Clinical trial results:
Carriage of 3GCREB in patients at risk for relapsing infection: randomized controlled trial of intestinal decolonization with colistin plus rifaximin.

Summary

EudraCT number	2014-000180-41
Trial protocol	DE
Global end of trial date	02 December 2016

Results information

Result version number	v1 (current)
This version publication date	03 September 2020
First version publication date	03 September 2020

Trial information

Trial identification

Sponsor protocol code	P000176

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	German Clinical Trials Register: DRKS00006330

Notes:

Sponsors

Sponsor organisation name	Medical Center - University of Freiburg
Sponsor organisation address	Breisacher Str. 153, Freiburg, Germany, 79110
Public contact	Clinical Trial Information, Clinical Trials Unit of the Medical Center - University of Freiburg, 49 761270-73800, andrea.kunzmann@uniklinik-freiburg.de
Scientific contact	Clinical Trial Information, Clinical Trials Unit of the Medical Center - University of Freiburg, 49 761270-73800, andrea.kunzmann@uniklinik-freiburg.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	02 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 December 2016
Global end of trial reached?	Yes
Global end of trial date	02 December 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess whether decolonization treatment with oral non-absorbable drugs is superior to watch & wait in eradicating 3GCREB from the intestinal tract and prevent infection

Protection of trial subjects:

The underlying principles for the independent Data Safety Monitoring Committee are ethical and safety aspects for the patients. The DSMC examines, whether the conduct of the trial is still ethically justifiable, whether security of the patients is ensured, and whether the process of the trial is acceptable. The DSMC will be informed about the adherence to the protocol, the patient recruitment, and the observed serious adverse events. This clinical trial was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 4
Worldwide total number of subjects	4
EEA total number of subjects	4

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)	1

From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Six patients were enrolled to the trial within 12 months, 4 of them were randomized (3 to placebo/control group, 1 to interventional group) and evaluated in this CSR; two patients were screening failures, one of them due to planned pregnancy. First patient in: 16.11.2015, last patient out: 04.02.2017

Pre-assignment

Screening details:

Patients with relapsing infection and gut colonization with 3GCREB of both genders

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Colistin and rifaximin

Arm description:

4 x 2 million units per day colistin and 2 x 400 mg rifaximin

Arm type	Experimental
Investigational medicinal product name	Colistin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

4 x 2 million units per day, daily during 3 weeks

Investigational medicinal product name	Rifaximin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 x 400 mg per day, daily during 3 weeks

Arm title	Watch and wait

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Colistin and rifaximin	Watch and wait
Started	1	3
Completed	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Colistin and rifaximin
Reporting group description:	
4 x 2 million units per day colistin and 2 x 400 mg rifaximin	
Reporting group title	Watch and wait
Reporting group description: -	

Reporting group values	Colistin and rifaximin	Watch and wait	Total
Number of subjects	1	3	4
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)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	1	1
From 65-84 years	1	2	3
85 years and over	0	0	0
Years of age	0	0	0
Gender categorical Units: Subjects			
Female	0	2	2
Male	1	1	2

End points

End points reporting groups

Reporting group title	Colistin and rifaximin
Reporting group description:	
4 x 2 million units per day colistin and 2 x 400 mg rifaximin	
Reporting group title	Watch and wait
Reporting group description: -	

Primary: 3GCREB eradication

End point title	3GCREB eradication[1]
End point description:	
No evidence for colonization with 3GCREB by rectal swab (preferably; alternatively stool cultures) performed at visit 3 (EOT)	
End point type	Primary
End point timeframe:	
Visit 3 (EOT)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analysis could be performed due to the small number of patients.

End point values	Colistin and rifaximin	Watch and wait		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	3		
Units: Number of patients	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Early 3GCREB decolonization

End point title	Early 3GCREB decolonization
End point description:	
Early 3GCREB decolonization on days 8-12 after treatment initiation (visit 2)	
End point type	Secondary
End point timeframe:	
8-12 days after treatment initiation (Visit 2)	

End point values	Colistin and rifaximin	Watch and wait		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[2]	3		
Units: Number of patients	1	1		

Notes:

[2] - antibiotics use for urinary infection

Statistical analyses

No statistical analyses for this end point

Secondary: Late 3GCREB decolonization

End point title	Late 3GCREB decolonization

End point description:

Late 3GCREB decolonization 9 weeks after EOT (visit 5)

End point type	Secondary

End point timeframe:

9 weeks after EOT (visit 5)

End point values	Colistin and rifaximin	Watch and wait		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	3		
Units: Number of patients		0		

Notes:

[3] - unclear, visit not performed

Statistical analyses

No statistical analyses for this end point

Secondary: Any infection which requires antibiotic therapy

End point title	Any infection which requires antibiotic therapy

End point description:

Any infection which requires antibiotic therapy until 9 weeks after EOT visit (visit 5)

End point type	Secondary

End point timeframe:

Until 9 weeks after EOT (visit 5)

End point values	Colistin and rifaximin	Watch and wait		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	3		
Units: Infection occured	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Infection originating from gastrointestinal tract microflora

End point title	Infection originating from gastrointestinal tract microflora

End point description:

Infection originating from gastrointestinal tract microflora (including urinary tract infection) which requires antibiotic therapy until 9 weeks after EOT visit (visit 5)

End point type	Secondary

End point timeframe:

Until 9 weeks after EOT visit (visit 5)

End point values	Colistin and rifaximin	Watch and wait		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	3		
Units: Infection occured	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Intestinal carriage of colistin- and rifaximin-resistant 3GCREB

End point title	Intestinal carriage of colistin- and rifaximin-resistant 3GCREB

End point description:

End point type	Secondary

End point timeframe:

9 weeks after EOT (visit 5)

End point values	Colistin and rifaximin	Watch and wait		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	3		
Units: 3GCREB carriage present		3		

Notes:

[4] - unclear, visit not performed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Until 9 weeks after EOT visit (visit 5)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20

Reporting groups	
Reporting group title	Colistin plus rifaximin
Reporting group description: -	
Reporting group title	Watch and wait
Reporting group description: -	

Serious adverse events	Colistin plus rifaximin	Watch and wait	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	0 / 3 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Colistin plus rifaximin	Watch and wait	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
Gastrointestinal disorders			
Globus sensation in the throat			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Wound upper lip with bleeding and exanthema thighs and buttocks			
subjects affected / exposed	0 / 1 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

Pain in the lumbar spine area subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2015	The background of the first amendment was the discussion which has arisen after completion of the study protocol, which sample is the optimal starting material for the detection of multidrugresistant bacteria. Therefore, both materials, rectal swab and stool sample, were included as study material. In the former versions of the protocol, only rectal swab is mentioned.
02 February 2016	The background of the second amendment was to simplify the inclusion and exclusion criteria in order to enhance the recruitment. Therefore inclusion criteria number 3 was edited as follows: a second infection WITHOUT microbiological documentation can be accepted if it can be considered as relapsing infection with the same clinical focus based on clinical judgement and there has been no other relevant pathogen for this episode and the episode required antibiotic treatment considered adequate and clinically effective).

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.

The study has been early terminated by the Sponsor. The main reason for premature study termination was the lower than expected patient recruitment.

Notes: