



## Clinical trial results:

### Proton pump inhibition for secondary hemochromatosis in hereditary anemia, a phase III placebo controlled randomized cross-over clinical trial.

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2017-003777-34 |
| Trial protocol           | NL             |
| Global end of trial date | 12 April 2021  |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 21 May 2022  |
| First version publication date | 21 May 2022  |

#### Trial information

##### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | NL63198.041.17 |
|-----------------------|----------------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | UMC Utrecht   |
| Sponsor organisation address | Heidelberglaan 100, Utrecht, Netherlands,                                     |
| Public contact               | Van Creveldkliniek, UMC Utrecht, 0031 088-7558450, vck-research@umcutrecht.nl |
| Scientific contact           | Van Creveldkliniek, UMC Utrecht, 0031 088-7558450, vck-research@umcutrecht.nl |

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                       | 12 April 2021 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 12 April 2021 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 12 April 2021 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

To show that PPIs compared to placebo are an effective treatment of secondary hemochromatosis in a relative large number of patients with hereditary anemia and mild to moderate iron overload.

Protection of trial subjects:

Strict monitoring scheme according to trial protocol.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 14 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: 30 |
| Worldwide total number of subjects   | 30              |
| EEA total number of subjects         | 30              |

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)                      | 26 |
| From 65 to 84 years                       | 4  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Not applicable.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | First trial year (12 months)                                  |
| Is this the baseline period? | Yes   |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind  |
| Roles blinded                | Investigator, Monitor, Subject, Data analyst, Carer, Assessor |

### Arms

|                              |              |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes          |
| <b>Arm title</b>             | Esomeprazole |

Arm description:

Esomeprazole 40mg BID

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Esomeprazole |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

40 milligram twice daily

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description: -

|   |         |
|---|---------|
| Arm type  | placebo |
| No investigational medicinal product assigned in this arm |         |

| Number of subjects in period 1 | Esomeprazole | Placebo |
|--------------------------------|--------------|---------|
| Started                        | 16           | 14      |
| Completed                      | 14           | 14      |
| Not completed                  | 2            | 0       |
| Consent withdrawn by subject   | 2            | -       |

**Period 2**

|                              |   |
|------------------------------|---|
| Period 2 title               | Second trial year (12 months)                                 |
| Is this the baseline period? | No  |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

**Arms**

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description: -

|          |         |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

|  |         |
|--|---------|
| Investigational medicinal product name | Placebo |
|--|---------|

|  |  |
|--|--|
| Investigational medicinal product code |  |
|--|--|

|            |  |
|------------|--|
| Other name |  |
|------------|--|

|                      |         |
|----------------------|---------|
| Pharmaceutical forms | Capsule |
|----------------------|---------|

|                          |          |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

Twice daily 1 capsule

|                  |              |
|------------------|--------------|
| <b>Arm title</b> | Esomeprazole |
|------------------|--------------|

Arm description:

Esomeprazole 40mg BID

|          |              |
|----------|--------------|
| Arm type | experimental |
|----------|--------------|

No investigational medicinal product assigned in this arm

| <b>Number of subjects in period 2</b> | Placebo | Esomeprazole |
|---------------------------------------|---------|--------------|
| Started                               | 14      | 14           |
| Completed                             | 12      | 12           |
| Not completed                         | 2       | 2            |
| Consent withdrawn by subject          | 2       | 2            |

## Baseline characteristics

### Reporting groups

|   |              |
|---|--------------|
| Reporting group title                                 | Esomeprazole |
| Reporting group description:<br>Esomeprazole 40mg BID |              |
| Reporting group title                                 | Placebo      |
| Reporting group description: -                        |              |

| Reporting group values                             | Esomeprazole | Placebo  | Total |
|--|--------------|----------|-------|
| Number of subjects                                 | 16           | 14       | 30    |
| Age categorical                                    |              |          |       |
| 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)                               | 14           | 14       | 28    |
| From 65-84 years                                   | 2            | 0        | 2     |
| 85 years and over                                  | 0            | 0        | 0     |
| Age continuous                                     |              |          |       |
| Age continuous                                     |              |          |       |
| Units: years                                       |              |          |       |
| median   | 47           | 35       |       |
| inter-quartile range (Q1-Q3)                       | 19 to 66     | 23 to 59 | -     |
| Gender categorical                                 |              |          |       |
| Units: Subjects                                    |              |          |       |
| Female   | 9            | 6        | 15    |
| Male   | 7            | 8        | 15    |
| Deferasirox (DFX) use                              |              |          |       |
| Units: Subjects                                    |              |          |       |
| No DFX   | 10           | 9        | 19    |
| DFX  | 6            | 5        | 11    |

## End points

### End points reporting groups

|                                |              |
|--------------------------------|--------------|
| Reporting group title          | Esomeprazole |
| Reporting group description:   |              |
| Esomeprazole 40mg BID          |              |
| Reporting group title          | Placebo      |
| Reporting group description: - |              |
| Reporting group title          | Placebo      |
| Reporting group description: - |              |
| Reporting group title          | Esomeprazole |
| Reporting group description:   |              |
| Esomeprazole 40mg BID          |              |

### Primary: Change in delta liver iron content (delta LIC)

|   |  |
|---|--|
| End point title   | Change in delta liver iron content (delta LIC) |
| End point description:  |  |
| Cross-over design. Difference in change when comparing both treatments. |  |
| End point type  | Primary  |
| End point timeframe:  |  |
| Comparison of two treatments of both 12 months.                         |  |

| End point values                     | Esomeprazole      | Placebo           |  |  |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed          | 16 <sup>[1]</sup> | 14 <sup>[2]</sup> |  |  |
| Units: mg Fe/g dw                    |                   |                   |  |  |
| arithmetic mean (standard deviation) | -0.11 (± 0.75)    | -0.57 (± 1.20)    |  |  |

Notes:

[1] - All esomeprazole periods.

[2] - All placebo periods.

### Statistical analyses

|  |                                |
|--|--------------------------------|
| Statistical analysis title   | Primary efficacy analysis      |
| Statistical analysis description:  |                                |
| Linear mixed model with delta LIC as dependent variable, a random intercept at patient level and treatment as independent variable. Sex, iron chelator use, (period) baseline LIC and randomized order of treatment were included as covariates. |                                |
| Comparison groups  | Placebo v Esomeprazole         |
| Number of subjects included in analysis  | 30                             |
| Analysis specification   | Pre-specified                  |
| Analysis type  | superiority                    |
| P-value  | < 0.05                         |
| Method   | Mixed models analysis          |
| Parameter estimate   | Mean difference (final values) |
| Point estimate   | -0.55                          |

| Confidence interval |         |
|---------------------|---------|
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -1.06   |
| upper limit         | -0.05   |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Length of trial.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |       |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

|                    |   |
|--------------------|---|
| Dictionary version | 4 |
|--------------------|---|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Esomeprazole |
|-----------------------|--------------|

Reporting group description:

All patients that received esomeprazole.

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

All patients that received placebo.

| Serious adverse events                            | Esomeprazole    | Placebo         |  |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events |                 |                 |  |
| subjects affected / exposed                       | 5 / 30 (16.67%) | 3 / 26 (11.54%) |  |
| number of deaths (all causes)                     | 0               | 0               |  |
| number of deaths resulting from adverse events    |                 |                 |  |
| Investigations                                    |                 |                 |  |
| Abdominal pain                                    |                 |                 |  |
| subjects affected / exposed                       | 1 / 30 (3.33%)  | 0 / 26 (0.00%)  |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders              |                 |                 |  |
| Vaso-occlusive crisis                             |                 |                 |  |
| subjects affected / exposed                       | 0 / 30 (0.00%)  | 2 / 26 (7.69%)  |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 6           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Rectus hematoma                                   |                 |                 |  |
| subjects affected / exposed                       | 1 / 30 (3.33%)  | 0 / 26 (0.00%)  |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                           |                 |                 |  |
| Cholecystitis acute                               |                 |                 |  |

|   |   |                |  |
|---|---|----------------|--|
| subjects affected / exposed                     | 1 / 30 (3.33%)                          | 0 / 26 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1                                   | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0                                   | 0 / 0          |  |
| Infections and infestations                     |   |                |  |
| Endocarditis bacterial                          | Additional description: Mechanic valve. |                |  |
| subjects affected / exposed                     | 1 / 30 (3.33%)                          | 1 / 26 (3.85%) |  |
| occurrences causally related to treatment / all | 0 / 2                                   | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0                                   | 0 / 0          |  |
| Pneumonia                                       |   |                |  |
| subjects affected / exposed                     | 1 / 30 (3.33%)                          | 0 / 26 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1                                   | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0                                   | 0 / 0          |  |
| Enterococcal bacteraemia                        |   |                |  |
| subjects affected / exposed                     | 0 / 30 (0.00%)                          | 1 / 26 (3.85%) |  |
| occurrences causally related to treatment / all | 0 / 0                                   | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0                                   | 0 / 0          |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                     | <b>Esomeprazole</b> | <b>Placebo</b>   |  |
|---|---------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                     |                  |  |
| subjects affected / exposed                           | 15 / 30 (50.00%)    | 17 / 26 (65.38%) |  |
| Social circumstances                                  |                     |                  |  |
| Malaise   |                     |                  |  |
| subjects affected / exposed                           | 3 / 30 (10.00%)     | 1 / 26 (3.85%)   |  |
| occurrences (all)                                     | 3                   | 1                |  |
| Fatigue   |                     |                  |  |
| subjects affected / exposed                           | 1 / 30 (3.33%)      | 2 / 26 (7.69%)   |  |
| occurrences (all)                                     | 1                   | 2                |  |
| Gastrointestinal disorders                            |                     |                  |  |
| Nausea  |                     |                  |  |
| subjects affected / exposed                           | 1 / 30 (3.33%)      | 3 / 26 (11.54%)  |  |
| occurrences (all)                                     | 1                   | 3                |  |
| Epigastric discomfort                                 |                     |                  |  |

|  |                        |                        |  |
|--|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 30 (3.33%)<br>1    | 2 / 26 (7.69%)<br>2    |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 6 / 30 (20.00%)<br>6   | 2 / 26 (7.69%)<br>2    |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)   | 3 / 30 (10.00%)<br>3   | 0 / 26 (0.00%)<br>0    |  |
| Respiratory, thoracic and mediastinal disorders<br>Lower respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 3 / 30 (10.00%)<br>3   | 4 / 26 (15.38%)<br>4   |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)  | 10 / 30 (33.33%)<br>17 | 10 / 26 (38.46%)<br>23 |  |
| Renal and urinary disorders<br>Acute kidney injury<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 30 (0.00%)<br>0    | 1 / 26 (3.85%)<br>1    |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 30 (3.33%)<br>1    | 0 / 26 (0.00%)<br>0    |  |
| Infections and infestations<br>Flue<br>subjects affected / exposed<br>occurrences (all)  | 2 / 30 (6.67%)<br>2    | 1 / 26 (3.85%)<br>1    |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 09 April 2018     | Addition of one additional participating center.<br>Minor adjustments inclusion criteria. |
| 06 June 2018      | Addition of one additional participating center.  |
| 26 September 2018 | Adjustment inclusion criteria: deletion of transferrin saturation criterion.              |
| 08 April 2019     | Adjustment/correction sample size calculation.  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported