



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 | Subject, Investigator |

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 | Rifaximin 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>