



Clinical trial results:

Safety and Efficacy of Rifaximin Delayed Release 400 mg Tablets in Patients with Moderate-to-Severe Papulopustular Rosacea and Positive Lactulose Breath Test. A Multicenter Double-Blind, Placebo-Controlled Randomized Clinical Trial.

Summary

EudraCT number	2017-003722-33
Trial protocol	IT DE
Global end of trial date	21 March 2022

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	REROS/001/17
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Alfasigma
Sponsor organisation address	Via Ragazzi del '99 5, Bologna, Italy,
Public contact	Nicola Gargano, Alfasigma, nicola.gargano@alfasigma.com
Scientific contact	Nicola Gargano, Alfasigma, 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	29 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 March 2022
Global end of trial reached?	Yes
Global end of trial date	21 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the safety and efficacy of oral Rifaximin-EIR (rifaximin delayed release) versus placebo in adults with moderate-to-severe papulopustular rosacea (a.k.a. subtype II).

Protection of trial subjects:

Before initiating the trial, the Sponsor and the Investigators/institutions obtained written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent and assent forms and any other written/oral information provided to the subjects. The Sponsor provided the IRB/IEC with a current copy of the Investigator's Brochure and any updated copy prepared during the trial, when requested. The Sponsor and the Investigators/institutions obtained approval/favourable opinion from the IRB/IEC for change(s) to any aspect of the trial, such as modification(s) of the protocol, written informed consent form (ICF), written information provided to subjects.

The Sponsor had to promptly report any new information that could affect the safety of the subjects or the conduct of the trial to both the IRB/IEC and the Regulatory Authorities, if applicable.

This study was conducted in compliance with the study protocol, the recommendations on biomedical research on human subjects of the Declaration of Helsinki, ICH GCP E6 (R2) Guidelines, and all applicable national laws and regulations.

Agreement to adhere to the protocol was indicated by Investigators signing and returning the protocol signature page.

Subject identities were kept confidential by assigning each subject a unique identifier consisting of a subject-specific numeric code, which was used throughout the study instead of the subject's name.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 June 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	Germany: 103
Country: Number of subjects enrolled	Italy: 42
Country: Number of subjects enrolled	Russian Federation: 87
Country: Number of subjects enrolled	Ukraine: 11
Worldwide total number of subjects	243
EEA total number of subjects	145

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)	229
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were planned to be competitively enrolled at approximately 50 study sites in Italy, Germany, Russia and Ukraine.

Pre-assignment

Screening details:

A total of 661 subjects provided written informed consent to participate in this study. Two hundred and forty-three subjects completed screening successfully and 418 were screening failures.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

2 rifaximin-EIR 400 mg tablets BID for 10 days and 2 tablets of placebo BID for the following 20 days

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

Dosage and administration details:

2 tablets BID (10 days)

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

Dosage and administration details:

2 tablets BID (20 days)

Arm title	Arm B
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Arm description:

1 rifaximin-EIR 400 mg tablet and 1 placebo tablet BID for 30 days

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

Dosage and administration details:

1 tablets BID (30 days)

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
1 tablets BID (30 days)	
Arm title	Arm C
Arm description:	
1 rifaximin-EIR 400 mg tablet and 1 placebo tablet BID for 10 days and 2 tablets of placebo BID for the following 20 days	
Arm type	Experimental
Investigational medicinal product name	Rifaximin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
1 tablet BID (10 days)	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
1 tablet BID (10 days) and 2 tablets BID (20 days)	
Arm title	Arm D
Arm description:	
2 tablets of placebo BID for 30 days.	
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:	
2 tablets BID (30 days)	

Number of subjects in period 1	Arm A	Arm B	Arm C
Started	60	61	60
Completed	55	54	52
Not completed	5	7	8
Consent withdrawn by subject	2	3	5
Adverse event, non-fatal	1	-	2
other	1	1	1
Lost to follow-up	1	3	-

Number of subjects in period 1	Arm D
Started	62
Completed	55
Not completed	7
Consent withdrawn by subject	4
Adverse event, non-fatal	-
other	-
Lost to follow-up	3

Baseline characteristics

Reporting groups

Reporting group title	Arm A
Reporting group description: 2 rifaximin-EIR 400 mg tablets BID for 10 days and 2 tablets of placebo BID for the following 20 days	
Reporting group title	Arm B
Reporting group description: 1 rifaximin-EIR 400 mg tablet and 1 placebo tablet BID for 30 days	
Reporting group title	Arm C
Reporting group description: 1 rifaximin-EIR 400 mg tablet and 1 placebo tablet BID for 10 days and 2 tablets of placebo BID for the following 20 days	
Reporting group title	Arm D
Reporting group description: 2 tablets of placebo BID for 30 days.	

Reporting group values	Arm A	Arm B	Arm C
Number of subjects	60	61	60
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	41.2	44.6	43.8
standard deviation	± 11.46	± 11.75	± 11.09
Gender categorical Units: Subjects			
Female	45	45	45
Male	15	16	15

Reporting group values	Arm D	Total	
Number of subjects	62	243	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days)		0 0 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	43.6		
standard deviation	± 11.16	-	
Gender categorical			
Units: Subjects			
Female	39	174	
Male	23	69	

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description: 2 rifaximin-EIR 400 mg tablets BID for 10 days and 2 tablets of placebo BID for the following 20 days	
Reporting group title	Arm B
Reporting group description: 1 rifaximin-EIR 400 mg tablet and 1 placebo tablet BID for 30 days	
Reporting group title	Arm C
Reporting group description: 1 rifaximin-EIR 400 mg tablet and 1 placebo tablet BID for 10 days and 2 tablets of placebo BID for the following 20 days	
Reporting group title	Arm D
Reporting group description: 2 tablets of placebo BID for 30 days.	

Primary: Mean change in number of rosacea inflammatory lesions

End point title	Mean change in number of rosacea inflammatory lesions
End point description: Co-primary endpoint: Mean change from Baseline/Randomization in number of rosacea inflammatory lesions at Day 30	
End point type	Primary
End point timeframe: 30 days	

End point values	Arm A	Arm B	Arm C	Arm D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	61	60	62
Units: change				
arithmetic mean (standard deviation)	-8.4 (± 12.71)	-6.7 (± 13.92)	-12.3 (± 17.07)	-8.6 (± 13.13)

Statistical analyses

Statistical analysis title	1st co-primary endpoint (A vs D)
Comparison groups	Arm A v Arm D
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Statistical analysis title	1st co-primary endpoint (B vs D)
Comparison groups	Arm B v Arm D
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Statistical analysis title	1st co-primary endpoint (C vs D)
Comparison groups	Arm C v Arm D
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Primary: Treatment success	
End point title	Treatment success
End point description:	
Co-primary endpoint:	
Percent of participants showing treatment success (IGA score) at Day 30	
End point type	Primary
End point timeframe:	
30 days	

End point values	Arm A	Arm B	Arm C	Arm D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	61	60	62
Units: percent				
number (not applicable)	11.7	11.5	8.3	14.5

Statistical analyses

Statistical analysis title	2nd co-primary endpoint
Comparison groups	Arm A v Arm B v Arm C v Arm D

Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Cochran-Mantel-Haenszel

Adverse events

Adverse events information

Timeframe for reporting adverse events:

60 days

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Arm A SAF
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Reporting group description:

All randomized subjects are included in the Safe Analysis Set (SAF).

Subjects affected by non-serious adverse events: number of subjects with at least 1 most common Treatment Emergent Adverse Event (TEAE), i.e. at least 2% in any treatment group, is reported.

Reporting group title	Arm B SAF
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Reporting group description:

All randomized subjects are included in the Safe Analysis Set (SAF).

Subjects affected by non-serious adverse events: number of subjects with at least 1 most common Treatment Emergent Adverse Event (TEAE), i.e. at least 2% in any treatment group, is reported.

Of note, the treatment kit of Group C was wrongly dispensed to 1 subject randomized to Group B; therefore, the subject is included in Group C of the SAF for the analysis.

Reporting group title	Arm C SAF
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Reporting group description:

All randomized subjects are included in the Safe Analysis Set (SAF).

Subjects affected by non-serious adverse events: number of subjects with at least 1 most common Treatment Emergent Adverse Event (TEAE), i.e. at least 2% in any treatment group, is reported.

Of note, the treatment kit of Group C was wrongly dispensed to 1 subject randomized to Group B; therefore, the subject is included in Group C of the SAF for the analysis.

Reporting group title	Arm D SAF
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Reporting group description:

All randomized subjects are included in the Safe Analysis Set (SAF).

Subjects affected by non-serious adverse events: number of subjects with at least 1 most common Treatment Emergent Adverse Event (TEAE), i.e. at least 2% in any treatment group, is reported.

Serious adverse events	Arm A SAF	Arm B SAF	Arm C SAF
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	1 / 61 (1.64%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Gastrointestinal motility disorder			

subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronavirus infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 61 (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

Serious adverse events	Arm D SAF		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 62 (1.61%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronavirus infection			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Arm A SAF	Arm B SAF	Arm C SAF
Total subjects affected by non-serious adverse events subjects affected / exposed	16 / 60 (26.67%)	14 / 60 (23.33%)	8 / 61 (13.11%)
Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3	2 / 60 (3.33%) 2	3 / 61 (4.92%) 3
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) pyrexia subjects affected / exposed occurrences (all) Vaccination site pain subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2 2 / 60 (3.33%) 2 0 / 60 (0.00%) 0	1 / 60 (1.67%) 1 1 / 60 (1.67%) 1 2 / 60 (3.33%) 2	0 / 61 (0.00%) 0 0 / 61 (0.00%) 0 0 / 61 (0.00%) 0
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1 0 / 60 (0.00%) 0	2 / 60 (3.33%) 2 1 / 60 (1.67%) 2	1 / 61 (1.64%) 1 1 / 61 (1.64%) 2
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2	0 / 60 (0.00%) 0	0 / 61 (0.00%) 0
Skin and subcutaneous tissue disorders Rosacea subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	0 / 60 (0.00%) 0	1 / 61 (1.64%) 1
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Conjunctivitis	5 / 60 (8.33%) 5	3 / 60 (5.00%) 4	2 / 61 (3.28%) 2

subjects affected / exposed	1 / 60 (1.67%)	2 / 60 (3.33%)	0 / 61 (0.00%)
occurrences (all)	1	2	0

Non-serious adverse events	Arm D SAF		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 62 (17.74%)		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
pyrexia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences (all)	1		
Vaccination site pain			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences (all)	2		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Rosacea			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences (all)	2		
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences (all)	4		
Conjunctivitis			
subjects affected / exposed	0 / 62 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 February 2019	The protocol was first amended (version 2.0) mainly to improve inclusion/exclusion criteria and statistical analysis.
04 December 2019	The version 2.0 of protocol was amended into version 3.0 to report administrative changes, to update the number of enrolling sites, to better define concomitant medications and helicobacter pylori infection assessment, to add the English version of some of the Protocol Appendices and to amend the "Subject screening and enrolment log".
06 April 2021	The version 3.0 of protocol was amended into version 4.0 to to revise some inclusion criteria and to include further stratification analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported