Clinical trial results:
A double-blind, controlled, parallel-group, randomized, multicenter clinical trial to assess the efficacy and safety of a herbal drug containing centaury, lovage root, and rosemary leaf (CLR) in comparison to fosfomycin trometamol for the treatment of acute lower uncomplicated urinary tract infections (uUTIs) in women

Summary

EudraCT number	2013-004529-99
Trial protocol	DE
Global end of trial date	29 June 2017

Results information

Result version number	v1 (current)
This version publication date	06 January 2023
First version publication date	06 January 2023

Trial information

Trial identification

Sponsor protocol code	CanUTI-7

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bionorica SE
Sponsor organisation address	Kerschensteinerstraße 11-15, Neumarkt, Germany, 92318
Public contact	Head of cooperate communication, Bionorica SE, info@bionorica.de
Scientific contact	Head of Research and Development, Bionorica SE, research.development@bionorica.de

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	15 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 June 2017
Global end of trial reached?	Yes
Global end of trial date	29 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate non-inferiority of a non-antibiotic therapy with CLR versus an antibiotic treatment with fosfomycin trometamol in women suffering from acute lower uUTIs as measured by the proportion of patients who received an additional antibiotic treatment for acute lower uUTIs during the trial.

Protection of trial subjects:

This study was conducted in compliance with the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice, including the archiving of essential documents.

Background therapy: -

Evidence for comparator:

The trial was designed as a comparison of two different versus AB - in order to look for alternatives to AB treatment of uncomplicated UTIs. Thus, the aim was to reduce AB use and furthermore to demonstrate the advantage of using CLR therapy for decreasing the pressure of developing bacterial resistance against ABs due to widespread use, which is an additional advantage of the CLR therapy. Besides, and in accordance with the EAU guidelines 2015, uncomplicated UTIs could be considered a benign infection not leading to more serious outcome and requiring additional attention. Hence, from medical point of view there was no enhanced risk for the patient when not treating with ABs.

Actual start date of recruitment	20 February 2016
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	Poland: 135
Country: Number of subjects enrolled	Germany: 117
Country: Number of subjects enrolled	Ukraine: 416
Worldwide total number of subjects	668
EEA total number of subjects	252

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	568
From 65 to 84 years	100
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 668 patients were enrolled; of these, 9 were not randomized and not treated. In total, 659 (98.7% of the enrolled population) patients were randomized, 325 to treatment with CLR (test IMP) and 334 to treatment with FT (reference IMP). All randomized patients were treated with the IMP they were allocated to.

Pre-assignment

Screening details:

This trial does not include a screening phase. Only patients who had symptoms of lower uUTIs developed within not more than 6 days prior to screening at Visit 1 were eligible for this trial.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	CLR_group

Arm description:

CLR coated tablets and FT-matched placebo

Arm type	Experimental
Investigational medicinal product name	Canephron® N (CLR)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 coated tablets t.i.d. for 7 days

Investigational medicinal product name	FT-matched placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules for oral solution in sachet
Routes of administration	Oral use

Dosage and administration details:

1 sachet of granules; single dose (Day 1)

Arm title	FT_group

Arm description:

FT granulates 3 g and CLR-matched placebo

Arm type	Active comparator
Investigational medicinal product name	Monuril® 3000 mg granules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules for oral solution in sachet
Routes of administration	Oral use

Dosage and administration details:

1 sachet of 8 g of granules; single dose (Day 1)

Investigational medicinal product name	CLR-matched placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 coated tablets t.i.d. for 7 days

Number of subjects in period 1[1]	CLR_group	FT_group
Started	325	334
End of treatment	325	334
End of observation	313	329
Completed	313	329
Not completed	12	5
Consent withdrawn by subject	4	-
Lost to follow-up	6	4
not specified	2	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 668 patients were enrolled; of these, 9 were not randomized and not treated. In total, 659 (98.7% of the enrolled population) patients were randomized, 325 to treatment with CLR (test IMP) and 334 to treatment with FT (reference IMP). All randomized patients were treated with the IMP they were allocated to.

Baseline characteristics

Reporting groups	
Reporting group title	CLR_group
Reporting group description:	
CLR coated tablets and FT-matched placebo	
Reporting group title	FT_group
Reporting group description:	
FT granulates 3 g and CLR-matched placebo	

Reporting group values	CLR_group	FT_group	Total
Number of subjects	325	334	659
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	43.9	45.2	
standard deviation	± 15.60	± 16.24	-
Gender categorical Units: Subjects			
Female	325	334	659

Subject analysis sets	
Subject analysis set title	CLR - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients randomized and treated at least once with IMP after randomization. Following the intent-to-treat principle all patients were analyzed according to the treatment group they were randomized to.	
Subject analysis set title	FT - FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients randomized and treated at least once with IMP after randomization. Following the intent-to-treat principle all patients were analyzed according to the treatment group they were randomized to.	
Subject analysis set title	CLR - SAF
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients treated at least once with IMP. The assignment of patients to the treatment groups was as actually treated. Patients treated with more than one type of IMP by mistake were to be analyzed	

according to the IMP they received the longest.

Subject analysis set title	FT - SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients treated at least once with IMP. The assignment of patients to the treatment groups was as actually treated. Patients treated with more than one type of IMP by mistake were to be analyzed according to the IMP they received the longest.

Subject analysis set title	CLR - PPS
Subject analysis set type	Per protocol

Subject analysis set description:

All patients from the FAS who had no major protocol deviations.

Subject analysis set title	FT - PPS
Subject analysis set type	Per protocol

Subject analysis set description:

All patients from the FAS who had no major protocol deviations.

Reporting group values	CLR - FAS	FT - FAS	CLR - SAF
Number of subjects	325	332	325
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	43.9	45.1	43.9
standard deviation	± 15.60	± 16.26	± 15.60
Gender categorical			
Units: Subjects			
Female	325	332	325

Reporting group values	FT - SAF	CLR - PPS	FT - PPS
Number of subjects	334	285	303
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			

From 65-84 years			
85 years and over			

Age continuous			
Units: years			
arithmetic mean	45.2	43.7	45.0
standard deviation	± 16.24	± 15.57	± 16.41
Gender categorical			
Units: Subjects			
Female	334	285	303

End points

End points reporting groups

Reporting group title	CLR_group
Reporting group description: CLR coated tablets and FT-matched placebo	
Reporting group title	FT_group
Reporting group description: FT granulates 3 g and CLR-matched placebo	
Subject analysis set title	CLR - FAS
Subject analysis set type	Full analysis
Subject analysis set description: All patients randomized and treated at least once with IMP after randomization. Following the intent-to-treat principle all patients were analyzed according to the treatment group they were randomized to.	
Subject analysis set title	FT - FAS
Subject analysis set type	Full analysis
Subject analysis set description: All patients randomized and treated at least once with IMP after randomization. Following the intent-to-treat principle all patients were analyzed according to the treatment group they were randomized to.	
Subject analysis set title	CLR - SAF
Subject analysis set type	Safety analysis
Subject analysis set description: All patients treated at least once with IMP. The assignment of patients to the treatment groups was as actually treated. Patients treated with more than one type of IMP by mistake were to be analyzed according to the IMP they received the longest.	
Subject analysis set title	FT - SAF
Subject analysis set type	Safety analysis
Subject analysis set description: All patients treated at least once with IMP. The assignment of patients to the treatment groups was as actually treated. Patients treated with more than one type of IMP by mistake were to be analyzed according to the IMP they received the longest.	
Subject analysis set title	CLR - PPS
Subject analysis set type	Per protocol
Subject analysis set description: All patients from the FAS who had no major protocol deviations.	
Subject analysis set title	FT - PPS
Subject analysis set type	Per protocol
Subject analysis set description: All patients from the FAS who had no major protocol deviations.	

Primary: Non-AB rate

End point title	Non-AB rate
End point description: Non-AB rate as proportion of patients who did not receive additional antibiotic treatment for acute lower uUTI between Visit 1 and Visit 4	
End point type	Primary
End point timeframe: Between day 1 (visit 1) and day 38 +/- 3 (visit 4) after start of treatment	

End point values	CLR - PPS	FT - PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	285	303		
Units: number of patients	238	272		

Statistical analyses

Statistical analysis title	Non-inferiority
Comparison groups	CLR - PPS v FT - PPS
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0014
Method	Farrington's and Manning's test
Parameter estimate	Risk difference (RD)
Point estimate	-0.0626
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1199
upper limit	-0.0053

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs ocurring between V1 (randomisation) and V4 (end of observation) are reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	FT_group
Reporting group description: -	
Reporting group title	CLR_group

Reporting group description: -

Serious adverse events	FT_group	CLR_group	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 334 (0.30%)	1 / 325 (0.31%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis chronic			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyelonephritis			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
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	FT_group	CLR_group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 334 (12.57%)	48 / 325 (14.77%)	
General disorders and administration site conditions			
Asthenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
Drug intolerance			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
Localised oedema			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Menorrhagia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences (all)	1	0	
Ovarian cyst			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
Pruritus genital			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
Vaginal discharge			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	2 / 325 (0.62%)	
occurrences (all)	0	2	
Vaginal haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
Rhinorrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	1 / 325 (0.31%)	
occurrences (all)	1	1	
Aspartate aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences (all)	1	0	
Blood alkaline phosphatase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
Blood pressure increased			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
C-reactive protein increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	3 / 325 (0.92%)	
occurrences (all)	0	3	
Gamma-glutamyltransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	2 / 325 (0.62%)	
occurrences (all)	1	2	
Nervous system disorders			
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences (all)	1	0	
Dysgeusia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	2 / 325 (0.62%)	
occurrences (all)	0	2	
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 334 (0.60%)	4 / 325 (1.23%)	
occurrences (all)	2	5	
Somnolence			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Leukopenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
Splenomegaly			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
Thrombocytopenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Eye irritation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal distension			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 334 (1.20%)	0 / 325 (0.00%)	
occurrences (all)	4	0	
Abdominal pain lower			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	2 / 325 (0.62%)	
occurrences (all)	0	2	
Abdominal pain upper			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 334 (0.60%)	1 / 325 (0.31%)	
occurrences (all)	2	1	
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 334 (2.99%)	3 / 325 (0.92%)	
occurrences (all)	11	3	
Dyspepsia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	1 / 325 (0.31%)	
occurrences (all)	1	1	
Enteritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences (all)	1	0	
Epigastric discomfort			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences (all)	1	0	
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 334 (1.20%)	2 / 325 (0.62%)	
occurrences (all)	4	2	
Oral discomfort			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	

Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	2 / 325 (0.62%)	
occurrences (all)	1	2	
Skin and subcutaneous tissue disorders			
Pruritus			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Dysuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences (all)	1	0	
Glycosuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	2 / 325 (0.62%)	
occurrences (all)	0	2	
Nephrolithiasis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences (all)	1	0	
Pyelocaliectasis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
Back pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	1 / 325 (0.31%)	
occurrences (all)	1	1	

Joint range of motion decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
Muscle spasms			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
Osteoarthritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences (all)	1	0	
Spinal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Gastroenteritis viral			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences (all)	1	0	
Hepatitis viral			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
Influenza			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
Laryngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 334 (0.60%)	0 / 325 (0.00%)	
occurrences (all)	2	0	
Otitis media			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences (all)	1	0	
Periodontitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	
Pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences (all)	1	0	
Pyelonephritis acute			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	2 / 325 (0.62%)	
occurrences (all)	0	2	
Pyelonephritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	2 / 325 (0.62%)	
occurrences (all)	1	2	
Respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	2 / 325 (0.62%)	
occurrences (all)	0	2	
Respiratory tract infection viral			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 334 (0.60%)	1 / 325 (0.31%)	
occurrences (all)	2	1	
Vaginal infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	1 / 325 (0.31%)	
occurrences (all)	0	1	

Viral upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 334 (2.40%)	5 / 325 (1.54%)	
occurrences (all)	8	5	
Metabolism and nutrition disorders			
Glucose tolerance impaired			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 334 (0.00%)	2 / 325 (0.62%)	
occurrences (all)	0	2	
Increased appetite			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 325 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 March 2016	This amendment was implemented at the request of the sponsor and aimed to introduce the following changes in the conduct of the trial: - An analysis of prostaglandins in urine samples collected at Visits 1 and 3 from patients at selected centers in Poland in Germany was added. - Number and volume of urine samples were corrected due to the newly introduced analysis of prostaglandins in these samples. - Inclusion criterion No. 3 was further specified for clarity as follows: Sum-score of the three main uUTI symptoms (dysuria ["feeling pain or burning when passing urine", No. 3], pollakisuria ["frequent urination of small volumes of urine", No. 1], and urgency ["Urgent urination", No. 2]) reported on the ACSS-Typical domain at Visit 1 is ≥ 6. - Inclusion criterion No. 3 was further specified as follows: Patients who took anti-inflammatory or analgesic drugs (eg, ibuprofen, paracetamol, acetylsalicylic acid) or spasmolytics for any reason within 24 hours prior to Visit 1, and/or are not willing to stop the intake of any of the following medication not permitted for use during the trial: Rosmarini folium, Levistici radix, and Centaurii herba supplements other than the CLR (IMP), antiinflammatory or analgesic drugs (eg, ibuprofen, acetylsalicylic acid, with exception of paracetamol), spasmolytics, herbal drugs or supplements, cranberry juice, and kidney or bladder teas. - The analgesic drugs added to exclusion criterion 10 were included in the list of prohibited concomitant medications.
10 January 2017	The main objective of this amendment was to introduce changes in CTP Version 4, 11-MAR-2016, following from the sponsor's decision to cancel the planned interim analysis. The decision for withdrawal of the interim analysis was justified with the markedly increased recruitment rates over the last 4 months of the trial conduct (up to 2 patients per trial site per month) and the expectation of a further increasing recruitment rate due to additionally initiated sites (see below). Other relevant changes implemented in CTP Version 5 with Amendment No. 2 included: - Prolongation of recruitment period by 4 months and of overall trial duration by 6 months accordingly. - Romania was excluded from the list of participating countries, because the conduct of- the trial in this country was disapproved by the local competent authority; consequently, the sponsor decided to increase the number of trial sites in Germany, Ukraine and Poland. - The list of concomitant medications not permitted during the trial was further specified by including an exception rule for spasmolytics, anti-inflammatory or analgesic drugs, and any additional AB therapy for other than acute lower uUTI indications. - The range of kit-No was updated since new IMP had been produced (the IMP for Ukraine had expired and not enough IMP was available for all countries). - Benefit-risk information with regard to the use of fosfomycin in the trial was updated in accordance with the latest version of the Summary of Product Characteristics of fosfomycin.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported