Clinical trial results:
Effects of Mg-orotate on cardiocirculatory performance and adaptations at the muscular level: A double-blind, randomized, explorative, placebo-controlled, cross-over pilot study

Summary

EudraCT number	2013-003418-42
Trial protocol	DE
Global end of trial date	14 February 2018

Results information

Result version number	v1 (current)
This version publication date	01 March 2022
First version publication date	01 March 2022
Summary attachment (see zip file)	Trial Report Summary (200623_WOE-2013-TUE_Synopsis_Final1.1_of_Study_Report_Final1.0_geschw.pdf)

Trial information

Trial identification

Sponsor protocol code	WOE_2013_TUE

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Wörwag Pharma GmbH & Co. KG
Sponsor organisation address	Flugfeld-Allee 24, 71034 Böblingen, Germany,
Public contact	Global Clinical Research, Wörwag Pharma GmbH & Co. KG, +49 70316204416, claudia.reule@woerwagpharma.com
Scientific contact	Global Clinical Research, Wörwag Pharma GmbH & Co. KG, +49 70316204416, claudia.reule@woerwagpharma.com

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	13 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 February 2018
Global end of trial reached?	Yes
Global end of trial date	14 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

We performed an explorative pilot study in healthy individuals to address the question whether Mg-orotate might generally affect parameters of cardiorespiratory fitness during a 4 week training intervention period. We further analyzed skeletal muscle expression levels of a panel of genes known to be involved in structural, functional, and metabolic adaptation pathways in order to elucidate potential impacts of Mg-orotate supplementation on skeletal muscle remodeling processes.

Protection of trial subjects:

Before study initialization, favourable opinion was received from the Ethics Committee of the University Hospital of Tübingen and approval from the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte). This study is registered at EudraCT (2013-003418-42). The study was performed in compliance with ICH Good Clinical Practice (GCP) and the Declaration of Helsinki, including the archiving of essential documents.
All subjects provided written informed consent to participate in the study prior to being screened.
The subject information sheet detailed the procedures involved in the study (aims, methodology, potential risks, anticipated benefits) and the investigator explained these to each subject. Each subject signed the consent form to indicate that the information had been explained and understood. Every subject was then allowed time to consider the information presented before signing and dating the informed consent form to indicate that they fully understood the information, and willingly volunteered to participate in the study.
Before the intake phase, 2 dropouts occured due to acute illness. These subjects were later reincluded after their recovery.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 September 2016
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	Germany: 12
Worldwide total number of subjects	12
EEA total number of subjects	12

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	12
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at University Hospital Tübingen (Germany) at the Department of Sports Medicine. A total of 12 healthy men between 18 and 35 were assessed for eligibility and randomized. No exclusions and 2 dropouts occured. The first participant was enrolled on September 27th, 2016, and the last study visit took place on February 14th, 2018

Pre-assignment

Screening details:

All subjects provided written informed consent to participate prior to being screened. At visit 1 a physical examination took place, vital signs were measured, lactate diagnostics based on spiroergometry were concluded, and blood samples were taken. At visit 2 the randomisation took place.

Period 1

Period 1 title	Visit 2 - 4
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Verum, Placebo + Training

Arm description:

4500mg magnesium orotate dihydrate per day for 28 days with training.

Arm type	Experimental
Investigational medicinal product name	Magnesium orotate dihydrate
Investigational medicinal product code	
Other name	Magnerot Classic N
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral intake of three tablets of 500mg Magnerot Classic N (Magnesium orotate dihydrate), three times per day (=4500mg/d) for 28 days.

Arm title	Placebo, Verum + Training

Arm description:

Placebo for 28 days, with training

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Three tablets of placebo, three times per day for 28 days.

Arm title	Verum, Placebo

Arm description:

4500mg magnesium orotate dihydrate per day for 28 days without training.

Arm type	Experimental

Investigational medicinal product name	Magnesium orotate dihydrate
Investigational medicinal product code	
Other name	Magnerot Classic N
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral intake of three tablets of 500mg Magnerot Classic N (Magnesium orotate dihydrate), three times per day (=4500mg/d) for 28 days.

Arm title	Placebo, Verum

Arm description:

Placebo for 28 days, without training

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Three tablets of placebo, three times per day for 28 days.

Number of subjects in period 1	Verum, Placebo + Training	Placebo, Verum + Training	Verum, Placebo
Started	3	3	3
Completed	3	3	3

Number of subjects in period 1	Placebo, Verum
Started	3
Completed	3

Period 2

Period 2 title	Visit 6 - 8
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes

Arm title	Verum, Placebo + Training

Arm description:

Placebo for 28 days, with training.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Three tablets of placebo, three times per day for 28 days.

Arm title	Placebo, Verum + Training

Arm description:

4500mg magnesium orotate dihydrate per day for 28 days with training.

Arm type	Experimental
Investigational medicinal product name	Magnesium orotate dihydrate
Investigational medicinal product code	
Other name	Magnerot Classic N
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral intake of three tablets of 500mg Magnerot Classic N (Magnesium orotate dihydrate), three times per day (=4500mg/d) for 28 days.

Arm title	Verum, Placebo

Arm description:

Placebo for 28 days, without training.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Three tablets of placebo, three times per day for 28 days.

Arm title	Placebo, Verum

Arm description:

4500mg magnesium orotate dihydrate per day for 28 days without training.

Arm type	Experimental
Investigational medicinal product name	Magnesium orotate dihydrate
Investigational medicinal product code	
Other name	Magnerot Classic N
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral intake of three tablets of 500mg Magnerot Classic N (Magnesium orotate dihydrate), three times per day (=4500mg/d) for 28 days.

Number of subjects in period 2	Verum, Placebo + Training	Placebo, Verum + Training	Verum, Placebo
Started	3	3	3
Completed	3	3	3

Number of subjects in period 2	Placebo, Verum
Started	3
Completed	3

Period 3	
Period 3 title	Visit 1
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	No Training

Arm description:

Subjects performed no training parallel to the intake of the verum/placebo.

Arm type	Screening
Investigational medicinal product name	Magnesium orotate dihydrate
Investigational medicinal product code	
Other name	Magnerot Classic N
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

No intake yet.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

No intake yet.

Arm title	Training

Arm description:

Subjects performed aerobic training parallel to the intake of the verum/placebo.

Arm type	Screening

Investigational medicinal product name	Magnesium orotate dihydrate
Investigational medicinal product code	
Other name	Magnerot Classic N
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

No intake yet.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

No intake yet.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The baseline period was added subsequently as a separate period and could not be set as period 1 due to the system structure.

Number of subjects in period 3	No Training	Training
Started	6	6
Completed	6	6

Baseline characteristics

Reporting groups	
Reporting group title	No Training
Reporting group description:	
Subjects performed no training parallel to the intake of the verum/placebo.	
Reporting group title	Training
Reporting group description:	
Subjects performed aerobic training parallel to the intake of the verum/placebo.	

Reporting group values	No Training	Training	Total
Number of subjects	6	6	12
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)	6	6	12
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	26.67	24.50	
standard deviation	± 3.83	± 5.32	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	6	6	12
Weight Units: kilogram(s)			
arithmetic mean	77.88	72.58	
standard deviation	± 18.69	± 14.90	-
BMI Units: kilogram(s)/square meter			
arithmetic mean	24.08	22.86	
standard deviation	± 4.45	± 4.12	-

End points

End points reporting groups

Reporting group title	Verum, Placebo + Training
Reporting group description: 4500mg magnesium orotate dihydrate per day for 28 days with training.	
Reporting group title	Placebo, Verum + Training
Reporting group description: Placebo for 28 days, with training	
Reporting group title	Verum, Placebo
Reporting group description: 4500mg magnesium orotate dihydrate per day for 28 days without training.	
Reporting group title	Placebo, Verum
Reporting group description: Placebo for 28 days, without training	
Reporting group title	Verum, Placebo + Training
Reporting group description: Placebo for 28 days, with training.	
Reporting group title	Placebo, Verum + Training
Reporting group description: 4500mg magnesium orotate dihydrate per day for 28 days with training.	
Reporting group title	Verum, Placebo
Reporting group description: Placebo for 28 days, without training.	
Reporting group title	Placebo, Verum
Reporting group description: 4500mg magnesium orotate dihydrate per day for 28 days without training.	
Reporting group title	No Training
Reporting group description: Subjects performed no training parallel to the intake of the verum/placebo.	
Reporting group title	Training
Reporting group description: Subjects performed aerobic training parallel to the intake of the verum/placebo.	
Subject analysis set title	Verum
Subject analysis set type	Full analysis
Subject analysis set description: Analysis of period with magnesium orotate dihydrate administration	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description: Analysis of period with placebo administration	

Primary: Delta VO2max

End point title	Delta VO2max
End point description: Change of maximal oxygen uptake (VO2max) from start to end of period	
End point type	Primary
End point timeframe: start to end of period; between visit 2 and between 4 and visits 6 and 8 respectively	

End point values	No Training	Training	Verum	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	12	12
Units: millilitre(s)/kilogramBW/minute				
arithmetic mean (confidence interval 95%)	-0.50 (-4.03 to 3.03)	2.25 (-0.32 to 4.82)	0.17 (-2.53 to 2.86)	1.58 (-0.40 to 3.56)

Statistical analyses

Statistical analysis title	3-way ANOVA Training v No Training

Statistical analysis description:

3-way variance analysis with fixed effects for medication and training and random effects for subjects. Subject and medication effects are combined. Cross-over design is considered by using intra-individual differences. Period effect and cross-over effects are checked. All parameters are described with descriptive statistcs (sample size, frequency, relative frequency, maximum, minimum, median, standard deviation, 95% confidence interval).
This method was used for all endpoints.

Comparison groups	Training v No Training
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.0789 [2]
Method	ANOVA

Notes:

[1] - Linear additive mixed model for explanatory data analysis.

[2] - 3-way ANOVA

Statistical analysis title	3-way ANOVA Verum v Placebo

Statistical analysis description:

3-way variance analysis with fixed effects for medication and training and random effects for subjects. Subject and medication effects are combined. Cross-over design is considered by using intra-individual differences. Period effect and cross-over effects are checked. All parameters are described with descriptive statistcs (sample size, frequency, relative frequency, maximum, minimum, median, standard deviation, 95% confidence interval).
This method was used for all endpoints.

Comparison groups	Verum v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.337 [4]
Method	ANOVA

Notes:

[3] - Linear additive mixed model for explanatory data analysis.
Regarding "number of subjects included": Due to the crossover design the subjects are part of both analyzed groups. Hence, the correct number of subjects included is 12.

[4] - 3-way ANOVA

Secondary: Delta AT

End point title	Delta AT

End point description:	
Change of oxygen uptake (VO2) at anaerobic threshold (AT)	
End point type	Secondary
End point timeframe:	
start to end of period; between visit 2 and between 4 and visits 6 and 8 respectively	

End point values	No Training	Training	Verum	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	12	12
Units: millilitre(s)/kilogramBW/min				
arithmetic mean (confidence interval 95%)	-0.33 (-1.81 to 1.14)	1.00 (-2.74 to 4.74)	1.00 (-1.48 to 3.48)	-0.33 (-3.07 to 2.41)

Statistical analyses

No statistical analyses for this end point

Secondary: Delta LT

End point title	Delta LT
End point description:	
Change of lactate threshold (LT)	
End point type	Secondary
End point timeframe:	
start to end of period; between visit 2 and between 4 and visits 6 and 8 respectively	

End point values	No Training	Training	Verum	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	12	12
Units: watt/kilogrammBW				
arithmetic mean (confidence interval 95%)	-0.02 (-0.07 to 0.03)	0.10 (0.00 to 0.20)	-0.03 (-0.10 to 0.04)	0.12 (-0.01 to 0.24)

Statistical analyses

No statistical analyses for this end point

Secondary: Delta Pmax

End point title	Delta Pmax
End point description:	
Change of maximal power from start to end of period	
End point type	Secondary

End point timeframe:

start to end of period; between visit 2 and between 4 and visits 6 and 8 respectively

End point values	No Training	Training	Verum	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	12	12
Units: watt				
arithmetic mean (confidence interval 95%)	1.75 (-7.83 to 11.33)	26.17 (13.08 to 39.25)	11.17 (-0.79 to 23.12)	16.75 (5.52 to 27.98)

Statistical analyses

No statistical analyses for this end point

Secondary: FC MSTN

End point title	FC MSTN

End point description:

Fold change of muscular myostatin mRNA, log2-transformed (MSTN gene expression)

End point type	Secondary

End point timeframe:

Start to end of period; between visit 2 and between 4 and visits 6 and 8 respectively

End point values	No Training	Training	Verum	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	12	12
Units: log2 fold change				
arithmetic mean (confidence interval 95%)	-0.25 (-0.61 to 0.11)	-0.75 (-1.01 to -0.49)	-0.63 (-0.93 to -0.34)	-0.37 (-0.63 to -0.11)

Statistical analyses

No statistical analyses for this end point

Secondary: FC LDHB

End point title	FC LDHB

End point description:

Fold change of muscular lactate dehydrogenase B mRNA, log2-transformed (LDHB gene expression)

End point type	Secondary

End point timeframe:

Start to end of period; between visit 2 and between 4 and visits 6 and 8 respectively

End point values	No Training	Training	Verum	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	12	12
Units: log2 fold change				
arithmetic mean (confidence interval 95%)	-0.04 (-0.37 to 0.28)	0.37 (0.13 to 0.61)	0.20 (-0.05 to 0.46)	0.12 (-0.14 to 0.39)

Statistical analyses

No statistical analyses for this end point

Secondary: FC TRIM63

End point title	FC TRIM63

End point description:

Fold change of muscular Tripartite Motif Containing 63 / muscle-specific RING finger protein 1 mRNA, log2-transformed (TRIM63 gene expression)

End point type	Secondary

End point timeframe:

Start to end of period; between visit 2 and between 4 and visits 6 and 8 respectively

End point values	No Training	Training	Verum	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	12	12
Units: log2 fold change				
arithmetic mean (confidence interval 95%)	-0.12 (-0.58 to 0.33)	-0.48 (-0.85 to -0.11)	-0.52 (-0.91 to -0.13)	-0.08 (-0.37 to 0.21)

Statistical analyses

No statistical analyses for this end point

Secondary: FC FBXO32

End point title	FC FBXO32

End point description:

Fold change of period of muscular F-Box Protein 32 / Atrogin-1 mRNA, log2-transformed (FBXO32 gene expression)

End point type	Secondary

End point timeframe:

Start to end of period; between visit 2 and between 4 and visits 6 and 8 respectively

End point values	No Training	Training	Verum	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	12	12
Units: log2 fold change				
arithmetic mean (confidence interval 95%)	-0.32 (-0.57 to -0.08)	-0.59 (-1.07 to -0.11)	-0.66 (-1.09 to -0.23)	-0.26 (-0.54 to 0.02)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected from visit 1 until the end of the trial.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1
Reporting groups	
Reporting group title	Verum
Reporting group description:	
Reported adverse events during intake of Magnesium orotate dihydrate	
Reporting group title	Placebo
Reporting group description:	
Reported adverse events during intake of placebo	

Serious adverse events	Verum	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Verum	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 12 (25.00%)	3 / 12 (25.00%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Presyncope			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Toothache			

subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Infections and infestations			
Pulpitis dental			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 May 2015	Investigator change

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Small number of patients (pilot study);

Notes: