Clinical Study Protocol
Oxalobacter formigenes (Oxabact®)

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

Protocol Number	OC5-OL-01
EudraCT Number	2013- 004368-74
Sponsor:	OxThera Intellectual Property AB Regeringsgatan 111 SE-111 39 Stockholm Sweden
Sponsor signee:	Bastian Dehmel, MD, Chief Medical Officer
Protocol Date:	14 October 2019
Protocol Version:	12, including amendment XIII

Revision History

Rev.:	Description:	Effective Date:
000	New document	2013-10-14
001	Amendment I: • Addition of a new inclusion criterion; this details the minimum age of the patients (≥ 2 years) and that they they must be able to swallow the capsules or can use a gastric tube that allows for administration of the capsules. • Addition of a new exclusion criterion concerning inability to take study medication. • Clarification that patients may receive capsules through a gastric tube. • Information on the number of patients expected to be children in the study. • Information provided on the dose justification. • Information on the risks, burdens and expected benefit of Oxabact OC5 administration to patients. A benefit risk assessment now provided. • Clarification that children will not be treated with Oxabact OC5 until the 4-week safety data from at least two adult patients in the earlier OC5-DB-01 study has been reviewed and raises no safety concerns. • Clarification of the maximum volume of blood draws at each visit. • Minor non-substantial corrections and/or clarifications	2014-02-14
002	Amendment II – US specific	2014-03-26
003	Amendment III – US specific	2014-05-09
004	Amendment IV: • After the follow-up period, patients will be offered to continue on study drug treatment until transplantation. During this period of time, monthly clinic visits will be performed including plasma	2014-10-21

	oxalate sampling and safety labs. Stool samples will be taken every 8th week. • Addition of a secondary endpoint to evaluate the efficacy and safety of long-term treatment for patients who continue on study drug after the follow-up period. • Speckle Tracking Echocardiography will be performed at screening or week 14 visit and repeated every 6 months during the continued treatment period. Speckle Tracking Echocardiography will be done at sites that routinely do this examination and will be evaluated for clinically significant changes during the study period. • Addition of analysis of Calcium, Magnesium, Citrate and Creatinine for 24h urine samples – only for patients in the sub-study (US). • Additional information regarding current clinical studies added in the section about clinical experience with Oxabact.	
005	Amendment V • The length of the continued treatment period has been limited to a maximum of 12 months. • An individual benefit/risk assessment will be done by the investigator before the start of the continued treatment and every third month during the continued treatment period. • Section 4.6 Overall risk and benefit assessment has been updated.	2014-12-14
006	Amendment VI • Country specific amendment for France.	2015-02-20
007	Amendment VII • The timeline for evaluation of the primary endpoint (change in plasma oxalate from baseline) has been amended. • The timeline for evaluation for some of the secondary endpoints (safety and change in number of *O. formigenes* in faeces) has been amended. • The length of the continued treatment period has been extended by an additional 12 month period (i.e. to a maximum of 24 months).	2016-03-08

	• The efficacy results from the OC5-DB-01 study have been included. • Safety data has been updated for the OC5-DB-01 and OC5-OL-01 studies. • In addition to the analyses of total plasma oxalate by the AMC laboratory, the Bonn laboratory will analyse free plasma oxalate using a standard plasma oxalate Ion Chromatography (IC) method.	
008	Amendment VIII • Updated Emergency Contact Information in Table 1. • Updated contact information for reporting of SAEs in section 11.4	2016-05-31
008	Amendment IX • Added oxalate removal sub-study to Secondary Objectives in synopsis which had been omitted by mistake. • Correction of inclusion/exclusion criteria regarding swallowing capsules to remove the 6 weeks time-frame. • Clarifying the analysis of plasma oxalate by IC method at local lab or Central lab in Bonn. • Revision of section 9 Study Drug Materials and Management to reflect a change of number of capsules in each vial from 18 to 14 capsules per vial. • Updated data on reported Adverse Events in section 11.5.1.2. • Minor corrections and administrative changes.	2016-09-20
009	Amendment X • The length of the continued treatment period has been extended by an additional 12-month period (i.e. to a maximum of 36 months). • Coordinating investigator has been changed to Prof Hoppe, UKB, Bonn, Germany. • Updated safety results for the study. • Minor corrections and administrative changes.	2017-04-04
010	Amendment XI • Clarified that the primary endpoint will evaluate total plasma oxalate values.	2017-11-24

	• Added analysis of change in free plasma oxalate values as a secondary endpoint. • Visit frequency for continued treatment year three changed from once monthly to once every third month. • Removed sub-study on oxalate removal, since no patients have been included into the sub-study. • Revised exclusion criteria 11 and section 8.2.2 Prohibited medications to allow for standard of care vitamin supplements for patients on dialysis. • An interim analysis will be done to analyse results from the first 12 months of continued treatment. • A transition from 14 capsules per vial to 18 capsules per vial will be done during 2018, to include some overage medication in each vial. • Clarification of the stability period for study drug stored in refrigerator. • Available local lab results for free plasma oxalate before effective date of Amendment VII will be captured retrospectively (see section 10.1) and included in the analysis. • Revised description of parameters to be evaluated for Speckle Tracking Echocardiography and traditional echocardiography. STE and traditional echocardiography evaluations performed before the effective date of this amendment will be re-evaluated to capture and analyse the same parameters. • Updated safety information in section 11.5.1.2. • Minor administrative and corrective changes.	
011	Amendment XII • Final visit after completion of year 3 has been corrected from week 152 to week 156. • Central reading of echocardiography examinations has been added.	2018-01-18
012	Amendment XIII • Information on the ongoing studies OC5-DB-02 and OC5-OL-02 was added to section 4.4 (including Table 3), 4.6.2, 4.6.3 and 4.6.4. • Information on current study updated in Table 3.	2019-10-14

	• Information on another compassionate use patient was added to section 4.4.1.3. • Clarification in section 6.1 to add "dry weight" as part of dialysis regimen monitoring. • Removal of the term "pre-dialysis" and addition of a clarification of the sampling time-point in inclusion criteria (section 7.1), primary endpoint /efficacy parameters (section 10) and throughout the document. • Addition of transplantation to section 7.3 as an explicit reason for withdrawal. • Update of section 11.1 to include definition of events that are not to be reported as AEs. The update is done to harmonise with the protocols of studies OC5-DB-02 and OC5-OL-02. • Update of section 11.5.1.1 and 11.5.1.2 to add information on the other ongoing studies OC5-DB-02 and OC5-OL-02. • Update of section 11.5.1.2 to refer to Investigator Brochure, to harmonise with the protocol of the OC5-OL-02 study. • Addition of interim analysis at 24 months of continued treatment to section 12.1 and to the Synopsis. • Change of coordinating investigator implemented. • Minor corrections and administrative changes.	

Study protocol approval

Protocol number: OC5-OL-01

Protocol Date: 2019-10-14

Protocol Version: 12, including Amendment XIII

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

Sponsor:
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This protocol has been approved by:

Bastian Dehmel, MD
Chief Medical Officer
OxThera AB, Stockholm, Sweden
Sponsor's representative

Signature: B. Dehmel

Date: 2019-10-17
(YYYY – MM – DD)

Dr. Gesa Schalk
Coordinating Investigator
University Hospital, Bonn, Germany.

Signature:

Date: 2019-10-30
(YYYY – MM - DD)

Procedures in Case of Emergency

Table 1: Emergency Contact Information

Role in Study	Name	Telephone number	Fax number
Drug Safety Physician/ Medical Monitor	Yves Miclo	+44 1223 402660	+44 1223 413689
Clinical Study Leader at sponsor	Maria Norling	+46 73 987 00 78	

1 SYNOPSIS

Name of Sponsor/Company: OxThera Intellectual Property AB
Name of Investigational Product: Oxabact® (OC5)
Name of Active Ingredient: *Oxalobacter formigenes*, strain HC-1
Title of Study: A phase 2, open-label, multi-centre study to evaluate the efficacy and safety of OC5 to reduce plasma oxalate in patients with primary hyperoxaluria who are on dialysis.
Coordinating Investigator: Dr. Gesa Schalk, Universitätsklinikum Bonn, Germany.
Participating countries and number of sites: The study will be conducted in one site in Germany.
Studied period: Estimated date first patient enrolled: Q2 2014 Estimated date last patient completed: Q1 2020. After the first 14 weeks of the study, patients will be offered to continue on study drug for up to 36 months or until transplantation.
Phase of development: 2
Objectives: Primary: o To evaluate the efficacy of OC5 to reduce total plasma oxalate levels during OC5 treatment in patients with Primary Hyperoxaluria (PH) who are on dialysis. Secondary: o To evaluate the efficacy of OC5 to reduce free plasma oxalate levels during OC5 treatment in patients with Primary Hyperoxaluria (PH) who are on dialysis. o To evaluate the safety of OC5 in patients with PH who are on dialysis. o To evaluate changes in number of *O. formigenes* in faeces following administration of OC5. o To evaluate effect of stopping OC5 treatment for 4 weeks after the first 6 weeks of treatment. o To evaluate results from Speckle Tracking Echocardiography and traditional echocardiography.

Methodology:

This open-label study will evaluate the safety and efficacy of OC5 in patients with PH who are on dialysis. Patients will initially be treated for 6 weeks with OC5. The study patients will be monitored for 4 weeks prior to initiation of study medication, as well as 4 weeks of follow-up after termination of study medication. If the patient, in the investigator's opinion, has a positive effect of the study drug, patients will be offered to continue treatment with study drug after the 4-week follow-up period until transplantation (maximum length of the continued treatment period will be 36 months). The investigator should confirm that the benefit/risk assessment for the individual patient is considered to be positive and that there are no complications or adverse events that could adversely affect the benefit/risk ratio. A repeated benefit/risk assessment for the patient will be done and documented every three months throughout the continued treatment period.

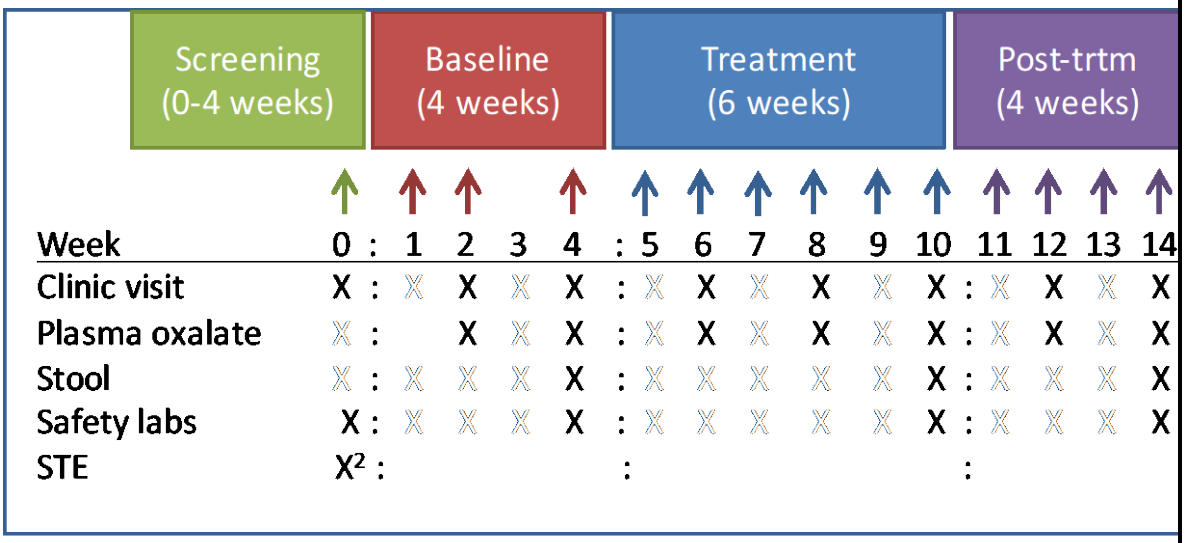
Patients will be on a stable dialysis regimen. This could be only haemodialysis (HD), only peritoneal dialysis (PD) or combined HD and PD. The choice of dialysis regimen will be decided upon by the investigator and individualized to remove adequate oxalate to minimise the risk for systemic oxalosis. The PD regimen (number of days/week, hours per treatment, volume of dialysis buffer) and HD regimen (number of days/week; hours per treatment; blood and dialysate flow rates; and HD membrane) will be maintained for the duration of the study. This will be monitored and recorded by measuring volume of spent dialysate from HD and PD and quantifying dialysis dose of each HD session in terms of Kt/V measurement using an online clearance monitor.

The plasma oxalate levels (the primary end point of this study) will be measured at weeks 2, 4, 6, 8, 10, 12, 14 during the first 14 weeks of the study, monthly throughout years 1 and 2 in the continued treatment period and every third or fourth month throughout year 3 of the continued treatment period (see illustrations of the study design below). A blood sample will be obtained after two consecutive days of dialysis on the preceding days but prior to the dialysis session on the day of sampling.

Faecal samples will be collected at weeks 4, 10, 14 during the first 14 weeks of the study, every 2 months throughout years 1 and 2 in the continued treatment period and every 3-4 months throughout year 3 of the continued treatment period. Faecal samples are analysed for determination of *O. formigenes.* Safety evaluation will include safety labs at weeks 0, 4, 10, 14 during the first 14 weeks of the study, monthly throughout years 1 and 2 in the continued treatment period and every 3-4 months throughout year 3 of the continued treatment period. Adverse events will be monitored throughout the study.

Speckle Tracking Echocardiography will be performed during baseline if possible. If the examination could not be performed during baseline, an effort will be made to perform the Speckle Tracking Echocardiography before start of continued treatment (if applicable). The procedure will be repeated every 6 months throughout the continued treatment period, if possible.

Illustration of the study design – the first 14 weeks of the study

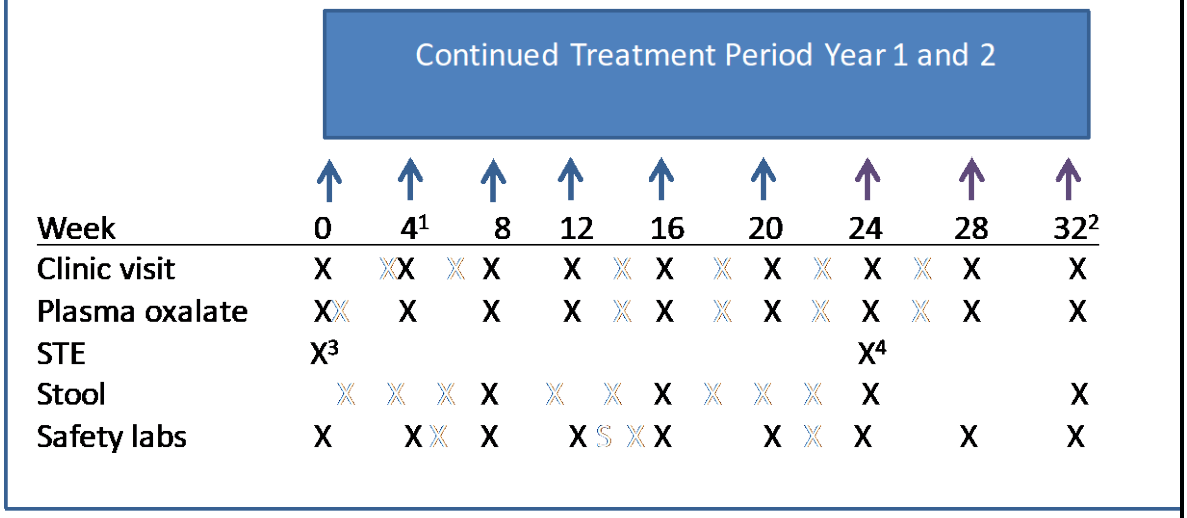


Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Clinic visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma oxalate	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Stool	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety labs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
STE	X[2]														

[1] After the post-treatment period, patients will be offered continous treatment for 36 months or until transplantation.
2 Speckle Tracking/Traditional Echocardiography should be done at screening visit +/- 1 month.

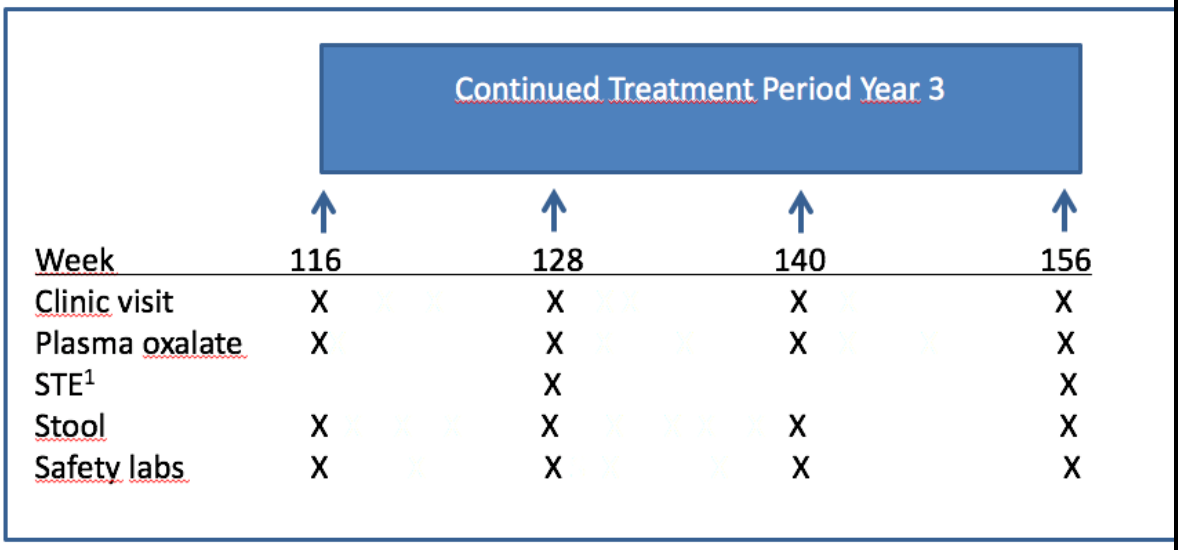
For patients continuing on treatment with study drug after week 14, monthly clinic visits will be performed including plasma oxalate sampling and safety labs during years 1 and 2. Stool samples will be taken every 8th week. During year 3 of the continued treatment period clinical visits and collection of stool samples will be done every third or fourth month.

Illustration of the study design - continued treatment Year 1 and 2



[1] Visit week 4 will be scheduled 28 days (+/- 3 days) after first day of continued treatment after study week 14.
2 Treatment Year 1 and 2 will continue with the same frequency of visits and collections until week 104 or until the patient i transplanted. Visit intervals and examinations/samplings will be kept the same throughout year 1 and 2 of the continued treatment period.
3 For patients who did not have a Speckle Tracking/Traditional Echocardiography performed at screening, an effort will be made to perform this examination before start of continued treatment.
4 Speckle Tracking/Traditional Echocardiography will be repeated every 6th month during year 1 and 2 of the continued treatment period in weeks 0, 24, 48, 72 and 104.

Illustration of the study design - continued treatment Year 3



1 Speckle Tracking/Traditional Echocardiography will be repeated every 6th month during the continued treatment period ye 3, in weeks 128 and 156.

Number of patients (planned):

Approximately 6 to 12 patients will be enrolled in the study, it is estimated that 2 of these patients will be children.

Diagnosis and main criteria for inclusion:

Main Inclusion Criteria:

1. Signed informed consent (as applicable for the age of the patient). An appendix to the informed consent form will be signed by patients continuing on treatment after week 14.
2. Male or female patients ≥ 2 years of age. Patients have to be able to swallow size 4 capsules twice daily, or use a gastric tube that allows for administration of size 4 capsules.
3. A diagnosis of PH (as determined by standard diagnostic methods).
4. Patient should be on a stable dialysis regimen for at least two weeks before baseline.
5. Plasma oxalate ≥40 micromole/L prior to the dialysis session.
6. Patients receiving vitamin B6 must be receiving a stable dose for at least 3 months prior to screening and must remain on the stable dose during the study. Patients not receiving vitamin B6 at study entry must be willing to refrain from initiating vitamin B6 during study participation.

Main Exclusion Criteria:

7. Inability to swallow size 4 capsules twice daily, or using a gastric tube not suited for administration of size 4 capsules via the tube.
8. Ongoing treatment with immunosuppressive medication.
9. The existence of secondary hyperoxaluria, e.g. hyperoxaluria due to bariatric surgery or chronic gastrointestinal diseases such as cystic fibrosis, chronic inflammatory bowel disease and short-bowel syndrome.
10. Use of antibiotics to which *O. formigenes* is sensitive, including current antibiotic use, or antibiotics use within 14 days of initiating study medication.
11. Current treatment with a separate ascorbic acid preparation. Standard of care vitamin supplement for patients on dialysis are allowed.
12. Pregnancy.
13. Women of childbearing potential who are not using adequate contraceptive precautions. Sexually active females, unless surgically sterile or at least 2 years post-menopausal, must be using a highly effective contraception (including oral, transdermal, injectable, or implanted contraceptives, IUD, abstinence, use of a condom by the sexual partner or sterile sexual partner) for 30 days prior to the first dose of OC5 and must agree to continue using such precautions during the clinical study.
14. Presence of a medical condition that the Investigator considers likely to make the patient susceptible to adverse effect of study treatment or unable to follow study procedures.
15. Participation in any study of an investigational product, biologic, device, or other agent within 30 days prior to the first dose of OC5 or not willing to forego other forms of investigational treatment during this study.

Investigational product, dosage and mode of administration:

The study drug consists of OC5. The dose will be administrated orally with breakfast and dinner as one enteric-coated capsule two times per day. For patients using a gastric tube the capsules may be administered through the tube. The dose will be NLT ≥1E+09 colony forming units (CFU) per capsule.

Duration of treatment:

Patients will initially be treated for 6 weeks with OC5. Prior to initiation of study medication, the patients will be monitored for 4 weeks. After termination of study medication for the 6-week period the patients will be followed for a 4 weeks follow-up period.

After the end of the 4 weeks follow-up period, the patients will be offered to continue treatment until transplantation. The maximal length of the continued treatment period will be 36 months. A repeated benefit/risk assessment for the patient will be done and documented every three months throughout the continued treatment period.

Criteria for evaluation:

Efficacy:

Primary endpoint:

- Change in plasma oxalate (total plasma oxalate) level during OC5 treatment, compared with baseline.

Secondary endpoints:

- Change in plasma oxalate (free plasma oxalate) level during OC5 treatment, compared with baseline.
- Change in plasma oxalate (total plasma oxalate) values from week 10 to week 14, following the 4 week off-treatment period.
- Change in number of *O. formigenes* in faeces during OC5 treatment.
- To evaluate results from Speckle Tracking Echocardiography and traditional echocardiography.

Safety:

- Adverse events (AEs), haematology, clinical chemistry, urinalysis.

Statistical methods: Evidence for efficacy will be provided as the combined evaluation of individual case studies.

Efficacy: The primary endpoint, change in total plasma oxalate from baseline, will be evaluated over time for each patient. Plasma oxalate levels will be measured on a monthly basis for the initial part of the study and the first 24 months of the continued treatment period, and once every three or four months for the last 12 months of the continued treatment. The duration of treatment will depend on the individual treatment time for each patient. All secondary endpoints will be analysed using the same methodology.

Two interim analyses will be performed: The first analysis will be based on patients who complete the first year of continued treatment. The second interim analysis will be based on all study data obtained up to 24 months. Both interim analyses will evaluate all captured efficacy and safety parameters.

The study involves a small number of patients and natural history data on changes in total and free plasma oxalate for this population is limited. Response to treatment is likely to vary depending on the baseline plasma oxalate level, individual hepatic oxalate production and age of each patient. Accordingly, the sample size is not based on assumptions of efficacy outcome and statistical power. Any inferences from the data will be based on clinical relevance rather than statistical significance.

Safety: The safety will be summarised using descriptive statistics based on frequency, seriousness and severity of treatment emergent AEs. Clinically relevant changes in safety laboratory parameters will also be summarised.

2 TABLE OF CONTENTS

2.1 List of Tables

2.2 List of figures

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and specialist terms

Abbreviation or specialist term	Explanation
AE	Adverse Event
AGT	Alanine/glyoxylate aminotransferase
CAPD	Chronic Ambulatory Peritoneal Dialysis.
CCPD	Continuous Cycling Peritoneal Dialysis
CFU	Colony Forming Units
CRF	Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GRHPR	Glyoxylate reductase / hydroxypyruvate reductase
HD	Haemodialysis
HOGA	4-hydroxy-2-oxoglutarate aldolase
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
NLT	Not Less Than
NMT	Not More Than
OC3	Old Investigational Drug, evaluated in earlier clinical studies.
OC5	Investigational Drug
PD	Peritoneal Dialysis
PH	Primary Hyperoxaluria
PI	Principal Investigator The investigator who leads the study conduct at an individual study centre.
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction

4 INTRODUCTION

4.1 Primary hyperoxaluria

4.1.1 Aetiology, clinical features and epidemiology

Primary hyperoxaluria (PH) type I, II and III are rare autosomal recessive inborn errors of glyoxylate metabolism. PH type I is caused by deficient or absent activity of liver specific peroxisomal alanine/glyoxylate aminotransferase (AGT). In some patients with PH type I, enzyme is present but mis-targeted to mitochondria where it is metabolically inactive. PH type II occurs as a result of deficient glyoxylate reductase -hydroxy-pyruvate reductase (GRHPR) enzyme activity. Oxalate overproduction in patients with PH type III is caused by loss-of-function of the mitochondrial 4-hydroxy-2-oxoglutarate aldolase (HOGA) enzyme.[1]

All types of PH are characterised by severe hyperoxaluria. Oxalate cannot be metabolised by human cells and is primarily eliminated through the kidneys and the gastrointestinal tract as an end product of metabolism. Oxalate is freely filtered at the glomerulus, reabsorbed in proximal tubules and secreted by the distal tubules. Urinary oxalate excretion levels in PH patients are extremely high (>1.0 mmol/day/1.73m^2) as compared to normal levels (< 0.5 mmol/day) and such high oxalate concentration levels damage the renal parenchymal cells both as free oxalate and as calcium-oxalate crystals.[1] In addition to calcium-oxalate deposition, chronic hyperoxaluria is associated with parenchymal inflammation and interstitial fibrosis.[1,2]

In PH, marked hyperoxaluria is present from birth. There is however a marked interfamilial as well as intrafamilial heterogeneity of disease expression, where the individual hepatic oxalate production and time for exposure to high oxalate (age) are important factors.[3] The majority of patients are symptomatic during childhood and mostly before 10 years of age. In some cases, however, the disease may go unrecognised until patients reach 30-50 years of age. Overall, the risk for end-stage renal disease (ESRD) is 50% by age of 15 and 80% by age 30. The median age at death is around 30.[2]

PH is an ultra-rare disease with a prevalence for PH type I of 1-5 per million and an incidence rate of approximately 1 per 120 000 births in Europe. PH type I is the most common variant, accounting for 70-80% of all cases. Available prevalence and incidence rates may however be underestimated because of the diagnosis being delayed or overlooked.[4] Early diagnosis, molecular subtyping and prompt initiation of conservative treatment are of vital importance for PH patients.

The clinical hallmark of the disease is recurrent calcium-oxalate urolithiasis and/or nephrocalcinosis with progressive decline in renal function. Patients with end stage renal disease receive dialysis while waiting for transplantation. So far dialysis has not been shown to overcome the problems of ongoing oxalate production and deposition at extra-renal sites. Even the most intensified dialysis regimen is not able to cope with the increasing oxalosis that often leads to multiple organ dysfunction including ischemic ulcers of the skin, metabolic bone disease, refractory anaemia, cardiomyopathy and cardiac conduction system abnormalities causing severe morbidity and mortality.[1,2]

4.1.2 Unmet medical need

The clinical management of PH patients is very challenging particularly when they reach ESRD. Once the patient reaches ESRD it is very difficult to achieve adequate removal of endogenous oxalate using the current dialysis techniques. Neither haemodialysis nor

peritoneal dialysis is able to keep pace with the endogenous production of oxalate. Accumulation of oxalate in plasma and in blood vessels start early and accumulation in extra-renal tissues starts when the local critical saturation point for plasma oxalate level is reached.[5] Saturation limits ranging from 30-60 micromoles/L have been reported depending on the fluid composition in the local environment. Intensified five-hour sessions of haemodialysis for 5 or 6 days/week are often performed until transplantation.[6]
A medical treatment, which can enhance or contribute to the removal of oxalate in addition to dialysis could be of immense importance in management of these patients.

4.2 Oxabact®

The active study drug Oxabact® consists of lyophilised *O. formigenes* strain HC1 in an enteric-coated capsule for oral administration.

O. formigenes is a strict anaerobe that relies exclusively on oxalate as a substrate to obtain energy for its survival and growth. Three proteins involved in oxalate degradation have been purified, their genes isolated and expressed to understand the physiological significance of this bacterium.[7] It is currently believed to be the most efficient oxalate degrading enzymatic system that operates at neutral pH. *O. formigenes* is a part of the normal intestinal flora in humans; it is non-pathogenic and has never been isolated systemically as a pathogen.

4.3 Oxabact® treatment for PH patients

Oxalobacter formigenes, given orally, has the potential to modify the course of PH by enhancing enteric elimination of oxalate, thereby potentially mobilising the oxalate stores and decreasing total body burden and serum levels of oxalate. This then could have significant benefit on the heart, the joints and the kidney, especially on the tubular function, as well as other affected organs such as skin, skeleton and eyes.

Although kidneys are believed to be the principal route for oxalate excretion, considerable intestinal excretion of oxalate has been shown in animal models. Colonic secretion of oxalate is an extra-renal route for oxalate elimination in rats with hyperoxalemia with or without chronic renal failure, which is also a clinical feature seen in patients with Primary Hyperoxaluria.[8] Administration of the bacteria *O. formigenes* is proven to create a suitable trans-epithelial gradient for oxalate flux from the blood stream over to the small intestines, to increase degradation of oxalate in the gastrointestinal tract, thus promoting enteric elimination of oxalate. The bacteria have also been shown to actively promote enteric elimination of oxalate through its secretion of a signal to epithelial cells to transport oxalate from plasma to intestines in animal models [9]

Incremental secretion of oxalate into the gut can be maintained by constantly degrading the secreted oxalate with the help of *O. formigenes* in the GI tract. Thus *O. formigenes* treatment is a potential therapy to promote the removal of endogenously produced plasma oxalate by enteric elimination thereby lowering the body burden of oxalate in PH patients in ESRD.

4.4 Clinical experience with Oxabact®

Five clinical studies in PH patients have been performed with older Oxabact® products (OC2 and OC3): two phase I/II studies and two phase II/III studies, plus an open-label extension study following the first phase II/III study, see Table 3.

In addition, a placebo-controlled, double-blind randomised Phase I/II study (OC5-DB-01: EudraCT No. 2012-005606-22) has been performed with the new OC5 product in 8 clinical sites in Europe. This study enrolled 28 PH patients with maintained renal function and evaluated the efficacy and safety of Oxabact® OC5 to reduce urinary oxalate and plasma oxalate in patients with PH. OC5-DB-01 started in December 2013 and the study ended in Jan 2015.

Three studies are currently ongoing, all with the Oxabact® OC5 product: these include the current study (OC5-OL-01), a placebo-controlled, double-blind randomised phase III study (OC5-DB-02) and a single-arm, open-label extension study to the latter (OC5-OL-02). For further details, please see Table 3.

Table 3: Summary of clinical studies

Study	Sites/Patients	Study drug	Outcome
CTIxOC.002 Phase I/II, open-label, non-comparative. **4 weeks treatment**	- Single site, n=9 - PH type I - 5 males, 4 females - Mean age 14, range 3-49	**OC2:** *Oxalobacter formigenes* frozen cell paste, containing 1000 mg (NLT 1E+10 CFU), given orally b.i.d. with meals.	- Reduction in plasma oxalate in some patients on dialysis - No safety concerns
CTIxOC.002 A 2-3 Phase I/II, open-label, non-comparative. **4 weeks treatment**	- Single site, n=9 - PH type I - 5 males, 4 females - Mean age 16, range 5-50	**OC3a*:** Enteric coated capsule, containing 137 mg (NLT 1E+07 CFU) of lyophilised powder. Two capsules were given orally b.i.d. with meals.	- Significant reduction in urinary oxalate in nearly all patients - No safety concerns
OC3-DB-01 Phase II/III, double-blind, placebo-controlled. **24 weeks treatment**	- 9 sites, n=42 - PH type 1/2 - 19 males, 23 females - Mean age 13, range 6-39	**OC3b**:** Enteric coated capsule, containing 137 mg (NLT 1E+07 CFU) of lyophilised powder. One capsule was given orally b.i.d. with meals.	- Post hoc analyses showed trends toward reduction in urinary oxalate - No safety concerns - Questionable 24-hour urine collections
OC3-OL-01 Open-label extension study, non-comparative. **12 to 24 weeks treatment**	- 8 sites, n=37 - PH type 1/2 - 16 males, 21 females - Mean age 14, range 6-38	**OC3b**:** Enteric coated capsule, containing 137 mg (NLT 1E+07 CFU) of lyophilised powder. One capsule was given orally b.i.d. with meals.	- No trends towards reduction in urinary oxalate - No safety concerns - Questionable 24-hour urine collections
OC3-DB-02 Phase II/III, double-blind, placebo-controlled. **24 weeks treatment**	- 3 sites, n=34 - PH type 1/2 - 17 males, 17 females - Mean age 22, range 3-62	**OC3b buffer**:** Buffer formulation, containing 500 mg (NLT 1E+07 CFU) of lyophilised powder. One sachet, reconstituted with water and bicarbonate buffer, given orally b.i.d. before meals.	- No trends towards reduction in urinary oxalate - No safety concerns - Improved 24-hour urine collections

OC5-DB-01 Phase I/II, double-blind, placebo-controlled, multi-centre **8-10 weeks treatment**	– 8 sites, n=28 – PH type 1 / 2 / 3 – 15 males, 13 females Mean age 14.5, range 3-27	**OC5#:** Enteric coated gelatin capsule, containing 80 mg (NLT 1E+09 CFU) of lyophilised powder. One capsule was given orally b.i.d. with meals.	– No significant difference for primary endpoint (urinary oxalate excretion) – Marked patient heterogeneity with indication that oxalate deposits may be dissolving in OC5-treated patients – Post hoc analyses identified a small, but statistically significant increase of oxalate excretion per creatinine excretion and a statistically significant correlation between change in plasma oxalate and change in *Oxalobacter*. – No safety concerns
OC5-OL-01 (ongoing) Phase I/II, open-label, non-comparative, multi-centre 6 weeks + up to 36 months.	– 1 site – 6-8 PH patients who are on dialysis	**OC5#:** Enteric coated gelatine capsule, containing 80 mg (NLT 1E+09 CFU) of lyophilised powder. One capsule given orally b.i.d. with meals.	– Study ongoing – Study started in May 2014; 12 patients received study drug, and 1 patient is still ongoing. Interim analysis findings show decreased plasma oxalate and signs of improved myocardial function in patients with low baseline cardiac function.

OC5-DB-02 (ePHex, ongoing) Phase III, double-blind, placebo-controlled, multi-centre 52 weeks treatment	– 11 sites – Plan to recruit 22 PH patients with eGFR <90ml/hr/1.73m^2 and plasma oxalate ≥10µmol	**OC5#:** Enteric coated gelatin capsule, containing 80 mg (NLT 1E+09 CFU) of lyophilised powder. One capsule is given orally b.i.d. with meals.	– Study ongoing – Study started in January 2018 and is ongoing. 16 patients have been randomised.
OC5-OL-02 (ePHex-OLE, on-going) Phase III, open-label, single-arm, multi-centre, 104 weeks treatment	– 11 sites – PH patients who completed ePHex will be offered participation – Planning to recruit 16 patients	**OC5#:** Enteric coated gelatin capsule, containing 80 mg (NLT 1E+09 CFU) of lyophilised powder. One capsule is given orally b.i.d. with meals.	– Study ongoing – Study started in April 2019 – 4 patients have started open-label treatment

** OC3a: OC3 active ingredient prior to technology transfer and scale-up*
*** OC3b: OC3 active ingredient after technology transfer and scale-up*
 # OC5: OC5 active ingredient after process development and transfer

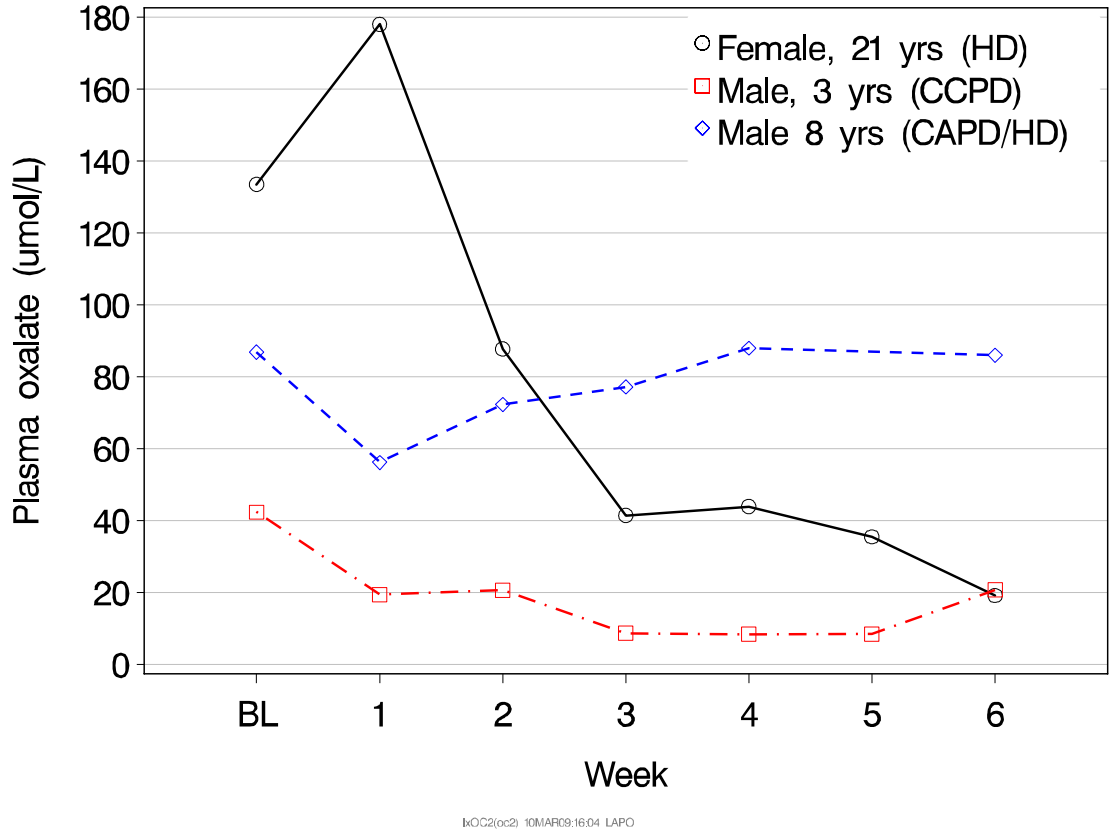
4.4.1 Clinical experience in PH patients on Dialysis

4.4.1.1 CTIx.002:

The first phase I/II study (CTIx.0002) was conducted in 9 patients using a frozen cell paste formulation of *O. formigenes* (OC2). Patients were given two doses of OC2 with two main meals per day for four weeks. Three PH I patients in ESRD who were undergoing dialysis were included in this study.[10]

Figure 1 shows the change in plasma oxalate in these patients. Plasma oxalate measurements were made once a week from samples taken before the dialysis session. A substantial decrease in plasma oxalate was observed in two of the patients in ESRD and no safety concerns were observed[10]. In one of the patients (Female 21 years on HD) the treatment was prolonged to 5 weeks since the therapeutic effect was quite significant and this patient also reported amelioration of clinical symptoms under therapy with less pain due to oxalate osteopathy.

Figure 1: Effect of *O. formigenes* treatment on plasma oxalate levels in patients with end-stage renal disease treated with *O. formigenes* delivered as frozen cell paste (OC2).



Note: The eight year-old male did not take all study medication per protocol after second week of treatment. HD=Haemodialysis, CCPD=Continuous Cycling Peritoneal Dialysis; CAPD=Chronic Ambulatory Peritoneal Dialysis.

4.4.1.2 CTIx.002 Amendments 2 and 3

The second phase I/II study was a single arm, single centre study conducted under an amendment of the same protocol (CTIx.002 A2-3) and enrolled 9 patients. In this study, *O. formigenes* was lyophilised and administered as an enteric-coated capsule (OC3a active ingredient). The dose was NLT 1E+07 CFU given twice a day for 4 weeks. In eight patients with measureable urine, there was a reduction in 24-hour urinary oxalate excretion by a median 58% (p=0.0078, Wilcoxon rank-sum test), ranging from 4% to 95%. Plasma oxalate decreased overall by a median 26% and the reduction ranged from 22% to 84% in 6 of these patients. The plasma oxalate decreased by 26 µmol/L in the patient with end-stage renal disease. OC3a treatment was well tolerated.

4.4.1.3 Compassionate use

Oxabact has also been evaluated during compassionate use in two 11-month-old girls with infantile oxalosis and ESRD (see Figure 2 and Figure 3). They received OC3b (administered together with esomeprazole via gastric tube) twice a day up to 4 weeks during two treatment periods. Dialysis regimens were unchanged. Plasma oxalate levels decreased from >110 µmol/L before to 72 µmol/L following treatment in patient 1 and from >90 to 69 µmol/L (first treatment period) and 50 µmol/L (second treatment period) in patient 2.[11]

Compassionate use of OC3b (broken capsules, 137-276 mg, mixed with a local buffer, reconstituted with 50-100 mL water and administered via gastric tube) twice a day up to 8 weeks have been evaluated in two other patients with infantile oxalosis at two other sites in the United States and the United Kingdom, without any reduction in plasma oxalate (unpublished data). Recent analysis has shown that the buffer used at the time was not reconstituted properly and therefore was unsuitable for supporting survival of *Oxalobacter* in the stomach.

OC3b and OC3 buffer were well tolerated and no serious side effects were reported during compassionate use.

Figure 2: Follow up of plasma oxalate levels in patient 1 during treatment with *Oxalobacter formigenes*.

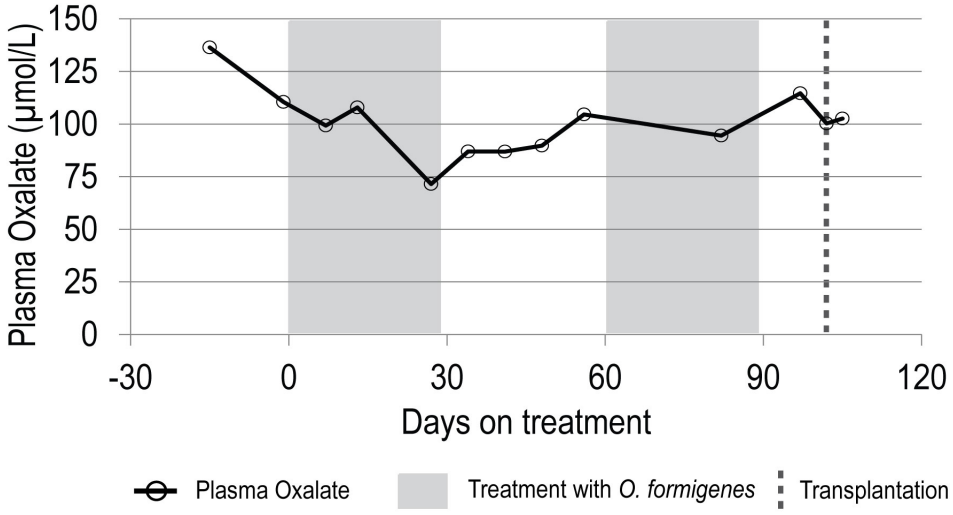
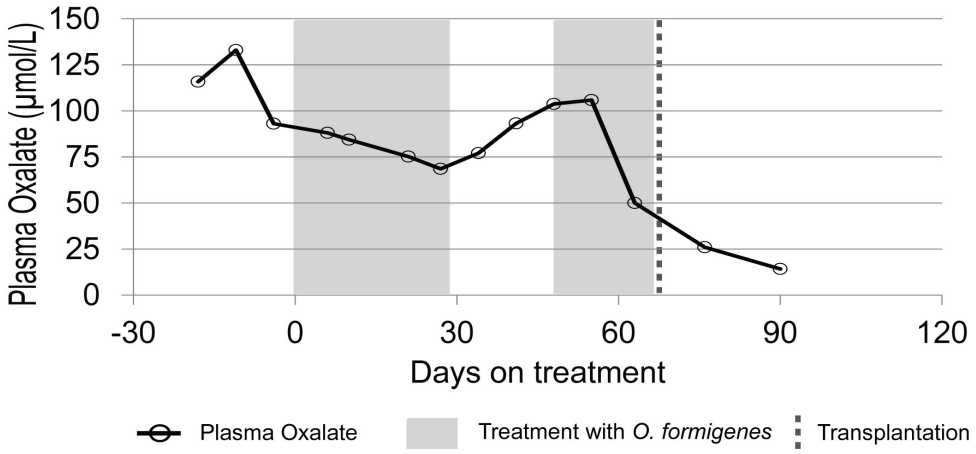


Figure 3: Follow up of plasma oxalate levels in patient 2 during treatment with *Oxalobacter formigenes*



OC5 is currently being provided under named-patient use to a young girl with infantile oxalosis, in Germany. She developed end-stage renal disease shortly after birth and was treated with daily peritoneal and 3 times/week haemodialysis. Treatment with OC5 (in buffer solution) started in December 2017, when the child was 3 months old, and is ongoing (September 2019). The patient recently turned two years of age and is on the waiting list for a combined liver/kidney transplantation. According to the treating physician, there are clear indications that disease progression has slowed down during the course of treatment and that plasma oxalate levels have reduced and stabilised. OC5 has been tolerated well by the patient. It is planned that the child will continue OC5 Oxabact treatment until a combined liver/kidney transplantation can be performed.

4.4.2 Clinical Experience with Oxabact® OC5 in PH patients with maintained renal function (results from the OC5-DB-01 study)

The OC5-DB-01 study was a double-blind, randomised, placebo-controlled, multi-centre study to evaluate the efficacy and safety of Oxabact® OC5 in PH patients with maintained renal function (i.e. eGFR or a creatinine clearance of ≥ 40 mL/min normalised to 1.73m^2 body surface area). The patients were randomised to treatment with Oxabact® or placebo and were administered one capsule twice a day for 8 - 10 weeks. Each dose of Oxabact® corresponded to not less than 10^9 CFU *O. formigenes.* The primary objective of the study was to evaluate the efficacy of Oxabact® drug product to reduce urinary oxalate excretion following 8 - 10 weeks of treatment.

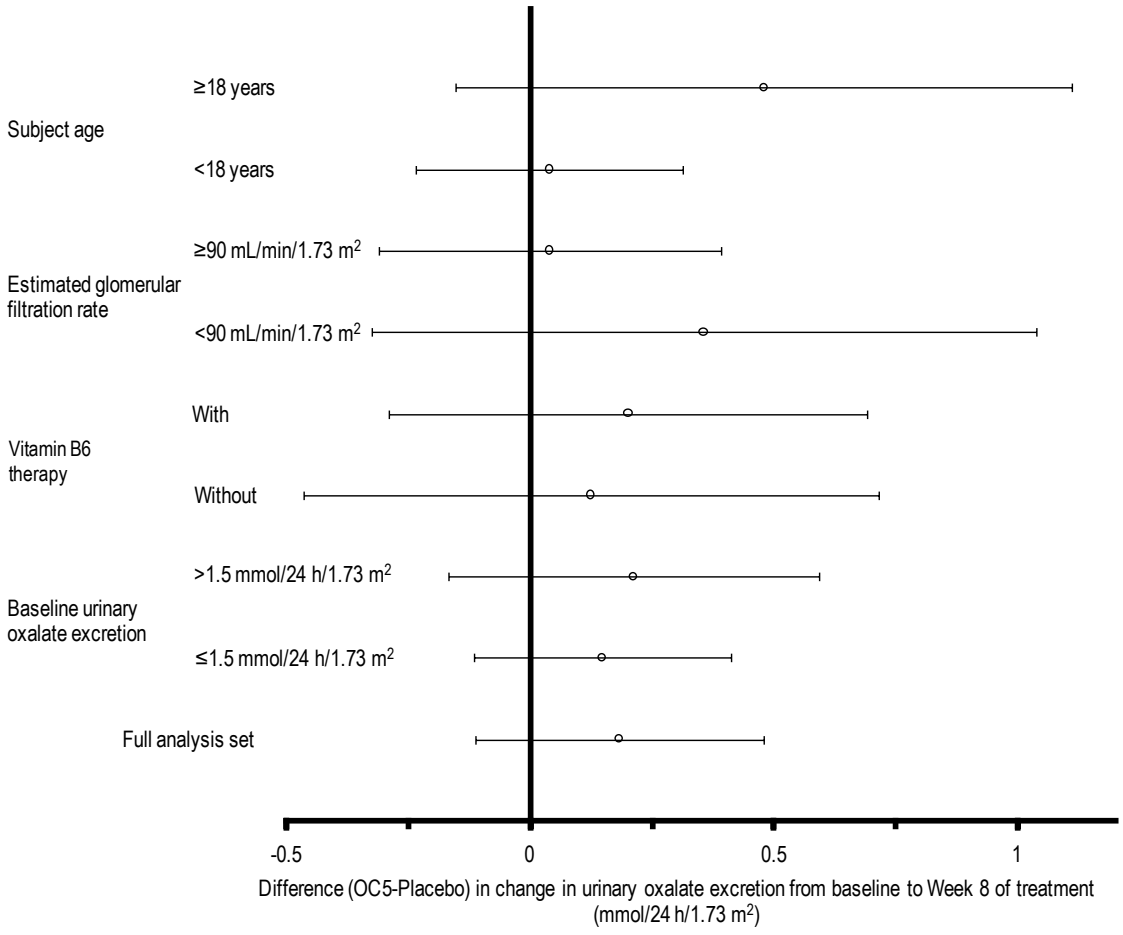
In total, 44 patients from 8 sites in Germany, France, and the United Kingdom were screened for inclusion in the study. 28 of these were randomised; 14 were randomised to receive Oxabact® and 14 randomised to receive placebo. All 28 patients fulfilled the FAS and Safety set criteria, received the treatment and completed the study.

The primary analysis for the OC5-DB-01 study did not identify a statistically significant difference between the OC5 treatment and placebo in terms of its effect on urinary oxalate excretion. After 8 weeks' treatment, the change in urinary oxalate excretion appeared slightly higher (0.182 mmol/24 h/1.73 m^2) in the OC5 group than in the

placebo group; this difference did not achieve statistical significance (p=0.22). OC5 treatment did lead to a statistically significant increase in the number of *O. formigenes* cells in the faeces of patients compared with placebo (p=0.00023). In all other secondary and exploratory endpoints, no significant differences were observed between OC5 and placebo.

Subgroup analysis of the primary endpoint based on baseline urinary oxalate excretion, baseline eGFR, age or concomitant use of vitamin B6 therapy did not reveal any statistically significant differences between the treatment groups, but the magnitude of the least square difference between OC5 and placebo was larger in the eGFR<90 ml/min/1.73 m^2 subgroup than in the eGFR>90 ml/min/1.73 m^2 subgroup (0.356 vs 0.040 mmol/24 h/1.73 m^2) and larger in the subgroup of patients aged 18 years or older than in the subgroup of patients younger than 18 years (0.480 vs 0.039 mmol/24 h/1.73 m^2). A Forest plot of difference in change in urinary oxalate excretion from baseline to Week 8 of treatment in different subgroups is shown in the figure below.

Figure 4: A Forest plot of difference in change in urinary oxalate excretion from baseline to Week 8 of treatment in different subgroups in the OC5-DB-01 study.



The figure displays estimate and 95 percent confidence intervals (Full analysis set).

Despite a stratification of the two treatment groups (below/above 1.5 mmol/24 h/1.73 m^2), the patients in the OC5 group had more impaired renal function than the placebo patients. Mean baseline eGFR was lower in the OC5 group than in the placebo group (97.5±38.7 versus 123.1±45.4 mL/min/1.73 m^2), and renal and urinary disorders were more common in the OC5 group (11 cases versus eight cases); most notably, four patients in the OC5 group had a history of chronic renal failure, whereas no patients in the placebo group had been affected by this condition. In light of the observed difference in renal function between the two groups, ad hoc analyses were conducted to investigate the relationship between efficacy parameters and indicators of renal health.

An analysis of the change in urinary oxalate excretion per urinary creatinine excretion showed a small (+5.4 mg oxalate/g creatinine), but statistically significant increase of oxalate excretion in the active group versus placebo, p=0.023 (FAS).
Significant correlations were observed between renal function and the effect of OC5 treatment on urinary oxalate concentration. Overall, the OC5-induced increase in urinary oxalate excretion was larger in patients with impaired renal function. The analyses also demonstrated that plasma oxalate concentration decreased as the number of *O. formigenes* increased in the OC5 treated patients, p=0.04. This suggests that the bacteria metabolise free oxalate that originates from plasma, thereby supporting that enteric elimination of oxalate has occurred.

It is hypothesised that this reduction in free plasma oxalate disturbs the endogenous equilibrium between free plasma oxalate, plasma protein-bound oxalate and deposited oxalate and forces a dissolution of oxalate deposits in plasma-proteins and vessels, which leads to increased excretion of urinary oxalate. An analogous relationship between plasma urate levels and solid urate dissolution has been observed in patients with gout, where effective treatment leads to initially increased urinary urate excretion[12]. Because oxalate deposits are expected to be more pronounced in patients with impaired renal function, this hypothesis also explains why the effect of OC5 treatment was greater in patients with more advanced kidney disease. A statistically significant decrease in urine output in the OC5-treated patients may also suggest that *O. formigenes* confers some beneficial effect on water reabsorption and urine concentrating-ability in the tubules of these patients.

4.5 Rationale for current phase 2 study

4.5.1 Overall objective

The overall objective of this study is to study the efficacy of Oxabact® to reduce plasma oxalate in PH patients in ESRD who are undergoing dialysis. Oxabact® has not been tested in a clinical trial designed for this patient population. Patients in ESRD who are on dialysis is a population with a significant unmet medical need for lowering the morbidity associated with oxalosis while the patients are waiting for a liver / kidney transplant.

As described in section 4.4 although a positive efficacy outcome was seen in some of the ESRD patients enrolled in CTIxOC.002 (using the frozen cell paste OC2 formulation), the results from patients treated with the OC3b formulation in patients with maintained renal function were less substantial (Table 3: Summary of clinical studies).

OxThera has made significant improvements in the Oxabact® formulation to develop the OC5 product that has a one hundred times higher cell concentration and oxalate degrading activity as compared to OC3b. The new OC5 product has been evaluated in a multicentre double-blind controlled trial in PH patients with a GFR >40 ml/min/1.73 m^2 where urinary oxalate was the primary end-point (OC5-DB-01). In this current trial, OC5-OL-01, the OC5 product with higher concentration and faster recovery from the lyophilised state is tested in the PH patients in ESRD where plasma oxalate is the primary end-point.

4.5.2 OC5 development

OxThera has made changes to the culture conditions, cell harvesting procedures and optimization of excipients used for the freeze-drying process to develop the new highly concentrated product OC5. As compared to OC3b, the OC5 product has hundred-fold higher concentration of viable cells and these cells show a rapid recovery of their oxalate degrading activity from the lyophilised state.

OC5 is derived from the same cGMP Master Cell Bank as the earlier product. However, the cell bank has been sub-cloned to meet stringent requirements with regard to viable cell count and oxalate degrading activity. Furthermore, culture conditions and harvest criteria in the fermentation process have been refined to improve the capability of the cells to degrade oxalate at end of fermentation. Together with optimised excipients and relative amounts of these and cells, the product is now also better protected from the lyophilisation process, which in itself has also been improved. A significantly higher number of viable cells are recovered from the lyophilised state than previously recovered for the OC3b product.

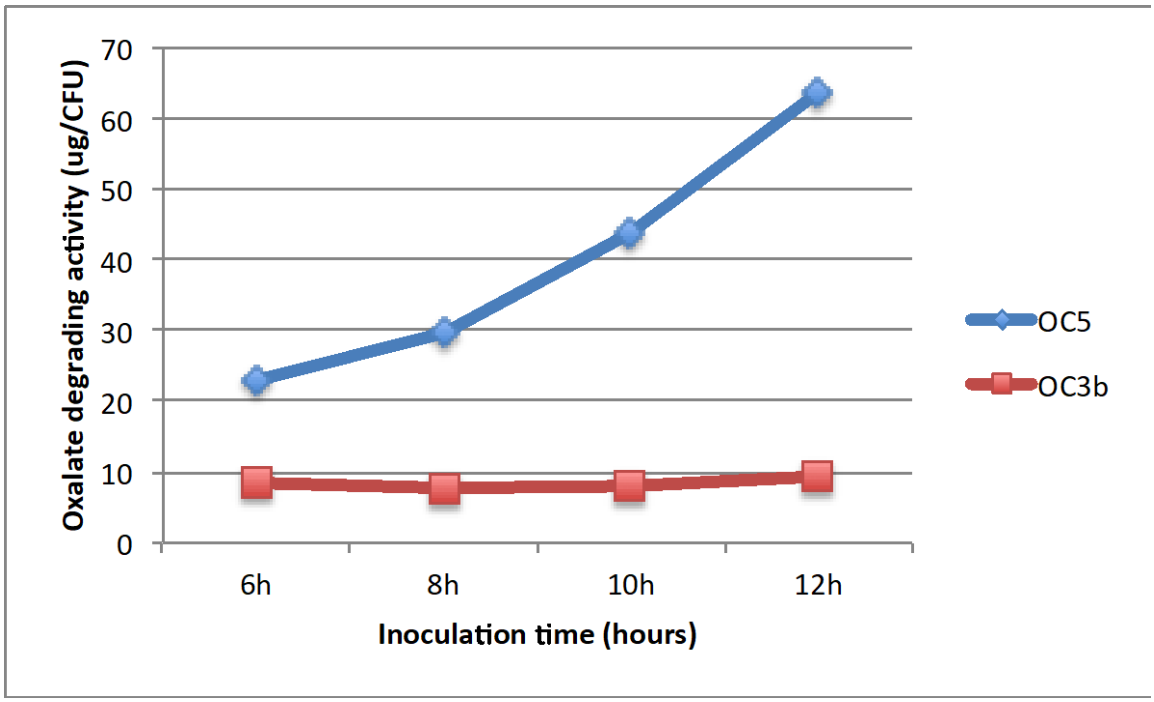
In addition, product-related analytical methods have been refined since the previous production process; Content (viable cell count, CFU/g) and Potency (oxalate degrading activity, mg oxalate degraded/capsule at 19h). The previous assays for OC3 did not differentiate very well between products with high or low potency.

The higher concentration of viable cells and higher oxalate degrading activity in OC5 allows for use of less lyophilised powder per dose. Thus, a smaller capsule, size 4 instead of size 2, will be used.

OC5 is formulated as enteric-coated capsules designed to protect the *O. formigenes* bacteria from gastric juice and to deliver the active ingredient to its natural habitat and site of action, the small intestines. The disintegration time for the coated OC5 capsules is shortened in comparison to OC3b to better mimic the disintegration profile of a previous version of the product, OC3a.

As can be seen in Figure 5, the OC5 material begins replicating much quicker than does the OC3b material. In essence, with an improved cell bank, harvesting technique and freeze-drying strategy the quality of the product has been greatly improved.

Figure 5: Potency of OC5 compared to OC3.



4.5.3 Dose justification

Based on toxicity studies it should be within the NOAEL to administer up to 9 x 10^{11} CFU of OC5 twice daily to human patients. The OC5-OL-01 study will administer a 10^9 CFU twice daily dose to all patients.

It needs to be taken into account that the oxalate degrading capacity, or potency, of Oxabact® is limited by the availability of endogenous oxalate. The daily plasma production of endogenous oxalate is 4–7 mmol/1.73m^2 in PH patients. The optimal (i.e. *in vitro*) oxalate degrading capacity of the OC5 Oxabact® capsules according to drug product specifications is approximately 15-25 times higher than the daily endogenous production of oxalate in PH patients (i.e. ≥100 mmol/capsule/19h). However, the amount of available oxalate cannot support this capacity and no difference in safety is anticipated with varying oxalate degrading capacity due to the limited availability of endogenous oxalate.

It is necessary to provide an exaggerated dose of Oxabact® to ensure delivery of sufficient viable *O. formigenes* to the relevant part of the gastrointestinal tract. The bacteria need to survive transit through the stomach and upper small intestine and withstand the dilution effect from the normal gut microbiota. It is a competitive environment particularly given that *O. formigenes* are anaerobic and utilise only oxalate as an energy source. The dosing strategy supports the use of the same dose across age groups.

The OC5 drug product in the recent OC5-DB-01 (also dosed at NLT 10^9 CFU twice daily) study has been well tolerated with no safety concerns.

4.6 Overall risk and benefit assessment

4.6.1 Burden

Patients are requested to provide three faecal samples during the first 14 weeks of the study, one sample every second month during the first 24 months of the continued treatment period and one sample every third or fourth month for the final 12 months of the continued treatment period. Faecal samples will be collected at patients' homes or at the clinic whichever is the most convenient for the patient. For samples collected at home, a designated courier will deliver collection kits and pickup collections at times agreed with the patients even during weekends if requested.

Patients will attend clinical visits at eight times throughout the first 14 weeks of the study, once monthly during the first 24 months of the continued treatment period and once every third or fourth month for the final 12 months of the continued treatment period. This will involve time travelling to the hospital and the time required to see the investigator/study nurse. Since the patients are on dialysis, these visits may to a great extent be combined with regular visits to the clinic for dialysis treatment. Blood samples will be collected during the clinical visits for safety laboratory evaluations (four times during the first 14 weeks of the study, once monthly during the first 24 months of the continued treatment period and once every third or fourth month for the final 12 months of the continued treatment period and for plasma oxalate analysis (seven times during the first 14 weeks of the study, once monthly during the first 24 months of the continued treatment period and once every third or fourth month for the final 12 months of the study. Approximately 20 mL of blood will be needed for the safety lab sample and approximately 5 mL for the plasma oxalate sample.

Study medication will be administrated orally with breakfast and dinner as one capsule two times per day, for 6 weeks and during the continued treatment period until the patient is transplanted or until a maximal length of the continued treatment period of 36 months). The capsule size is quite small (size 4) and should be relatively easy to swallow even for younger patients. For patients using a gastric tube the capsules may be administered through the tube. The patients will be asked to complete a simple diary to record the study drug taken and any missed doses.

Speckle Tracking Echocardiography and traditional echocardiography will be done during baseline and repeated every 6 months during the continued treatment period of maximum 36 months. The examination is non-invasive.

4.6.2 Risk threshold

Detailed information on the anticipated adverse events of the OC5-OL-01 study is outlined in section 10.5. In brief these potential risks may include:

- Displacement of indigenous *O. formigenes* or changes in the normal gut microbiota
- Infections
- Elevated plasma formate
- Gastrointestinal symptoms

While the potential for these risks do exist, non-clinical and clinical data to date has not indicated that the Oxabact® product is associated with any changes in the gut microbiota, local or systemic infection or elevated plasma formate levels. Previous studies (OC3-DB-01 and OC3-DB-02) have also found that the OC3 product was safe and

well tolerated with an adverse event profile similar to the placebo, even for gastrointestinal symptoms. While the OC5 product is more concentrated than the OC3 product, the safety profile is still favourable, as supported by the concluded bridging toxicology study (DP-1002). Twenty-eight consecutive days of twice daily oral administration by capsule of OC3 at 2E+08 CFU or OC5 at 9E+09 CFU to male and female rats was well tolerated with no test article-related changes or differences being noted between the two product formulations. The safety profile for OC5 was comparable to OC3, i.e. no changes observed on clinical observation, laboratory parameters, or histopathology considered specific to the treatment with OC5.

Data collected to date for the completed OC5-DB-01 study, the current OC5-OL-01 study and the ongoing OC5-DB-02 and OC5-OL-02 studies indicate that the product is safe and well tolerated. No Oxabact® -related severe or serious adverse events have been reported so far in these on-going studies, see section 11.5.1.

Overall the safety data accrued to date would suggest that the OC5 drug product is safe and well tolerated and appears to have a similar safety profile as the earlier OC3 drug product.

In conclusion, the burden and risk threshold is deemed to be acceptable for the study and many efforts have been made to minimise burden and potential risks to the patients. Furthermore, the patients will visit the clinic 8 times during the first 14 weeks of the study, once monthly during the first 24 months continued treatment and once every third or fourth month for the last 12 months of the continued treatment period for study specific visits in order to monitor adverse events and to make sure the patient is able to follow study procedures.

4.6.3 Benefits

PH is a devastating, life-threatening disease for which there are no approved pharmaceutical therapies. It is particularly emotive since it primarily affects a paediatric population. Consequently, there is a significant unmet medical need in treating this disease. Oral administration of *Oxalobacter formigenes* is a promising potential treatment for patients with PH. Clear beneficial effects of *Oxalobacter formigenes* have been demonstrated in animal models of PH and in earlier Phase I/II clinical studies.

Based on analysis of the nonclinical and clinical safety data generated to date, Oxabact® has been well tolerated. The older OC2 and OC3 Oxabact® products have been given to more than 80 people for time periods of 4 weeks to 12 months (with the majority of patients having been treated for 6 months). Administration of *O. formigenes* as a frozen cell paste, capsule or buffered powder for suspension was well tolerated in patients with primary hyperoxaluria. No SUSARs have been reported in any of these studies for Oxabact® and the product has had a favourable safety profile.

The safety data available with the OC5 drug product from the completed OC5-DB-01 study and the ongoing OC5-OL-01, OC5-DB-02 and OC5-OL-02 studies would also support the favourable safety profile. OC5 has been administered to 14 patients in the OC5-DB-01 study and to 12 patients in the OC5-OL-01 study. Sixteen patients have been randomised in the ongoing OC5-DB-02 study. Four of these have entered the follow-up study OC5-OL-02 and are now receiving open-label Oxabact®. In OC5-DB-02, patients are randomised 1:1 to receive Oxabact® or

placebo; hence, it can be estimated that approximately 8 of the 16 randomised patients receive Oxabact®. No SUSAR has been reported in these studies for the Oxabact® product. Only 3 SAEs were reported in OC5-DB-01 and nine SAEs in OC5-OL-01 to date. In OC5-DB-02, there have been 8 SAEs reported to-date; none of them was considered related to study drug. There have been no reported SAEs in the OC5-OL-02 study. The majority of AEs are mild and not related to the study drug.

The OC5-OL-01 study should provide valuable information on the ability of the improved OC5 Oxabact® product to reduce plasma oxalate and confer clinical benefit in patients with PH who are on dialysis. A reduction of plasma oxalate may cause endogenous oxalate deposits to dissolve and thus treat systemic oxalate-related complications. It will also generate further safety information on the product. Since PH patients on dialysis have a more severe form of the disease, they typically have higher plasma oxalate levels, more oxalate deposits and higher urinary oxalate levels (if not anuric) than PH patients with maintained renal function. OxThera believe that it is beneficial to have a 36-month continued treatment period for these patients. It may take some time to reduce the elevated plasma oxalate levels (which can be exceptionally high in these patients). Furthermore, the widespread oxalate deposits may start to dissolve once plasma oxalate levels decrease under saturation and prolongation of OC5 treatment may help in reducing the oxalate deposits in the body.

4.6.4 Benefit:Risk Assessment

There is an unmistaken need for additional therapeutic measures to treat patients with PH. These patients are at high risk for kidney damage due to over-production of oxalate and oxalate crystallisation and currently there are limited treatments available for this disease. This is particularly so for PH patients on dialysis who typically have extremely high plasma oxalate levels and widespread oxalate deposits in the body. The efficacy of Oxabact® in PH patients is still to be proven. It is hoped that improvements in the OC5 formulation will result in a possible treatment for patients with PH.

All nonclinical and clinical safety data to date indicate that Oxabact® has been well tolerated. There have been no SUSARs reported for Oxabact® in any clinical study with *O. formigenes*. Older studies with OC2 and OC3 drug product have been performed in over 80 patients with treatment times of 4 weeks to 12 months. The 2 larger placebo-controlled studies (OC3-DB-01 and OC3-DB-02) found that the OC3 product was safe and well tolerated with an adverse event profile similar to the placebo. In addition, the improved product, OC5, has been administered to 14 patients in the OC5-DB-01 study and to 12 patients in the OC5-OL-01 study. Sixteen patients have been randomised in the ongoing OC5-DB-02 study, and 4 of these have entered the open-label extension study OC5-OL-02. Safety data from the completed OC5-DB-01 study and safety reporting of the on-going double-blind OC5-DB-02, the open-label OC5-OL-01 and the OC5-OL-02 studies suggest that OC5 has a favourable safety profile and would not be expected to differ from that of the earlier OC3 drug product in terms of safety.

Thus, based on the mechanism of action of OC5 (removal of free oxalate from plasma by enhancing the oxalate secretion from plasma to the gut), a naturally occurring and non-pathogenic bacteria that relies exclusively on oxalate for its metabolism within the gut, and the available non-clinical and clinical data, the Sponsor believes that the

benefit/risk evaluation of conducting this Phase II trial for treatment in patients with PH is considered favourable.

All in all, the potential clinical benefit to the target population (and study participants in this trial) is deemed to outweigh the potential risks implied and the study is therefore medically and ethically justifiable.

5 TRIAL OBJECTIVES AND PURPOSE

5.1 Primary objective

- To evaluate the efficacy of OC5 to reduce total plasma oxalate levels during OC5 treatment in patients with Primary Hyperoxaluria (PH) who are on dialysis.

5.2 Secondary objectives

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

6 INVESTIGATIONAL PLAN

6.1 Overall study design and plan

This study is an open label multi-centre study to evaluate the efficacy and safety of OC5 (*O. formigenes*) to reduce plasma oxalate in PH patients on dialysis. It is hypothesised that daily administration of *O. formigenes* facilitates the secretion of endogenously produced oxalate from plasma to the GI tract. The enteric elimination of oxalate in addition to dialysis may help to lower the build-up of extra-renal oxalate in PH patients in ESRD.

Patients will initially be treated for 6 weeks with OC5. The study patients will be monitored for 4 weeks prior to initiation of study medication, as well as 4 weeks of follow-up after termination of study medication. If the patient, in the opinion of the responsible investigator, has a positive effect of the study drug, patients will be offered to continue treatment with study drug after the 4-week follow-up period until transplantation (maximum length of the continued treatment period will be 36 months).

The investigator should confirm that the benefit/risk assessment for the individual patient is considered to be positive and that there are no complications or adverse events that could adversely affect the benefit/risk ratio. A repeated benefit/risk

assessment for the patient will be done and documented every three months throughout the continued treatment period.

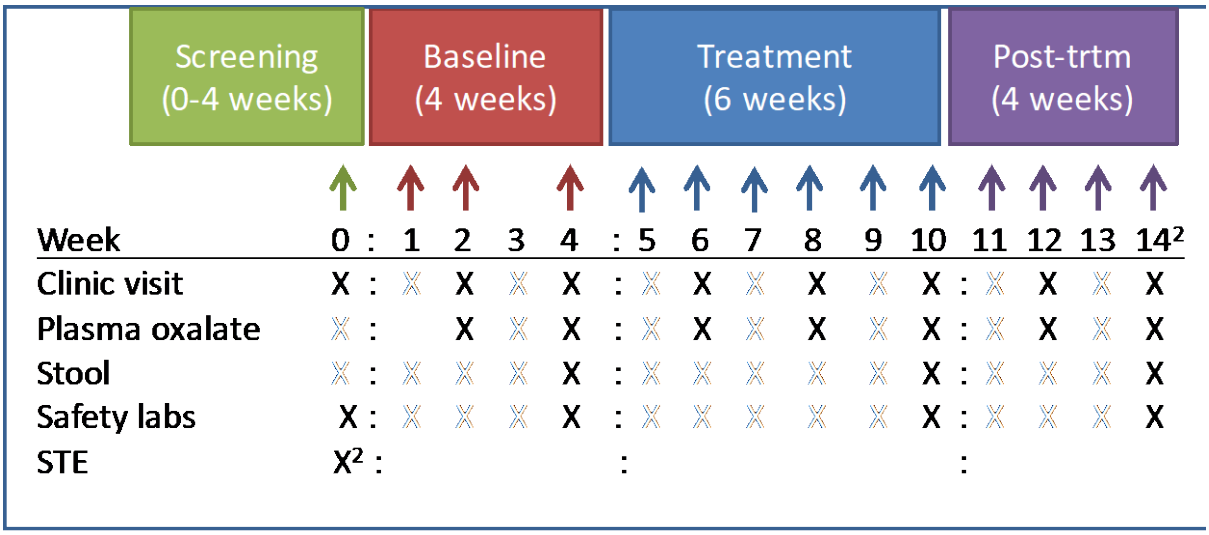
Following screening and baseline evaluations eligible patients will receive Oxabact® twice daily for 6 weeks. The dose will be administrated orally with meals as one enteric-coated capsule two times per day preferably with breakfast and dinner. For patients using a gastric tube the capsules may be administered through the tube. The dose will be NLT 1E+09 CFU/capsule.

Prior to enrollment patients will be on a stable dialysis regimen. This could be only haemodialysis (HD), only peritoneal dialysis (PD) or combined HD and PD. The choice of dialysis regimen will be decided upon by the investigator and individualised to remove adequate oxalate to minimise the risk for systemic oxalosis. The PD regimen (number of days/week, hours per treatment, volume of dialysis buffer) and HD regimen (number of days/week; hours per treatment; blood and dialysate flow rates; and HD membrane) will be maintained for the duration of the study. This will be monitored and recorded by measuring volume of spent dialysate from HD and PD and quantifying dialysis dose of each HD session in terms of Kt/V measurement using an online clearance monitor. Each patient's dry weight (target bodyweight after the dialysis session) will also be recorded.

The total plasma oxalate (the primary end point of this study) will be measured at weeks 2, 4, 6, 8, 10, 12, 14, thereafter monthly for the first 24 months of continued treatment and every third or fourth month during the last 12 months of the continued treatment period (Figure 6 and Figure 7). A blood sample will be obtained after two consecutive days of completed dialysis regimen the preceding days, but prior to the dialysis session on the day of sampling. The plasma samples will be processed at each clinical site and analysed for total plasma oxalate at the Academic Medical Center, Amsterdam and for free plasma oxalate at the local lab (Bonn University Clinical laboratory).

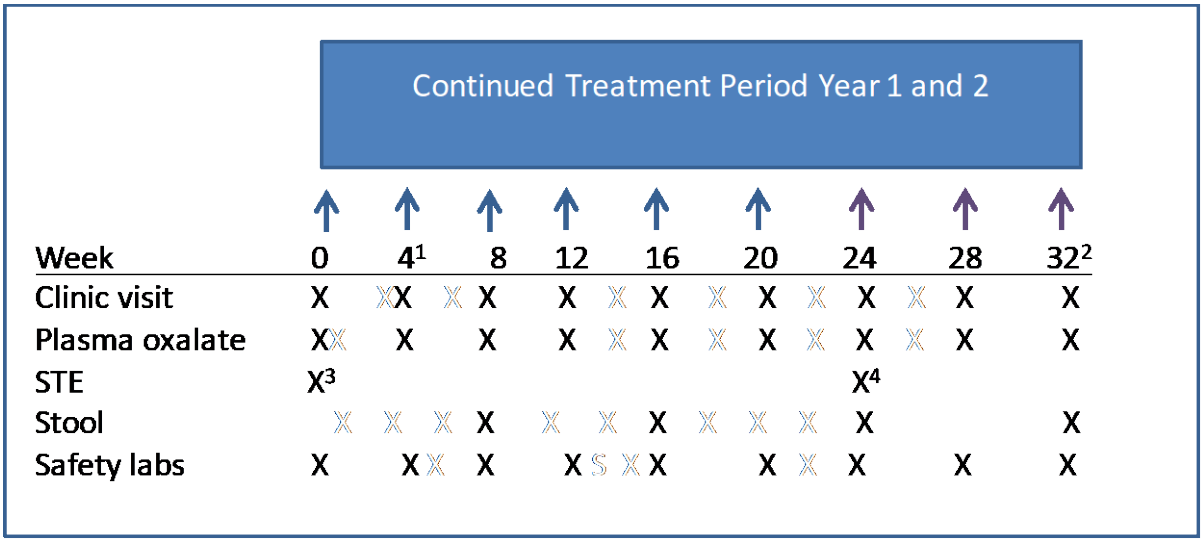
Speckle Tracking Echocardiography and traditional echocardiography will be performed, if possible, at screening visit (+/- 1 month) or before start of continued treatment period (at visit week 14). Speckle Tracking Echocardiography and traditional echocardiography will then be repeated at week 24 in the continued treatment period and thereafter every 6 months until end of treatment, if possible.

Figure 6: Study design for OC5-OL-01 - the first 14 weeks of the study.



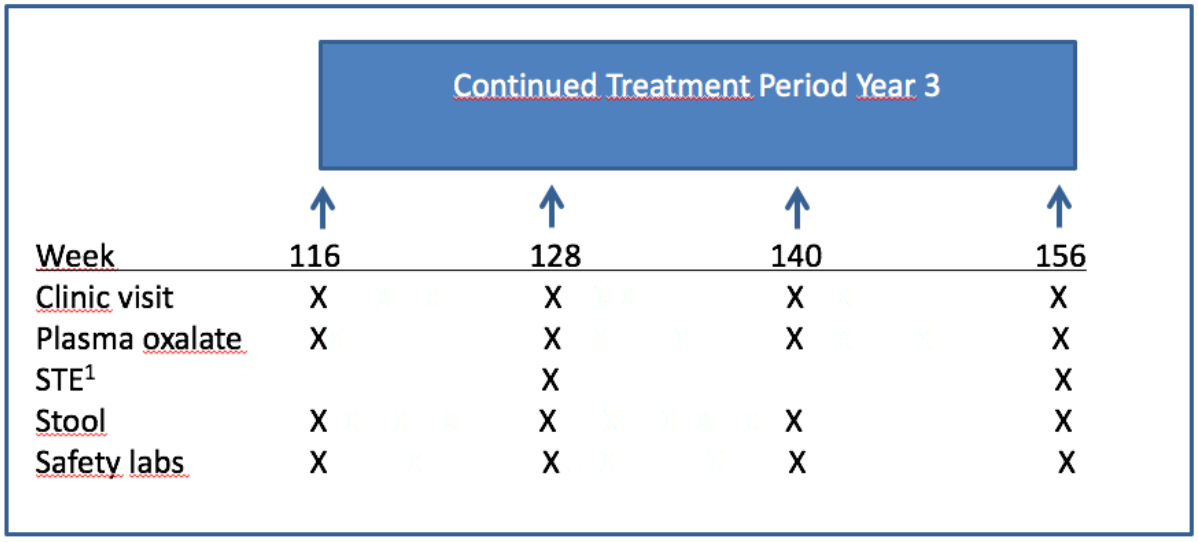
[1] After the post-treatment period, patients will be offered continous treatment for 36 months or until transplantation.
2 Speckle Tracking/Traditional Echocardiography should be done at screening visit +/- 1 month.

Figure 7: Study design for OC5-OL-01 continued treatment period Year 1 and 2



[1] Visit week 4 will be scheduled 28 days (+/- 3 days) after first day of continued treatment after study week 14.
2 Treatment Year 1 and 2 will continue with the same frequency of visits and collections until week 104 or until the patient is transplanted. Visit intervals and examinations/samplings will be kept the same throughout year 1 and 2 of the continued treatment period.
3 For patients who did not have a Speckle Tracking/Traditional Echocardiography performed at screening, an effort will be made to perform this examination before start of continued treatment.
4 Speckle Tracking/Traditional Echocardiography will be repeated every 6th month during year 1 and 2 of the continued treatment period in weeks 0, 24, 48, 72 and 104.

Figure 8: Study design for OC5-OL-01 continued treatment period Year 3



1 Speckle Tracking/Traditional Echocardiography will be repeated every 6th month during the continued treatment period year 3, in weeks 128 and 156.

Faecal samples will be collected for determination of *O. formigenes* at weeks 4, 10, 14, every 2 months throughout the first 24 months of the continued treatment period and every 3-4 months for the last 12 months of the continued treatment period. Faeces samples will be analysed at Institut fur Mikroökologie in Herborn, Germany.

Safety evaluation will include safety labs at weeks 0, 4, 10, 14, monthly throughout the first 24 months of the continued treatment period and every 3-4 months for the last 12 months of the continued treatment period. Physical examination will be done at weeks 0, 4, 10, 14, every second month during continued treatment year 1 and 2 and every 3-4 months during continued treatment year 3. Adverse events will be monitored throughout the study. Specimen samples will be analysed at a local laboratory.

For the course of the study, the patients should be instructed to maintain their normal diet and fluid intake as prescribed under their standard clinical care.

All patients will be monitored for safety and concomitant medication usage throughout the study period.

Monitoring of adverse events, concomitant medication and compliance with the administration of study drug will be performed at least once monthly at each study visit for the first two years of continued treatment and at least every 3-4 months during the last year of the continued treatment period.

6.2 Schedule of assessments

The assessments to be performed during the study are described in Table 4: Schedule of assessments – the first 14 weeks of the study, Table 5: Schedule of assessments – continued treatment Year 1 and 2 and Table 6: Schedule of assessments – continued treatment Year 3. The procedures are further described in Sections 6.2.1– 6.2.5.

Table 4: Schedule of assessments – the first 14 weeks of the study

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

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

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

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

Table 5: Schedule of assessments – continued treatment Year 1 and 2

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

1. Treatment will continue until the patient is transplanted. The maximal length of the continued treatment period will be 36 months. Visit intervals and examinations/samplings will be kept the same throughout the year 1 and 2 of the continued treatment period.
2 Visit 9 may coincide with visit 8 for patients continuing on treatment immediately after week 14 visit.
3. Visit 10 will be scheduled 28 days (+/- 3 days) after first day of continued treatment after study week 14.
4. Safety labs include: haematology analysis, clinical chemistry analysis and urinalysis and will be analysed at the local lab.
5. Pregnancy test will be repeated every 6 months during the continued treatment period.
6. For patients who did not have a Speckle Tracking/Traditional Echocardiography performed at screening, an effort will be made to perform this examination before start of continued treatment.
7. Speckle Tracking/Traditional Echocardiography will be repeated every 6th month during the continued treatment period in weeks 0, 24, 48, 72 and 104.

Table 6 Schedule of assessments – continued treatment Year 3

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

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

6.2.1 Screening

Patient Information must be given and the Informed Consent form must be signed prior to any study related procedures being performed. The investigator shall list all patients who are considered for participation in the study and who have signed the Informed Consent on a Screening and Inclusion log.

The inclusion and exclusion criteria should be reviewed. Demographics and baseline data will be collected. These include:

- Birthdate, height, weight.
- Physical examination and Vital Signs.
- PH medical history (including diagnosis, historical levels of urinary oxalate, renal function).
- Other medical history, including concurrent illnesses and symptoms.
- Concomitant medication.

The following samples should be taken and sent for analysis:

- Haematology analyses, clinical chemistry analyses and pregnancy test.
- Urine sample for urinalysis, if possible.

The patient should be on a stable dialysis regimen individualised to remove adequate oxalate to minimise the risk for systemic oxalosis for at least two weeks prior to baseline (two weeks before visit week 2). The regimen could be either HD or PD or a combination of HD and PD. The PD regimen (number of days/week, hours per treatment, volume of dialysis buffer) and HD regimen (number of days/week; hours per treatment; blood and dialysate flow rates; and HD membrane) will be maintained unchanged for the duration of the study. This will be monitored and recorded by measuring volume of spent dialysate from HD and PD and quantifying dialysis dose of each HD session in terms of Kt/V measurement using an online clearance monitor.

Speckle Tracking Echocardiography and traditional echocardiography will be performed, if possible, at screening visit (+/- 1 month) or before start of continued treatment period (at visit week 14). Speckle Tracking Echocardiography will then be repeated at week 24 in the continued treatment period and thereafter every 6 months until end of treatment, if possible.

The patient (and parents when applicable) will be instructed how to collect faeces samples, and dates for collection will be scheduled. See section 6.3 for further information on collections at patient´s home. For the course of the study, the patient should be instructed to maintain their normal diet and fluid intake as prescribed under their standard clinical care. The patient will be asked to avoid taking ascorbic acid preparations or multivitamin preparations during the study period. The patient will be scheduled for a week 2 visit.

6.2.2 Baseline

During baseline plasma oxalate sampling will be done at week 2 and 4. The blood sample will be taken after two consecutive days of dialysis on the preceding days, but prior to the dialysis session on the day of sampling. The blood sample will be processed at the clinical site and the acidified plasma will be shipped frozen to the central

laboratory (Academical Medical Center, Amsterdam, The Netherlands) for determination of oxalate using the Isotope dilution Gas Chromatography with mass selective detection (GC-MSD). Plasma oxalate will also be determined using the Ion Chromatography method at Bonn University Clinical laboratory, Germany.

Safety labs and faecal testing for *O. formigenes* will be performed in week 4.

The faeces sample will be collected either at patient´s home or at the clinic and shipped for analysis at Institut für Mikroökologie, Herborn, Germany.

Any changes in concomitant medication will be recorded in the CRF at visit week 2 and 4. At week 4 each patient's eligibility will be reviewed to assure that no exclusionary conditions have developed since the screening visit. The result from the week 2 plasma oxalate sample (total plasma oxalate) will be reviewed for patient eligibility at this point.

For patients who fail any of the inclusion or exclusion criteria, applicable parts of the CRF should be completed and they should be recorded as screening failures in the Screening and Inclusion log.

After verification of the inclusion and exclusion criteria, the patient will be included in the study to receive study treatment.

At the clinical visit week 4 the patient and/or the parents will be instructed about the administration procedures for the study drug. See section 8.1 regarding dose administration. The patient will be scheduled for clinic visits at week 6, 8, 10, 12 and week 14.

6.2.3 Treatment period – the first 6-week treatment period (study week 5-10)

During the initial 6 weeks treatment period, the patient will be followed by clinic visits at week 6, 8 and 10, according to Table 4: Schedule of assessments – the first 14 weeks of the study.

At the clinic visits, a blood sample for plasma oxalate will be taken prior to the dialysis session.

At week 10, faecal sample will be taken as well as safety labs.

At each clinic visit the patient will be assessed for the presence or absence of Adverse Events and changes in concomitant medications.

The patient will receive shipments of study drug bi-weekly at week 4, 6 and 8. Remaining study drug will be returned to the clinic or site pharmacy at clinical visits weeks 6, 8, 10 and 12.

6.2.4 Post treatment period – 4 weeks without study drug (study week 11-14)

During the post-treatment period study visits will take place at week 12 and 14. A blood sample will be taken for determination of plasma oxalate prior to the dialysis session in week 12 and 14.

At week 14 faecal sample will be taken as well as safety labs.

At each clinic visit the patient will be assessed for the presence or absence of Adverse Events and changes in concomitant medications. At the clinical visit week 14 a physical examination including vital signs will be performed.

Adverse Drug Reactions (i.e. AEs that are possibly or probably related to study treatment, see section 11.1), which are unresolved at the time of week 14 clinic visit, should be followed until the event has resolved or, if persistent, has been assessed as "chronic" or "stable" for patients not participating in the continued treatment period.

6.2.5 Continued treatment period

Addendum to the ICF needs to be signed for patients who agree to continue on treatment with study drug after the week 14 visit. During the first 24 months of the continued treatment period the patient will be followed by clinic visits every 4th week and during the last 12 months every third or fourth month, please see Table 5: Schedule of assessments – continued treatment Year 1 and 2 and Table 6 : Continued treatment Year 3. Patients who are already treated in year 3 of continued treatment at the time of implementation of this amendment will continue on the previous monthly visit schedule for year 3.

At the clinic visits, blood samples will be taken, prior to the dialysis session, for plasma oxalate as well as for safety labs. Pregnancy test will be taken at continued treatment week 0 (clinic visit 9) and repeated every 6 months during the continued treatment period, for women of childbearing potential.

Faecal sample will be taken every 8th week for the first 24 months of the continued treatment period and thereafter every 12th or 16th week.

At each clinic visit the patient will be assessed for the presence or absence of Adverse Events and changes in concomitant medications.

The patient will receive a shipment of study drug bi-weekly throughout the treatment period. Remaining study drug/empty vials will be returned to the clinic or site pharmacy at the next clinical visit, or the visit thereafter if new supply has not yet been received by the patient.

Speckle Tracking Echocardiography and traditional echocardiography will be done. If the examination could not be done at screening, an effort will be made to perform the examination before start of continued treatment period (at week 0 of the continued treatment, clinic visit 9). The examination will then be repeated at week 24 in the continued treatment period and thereafter every 6 months until end of treatment.

6.3 Specimen collection at patient's homes

The collections of faeces will be performed by the patients either in their home environment or at the clinic, and should be performed according to Table 4: Schedule of assessments – the first 14 weeks of the study, Table 5: Schedule of assessments – continued treatment Year 1 and 2 and Table 6: Schedule of assessments – continued treatment Year 3. The sponsor will provide collection kits and a Patient Handbook describing the collection procedures. The delivery of collection kits to patients´ homes and pick-up of collections, if applicable, will be done by a courier.

6.4 Diet

For the course of the study, the patients will be instructed to maintain their normal diet and fluid intake as prescribed under their standard clinical care. They will be asked to avoid making significant changes in their diet during the study specially related to high oxalate foods and fluid intake.

The patients will be asked to refrain from ascorbic acid preparations or multivitamin preparations during the study. Vitamins given as standard of care for patients on dialysis are allowed during the study.

7 SELECTION AND WITHDRAWAL OF PATIENTS

7.1 Patient inclusion criteria

1. Signed informed consent (as applicable for the age of the patient). An appendix to the informed consent form will be signed by patients continuing on treatment after week 14.
2. Male or female patients≥ 2 years of age. Patients have to be able to swallow size 4 capsules twice daily, or use a gastric tube that allows for administration of size 4 capsules.
3. A diagnosis of PH (as determined by standard diagnostic methods).
4. Patient should be on a stable dialysis regimen for at least two weeks before baseline.
5. Plasma oxalate ≥40 micromole/L prior to the dialysis session.
6. Patients receiving vitamin B6 must be receiving a stable dose for at least 3 months prior to screening and must remain on the stable dose during the study. Patients not receiving vitamin B6 at study entry must be willing to refrain from initiating vitamin B6 during study participation.

7.2 Patient exclusion criteria

7. Inability to swallow size 4 capsules twice daily, or using a gastric tube not suited for administration of size 4 capsules via the tube.
8. Ongoing treatment with immunosuppressive medication.
9. The existence of secondary hyperoxaluria, e.g. hyperoxaluria due to bariatric surgery or chronic gastrointestinal diseases such as cystic fibrosis, chronic inflammatory bowel disease and short-bowel syndrome.
10. Use of antibiotics to which *O. formigenes* is sensitive (see section 8.2.2), including current antibiotic use, or antibiotics use within 14 days of initiating study medication.
11. Current treatment with a separate ascorbic acid preparation. Standard of care vitamin supplement for patients on dialysis are allowed.
12. Pregnancy.
13. Women of childbearing potential who are not using adequate contraceptive precautions. Sexually active females, unless surgically sterile or at least 2 years post-menopausal, must be using a highly effective contraception (including oral, transdermal, injectable, or implanted contraceptives, IUD, abstinence, use of a condom by the sexual partner or sterile sexual partner) for 30 days prior to the first dose of OC5 and must agree to continue using such precautions during the clinical study.

14. Presence of a medical condition that the Principal Investigator considers likely to make the patient susceptible to adverse effect of study treatment or unable to follow study procedures.
15. Participation in any study of an investigational product, biologic, device, or other agent within 30 days prior to the first dose of OC5 or not willing to forego other forms of investigational treatment during this study.

7.3 Patient withdrawal criteria

If a patient fails to return for a scheduled study visit the investigator will make a reasonable effort to contact the patient and determine why the patient failed to return and to schedule a new study visit. Any information obtained during this contact will be documented in the study records.

A study patient will be discontinued from participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, illness, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the patient.
- OxThera or the Principal Investigator in consultation with OxThera may discontinue the patient at any time for medical and/or administrative reasons.
- The patient withdraws consent from participating in the study at any time.
- The patient undergoes a transplantation procedure.
- There are major protocol violations.

Any patient who withdraws prematurely from the first 14 weeks of the study will be asked to complete all study assessments described for the week 14 clinical visit. For patients who withdraw during the continuation phase of the study, the last data collected will be that from the last performed study visit.

For any patient who has withdrawn, the date of withdrawal from the study and the reason for withdrawal will be recorded in the source data and CRF. Adverse Drug Reactions (i.e. AEs that are possibly or probably related to study treatment, see section 11.2), which are unresolved at the time of withdrawal, should be followed until the event has resolved or, if persistent, has been assessed as “chronic” or “stable”.

Withdrawn patients should not be re-entered into the study. Additional patients, if available, may be enrolled at the discretion of the Sponsor.

8 TREATMENT OF PATIENTS

8.1 Description of study treatment

The study drug consists of OC5 as the active treatment. The study drug is supplied as enteric-coated capsules. One capsule shall be administered orally with water twice daily with breakfast and dinner. For patients using a gastric tube the capsules may be administered through the tube. The study product is described in more detail in section 9.

8.2 Concomitant medications

Any medications including over-the-counter medications or herbal supplements will be recorded as concomitant drug therapy on the case report form. Patients will continue any medications they are receiving at study entry for underlying medical conditions and the medications will be recorded at screening and changes will be noted throughout the study.

8.2.1 Concomitant treatment with vitamin B6

Patients receiving vitamin B6 (pyridoxine) prior to study entry must be on a stable dose for at least 3 months prior to the screening visit. Patients who are not receiving vitamin B6 at study entry will not be allowed to initiate vitamin B6 during study participation. Patients will be encouraged not to change the dosing of vitamin B6 or discontinue vitamin B6 during study participation except for any safety events considered related to vitamin B6.

8.2.2 Prohibited medications

Patients are not allowed to receive any other investigational therapies during study participation.

Other prohibited medications are:

- Ascorbic acid preparations: Ascorbic acid preparations must not be used during the study period. Standard of care vitamin supplements for patients on dialysis are allowed.
- Multiple dosing antibiotics: Patients that require chronic antibiotics, or more than two courses of acute antibiotics, to which *O. formigenes* is sensitive will discontinue study drug and be followed for safety. If a short-term antibiotics therapy is indicated to treat acute bacterial infections, patients should receive standard of care.
    - *O. formigenes* has shown resistance to ceftizoxime, imipenem, ampicillin, amoxicillin and penicillin. These are the preferred antibiotics for standard of care.
    - *O. formigenes* has shown sensitivity to chloramphenicol, doxycycline, erythromycin, and tetracycline.
- Immune suppressive therapy

8.3 Treatment compliance

Patients will be provided with a study drug diary to record doses taken/missed. Compliance to study treatment will be questioned at each visit to the clinic. Any missed doses or doses lost during handling will be registered.

Unused medication will be returned to the clinic or site pharmacy at clinical visits weeks 6, 8, 10 and 12 during the first 14 weeks of the study. The unused medication will be accounted for an overall check of compliance.

For the continued treatment period, study drug will be returned to the clinic or site pharmacy at the next clinical visit, or the visit thereafter if new supply has not yet been received by the patient.

9 STUDY DRUG MATERIALS AND MANAGEMENT

9.1 Study drug

OC5 is the active treatment and is supplied as enteric-coated, size 4, gelatine capsules. One capsule contains NLT 1E+09 CFU. Details on the product are described in Table 7 below.

Table 7: Details of the study drug in the OC5-OL-01 study

Parameter	**High Dose**
Active Substance	Lyophilised *O. formigenes*, strain HC-1
Name	Oxabact® (OC5)
Route of Administration	Oral
Dose form	Enteric-coated capsule
Viable cell count	NLT 1E+09 CFU/dose, NMT 5E+10 CFU/dose
Excipients	Oligofructose, Maltodextrin, Alginate, Sucrose, Microcrystalline cellulose

9.2 Study drug packaging and labelling

Capsules will be filled into sealed aluminium tubes. A transition to tubes containing 18 capsules rather than 14 capsules was done during 2019, to include some overage medication in each tube. A desiccant will be present in the lid of the tube.

The label, including patient number, will be placed on the aluminium tube and on secondary packaging (transparent bag) holding the aluminium tubes.

The product will be labelled to meet each country´s regulatory requirement.

9.3 Study drug storage

Study medication provided by the sponsor must be stored in a temperature-controlled freezer (-20°C +/- 5°C), in a locked area at site pharmacies before dispensing and delivery to patients. Study medication should be stored refrigerated (2°C to 8°C) at the patients' home, current stability data supports up to 4 weeks refrigerated storage.

9.4 Study drug accountability, handling and disposal

OxThera will supply study medication through the designated drug depot to all sites in the study.

The drug depot will complete a drug inventory log to document receipt and distribution of study drug. They will send study drug to the site pharmacies as a controlled shipment at -20°C +/- 5°C. The site pharmacies will store study medication in a temperature-controlled freezer (-20°C +/- 5°C), in a locked area. The site pharmacies will distribute study drug to patients and will inform patients that study capsules should be stored refrigerated (2°C to 8°C) at their homes in securely sealed tubes. Patients will be supplied with sufficient capsules for two weeks treatment, every second week.

Unused study medication and empty vials will be returned to the clinic or site pharmacy at clinical visits weeks 6, 8, 10 and 12 for the first 14 weeks. For the continued treatment period, remaining unused study drug and empty vials will be returned to the clinic or site pharmacy at the next scheduled visit to the clinic after each delivery of new supply. The pharmacy will document receipt of unused study medication. Any surplus of study medication will be reviewed and properly documented by the study monitor, and returned to the sponsor.

Investigational products deliberately and/or accidentally destroyed in transit or at a study site should be accounted for and documented.

10 ASSESSMENT OF EFFICACY

The main efficacy parameter to be assessed is:

- Change in total plasma oxalate level during OC5 treatment, compared with an average of the baseline values.

Secondary efficacy parameters to be assessed are:

- To evaluate the efficacy of OC5 to reduce free plasma oxalate levels during OC5 treatment in patients with Primary Hyperoxaluria (PH) who are on dialysis.
- Change in number of *O. formigenes* in faeces during OC5 treatment.
- Change in plasma oxalate values from week 10 to week 14, following the 4-week off-treatment period.
- To evaluate results from Speckle Tracking Echocardiography and traditional echocardiography for patients where this examination could be performed.

10.1 Plasma oxalate

Samples for plasma oxalate will be collected during clinical visits, as specified in Table 4: Schedule of assessments – the first 14 weeks of the study, Table 5: Schedule of assessments – continued treatment Year 1 and 2 and Table 6: Schedule of assessments Year 3. These samples have to be taken after two consecutive days of patient's standard dialysis regimen, but prior to the dialysis session on the day of sampling.

Samples for plasma oxalate will be processed at the clinical site and analysed for total plasma oxalate concentration at Academic Medical Center, Amsterdam, the Netherlands using Isotope dilution Gas Chromatography with mass selective detection (GC-MSD). Samples will also be analysed for free plasma oxalate at the University Clinical laboratory in Bonn using Ion Chromatography (IC). Each site will be provided with kits and supplies for collection, processing and shipping of blood samples for determination of plasma oxalate. Complete instructions for the collection, processing, storage and shipping of sample will be provided in the site manual. Available local lab results for free plasma oxalate performed as standard of care during the study, but before the effective date for Amendment VII (which introduced this analysis method in the protocol) will be captured retrospectively and included in the statistical analysis.

10.2 Quantification of *O. formigenes*

The possibility to monitor the natural occurrence of *O. formigenes* bacteria and the presence of the *O. formigenes* bacteria during and after treatment with OC5 is an important tool for control of the pharmacodynamics of the drug. A real-time quantitative PCR assay will be used that permits determination of the levels of *O. formigenes* and its change over time in faecal samples.

Faecal samples will be collected either at patients' home or at the clinic and shipped to central laboratory MVZ Institut für Mikroökologie GmbH, Auf den Lüppen 8, 35745 Herborn, Germany.

10.3 Speckle Tracking Echocardiography and Traditional Echocardiography

Speckle Tracking Echocardiography is currently evaluated as a method to detect and quantify oxalate deposits in the heart muscle.[13] Speckle Tracking Echocardiography and traditional echocardiography will be performed at screening (alternatively before start of continued treatment) and repeated every 6 months during the continued treatment period, if possible. The examination will be performed locally using specific equipment. Images will be interpreted by a central reader who is blinded to plasma oxalate and examination date.

Speckle Tracking Echocardiography results will be evaluated for changes in Global Longitudinal Strain, including segmental changes, Short-Axis Myocardial Function, Rotational Displacement and Apical Sparing Patterns. Traditional echocardiographic parameters will also be evaluated (Ejection Fraction, End Diastolic Volume, e/é, e/a, Left Ventricular End Diastolic Dimension, Fractional Shortening, Tricuspid Regurgitation by Doppler as an indicator of RV/pulmonary pressure). A positive treatment effect would be an improved myocardial function based on the above-mentioned parameters, decreased Global Longitudinal Strain, improved Rotational Displacement and reduced/removed Apical Sparing Pattern. The treatment effect on STE parameters will be compared to traditional echocardiography parameters of LV and RV function to determine which assessment of cardiac function is more sensitive in these patients.

Speckle Tracking Echocardiography examinations performed during the study, but before this amendment´s effective date will be re-evaluated to retrospectively capture the above-mentioned parameters to be included in the statistical analysis.

11 ASSESSMENT OF SAFETY

The safety parameters to be assessed are:

- Adverse Events
- Laboratory safety measurements

11.1 Definition of Adverse Events

Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical study patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including 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 include 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 are within what is normally experienced they should not be recorded as adverse events. If the symptoms are worse than what is normally experienced, then they should be recorded as adverse events.

An AE does **not** include:

• Symptoms of the underlying disease 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 patient'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 drug 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. Abnormal laboratory values will be recorded in the study database.

Adverse Drug Reaction (ADR)

An AE is defined as an adverse drug reaction (ADR) if further analyses prove that the AE is 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 drug, expected from analogue conclusions or theoretical considerations related to toxicological, pharmacological or kinetic characteristics.

Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is one that suggests a significant hazard, contraindication, side effect or precaution that results in:

- the patient'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 other important medical event as determined by the Investigator.

* 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.

** Hospitalisation requires over-night 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.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected Unexpected Serious Adverse Reaction (SUSAR) is a suspected unexpected serious adverse reaction

In cases of doubt on this issue, it is suggested that there should be a predisposition to report rather than not to report (see section 11.4).

11.2 Relationship to study drug

The following relationships to study drug will be used in the study. Events classified as possible, probable, or definitely will be considered related to study drug.

Not related:

The event does not follow a plausible chronological sequence relative to trial medication administration and can be clearly assigned to other factors, such as patient's clinical condition, therapeutic procedures or administration of concomitant medications.

Possible:

There is sufficient information to accept the possibility of a causal relationship, although the connection is uncertain or doubtful, i.e. causal relationship is not impossible and not unlikely. The event follows a plausible chronological sequence relative to trial medication administration and/or presents the usual response to the drug tested. The event might also be caused by other factors, such as the patient's clinical condition, therapeutic procedures or administration of concomitant medications.

Probable:

There are good reasons and sufficient documentation to assume a causal relationship in the sense of plausible, conceivable, likely, but not necessarily highly probable. The event follows a plausible chronological sequence relative to trial medication administration and/or presents an unexpected response to the trial drug and cannot reasonably be explained by other factors, such as the patient´s clinical condition, therapeutic procedures or administration of concomitant medications.

Definitely:

When the event cannot be attributed to the patient's underlying medical condition or other concomitant therapy and there is compelling temporal relationship between the onset of the event and the study investigational product administration that leads the PI to believe there is evidence of a reasonable causal relationship.

11.3 Recording Adverse Events

Each patient will be questioned about AEs at each clinic visit/ following initiation of treatment. The question asked will be "Since your last clinic visit have you had any health problems?" The information can also be obtained from signs and symptoms detected during each examination, observed by the study personnel or spontaneous reports from the study patients or by lab results.

The investigator is to record in the CRFs all directly observed AEs, all AEs as a response of the open question and all AEs spontaneously reported by the patient during the study.

The investigator will record all AEs by:

- Description of event (recorded in standard medical terminology and avoiding abbreviations),
- Start and end date,
- Intensity* (mild, moderate or severe),
- Seriousness (serious or not serious, according to definition),
- Causal relationship, (definitely, possible, probable, unrelated)
- Action taken, (none, treatment required, patient withdrawn, other)
- Outcome of the AE (recovered, recovered with sequelae, death, not recovered)

The Sponsor or delegate will code all AEs and SAEs using MedDRA.

* For each reported AE, the intensity will be recorded. The following definitions of intensity are to be used:

  - *Mild:* A mild AE means awareness of symptoms or signs, but easily tolerated (acceptable).
  - *Moderate:* A moderate AE means enough discomfort to interfere with usual activity (disturbing).
  - *Severe:* A severe AE means incapacity to work or to do usual activity (unacceptable)

If the intensity changes within 24 hours the maximum intensity should be recorded. If the intensity changes over a longer period of time, the changes should be recorded in the CRF.

11.4 Reporting Adverse Events

Adverse Event reporting on each patient shall start at the initiation of study treatment. The reporting shall continue during the course of the study. Spontaneously reported events by study patients in between planned visits shall also be reported. Adverse Drug Reactions, which are unresolved at the time of the last follow-up visit should be followed until the event has resolved or, if persistent, has been assessed as “chronic” or “stable”. AEs should be reported for all patients, independent of treatment assignment.

NON-SERIOUS AEs are to be reported in the CRF.

SAEs are to be reported by the investigator to ProductLife Department via the form in the eCRF or via fax (+**44 1223 413689**) or email (**safety@productlife-group.com**).

In case of any question related to SAE reporting please contact Drug Safety Physician/ Medical Monitor, see contact information in Table 1. The initial SAE form (provided in the eCRF and in the Investigational Site File (ISF)) should be completed within 24 hours of awareness of the event. All SAEs must be reported whether or not considered drug related. SAEs should also be reported in the CRF.

Completed Serious Adverse Event Reports should be submitted to ProductLife Pharmacovigilance Department within 24 hours of awareness by eCRF, fax (**+44(0) 1223 413 689**) or email (**safety@productlife-group.com**).

After receipt of the initial report, ProductLife Pharmacovigilance Department will forward the information to OxThera. Timelines for reporting and forwarding information are detailed in the Safety Management Plan. ProductLife Pharmacovigilance Department will work with OxThera to review the information received and contact the site to request any missing information/amendments needed. When follow-up information is obtained by the investigator it should also be forwarded to the Medical Monitor within 24 hours. The report should be marked "Follow-up report". Any follow-up received should be treated in the same way as initial reports.

The investigator will submit copies of SAE reports to the independent ethics committee concerned as required by local regulations. All serious and unexpected adverse events will be reported to the European authorities as per regulations.

An Unexpected Adverse Reaction is any adverse reaction, the specificity or severity of which is not specified in the current Investigator's Brochure for the study drug.

A SUSAR is a Suspected Unexpected Serious Adverse Reaction. All SUSARs that are possibly, probably or definitely related to OC5 are subject to expedited reporting to Regulatory Authorities, Ethic Committees and participating investigators in accordance with local requirements in force and the ICH guidelines for Good Clinical Practice (GCP) and the EU Directive 2001/20/EC. ProductLife Pharmacovigilance Department will be responsible for ensuring expedited reporting of SUSARs.

The investigator is responsible for ensuring that there are procedures and expertise available to handle emergencies during the study.

11.5 Anticipated Adverse Events

11.5.1 Review of available data

OC3 has been evaluated in several clinical studies in patients with PH; one 28-day phase I/II study (OC3a), one 24-week double blind placebo-controlled multicentre international phase II/III clinical study including a 24-week open-label extension study (OC3b), and one 24-week double-blind placebo-controlled multicentre international phase II/III clinical study (OC3b buffer formulation), see Table 3. OC5 has been evaluated in one completed double-blind placebo-controlled multicentre international phase II study, the current ongoing phase II open-label study, and two ongoing phase III trials, see Table 3. In summary OC3 and OC5 have been evaluated in over 100 subjects receiving a dose of up to 10^9 CFU twice a day. The continuous exposure to study drug ranged from 4 weeks up to 3 years. Both OC3 and OC5 were considered safe and well tolerated in all clinical studies.

Review of the safety data from all the completed studies indicate that patients may experience headache and gastrointestinal symptoms including abdominal pain,

constipation, nausea, vomiting, diarrhoea, and flatulence.

No treatment related serious adverse events for Oxabact® were reported in patients with PH. In all studies, the majority of adverse events were reported as mild and unlikely related to the treatment. In the placebo-controlled studies, the adverse events were equally distributed between Oxabact® and placebo.

As a safety precaution, children were not treated with OC5 in the OC5-OL-01 study until the 4-week safety data from at least two adult patients in the OC5-DB-01 study had been reviewed.

11.5.1.1 Safety data for OC5-DB-01 study

28 patients were randomised in the OC5-DB-01 trial; 14 patients received OC5 and 14 patients received placebo. The first patient was enrolled in December 2013 and the last patient last visit (LPLV) was in January 2015.

There were 67 adverse events (AEs) and three serious adverse events (SAEs) reported throughout the OC5-DB-01 study. These are summarised in Table 8 and Table 9 below.

Table 8: Summary of all adverse events in OC5-DB-01 (safety analysis set).

	OC5 (N=14)		Placebo (N=14)		Total (N=28)	
	n (%)	m	n (%)	m	n (%)	m
Any adverse events	10 (71.4)	41	12 (85.7)	26	22 (78.6)	67
Any serious adverse events	3 (21.4)	3	0	0	3 (10.7)	3
Adverse events by relationship						
Not related	9 (64.3)	26	10 (71.4)	15	19 (67.9)	41
Possible	6 (42.9)	14	6 (42.9)	10	12 (42.9)	24
Probable	0	0	0	0	0	0
Definitely	1 (7.1)	1	1 (7.1)	1	2 (7.1)	2
Adverse events by intensity						
Mild	9 (64.3)	28	12 (85.7)	23	21 (75.0)	51
Moderate	6 (42.9)	11	2 (14.3)	2	8 (28.6)	13
Severe	2 (14.3)	2	1 (7.1)	1	3 (10.7)	3
Adverse event leading to withdrawal	0	0	0	0	0	0
Adverse event leading to death	0	0	0	0	0	0

n: Number of patients; m: Number of mentions
Percentage is based on number of patients in safety analysis set

Three patients (all in the OC5 group) experienced SAEs. No SAE was judged to be related to the treatment and none required a change in dose. Brief summaries of the SAEs are presented as follows:

- Patient SCR01-0009: a 16-year-old male experienced radius fracture approximately 1 month after initiation of OC5 treatment.
- Patient SCR02-0001: a 13-year-old female experienced pyelonephritis approximately 7 weeks after initiation of OC5 treatment. Her condition was judged to be severe and unrelated to the study treatment.

- Patient SCR03-0005: an 18-year-old male experienced renal colic approximately 6 weeks after initiation of OC5 treatment. His condition was judged to be severe and unrelated to study treatment.

Table 9: Summary of types of adverse events experienced in OC5-DB-01 (Safety analysis set).

	OC5 (N=14)		Placebo (N=14)		Total (N=28)	
	n (%)	m	n (%)	m	n (%)	m
Any adverse event	10 (71.4)	41	12 (85.7)	26	22 (78.6)	67
Gastrointestinal disorders	6 (42.9)	14	5 (35.7)	7	11 (39.3)	21
Infections and infestations	3 (21.4)	3	4 (28.6)	5	7 (25.0)	8
Nervous system disorders	1 (7.1)	2	5 (35.7)	5	6 (21.4)	7
Respiratory, thoracic and mediastinal disorders	2 (14.3)	3	3 (21.4)	4	5 (17.9)	7
Renal and urinary disorders	4 (28.6)	7	0	0	4 (14.3)	7
Renal colic	2 (14.3)	3	0	0	2 (7.1)	3
Renal pain	2 (14.3)	2	0	0	2 (7.1)	2
Calculus urethral	1 (7.1)	1	0	0	1 (3.6)	1
Pyelonephritis	1 (7.1)	1	0	0	1 (3.6)	1
General disorders and administration site conditions	3 (21.4)	6	1 (7.1)	1	4 (14.3)	7
Skin and subcutaneous tissue disorders	3 (21.4)	3	0	0	3 (10.7)	3
Musculoskeletal and connective tissue disorders	1 (7.1)	1	1 (7.1)	1	2 (7.1)	2
Injury, poisoning and procedural complications	1 (7.1)	1	0	0	1 (3.6)	1
Psychiatric disorders	1 (7.1)	1	0	0	1 (3.6)	1
Ear and labyrinth disorders	0	0	1 (7.1)	1	1 (3.6)	1
Investigations	0	0	1 (7.1)	1	1 (3.6)	1
Reproductive system and breast disorders	0	0	1 (7.1)	1	1 (3.6)	1

n: Number of patients; m: Number of mentions
Adverse events are coded according to MedDRA version 16.1
Percentage is based on number of patients in safety analysis set

Ten patients (71%) in the OC5 group experienced an AE, which was similar to the number in the Placebo group (12; 86%). A greater number of individual AEs were mentioned in the OC5 group than in the Placebo group (41 versus 26). Four patients in the OC5 group experienced renal and urinary disorders (seven mentions in total); no AEs in this system organ class were reported in the Placebo group.

The occurrence of AEs was similar in the two groups. Although more renal and urinary disorders were experienced by patients in the OC5 group than in the Placebo group (four patients [29%] versus no patients [0%]), only one occurrence was considered related to the treatment (Patient SCR01-0002; kidney pains, moderate, possibly related).
Two AEs were judged to be definitely related to treatment. Patient SCR01-0001 (OC5) experienced a case of mild rumbling stomach, which began the day that treatment commenced and resolved the day after treatment ended. Patient SCR07-0004 (Placebo) experienced a case of mild diarrhoea the day after treatment started.

Four AEs were of at least moderate severity and judged to be possibly related to the treatment: a moderate case of gastroenteritis (OC5; SCR01-0018), the aforementioned case of kidney pains (OC5; SCR01-0002), a moderate case of increased bowel movements (OC5; SCR03-0005) and a case of severe headaches (Placebo; SCR07-0004). No AEs required changes of dose.

Overall the safety data accrued to date would suggest that the OC5 drug product is safe and well tolerated and appears to have a similar safety profile as the earlier OC3 drug product.

11.5.1.2 Safety data for the ongoing studies OC5-OL-01, OC5-DB-02 and OC5-OL-02

The current OC5-OL-01 study started in May 2014 and is ongoing in Germany. Fourteen subjects were screened and 12 subjects have been enrolled in the study and received study drug. This study includes late-stage patients with ESRD who are on dialysis. Most of these patients are on a waiting list for transplantation. Eight subjects continued into the continued treatment phase of the study, and one subject currently remains in the study (as of September 2019). There have been no severe nor serious related AEs for Oxabact® in this ongoing study.

In the ongoing, double-blind OC5-DB-02 study in patients with retained but reduced kidney function (eGFR <90ml/hr/1.73m^2), 16 patients have been randomised. There have been 8 SAEs reported to-date; none of them was considered related to study drug. There have been no reported SAEs in the ongoing open-label OC5-OL-02 study (currently 4 enrolled patients).

Overall, the safety data accrued to date would suggest that the OC5 drug product is safe and well tolerated and appears to have a similar safety profile as the earlier OC3 drug product. Further safety information of the OC5-OL-01, OC5-DB-02 and OC5-OL-02 studies has been detailed in the current version of the Oxabact® Investigator's Brochure.

11.5.2 Systemic infections due to *O. formigenes*

O. formigenes is a commensal bacterium in the intestinal tract and is a strict anaerobe. Following an extensive search of the literature, there have been no reports of local or systemic infections where *O. formigenes* have been isolated. Preparations of *O. formigenes* have been administered to rats, pigs and humans without any apparent toxicity or side effects including local or systemic infections. In the completed clinical studies, no patient experienced any infection due to *O. formigenes*.

Any patient who develops signs and symptoms of bacteremia requiring hospitalisation should be evaluated to identify the source of infection (e.g., lung, GI tract, meningeal, etc.). Evaluation for the source of bacterial infection should include clinical and laboratory tests and cultures for common pathogens. Empiric antibiotic treatment should include coverage for common pathogens. It is recommended that an Infectious Diseases Specialist be consulted to assist in the assessment and management of the patient.

O. formigenes has shown sensitivity to chloramphenicol, doxycycline, erythromycin, and tetracycline. In the event of unexpected infection caused by the study medication erythromycin is the recommended first line antibiotic therapy in children and adults, and tetracycline is the recommended second line antibiotic therapy in older children and adults. If common pathogens have been excluded or if the infection is not

responding to erythromycin or tetracycline the study medication should be stopped until further evaluation.

11.5.3 Elevated levels of plasma formate

Since *Oxalobacter formigenes* converts oxalate to formate, there may be the possibility of elevated plasma formate levels following administration of high doses of OC5. Formate is a metabolite of methanol responsible for the toxicity observed with methanol poisoning. Typically, toxic effects require prolonged exposure to elevated plasma formate levels.

Previous studies with Oxabact® (including OC2, OC3 and OC5) in over 100 patients with doses ranging from NLT 10^7 to NLT 10^9 CFU have not indicated any signs or symptoms of elevated formate plasma levels, metabolic acidosis or methanol poisoning. The main manifestations of methanol poisoning are metabolic acidosis and ocular toxicity. Any patient who develops signs and symptoms of metabolic acidosis should be evaluated to identify the source (e.g. evaluation of serum bicarbonate, blood pH, anion gap, osmolality gap and plasma formate).

Formate accumulation in plasma is the main reason for acidosis in early, uncomplicated stages of metabolic acidosis.[14] Metabolic acidosis is characterised by low blood pH (arterial pH < 7.38 or venous pH < 7.34) or low levels of serum bicarbonate, HCO_3^- (< 18 mmol/L). Decreased levels of serum bicarbonate or blood pH will serve as an indication of elevated levels of formate. The OC5-OL-01 study will investigate these early signs of elevated plasma formate as part of routine safety labs. Low levels of serum bicarbonate or blood pH should trigger determination of the anion gap and the osmotic gap in order to confirm or rule out the diagnosis of metabolic acidosis due to elevated formate levels.

If metabolic acidosis is diagnosed, the acidosis should be corrected as quickly as possible and therapy provided, if appropriate. If a diagnosis due to elevated formate levels cannot be excluded or if the metabolic acidosis cannot be corrected by standard of care the study medication should be stopped until further evaluation. Further evaluation should then include levels of plasma formate and visual disturbance test.

11.6 Laboratory safety measurements

The laboratory safety tests include:

- Haematology: Complete Blood Count (CBC) with differential and platelet count.
- Chemistry: Blood Urea Nitrogen (BUN), creatinine, electrolytes (Na+, K+, Mg++, Ca++, HCO_3^-, Cl), glucose, pH, albumin, alkaline phosphatase, ALT, AST, total bilirubin, and total protein.
- Random Urine (Urinalysis): protein, glucose, pH.

Laboratory parameters from haematology, chemistry and urinalysis will be assessed at the local laboratory at each clinic. Laboratory safety tests will be performed as specified in Table 4: Schedule of assessments – the first 14 weeks of the study, Table 5: Schedule of assessments – continued treatment Year 1 and 2 and Table 6: Schedule of assessments – continued treatment Year 3.

12 STATISTICS

12.1 Statistical methods

Efficacy: The primary endpoint, change in total plasma oxalate from baseline, will be evaluated over time for each patient. Evidence for efficacy will be provided as the combined evaluation of individual case studies. Plasma oxalate levels will be measured on a monthly basis throughout the first 24 months of the continued treatment period and once every 3-4 months during the last 12 months of the continued treatment period. All secondary endpoints will be analysed using the same methodology.

For the primary endpoint the change in total plasma oxalate levels will be based on the average from two baseline measurements (week 2 and week 4) and one measurement every 4th week throughout the first 24 months of the continued treatment period and every 3-4 months during the last 12 months of the continued treatment period.

The change in plasma oxalate during 4 weeks follow-up period after the end of the 6 weeks treatment period with OC5, will be based on one measurement at week 10 and one measurement at week 14. The last observation will be carried forward in case of missing values at week 14 and/or week 10.

Two interim analyses will be performed: The first analysis will be based on patients who complete the first year of continued treatment. The second interim analysis will be based on all study data obtained up to 24 months. Both interim analyses will evaluate all captured efficacy and safety parameters.

The individual changes in plasma oxalate per week will also be calculated as an average slope using regression of plasma oxalate by week.

The study involves a small number of patients and natural history data on changes in total and free plasma oxalate for this population is limited. Response to treatment is likely to vary depending on the baseline plasma oxalate level, individual hepatic oxalate production and age of each patient. Accordingly, the sample size is not based on assumptions of efficacy outcome and statistical power, and the definition of analysis populations is not applicable. Any inferences from the data will be based on clinical relevance rather than statistical significance.

Safety: The safety will be summarised using descriptive statistics based on frequency, seriousness and severity of treatment emergent AEs. Clinically relevant changes in safety laboratory parameters will also be summarised.

All statistical analyses will be further defined in a Statistical Analysis Plan.

13 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution should permit study-related monitoring, audits, IEC review and regulatory inspections, and should provide direct access to the source data/medical record.

The monitor should verify that each patient has consented in writing to direct access to the original medical record/source data (by the use of written patient information and signed informed consent). During the monitoring, the data recorded in the CRFs by the investigator will be checked for consistency with the source documents/medical record by the study monitor (source data verification). Any discrepancies of data should be documented and explained in the monitoring reports.

For every patient, the medical records should include the minimum following information:

- patient number and study id
- date for information given, signing informed consent, screening
- treatments given, including investigational product(s)
- visits to the clinic
- AE/SAE, if any
- concomitant medication
- time and reason for discontinuation, if any

There are data that are recorded only on the CRF, which are associated with protocol-specific procedures and not with normal clinical care practice. For such clinical data the investigator would not be expected to duplicate the information. Source data location will then be specified in the Investigator file.

14 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Monitoring and audits

Monitoring of the study will be arranged by the sponsor according to GCP guidelines. Monitoring visits will be performed regularly to the study sites during the study, to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of consistency with data recorded on the Case Report Forms and product accountability will be performed as a part of the monitoring visits.

The study site may also be subject to quality assurance audits by the sponsor as well as inspection by the appropriate regulatory agencies.

It is important that the investigator and their relevant personnel are available during the monitoring visits and possible audits/inspections, that study related records are made available, and that sufficient time is devoted to the monitoring process.

14.2 Site personnel

Investigators and other key personnel shall provide curriculum vitae or equivalent, that will confirm their suitability for the clinical study. All investigators and key personnel

should be listed together with their responsibilities in the study on a signature and delegation log.

It is the responsibility of the Investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed.

15 ETHICS AND REGULATORY REQUIREMENTS

15.1 Ethics review

It is the responsibility of the investigator to obtain written approval of the study protocol (incl. the patient information and informed consent) and subsequent protocol amendments from the IEC. The investigator should file all correspondence with the IEC, and a list of the IEC composition (names and position) should be filed in the Investigator File. A copy of the IEC approval should be forwarded to the sponsor.

15.2 Ethical conduct of the study

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human patients adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions and applicable ICH GCP guidelines.

The investigator is responsible for complying with all reporting procedures applicable to their IEC such as the reporting of SAEs and the final study report.

15.3 Written informed consent

It is the responsibility of the investigator to give each patient, prior to inclusion in the study, full and adequate verbal and written information regarding the purpose and procedures of the study and the possible risks involved. The patients must be informed about their right to withdraw from the study at any time, and that such withdrawal will not affect their future medical care, treatment or benefits to which the patient is otherwise entitled. The patients should be informed that the results will be stored and analysed digitally, maintaining confidentiality in accordance with local data protection laws.

Furthermore, it is the responsibility of the investigator to obtain signed informed consent from all patients prior to initiation of any study-related activity. As the study involves children, age specific patient information sheets and parent information sheets should be prepared, and patient and/or parental consenting should depend on the age of the patient. The investigator or his/her designated representative, who gave the verbal and written information about the study to the patient, must also sign the informed consent form. A copy of the written patient information must be handed to each patient, to bring home. The investigator will confirm the receipt of informed consent from each patient by a recording in the CRF. The signed Informed Consent forms should be filed by the Investigator in the Investigator File for possible future audits and inspections.

The investigator must always use the current IEC approved Patient Information/Informed Consent Form and it must not be changed without prior discussion with the sponsor and approval from the IEC.

15.4 Regulatory requirements

The study will be performed in compliance with each country's regulatory requirements. As with the IEC, clinical trial authorisation from the appropriate Regulatory Authority(ies) must be sought and obtained (as applicable to local country regulations), prior to the start of the study. The investigational product for this study will not be shipped to a study site until a copy of the applicable Regulatory Authority approval has been received by the sponsor. In addition, the Regulatory Authority(ies) must approve amendments (as instructed by OxThera), receive SUSAR reports and annual safety updates or as required by local country regulations, and be notified of the end of the trial.

16 DATA HANDLING AND RECORDKEEPING

16.1 Case report forms

A Case Report Form (CRF) is required and should be completed for each included patient. The CRF must be signed and dated by the investigator who takes responsibility for the accuracy, completeness and legibility of the data reported to the sponsor in the CRFs.

Data validation will be performed after data have been entered, signed and monitored by computerised logical checks. Any discrepancies found in the data will generate queries. The queries will be sent to the site personnel and the responsible site monitor for further action.

16.2 Retention of records

All essential documents must be safely retained by the investigator for at least 2 years following the date a marketing application is approved for the drug, for the indication for which it is being investigated; or if no application is filed or if the application is not approved for such indication for 15 years after the investigation is discontinued and the regulatory authorities are notified.

16.3 Protection of personal data

The completion of the Study involves the collection and processing of Personal Data. All processing of Personal Data at the clinic and by the sponsor must be carried out in accordance with national legislation concerning the protection of Personal Data.

The investigator must ensure that the patient's privacy is maintained. On the CRF or other documents submitted to OxThera, patients will be identified by a patient ID number only. Documents that are not submitted to OxThera (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator.

The investigator shall permit direct access to patient s' records and source document for the purposes of monitoring, auditing, or inspection by OxThera, authorised representatives of OxThera, Regulatory Authorities and IECs.

As part of the required content of the informed consent, patients will be informed that their records may be reviewed by OxThera's designee and by regulatory agencies. Should access to medical record require a separate waiver or authorisation, it is the Investigator's responsibility to obtain such permission from the patient in writing before the patient is entered into the study.

17 FINANCING, INDEMNIFICATION AND INSURANCE

The Clinical Trial Agreement (CTA) outlines the compensation and payment terms of the study. The CTA must be signed before the start of the study. If there are differences between the CTA and the Protocol regarding certain rights and obligations the CTA is the prevailing document. Indemnification is covered by the CTA and by a separate Indemnification Agreement between the sponsor and the Institution if applicable.

OxThera has civil liability insurance, which covers this study in all participating countries.

18 CONFIDENTIALITY, INTELLECTUAL PROPERTY AND PUBLICATION POLICY

Investigator's, Institution's and OxThera IP AB's obligations regarding intellectual property, confidentiality and publication are described in detail in the CTA. They can be summarised as follows;

All information (whatever form) disclosed by OxThera to Institution, or generated pursuant to this study, shall be deemed to be confidential information. Except as required by applicable law, Institution shall not use or disclose to any party OxThera 's confidential information received pursuant to this study or otherwise, without the prior written consent of OxThera. All data generated or arising from the performance of the study shall be the exclusive property of OxThera.

It is intended to publish the results of the study as a whole once all patients have completed the study and the study has been analysed. If there is a publication, the Investigator that has the highest number of treated patients will be the lead author. The investigator may not publish the results of their cohort of patients until the full study has been submitted for publication. The investigator may not submit for publication or present the results of this study without allowing OxThera 30 days in which to review and comment on the pre-publication manuscript. The investigator may not submit the results of the study for publication without the prior consent of OxThera, unless the review period has passed and there has been no reaction from the sponsor.

19 CHANGES TO THE STUDY PROTOCOL

The investigator should not implement any deviation from or changes to the protocol without agreement with the sponsor and prior review and documented approval from the IEC and Regulatory Authorities, except where necessary to eliminate an immediate hazard to the patients. All changes to the final study protocol must be documented in a written protocol amendment.

20 REFERENCES

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21 APPENDICES

Appendix 1: Study protocol approval by investigator

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Protocol number: OC5-OL-01

Protocol Date: 2019-10-14

Protocol Version: 12, including Amendment XIII

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

Sponsor: OxThera Intellectual Property AB
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I, the undersigned, have read and understand the protocol specified above, and agree on the contents. The Study Protocol, the Clinical Trial Agreement/ Financial Agreement, and GCP Guidelines will serve as a basis for co-operation in this study.

Investigator: Gesa Schalk

Affiliation: Universitätsklinikum Bonn
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Signature:

Date: 2019-10-30
YYYY – MM – DD