



Clinical trial results:

A Study to Assess Repeat Treatment Efficacy and Safety of Rifaximin 550 mg TID in Subjects with Irritable Bowel Syndrome with Diarrhoea (IBS-D)

Summary

EudraCT number	2013-002394-22
Trial protocol	GB DE
Global end of trial date	12 June 2014

Results information

Result version number	v1 (current)
This version publication date	27 November 2021
First version publication date	27 November 2021

Trial information

Trial identification

Sponsor protocol code	RFIB3053
-----------------------	----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01543178
WHO universal trial number (UTN)	-
Other trial identifiers	Name: TARGET3

Notes:

Sponsors

Sponsor organisation name	Salix Pharmaceuticals Inc.
Sponsor organisation address	400 Somerset Corporate Blvd. , Bridgewater, United States, NJ 08807
Public contact	Customer Support, Salix Pharmaceuticals Inc., 1 800-321-4576,
Scientific contact	Customer Support, Salix Pharmaceuticals Inc., 1 800-321-4576,

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	27 August 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 June 2014
Global end of trial reached?	Yes
Global end of trial date	12 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of repeat treatment with rifaximin 550mg TID in subjects with IBS-D who responded to initial treatment with rifaximin 550 mg TID.

Protection of trial subjects:

No specific measures

Background therapy:

None

Evidence for comparator:

Placebo used in order to demonstrate a treatment effect

Actual start date of recruitment	17 February 2012
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	United Kingdom: 12
Country: Number of subjects enrolled	United States: 2567
Worldwide total number of subjects	2579
EEA total number of subjects	12

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)	2339
From 65 to 84 years	239
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participating sites were located in the USA, UK and Germany, although no patients were recruited in Germany

Pre-assignment

Screening details:

Subjects were screening over 10 ± 3 days, when they received single-blind placebo and completed a daily irritable bowel syndrome (IBS) symptom diary. Average daily symptom scores ≥ 3 for abdominal pain and for bloating, and ≥ 2 days/week with stool consistency of 6-7 (Bristol Stool-Form Scale), were required to start open-label rifaximin

Period 1

Period 1 title	Open-label phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Open-label rifaximin
------------------	----------------------

Arm description:

Subjects received open-label rifaximin for 2 weeks with a 4-week treatment-free follow-up. Responders continued into Maintenance Phase 1 (treatment free). Non-responders were withdrawn from the study. Subjects continued in Maintenance Phase 1 for up to 18 weeks, depending upon recurrence. Subjects who met the criteria for recurrence were scheduled to enter the Double-Blind Repeat (DBR) Treatment Phase. Subjects who did not meet the recurrence criteria by the end of Maintenance Phase 1 were withdrawn from the study.

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

Dosage and administration details:

One 550 mg tablet three times daily (TID)

Number of subjects in period 1	Open-label rifaximin
Started	2579
Completed	636
Not completed	1943
Consent withdrawn by subject	135
No recurrence	133
Adverse event, non-fatal	80
Other	20
Pregnancy	2
Randomization closed	171

Non-compliance	44
Lost to follow-up	101
Non-responder	1257

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-blind rifaximin

Arm description:

Subjects received rifaximin for 2 weeks with a 4-week treatment-free follow-up (Double-blind Repeat [DBR] Treatment Phase). The 4-week follow-up phase was the Primary Evaluation Period (PEP) for repeat treatment efficacy. Subjects then entered into Maintenance Phase 2 (6-weeks treatment-free period) followed by a second retreatment with rifaximin for 2 weeks with a 4-week treatment-free follow-up (Second Repeat Treatment [SRT] Phase).

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

Dosage and administration details:

One 550 mg tablet three times daily (TID)

Arm title	Double-blind placebo
------------------	----------------------

Arm description:

Subjects received placebo rifaximin for 2 weeks with a 4-week treatment-free follow-up (Double-blind Repeat [DBR] Treatment Phase). The 4-week follow-up phase was the Primary Evaluation Period (PEP) for repeat treatment efficacy. Subjects then entered into Maintenance Phase 2 (6-weeks treatment-free period) followed by a second retreatment with placebo rifaximin for 2 weeks with a 4-week treatment-free follow-up (Second Repeat Treatment [SRT] Phase).

Arm type	Placebo
Investigational medicinal product name	Rifamaxin placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One tablet three time daily (TID)

Number of subjects in period 2	Double-blind rifaximin	Double-blind placebo
Started	328	308
Second repeat treatment started	295	283
Completed	284	271
Not completed	44	37
Consent withdrawn by subject	23	19
Adverse event, non-fatal	1	2
Other	4	3
Non-compliance	6	7
Lost to follow-up	10	6

Baseline characteristics

Reporting groups

Reporting group title	Open-label phase
-----------------------	------------------

Reporting group description: -

Reporting group values	Open-label phase	Total	
Number of subjects	2579	2579	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	2339	2339	
From 65-84 years	239	239	
85 years and over	1	1	
Age continuous			
Units: years			
median	47.0		
full range (min-max)	18 to 85	-	
Gender categorical			
Units: Subjects			
Female	1760	1760	
Male	819	819	
Race			
Units: Subjects			
American Indian/Alaskan Native	20	20	
Asian	101	101	
Black/African American	289	289	
Native Hawaiian/Pacific Islander	5	5	
White	2155	2155	
Other	9	9	
Ethnicity			
Units: Subjects			
Hispanic or Latino	644	644	
Not Hispanic or Latino	1933	1933	
Missing	2	2	
Body mass index			
Units: kg/m ²			
arithmetic mean	30.1		
standard deviation	± 8.0	-	

Subject analysis sets

Subject analysis set title	Double-blind rifaximin
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients at baseline who were later randomized to rifaximin in the DBR phase

Subject analysis set title	Double-blind placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients at baseline who were later randomized to placebo rifaximin in the DBR phase

Reporting group values	Double-blind rifaximin	Double-blind placebo	
Number of subjects	328	308	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	289	279	
From 65-84 years	38	29	
85 years and over	1	0	
Age continuous			
Units: years			
median	50.0	46.0	
full range (min-max)	19 to 85	18 to 78	
Gender categorical			
Units: Subjects			
Female	222	219	
Male	106	89	
Race			
Units: Subjects			
American Indian/Alaskan Native	1	2	
Asian	15	9	
Black/African American	37	31	
Native Hawaiian/Pacific Islander	0	2	
White	273	262	
Other	2	2	
Ethnicity			
Units: Subjects			
Hispanic or Latino	74	76	
Not Hispanic or Latino	253	232	
Missing	1	0	
Body mass index			
Units: kg/m ²			
arithmetic mean	29.9	29.7	
standard deviation	± 7.6	± 6.5	

End points

End points reporting groups

Reporting group title	Open-label rifaximin
Reporting group description: Subjects received open-label rifaximin for 2 weeks with a 4-week treatment-free follow-up. Responders continued into Maintenance Phase 1 (treatment free). Non-responders were withdrawn from the study. Subjects continued in Maintenance Phase 1 for up to 18 weeks, depending upon recurrence. Subjects who met the criteria for recurrence were scheduled to enter the Double-Blind Repeat (DBR) Treatment Phase. Subjects who did not meet the recurrence criteria by the end of Maintenance Phase 1 were withdrawn from the study.	
Reporting group title	Double-blind rifaximin
Reporting group description: Subjects received rifaximin for 2 weeks with a 4-week treatment-free follow-up (Double-blind Repeat [DBR] Treatment Phase). The 4-week follow-up phase was the Primary Evaluation Period (PEP) for repeat treatment efficacy. Subjects then entered into Maintenance Phase 2 (6-weeks treatment-free period) followed by a second retreatment with rifaximin for 2 weeks with a 4-week treatment-free follow-up (Second Repeat Treatment [SRT] Phase).	
Reporting group title	Double-blind placebo
Reporting group description: Subjects received placebo rifaximin for 2 weeks with a 4-week treatment-free follow-up (Double-blind Repeat [DBR] Treatment Phase). The 4-week follow-up phase was the Primary Evaluation Period (PEP) for repeat treatment efficacy. Subjects then entered into Maintenance Phase 2 (6-weeks treatment-free period) followed by a second retreatment with placebo rifaximin for 2 weeks with a 4-week treatment-free follow-up (Second Repeat Treatment [SRT] Phase).	
Subject analysis set title	Double-blind rifaximin
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients at baseline who were later randomized to rifaximin in the DBR phase	
Subject analysis set title	Double-blind placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients at baseline who were later randomized to placebo rifaximin in the DBR phase	

Primary: Repeat treatment responders

End point title	Repeat treatment responders
End point description: Percentage of subjects who are responders to repeat treatment in both IBS-related abdominal pain AND stool consistency. Intent-to-treat (ITT) analysis, with a worse case approach (patients with < 4 days of IBS symptom data in a given week were considered as non-responders for that week).	
End point type	Primary
End point timeframe: The 4-week treatment-free period (the PEP) following 2 weeks of double-blind repeat treatment (DBR Treatment Phase)	

End point values	Double-blind rifaximin	Double-blind placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	328	308		
Units: Number of subjects	107	77		

Statistical analyses

Statistical analysis title	Treatment difference
Comparison groups	Double-blind rifaximin v Double-blind placebo
Number of subjects included in analysis	636
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0232
Method	Cochran-Mantel-Haenszel

Secondary: Prevention of recurrence

End point title	Prevention of recurrence
End point description: Key secondary endpoint #1: Percentage of subjects who demonstrated adequate relief in both IBS-related abdominal pain AND stool consistency during the PEP in the DBR Treatment Phase AND had no recurrence through the end of Maintenance Phase 2 AND continued to respond without recurrence through the end of Week 6 of the SRT Phase. A worst case analysis was performed, in which patients with < 4 days of IBS symptom data in a given week were considered as non-responders for that week.	
End point type	Secondary
End point timeframe: The entire double-blind phase	

End point values	Double-blind rifaximin	Double-blind placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	295	283		
Units: Number of subjects	39	20		

Statistical analyses

Statistical analysis title	Treatment difference
Comparison groups	Double-blind rifaximin v Double-blind placebo
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0068
Method	Cochran-Mantel-Haenszel

Secondary: Durable response

End point title	Durable response
-----------------	------------------

End point description:

Key secondary endpoint #2: Percentage of subjects with adequate relief who were responders to repeat treatment in both IBS-related abdominal pain AND stool consistency during the PEP in the DBR Treatment Phase and had no recurrence through the end of Maintenance Phase 2. A worst case analysis was performed, in which patients with < 4 days of IBS symptom data in a given week were considered as non-responders for that week.

End point type	Secondary
----------------	-----------

End point timeframe:

The first 12 weeks of evaluation during the double-blind phase.

End point values	Double-blind rifaximin	Double-blind placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	328	308		
Units: Number of subjects	56	36		

Statistical analyses

Statistical analysis title	Treatment difference
----------------------------	----------------------

Comparison groups	Double-blind placebo v Double-blind rifaximin
-------------------	---

Number of subjects included in analysis	636
---	-----

Analysis specification	Pre-specified
------------------------	---------------

Analysis type	superiority
---------------	-------------

P-value	= 0.0419
---------	----------

Method	Cochran-Mantel-Haenszel
--------	-------------------------

Secondary: IBS-related Bloating

End point title	IBS-related Bloating
-----------------	----------------------

End point description:

Key secondary endpoint #3: Percentage of subjects who were responders to repeat treatment for IBS-related bloating during the PEP in the DBR Treatment Phase. Subjects were IBS-related bloating responders if they had at least a 1 point decrease from baseline in their weekly average bloating score for at least 2 weeks during the PEP. A worst case analysis was performed, in which patients with < 4 days of IBS symptom data in a given week were considered as non-responders for that week.

End point type	Secondary
----------------	-----------

End point timeframe:

The 4-week treatment-free period (the PEP) following 2 weeks of double-blind repeat treatment (DBR Treatment Phase)

End point values	Double-blind rifaximin	Double-blind placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	328	308		
Units: Number of subjects	153	127		

Statistical analyses

Statistical analysis title	Treatment difference
Comparison groups	Double-blind rifaximin v Double-blind placebo
Number of subjects included in analysis	636
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1429
Method	Cochran-Mantel-Haenszel

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 24 weeks for the open-label period. Up to 18 weeks for the double-blind period.

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	15
--------------------	----

Reporting groups

Reporting group title	Open-label rifaximin
-----------------------	----------------------

Reporting group description:

During treatment with open-label rifaximin 550 mg TID

Reporting group title	Double-blind rifaximin
-----------------------	------------------------

Reporting group description:

During treatment with double-blind rifaximin 550 mg TID

Reporting group title	Double-blind placebo
-----------------------	----------------------

Reporting group description:

During treatment with double-blind rifaximin placebo

Serious adverse events	Open-label rifaximin	Double-blind rifaximin	Double-blind placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 2579 (1.09%)	4 / 328 (1.22%)	4 / 308 (1.30%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 2579 (0.00%)	1 / 328 (0.30%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal cancer			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Uterine leiomyoma			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	4 / 2579 (0.16%)	0 / 328 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Dysfunctional uterine bleeding			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			

subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 2579 (0.00%)	1 / 328 (0.30%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hilum mass			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 2579 (0.00%)	1 / 328 (0.30%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gun shot wound			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Coronary artery occlusion			
subjects affected / exposed	0 / 2579 (0.00%)	0 / 328 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	2 / 308 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diverticulum			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Irritable bowel syndrome			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	2 / 2579 (0.08%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone cyst			

subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc degeneration			
subjects affected / exposed	2 / 2579 (0.08%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 2579 (0.00%)	1 / 328 (0.30%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis viral			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin abscess			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			

subjects affected / exposed	1 / 2579 (0.04%)	0 / 328 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Open-label rifaximin	Double-blind rifaximin	Double-blind placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	198 / 2579 (7.68%)	74 / 328 (22.56%)	69 / 308 (22.40%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	24 / 2579 (0.93%)	9 / 328 (2.74%)	4 / 308 (1.30%)
occurrences (all)	25	10	5
Aspartate aminotransferase increased			
subjects affected / exposed	24 / 2579 (0.93%)	7 / 328 (2.13%)	4 / 308 (1.30%)
occurrences (all)	26	8	4
Blood creatine phosphokinase increased			
subjects affected / exposed	31 / 2579 (1.20%)	9 / 328 (2.74%)	3 / 308 (0.97%)
occurrences (all)	31	9	3
Nervous system disorders			
Headache			
subjects affected / exposed	42 / 2579 (1.63%)	4 / 328 (1.22%)	9 / 308 (2.92%)
occurrences (all)	45	5	9
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	52 / 2579 (2.02%)	12 / 328 (3.66%)	7 / 308 (2.27%)
occurrences (all)	54	14	7
Diarrhoea			
subjects affected / exposed	20 / 2579 (0.78%)	7 / 328 (2.13%)	3 / 308 (0.97%)
occurrences (all)	22	9	3
Vomiting			
subjects affected / exposed	24 / 2579 (0.93%)	2 / 328 (0.61%)	5 / 308 (1.62%)
occurrences (all)	27	2	6
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all)	17 / 2579 (0.66%) 18	3 / 328 (0.91%) 3	8 / 308 (2.60%) 9
Infections and infestations			
Influenza subjects affected / exposed occurrences (all)	33 / 2579 (1.28%) 33	7 / 328 (2.13%) 7	2 / 308 (0.65%) 2
Bronchitis subjects affected / exposed occurrences (all)	15 / 2579 (0.58%) 15	9 / 328 (2.74%) 10	5 / 308 (1.62%) 6
Sinusitis subjects affected / exposed occurrences (all)	34 / 2579 (1.32%) 34	7 / 328 (2.13%) 7	7 / 308 (2.27%) 7
Upper respiratory tract infection subjects affected / exposed occurrences (all)	41 / 2579 (1.59%) 47	12 / 328 (3.66%) 13	8 / 308 (2.60%) 8
Nasopharyngitis subjects affected / exposed occurrences (all)	36 / 2579 (1.40%) 36	10 / 328 (3.05%) 10	9 / 308 (2.92%) 11
Urinary tract infection subjects affected / exposed occurrences (all)	35 / 2579 (1.36%) 36	11 / 328 (3.35%) 12	15 / 308 (4.87%) 19

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 April 2012	<p>Clarification on nonresponder follow-up and end-of-study assessments was added. Key secondary endpoints were added as components of the primary endpoint. The weekly diary subject global assessment (SGA) questions were added as a requirement with details about how responsiveness and validity of the SGA would be evaluated.</p> <p>The following secondary endpoints were added:</p> <ul style="list-style-type: none">- Responsiveness of the weekly SGA question in detecting daily IBS symptom changes each week.- Validity of the weekly SGA question in correlating with daily IBS symptoms each week.- Proportion of subjects who are monthly responders by month during the DBR Treatment Phase, the Maintenance Phase 2, and the SRT Phase.- Proportion of subjects who are weekly responders by week during Treatment 2 Phase, Maintenance Phase 1, DBR Treatment Phase, Maintenance Phase 2 and SRT Phase- Proportion of subjects who are responders during PEP in the DBR Treatment Phase for the complete recurrence subjects during the Maintenance Phase 1. <p>"Treatment Success" was replaced with "Weekly Responder" and both terms were clarified.</p> <p>Recurrence was redefined.</p> <p>Additional information was added regarding potential substudies.</p> <p>Exclusion criterion #6 was modified.</p> <p>"Prohibited medications" were redefined as "restricted medications" with clarification on handling the latter.</p> <p>Additional instructions and explanation for the requirement for stool samples was added.</p> <p>Weekly nonresponder was redefined.</p> <p>Subjects who were responders during the 4-week follow-up period in the DBR Treatment Phase (PEP) and experienced recurrence during the Maintenance Phase 2 were considered having "recurrence at the first non-responding week" within a 4-week assessment period during which the recurrence occurs, as opposed to "no treatment success" as defined in the original protocol.</p> <p>Worst case analysis method was added to the methods of handling dropouts and missing data.</p> <p>Subgroup analyses were added to Section 8.3.3</p>
27 August 2012	<p>The skin swab sub-study was added, noting instruction for collection of samples and that further details would be provided in a separate protocol.</p> <p>The 14 day window after signing the informed consent form (ICF) for colonoscopy was removed.</p> <p>Exclusion criterion #16 was removed as creatinine clearance was not a concern while using rifaximin in this study population.</p> <p>The window for taking antibiotics was reduced from 60 to 14 days prior to signing the ICF.</p> <p>Simethicone was added as a restricted therapy.</p> <p>Visit windows were defined for colonoscopy requirements.</p>
26 February 2013	<p>Added a standard of care approach to endoscopic examination and removed the 7 day waiting period between colonoscopy and Screening Phase.</p>
20 June 2013	<p>Added European Union investigative sites to the study design and incorporated required statements for submission of the protocol in Europe.</p>

11 February 2014	<p>The DBR population was clarified as the ITT population. DBR phase noted as the randomization phase and is the basis for analysis of ITT population.</p> <p>Key secondary endpoints were re-ranked to reflect the study design objectives and clarification for the analysis thereof was added.</p> <p>Decreased the sample size from 800 to 600 based on a change in the PEP in DBR Treatment phase. The new assumption accounts for the enrichment aspects of the study design and is supported by literature regarding a repeat treatment study.</p> <p>Post-marketing experience information, prohibited medications, and updates to birth control methods was added per country specific requests made by the German Competent Authority (BfArM).</p> <p>"Recurrence" definition was clarified for partial recurrence and definition of "durability" of response was added.</p>
------------------	--

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27528177>