Clinical trial results:
Efficacy of zinc on human hepatic copper uptake: A randomized intervention study

Summary

EudraCT number	2019-000905-57
Trial protocol	DK
Global end of trial date	01 October 2020

Results information

Result version number	v1 (current)
This version publication date	07 October 2021
First version publication date	07 October 2021

Trial information

Trial identification

Sponsor protocol code	N/A

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Department of Hepatology & Gastroenterology
Sponsor organisation address	Palle Juul-Jensens Boulevard 99, Aarhus N, Denmark, 8200
Public contact	Thomas Sandahl, Aarhus University Hospital , thomsand@rm.dk
Scientific contact	Thomas Sandahl, Aarhus University Hospital , thomsand@rm.dk

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	19 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 September 2020
Global end of trial reached?	Yes
Global end of trial date	01 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy of zinc on blocking human gut copper uptake in relation to the type of zinc (zinc acetate/zinc gluconate) and the dose regimen (once a day/ thrice a day). This is quantified by 64CuCl2 PET/CT scans.

Protection of trial subjects:

Blood samples to exclude unknown liver/kidney disease at inclusion
Medical observation for at least 30 minutes after tracer intake
Medical observation during scans including stethoscopy and blood pressure before and after the scan

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 May 2019
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	Denmark: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	27
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were included from the 30th of May 2019 to the 28th of January 2020 by advertisements at the hospital, on a trial participant recruitment website and in a local newspaper.

Pre-assignment

Screening details:

Interested volunteers would send an e-mail and have the participant information forwarded. If still interested after reading this, they would receive a phone call to set a date for the inclusion conversation.

Pre-assignment period milestones

Number of subjects started	40
Number of subjects completed	40

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Zinc acetate 50 mg x 3

Arm description:

Control treatment

Arm type	Active comparator
Investigational medicinal product name	Wilzin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

50 mg thrice daily, one hour fast before and after oral intake

Arm title	Zinc acetate 150 mg x 1

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Wilzin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

150 mg once daily, one hour fast before and after oral intake

Arm title	Zinc gluconate 50 mg x 3

Arm description: -

Arm type	Experimental

Investigational medicinal product name	Zink "Natur-Drogeriet"
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

50 mg thrice daily, one hour fast before and after oral intake

Arm title	Zinc gluconate 150 mg x 1

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Zink "Natur-Drogeriet"
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg once daily, one hour fast before and after oral intake

Number of subjects in period 1	Zinc acetate 50 mg x 3	Zinc acetate 150 mg x 1	Zinc gluconate 50 mg x 3
Started	10	10	10
Completed	10	9	9
Not completed	0	1	1
Technical error before end-of-treatment scan	-	1	-
Other illness before baseline scan	-	-	1

Number of subjects in period 1	Zinc gluconate 150 mg x 1
Started	10
Completed	10
Not completed	0
Technical error before end-of-treatment scan	-
Other illness before baseline scan	-

Baseline characteristics

Reporting groups	
Reporting group title	Zinc acetate 50 mg x 3
Reporting group description: Control treatment	
Reporting group title	Zinc acetate 150 mg x 1
Reporting group description: -	
Reporting group title	Zinc gluconate 50 mg x 3
Reporting group description: -	
Reporting group title	Zinc gluconate 150 mg x 1
Reporting group description: -	

Reporting group values	Zinc acetate 50 mg x 3	Zinc acetate 150 mg x 1	Zinc gluconate 50 mg x 3
Number of subjects	10	10	10
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)	9	6	5
From 65-84 years	1	4	5
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	6	6	6
Male	4	4	4
Body mass index Units: N/A			
arithmetic mean	23.2	23.4	24.3
standard deviation	± 3.3	± 2.5	± 2.3
Plasma zinc Units: Micromole/L			
arithmetic mean	11.3	12.3	11.0
standard deviation	± 1.7	± 2.5	± 1.0
Alanine aminotransferase Units: U/L			
arithmetic mean	25.2	27.8	20.7
standard deviation	± 13.2	± 10.1	± 7.5
Bilirubin Units: micromole(s)/litre			
arithmetic mean	10.4	12.2	14.4
standard deviation	± 2.8	± 6.0	± 4.7
Creatinine			

Units: micromole(s)/litre			
arithmetic mean	69.6	61.9	65.9
standard deviation	± 13.1	± 11.6	± 10.9

Reporting group values	Zinc gluconate 150 mg x 1	Total	
Number of subjects	10	40	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	7	27	
From 65-84 years	3	13	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	9	27	
Male	1	13	
Body mass index			
Units: N/A			
arithmetic mean	23.6		
standard deviation	± 3.1	-	
Plasma zinc			
Units: Micromole/L			
arithmetic mean	11.4		
standard deviation	± 1.6	-	
Alanine aminotransferase			
Units: U/L			
arithmetic mean	24.7		
standard deviation	± 8.8	-	
Bilirubin			
Units: micromole(s)/litre			
arithmetic mean	11.3		
standard deviation	± 5.7	-	
Creatinine			
Units: micromole(s)/litre			
arithmetic mean	61.1		
standard deviation	± 7.0	-	

Subject analysis sets	
Subject analysis set title	All completed participants
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All participants with baseline and end-of-treatment scan	

Reporting group values	All completed participants		
Number of subjects	37		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Gender categorical Units: Subjects			
Female	24		
Male	13		
Body mass index Units: N/A arithmetic mean standard deviation	±		
Plasma zinc Units: Micromole/L arithmetic mean standard deviation	±		
Alanine aminotransferase Units: U/L arithmetic mean standard deviation	±		
Bilirubin Units: micromole(s)/litre arithmetic mean standard deviation	±		
Creatinine Units: micromole(s)/litre arithmetic mean standard deviation	±		

End points

End points reporting groups	
Reporting group title	Zinc acetate 50 mg x 3
Reporting group description: Control treatment	
Reporting group title	Zinc acetate 150 mg x 1
Reporting group description: -	
Reporting group title	Zinc gluconate 50 mg x 3
Reporting group description: -	
Reporting group title	Zinc gluconate 150 mg x 1
Reporting group description: -	
Subject analysis set title	All completed participants
Subject analysis set type	Intention-to-treat
Subject analysis set description: All participants with baseline and end-of-treatment scan	

Primary: Ratio (mean hepatic SUV)	
End point title	Ratio (mean hepatic SUV)
End point description: Mean hepatic SUV on follow-up scan divided by mean hepatic SUV on baseline scan yielding a ratio between the two	
End point type	Primary
End point timeframe: Continuous assessment of PET data during the study	

End point values	Zinc acetate 50 mg x 3	Zinc acetate 150 mg x 1	Zinc gluconate 50 mg x 3	Zinc gluconate 150 mg x 1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	9	9	9
Units: N/A				
arithmetic mean (standard deviation)	0.57 (± 0.34)	0.63 (± 0.33)	0.50 (± 0.22)	0.85 (± 0.41)

Statistical analyses

Statistical analysis title	Difference in ratio among the groups
Statistical analysis description: Oneway ANOVA	
Comparison groups	Zinc acetate 50 mg x 3 v Zinc acetate 150 mg x 1 v Zinc gluconate 50 mg x 3 v Zinc gluconate 150 mg x 1

Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.15
Method	ANOVA

Primary: Noninferiority test

End point title	Noninferiority test[1]

End point description:

Difference between means (standard treatment vs. test treatment)
Non-inferiority margin of 25% (based on the lower 95% confidence interval around the estimated difference between standard treatment and no treatment and a clinical judgement about how much of the margin should be preserved).

End point type	Primary

End point timeframe:

PET data was analysed through out the study. The analysis was performed after all data was collected.

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The noninferiority test compares test treatments against standard treatment, thus no values are appropriate for standard treatment baseline arm

End point values	Zinc acetate 150 mg x 1	Zinc gluconate 50 mg x 3	Zinc gluconate 150 mg x 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	9	
Units: percent				
arithmetic mean (confidence interval 95%)	5.7 (-26.6 to 38.1)	-7.3 (-35.0 to 20.4)	28.5 (-7.4 to 64.4)	

Statistical analyses

Statistical analysis title	Noninferiority

Statistical analysis description:

Non-inferiority analysis with a non-inferiority margin of 25% (based on the lower 95% confidence interval around the estimated difference between standard treatment and no treatment and a clinical judgement about how much of the margin should be preserved (75%)).

Comparison groups	Zinc gluconate 50 mg x 3 v Zinc acetate 150 mg x 1 v Zinc gluconate 150 mg x 1
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.01 [2]
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	-7.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-35
upper limit	20.4

Notes:

[2] - For only non inferior treatment zinc gluconate 50 mg x 3

Secondary: Adverse events

End point title	Adverse events

End point description:

End point type	Secondary

End point timeframe:

Collected through out the study

End point values	Zinc acetate 50 mg x 3	Zinc acetate 150 mg x 1	Zinc gluconate 50 mg x 3	Zinc gluconate 150 mg x 1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	9	9	9
Units: Numbers				
Gastric discomfort	2	4	0	1
Nausea	5	5	1	2
Headache	0	2	0	0
Palpitation	0	1	0	0
Obstipation	0	2	0	0

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Compliance

End point title	Compliance

End point description:

End point type	Other pre-specified

End point timeframe:

Assessment after study termination

End point values	Zinc acetate 50 mg x 3	Zinc acetate 150 mg x 1	Zinc gluconate 50 mg x 3	Zinc gluconate 150 mg x 1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	9	9	9
Units: percent				
median (full range (min-max))	97.5 (96 to 100)	87.6 (46 to 100)	96 (90 to 100)	99.2 (96 to 100)

Statistical analyses

Statistical analysis title	Difference between groups
Comparison groups	Zinc acetate 50 mg x 3 v Zinc acetate 150 mg x 1 v Zinc gluconate 50 mg x 3 v Zinc gluconate 150 mg x 1
Number of subjects included in analysis	37
Analysis specification	Post-hoc
Analysis type	other
P-value	> 0.05
Method	ANOVA

Post-hoc: Plasma zinc after treatment

End point title	Plasma zinc after treatment

End point description:

End point type	Post-hoc

End point timeframe:

Continuous assessment during the study

End point values	Zinc acetate 50 mg x 3	Zinc acetate 150 mg x 1	Zinc gluconate 50 mg x 3	Zinc gluconate 150 mg x 1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	5	9	5
Units: Micromole/L				
arithmetic mean (standard deviation)	25.2 (± 5.0)	20.4 (± 4.0)	18.9 (± 4.3)	17.3 (± 1.5)

Statistical analyses

Statistical analysis title	Difference among groups
Comparison groups	Zinc acetate 50 mg x 3 v Zinc acetate 150 mg x 1 v Zinc gluconate 50 mg x 3 v Zinc gluconate 150 mg x 1

Number of subjects included in analysis	24
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.04
Method	ANOVA

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
14 days after last scan	
Adverse event reporting additional description:	
By the participant calling an investigator - registered in REDCap directly By the participant noting it on sheet handed out for drug and adverse event registration - registered in REDCap after trial completion	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups	
Reporting group title	Zinc acetate 50 mg x 3
Reporting group description: -	
Reporting group title	Zinc acetate 150 mg x 1
Reporting group description: -	
Reporting group title	Zinc gluconate 50 mg x 3
Reporting group description: -	
Reporting group title	Zinc gluconate 150 mg x 1
Reporting group description: -	

Serious adverse events	Zinc acetate 50 mg x 3	Zinc acetate 150 mg x 1	Zinc gluconate 50 mg x 3
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Zinc gluconate 150 mg x 1		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Zinc acetate 50 mg x 3	Zinc acetate 150 mg x 1	Zinc gluconate 50 mg x 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 10 (70.00%)	8 / 9 (88.89%)	1 / 9 (11.11%)
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Headache			
subjects affected / exposed	0 / 10 (0.00%)	2 / 9 (22.22%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Discomfort			
subjects affected / exposed	2 / 10 (20.00%)	4 / 9 (44.44%)	0 / 9 (0.00%)
occurrences (all)	2	4	0
Nausea			
subjects affected / exposed	5 / 10 (50.00%)	5 / 9 (55.56%)	1 / 9 (11.11%)
occurrences (all)	5	5	1
Obstipation			
subjects affected / exposed	0 / 10 (0.00%)	2 / 9 (22.22%)	0 / 9 (0.00%)
occurrences (all)	0	2	0

Non-serious adverse events	Zinc gluconate 150 mg x 1		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)		
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Headache			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Discomfort			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		

Nausea subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2		
Obstipation subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 November 2019	We added an additional treatment arm with zinc gluconate 50 mg x 3 daily (10 participants). This to be able to compare the zinc formula if taken thrice daily similar to the control treatment. Furthermore, a plasma zinc sample on all remaining participants was added. This to investigate if the variance in effect of zinc on hepatic copper uptake could by explained by zinc levels. The amendment was not considered to modify any ethical considerations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported