# 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 |

### 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 |

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<br>Units: Subjects | | | |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 41.2 | 44.6 | 43.8 |
| standard deviation | ± 11.46 | ± 11.75 | ± 11.09 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 45 | 45 | 45 |
| Male | 15 | 16 | 15 |

| Reporting group values | Arm D | Total | |
|---|---|---|---|
| Number of subjects | 62 | 243 | |
| Age categorical<br>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 | 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:<br>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:<br>Co-primary endpoint:<br>Percent of participants showing treatment success (IGA score) at Day 30 | |
| End point type | Primary |
| End point timeframe:<br>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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 24.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Arm A SAF |

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 |

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 |

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 |

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 | 3 / 60 (5.00%) | 2 / 60 (3.33%) | 3 / 61 (4.92%) |
| occurrences (all) | 3 | 2 | 3 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 1 / 60 (1.67%) | 0 / 61 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| pyrexia | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 1 / 60 (1.67%) | 0 / 61 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Vaccination site pain | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 2 / 60 (3.33%) | 0 / 61 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 2 / 60 (3.33%) | 1 / 61 (1.64%) |
| occurrences (all) | 1 | 2 | 1 |
| Nausea | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 60 (1.67%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 2 | 2 |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 0 / 60 (0.00%) | 0 / 61 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rosacea | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 60 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 5 / 60 (8.33%) | 3 / 60 (5.00%) | 2 / 61 (3.28%) |
| occurrences (all) | 5 | 4 | 2 |
| Conjunctivitis | | | |

| | | | |
|---|---|---|---|
| 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<br>subjects affected / exposed<br>occurrences (all) | 3 / 62 (4.84%)<br>4 | | |
| Conjunctivitis<br>subjects affected / exposed<br>occurrences (all) | 0 / 62 (0.00%)<br>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