



## 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 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
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##### 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
<b>Arm title</b>	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

<b>Arm title</b>	Placebo
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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

<b>Number of subjects in period 1</b>	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
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Reporting group description:

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

Reporting group title	Placebo
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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
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Subject analysis set type	Safety analysis
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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
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Subject analysis set type	Intention-to-treat
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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
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Subject analysis set type	Modified intention-to-treat
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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 $\geq$ 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

<b>Statistical analysis title</b>	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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	20
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### Reporting groups

Reporting group title	Safety analysis population
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Reporting group description: -

<b>Serious adverse events</b>	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 %

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

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

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### 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: