



## Clinical trial results: Proof of Concept Study of Eurartesim® in Patients with Imported Uncomplicated Plasmodium Vivax Malaria Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2013-003763-56   |
| Trial protocol           | IT ES NL DE      |
| Global end of trial date | 23 November 2016 |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 11 July 2020 |
| First version publication date | 11 July 2020 |

### Trial information

#### Trial identification

|                       |                        |
|-----------------------|------------------------|
| Sponsor protocol code | ST3073-ST3074-DM13-001 |
|-----------------------|------------------------|

#### 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, Bologna, Italy,                                    |
| Public contact               | Giovanni Valentini - Medical Expert, Alfasigma S.p.A., 0039 0691393916, |
| Scientific contact           | Giovanni Valentini - Medical Expert, Alfasigma S.p.A., 0039 0691393916, |

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                       | 21 December 2018 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 02 November 2016 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 23 November 2016 |
| Was the trial ended prematurely?                     | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of an Eurartesim® treatment course in patients with imported uncomplicated P. vivax malaria. The efficacy will be primarily assessed as uncorrected Adequate Clinical and Parasitological Response (ACPR) at Day 21 of follow-up.

Protection of trial subjects:

This study was conducted in accordance with the World Medical Association Declaration of Helsinki and ICH Topic E6, Guideline for Good Clinical Practice

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 18 June 2014 |
| 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 | Spain: 2       |
| Country: Number of subjects enrolled | Germany: 5     |
| Country: Number of subjects enrolled | Italy: 18      |
| Country: Number of subjects enrolled | Switzerland: 2 |
| Worldwide total number of subjects   | 27             |
| EEA total number of subjects         | 25             |

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)                 | 1  |
| Adults (18-64 years)                      | 26 |
| From 65 to 84 years                       | 0  |

|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details:

All patients were recruited from seven study centers of four countries: Italy (Rome, Brescia and Reggio Emilia), Germany (Munich and Berlin), Spain (Barcelona) and Switzerland (Bern)

### Pre-assignment

Screening details:

Subjects screened for inclusion= 29; Subjects enrolled= 27

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

Blinding implementation details:

This was an open label study not requiring blinding conditions

### Arms

|  |  |
|--|--|
| Arm title                              | Eurartesim® oral film coated tablet                |
| Arm description: -                     |  |
| Arm type                               | Experimental                                       |
| Investigational medicinal product name | Eurartesim® (320/40mg PQP/DHA) film coated tablets |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Film-coated tablet                                 |
| Routes of administration               | Oral use   |

Dosage and administration details:

Each patient received a specific amount of drug according to his/her body weight once a day for 3 consecutive days. In case the patient was hospitalized, appropriately trained personnel administered the study treatment. Outpatients were instructed to take Eurartesim® with a dose regimen of 1 administration every 24 hours over a period of 3 days, i.e. at Day 0 at the hospital under medical supervision, then after 24 hours (Day 1) and after 48 hours (Day 2) from the first administration. The daily dose of Eurartesim® was administered with water and without food (between meals) over 3 consecutive days for a total of 3 doses taken at the same time each day.

| Number of subjects in period 1                    | Eurartesim® oral film coated tablet |
|---|-------------------------------------|
| Started   | 27                                  |
| Completed   | 20                                  |
| Not completed                                     | 7                                   |
| Major violation due to age < 18                   | 1                                   |
| Lost to follow-up                                 | 5                                   |
| Subj. left the hospital w/o medical authorization | 1                                   |



## Baseline characteristics

### Reporting groups

|   |               |
|---|---------------|
| Reporting group title   | Overall trial |
| Reporting group description:<br>The reporting group corresponds to the Intention to Treat (ITT) population that includes all patients taking at least one dose of the study drug. |               |

| Reporting group values  | Overall trial    | Total |  |
|---|------------------|-------|--|
| Number of subjects  | 27               | 27    |  |
| Age categorical<br>Units: Subjects                                      |                  |       |  |
| Adolescents (12-17 years)   | 1                | 1     |  |
| Adults (18-64 years)  | 26               | 26    |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 35.26<br>± 13.52 | -     |  |
| Gender categorical<br>Units: Subjects                                   |                  |       |  |
| Female  | 9                | 9     |  |
| Male  | 18               | 18    |  |

### Subject analysis sets

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | Per protocol (PP) |
| Subject analysis set type  | Per protocol      |

Subject analysis set description:

The Per Protocol (PP) population includes all patients who took the complete treatment and who did not meet any major protocol violations. The PP Population is the primary population for the efficacy analysis

|                            |                            |
|----------------------------|----------------------------|
| Subject analysis set title | Per protocol (PP) baseline |
| Subject analysis set type  | Per protocol               |

Subject analysis set description:

In order to be able to complete the mandatory statistical analysis section also for a single arm clinical trial a "PP baseline subject analysis set" has been created.

| Reporting group values  | Per protocol (PP) | Per protocol (PP) baseline |  |
|---|-------------------|----------------------------|--|
| Number of subjects  | 22                | 22                         |  |
| Age categorical<br>Units: Subjects                                      |                   |                            |  |
| Adolescents (12-17 years)   | 0                 | 0                          |  |
| Adults (18-64 years)  | 22                | 22                         |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 36.77<br>± 13.83  | 36.77<br>± 13.83           |  |
| Gender categorical<br>Units: Subjects                                   |                   |                            |  |
| Female  | 7                 | 7                          |  |

|      |    |    |  |
|------|----|----|--|
| Male | 15 | 15 |  |
|------|----|----|--|

|  |
|--|
|  |
|  |

## End points

### End points reporting groups

|  |                                     |
|--|-------------------------------------|
| Reporting group title  | Eurartesim® oral film coated tablet |
| Reporting group description:   | -                                   |
| Subject analysis set title   | Per protocol (PP)                   |
| Subject analysis set type  | Per protocol                        |
| Subject analysis set description:  |                                     |
| The Per Protocol (PP) population includes all patients who took the complete treatment and who did not meet any major protocol violations. The PP Population is the primary population for the efficacy analysis |                                     |
| Subject analysis set title   | Per protocol (PP) baseline          |
| Subject analysis set type  | Per protocol                        |
| Subject analysis set description:  |                                     |
| In order to be able to complete the mandatory statistical analysis section also for a single arm clinical trial a "PP baseline subject analysis set" has been created.   |                                     |

### Primary: Proportion of Subjects with Uncorrected Adequate Clinical and Parasitological Response (ACPR) at Day 21

|                        |   |
|------------------------|---|
| End point title        | Proportion of Subjects with Uncorrected Adequate Clinical and Parasitological Response (ACPR) at Day 21 |
| End point description: |   |
| End point type         | Primary   |
| End point timeframe:   |   |
| Day 21                 |   |

| End point values            | Per protocol (PP)    | Per protocol (PP) baseline |  |  |
|-----------------------------|----------------------|----------------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set       |  |  |
| Number of subjects analysed | 22                   | 22                         |  |  |
| Units: Subjects             | 18                   | 0                          |  |  |

### Statistical analyses

|  |  |
|--|--|
| Statistical analysis title   | Efficacy endpoints analysis                    |
| Statistical analysis description:  |  |
| The efficacy analysis was performed in the ITT and PP populations; however, given the nature of the study, the latter one was primary. The analysis for all the efficacy endpoints was descriptive. In addition, 95% Confidence Interval (CI) was computed with reference to the proportion of patients having Day 21 Uncorrected ACPR. The Confidence Interval for the primary end-point had a precision of 5%. |  |
| Comparison groups  | Per protocol (PP) v Per protocol (PP) baseline |

|   |                      |
|---|----------------------|
| Number of subjects included in analysis | 44                   |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | other <sup>[1]</sup> |
| Parameter estimate                      | Percentage           |
| Point estimate                          | 81.8                 |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | 59.7                 |
| upper limit                             | 94.8                 |

Notes:

[1] - In order to complete the mandatory statistical section for a single arm clinical trial the following data have been imputed: 1) the "PP baseline subject analysis set" is considered one group and the "PP subject analysis set" another group and, consequently, the n° of subjects in this analysis is 22 and not 44; 2) for the "PP baseline subject analysis set" the n° of subjects with uncorrected ACPR has been indicated as 0, as at baseline the n° of aparasitaemic subjects in the PP population was 0.

### Secondary: Proportion of Aparasitaemic Subjects at Day 1

|                        |   |
|------------------------|---|
| End point title        | Proportion of Aparasitaemic Subjects at Day 1 |
| End point description: |   |
| End point type         | Secondary                                     |
| End point timeframe:   |   |
| Day 1                  |   |

| End point values            | Per protocol (PP)    |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 22                   |  |  |  |
| Units: Subjects             | 9                    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Aparasitaemic Subjects at Day 2

|                        |   |
|------------------------|---|
| End point title        | Proportion of Aparasitaemic Subjects at Day 2 |
| End point description: |   |
| End point type         | Secondary                                     |
| End point timeframe:   |   |
| Day 2                  |   |

| End point values            | Per protocol (PP)    |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 22                   |  |  |  |
| Units: Subjects             | 20                   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Aparasitaemic Subjects at Day 7

|                        |   |
|------------------------|---|
| End point title        | Proportion of Aparasitaemic Subjects at Day 7 |
| End point description: |   |
| End point type         | Secondary                                     |
| End point timeframe:   |   |
| Day 7                  |   |

| End point values            | Per protocol (PP)    |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 22                   |  |  |  |
| Units: Subjects             | 21                   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Aparasitaemic Subjects at Day 21

|                        |  |
|------------------------|--|
| End point title        | Proportion of Aparasitaemic Subjects at Day 21 |
| End point description: |  |
| End point type         | Secondary                                      |
| End point timeframe:   |  |
| Day 21                 |  |

| End point values            | Per protocol (PP)    |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 22                   |  |  |  |
| Units: Subjects             | 18                   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Aparasitaemic Subjects at Day 42

|                 |  |
|-----------------|--|
| End point title | Proportion of Aparasitaemic Subjects at Day 42 |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 42

| End point values            | Per protocol (PP)    |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 22                   |  |  |  |
| Units: Subjects             | 16                   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Afebrile Subjects at Day 1

|                 |  |
|-----------------|--|
| End point title | Proportion of Afebrile Subjects at Day 1 |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1

| End point values            | Per protocol (PP)    |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 22                   |  |  |  |
| Units: Subjects             | 18                   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Afebrile Subjects at Day 2

|                 |  |
|-----------------|--|
| End point title | Proportion of Afebrile Subjects at Day 2 |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 2

| End point values            | Per protocol (PP)    |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 22                   |  |  |  |
| Units: Subjects             | 22                   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Afebrile Subjects at Day 7

|                 |  |
|-----------------|--|
| End point title | Proportion of Afebrile Subjects at Day 7 |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 7

| End point values            | Per protocol (PP)    |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 22                   |  |  |  |
| Units: Subjects             | 21                   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Afebrile Subjects at Day 21

|                 |   |
|-----------------|---|
| End point title | Proportion of Afebrile Subjects at Day 21 |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 21

| End point values            | Per protocol (PP)    |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 22                   |  |  |  |
| Units: Subjects             | 18                   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Afebrile Subjects at Day 42

|                 |   |
|-----------------|---|
| End point title | Proportion of Afebrile Subjects at Day 42 |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 42

|                             |                      |  |  |  |
|-----------------------------|----------------------|--|--|--|
| <b>End point values</b>     | Per protocol (PP)    |  |  |  |
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 22                   |  |  |  |
| Units: Subjects             | 16                   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Subjects with Uncorrected Adequate Clinical and Parasitological Response (ACPR) at Day 42

|                        |   |
|------------------------|---|
| End point title        | Proportion of Subjects with Uncorrected Adequate Clinical and Parasitological Response (ACPR) at Day 42 |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| Day 42                 |   |

|                             |                      |  |  |  |
|-----------------------------|----------------------|--|--|--|
| <b>End point values</b>     | Per protocol (PP)    |  |  |  |
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 22                   |  |  |  |
| Units: Subjects             | 16                   |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Subjects with Treatment Failure (TF) at Day 21

|                        |  |
|------------------------|--|
| End point title        | Proportion of Subjects with Treatment Failure (TF) at Day 21 |
| End point description: |  |
| End point type         | Secondary  |
| End point timeframe:   |  |
| Day 21                 |  |

|                             |                      |  |  |  |
|-----------------------------|----------------------|--|--|--|
| <b>End point values</b>     | Per protocol (PP)    |  |  |  |
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 22                   |  |  |  |
| Units: Subjects             | 1                    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Subjects with Treatment Failure (TF) at Day 42

|                 |  |
|-----------------|--|
| End point title | Proportion of Subjects with Treatment Failure (TF) at Day 42 |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 42

|                             |                      |  |  |  |
|-----------------------------|----------------------|--|--|--|
| <b>End point values</b>     | Per protocol (PP)    |  |  |  |
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 22                   |  |  |  |
| Units: Subjects             | 1                    |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Overall trial

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | ITT/Safety population |
|-----------------------|-----------------------|

Reporting group description:

The Intention to Treat (ITT) population includes all patients taking at least one dose of the study drug. This population is used for the safety analysis. As for the safety data presentation, it is referenced as Safety Population.

| Serious adverse events                            | ITT/Safety population |  |  |
|---|-----------------------|--|--|
| Total subjects affected by serious adverse events |                       |  |  |
| subjects affected / exposed                       | 0 / 27 (0.00%)        |  |  |
| number of deaths (all causes)                     | 0                     |  |  |
| number of deaths resulting from adverse events    | 0                     |  |  |

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

| Non-serious adverse events                            | ITT/Safety population |  |  |
|---|-----------------------|--|--|
| Total subjects affected by non-serious adverse events |                       |  |  |
| subjects affected / exposed                           | 14 / 27 (51.85%)      |  |  |
| Investigations  |                       |  |  |
| Alanine aminotransferase increased                    |                       |  |  |
| subjects affected / exposed                           | 2 / 27 (7.41%)        |  |  |
| occurrences (all)                                     | 2                     |  |  |
| Hepatic enzyme increased                              |                       |  |  |
| subjects affected / exposed                           | 1 / 27 (3.70%)        |  |  |
| occurrences (all)                                     | 1                     |  |  |
| Transaminases abnormal                                |                       |  |  |
| subjects affected / exposed                           | 1 / 27 (3.70%)        |  |  |
| occurrences (all)                                     | 1                     |  |  |
| Transaminases increased                               |                       |  |  |

|  |   |  |  |
|--|---|--|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 27 (3.70%)<br>1   |  |  |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)   | 1 / 27 (3.70%)<br>1   |  |  |
| Cardiac disorders<br>Palpitations<br>subjects affected / exposed<br>occurrences (all)  | 1 / 27 (3.70%)<br>1   |  |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)   | 1 / 27 (3.70%)<br>1   |  |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspepsia<br>subjects affected / exposed<br>occurrences (all)<br><br>Vomiting<br>subjects affected / exposed<br>occurrences (all) | 1 / 27 (3.70%)<br>1<br><br>1 / 27 (3.70%)<br>1<br><br>1 / 27 (3.70%)<br>1<br><br>4 / 27 (14.81%)<br>5 |  |  |
| Hepatobiliary disorders<br>Hypertransaminasaemia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 27 (3.70%)<br>1   |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)   | 2 / 27 (7.41%)<br>2   |  |  |
| Skin and subcutaneous tissue disorders   |   |  |  |

|  |   |  |  |
|--|---|--|--|
| Rash maculo-papular<br>subjects affected / exposed<br>occurrences (all)  | 1 / 27 (3.70%)<br>1   |  |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 27 (3.70%)<br>1   |  |  |
| Infections and infestations<br>Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Pneumonia<br>subjects affected / exposed<br>occurrences (all) | 1 / 27 (3.70%)<br>1<br><br>1 / 27 (3.70%)<br>1<br><br>1 / 27 (3.70%)<br>1 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date             | Interruption   | Restart date |
|------------------|--|--------------|
| 23 November 2016 | A total of 100 male and female patients satisfying the inclusion criteria and presenting none of the exclusion criteria had to be enrolled in the study. However, the study was prematurely interrupted due to a very low rate of recruitment. | -            |

Notes:

### Limitations and caveats

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

A total of 100 male and female patients satisfying the inclusion criteria and presenting none of the exclusion criteria had to be enrolled in the study. However, the study was prematurely interrupted due to a very low rate of recruitment.

Notes: