



Clinical trial results:

A Phase 1/2, randomised, placebo-controlled, double-blind, multi-centre study to evaluate the efficacy and safety of OC5 to reduce urinary oxalate in subjects with primary hyperoxaluria

Summary

EudraCT number	2012-005606-22
Trial protocol	DE GB
Global end of trial date	23 January 2015

Results information

Result version number	v1 (current)
This version publication date	19 May 2017
First version publication date	19 May 2017

Trial information

Trial identification

Sponsor protocol code	OC5-DB-01
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02012985
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	OxThera IP AB
Sponsor organisation address	Sturegatan 56, Stockholm, Sweden, 11436
Public contact	Director of Clinical Operations, OxThera AB, +46 86600223, anna.sjogren@oxthera.com
Scientific contact	Director of Clinical Operations, OxThera AB, +46 86600223, anna.sjogren@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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 January 2015
Global end of trial reached?	Yes
Global end of trial date	23 January 2015
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 urinary oxalate levels during 8 weeks in subjects with Primary Hyperoxaluria (PH).

Protection of trial subjects:

Patients were observed in the clinics during the study visits. Physical exam and vital signs were taken at screening and at last study visit to the clinic. Local laboratory safety tests included haematology, chemistry and urinalysis were assessed at each study visit (week 0, 5, 10, 14).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 December 2013
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	United Kingdom: 3
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 13
Worldwide total number of subjects	28
EEA total number of subjects	28

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)	9
Adolescents (12-17 years)	10
Adults (18-64 years)	9
From 65 to 84 years	0

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

This was a randomised, placebo-controlled, double-blind, multi-centre study conducted at 8 sites in Germany, France and the UK. First patient enrolled 06 Dec 2013, and last patient completed 23 Jan 2015. In total 44 patients were screened of which 28 patients were randomised.

Pre-assignment

Screening details:

Male and females aged 2 year or above (at least 5 years old in the UK) with a diagnosis of primary hyperoxaluria type I, II or III were to be screened for the study. Patients were screened and followed during a 4-week baseline period before randomised 1:1 to receive 8 to 10 weeks of treatment with OC5 or placebo.

Period 1

Period 1 title	Randomisation
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Placebo capsules had the same appearance and mode of administration as the active product and were filled with microcrystalline cellulose.

Arms

Are arms mutually exclusive?	Yes
Arm title	Baseline OC5

Arm description:

Patients randomised to receive 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 in enteric-coated size-4 capsule at a dose of minimum 10^9 colony-forming units (CFU) per capsule. Administration orally with breakfast and dinner as one capsule twice daily, during 8-10 weeks.

Arm title	Baseline Placebo
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Arm description:

Patients randomised to placebo treatment.

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

Dosage and administration details:

Placebo in enteric-coated size-4 capsule filled with microcrystalline cellulose. Administration orally with breakfast and dinner as one capsule twice daily, during 8-10 weeks.

Number of subjects in period 1	Baseline OC5	Baseline Placebo
Started	14	14
Completed	14	14

Period 2

Period 2 title	Treatment
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	OC5 group

Arm description:

Patients randomised to receive 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 in enteric-coated size-4 capsule at a dose of minimum 10^9 colony-forming units (CFU) per capsule. Administration orally with breakfast and dinner as one capsule twice daily, during 8-10 weeks.

Arm title	Placebo
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Arm description:

Patients randomised to placebo treatment.

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

Dosage and administration details:

Placebo in enteric-coated size-4 capsule filled with microcrystalline cellulose.

Administration orally with breakfast and dinner as one capsule twice daily, during 8-10 weeks.

Number of subjects in period 2	OC5 group	Placebo
Started	14	14
Completed	14	14

Baseline characteristics

Reporting groups

Reporting group title	Baseline OC5
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Reporting group description:

Patients randomised to receive treatment with OC5.

Reporting group title	Baseline Placebo
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Reporting group description:

Patients randomised to placebo treatment.

Reporting group values	Baseline OC5	Baseline Placebo	Total
Number of subjects	14	14	28
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	4	5	9
Adolescents (12-17 years)	5	5	10
Adults (18-64 years)	5	4	9
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	4	9	13
Male	10	5	15
Primary hyperoxaluria medical history			
Units: Subjects			
Type I	13	13	26
Type II	0	1	1
Type III	1	0	1
PH Diagnosis confirmed by			
Units: Subjects			
DNA screening	11	12	23
Enzyme deficiency	3	1	4
Elevated urine glycolate	0	1	1
Time since diagnosis			
Units: Days			
arithmetic mean	3193.3	3358.5	-
standard deviation	± 2038.3	± 1921.4	-
Baseline plasma oxalate			
Units: micromole(s)/litre			
arithmetic mean	14.755	14.664	-
standard deviation	± 8.935	± 11.2	-
Baseline estimated Glomerular Filtration Rate			
Units: mL/min/1.73 m2			

arithmetic mean	97.471	123.111	
standard deviation	± 38.666	± 45.425	-
Baseline urinary oxalate excretion (without centrifuging)			
Centrifuging the urine removed larger calcium oxalate crystals and thus reduced spontaneous variability due to random sampling of larger crystals.			
Units: mmol/24 h/1.73 m ²			
arithmetic mean	1.733	1.737	
standard deviation	± 0.488	± 0.696	-
Baseline urinary oxalate excretion (with centrifuging)			
Centrifuging the urine removed larger calcium oxalate crystals and thus reduced spontaneous variability due to random sampling of larger crystals.			
Units: mmol/24 h/1.73 m ²			
arithmetic mean	1.396	1.456	
standard deviation	± 0.521	± 0.776	-

End points

End points reporting groups

Reporting group title	Baseline OC5
Reporting group description: Patients randomised to receive treatment with OC5.	
Reporting group title	Baseline Placebo
Reporting group description: Patients randomised to placebo treatment.	
Reporting group title	OC5 group
Reporting group description: Patients randomised to receive treatment with OC5.	
Reporting group title	Placebo
Reporting group description: Patients randomised to placebo treatment.	

Primary: Efficacy of OC5 in reducing urinary oxalate excretion levels during 8 weeks

End point title	Efficacy of OC5 in reducing urinary oxalate excretion levels during 8 weeks
End point description: The primary endpoint was defined as absolute change in urinary oxalate excretion (mmol/24 h/1.73 m ²) after 8 weeks treatment from baseline. Patients had to have daily urinary excretion of minimum 1 mmol/24 h/1.73 m ² to meet the inclusion criteria for the protocol. Patients were stratified for daily urinary oxalate excretion above and below 1.5 mmol/24 h/1.73 m ² .	
End point type	Primary
End point timeframe: Change after 8 weeks of treatment compared to baseline	

End point values	OC5 group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: mmol/24 h/1.73 m ²				
least squares mean (confidence interval 95%)	0.042 (-0.162 to 0.245)	-0.14 (-0.355 to 0.076)		

Statistical analyses

Statistical analysis title	OC5 difference to placebo
Statistical analysis description: Based on a mixed-model repeated measures analysis of variance including treatment, visit and visit-by-treatment interaction and baseline crystal-bound oxalate as covariate	
Comparison groups	OC5 group v Placebo

Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2174
Method	Mixed models analysis

Secondary: Change in number of O. formigenes in faeces after 8 weeks of treatment

End point title	Change in number of O. formigenes in faeces after 8 weeks of treatment
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End point description:

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. One subject in the study had detectable O. formigenes type 1 at the start of the study, albeit very low (SCR03-0005, in the active group). Three subjects in the active group and three subjects in the placebo group had detectable levels of O. formigenes type 2 during baseline. All subjects but one in the active group increased in O. formigenes type 1 count; the subject with no increase in O. formigenes type 1 had undetectable levels of any Oxalobacter. No O. formigenes type 1 were detectable in the placebo group during any time of the study. In terms of absolute change in number of O. formigenes in faeces, the LS mean difference from baseline after 8 weeks of treatment was 12,723,497 greater in the OC5 group than in the Placebo group (95% CI: 4,788,219–20,658,775; p=0.00023).

End point type	Secondary
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End point timeframe:

Change in faeces after 8 weeks of treatment compared to baseline

End point values	OC5 group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: amount				
number (confidence interval 95%)	13814394 (7992437 to 19636352)	1090897 (-4293285 to 6475081)		

Statistical analyses

Statistical analysis title	OC5 difference to placebo
Comparison groups	OC5 group v Placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.00023
Method	Mixed models analysis

Notes:

[1] - Based on a mixed-model repeated measures analysis of variance including treatment, visit and visit-by-treatment interaction and baseline number of O.formigenes as a covariate.

Secondary: Change in plasma oxalate concentration after 8 weeks of treatment

End point title	Change in plasma oxalate concentration after 8 weeks of
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	treatment
End point description:	
The LS mean difference between plasma oxalate concentration at baseline and after 8 weeks of treatment was 0.894 µmol/L (95% CI: -0.636, 2.423) in the OC5 group and 0.053 µmol/L (95% CI: -1.534, 1.640) in the Placebo group. The difference between the groups did not achieve statistical significance (0.841 µmol/L; 95% CI: -1.363, 3.045; p=0.4383).	
End point type	Secondary
End point timeframe:	
Change after 8 weeks of treatment	

End point values	OC5 group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: micromole(s)/litre				
least squares mean (confidence interval 95%)	0.894 (-0.636 to 2.423)	0.053 (-1.534 to 1.64)		

Statistical analyses

Statistical analysis title	OC5 difference to placebo
Statistical analysis description:	
Based on a mixed-model repeated measures analysis of variance including treatment, visit and visit-by-treatment interaction and baseline plasma oxalate as covariate.	
Baseline level of plasma oxalate is defined as last non-missing and valid assessment before first dose of study drug.	
Comparison groups	OC5 group v Placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4383
Method	Mixed models analysis

Secondary: Change in urinary oxalate excretion after 4 weeks of treatment compared with baseline

End point title	Change in urinary oxalate excretion after 4 weeks of treatment compared with baseline
End point description:	
The LS mean difference between urinary oxalate excretion at baseline and after 4 weeks of treatment was 0.007 mmol/24 h/1.73 m ² (95% CI: -0.186, 0.201) in the OC5 group and -0.177 (95% CI: -0.358, 0.005) in the Placebo group. The difference of 0.184 mmol/24 h/1.73 m ² (95% CI: -0.079, 0.448) failed to achieve statistical significance (p=0.1617). Similar results were obtained when the samples were centrifuged.	
End point type	Secondary
End point timeframe:	
Change after 4 weeks of treatment compared with baseline	

End point values	OC5 group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: mmol/24 h/1.73 m2				
least squares mean (confidence interval 95%)	0.007 (-0.186 to 0.201)	-0.177 (-0.358 to 0.005)		

Statistical analyses

Statistical analysis title	OC5 difference to placebo
Statistical analysis description:	
Based on a mixed-model repeated measures analysis of variance including treatment, stratification variable, visit and visit-by-treatment interaction.	
Baseline level of urinary oxalate is the mean from eligible 24-h urine collections taken before first dose of study drug.	
Comparison groups	OC5 group v Placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1617
Method	Mixed models analysis

Secondary: Estimated glomerular filtration rate

End point title	Estimated glomerular filtration rate
End point description:	
Estimated glomerular filtration rate reported as absolut change after 8 weeks of treatment compared to baseline value.	
End point type	Secondary
End point timeframe:	
Change after 8 weeks of treatment compared to baseline	

End point values	OC5 group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: mL/min/1.73 m2				
arithmetic mean (standard deviation)	-3.199 (± 13.594)	-6.529 (± 15.135)		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of nephrocalcinosis

End point title	Occurrence of nephrocalcinosis
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End point description:

Nephrocalcinosis was diagnosed using renal ultrasound.

At baseline, nephrocalcinosis was observed in a total of 19 kidneys in the OC5 group and in 11 kidneys in the Placebo group. No difference was observed between OC5 and Placebo with respect to reduction in nephrocalcinosis cases. In both treatment groups, nephrocalcinosis was observed in two fewer kidneys at the Week 8 clinical visit than at baseline.

End point type	Secondary
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End point timeframe:

Number of occurrences at study baseline and after 8 weeks of treatment

End point values	Baseline OC5	Baseline Placebo	OC5 group	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14 ^[2]	14 ^[3]	14 ^[4]	14 ^[5]
Units: number of nephrocalcinosis				
Left kidney	10	6	9	5
Right kidney	9	5	8	4

Notes:

[2] - Baseline

[3] - Baseline

[4] - 8 weeks treatment

[5] - 8 weeks treatment

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.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	OC5 group
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Reporting group description:

Patients randomised to receive treatment with OC5.

Reporting group title	Placebo
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Reporting group description:

Patients randomised to placebo treatment.

Serious adverse events	OC5 group	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 14 (21.43%)	0 / 14 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Pyelonephritis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			

subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	OC5 group	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 14 (71.43%)	12 / 14 (85.71%)	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	
occurrences (all)	4	1	
Influenza like illness			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	2 / 14 (14.29%)	1 / 14 (7.14%)	
occurrences (all)	2	1	
Cough			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
Epistaxis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Asthma			

subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 14 (7.14%) 1	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 14 (0.00%) 0	
Investigations Red blood cells urine positive subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 14 (7.14%) 1	
Injury, poisoning and procedural complications Radius fracture subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 14 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1 1 / 14 (7.14%) 1	5 / 14 (35.71%) 5 0 / 14 (0.00%) 0	
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 14 (7.14%) 1	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Diarrhoea	3 / 14 (21.43%) 3 1 / 14 (7.14%) 4 2 / 14 (14.29%) 3	2 / 14 (14.29%) 2 1 / 14 (7.14%) 2 0 / 14 (0.00%) 0	

subjects affected / exposed	0 / 14 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Abdominal discomfort			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Change of bowel habit			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Frequent bowel movements			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Skin reaction			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	2 / 14 (14.29%)	0 / 14 (0.00%)	
occurrences (all)	3	0	
Renal pain			
subjects affected / exposed	2 / 14 (14.29%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Calculus urethral			

subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Pyelonephritis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Infections and infestations			
Rhinitis			
subjects affected / exposed	0 / 14 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	3	
Gastroenteritis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Laryngitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 May 2013	Amendment 1 (which related to Rev 3 of the protocol and was the first submitted protocol in France and the United Kingdom): This amendment removed inclusion criterion 4 (historic values of urinary oxalate); clarified details on telephone follow-up, clarified that ascorbic acid preparations were to be avoided during the study period, and defined abnormal safety laboratory limits for serum bicarbonate and blood pH.
04 September 2013	Amendment 2 (which related to Version 4 of the protocol): This amendment defined criteria of the early termination of the study, corrected an error in the table of drug potency, clarified instructions on how to handle potential infections due to study medication, included information on burden, risk threshold and risk:benefit assessment, and clarified instructions on how to handle any elevated formate levels.
04 September 2013	Amendment 3 and 4 (which related to Version 5 and 6 of the protocol in Germany and the United Kingdom respectively): These amendments were local to Germany and the UK, respectively. In Germany, Amendment 3 concerned sequential enrolment with adult subjects being recruited before children. In the UK, amendment 4 included a change of inclusion criterion 2 to state "Male or female subjects ≥ 5 years of age".
10 June 2014	Amendment 5 (which related to Version 7, 8 and 9 of the protocol in France, Germany and the United Kingdom respectively): This amendment included the following changes: • Change in inclusion criteria number 3 to also include subjects with PH type II or III. • Correction of inclusion criteria number 4 to a mean urinary oxalate excretion ≥ 1 mmol/24 h/1.73 m² (previously >1 mmol/24 h/1.73 m²). • Update of Section 7.2.2 (Prohibited Medications), Section 10.5.2 (Systemic Infections) and Section 11.1 (Study Population), with regard to antibiotic treatment. • Clarification in Section 5.2.2 and Section 9.1 that an additional urine collection during baseline may be scheduled in case of incomplete collection(s) or accidental loss of a collection during baseline. • Clarification of data imputation for end of treatment (Week 14) in Section 11.8.3. • Adjustment of the study timelines in line with actual study progress. Furthermore, due to issues with subject recruitment, it was necessary to add an eighth clinical site (Hôpital Robert Debré, Paris). A substantial amendment with information on the new site was sent to the French Ethics Committee SudEst II on 04 June 2014. Approval was given by SudEst II for the new site on 18 June 2014. A notification was also sent to ANSM on 04 June 2014 regarding the new clinical site. Approval was not required from ANSM. However, no subjects were recruited at this site.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported