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