Clinical trial results:
A Phase II, multicentre, double-blind, randomised, placebo-controlled study of Rifaximin delayed release 400 mg tablet: clinical efficacy and safety in the prevention of post-operative endoscopic Crohn's disease recurrence

Summary

EudraCT number	2017-002258-36
Trial protocol	DE BE ES NL PL IT
Global end of trial date	29 July 2020
Results information	
Result version number	v1 (current)
This version publication date	14 August 2021
First version publication date	14 August 2021

Trial information

Trial identification	
Sponsor protocol code	RETIPC/01/17
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	NA: NA

Notes:

Sponsors	
Sponsor organisation name	Alfasigma S.p.A.
Sponsor organisation address	Via Ragazzi del '99, 5, Bologna, Italy, 40122
Public contact	Cecilia Renzulli, Alfasigma S.p.A, cecilia.renzulli@alfasigma.com
Scientific contact	Cecilia Renzulli, Alfasigma S.p.A, cecilia.renzulli@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	25 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 July 2020
Global end of trial reached?	Yes
Global end of trial date	29 July 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study primarily aimed to demonstrate the efficacy of Rifaximin-EIR 400 mg tablet (800 mg/B.I.D., total daily dose 1600 mg) vs. Placebo in the prevention of Endoscopic Crohn's Disease Recurrence following ileocolonic resection.

Protection of trial subjects:

This study was conducted in compliance with the Declaration of Helsinki and the standards of Good Clinical Practice as defined in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 (R2) "Guideline for Good Clinical Practice".

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 March 2018
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	Netherlands: 5
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 5
Worldwide total number of subjects	43
EEA total number of subjects	43

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)	40
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total, 50 patients were screened for the study during approximately 26 months – from 17 November 2017 to 31 December 2019 in 14 out of the 25 activated study sites in 6 European countries (Belgium, France, Germany, Italy, the Netherlands, Poland).

Pre-assignment

Screening details:

In total, 50 patients were screened for the study. Eight patients (16.0%) were recorded as screening failures (SF). Among these 8 patients, 1 has been randomised in the study but has not received study drug.

Period 1

Period 1 title	Overall period (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	Rifaximin-EIR 400 mg

Arm description:

Rifaximin-EIR 400 mg film coated tablets, 2 tablets taken orally B.I.D. (1600 mg/daily)

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

Dosage and administration details:

Rifaximin-EIR 400 mg film coated tablets, 2 tablets taken orally B.I.D. (1600 mg/daily) for 26 weeks

Arm title	Placebo

Arm description:

Placebo matching Rifaximin-EIR 400 mg film coated tablets

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

Dosage and administration details:

Placebo film coated tablets: 2 tablets taken orally B.I.D. for 26 weeks

Number of subjects in period 1	Rifaximin-EIR 400 mg	Placebo
Started	21	22
Completed	17	21
Not completed	4	1
Investigator's decision	1	1
Adverse event, non-fatal	1	-
Exclusion Criteria	1	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	Rifaximin-EIR 400 mg

Reporting group description:

Rifaximin-EIR 400 mg film coated tablets, 2 tablets taken orally B.I.D. (1600 mg/daily)

Reporting group title	Placebo

Reporting group description:

Placebo matching Rifaximin-EIR 400 mg film coated tablets

Reporting group values	Rifaximin-EIR 400 mg	Placebo	Total
Number of subjects	21	22	43
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	20	20	40
From 65-84 years	1	2	3
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	9	7	16
Male	12	15	27

Subject analysis sets

Subject analysis set title	Safety Analysis (SAF) Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Of all 43 patients that were randomised, 42 patients (97.7%) were included in the SAF Population: with 20 patients (95.2%) in the Rifaximin-EIR and 22 patients (100.00%) in the Placebo group.
1 out of the 43 randomised subjects was randomised to the Rifaximin-EIR group but did not receive any study drug, so the patient was recorded as Screening failure.

Subject analysis set title	Intention to Treat (ITT) population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Of all 43 patients that were randomised, 42 patients (97.7%) were included in the ITT Population: with 20 patients (95.2%) in the Rifaximin-EIR and 22 patients (100.00%) in the Placebo group.
1 out of the 43 randomised subjects was randomised to the Rifaximin-EIR group but did not receive any study drug, so the patient was recorded as screening failure.

Subject analysis set title	Modified Intention to Treat (mITT) population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Within the ITT Population, subjects who had the endoscopic evaluation at Week 26 were included in

the mITT Population

Subject analysis set title	Per Protocol (PP) population
Subject analysis set type	Per protocol

Subject analysis set description:

Reasons for exclusion from the PP Population were the violation of inclusion/exclusion criteria, the use of prohibited medications and treatment compliance.

Reporting group values	Safety Analysis (SAF) Population	Intention to Treat (ITT) population	Modified Intention to Treat (mITT) population
Number of subjects	42	42	36
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	39	39	33
From 65-84 years	3	3	3
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	23	23	20
Male	19	19	16

Reporting group values	Per Protocol (PP) population		
Number of subjects	28		
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)	25		
From 65-84 years	3		
85 years and over	0		
Gender categorical Units: Subjects			
Female	16		
Male	12		

End points

End points reporting groups

Reporting group title	Rifaximin-EIR 400 mg

Reporting group description:

Rifaximin-EIR 400 mg film coated tablets, 2 tablets taken orally B.I.D. (1600 mg/daily)

Reporting group title	Placebo

Reporting group description:

Placebo matching Rifaximin-EIR 400 mg film coated tablets

Subject analysis set title	Safety Analysis (SAF) Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Of all 43 patients that were randomised, 42 patients (97.7%) were included in the SAF Population: with 20 patients (95.2%) in the Rifaximin-EIR and 22 patients (100.00%) in the Placebo group.
1 out of the 43 randomised subjects was randomised to the Rifaximin-EIR group but did not receive any study drug, so the patient was recorded as Screening failure.

Subject analysis set title	Intention to Treat (ITT) population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Of all 43 patients that were randomised, 42 patients (97.7%) were included in the ITT Population: with 20 patients (95.2%) in the Rifaximin-EIR and 22 patients (100.00%) in the Placebo group.
1 out of the 43 randomised subjects was randomised to the Rifaximin-EIR group but did not receive any study drug, so the patient was recorded as screening failure.

Subject analysis set title	Modified Intention to Treat (mITT) population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Within the ITT Population, subjects who had the endoscopic evaluation at Week 26 were included in the mITT Population

Subject analysis set title	Per Protocol (PP) population
Subject analysis set type	Per protocol

Subject analysis set description:

Reasons for exclusion from the PP Population were the violation of inclusion/exclusion criteria, the use of prohibited medications and treatment compliance.

Primary: Proportion of patients with Endoscopic Recurrence at Week 26

End point title	Proportion of patients with Endoscopic Recurrence at Week 26

End point description:

Proportion of patients with Endoscopic Recurrence at Week 26 after Randomisation, defined as Rutgeerts score ≥ i2

End point type	Primary

End point timeframe:

26 weeks

End point values	Rifaximin-EIR 400 mg	Placebo	Intention to Treat (ITT) population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	20	22	42	
Units: Subjects	19	19	38	

Statistical analyses

Statistical analysis title	Efficacy statistical analysis
Comparison groups	Placebo v Rifaximin-EIR 400 mg
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Fisher exact
Confidence interval	
level	95 %
sides	2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 28 weeks	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20
Reporting groups	
Reporting group title	Safety analysis population

Reporting group description: -

Serious adverse events	Safety analysis population		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 42 (2.38%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety analysis population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 42 (85.71%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		

Hypertension subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 3 / 42 (7.14%) 3 1 / 42 (2.38%) 1 1 / 42 (2.38%) 1		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	 1 / 42 (2.38%) 1		
Reproductive system and breast disorders Galactorrhoea subjects affected / exposed occurrences (all) Gynaecomastia subjects affected / exposed occurrences (all) Vulvovaginal pruritus subjects affected / exposed occurrences (all)	 1 / 42 (2.38%) 1 1 / 42 (2.38%) 1 1 / 42 (2.38%) 1		
Respiratory, thoracic and mediastinal disorders Emphysema subjects affected / exposed occurrences (all) Rhinitis allergic subjects affected / exposed occurrences (all)	 1 / 42 (2.38%) 1 1 / 42 (2.38%) 1		
Investigations			

Blood testosterone decreased subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Neutrophil count increased subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Red blood cell sedimentation rate increased subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
White blood cell count increased subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Injury, poisoning and procedural complications Animal scratch subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Muscle injury subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Lymphopenia subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Neutropenia subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	5 / 42 (11.90%) 6		
Anal fissure subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 4		

Nausea				
subjects affected / exposed	3 / 42 (7.14%)			
occurrences (all)	4			
Abdominal distension				
subjects affected / exposed	2 / 42 (4.76%)			
occurrences (all)	3			
Diarrhoea				
subjects affected / exposed	2 / 42 (4.76%)			
occurrences (all)	3			
Dyspepsia				
subjects affected / exposed	2 / 42 (4.76%)			
occurrences (all)	2			
Haematochezia				
subjects affected / exposed	2 / 42 (4.76%)			
occurrences (all)	2			
Proctalgia				
subjects affected / exposed	2 / 42 (4.76%)			
occurrences (all)	2			
Anal skin tags				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Cheilosis				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Flatulence				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Gastric mucosa erythema				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Gastritis				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Rectal haemorrhage				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			

Umbilical hernia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	5		
Gastroenteritis			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Bronchitis			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	3		
Cystitis			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Ear infection			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Gastroenteritis viral			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Oral fungal infection			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Osteomyelitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Tinea pedis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Hypokalaemia			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Hypophosphataemia			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		

Decreased appetite			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Gout			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Iron deficiency			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Malnutrition			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Vitamin B12 deficiency			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 September 2017	Amended versions of the study protocol (2.0 and 3.0) contained minor administrative updates, additions or clarifications regarding exclusion criteria and clarifications concerning schedule of assessments and secondary endpoint.
11 October 2018	Amended versions of the study protocol (2.0 and 3.0) contained minor administrative updates, additions or clarifications regarding exclusion criteria and clarifications concerning schedule of assessments and secondary endpoint.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was prematurely terminated due to the difficulties in patient recruitment.

Notes: