Clinical trial results:
A double-blind, randomised, multi-centre, controlled clinical trial to compare D-mannose versus antibiotic in the treatment of acute uncomplicated lower urinary tract infections in female patients

Summary

EudraCT number	2021-003466-12
Trial protocol	DE
Global end of trial date	25 August 2023

Results information

Result version number	v1 (current)
This version publication date	13 September 2024
First version publication date	13 September 2024

Trial information

Trial identification

Sponsor protocol code	MCMK0220

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	MCM Klosterfrau Vertriebsgesellschaft mbH
Sponsor organisation address	Gereonsmuehlengasse 1-11, Cologne, Germany, 50670
Public contact	Clinical Operations, MCM Klosterfrau Vertriebsgesellschaft mbH, clinical.operations@klosterfrau.de
Scientific contact	Clinical Operations, MCM Klosterfrau Vertriebsgesellschaft mbH, clinical.operations@klosterfrau.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	25 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 August 2023
Global end of trial reached?	Yes
Global end of trial date	25 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

At start of trial the European Association of Urology guidelines on urological infections (EAU Guidelines 2020) recommend oral antibiotics (e.g. fosfomycin trometamol, pivmecillinam, nitrofurantoin) as first-line treatment for acute lower urinary tract infection (UTI, also called cystitis) in women. This randomised controlled clinical trial aims to investigate D-mannose (Femannose® N) as stand-alone therapy for acute uncomplicated UTI to point out possible strategies for the avoidance of so far common antibiotic use.

Protection of trial subjects:

In this study subjects with a diagnosed acute cystitis received a well established and approved treatment. Each subject was fully informed of all aspects of the study and provided informed consent prior to start of any study procedures. Subjects could withdraw from treatment at any time and for any reason. No specific additional measures were required to minimize distress given the nature of study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 May 2022
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	Germany: 118
Worldwide total number of subjects	118
EEA total number of subjects	118

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)	108
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adult female subjects were screened for study participation during regular visits when they attended the investigational site with symptoms of acute uncomplicated cystitis. Methods of subject recruitment could include, but were not limited to, e-mails, posters, advertisements on various channels.

Pre-assignment

Screening details:

Sixteen out of 134 subjects failed to meet the inclusion and /or exclusion criteria or were excluded due to other reasons and therefore were not randomised or treated with the IMP or IMD.

Period 1

Period 1 title	overall trial (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	Arm 1

Arm description:

D-mannose

Arm type	medical device
Investigational medicinal product name	D-mannose
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules for oral solution in sachet
Routes of administration	Oral use

Dosage and administration details:

Subjects in Arm 1 (D-mannose) received one sachet of IMP-matched placebo once on Day 1 and repeated doses of IMD (2 g of D-mannose per sachet) for 5 days. Subjects had to take one sachet of the IMD three times a day from Day 1 to Day 3 and one sachet two times a day on Day 4 and Day 5 (13 sachets).

Arm title	Arm 2

Arm description:

Fosfomycin

Arm type	Active comparator
Investigational medicinal product name	Fosfomycin
Investigational medicinal product code	J01XX01
Other name	
Pharmaceutical forms	Powder for oral solution in sachet
Routes of administration	Oral use

Dosage and administration details:

Subjects in Arm 2 (Fosfomycin) received one sachet of IMP (3 g of Fosfomycin per sachet) once on Day 1 and repeated doses of IMD-matched placebo for 5 days. Subjects had to take one sachet of the IMD-matched placebo three times a day from Day 1 to Day 3 and one sachet two times a day on Day 4 and Day 5 (13 sachets).

Number of subjects in period 1	Arm 1	Arm 2
Started	61	57
Day 8	58	56
Completed	47	46
Not completed	14	11
Physician decision	-	1
e.g.need for additional antibiotic therapy for UTI	11	9
Adverse event, non-fatal	2	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm 1
Reporting group description: D-mannose	
Reporting group title	Arm 2
Reporting group description: Fosfomycin	

Reporting group values	Arm 1	Arm 2	Total
Number of subjects	61	57	118
Age categorical Units: Subjects			
Adults (18-64 years)	57	51	108
From 65-84 years	4	6	10
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	61	57	118
Male	0	0	0

Subject analysis sets	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol
Subject analysis set description: The PPS for the efficacy analyses included all subjects who did not show any relevant protocol deviation and were classified as clinically evaluable. The PPS cohort could be considered as the more conservative cohort with respect to study results in a non-inferiority setting and the primary analysis set in this study.	
Subject analysis set title	Safety Evaluation Population
Subject analysis set type	Safety analysis
Subject analysis set description: identical to full analysis set	

Reporting group values	Per protocol	Safety Evaluation Population	
Number of subjects	111	118	
Age categorical Units: Subjects			
Adults (18-64 years)	101	108	
From 65-84 years	10	10	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	111	118	
Male	0	0	

End points

End points reporting groups

Reporting group title	Arm 1
Reporting group description: D-mannose	
Reporting group title	Arm 2
Reporting group description: Fosfomycin	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol
Subject analysis set description: The PPS for the efficacy analyses included all subjects who did not show any relevant protocol deviation and were classified as clinically evaluable. The PPS cohort could be considered as the more conservative cohort with respect to study results in a non-inferiority setting and the primary analysis set in this study.	
Subject analysis set title	Safety Evaluation Population
Subject analysis set type	Safety analysis
Subject analysis set description: identical to full analysis set	

Primary: Clinical cure at Day 8

End point title	Clinical cure at Day 8
End point description: For this pilot study a range of different endpoints, analyzed individually or in combination in the acute phase (until Day 8, Visit 2) or overall, was defined containing percentage of subjects with "clinical cure-main variation". Missings at visit 2 were replaced by data from Day 8 (+/-1Day) or - if data not available - excluded from analysis. Once clinical cure was reached on a specific study day, clinical cure was considered to persist on all following days until recurrence of UTI was observed or until the day of study termination.	
End point type	Primary
End point timeframe: Day 8 (+/- 1day)	

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	54		
Units: percent				
number (confidence interval 95%)	82.5 (72.6 to 92.3)	92.6 (85.6 to 99.6)		

Statistical analyses

Statistical analysis title	Risk-difference

Statistical analysis description:

Non-inferiority of D-mannose versus Fosfomycin was analyzed using the test on so-called ‘risk-difference’ (in the current study, i.e. a difference in clinical cure rates) including 95% two-sided Wald confidence intervals (CIs).
Non-inferiority could be concluded in case the lower limit of CI of above p-differences does not cross

-0.15.

Comparison groups	Arm 1 v Arm 2
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk difference (RD)
Point estimate	-10.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.2
upper limit	2

Secondary: Global judgement of tolerability (by investigator)

End point title	Global judgement of tolerability (by investigator)

End point description:

Missing data at Visit 2 is imputed with the worst category in case the missingness is due to the withdrawal reason 'Appearance of non-tolerable adverse events',which is associated with a lack of tolerability.

End point type	Secondary

End point timeframe:

Visit 2 (Day 8)

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	57		
Units: percent				
number (not applicable)				
Very good	73.8	56.1		
Good	18.0	26.3		
Moderate	0	7.0		
Poor	0	1.8		
Very poor	3.3	1.8		
Missing	1.6	7.0		
Drop-out	3.3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Global judgement of tolerability (by subject)

End point title	Global judgement of tolerability (by subject)

End point description:

Missing data at Visit 2 is imputed with the worst category in case the missingness is due to the

withdrawal reason 'Appearance of non-tolerable adverse events',which is associated with a lack of tolerability.

End point type	Secondary

End point timeframe:

Visit 2 (Day 8)

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	57		
Units: percent				
number (not applicable)				
Very good	75.4	50.9		
Good	14.8	31.6		
Moderate	0	7.0		
Poor	0	1.8		
Very poor	4.9	1.8		
Missing	1.6	7.0		
Drop-out	3.3	0		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Post-hoc Clinical Cure at Day 8 (non-inferiority)

End point title	Post-hoc Clinical Cure at Day 8 (non-inferiority)

End point description:

clinical cure-main variation estimated with multiple imputations for missing data; persistence was not applied. Non-inferiority margin 15% as per protocol.

End point type	Post-hoc

End point timeframe:

Day 8 (+/-1 day)

End point values	Arm 1	Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	54		
Units: percent				
number (confidence interval 95%)	84.2 (72.1 to 92.5)	83.5 (70.9 to 92.2)		

Statistical analyses

Statistical analysis title	Risk-difference
Comparison groups	Arm 1 v Arm 2
Number of subjects included in analysis	111
Analysis specification	Post-hoc
Analysis type	non-inferiority
Parameter estimate	Risk difference (RD)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.11
upper limit	14.57

Adverse events

Adverse events information	
Timeframe for reporting adverse events: overall trial	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0
Reporting groups	
Reporting group title	Arm 1
Reporting group description: D-mannose	
Reporting group title	Arm 2
Reporting group description: Fosfomycin	

Serious adverse events	Arm 1	Arm 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 61 (0.00%)	1 / 57 (1.75%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	0 / 61 (0.00%)	1 / 57 (1.75%)	
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	Arm 1	Arm 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 61 (32.79%)	25 / 57 (43.86%)	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 61 (8.20%)	6 / 57 (10.53%)	
occurrences (all)	5	6	
Orthostatic intolerance			

subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Sciatica			
subjects affected / exposed	0 / 61 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 61 (3.28%)	0 / 57 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 61 (1.64%)	12 / 57 (21.05%)	
occurrences (all)	1	12	
Abdominal discomfort			
subjects affected / exposed	0 / 61 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Abdominal distension			
subjects affected / exposed	0 / 61 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	2 / 61 (3.28%)	0 / 57 (0.00%)	
occurrences (all)	2	0	
Abdominal pain lower			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 61 (1.64%)	1 / 57 (1.75%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 61 (1.64%)	1 / 57 (1.75%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal			

disorders			
Cough			
subjects affected / exposed	0 / 61 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Sacroiliac joint dysfunction			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 61 (4.92%)	4 / 57 (7.02%)	
occurrences (all)	3	4	
Acute sinusitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	0 / 61 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 61 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	1 / 61 (1.64%)	1 / 57 (1.75%)	
occurrences (all)	1	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 57 (0.00%)	
occurrences (all)	1	0	

Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	2 / 61 (3.28%) 2	0 / 57 (0.00%) 0	
Metabolism and nutrition disorders Hyperlipidaemia subjects affected / exposed occurrences (all)	0 / 61 (0.00%) 0	1 / 57 (1.75%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 October 2022	Substantial changes: Since the ACSS questionnaire is a fully validated instrument to confirm the appearance of an acute UTI, the sponsor decided to delete inclusion criterion no. 6 'Urine culture (MSU) is positive for bacteria defined as ≥10^3 colony forming units (CFU) per mL urine of single or mixed culture of uropathogens'. This step had to ensure also for the future the inclusion of the correct subject population, but avoid any delayed exclusion for example due to false-positive or false-negative laboratory results. Nevertheless, the urine samples were still taken and results analysed statistically at study end. Thus, these changes did not impact methodology or data recording.
18 August 2023	Substantial changes: Sample size calculation was adapted and a statistical power approach incorporated. This was a pilot study in order to provide good estimators of endpoints and provide promising results, in specific with regard to clinical cure. Specifications in the endpoints were made additionally. These changes did not impact data recording.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported