn in the genital area (3% of body surface)	Burns second degree	Injury, poisoning and procedural complications	2020-08-18	2020-08-31	Grade 2 (Moderate)	Unlikely	Treatment required	Recovered
3401-05	10/Female	Acute pyelonephritis	Pyelonephritis acute	Infections and infestations	2020-08-20	2020-08-25	Grade 2 (Moderate)	Unlikely	Treatment required	Recovered
		Fever	Pyrexia	General disorders and administration site conditions	2021-01-12	2021-01-15	Grade 2 (Moderate)	Unlikely	Treatment required	Recovered
		Presumably Acute phyelonefritis not confirmed (urine culture negative)	Pyelonephritis	Infections and infestations	2021-01-13	2021-01-18	Grade 3 (Severe)	Unlikely	Treatment required	Recovered
3401-06	15/Female	Renal Calculi	Nephrolithiasis	Renal and urinary disorders	2021-02-05	2021-05-20	Grade 3 (Severe)	Unlikely	Other	Recovered
P-O group										
4401-01	28/Male	Bilateral renal colic	Renal colic	Renal and urinary disorders	2019-12-28	2019-12-30	Grade 3 (Severe)	Unlikely	None	Recovered
		Stone event requiring urgent treatment	Nephrolithiasis	Renal and urinary disorders	2020-05-14	2020-05-20	Grade 3 (Severe)	Unlikely	Study drug interrupted	Recovered

Abbreviations: AE=adverse event; D=day; M=month; MedDRA=Medical Dictionary for Regulatory Activities; SAF=safety population; O-O=group receiving Oxabact in study OC5-DB-02 and study OC5-OL-02; PT=preferred term; P-O=group receiving placebo in study OC5-DB-02 and Oxabact in study OC5-OL-02; SOC=system organ class; Y=year.
[a] Age at the time of consent.
Source: Appendix 16.2.7.1.
AEs are coded according to MedDRA version 24.0.

5.1.1.3 Other Significant Adverse Events

No subjects discontinued the study due to an AE (Table 9).

12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

Subjects 3401-05 and 3401-06, both participating in study OC5-OL-02 study site 3401, showed substantial increases in Pox in the presence of declining eGFR values. A manual review of all available study data included in the clinical database was conducted and the following observations can be made:

Subject 3401-05 was a 10-year-old female subject who was randomised to receive Oxabact during the OC5-DB-02 study. Her baseline Uox in this study was 1.8 mmol/24h/1.73 m^2. During study OC5-DB-02, total Pox initially increased and then decreased. eGFR remained relatively stable throughout the study and Uox decreased slightly. At Month 4 of the OC5-OL-02 study, a peak in Uox was seen at 5.36 mmol/24h/1.73 m^2. Between Months 6 and 12 of the OC5-OL-02 study, considerable swings in Pox were observed, as well as a decline in eGFR. The decrease in eGFR is reflected by an increase in cystatin c and creatinine. During Months 6 through 12, a slight shift in haemoglobin and haematocrit was seen, but physical examination, urinalysis, c-reactive protein (CRP), electrolytes, protein and albumin all remained within normal range. Stool analysis did not reveal any abnormal findings. On Day 227 (Month 7), the subject experienced the SAE of pyrexia, which resulted in hospitalisation/prolongation of hospitalisation. The event was of severity Grade 2 (moderate) and the subject had recovered on Day 230 (Month 7). On Day 228 (Month 7), the subject experienced pyelonephritis with a negative urine culture, which resulted in hospitalisation/prolongation of hospitalisation. The event was of severity Grade 3 (severe) and the subject had recovered on Day 233 (Month 7). This event was considered a suspected stone event. On Day 297 (Month 10), the subject experienced the AEs of abdominal pain and urinary tract infection. The subject had recovered on, respectively, Day 297 (Month 10) and Day 308 (Month 10). None of the (S)AEs was considered related to study medication. Use of antibiotics which were not listed as allowed in the protocol (cefotaxime, cefixime and fosfomycin) was recorded in the study database during Months 6 through 10. No treatment compliance issues were documented for this subject.

Subject 3401-06 was a 15-year-old female subject who was randomised to receive Oxabact during the OC5-DB-02 study. Her baseline Uox in this study was 1.20 mmol/24h/1.73 m^2. During study OC5-DB-02, total Pox, eGFR and Uox all showed an initial increase, followed by a decrease. Between Month 8 and Month 12 of study OC5-OL-02 a steep linear increase in total Pox and a decline in eGFR were seen. During this time window, one abnormal urinalysis result was seen at Month 8 (high pH and protein found in urine, assessed as not clinically significant by principal investigator), as well as a decrease in haemoglobin and haematocrit at Month 12, and elevated eosinophils, CRP, cystatin c and creatinine at Month 12 (both not clinically significant). No abnormalities in bicarbonate BUN or electrolytes were seen. A peak in total and free Pox, as well as total glycolate was seen at Month 12. Uox was measured only once during the study, at Month 4, at which time it was 1.86 mmol/24h/1.73 m^2. On study Day 253 (Month 8), the subject experienced an SAE of nephrolithiasis, which resulted in hospitalisation/prolongation of hospitalisation. The event was of severity Grade 3 (severe) and the subject had recovered on study Day 357 (Month 11).

This was considered a suspected stone event. On study Day 270 (Month 8), the subject experienced an AE of dysuria. The event was of severity Grade 1 (mild) and the subject had recovered on study Day 270 (Month 8). On study Day 292 (Month 9), the subject experienced an AE of renal colic. The event was of severity Grade 3 (severe) and the subject had recovered on study Day 296 (Month 9). This was considered a suspected stone event. None of the (S)AEs was considered related to study treatment. Use of antibiotics which were not listed as allowed in the protocol (fosfomycin) was recorded in the study database during Months 8 through 12. No treatment compliance issues were documented for this subject.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

The number of events was too small for analysis. No deaths occurred during the course of this study.

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value

Haematology and clinical chemistry parameters were determined at baseline and at Months 2, 4, 6, 8, 10, 12, 15, 18, 21 and 24. Urinalysis was performed at the same time points.

Out-of-range values were judged by the investigator as either ‘abnormal with clinical significance’ or ‘abnormal without clinical significance’. Clinically significant laboratory findings considered to be unrelated to the subject’s underlying disease were to be reported as AEs. Out-of-range safety laboratory values are listed by subject in Appendix 14.3.2.1.

12.4.2 Evaluation of Each Laboratory Parameter

Haematology

Subject listings for the haematology panel are presented in Appendix 16.2.8.1.

In several study subjects (e.g., subjects 3401-04, 3401-05 and 3401-06), an elevated eosinophil count was observed during study OC5-OL-02. The count was considered not clinically significant by the investigator. As these subjects were all enrolled at the same site, the findings were discussed with the investigator and the OxThera medical monitor. No definitive cause for the elevated eosinophil count was reported to OxThera.

No additional notable findings were seen.

Clinical Chemistry

Subject listings for the clinical chemistry panel are provided in Appendix 16.2.8.2. No notable findings were seen.

Urinalysis

Subject listings for the urinalysis panel are provided in Appendix 16.2.8.3. No notable findings were seen.

12.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital Signs

Vital signs measurements were performed at baseline and at Months 2, 4, 6, 8, 10, 12, 15, 18, 21 and 24.

Vital signs were assessed by the investigator as normal or abnormal. Abnormal findings were then judged as clinically significant or clinically insignificant. Clinically significant physical findings considered to be unrelated to the subject's underlying disease were to be reported as AEs.

Vital signs data are listed by subject in Appendix 16.2.7.2. No notable findings were seen.

Pregnancy

None of the female subjects returned a positive pregnancy test during this study.

12.6 Safety Conclusions

A total of 78 TEAEs were reported in 15 subjects. Most TEAEs were considered to be unrelated to the study treatment and Grade 1 (mild) to Grade 2 (moderate) in intensity. Of these TEAEs, 12 were considered to be at least possibly related to study treatment. Seven TEAEs, reported in 4 subjects, were serious. No related treatment-emergent SAEs nor fatal AEs were observed during the study. There were no AEs that lead to study or treatment discontinuation.

The most frequently reported AEs were in the SOCs infections and infestations (45.5%), gastrointestinal disorders (31.8%), renal and urinary disorders (27.3%), general disorders and administration site conditions (18.2%), musculoskeletal and connective tissue disorders (18.2%), nervous system disorders (18.2%), investigations (13.6%) and skin and subcutaneous tissue disorders (13.6%). AEs in the SOC renal and urinary disorders were reported in 6 subjects (18.2%, 4 events). Most AEs were considered to be Grade 1 (mild, 63.6%) to Grade 2 (moderate, 36.4%) in intensity.

13 DISCUSSION AND OVERALL CONCLUSIONS

The current study is an open-label, single-arm treatment extension study to evaluate the long-term efficacy and safety of Oxabact for patients with PH who completed study OC5-DB-02.

Twenty-two subjects from study OC5-DB-02 were enrolled into the OC5-OL-02 study. Eighteen subjects (81.8%) discontinued due to study termination by sponsor. Two subjects (9.1%) discontinued due to physician decision and one subject (4.5%) discontinued due to another reason. One subject (4.5%) completed the study.

PH is an extremely rare orphan disease with very small patient numbers available for clinical studies. Therefore, this study included a small population, with 5 centres recruiting only 1 subject. In addition, the clinical, biochemical, and genetic heterogeneity of PH I is large, with some patients presenting in infancy with renal failure and others experiencing only occasional passage of stones in adult life with maintained renal function. This further complicates interpretation of the data. Moreover, given the early termination of the study, subjects only reached a mean of 10.5 months of observation instead of the planned 24 months, which limits interpretability of the data. It is worth noting that several subjects in the O-O group (e.g., subjects 3401-04, 3401-05 and 3401-06) showed substantial increases in total Pox during the OC5-OL-02 study. Upon detailed review of these subjects, antibiotic use as treatment for AEs/SAEs of suspected stone events may represent a possible explanation for the observed rise in Pox.

Overall, Oxabact was safe and well tolerated. Most TEAEs were considered to be unrelated to the study treatment and Grade 1 (mild) to Grade 2 (moderate) in intensity. No related treatment-emergent SAEs nor fatal AEs were observed during the study. No subjects were withdrawn due to AEs.

16.1.5 Signatures of Principal Investigator, Sponsor's Responsible Medical Officer and Statistician

Study title:	A phase III double-blind, randomised study to evaluate the long-term efficacy and safety of Oxabact® in patients with primary hyperoxaluria.
Study Number	OC5-OL-02
Report Version	17-Sep-2021 (Final)

STUDY AUTHORS:

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

PRINCIPAL INVESTIGATOR: Dr. Gesa Schalk

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Date: 21. September 2021

STATISTICIAN: Corine Baljé-Volkers

Signature:

Affiliation: Author! et al. B.V.

Date: 20 September 2021

SPONSOR RESPONSIBLE MEDICAL OFFICER: Dr. Bastian Dehmel

Signature:

Affiliation: OxThera Intellectual Property AB

Date: 21. September 2021