



Clinical trial results:

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

Summary

EudraCT number	2013-004368-74
Trial protocol	DE
Global end of trial date	29 January 2020

Results information

Result version number	v1 (current)
This version publication date	02 August 2020
First version publication date	02 August 2020

Trial information

Trial identification

Sponsor protocol code	OC5-OL-01
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02000219
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	OxThera Intellectual Property AB
Sponsor organisation address	Regeringsgatan 111, Stockholm, Sweden, 11139
Public contact	Director of Regulatory Affairs, OxThera Intellectual Property AB, 0046 86600223, orla.mccallion@oxthera.com
Scientific contact	Chief Medical Officer, OxThera Intellectual Property AB, 0046 86600223, bastian.dehmel@oxthera.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 January 2020
Global end of trial reached?	Yes
Global end of trial date	29 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The initial 14 weeks phase of the study: Following a 4-week baseline period, patient received OC5 (Oxalobacter formigenes) twice daily for a 6-week treatment period (week 10). Patients were subsequently followed for 4 weeks without study-drug (week 14).

Continued treatment (CT) phase of the study: At the end of the initial 14-week period, patients were offered to continue OC5 treatment for up to 3 years (156 weeks).

Patients were observed in the clinics during the study visits. Physical exam and vital signs were taken at screening and up to last study visit to the clinic. Laboratory safety tests included haematology, chemistry and urinalysis were assessed at weeks 0, 4, 10 and 14 during the initial 14-week study, monthly throughout year 1 and 2, and every third and fourth month throughout year 3 of the continued treatment period. Adverse events (AEs) and concomitant medication were monitored throughout the study during study visits. Patients' personal data were collected and processed in line with national requirements and subsequent GDPR regulations since 2018.

Background therapy:

Dialysis

Evidence for comparator:

N/A; only active drug

Actual start date of recruitment	19 May 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 11
Worldwide total number of subjects	12
EEA total number of subjects	12

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	2
Adolescents (12-17 years)	0
Adults (18-64 years)	10
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Open-label study initially conducted at 4 sites (Germany, USA, 2 sites in France). Sites in the USA and France closed during 2017. No patients recruited at US site; subject enrolled in France left study early. First patient enrolled 19 May 2014; last patient completed study 29 Jan 2020. In total: 14 patients screened, 12 patients enrolled.

Pre-assignment

Screening details:

Male or female PH patients, ≥ 2 years, on a stable dialysis regimen with plasma oxalate ≥ 40 $\mu\text{mol/L}$ were included in the study. Patients should be able to take size-4 capsules twice daily by swallowing or via gastric tube. Inclusion/exclusion criteria were assessed during screening.

NB: Baseline characteristics only detailed for enrolled patients.

Pre-assignment period milestones

Number of subjects started	14 ^[1]
Number of subjects completed	12

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen failure: 2
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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: There were 2 screen failures that participated in baseline but were not enrolled into 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:

N/A; the study was open-label

Arms

Arm title	Baseline OC5
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Oxabact
Investigational medicinal product code	OC5
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

OC5 was provided as enteric-coated size-4 capsule containing at least $1\text{E}+09$ colony-forming units (CFU) *O. formigenes* per capsule. After the 4-week baseline period, administration was orally as one capsule twice daily (breakfast and dinner), for 6 weeks in the initial phase of the study and for up to 156 weeks during the continued treatment phase.

Number of subjects in period 1	Baseline OC5
Started	12
Completed	12

Period 2

Period 2 title	Initial 6-wk treatment + 4-wks off drug
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N/A; the study was open-label

Arms

Arm title	OC5 (initial phase)
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Arm description:

Patients received open-label treatment with OC5.

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

Dosage and administration details:

OC5 was provided as enteric-coated size-4 capsule containing at least 1E+09 colony-forming units (CFU) *O. formigenes* per capsule. After the 4-week baseline period, administration was orally as one capsule twice daily (breakfast and dinner), for 6 weeks in the initial phase of the study and for up to 156 weeks during the continued treatment phase.

Number of subjects in period 2	OC5 (initial phase)
Started	12
Completed	9
Not completed	3
Adverse event, non-fatal	1
Transplantation	2

Period 3

Period 3 title	Continued treatment (up to 156 weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Blinding implementation details: N/A; this was an open-label study	

Arms

Arm title	OC5 (continued treatment)
Arm description: Patients received open-label treatment with OC5.	
Arm type	Experimental
Investigational medicinal product name	Oxabact
Investigational medicinal product code	OC5
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

OC5 was provided as enteric-coated size-4 capsule containing at least 1E+09 colony-forming units (CFU) *O. formigenes* per capsule. After the 4-week baseline period, administration was orally as one capsule twice daily (breakfast and dinner), for 6 weeks in the initial phase of the study and for up to 156 weeks during the continued treatment phase.

Number of subjects in period 3^[2]	OC5 (continued treatment)
Started	8
Completed	3
Not completed	5
Non-compliance with study protocol/study drug	2
Consent withdrawn by subject	1
Transplantation	2

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: One patient who completed the initial 14-weeks of the study declined participation in the continued treatment phase of the study.

Baseline characteristics

Reporting groups

Reporting group title	Baseline
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Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	12	12	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	2	2	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	10	10	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	4	4	
Male	8	8	
Primary Hyperoxaluria medical history			
Units: Subjects			
Type I	12	12	
Type II	0	0	
Type III	0	0	
Time since diagnosis			
Units: months			
arithmetic mean	59.9		
standard deviation	± 88.2	-	
Baseline total plasma oxalate			
Units: micromole(s)/litre			
arithmetic mean	147.572		
standard deviation	± 39.634	-	
Baseline free plasma oxalate			
Units: micromole(s)/litre			
arithmetic mean	106.908		
standard deviation	± 32.502	-	
Baseline Oxalobacter formigenes type 1			
Units: colony forming unit(s)/dose (x 1E+06)			
arithmetic mean	0.091		
standard deviation	± 0.027	-	
Baseline Speckle Tracking Echocardiography, GLS (global longitudinal strain)			

Units: percent			
arithmetic mean	-17.368		
standard deviation	± 5.301	-	
Baseline Traditional Echocardiography, LVEF (left ventricular ejection fraction)			
Units: percent			
arithmetic mean	50.200		
standard deviation	± 10.261	-	

End points

End points reporting groups

Reporting group title	Baseline OC5
Reporting group description: -	
Reporting group title	OC5 (initial phase)
Reporting group description: Patients received open-label treatment with OC5.	
Reporting group title	OC5 (continued treatment)
Reporting group description: Patients received open-label treatment with OC5.	

Primary: Change in total plasma oxalate concentration during OC5 treatment, compared with baseline - week 10 (after 6 weeks of OC5 treatment)

End point title	Change in total plasma oxalate concentration during OC5 treatment, compared with baseline - week 10 (after 6 weeks of OC5 treatment) ^[1]
End point description: For the primary endpoint, the change in total plasma oxalate concentration from baseline during OC5 treatment was calculated using the average from the 2 pre-treatment values as the baseline value. The change from baseline was determined for each post-baseline measurement, i.e., throughout the initial 6-week treatment period, the 4-week off-treatment period and the continued treatment period for up to 3 years (156 weeks). The primary endpoint was evaluated using descriptive statistics.	
End point type	Primary
End point timeframe: Change from baseline after 6 weeks of OC5 treatment (i.e. at week 10 of the initial 14-week phase of the study)	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: The statistical analysis was descriptive and therefore, no formal statistical significance testing was performed.	

End point values	OC5 (initial phase)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: micromole(s)/litre				
arithmetic mean (standard deviation)	-5.675 (± 21.020)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in total plasma oxalate concentration during OC5 treatment, compared with baseline - week 14 (after 4 weeks off treatment)

End point title	Change in total plasma oxalate concentration during OC5 treatment, compared with baseline - week 14 (after 4 weeks off treatment) ^[2]
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End point description:

For the primary endpoint, the change in total plasma oxalate concentration from baseline during OC5 treatment was calculated using the average from the 2 pre-treatment values as the baseline value. The change from baseline was determined for each post-baseline measurement, i.e., throughout the initial 6-week treatment period, the 4-week off-treatment period and the continued treatment period for up to 3 years (156 weeks). The primary endpoint was evaluated using descriptive statistics.

End point type	Primary
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End point timeframe:

Change from baseline after 6 weeks of OC5 treatment + 4 weeks off treatment (i.e. at week 14 of the initial 14-week phase of the study)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis was descriptive and therefore, no formal statistical significance testing was performed.

End point values	OC5 (initial phase)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: micromole(s)/litre				
arithmetic mean (standard deviation)	-8.410 ($\pm$ 19.258)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in total plasma oxalate concentration during OC5 treatment, compared with baseline - week 52

End point title	Change in total plasma oxalate concentration during OC5 treatment, compared with baseline - week 52 ^[3]
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End point description:

For the primary endpoint, the change in total plasma oxalate concentration from baseline during OC5 treatment was calculated using the average from the 2 pre-treatment values as the baseline value. The change from baseline was determined for each post-baseline measurement, i.e., throughout the initial 6-week treatment period, the 4-week off-treatment period and the continued treatment period for up to 3 years (156 weeks). The primary endpoint was evaluated using descriptive statistics.

End point type	Primary
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End point timeframe:

Change from baseline after 52 weeks of continued OC5 treatment

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis was descriptive and therefore, no formal statistical significance testing was performed.

End point values	OC5 (continued treatment)			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: micromole(s)/litre				
arithmetic mean (standard deviation)	-33.990 ($\pm$ 34.780)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in total plasma oxalate concentration during OC5 treatment, compared with baseline - week 104

End point title	Change in total plasma oxalate concentration during OC5 treatment, compared with baseline - week 104 ^[4]
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End point description:

For the primary endpoint, the change in total plasma oxalate concentration from baseline during OC5 treatment was calculated using the average from the 2 pre-treatment values as the baseline value. The change from baseline was determined for each post-baseline measurement, i.e., throughout the initial 6-week treatment period, the 4-week off-treatment period and the continued treatment period for up to 3 years (156 weeks). The primary endpoint was evaluated using descriptive statistics.

End point type	Primary
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End point timeframe:

Change from baseline after 104 weeks of continued OC5 treatment

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis was descriptive and therefore, no formal statistical significance testing was performed.

End point values	OC5 (continued treatment)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: micromole(s)/litre				
arithmetic mean (standard deviation)	-67.358 (± 47.769)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in total plasma oxalate concentration during OC5 treatment, compared with baseline - week 156

End point title	Change in total plasma oxalate concentration during OC5 treatment, compared with baseline - week 156 ^[5]
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End point description:

For the primary endpoint, the change in total plasma oxalate concentration from baseline during OC5 treatment was calculated using the average from the 2 pre-treatment values as the baseline value. The change from baseline was determined for each post-baseline measurement, i.e., throughout the initial 6-week treatment period, the 4-week off-treatment period and the continued treatment period for up to 3 years (156 weeks). The primary endpoint was evaluated using descriptive statistics.

End point type	Primary
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End point timeframe:

Change from baseline after 156 weeks of continued treatment.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis was descriptive and therefore, no formal statistical significance testing was performed.

End point values	OC5 (continued treatment)			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: micromole(s)/litre				
arithmetic mean (standard deviation)	-44.647 ($\pm$ 54.752)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in free plasma oxalate concentration during OC5 treatment, compared with baseline - week 10 (after 6 weeks of OC5 treatment)

End point title	Change in free plasma oxalate concentration during OC5 treatment, compared with baseline - week 10 (after 6 weeks of OC5 treatment)
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End point description:

Change in free plasma oxalate concentration during OC5 treatment, compared with baseline.

End point type	Secondary
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End point timeframe:

Change from baseline after 6 weeks of OC5 treatment (i.e. at week 10 of the initial 14-week phase of the study)

End point values	OC5 (initial phase)			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: micromole(s)/litre				
arithmetic mean (standard deviation)	1.590 ($\pm$ 18.771)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in free plasma oxalate concentration during OC5 treatment, compared with baseline - week 14 (after 4 weeks off treatment)

End point title	Change in free plasma oxalate concentration during OC5 treatment, compared with baseline - week 14 (after 4 weeks
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off treatment)

End point description:

Change in free plasma oxalate concentration during OC5 treatment, compared with baseline.

End point type Secondary

End point timeframe:

Change from baseline after 6 weeks of OC5 treatment + 4 weeks off drug (i.e. at week 14 of the initial 14-week phase of the study)

End point values	OC5 (initial phase)			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: microcurie(s)/litre				
arithmetic mean (standard deviation)	-6.497 ($\pm$ 17.306)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in free plasma oxalate concentration during OC5 treatment, compared with baseline - week 52

End point title Change in free plasma oxalate concentration during OC5 treatment, compared with baseline - week 52

End point description:

Change in free plasma oxalate concentration during OC5 treatment, compared with baseline.

End point type Secondary

End point timeframe:

Change from baseline after 52 weeks of continued treatment

End point values	OC5 (continued treatment)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: micromole(s)/litre				
arithmetic mean (standard deviation)	2.524 ($\pm$ 13.789)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in free plasma oxalate concentration during OC5 treatment,

compared with baseline - week 104

End point title	Change in free plasma oxalate concentration during OC5 treatment, compared with baseline - week 104
End point description: Change in free plasma oxalate concentration during OC5 treatment, compared with baseline.	
End point type	Secondary
End point timeframe: Change from baseline after 104 weeks of continued treatment	

End point values	OC5 (continued treatment)			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: micromole(s)/litre				
arithmetic mean (standard deviation)	-47.293 ($\pm$ 30.462)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in free plasma oxalate concentration during OC5 treatment, compared with baseline - week 156

End point title	Change in free plasma oxalate concentration during OC5 treatment, compared with baseline - week 156
End point description: Change in free plasma oxalate concentration during OC5 treatment, compared with baseline.	
End point type	Secondary
End point timeframe: Change from baseline after 156 weeks of continued treatment	

End point values	OC5 (continued treatment)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: microcurie(s)/litre				
arithmetic mean (standard deviation)	-5.360 ($\pm$ 20.987)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in plasma oxalate (total plasma oxalate) values from week 10 to week 14, following the 4-week off-treatment period.

End point title	Change in plasma oxalate (total plasma oxalate) values from week 10 to week 14, following the 4-week off-treatment period.
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End point description:

Change in total plasma oxalate concentration after 4 weeks off OC5 treatment compared with week 10 (i.e. after 6 weeks of OC5 treatment).

End point type	Secondary
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End point timeframe:

Change from week 10 to week 14, i.e. after 4 weeks off-treatment. (Week 10: end of initial 6-week treatment following 4 weeks baseline period; week 14: end of 4-week wash-out period)

End point values	OC5 (initial phase)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: micromole(s)/litre				
arithmetic mean (standard deviation)	-6.549 ($\pm$ 25.769)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of O. formigenes in faeces during treatment - week 10 (after 6 weeks of OC5 treatment)

End point title	Number of O. formigenes in faeces during treatment - week 10 (after 6 weeks of OC5 treatment)
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End point description:

Number of O. formigenes observed in faeces during treatment.

Measurements provided the number of O. formigenes bacteria (genotypes 1 and 2), and OC5 consists of O. formigenes derived from the human strain HC-1 of O. formigenes genotype 1. At first baseline, O. formigenes genotype 1 and 2 were not detected in any patients, except for one patient who showed a (low) positive count of genotype 2. Baseline for this assessment was set at 4 weeks. Genotype 1 was observed in all patients during treatment.

End point type	Secondary
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End point timeframe:

Number of O. formigenes after 6 weeks of OC5 treatment (i.e. at week 10 of the initial 14-week phase of the study)

End point values	OC5 (initial phase)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: colony forming unit(s)/gram (1E+06)				
arithmetic mean (standard deviation)	16.009 ($\pm$ 29.766)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of *O. formigenes* in faeces during treatment - week 14 (after 4 weeks off treatment)

End point title	Number of <i>O. formigenes</i> in faeces during treatment - week 14 (after 4 weeks off treatment)
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End point description:

Number of *O. formigenes* observed in faeces during treatment.

Measurements provided the number of *O. formigenes* bacteria (genotypes 1 and 2), and OC5 consists of *O. formigenes* derived from the human strain HC-1 of *O. formigenes* genotype 1. At first baseline, *O. formigenes* genotype 1 and 2 were not detected in any patients, except for one patient who showed a (low) positive count of genotype 2. Baseline for this assessment was set at 4 weeks. Genotype 1 was observed in all patients during treatment.

End point type	Secondary
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End point timeframe:

Number of *O. formigenes* after 6 weeks of OC5 treatment + 4 weeks off treatment (i.e. at week 14 of the initial 14-week phase of the study)

End point values	OC5 (initial phase)			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: colony forming unit(s)/gram (1E+06)				
arithmetic mean (standard deviation)	19.892 ($\pm$ 52.997)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of *O. formigenes* in faeces during treatment - week 56

End point title	Number of <i>O. formigenes</i> in faeces during treatment - week 56
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End point description:

Number of *O. formigenes* observed in faeces during treatment.

Measurements provided the number of *O. formigenes* bacteria (genotypes 1 and 2), and OC5 consists of *O. formigenes* derived from the human strain HC-1 of *O. formigenes* genotype 1. At first baseline, *O.*

formigenes genotype 1 and 2 were not detected in any patients, except for one patient who showed a (low) positive count of genotype 2. Baseline for this assessment was set at 4 weeks. Genotype 1 was observed in all patients during treatment.

End point type	Secondary
End point timeframe:	
Number of O. formigenes after 56 weeks of continued OC5 treatment.	

End point values	OC5 (continued treatment)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: colony forming unit(s)/gram (1E+06)				
arithmetic mean (standard deviation)	36.404 ($\pm$ 31.532)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of O. formigenes in faeces during treatment - week 104

End point title	Number of O. formigenes in faeces during treatment - week 104
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End point description:

Number of O. formigenes observed in faeces during treatment.

Measurements provided the number of O. formigenes bacteria (genotypes 1 and 2), and OC5 consists of O. formigenes derived from the human strain HC-1 of O. formigenes genotype 1. At first baseline, O. formigenes genotype 1 and 2 were not detected in any patients, except for one patient who showed a (low) positive count of genotype 2. Baseline for this assessment was set at 4 weeks. Genotype 1 was observed in all patients during treatment.

End point type	Secondary
End point timeframe:	
Number of O. formigenes after 104 weeks of continued OC5 treatment.	

End point values	OC5 (continued treatment)			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: colony forming unit(s)/gram (1E+06)				
arithmetic mean (standard deviation)	120.622 ($\pm$ 217.752)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of O. formigenes in faeces during treatment - week 156

End point title	Number of O. formigenes in faeces during treatment - week 156
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End point description:

Number of O. formigenes observed in faeces during treatment.

Measurements provided the number of O. formigenes bacteria (genotypes 1 and 2), and OC5 consists of O. formigenes derived from the human strain HC-1 of O. formigenes genotype 1. At first baseline, O. formigenes genotype 1 and 2 were not detected in any patients, except for one patient who showed a (low) positive count of genotype 2. Baseline for this assessment was set at 4 weeks. Genotype 1 was observed in all patients during treatment.

End point type	Secondary
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End point timeframe:

Number of O. formigenes after 156 weeks of continued OC5 treatment.

End point values	OC5 (continued treatment)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: colony forming unit(s)/gram (1E+06)				
arithmetic mean (standard deviation)	4.025 (± 1.690)			

Statistical analyses

No statistical analyses for this end point

Secondary: To evaluate results from Speckle tracking echocardiography - week 52

End point title	To evaluate results from Speckle tracking echocardiography - week 52
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End point description:

Change in Global Longitudinal Strain - GLS (% , assessed by Speckle-tracking echocardiography) during treatment compared with baseline.

End point type	Secondary
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End point timeframe:

Change from baseline after 52 weeks of OC5 treatment. (No post-treatment data for the initial 14 weeks of the study.)

End point values	OC5 (continued treatment)			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: percent				
arithmetic mean (standard deviation)	-1.087 ($\pm$ 4.335)			

Statistical analyses

No statistical analyses for this end point

Secondary: To evaluate results from Speckle tracking echocardiography - week 104

End point title	To evaluate results from Speckle tracking echocardiography - week 104
End point description: Change in Global Longitudinal Strain - GLS (% , assessed by Speckle-tracking echocardiography) during treatment compared with baseline.	
End point type	Secondary
End point timeframe: Change from baseline after 104 weeks of OC5 treatment. (No post-treatment data for the initial 14 weeks of the study.)	

End point values	OC5 (continued treatment)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: percent				
arithmetic mean (standard deviation)	-4.238 ($\pm$ 1.959)			

Statistical analyses

No statistical analyses for this end point

Secondary: To evaluate results from Speckle tracking echocardiography - week 156

End point title	To evaluate results from Speckle tracking echocardiography - week 156
End point description: Change in Global Longitudinal Strain - GLS (% , assessed by Speckle-tracking echocardiography) during treatment compared with baseline	
End point type	Secondary
End point timeframe: Change from baseline after 156 weeks of OC5 treatment. (No post-treatment data for the initial 14 weeks of the study.)	

End point values	OC5 (continued treatment)			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: percent				
arithmetic mean (standard deviation)	-4.640 ($\pm$ 4.582)			

Statistical analyses

No statistical analyses for this end point

Secondary: To evaluate results from traditional echocardiography - week 52

End point title	To evaluate results from traditional echocardiography - week 52
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End point description:

Change in Left Ventricular Ejection Fraction - LVEF (% , assessed by traditional echocardiography) during treatment compared with baseline.

End point type	Secondary
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End point timeframe:

Change from baseline after 52 weeks of OC5 treatment. (No post-treatment data for the initial 14 weeks of the study.)

End point values	OC5 (continued treatment)			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: percent				
arithmetic mean (standard deviation)	10.833 ($\pm$ 7.834)			

Statistical analyses

No statistical analyses for this end point

Secondary: To evaluate results from traditional echocardiography - week 104

End point title	To evaluate results from traditional echocardiography - week 104
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End point description:

Change in Left Ventricular Ejection Fraction - LVEF (% , assessed by traditional echocardiography) during treatment compared with baseline.

End point type	Secondary
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End point timeframe:

Change from baseline after 104 weeks of OC5 treatment. (No post-treatment data for the initial 14 weeks of the study.)

End point values	OC5 (continued treatment)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: percent				
arithmetic mean (standard deviation)	12.000 ($\pm$ 6.557)			

Statistical analyses

No statistical analyses for this end point

Secondary: To evaluate results from traditional echocardiography - week 156

End point title	To evaluate results from traditional echocardiography - week 156
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End point description:

Change in Left Ventricular Ejection Fraction - LVEF (%), assessed by traditional echocardiography) during treatment compared with baseline.

End point type	Secondary
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End point timeframe:

Change from baseline after 156 weeks of OC5 treatment. (No post-treatment data for the initial 14 weeks of the study.)

End point values	OC5 (continued treatment)			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: percent				
arithmetic mean (standard deviation)	17.000 ($\pm$ 13.299)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Each subject was questioned about AEs at each clinic visit/telephone follow-up following initiation of treatment.

Adverse event reporting additional description:

Each subject was asked the question "Since your last clinic visit have you had any health problems?" The information could also be obtained from signs and symptoms detected during each examination, observed by the study personnel or spontaneous reports from the study subjects or by laboratory results.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	OC5 group
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Reporting group description: -

Serious adverse events	OC5 group		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 12 (58.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Arteriovenous fistula thrombosis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Shunt occlusion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Shunt stenosis			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Shunt thrombosis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related sepsis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	OC5 group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 12 (83.33%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Ovarian germ cell teratoma benign			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Hypertension			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hypovolaemic shock			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Thrombosis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Surgical and medical procedures			
Dialysis device insertion			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Aneurysm repair			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Angioplasty			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Medical device change			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Parathyroidectomy			

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
General disorders and administration site conditions Administration site haematoma subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all) Complication associated with device subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Social circumstances Tattoo subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Respiratory, thoracic and mediastinal disorders Dysphonia subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Nasal polyps subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Psychiatric disorders Depression subjects affected / exposed occurrences (all) Mixed anxiety and depressive disorder subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Product issues			

Device physical property issue subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Investigations Catheterisation cardiac subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Injury, poisoning and procedural complications Arteriovenous fistula aneurysm subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Burns second degree subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Concussion subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Dislocation of vertebra subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Hand fracture subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Humerus fracture subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Ligament sprain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Post-traumatic neck syndrome subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Postoperative wound complication subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Procedural headache			

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Shunt occlusion subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Cardiac disorders Cardiovascular disorder subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Myocardial infarction subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Tension headache subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Blood and lymphatic system disorders Coagulopathy subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Eye disorders Conjunctival haemorrhage subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Conjunctival hyperaemia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Hypermetropia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	5 / 12 (41.67%) 7		

Vomiting			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	5		
Abdominal pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastrointestinal pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Haematochezia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Intestinal atony			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Intestinal polyp			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Large intestine polyp			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

Nausea subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Tooth disorder subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Blister subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Dermatitis bullous subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Eczema subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Erythema subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Pruritus subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Urticaria subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Renal and urinary disorders			
Calculus bladder subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Musculoskeletal and connective tissue disorders			
Bursitis subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		

Muscle spasms			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Arthralgia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Rheumatic disorder			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Torticollis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	7 / 12 (58.33%)		
occurrences (all)	12		
Bacterial infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Chronic sinusitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Cystitis			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Gastrointestinal infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Infected bite			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Oral herpes			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	6		
Decreased appetite			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2014	Amendment 1 (which related to Version 1 of the Protocol in Germany and France): This amendment added a new inclusion criterion; this detailed the minimum age of the patients (≥ 2 years) and that they had to be able to swallow the capsules or could use a gastric tube that allowed for administration of the capsules. A new exclusion criterion concerning inability to take study medication was also added. This amendment further clarified that children would 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 had been reviewed and raised no safety concerns.
26 March 2014	Amendment 2 (which related to Version 2 of the Protocol in US): This amendment only concerned US (which did not enroll any subjects). This amendment clarified the exclusion criteria no. 8 and detailed that transplanted patients or patients requiring ongoing immunosuppressive treatment during the study were excluded. Moreover, the following was added: • Clarification of evaluation of infections during the study, • Change of recommended first-line antibiotics for treatment of unexpected infections caused by the study medication • Subjects experiencing a systemic infection with unknown origin or suspected to be caused by Oxalobacter formigenes will be taken off treatment.
09 May 2014	Amendment 3 (which related to Version 3 of the Protocol in US): This amendment only concerned US (which did not enroll any subjects). This amendment clarified that patients with elevated numbers of Oxalobacter formigenes at week 14 would be followed until values return to baseline levels or until they stabilise over two consecutive samples.
21 October 2014	Amendment 4 (which related to Version 4 of the Protocol in Germany): This amendment only concerned Germany. This amendment processed the following: after the end of the 4 weeks follow-up, patients would be offered to receive study drug until transplantation (continued treatment period). Moreover, the following additions were made: • Addition of a secondary endpoint to evaluate the efficacy and safety of long-term treatment for patients who would continue on study drug after the follow-up period, • Addition that Speckle Tracking Echocardiography would be performed at screening or week 14 visit and repeated every 6 months during the continued treatment period.
14 December 2014	Amendment 5 (which related to Version 5 of the Protocol in Germany). This amendment only concerned Germany. This amendment clarified that the length of the continued treatment had been prolonged to a maximum of 12 months.
20 February 2015	Amendment 6 (which related to Version 6 of the Protocol in France). This amendment only concerned France. This amendment clarified a new administration process for patients who would not be able to swallow capsules.

08 March 2016	Amendment 7 (which related to Version 7 of the Protocol in Germany). This Amendment only concerned Germany. This amendment clarified that the length of the continued treatment period had been extended by an additional 12-month period, i.e. to a maximum of 24 months. The timeline for evaluation of the primary endpoint (change in plasma oxalate from baseline) was also revised.
31 May 2016	Amendment 8 (which related to Version 8 of the Protocol). This amendment was submitted to Germany as a notification only, and included non-substantial amendments (administrative modifications).
20 September 2016	Amendment 9 (which related to Version 8 of the Protocol). This amendment was submitted to Germany as a notification only. The amendment included non-substantial amendments (administrative modifications).
04 April 2017	Amendment 10 (which related to Version 9 of the Protocol in Germany). This amendment only concerned Germany. This amendment clarified that the length of the continued treatment period had been extended by an additional 12-month period (i.e. to a maximum of 36 months).
27 November 2017	Amendment 11 (which related to Version 10 of the Protocol). This amendment was an internal document only, and not submitted to any authority. This amendment clarified that the primary endpoint will evaluate total plasma oxalate values, added analysis of change in free plasma oxalate values as a secondary endpoint, and further specified that an interim analysis of data would be performed after 12 months of continued treatment.
18 January 2018	Amendment 12 (which related to Version 11 of the Protocol in Germany). This amendment only concerned Germany. In addition to the revisions detailed in Version 10 of the protocol, this amendment clarified that final visit date after completion of 3 years was corrected from week 152 to week 156.
14 October 2019	Amendment 13 (which related to Version 12 of the Protocol in Germany). This amendment only concerned Germany. This amendment clarified transplantation as an explicit reason for withdrawal. It further defined events that would not be reported as Adverse Events, and detailed that an interim analysis of data would be performed after 24 months of continued treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 January 2014	The FDA temporarily put Version 1 of the OC5-OL-01 study protocol on clinical hold. Following modifications to the protocol (Version 2) and a commitment to further modify the protocol (Version 3), the clinical hold was removed.	30 April 2014

Notes:

Limitations and caveats

None reported