Clinical trial results:
A phase III double-blind, randomized study to evaluate the long-term efficacy and safety of Oxabact® in patients with primary hyperoxaluria

Summary

EudraCT number	2017-000684-33
Trial protocol	DE GB NL ES BE FR
Global end of trial date	15 April 2021

Results information

Result version number	v1 (current)
This version publication date	01 October 2021
First version publication date	01 October 2021

Trial information

Trial identification

Sponsor protocol code	OC5-DB-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03116685
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	OxThera Intellectual Property AB
Sponsor organisation address	Regeringsgatan 111, Stockholm, Sweden, 11139
Public contact	Chief Operating Officer, OxThera Intellectual Property AB, 0046 86600223, elisabeth.lindner@oxthera.com
Scientific contact	Chief Operating Officer, OxThera Intellectual Property AB, 0046 86600223, elisabeth.lindner@oxthera.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000370-PIP02-18
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 August 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 April 2021
Global end of trial reached?	Yes
Global end of trial date	15 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of Oxabact® following 52 weeks treatment in patients with primary hyperoxaluria who had maintained kidney function, but below the lower limit of the normal range (eGFR < 90 ml/min/1.73 m2) and a total plasma oxalate concentration ≥ 10 µmol/L at baseline.

Protection of trial subjects:

Before any study-related examinations were done, patients received detailed patient information, study procedures were explained to them and they had the opportunity to ask questions. Patients (and/or their parents/guardians in case of patients <18 years of age) had to sign an informed consent to be able to participate in the study.

The IMP has previously been given to over 130 people without any major side effects but there may be side effects that are unknown at this time. Subjects could get gastrointestinal adverse events such as stomach problems or nausea. Some patients have also reported headache, cough and cold-like symptoms during treatment. There is also a risk of the bacteria getting in the patient's blood and causing an infection. So far there have been no reports of such infections caused by the bacterium but if this happens it can be treated with antibiotics. To monitor potential adverse events, patients were observed in the clinics during the study visits. Physical exam, vital signs and laboratory safety tests were taken at screening and every study visit.

Oxalobacter formigenes metabolises oxalate and forms a substance called formate. There is a theoretical risk that this may enter the patient's blood and make them ill. So far there have been no reports of such illnesses caused by the bacterium.

Since the effects of the study medication on pregnancy are unknown, female patients of child-bearing age had a pregnancy test before taking part to exclude the possibility of pregnancy. All women of childbearing potential needed to use adequate contraceptive precautions during the study. If they became pregnant while taking part in the study, the were asked to immediately tell the doctor.

Study related data was collected in electronic Case Report Forms (eCRFs). All data was anonymised and was treated confidentially in line with national requirements and GDPR regulations.

Background therapy:

Patients were allowed to receive Standard of Care, preferably in a stable manner throughout the study. Standard of Care included hyperhydration, avoiding oxalate-rich foods, crystallisation inhibitors (alkali citrates, magnesium or phosphate ions) and Vitamin B6.

- Inclusion criteria 6: Subjects receiving vitamin B6 must be receiving a stable dose for at least 3 months prior to screening and must not change the dose during the study. Subjects not receiving vitamin B6 at study entry must be willing to refrain from initiating pyridoxine during study participation.

- Prohibited medication in line with exclusion criteria: Exclusion criterion 11: Use of antibiotics to which O. formigenes is sensitive. (This includes current antibiotic use, or antibiotics use within 14 days of initiating study medication.). Exclusion criterion 12: Current treatment with a separate ascorbic acid preparation. (Please note patients were asked to refrain from taking multivitamin supplements throughout the study as these contain ascorbic acid/Vitamin C.)

Evidence for comparator:

No comparator was used in the study; only the investigational drug and a placebo.

Actual start date of recruitment	09 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Tunisia: 4
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	25
EEA total number of subjects	17

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	12
Adolescents (12-17 years)	6
Adults (18-64 years)	7
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started on 17 Jan 2018 in Europe (8 sites) and the USA (3 sites) and ended on 07 May 2020. At a late stage in the trial, 3 sites were added in Tunisia and started patients recruiting in Dec 2019. In France, the Netherlands and at two US sites patients were screened but not randomized as they were screen failures.

Pre-assignment

Screening details:

There were 3 visits over 4-8 weeks to assess if the patient was suitable to receive study medicine (screening/baseline period). Screening was performed to assure eligibility as per inclusion/exclusion criteria especially for eGFR and Pox (these were the main reasons for screen failures). 43 patients were screened (2 re-screened); 25 were enrolled.

Pre-assignment period milestones

Number of subjects started	43[1]
Number of subjects completed	25

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 2
Reason: Number of subjects	Failed IC 3 (eGFR) and IC 4 (Pox): 4
Reason: Number of subjects	Failed IC 6 (Vitamin B6): 1
Reason: Number of subjects	Met EC 15 (Unable to follow study procedures): 1
Reason: Number of subjects	Failed IC 4 (Pox): 7
Reason: Number of subjects	Failed IC 3 (eGFR): 3

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 43 patients were screened in the OC5-DB-02 study. 18 of these patients were considered screen failures and were not eligible for inclusion in the study (15 did not satisfy requisite inclusion criteria, 2 withdrew consent during screening and 1 was unable to follow study procedures). Consequently only 25 patients completed screening and entered the treatment phase of the study.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No blinding during screening/baseline as patients did not yet receive study treatment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Oxabact OC5

Arm description:

During the baseline period, subjects did not receive any study treatment. Randomization (1:1 to Oxabact OC5:Placebo) was done after completion of the baseline period. Disposition information at baseline is provided as by subsequent treatment arm. Subjects in the Oxabact OC5 arm received treatment with Oxabact OC5 twice daily for 52 weeks.

Arm type	Experimental

Investigational medicinal product name	Oxabact OC5
Investigational medicinal product code	OC5
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The study drug consists of Oxabact® OC5. The dose was administered orally as one enteric-coated size-4 capsule with breakfast and dinner twice daily. The dose was NLT 1E+09 colony forming units (CFU) Oxalobacter formigenes per capsule.

Arm title	Placebo

Arm description:

During the baseline period, subjects did not receive any study treatment. Randomization (1:1 to Oxabact OC5:Placebo) was done after completion of the baseline period. Disposition information at baseline is provided as by subsequent treatment arm. Subjects in the placebo arm received treatment with placebo twice daily for 52 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The placebo capsule was administered orally as one enteric-coated size-4 capsule with breakfast and dinner twice daily. Placebo capsules were of the same size and contained the same bulking agent as the Oxabact® OC5 capsule.

Number of subjects in period 1	Oxabact OC5	Placebo
Started	13	12
Completed	13	12

Period 2

Period 2 title	Treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes

Arm title	Oxabact OC5

Arm description:

During the baseline period, subjects did not receive any study treatment. Randomization (1:1 to Oxabact OC5:Placebo) was done after completion of the baseline period. Disposition information at baseline is provided as by subsequent treatment arm. Subjects in the Oxabact OC5 arm received treatment with Oxabact OC5 twice daily for 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Oxabact OC5
Investigational medicinal product code	OC5
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The study drug consists of Oxabact® OC5. The dose was administered orally as one enteric-coated size-4 capsule with breakfast and dinner twice daily. The dose was NLT 1E+09 colony forming units (CFU) Oxalobacter formigenes per capsule.

Arm title	Placebo

Arm description:

During the baseline period, subjects did not receive any study treatment. Randomization (1:1 to Oxabact OC5:Placebo) was done after completion of the baseline period. Disposition information at baseline is provided as by subsequent treatment arm. Subjects in the placebo arm received treatment with placebo twice daily for 52 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The placebo capsule was administered orally as one enteric-coated size-4 capsule with breakfast and dinner twice daily. Placebo capsules were of the same size and contained the same bulking agent as the Oxabact® OC5 capsule.

Number of subjects in period 2	Oxabact OC5	Placebo
Started	13	12
Completed	13	11
Not completed	0	1
Physician decision	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Oxabact OC5
Reporting group description:	
During the baseline period, subjects did not receive any study treatment. Randomization (1:1 to Oxabact OC5:Placebo) was done after completion of the baseline period. Disposition information at baseline is provided as by subsequent treatment arm. Subjects in the Oxabact OC5 arm received treatment with Oxabact OC5 twice daily for 52 weeks.	
Reporting group title	Placebo
Reporting group description:	
During the baseline period, subjects did not receive any study treatment. Randomization (1:1 to Oxabact OC5:Placebo) was done after completion of the baseline period. Disposition information at baseline is provided as by subsequent treatment arm. Subjects in the placebo arm received treatment with placebo twice daily for 52 weeks.	

Reporting group values	Oxabact OC5	Placebo	Total
Number of subjects	13	12	25
Age categorical			
Patients that were two years of age or older were eligible to participate in the study. The youngest enrolled patient was five years of age at baseline.			
Units: Subjects			
Children (2-11 years)	6	6	12
Adolescents (12-17 years)	4	2	6
Adults (18-64 years)	3	4	7
Age continuous			
Units: years			
arithmetic mean	12.9	18.3	
standard deviation	± 6.4	± 16.5	-
Gender categorical			
The study was open to both male and female patients.			
Units: Subjects			
Female	9	5	14
Male	4	7	11
Primary Hyperoxaluria Medical History - Type of PH			
Diagnosis of PH and PH type (i.e. PH type I, type II or type III)			
Units: Subjects			
Type I	13	11	24
Type II	0	1	1
Type III	0	0	0
Frequency of kidney stone events 1 yr prior to study start			
Investigator-reported / subject-reported stone events or symptoms of events during the year preceeding study start. Combined PH Medical History and/or Adverse Events reported during screening /baseline.			
Units: Subjects			
None	8	7	15
One event	2	2	4
Two events	3	1	4
Three or more events	0	2	2

Total plasma oxalate			
Mean value from the 3 screening /baseline visits. Samples for total plasma oxalate were processed at the clinical site and analysed at Academic Medical Centre, Amsterdam, the Netherlands (AMC). Total plasma oxalate was measured using isotope dilution gas chromatography with mass selective detection (GC-MSD).			
Units: micromole(s)/litre			
arithmetic mean	14.8	14.4	
standard deviation	± 5.7	± 5.4	-
Kidney function - eGFR			
Mean value of the 3 screening /baseline visits. Kidney function was evaluated based on eGFR calculation using the 2009 creatinine-based "Schwartz bedside" equation (for children below 18 years of age) (Schwartz et al., 2009) and 2009 creatinine-based CKD-EPI equation for adults (Levey et al., 2009). Subjects who turn 18 during the study period were continuously evaluated using the Schwartz equation, ie the equation used at baseline was kept throughout the study.			
Units: millilitres/minute/1.73m2			
arithmetic mean	70.29	62.36	
standard deviation	± 11.58	± 16.90	-
Free plasma oxalate			
Mean value of the 3 visits during screening /baseline. Ultrafiltered, acidified plasma samples for free plasma oxalate were processed at the clinical site and analysed at Academic Medical Centre, Amsterdam, the Netherlands (AMC) using isotope dilution gas chromatography with mass selective detection (GC-MSD).			
Units: micromole(s)/litre			
arithmetic mean	11.3	10.0	
standard deviation	± 6.6	± 5.2	-
Urinary oxalate excretion /24 hour collection			
Mean of two values during screening /baseline. Twenty-four-hour urine samples for analysis of urinary oxalate were taken at subject´s home and sent to central laboratory TDL, London, UK.			
Units: millimoles/24hours/1.73m2			
arithmetic mean	2.11	1.76	
standard deviation	± 0.93	± 0.94	-
Number of Oxalobacter formigenes genotype 1 in stool			
Only one stool sample was collected during screening /baseline. Faecal samples were collected at subject's home and shipped to central laboratory MVZ Institut für Mikroökologie GmbH, Herborn, Germany. A real-time quantitative PCR assay was used that permits determination of the numbers of both O. formigenes genotype 1 and genotype 2 in faecal samples.			
Units: 1E+06 cells/gram			
median	0.0834	0.0834	
inter-quartile range (Q1-Q3)	0.0834 to 0.0834	0.0834 to 0.0834	-
Number of Oxalobacter formigenes genotype 2 in stool			
Only one stool sample was collected during screening /baseline. Faecal samples were collected at subject's home and shipped to central laboratory MVZ Institut für Mikroökologie GmbH, Herborn, Germany. A real-time quantitative PCR assay was used that permits determination of the numbers of both O. formigenes genotype 1 and genotype 2 in faecal samples.			
Units: 1E+06 cells/gram			
median	0.0268	0.0268	
inter-quartile range (Q1-Q3)	0.0268 to 0.0268	0.0268 to 0.1415	-

End points

End points reporting groups

Reporting group title	Oxabact OC5
Reporting group description:	
During the baseline period, subjects did not receive any study treatment. Randomization (1:1 to Oxabact OC5:Placebo) was done after completion of the baseline period. Disposition information at baseline is provided as by subsequent treatment arm. Subjects in the Oxabact OC5 arm received treatment with Oxabact OC5 twice daily for 52 weeks.	
Reporting group title	Placebo
Reporting group description:	
During the baseline period, subjects did not receive any study treatment. Randomization (1:1 to Oxabact OC5:Placebo) was done after completion of the baseline period. Disposition information at baseline is provided as by subsequent treatment arm. Subjects in the placebo arm received treatment with placebo twice daily for 52 weeks.	
Reporting group title	Oxabact OC5
Reporting group description:	
During the baseline period, subjects did not receive any study treatment. Randomization (1:1 to Oxabact OC5:Placebo) was done after completion of the baseline period. Disposition information at baseline is provided as by subsequent treatment arm. Subjects in the Oxabact OC5 arm received treatment with Oxabact OC5 twice daily for 52 weeks.	
Reporting group title	Placebo
Reporting group description:	
During the baseline period, subjects did not receive any study treatment. Randomization (1:1 to Oxabact OC5:Placebo) was done after completion of the baseline period. Disposition information at baseline is provided as by subsequent treatment arm. Subjects in the placebo arm received treatment with placebo twice daily for 52 weeks.	

Primary: Change from baseline in total plasma oxalate concentration after 52 weeks of treatment

End point title	Change from baseline in total plasma oxalate concentration after 52 weeks of treatment
End point description:	
Samples for total plasma oxalate were processed at the clinical site and analysed at Academic Medical Centre, Amsterdam, the Netherlands (AMC). Total plasma oxalate was measured using isotope dilution gas chromatography with mass selective detection (GC-MSD).	
End point type	Primary
End point timeframe:	
Every 8 weeks starting from randomisation and until /including week 52. Change from baseline in total plasma oxalate concentration was calculated at each visit as the visit value minus the mean of the three measurements during baseline.	

End point values	Oxabact OC5	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[1]	12[2]		
Units: micromole(s)/litre				
least squares mean (standard error)	-0.78 (± 1.37)	3.01 (± 1.61)		

Notes:

[1] - 13 patients started Oxabact OC5. 12 patients were analysed for total plasma oxalate at wk 52.

[2] - 12 patients started treatment with placebo. 8 of them reported total plasma oxalate values at wk 52.

Statistical analyses

Statistical analysis title	Mixed-effect Repeated Measures Model - MRMM

Statistical analysis description:

The primary statistical analysis was performed using a mixed-effect repeated measures model (MRMM) on the change from baseline value at 52 weeks, with the following independent variables: treatment group, baseline total plasma oxalate concentration value, week and week*treatment interaction. First order autoregressive covariance structure, AR(1) was used. This analysis is considered the first analysis in the hierarchical approach.

Comparison groups	Oxabact OC5 v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.064
Method	Mixed models analysis

Secondary: Change from baseline in kidney function (eGFR) after 52 weeks of treatment.

End point title	Change from baseline in kidney function (eGFR) after 52 weeks of treatment.

End point description:

Change in kidney function was evaluated based on eGFR calculation using the 2009 creatinine-based "Schwartz bedside" equation (for children below 18 years of age) (Schwartz et al., 2009) and 2009 creatinine-based CKD-EPI equation for adults (Levey et al., 2009). Subjects who turn 18 during the study period were continuously evaluated using the Schwartz equation, ie the equation used at baseline was kept throughout the study.

End point type	Secondary

End point timeframe:

eGFR was determined every 8 weeks during the treatment phase. Change from baseline in kidney function (eGFR) was evaluated after 52 weeks treatment.

End point values	Oxabact OC5	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[3]	12[4]		
Units: millilitres/minute/1.73m2				
least squares mean (standard error)	-1.35 (± 2.68)	-0.06 (± 3.12)		

Notes:

[3] - 13 patients started Oxabact OC5. 12 of these patients were analysed for eGFR at week 52.

[4] - 13 patients started treatment with placebo. 8 of these patients reported eGFR values at week 52.

Statistical analyses

Statistical analysis title	Mixed-effect Repeated Measures Model - MRMM

Statistical analysis description:

A similar MRMM as for the primary endpoint was performed. A fixed order autoregressive covariance structure, AR(1) was used. The model provided a test of difference in slopes using the proposed time-by-treatment interaction, treatment slopes and slope differences on change through time. LS means were determined for each visit.

Comparison groups	Placebo v Oxabact OC5
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.744
Method	Mixed models analysis

Secondary: Frequency of kidney stone events - Adjudicated assessment

End point title	Frequency of kidney stone events - Adjudicated assessment

End point description:

The kidney stone data, including adverse events and renal ultrasound at week 48, were assessed by an independent adjudicator. A composite number of kidney stone events was provided for each patient.

End point type	Secondary

End point timeframe:

Stone event data collected throughout the 52-week treatment period.

End point values	Oxabact OC5	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	12		
Units: Number of kidney stone events	7	8		

Statistical analyses

Statistical analysis title	Analysis for adjudicated stone data

Statistical analysis description:

For comparison between treatments on the total number of kidney stone events as per adjudicated data, a zero-inflated Poisson model was used.

Comparison groups	Placebo v Oxabact OC5
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.117
Method	Poisson model

Other pre-specified: Percent change from baseline in total plasma oxalate concentration after 52 weeks of treatment

End point title	Percent change from baseline in total plasma oxalate concentration after 52 weeks of treatment

End point description:

End point type	Other pre-specified

End point timeframe:

Plasma oxalate was measured every 8 weeks throughout the treatment phase.

End point values	Oxabact OC5	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[5]	12[6]		
Units: Percent				
arithmetic mean (standard deviation)	-0.57 (± 27.42)	15.27 (± 16.36)		

Notes:

[5] - 13 patients started treatment with Oxabact OC5. 12 of them were analysed for % Pox at week 52

[6] - 12 patients started placebo. 8 of them were analysed for percentage plasma oxalate at wk 52.

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

Percent change from baseline in total plasma oxalate concentration after 52 weeks of treatment was analysed statistically using an ANOVA model.

Comparison groups	Oxabact OC5 v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.146
Method	ANOVA

Other pre-specified: Subjects achieving ‘near-normalisation’ of total plasma oxalate concentration (<10 µmol/L) at least twice during weeks 24 to 52 of treatment

End point title	Subjects achieving ‘near-normalisation’ of total plasma oxalate concentration (<10 µmol/L) at least twice during weeks 24 to 52 of treatment

End point description:

End point type	Other pre-specified

End point timeframe:

Plasma oxalate was measured every 8 weeks throughout the treatment phase.

End point values	Oxabact OC5	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	12		
Units: Number of subjects	2	3		

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel test

Statistical analysis description:

Statistical analysis to compare the treatment arms was done using a Cochran-Mantel-Haenszel test controlling for the stratification as applied in the randomisation.

Comparison groups	Oxabact OC5 v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.582
Method	Cochran-Mantel-Haenszel

Other pre-specified: Change from baseline in free plasma oxalate concentration after 52 weeks of treatment

End point title	Change from baseline in free plasma oxalate concentration after 52 weeks of treatment

End point description:

Ultrafiltered, acidified plasma samples for free plasma oxalate were processed at the clinical site and analysed at Academic Medical Centre, Amsterdam, the Netherlands (AMC) using isotope dilution gas chromatography with mass selective detection (GC-MSD).

End point type	Other pre-specified

End point timeframe:

Plasma oxalate was measured every 8 weeks during the treatment period.

End point values	Oxabact OC5	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[7]	12[8]		
Units: micromole(s)/litre				
least squares mean (standard error)	2.88 (± 1.87)	1.46 (± 2.06)		

Notes:

[7] - 13 patients started Oxabact OC5. 10 patients were analysed for free plasma oxalate at wk 52.

[8] - 12 patients started placebo. 8 of them were analysed for free plasma oxalate at wk 52.

Statistical analyses

Statistical analysis title	Mixed-effect Repeated Measures Model - MRMM

Statistical analysis description:

See Primary endpoint. A first order autoregressive covariance structure, AR(1) was used.

Comparison groups	Oxabact OC5 v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6
Method	Mixed models analysis

Other pre-specified: Change from baseline in urinary oxalate excretion after 52 weeks of treatment

End point title	Change from baseline in urinary oxalate excretion after 52 weeks of treatment

End point description:

24-hour urine collection for analysis of urinary oxalate were taken at subject´s home and sent to central laboratory TDL, London, UK.

End point type	Other pre-specified

End point timeframe:

24-hour urine collection was done at weeks 8, 24, 40 and 52 of the treatment phase.

End point values	Oxabact OC5	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[9]	12[10]		
Units: millimoles/24hours/1.73m2				
least squares mean (standard error)	0.082 (± 0.247)	-0.320 (± 0.263)		

Notes:

[9] - 13 patients started Oxabact OC5. 12 patients were analysed for Uox at wk 52.

[10] - 12 patients started placebo. 10 of them were analysed for Uox at wk 52.

Statistical analyses

Statistical analysis title	Mixed-effect Repeated Measures Model - MRMM

Statistical analysis description:

A first order autoregressive covariance structure, AR(1) was used.

Comparison groups	Oxabact OC5 v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.232
Method	Mixed models analysis

Other pre-specified: Change in number of Oxalobacter formigenes in stool - genotype 1

End point title	Change in number of Oxalobacter formigenes in stool - genotype 1

End point description:

Faecal samples were collected at subject’s home and shipped to central laboratory MVZ Institut für Mikroökologie GmbH, Herborn, Germany. A real-time quantitative PCR assay was used that permits determination of the numbers of both O. formigenes genotype 1 and genotype 2 in faecal samples.

End point type	Other pre-specified

End point timeframe:

Stool samples were collected at weeks 24, 40 and 52 of the treatment period.

End point values	Oxabact OC5	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[11]	12[12]		
Units: x 1E+06 cells/g				
median (inter-quartile range (Q1-Q3))	0.6906 (-0.0025 to 3.1566)	0.000 (0.0000 to 0.0000)		

Notes:

[11] - 13 patients started Oxabact OC5. 11 patients were analysed for O. formigenes genotype 1 at wk 52.
[12] - 12 patients started placebo. 10 of them were analysed for O. formigenes genotype 1 at wk 52.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in number of Oxalobacter formigenes in stool - genotype 2

End point title	Change in number of Oxalobacter formigenes in stool - genotype 2

End point description:

Faecal samples were collected at subject’s home and shipped to central laboratory MVZ Institut für Mikroökologie GmbH, Herborn, Germany. A real-time quantitative PCR assay was used that permits determination of the numbers of both O. formigenes genotype 1 and genotype 2 in faecal samples.

End point type	Other pre-specified

End point timeframe:

Stool samples were collected at weeks 24, 40 and 52 of the treatment period.

End point values	Oxabact OC5	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13[13]	12[14]		
Units: x 1E+06 cells/g				
median (inter-quartile range (Q1-Q3))	0.0000 (0.0000 to 0.0000)	0.0000 (0.0000 to 0.0000)		

Notes:

[13] - 13 patients started Oxabact OC5. 11 patients were analysed for O. formigenes genotype 2 at wk 52.
[14] - 12 patients started placebo. 10 of them were analysed for O. formigenes genotype 2 at wk 52.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Event reporting for each subject started at the initiation of study treatment, (i.e. from First Dose Date). The reporting continued during the course of the study (i.e. until End Of Study).

Adverse event reporting additional description:

Patients were asked about adverse events at least at each visit, and these were reported in the eCRF by the investigator. Serious AEs were reported within 24 hours of awareness directly to the sponsor's safety vendor. End of Study was defined as End of Treatment (i.e. last dose date) + maximum 14 days of safety follow-up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Oxabact OC5

Reporting group description:

During the baseline period, subjects did not receive any study treatment. Randomization (1:1 to Oxabact OC5:Placebo) was done after completion of the baseline period. Disposition information at baseline is provided as by subsequent treatment arm. Subjects in the Oxabact OC5 arm received treatment with Oxabact OC5 twice daily for 52 weeks.

Reporting group title	Placebo

Reporting group description:

During the baseline period, subjects did not receive any study treatment. Randomization (1:1 to Oxabact OC5:Placebo) was done after completion of the baseline period. Disposition information at baseline is provided as by subsequent treatment arm. Subjects in the placebo arm received treatment with placebo twice daily for 52 weeks.

Serious adverse events	Oxabact OC5	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 13 (23.08%)	4 / 12 (33.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 13 (0.00%)	2 / 12 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 13 (7.69%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			

subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Escherichia urinary tract infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial pyelonephritis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Oxabact OC5	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)	11 / 12 (91.67%)	
Surgical and medical procedures			
Bladder catheterisation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Renal stone removal			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Catheter placement			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 13 (15.38%)	2 / 12 (16.67%)	
occurrences (all)	3	4	
Chest pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 13 (7.69%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Asthma			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	1 / 13 (7.69%)	1 / 12 (8.33%)	
occurrences (all)	1	1	

Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 12 (8.33%) 1	
Investigations C-reactive protein increased subjects affected / exposed occurrences (all) Eosinophilia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0 1 / 13 (7.69%) 1	1 / 12 (8.33%) 1 0 / 12 (0.00%) 0	
Injury, poisoning and procedural complications Ankle fracture subjects affected / exposed occurrences (all) Hand fracture subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0 0 / 13 (0.00%) 0	1 / 12 (8.33%) 1 1 / 12 (8.33%) 1	
Cardiac disorders Ventricular extrasystoles subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 12 (8.33%) 1	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2	0 / 12 (0.00%) 0	
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 12 (8.33%) 1	
Eye disorders Myopia subjects affected / exposed occurrences (all) Optic disc drusen subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0 1 / 13 (7.69%) 1	1 / 12 (8.33%) 1 0 / 12 (0.00%) 0	
Gastrointestinal disorders			

Vomiting			
subjects affected / exposed	1 / 13 (7.69%)	4 / 12 (33.33%)	
occurrences (all)	1	6	
Abdominal pain			
subjects affected / exposed	2 / 13 (15.38%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Abdominal distension			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Aphthous ulcer			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Renal colic			

subjects affected / exposed	2 / 13 (15.38%)	0 / 12 (0.00%)	
occurrences (all)	5	0	
Nephrolithiasis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	2 / 13 (15.38%)	1 / 12 (8.33%)	
occurrences (all)	3	1	
Back pain			
subjects affected / exposed	1 / 13 (7.69%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Arthralgia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Foot deformity			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Infections and infestations			
Tonsillitis			
subjects affected / exposed	2 / 13 (15.38%)	2 / 12 (16.67%)	
occurrences (all)	2	2	
Nasopharyngitis			
subjects affected / exposed	2 / 13 (15.38%)	2 / 12 (16.67%)	
occurrences (all)	2	2	
Urinary tract infection			
subjects affected / exposed	1 / 13 (7.69%)	2 / 12 (16.67%)	
occurrences (all)	1	3	
Upper respiratory tract infection			
subjects affected / exposed	1 / 13 (7.69%)	1 / 12 (8.33%)	
occurrences (all)	2	2	
COVID-19			

subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Dientamoeba infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Infected bite			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	2 / 13 (15.38%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Hyperkalaemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Iron deficiency			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2017	Amendment 1: UK specific amendment • Added information on the process for emergency unblinding • Clarified that separate regulatory approval would be sought for the open-label follow up study
21 September 2017	Amendment 2: • Spain and Belgium added to list of participating countries. • Clarified that a separate Clinical Trial Application would be issued for the follow-up study. • Safety analyses performed at a central lab instead of at the local lab. • Clarified process for patients with AKI during baseline. • Clarified that in the event there is a need to know the identity of the drug given to a patient, the decision to unblind the treatment resides solely with the investigator.
28 March 2018	Amendment 3: • Reporting of Pregnancy during the study added to the Safety section. • Information added about the Data and Safety Monitoring Board. • Sample size section updated. • Schedule of assessments updated. • The previous numbering of references (superscription format) have been replaced by Author name and year. • Reference list corrected and updated in alphabetical order. • Minor corrections and clarifications.
15 October 2018	Amendment 4: • Secondary and exploratory endpoints were reorganised. • Frequency of kidney stone events was added under key secondary endpoints. • Information added that kidney stone events and related symptoms were to be captured throughout the study. • Clarified that if an acute kidney injury/stone event occurred close to a scheduled visit, the visit would be rescheduled once the AKI/stone event was resolved. • Tunisia added to list of participating countries. • Statistical sections updated in line with revised endpoints. • Minor corrections and clarifications
06 September 2019	Amendment 5: • Clarification that for determination of eligibility, estimated Glomerular Filtration Rate (eGFR) could be calculated using Schwartz or CKD-EPI equations that include serum creatinine and/or cystatin C. Please note, that this amendment was a country-specific Amendment for Spain and the US.

19 December 2019	Amendment 6: • Included revisions made in Amendment 5 of 06 Sep 2019. • Implementation of post-treatment safety follow-up (mainly addressed in sections 6.2 and 6.3). Consequently, the definition of "End-of-Study" was updated and "End-of-Treatment" was defined. • Updated section 7.4. Withdrawal criteria to include "The subject requires dialysis". • Updated list of blind data and added clarifications in section 8.4. • Updated section 11.4 Reporting of Adverse Events to harmonise with the Safety Management plan for this study (Vs 4.0 dated 24 Jun 2019). • Updated section 11.5.3 to refer to Investigator Brochure; this was to harmonise with the protocol of the OC5-OL-01 and OC5-OL-02 studies. • Added updates and clarifications in section 12 Statistical Methods including tests of hypotheses and significance levels, information on methods used to analyse endpoints and definition of treatment-emergent AEs. Added additional subgroups. • Minor updates, corrections and clarifications throughout the protocol.
08 January 2021	Amendment 7: • Added clinical success criteria in section 5.3 • Updated section 7.4. Withdrawal criteria to clarify which assessments were to be done for early withdrawal. • Added 2 new other endpoints (Percent change from baseline in total plasma oxalate concentration and Subjects achieving 'near-normalisation' in total plasma oxalate concentration) in section 10. • Added updates and clarifications in section 12 relating to hierarchical testing. • Updated OC5-OL-01 study information throughout the protocol. • Minor updates, corrections and clarifications throughout the protocol. (N. B. "Patient" was replaced with "subject" throughout the protocol as appropriate).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported