Clinical trial results:
Rifaximin delayed release (400 mg tablet) for the prevention of recurrent acute diverticulitis and diverticular complications. A phase II, multicenter, double-blind, placebo-controlled, randomized clinical trial.

Summary

EudraCT number	2017-002708-28
Trial protocol	ES DE HU FR NL GB PT IT RO
Global end of trial date	22 December 2020

Results information

Result version number	v1 (current)
This version publication date	04 August 2023
First version publication date	04 August 2023

Trial information

Trial identification

Sponsor protocol code	REDIV/002/17

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Alfasigma S.p.A.
Sponsor organisation address	Via ragazzi del '99, 5, Bologna, Italy,
Public contact	Nicola Gargano, Alfasigma SpA, nicola.gargano@alfasigma.com
Scientific contact	Nicola Gargano, Alfasigma SpA, nicola.gargano@alfasigma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 December 2020
Global end of trial reached?	Yes
Global end of trial date	22 December 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to demonstrate that the rate of patients with recurrence/complications of diverticulitis is statistically different between patients treated with any of the two doses of Rifaximin-EIR and patients treated with placebo.

Protection of trial subjects:

Before initiating the trial, Alfasigma S.p.A. and the Investigator/Institution had to obtain written and dated approval/favourable opinion for the trial protocol, the written informed consent form, the patient recruitment procedures (e.g. adverts, if applicable), and any other written information to be provided to subjects from the relevant Independent Ethic Committee(s) (IEC(s)) and the Competent Regulatory Authorities, according to rules in force in each participant country. As part of the Investigator's/Institution's written application to the IEC(s), Alfasigma S.p.A. provided the IEC(s) with a current copy of the Investigator's Brochure. When the Investigator's Brochure was updated during the trial, Alfasigma S.p.A. supplied a copy of the updated Investigator’s Brochure to the IEC(s).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 33
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Spain: 54
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Italy: 97
Worldwide total number of subjects	236
EEA total number of subjects	235

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)	151
From 65 to 84 years	85
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was performed in a total of 52 investigational study sites, 22 in Italy, 3 in Germany, 9 in Spain, 5 in France, 2 in The Netherlands, 1 in Poland, 5 in Romania, 1 in Portugal, 3 in Hungary and 1 in the United Kingdom.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	236
Number of subjects completed	190

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screeining failure: 40
Reason: Number of subjects	subjects not dosed: 6

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	SAF Rifaximin EIR 400 mg

Arm description:

Safety (SAF) analysis set, defined as all randomized patients who signed informed consent and took at least one dose of the investigational product Rifaximin EIR 400 mg

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

Dosage and administration details:

Rifaximin-EIR 400 mg b.i.d. for 10 consecutive days a month, for 12 months

Arm title	SAF Rifaximin EIR 800 mg

Arm description:

Safety (SAF) analysis set, defined as all randomized patients who signed informed consent and took at least one dose of the investigational product - Rifaximin EIR 800 mg

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

Dosage and administration details:

Rifaximin-EIR 800 mg b.i.d. for 10 consecutive days a month, for 12 months

Arm title	SAF Placebo

Arm description:

Safety (SAF) analysis set, defined as all randomized patients who signed informed consent and took at least one dose of the investigational product - Placebo

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

Dosage and administration details:

Placebo for 10 consecutive days a month, for 12 months.

Number of subjects in period 1[1]	SAF Rifaximin EIR 400 mg	SAF Rifaximin EIR 800 mg	SAF Placebo
Started	63	62	65
Completed	42	41	47
Not completed	21	21	18
subjects not dosed	3	2	1
Subjects who prematurely discontinuated	18	19	17

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Demographic data and other baseline characteristics were presented for the SAF analysis set by treatment group.

Baseline characteristics

Reporting groups	
Reporting group title	SAF Rifaximin EIR 400 mg
Reporting group description:	
Safety (SAF) analysis set, defined as all randomized patients who signed informed consent and took at least one dose of the investigational product Rifaximin EIR 400 mg	
Reporting group title	SAF Rifaximin EIR 800 mg
Reporting group description:	
Safety (SAF) analysis set, defined as all randomized patients who signed informed consent and took at least one dose of the investigational product - Rifaximin EIR 800 mg	
Reporting group title	SAF Placebo
Reporting group description:	
Safety (SAF) analysis set, defined as all randomized patients who signed informed consent and took at least one dose of the investigational product - Placebo	

Reporting group values	SAF Rifaximin EIR 400 mg	SAF Rifaximin EIR 800 mg	SAF Placebo
Number of subjects	63	62	65
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	59.2	57.9	58.6
standard deviation	± 11.1	± 12.3	± 10.9
Gender categorical Units: Subjects			
Female	29	31	38
Male	34	31	27

Reporting group values	Total		
Number of subjects	190		
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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	98		
Male	92		

End points

End points reporting groups

Reporting group title	SAF Rifaximin EIR 400 mg
Reporting group description:	
Safety (SAF) analysis set, defined as all randomized patients who signed informed consent and took at least one dose of the investigational product Rifaximin EIR 400 mg	
Reporting group title	SAF Rifaximin EIR 800 mg
Reporting group description:	
Safety (SAF) analysis set, defined as all randomized patients who signed informed consent and took at least one dose of the investigational product - Rifaximin EIR 800 mg	
Reporting group title	SAF Placebo
Reporting group description:	
Safety (SAF) analysis set, defined as all randomized patients who signed informed consent and took at least one dose of the investigational product - Placebo	
Subject analysis set title	ITT Rifaximin EIR 400 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intention-to-Treat (ITT) analysis set, defined as all patients of the SAF set with at least one week of data filled in the patient’s diary -Rifaximin EIR 400 mg	
Subject analysis set title	ITT Rifaximin EIR 800 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intention-to-Treat (ITT) analysis set, defined as all patients of the SAF set with at least one week of data filled in the patient’s diary -Rifaximin EIR 800 mg	
Subject analysis set title	ITT Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intention-to-Treat (ITT) analysis set, defined as all patients of the SAF set with at least one week of data filled in the patient’s diary - Placebo	

Primary: Rate of patients with recurrence of diverticulitis or diverticular complications over the 12-month treatment period

End point title	Rate of patients with recurrence of diverticulitis or diverticular complications over the 12-month treatment period
End point description:	
End point type	Primary
End point timeframe:	
12 months	

End point values	ITT Rifaximin EIR 400 mg	ITT Rifaximin EIR 800 mg	ITT Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	61	59	62	
Units: number of patients				
number (not applicable)	10	7	6	

Statistical analyses

Statistical analysis title	Analysis of primary variables
Comparison groups	ITT Rifaximin EIR 400 mg v ITT Rifaximin EIR 800 mg v ITT Placebo
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 12 months	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0
Reporting groups	
Reporting group title	Rifaximin 400 mg
Reporting group description: -	
Reporting group title	Rifaximin 800 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Rifaximin 400 mg	Rifaximin 800 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 63 (6.35%)	1 / 62 (1.61%)	2 / 65 (3.08%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Pelvic fracture			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (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
Surgical and medical procedures			
Removal of foreign body			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (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
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (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			

Diverticular perforation			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 65 (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
Cholelithiasis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 65 (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
Respiratory, thoracic and mediastinal disorders			
Allergic cough			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (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
Infectious pleural effusion			

subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Rifaximin 400 mg	Rifaximin 800 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 63 (55.56%)	31 / 62 (50.00%)	42 / 65 (64.62%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	2	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 63 (1.59%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	1	1	0
Hypertensive crisis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Thrombophlebitis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 63 (3.17%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	2	0	1
Chest pain			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	1 / 65 (1.54%)
occurrences (all)	0	1	1
Fatigue			

subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Feeling hot			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	3	0	0
Pain			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	2 / 63 (3.17%)	2 / 62 (3.23%)	3 / 65 (4.62%)
occurrences (all)	2	3	3
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Ovarian cyst			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Prostatitis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	2 / 65 (3.08%)
occurrences (all)	0	1	2
Dyspnoea			

subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	1	0	1
Nasal polyps			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	2 / 65 (3.08%)
occurrences (all)	1	0	2
Anxiety disorder			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Apathy			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Somatic symptom disorder			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Blood triglycerides increased			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Blood Urea Increased			

subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Breath Sounds Abnormal			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
C-Reactive Protein Increased			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Faecal Calprotectin Increased			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	3 / 65 (4.62%)
occurrences (all)	0	0	3
Helicobacter Test Positive			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Prostatic Specific Antigen Increased			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Urinary tract infection			
subjects affected / exposed	1 / 63 (1.59%)	2 / 62 (3.23%)	3 / 65 (4.62%)
occurrences (all)	2	2	3
Accident at home			
subjects affected / exposed	1 / 63 (1.59%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	1	1	0
head injury			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Intentional product misuse			
subjects affected / exposed	3 / 63 (4.76%)	1 / 62 (1.61%)	2 / 65 (3.08%)
occurrences (all)	3	1	2
Limb injury			
subjects affected / exposed	1 / 63 (1.59%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	1	1	0
Muscle strain			

subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Patella fracture			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Product dispensing error			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Radius fracture			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Cardiac disorders			
Cardiac fibrillation			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Palpitations			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	0 / 63 (0.00%)	2 / 62 (3.23%)	0 / 65 (0.00%)
occurrences (all)	0	2	0
Facial paralysis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	0 / 63 (0.00%)	2 / 62 (3.23%)	1 / 65 (1.54%)
occurrences (all)	0	2	1
Migraine			
subjects affected / exposed	0 / 63 (0.00%)	2 / 62 (3.23%)	1 / 65 (1.54%)
occurrences (all)	0	3	1
Piriformis syndrome			

subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	2
Sciatica			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	2 / 65 (3.08%)
occurrences (all)	0	0	3
Syncope			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Normocytic anaemia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Thrombocytosis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	1 / 65 (1.54%)
occurrences (all)	0	1	1
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	2
Vitreous detachment			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	3 / 63 (4.76%)	2 / 62 (3.23%)	4 / 65 (6.15%)
occurrences (all)	6	2	7
Abdominal pain			
subjects affected / exposed	11 / 63 (17.46%)	9 / 62 (14.52%)	10 / 65 (15.38%)
occurrences (all)	16	17	17
Abdominal pain lower			
subjects affected / exposed	3 / 63 (4.76%)	4 / 62 (6.45%)	4 / 65 (6.15%)
occurrences (all)	6	10	7
Abdominal pain upper			

subjects affected / exposed	3 / 63 (4.76%)	3 / 62 (4.84%)	3 / 65 (4.62%)
occurrences (all)	5	4	3
Abdominal tenderness			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	1 / 65 (1.54%)
occurrences (all)	0	1	2
Anal pruritus			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	4 / 63 (6.35%)	7 / 62 (11.29%)	5 / 65 (7.69%)
occurrences (all)	4	14	8
Diarrhoea			
subjects affected / exposed	2 / 63 (3.17%)	2 / 62 (3.23%)	5 / 65 (7.69%)
occurrences (all)	2	4	5
Dyspepsia			
subjects affected / exposed	1 / 63 (1.59%)	1 / 62 (1.61%)	5 / 65 (7.69%)
occurrences (all)	2	3	6
Enteritis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	1	0	1
Faecaloma			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Faeces soft			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Flatulence			
subjects affected / exposed	2 / 63 (3.17%)	0 / 62 (0.00%)	2 / 65 (3.08%)
occurrences (all)	3	0	2
Gastritis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	1	0	1
Haemorrhoids			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Hiatus hernia			

subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Infrequent bowel movements			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	2 / 63 (3.17%)	3 / 62 (4.84%)	1 / 65 (1.54%)
occurrences (all)	2	3	1
Oesophagitis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Peptic ulcer			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	1 / 63 (1.59%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	1	1	0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Hepatic Steatosis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Alopecia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Dermatitis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Pruritus			

subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Skin disorder			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Renal colic			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Urinary retention			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 63 (3.17%)	0 / 62 (0.00%)	4 / 65 (6.15%)
occurrences (all)	2	0	4
Back pain			
subjects affected / exposed	2 / 63 (3.17%)	2 / 62 (3.23%)	3 / 65 (4.62%)
occurrences (all)	2	2	3
Fibromyalgia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	1	0	1
Pain in extremity			

subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Plantar fasciitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Tendonitis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	1 / 63 (1.59%)	1 / 62 (1.61%)	2 / 65 (3.08%)
occurrences (all)	1	2	2
Cystitis			
subjects affected / exposed	0 / 63 (0.00%)	2 / 62 (3.23%)	1 / 65 (1.54%)
occurrences (all)	0	3	1
Diverticulitis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Fungal infection			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	1	0	1
Gastroenteritis viral			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Helicobacter infection			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Hordeolum			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	2

Influenza			
subjects affected / exposed	4 / 63 (6.35%)	1 / 62 (1.61%)	3 / 65 (4.62%)
occurrences (all)	4	1	3
Nasopharyngitis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	1 / 65 (1.54%)
occurrences (all)	0	1	1
Oral candidiasis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	1 / 63 (1.59%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	1	1	0
Pneumonia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Testicular abscess			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Tooth abscess			
subjects affected / exposed	0 / 63 (0.00%)	2 / 62 (3.23%)	1 / 65 (1.54%)
occurrences (all)	0	2	1
Urinary tract infection viral			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Hyperlipidaemia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Hypertriglyceridaemia			

subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Hypovitaminosis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 November 2018	Main substantial amendment: Amendment to on exclusion criterion

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 November 2019	Recruitment rate was slower than expected.	-

Notes:

Limitations and caveats

None reported