



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 |
| Arm title | 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

| | |
|------------------|---------|
| Arm title | 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 |
|------------------------------|-----|

| | |
|------------------|---------|
| Arm title | 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

| | |
|------------------|--------------|
| Arm title | Esomeprazole |
|------------------|--------------|

Arm description:

Esomeprazole 40mg BID

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

No investigational medicinal product assigned in this arm

| Number of subjects in period 2 | 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: 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 ^[1] | 14 ^[2] | | |
| 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 %

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported