Clinical trial results:
A randomised, double-blind, double-dummy, multi-centre, comparative parallel-group study to evaluate the efficacy of oral Rifamycin SV-MMX® 400 mg b.i.d. vs. Rifamycin SV-MMX® 600 mg t.i.d. vs. placebo in the treatment of acute uncomplicated diverticulitis

Summary

EudraCT number	2012-003300-13
Trial protocol	HU DE IT RO LT SK LV
Global end of trial date	18 April 2017

Results information

Result version number	v1 (current)
This version publication date	26 January 2020
First version publication date	26 January 2020

Trial information

Trial identification

Sponsor protocol code	RIT-4/DIV

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01847664
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dr. Falk Pharma GmbH
Sponsor organisation address	Leinenweberstrasse 5, Freiburg, Germany, 79288
Public contact	Dept. of Clin. Res. & Development, Dr. Falk Pharma GmbH, +49 76115140, zentrale@drfalkpharma.de
Scientific contact	Dept. of Clin. Res. & Development, Dr. Falk Pharma GmbH, +49 76115140, zentrale@drfalkpharma.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	19 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare the efficacy of Rifamycin SV-MMX® 400 mg b.i.d. vs. Rifamycin SV-MMX® 600 mg t.i.d. vs. placebo, in patients with acute uncomplicated diverticulitis.

Protection of trial subjects:

Close supervision of subjects by implementing interim visits every 3 days to guarantee their safety and wellbeing. Prior to recruitment of patients, all relevant documents of the clinical study were submitted and approved by the Independent Ethics Committees (IECs) responsible for the participating investigators. Written consent documents embodied the elements of informed consent as described in the Declaration of Helsinki, the ICH Guidelines for Good Clinical Practice (GCP) and were in accordance with all applicable laws and regulations. The informed consent form and patient information sheet described the planned and permitted uses, transfers and disclosures of the patient's personal data and personal health information for purposes of conducting the study. The informed consent form and the patient information sheet further explained the nature of the study, its objectives and potential risks and benefits as well as the date informed consent was given. Before being enrolled in the clinical trial, every patient was informed that participation in this trial was voluntary and that he/she could withdraw from the study at any time without giving a reason and without having to fear any loss in his/her medical care. The patient’s consent was obtained in writing before the start of the study. By signing the informed consent, the patient declared that he/she was participating voluntarily and intended to follow the study protocol instructions and the instructions of the investigator and to answer the questions asked during the course of the trial.

Background therapy:

None

Evidence for comparator:

Not applicable

Actual start date of recruitment	07 June 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 13
Country: Number of subjects enrolled	Slovakia: 24
Country: Number of subjects enrolled	Germany: 78
Country: Number of subjects enrolled	Hungary: 42
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Lithuania: 38

Worldwide total number of subjects	201
EEA total number of subjects	201

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)	142
From 65 to 84 years	59
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 204 patients were randomised from Germany, Hungary, Italy, Lithuania, Romania and Slovakia.

Pre-assignment

Screening details:

Patients signing the informed consent form were screened for up to 4 days to evaluate eligibility for the study. A total of 300 patients was screened for enrolment into the study. 96 patients could not be randomised.

Period 1

Period 1 title	Double-blind, 10 days treatment phase (overall period)
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:

The study was to be conducted using the double-dummy technique to guarantee the double-blinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Rifamycin 400mg BID

Arm description:

10-day treatment with Rifamycin SV-MMX® 400 mg b.i.d., 800 mg/day

Arm type	Experimental
Investigational medicinal product name	Rifamycin SV-MMX®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Rifamycin SV-MMX® 400 mg b.i.d., 800 mg/day

Arm title	Rifamycin 600mg TID

Arm description:

10-day treatment with Rifamycin SV-MMX® 600 mg t.i.d., 1800 mg/day

Arm type	Experimental
Investigational medicinal product name	Rifamycin SV-MMX®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Rifamycin SV-MMX® 600 mg t.i.d., 1800 mg/day

Arm title	Placebo

Arm description:

10-day treatment with Rifamycin SV-MMX® placebo tablets

Arm type	Placebo

Investigational medicinal product name	Rifamycin SV-MMX® Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo

Number of subjects in period 1	Rifamycin 400mg BID	Rifamycin 600mg TID	Placebo
Started	82	79	40
Completed	70	70	35
Not completed	12	9	5
Adverse event, non-fatal	2	3	1
Lack of patient's cooperation	5	-	3
Non-eligibility detected after randomisation	1	4	1
Lack of efficacy	4	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Rifamycin 400mg BID
Reporting group description:	
10-day treatment with Rifamycin SV-MMX® 400 mg b.i.d., 800 mg/day	
Reporting group title	Rifamycin 600mg TID
Reporting group description:	
10-day treatment with Rifamycin SV-MMX® 600 mg t.i.d., 1800 mg/day	
Reporting group title	Placebo
Reporting group description:	
10-day treatment with Rifamycin SV-MMX® placebo tablets	

Reporting group values	Rifamycin 400mg BID	Rifamycin 600mg TID	Placebo
Number of subjects	82	79	40
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)	53	60	29
From 65-84 years	29	19	11
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	59.7	58.4	56.8
standard deviation	± 10.67	± 11.13	± 13.8
Gender categorical Units: Subjects			
Female	44	49	27
Male	38	30	13
Signs of inflammation of colonic wall Units: Subjects			
No	1	1	0
Yes	81	78	40
Presence of complications (US/CT) findings Units: Subjects			
No	82	79	40
Yes	0	0	0
Worst left lower quadrant pain over the last 24 hours (0-10cm VAS)			
Intensity of left lower quadrant pain was assessed by a 0 to 10cm visual analogue scale (VAS). Higher values indicate more pain.			
Units: cm			

arithmetic mean	5.91	5.36	5.46
standard deviation	± 2.095	± 2.142	± 2.193
C-reactive protein (CRP) at baseline [mg/l]			
Units: mg/l			
median	36.75	19.0	31.5
full range (min-max)	2.1 to 195.0	1.2 to 180	1.0 to 207

Reporting group values	Total		
Number of subjects	201		
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)	142		
From 65-84 years	59		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	120		
Male	81		
Signs of inflammation of colonic wall			
Units: Subjects			
No	2		
Yes	199		
Presence of complications (US/CT) findings			
Units: Subjects			
No	201		
Yes	0		
Worst left lower quadrant pain over the last 24 hours (0-10cm VAS)			
Intensity of left lower quadrant pain was assessed by a 0 to 10cm visual analogue scale (VAS). Higher values indicate more pain.			
Units: cm			
arithmetic mean			
standard deviation	-		
C-reactive protein (CRP) at baseline [mg/l]			
Units: mg/l			
median			
full range (min-max)	-		

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) includes all randomised patients who received at least one dose of IMP.

Reporting group values	Full analysis set		
Number of subjects	201		
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)	142		
From 65-84 years	59		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	58.6		
standard deviation	± 11.52		
Gender categorical Units: Subjects			
Female	120		
Male	81		
Signs of inflammation of colonic wall Units: Subjects			
No	2		
Yes	199		
Presence of complications (US/CT) findings Units: Subjects			
No	201		
Yes	0		
Worst left lower quadrant pain over the last 24 hours (0-10cm VAS)			
Intensity of left lower quadrant pain was assessed by a 0 to 10cm visual analogue scale (VAS). Higher values indicate more pain.			
Units: cm			
arithmetic mean	5.6		
standard deviation	± 2.137		
C-reactive protein (CRP) at baseline [mg/l] Units: mg/l			
median	29.9		
full range (min-max)	1.0 to 207.0		

End points

End points reporting groups

Reporting group title	Rifamycin 400mg BID
Reporting group description: 10-day treatment with Rifamycin SV-MMX® 400 mg b.i.d., 800 mg/day	
Reporting group title	Rifamycin 600mg TID
Reporting group description: 10-day treatment with Rifamycin SV-MMX® 600 mg t.i.d., 1800 mg/day	
Reporting group title	Placebo
Reporting group description: 10-day treatment with Rifamycin SV-MMX® placebo tablets	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis set (FAS) includes all randomised patients who received at least one dose of IMP.	

Primary: Rate of patients with treatment success at the day 10 visit (Primary Endpoint, Stage 1= Primary Analysis)

End point title	Rate of patients with treatment success at the day 10 visit (Primary Endpoint, Stage 1= Primary Analysis)

End point description:

Denominator: all patients in the analysis set.
Treatment success was 'Yes', if all of the following were fulfilled:
- Absence of fever (i.e., body temperature < 38°C) at the visit,
- Adequate relief of left lower quadrant pain defined as worst intensity during the last 24 h (visual analogue scale on day of visit) of < 4,
- Within the last 48 h, no intake of pain medication except for chronic low dose acetylsalicylic acid ≤ 100 mg/d for reasons other than pain,
- Leucocytes ≤ ULN at the visit,
- CRP ≤ ULN or at least 50% improvement compared to baseline at the visit,
- No complications of acute diverticulitis, No need for extra antimicrobial treatment due to acute diverticulitis, No need for surgical intervention of acute diverticulitis, No hospitalisation due to acute diverticulitis up to the visit.

Treatment success was 'No', if at least one of the above criteria was violated, and for patients withdrawn due to lack of efficacy.

End point type	Primary

End point timeframe:

Visit Day 10

End point values	Rifamycin 400mg BID	Rifamycin 600mg TID	Placebo	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	74[1]	74[2]	37[3]	185[4]
Units: Subjects				
Not assessable	4	10	8	22
No	22	26	11	59
Yes	48	38	18	104

Notes:

[1] - Stage 1 Results = Patients included in interim analysis

[2] - Stage 1 Results = Patients included in interim analysis

[3] - Stage 1 Results = Patients included in interim analysis

[4] - Stage 1 Results = Patients included in interim analysis

Statistical analyses

Statistical analysis title	Rifamycin 600mg TID versus Placebo

Statistical analysis description:

Rifamycin 600mg TID versus Placebo
Rifamycin 600mg TID versus Placebo was first to be tested according to the hierarchically ordered hypotheses.
Rifamycin 400mg BID versus Placebo was only to be tested if Rifamycin 600mg TID was statistically significantly superior to Placebo.
Unadjusted one-sided p-values were to be compared with the one-sided Stage 1 alpha of 0.0021.
The overall adjusted p-value adjusts for the adaptive design and considers the hierarchy of the hypotheses.

Comparison groups	Rifamycin 600mg TID v Placebo
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.562 [6]
Method	Normal approximation test for rates
Parameter estimate	Risk difference (RD)
Point estimate	0.027
Confidence interval	
level	Other: 99.58 %
sides	2-sided
lower limit	-0.2611
upper limit	0.3151

Notes:

[5] - Not assessable results were set to 'No' in this analysis.

[6] - Overall adjusted one-sided p-value calculated using ADDPLAN® Version 6.1.1 (licensed by ADDPLAN, Inc., an ICON Clinical Research, LLC company).
Unadjusted p-value: 0.3942

Statistical analysis title	Rifamycin 400mg BID versus Placebo

Statistical analysis description:

Rifamycin 400mg BID versus Placebo
Rifamycin 600mg TID versus Placebo was first to be tested according to the hierarchically ordered hypotheses.
Rifamycin 400mg BID versus Placebo was not to be tested as Rifamycin 600mg TID was not statistically significantly superior to Placebo.
The unadjusted one-sided p-value was exploratively compared with the one-sided Stage 1 alpha of 0.0021.
The overall adjusted p-value adjusts for the adaptive design and considers the hierarchy of the hypotheses.

Comparison groups	Rifamycin 400mg BID v Placebo
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.562 [8]
Method	Normal approximation test for rates
Parameter estimate	Risk difference (RD)
Point estimate	0.1622

Confidence interval	
level	Other: 99.58 %
sides	2-sided
lower limit	-0.1217
upper limit	0.446

Notes:

[7] - Not assessable results were set to 'No' in this analysis.

[8] - Overall adjusted one-sided p-value calculated using ADDPLAN® Version 6.1.1 (licensed by ADDPLAN, Inc., an ICON Clinical Research, LLC company).
Unadjusted p-value: 0.0505

Primary: Rate of patients with treatment success at the day 10 visit (Primary Endpoint, Stage 1 and Overrun)

End point title	Rate of patients with treatment success at the day 10 visit (Primary Endpoint, Stage 1 and Overrun)

End point description:

Denominator: all patients in the analysis set.
Treatment success was 'Yes', if all of the following were fulfilled:
- Absence of fever (i.e., body temperature < 38°C) at the visit,
- Adequate relief of left lower quadrant pain defined as worst intensity during the last 24 h (visual analogue scale on day of visit) of < 4,
- Within the last 48 h, no intake of pain medication except for chronic low dose acetylsalicylic acid ≤ 100 mg/d for reasons other than pain,
- Leucocytes ≤ ULN at the visit,
- CRP ≤ ULN or at least 50% improvement compared to baseline at the visit,
- No complications of acute diverticulitis, No need for extra antimicrobial treatment due to acute diverticulitis, No need for surgical intervention of acute diverticulitis, No hospitalisation due to acute diverticulitis up to the visit.

Treatment success was 'No', if at least one of the above criteria was violated, and for patients withdrawn due to lack of efficacy.

End point type	Primary

End point timeframe:

Visit Day 10

End point values	Rifamycin 400mg BID	Rifamycin 600mg TID	Placebo	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	82	79	40	201
Units: Subjects				
Not asessable	5	10	9	24
No	26	30	12	68
Yes	51	39	19	109

Statistical analyses

Statistical analysis title	Rifamycin 600mg TID versus Placebo

Statistical analysis description:

Rifamycin 600mg TID versus Placebo
Rifamycin 600mg TID versus Placebo was first to be tested according to the hierarchically ordered hypotheses.
Rifamycin 400mg BID versus Placebo was only to be tested if Rifamycin 600mg TID was statistically significantly superior to Placebo.
Unadjusted one-sided p-values were to be compared with the one-sided Stage 1 alpha of 0.0021.

The overall adjusted p-value adjusts for the adaptive design and considers the hierarchy of the hypotheses.

Comparison groups	Rifamycin 600mg TID v Placebo
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.5882 [10]
Method	Normal approximation test for rates
Parameter estimate	Risk difference (RD)
Point estimate	0.0187
Confidence interval	
level	Other: 99.58 %
sides	2-sided
lower limit	-0.2589
upper limit	0.2962

Notes:

[9] - Not assessable results were set to 'No' in this analysis.

[10] - Overall adjusted one-sided p-value calculated using ADDPLAN® Version 6.1.1 (licensed by ADDPLAN, Inc., an ICON Clinical Research, LLC company).
Unadjusted p-value: 0.4237

Statistical analysis title	Rifamycin 400mg BID versus Placebo

Statistical analysis description:

Rifamycin 400mg BID versus Placebo
Rifamycin 600mg TID versus Placebo was first to be tested according to the hierarchically ordered hypotheses.
Rifamycin 400mg BID versus Placebo was not to be tested as Rifamycin 600mg TID was not statistically significantly superior to Placebo.
The unadjusted one-sided p-value was exploratively compared with the one-sided Stage 1 alpha of 0.0021.
The overall adjusted p-value adjusts for the adaptive design and considers the hierarchy of the hypotheses.

Comparison groups	Placebo v Rifamycin 400mg BID
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.5882 [12]
Method	Normal approximation test for rates
Parameter estimate	Risk difference (RD)
Point estimate	0.147
Confidence interval	
level	Other: 99.58 %
sides	2-sided
lower limit	-0.1262
upper limit	0.4201

Notes:

[11] - Not assessable results were set to 'No' in this analysis.

[12] - Overall adjusted one-sided p-value calculated using ADDPLAN® Version 6.1.1 (licensed by ADDPLAN, Inc., an ICON Clinical Research, LLC company).
Unadjusted p-value: 0.0617

Statistical analysis title	Rifamycin 600mg TID versus Rifamycin 400mg BID

Statistical analysis description:

Exploratory comparison of Rifamycin 600mg TID versus Rifamycin 400mg BID

Comparison groups	Rifamycin 400mg BID v Rifamycin 600mg TID

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.1012 [14]
Method	Normal approximation test for rates
Parameter estimate	Risk difference (RD)
Point estimate	-0.1283
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2805
upper limit	0.0239

Notes:

[13] - Not assessable results were set to 'No' in this analysis.

[14] - Two-sided unadjusted p-value

Primary: Rate of patients with treatment success at the day 10 visit (sensitivity analysis using LOCF, Stage 1 and Overrun)

End point title	Rate of patients with treatment success at the day 10 visit (sensitivity analysis using LOCF, Stage 1 and Overrun)

End point description:

Denominator: all patients in the analysis set.
Sensitivity analysis for primary endpoint using last observation carried forward (LOCF).

End point type	Primary

End point timeframe:

Visit Day 10 (LOCF)

End point values	Rifamycin 400mg BID	Rifamycin 600mg TID	Placebo	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	82	79	40	201
Units: Subjects				
Not assessable	2	1	2	5
No	26	32	12	70
Yes	54	46	26	126

Statistical analyses

Statistical analysis title	Rifamycin 600mg TID versus Placebo

Statistical analysis description:

Rifamycin 600mg TID versus Placebo
Rifamycin 600mg TID versus Placebo was first to be tested according to the hierarchically ordered hypotheses.
Rifamycin 400mg BID versus Placebo was only to be tested if Rifamycin 600mg TID was statistically significantly superior to Placebo.
Unadjusted one-sided p-values were to be compared with the one-sided Stage 1 alpha of 0.0021.

Comparison groups	Rifamycin 600mg TID v Placebo

Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.7624 [16]
Method	Normal approximation test for rates

Notes:

[15] - Not assessable results were set to 'No' in this analysis.

[16] - Unadjusted one-sided p-value.

Statistical analysis title	Rifamycin 400mg BID versus Placebo

Statistical analysis description:

Rifamycin 400mg BID versus Placebo
Rifamycin 600mg TID versus Placebo was first to be tested according to the hierarchically ordered hypotheses.
Rifamycin 400mg BID versus Placebo was only to be tested if Rifamycin 600mg TID was statistically significantly superior to Placebo.
Unadjusted one-sided p-values were to be compared with the one-sided Stage 1 alpha of 0.0021.

Comparison groups	Placebo v Rifamycin 400mg BID
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.4629 [18]
Method	Normal approximation test for rates

Notes:

[17] - Not assessable results were set to 'No' in this analysis.

[18] - Unadjusted one-sided p-value.

Statistical analysis title	Rifamycin 600mg TID versus Rifamycin 400mg BID

Statistical analysis description:

Exploratory comparison of Rifamycin 600mg BID versus Rifamycin 400mg BID

Comparison groups	Rifamycin 400mg BID v Rifamycin 600mg TID
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.3187 [20]
Method	Normal approximation test for rates

Notes:

[19] - Not assessable results were set to 'No' in this analysis.

[20] - Two-sided unadjusted p-value.

Primary: Rate of patients with treatment success at the day 10 visit (sensitivity analysis based on patients with assessable treatment success at the day 10 visit, Stage 1 and Overrun)

End point title	Rate of patients with treatment success at the day 10 visit (sensitivity analysis based on patients with assessable treatment success at the day 10 visit, Stage 1 and Overrun)

End point description:

Denominator: Patients with assessable treatment success at the day 10 visit.
Sensitivity analysis for primary endpoint, excluding patients with not assessable treatment success at visit Day 10.

End point type	Primary

End point timeframe:

Visit Day 10

End point values	Rifamycin 400mg BID	Rifamycin 600mg TID	Placebo	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	77[21]	69[22]	31[23]	177[24]
Units: Subjects				
No	26	30	12	68
Yes	51	39	19	109

Notes:

[21] - Patients with assessable treatment success at the day 10 visit

[22] - Patients with assessable treatment success at the day 10 visit

[23] - Patients with assessable treatment success at the day 10 visit

[24] - Patients with assessable treatment success at the day 10 visit

Statistical analyses

Statistical analysis title	Rifamycin 600mg TID versus Placebo

Statistical analysis description:

Rifamycin 600mg TID versus Placebo
Rifamycin 600mg TID versus Placebo was first to be tested according to the hierarchically ordered hypotheses.
Rifamycin 400mg BID versus Placebo was only to be tested if Rifamycin 600mg TID was statistically significantly superior to Placebo.
Unadjusted one-sided p-values were to be compared with the one-sided Stage 1 alpha of 0.0021.

Comparison groups	Rifamycin 600mg TID v Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.6725 [26]
Method	Normal approximation test for rates

Notes:

[25] - Not assessable results were excluded from this analysis.

[26] - Unadjusted one-sided p-value.

Statistical analysis title	Rifamycin 400mg BID versus Placebo

Statistical analysis description:

Rifamycin 400mg BID versus Placebo
Rifamycin 600mg TID versus Placebo was first to be tested according to the hierarchically ordered hypotheses.
Rifamycin 400mg BID versus Placebo was only to be tested if Rifamycin 600mg TID was statistically significantly superior to Placebo.
Unadjusted one-sided p-values were to be compared with the one-sided Stage 1 alpha of 0.0021.

Comparison groups	Placebo v Rifamycin 400mg BID
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	= 0.3132 [28]
Method	Normal approximation test for rates

Notes:

[27] - Not assessable results were excluded from this analysis.

[28] - Unadjusted one-sided p-value.

	Rifamycin 600mg TID versus Rifamycin 400mg BID

Statistical analysis title	
Statistical analysis description:	
Exploratory comparison of Rifamycin 600mg BID versus Rifamycin 400mg BID	
Comparison groups	Rifamycin 400mg BID v Rifamycin 600mg TID
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.2283 [30]
Method	Normal approximation test for rates

Notes:

[29] - Not assessable results were excluded from this analysis.

[30] - Two-sided unadjusted p-value.

Secondary: Rate of patients with treatment success at visit Day 3

End point title	Rate of patients with treatment success at visit Day 3
End point description:	
Denominator: all patients in the analysis set. For definition of treatment success see description of primary endpoint.	
End point type	Secondary
End point timeframe:	
Visit Day 3	

End point values	Rifamycin 400mg BID	Rifamycin 600mg TID	Placebo	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	82	79	40	201
Units: Subjects				
Not assessable	4	2	6	12
No	51	57	20	128
Yes	27	20	14	61

Statistical analyses

Statistical analysis title	Rifamycin 600mg TID versus Placebo
Comparison groups	Rifamycin 600mg TID v Placebo
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.2693 [32]
Method	Normal approximation test for rates

Notes:

[31] - Not assessable results were set to 'No' in this analysis.

[32] - Exploratory unadjusted two-sided p-value.

Statistical analysis title	Rifamycin 400mg BID versus Placebo
Comparison groups	Placebo v Rifamycin 400mg BID

Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.82 [34]
Method	Normal approximation test for rates

Notes:

[33] - Not assessable results were set to 'No' in this analysis.

[34] - Exploratory unadjusted two-sided p-value.

Secondary: Rate of patients with treatment success at visit Day 7

End point title	Rate of patients with treatment success at visit Day 7

End point description:

Denominator: all patients in the analysis set.
For definition of treatment success see description of primary endpoint.

End point type	Secondary

End point timeframe:

Visit Day 7

End point values	Rifamycin 400mg BID	Rifamycin 600mg TID	Placebo	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	82	79	40	201
Units: Subjects				
Not assessable	7	3	6	16
No	30	36	13	79
Yes	45	40	21	106

Statistical analyses

Statistical analysis title	Rifamycin 600mg TID versus Placebo
Comparison groups	Rifamycin 600mg TID v Placebo
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	= 0.8474 [36]
Method	Normal approximation test for rates

Notes:

[35] - Not assessable results were set to 'No' in this analysis.

[36] - Exploratory unadjusted two-sided p-value.

Statistical analysis title	Rifamycin 400mg BID versus Placebo
Comparison groups	Placebo v Rifamycin 400mg BID

Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	= 0.8046 [38]
Method	Normal approximation test for rates

Notes:

[37] - Not assessable results were set to 'No' in this analysis.

[38] - Exploratory unadjusted two-sided p-value.

Secondary: Rate of patients with complete treatment success at visit Day 3

End point title	Rate of patients with complete treatment success at visit Day 3

End point description:

Complete treatment success is the same as treatment success, except that the criterion 'CRP ≤ ULN or at least 50% improvement compared to baseline at the visit' is 'CRP ≤ ULN at the visit'.

End point type	Secondary

End point timeframe:

Visit Day 3

End point values	Rifamycin 400mg BID	Rifamycin 600mg TID	Placebo	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	82	79	40	201
Units: Subjects				
Not assessable	1	2	3	6
No	72	67	37	176
Yes	9	10	0	19

Statistical analyses

Statistical analysis title	Rifamycin 600mg TID versus Placebo
Comparison groups	Placebo v Rifamycin 600mg TID
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	= 0.016 [40]
Method	Fisher exact

Notes:

[39] - Not assessable results were set to 'No' in this analysis.

[40] - Exploratory unadjusted two-sided p-value.

Statistical analysis title	Rifamycin 400mg BID versus Placebo
Comparison groups	Placebo v Rifamycin 400mg BID

Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	= 0.0296 [42]
Method	Fisher exact

Notes:

[41] - Not assessable results were set to 'No' in this analysis.

[42] - Exploratory unadjusted two-sided p-value.

Secondary: Rate of patients with complete treatment success at visit Day 7

End point title	Rate of patients with complete treatment success at visit Day 7

End point description:

Complete treatment success is the same as treatment success, except that the criterion 'CRP ≤ ULN or at least 50% improvement compared to baseline at the visit' is 'CRP ≤ ULN at the visit'.

End point type	Secondary

End point timeframe:

Visit Day 7

End point values	Rifamycin 400mg BID	Rifamycin 600mg TID	Placebo	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	82	79	40	201
Units: Subjects				
Not assessable	4	3	5	12
No	46	46	24	116
Yes	32	30	11	73

Statistical analyses

Statistical analysis title	Rifamycin 600mg TID versus Placebo
Comparison groups	Rifamycin 600mg TID v Placebo
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	= 0.3098 [44]
Method	Fisher exact

Notes:

[43] - Not assessable results were set to 'No' in this analysis.

[44] - Exploratory unadjusted two-sided p-value.

Statistical analysis title	Rifamycin 400mg BID versus Placebo
Comparison groups	Placebo v Rifamycin 400mg BID

Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority[45]
P-value	= 0.2325 [46]
Method	Fisher exact

Notes:

[45] - Not assessable results were set to 'No' in this analysis.

[46] - Exploratory unadjusted two-sided p-value.

Secondary: Rate of patients with complete treatment success at visit Day 10

End point title	Rate of patients with complete treatment success at visit Day 10

End point description:

Complete treatment success is the same as treatment success, except that the criterion 'CRP ≤ ULN or at least 50% improvement compared to baseline at the visit' is 'CRP ≤ ULN at the visit'.

End point type	Secondary

End point timeframe:

Visit Day 10

End point values	Rifamycin 400mg BID	Rifamycin 600mg TID	Placebo	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	82	79	40	201
Units: Subjects				
Not assessable	5	7	8	20
No	35	39	16	90
Yes	42	33	16	91

Statistical analyses

Statistical analysis title	Rifamycin 600mg TID versus Placebo
Comparison groups	Rifamycin 600mg TID v Placebo
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority[47]
P-value	= 1 [48]
Method	Fisher exact

Notes:

[47] - Not assessable results were set to 'No' in this analysis.

[48] - Exploratory unadjusted two-sided p-value.

Statistical analysis title	Rifamycin 400mg BID versus Placebo
Comparison groups	Placebo v Rifamycin 400mg BID

Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority[49]
P-value	= 0.2549 [50]
Method	Fisher exact

Notes:

[49] - Not assessable results were set to 'No' in this analysis.

[50] - Exploratory unadjusted two-sided p-value.

Secondary: Rate of patients with complete treatment success at visit Day 10 (LOCF)

End point title	Rate of patients with complete treatment success at visit Day 10 (LOCF)

End point description:

Complete treatment success is the same as treatment success, except that the criterion 'CRP ≤ ULN or at least 50% improvement compared to baseline at the visit' is 'CRP ≤ ULN at the visit'.

End point type	Secondary

End point timeframe:

Visit Day 10 (LOCF): Visit Day 10 analysis using last observation carried forward (LOCF).

End point values	Rifamycin 400mg BID	Rifamycin 600mg TID	Placebo	Full analysis set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	82	79	40	201
Units: Subjects				
Not assessable	1	1	2	4
No	37	41	17	95
Yes	44	37	21	102

Statistical analyses

Statistical analysis title	Rifamycin 600mg TID versus Placebo
Comparison groups	Rifamycin 600mg TID v Placebo
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority[51]
P-value	= 0.5677 [52]
Method	Fisher exact

Notes:

[51] - Not assessable results were set to 'No' in this analysis.

[52] - Exploratory unadjusted two-sided p-value.

Statistical analysis title	Rifamycin 400mg BID versus Placebo
Comparison groups	Placebo v Rifamycin 400mg BID

Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority[53]
P-value	= 1 [54]
Method	Fisher exact

Notes:

[53] - Not assessable results were set to 'No' in this analysis.

[54] - Exploratory unadjusted two-sided p-value.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Double-blind, 10 days treatment phase	
Adverse event reporting additional description:	
Treatment emergent adverse events are presented for the safety analysis set, which includes all randomised patients who received at least one dose of IMP and have at least one follow-up value for the safety variables to be analysed (n=199).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Rifamycin 400mg BID
Reporting group description:	
10-day treatment with Rifamycin SV-MMX® 400 mg b.i.d., 800 mg/day	
Reporting group title	Rifamycin 600mg TID
Reporting group description:	
10-day treatment with Rifamycin SV-MMX® 600 mg t.i.d., 1800 mg/day	
Reporting group title	Placebo
Reporting group description:	
10-day treatment with Rifamycin SV-MMX® placebo tablets	

Serious adverse events	Rifamycin 400mg BID	Rifamycin 600mg TID	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 81 (1.23%)	1 / 78 (1.28%)	0 / 40 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 81 (1.23%)	1 / 78 (1.28%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 1.5 %

Non-serious adverse events	Rifamycin 400mg BID	Rifamycin 600mg TID	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 81 (32.10%)	28 / 78 (35.90%)	10 / 40 (25.00%)

Injury, poisoning and procedural complications			
Muscle strain			
subjects affected / exposed	0 / 81 (0.00%)	0 / 78 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 81 (4.94%)	1 / 78 (1.28%)	1 / 40 (2.50%)
occurrences (all)	4	1	1
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 81 (9.88%)	4 / 78 (5.13%)	1 / 40 (2.50%)
occurrences (all)	8	4	1
General disorders and administration site conditions			
Facial pain			
subjects affected / exposed	0 / 81 (0.00%)	0 / 78 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 81 (1.23%)	3 / 78 (3.85%)	0 / 40 (0.00%)
occurrences (all)	1	3	0
Abdominal pain			
subjects affected / exposed	4 / 81 (4.94%)	2 / 78 (2.56%)	2 / 40 (5.00%)
occurrences (all)	4	2	2
Abdominal pain upper			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Colitis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 78 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	4 / 81 (4.94%)	2 / 78 (2.56%)	0 / 40 (0.00%)
occurrences (all)	4	2	0
Dry mouth			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Nausea			

subjects affected / exposed	3 / 81 (3.70%)	2 / 78 (2.56%)	2 / 40 (5.00%)
occurrences (all)	3	2	2
Vomiting			
subjects affected / exposed	2 / 81 (2.47%)	1 / 78 (1.28%)	0 / 40 (0.00%)
occurrences (all)	2	1	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 81 (2.47%)	1 / 78 (1.28%)	0 / 40 (0.00%)
occurrences (all)	2	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 81 (2.47%)	1 / 78 (1.28%)	0 / 40 (0.00%)
occurrences (all)	2	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 81 (0.00%)	0 / 78 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	0 / 81 (0.00%)	2 / 78 (2.56%)	0 / 40 (0.00%)
occurrences (all)	0	2	0
Myalgia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 78 (1.28%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 81 (0.00%)	3 / 78 (3.85%)	0 / 40 (0.00%)
occurrences (all)	0	3	0
Diverticulitis			
subjects affected / exposed	1 / 81 (1.23%)	2 / 78 (2.56%)	0 / 40 (0.00%)
occurrences (all)	1	2	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 81 (1.23%)	0 / 78 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Urinary tract infection			
subjects affected / exposed	0 / 81 (0.00%)	0 / 78 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1

Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 78 (0.00%) 0	1 / 40 (2.50%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2013	This amendment was primarily required to take into account the new information of the latest Investigator's Brochure (IB) for Rifamycin SV-MMX®. Additionally, the Federal Institute for Drugs and Medical Devices (BfArM) in Germany wished, during the approval process, to include a second ultrasonography or computed tomography after treatment end. Finally, some further changes were introduced to the protocol (e.g. inclusion criteria, concomitant medication etc.).
04 May 2015	This amendment was primarily required to take into account the new information of the latest Investigator's Brochure (IB) for Rifamycin SV-MMX®. In addition, some administrative amendments were introduced to the protocol to verbalize more detailed guidance as per the current status quo.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported