Clinical trial results:
Randomised, prospective, double-dummy double-blinded study to evaluate safety and efficacy of Angocin Anti-Infekt N versus standard antibiotics in the treatment of acute uncomplicated cystitis

Summary

EudraCT number	2010-022096-54
Trial protocol	DE
Global end of trial date	14 June 2013

Results information

Result version number	v1 (current)
This version publication date	06 July 2022
First version publication date	06 July 2022

Trial information

Trial identification

Sponsor protocol code	Repha_1344

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Repha GmbH
Sponsor organisation address	Alt-Godshorn 87, Langenhagen, Germany, 30855
Public contact	CRO, Mediconomics GmbH, 049 05115609980, info@mediconomics.com
Scientific contact	CRO, Mediconomics GmbH, 049 05115609980, info@mediconomics.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	14 June 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 June 2013
Global end of trial reached?	Yes
Global end of trial date	14 June 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Demonstration of the non-inferiority of ANGOCIN® Anti-Infekt N in comparison with two chemically defined standard antibiotics (cotrimoxazole and nitrofurantoin) in the therapy of acute, uncomplicated cystitis.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), which has its origins in the Declaration of Helsinki, and in strict compliance with the German German Drug Law (AMG) and the German Federal Data Protection Act (BDSG), in order to protect the rights, safety and well-being of patients.

Background therapy: -

Evidence for comparator:

The choice of the standard antibiotic was Kepinol® forte, as it is currently the most frequently prescribed antibiotic in
Germany for UTIs and is recommended by the DGGG (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe), among others. The comparison with cotrimoxazole and nitrofurantoin was planned in two stages:
1st stage : Kepinol® forte.
2nd stage : preparation with the active substance nitrofurantoin.
The 1st stage was terminated without the planned number of patients being reached, the 2nd stage was not started.

Actual start date of recruitment	18 May 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 96
Worldwide total number of subjects	96
EEA total number of subjects	96

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)	85
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in two parts: controlled phase and optional follow-up

Pre-assignment

Screening details:

When a patient was enrolled in the study, he or she was assigned a consecutive screening number within the centres. Via the patient number = "centre number / screening number", each patient in the study is clearly identifiable. In total, 96 patients were screened and 96 patients were randomized.

Period 1

Period 1 title	Controlled phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

As control and comparator differed with regard to the galenic properties, the trial was conducted in a doubly-dummy design. Despite differing treatment durations, the overall study medication intake was the same in both treatment arms as ensured by the double dummy design.

Arms

Are arms mutually exclusive?	Yes
Arm title	Investigational product

Arm description:

Group 1
morning: 5x Investigational product plus 1x placebo
noon: 5x investigational product
afternoon: 5x invstigatioal product
evening: 5x investigational product plus 1x placebo

Arm type	Experimental
Investigational medicinal product name	Angocin Anti-Infekt N
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

morning: 5x Investigational product plus 1x placebo
noon: 5x investigational product
afternoon: 5x invstigatioal product
evening: 5x investigational product plus 1x placebo

Arm title	Active Comparator

Arm description:

morning: 5x placebo + 1x active comparator
noon: 5 x placebo
afternoon: 5 x placebo
evening: 5 x placebo + 1x active comparator

Arm type	Active comparator

Investigational medicinal product name	Kepinol forte
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

morning: 5x placebo + 1x active comparator
noon: 5 x placebo
afternoon: 5 x placebo
evening: 5 x placebo + 1x active comparator

Number of subjects in period 1	Investigational product	Active Comparator
Started	45	51
Completed	22	29
Not completed	23	22
retrospective screening failure	18	20
missing screening results	-	1
Adverse event, non-fatal	1	-
need for antibiotics	2	-
personal reasons	-	1
Lack of efficacy	2	-

Period 2

Period 2 title	Optional follow-up phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Randomization was conducted in period 1

Arms

Are arms mutually exclusive?	Yes
Arm title	Investigational product

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Angocin Anti-Infekt N
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

no intervention during follow-up

Arm title	Active Comparator
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Kepinol forte
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

no intervention during follow-up

Number of subjects in period 2[1]	Investigational product	Active Comparator
Started	19	25
Completed	17	24
Not completed	2	1
follow-up is optional	2	1

Notes:

[1] - 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: The follow-up period was optional. The study was finished preliminary.

Baseline characteristics

End points

End points reporting groups

Reporting group title	Investigational product
Reporting group description:	
Group 1 morning: 5x Investigational product plus 1x placebo noon: 5x investigational product afternoon: 5x invstigatioal product evening: 5x investigational product plus 1x placebo	
Reporting group title	Active Comparator
Reporting group description:	
morning: 5x placebo + 1x active comparator noon: 5 x placebo afternoon: 5 x placebo evening: 5 x placebo + 1x active comparator	
Reporting group title	Investigational product
Reporting group description: -	
Reporting group title	Active Comparator
Reporting group description: -	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects from the intention-to-treat population without elevant protocol breaches	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
all subjects receiving study drug at least once. Same as the number of randomized subjects as well as safety population.	

Primary: Reduction in the number of lead cystitis germs from visit 1 (start of treatment) to visit 3 (follow-up 1), measured by the proportion of responders (definition: from > 10^5 cfu/mL midstream urine at visit 1 decrease to < 10^3 cfu/mL midstream urine

End point title	Reduction in the number of lead cystitis germs from visit 1 (start of treatment) to visit 3 (follow-up 1), measured by the proportion of responders (definition: from > 10^5 cfu/mL midstream urine at visit 1 decrease to < 10^3 cfu/mL midstream urine
End point description:	
Reduction in the number of lead cystitis germs from visit 1 (start of treatment) to visit 3 (follow-up 1), measured by the proportion of responders (definition: from > 10^5 cfu/mL midstream urine at visit 1 decrease to < 10^3 cfu/mL midstream urine at visit 3).	
End point type	Primary
End point timeframe:	
from visit 1 (start of treatment) to visit 3 (follow-up 1)	

End point values	Investigational product	Active Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	29		
Units: number of responders	10	15		

Statistical analyses

Statistical analysis title	Primary endpoint
Comparison groups	Investigational product v Active Comparator
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Mean difference (net)
Point estimate	-6.72
Confidence interval	
level	95 %
sides	1-sided
lower limit	-33.9

Notes:

[1] - The study was preliminary finished. However, based on the primary endpoint data available, a statistic analysis was performed. With a lower limit of the 95% CI of -33.90% of the treatment difference -6.27%, the non-inferiority of Angocin vs. Kepinol could not be concluded because the lower CI does not fulfil the condition -10.00% < lower CI. Keeping in mind that only 51 patients (instead of 356 patients planned) completed the study these results are limited.

Secondary: Change in general complaints and symptoms from visit 1 to visit 3

End point title	Change in general complaints and symptoms from visit 1 to visit 3

End point description:

Change in number of general symptoms or complaints

End point type	Secondary

End point timeframe:

visit 1 to visit 3

End point values	Investigational product	Active Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	51		
Units: percentage of patients	95	96		

Statistical analyses

Statistical analysis title	General complaints and symptoms

Statistical analysis description:

Decrease of signs of general complaints and symptoms

Comparison groups	Investigational product v Active Comparator
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9275
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Duration until being symptom-free

End point title	Duration until being symptom-free

End point description:

Median of the time until subjects are symptom-free. ITT population. The duration until freedom from symptoms is defined as the time span (number of treatment days) until the disappearance of all complaints/symptoms that the patient should record in the diary from visit 1 to visit 2.

End point type	Secondary

End point timeframe:

Visit 1 to Visit 2

End point values	Investigational product	Active Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[2]	51		
Units: median days	7	4		

Notes:

[2] - for one subject, diary was missing

Statistical analyses

Statistical analysis title	Time until being symptom-free

Statistical analysis description:

Time until being symptom-free in the ITT set.

Comparison groups	Investigational product v Active Comparator
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.11
Method	Chi-squared
Confidence interval	
level	95 %

Secondary: Physicians' assessment of effectiveness at visit 3

End point title	Physicians' assessment of effectiveness at visit 3

End point description: Number of patients who have recovered at visit 3 in the PP set.	
End point type	Secondary
End point timeframe: visit 3	

End point values	Investigational product	Active Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	29		
Units: Number of patients	17	29		

Statistical analyses

Statistical analysis title	Efficacy at visit 3
Comparison groups	Investigational product v Active Comparator
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0313
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided

Secondary: Relapse frequency or new infections between visit 3 and visit 4

End point title	Relapse frequency or new infections between visit 3 and visit 4
End point description: number of patients who experience a relapse (reoccurence of signs and symptoms within 14 days)	
End point type	Secondary
End point timeframe: visit 3 and visit 4	

End point values	Investigational product	Active Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	29		
Units: number of patients	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of the course of the disease by the physician on visit 2 (day 8)

End point title	Evaluation of the course of the disease by the physician on visit 2 (day 8)
End point description: Number of patients without symptoms at visit 2, ITT-set	
End point type	Secondary
End point timeframe: visit 2	

End point values	Investigational product	Active Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	51		
Units: number of patients recovered	30	41		

Statistical analyses

Statistical analysis title	Course of disease
Comparison groups	Active Comparator v Investigational product
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1067
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in dysuria from visit 1 to visit 3

End point title	Change in dysuria from visit 1 to visit 3
End point description: Decrease in signs of disease in dysuria	
End point type	Secondary
End point timeframe: visit 1 to visit 3	

End point values	Investigational product	Active Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	51		
Units: percentage of patients	95	94		

Statistical analyses

Statistical analysis title	Dysuria
Comparison groups	Investigational product v Active Comparator
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7585
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in pollakisuria from visit 1 to visit 3

End point title	Change in pollakisuria from visit 1 to visit 3
End point description: Decrease in signs of pollakisuria	
End point type	Secondary
End point timeframe: visit 1 to visit 3	

End point values	Investigational product	Active Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	51		
Units: percentage of patients	98	94		

Statistical analyses

Statistical analysis title	Pollakisuria
Statistical analysis description: Decrease in pollakisuria score	
Comparison groups	Investigational product v Active Comparator

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3508
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in nocturia from visit 1 to visit 3

End point title	Change in nocturia from visit 1 to visit 3
End point description: Decrease in signs of nocturia	
End point type	Secondary
End point timeframe: visit 1 to visit 3	

End point values	Investigational product	Active Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	51		
Units: percentage of patients	93	93		

Statistical analyses

Statistical analysis title	Nocturia
Statistical analysis description: Decrease in nocturia score	
Comparison groups	Investigational product v Active Comparator
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9302
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in urinary incontinence

End point title	Change in urinary incontinence
End point description: Decrease in signs of disease in urinary incontinence	
End point type	Secondary
End point timeframe: visit 1 to visit 3	

End point values	Investigational product	Active Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	51		
Units: percentage of subjects	90	94		

Statistical analyses

Statistical analysis title	Urinary incontinence
Statistical analysis description: Change in urinary incontinence score	
Comparison groups	Investigational product v Active Comparator
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6148
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: serious adverse events within 24 hours	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups	
Reporting group title	Investigational product
Reporting group description: Investigational drug	
Reporting group title	Active comparator
Reporting group description: Active comparator	

Serious adverse events	Investigational product	Active comparator	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 45 (2.22%)	1 / 51 (1.96%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Atrial fibrillation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 51 (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			
Appendicitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 51 (1.96%)	
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: 5 %

Non-serious adverse events	Investigational product	Active comparator	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 45 (8.89%)	6 / 51 (11.76%)	
Investigations			
C-reactive protein increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	1 / 51 (1.96%)	
occurrences (all)	1	1	
Disturbance in attention			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain lower			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal pain			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	2 / 51 (3.92%)	
occurrences (all)	0	2	
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 51 (0.00%)	
occurrences (all)	0	0	
Eczema			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Skin exfoliation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Skin disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Psychiatric disorders			
Restlessness			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

Flank pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 51 (1.96%)	
occurrences (all)	0	1	
Infections and infestations			
Pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 51 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Diabetes mellitus			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 51 (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 August 2011	mainly addition of new study sites, addition of beta-defensin 2 investigation in one study center, prolongation of trial duration
13 October 2011	mainly addition of further study centers, prolongation of trial duration
05 January 2012	mainly addition of further study centers
24 May 2012	mainly inclusion of patients >65 years, omission of positive nitrite as inclusion criterium, prolongation of study duration

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Study was prematurely finalized due to deficient recruitment. Only one center (03) fulfilled satisfying recruitment numbers. Responder rates in the remaining centres were below the rates of centre 03.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28352615